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Lutz F. Tietze, Theophil Eicher, Ulf Diederichsen,
Andreas Speicher, and Nina Schützenmeister

Reactions and Syntheses

in the Organic Chemistry Laboratory

Second, Completely Revised and Updated Edition

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Reactions and Syntheses

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Preface to the First Edition

1 Background

The book *Reaktionen und Synthesen im organisch-chemischen Praktikum und Forschungslaboratorium* was first published in German in 1981, with a second edition in 1991, and was translated into Japanese in 1984 (second edition 1995), English in 1989, Chinese in 1999, Russian in 2000, and Korean in 2002. The intention was

- to associate classes of compounds and functionalities with reaction types and mechanisms,
- to offer a great number of reliable preparative procedures of general importance, and
- to show the usefulness and robustness of the offered procedures for the synthesis of selected interesting compounds of relevance in biology, pharmacy, and medicine.

Since the last German edition, many new preparative procedures have been developed showing high chemo, regio, diastereo, and enantioselectivity, which frequently approach the selectivity of enzymatic transformations with the advantage of lower substrate specificity. In addition, new methods such as combinatorial chemistry, solid-phase chemistry, high-pressure chemistry, and the use of microwaves for heating have been introduced. Moreover, the efficiency of a synthesis, which can be defined as the increase in complexity per transformation, the avoidance of toxic reagents and solvents, and the preservation of resources are important issues in modern preparative organic chemistry. Significant developments in the last years have been realized in transition-metal catalysis, organocatalysis, and domino reactions. This progress has been impressively documented in *Classics of Total Synthesis* [1], *Organic Synthesis Highlights* [2], and *Domino Reactions in Organic Synthesis* [3].

As a consequence, we now present this book *Reactions and Syntheses in the Organic Chemistry Laboratory* in a new form with respect to its concept and organization and extensively renewed with respect to its content.

Its major highlights are as follows:

1. The basic units as well as the main objectives are *syntheses* (up to multistep

syntheses with more than five steps) of interesting and instructive target molecules from various fields of organic chemistry. Each synthesis is centered around one or more methods and reaction principles of general synthetic relevance.

2. As before, the users of the new book are provided with carefully elaborated experiments, which are described in preparative and analytical detail. However, experiments and syntheses are accompanied throughout in concentrated form by the required general, theoretical, and mechanistic background and explanations. Special attention is given to retrosynthetic analysis and alternative approaches of synthesis for a given target molecule.
3. To allow the inclusion of a representative and qualified spectrum of contemporary synthetic methods, more than 70% of the content of the former book has been replaced by more recent and more relevant experimental examples. The remaining (older) syntheses have been “updated” with respect to description of their general background.

Considering the various types of users of the book in the past, there has been a definite and broad acceptance among chemists and pharmacists on a more advanced level, besides graduate students and researchers in universities and industry. From these considerations, the following consequences have emerged for the third edition:

- General laboratory information, such as safety, first aid, performance of chemical reactions, instrumentation and standard apparatus, and isolation and purification of products, has been omitted. Methods for the formation and transformation of basic functional groups in organic compounds, regarded as important at the elementary education level in organic laboratory practice, are not described. These topics are comprehensively covered in other relevant textbooks [4–6].
- The deletion of these elementary aspects of organic chemistry has allowed us to describe in more detail of the advanced synthetic methods and to include mechanistic aspects and to incorporate total syntheses and retrosynthetic analyses.

2 Organization of the Book and Directions for Its Use

The book is divided into four chapters with several sections:

Chapter **1**: C–C bond formation

Chapter **2**: Oxidation and reduction

Chapter **3**: Heterocyclic compounds

Chapter **4**: Selected natural products.

The sections (e.g., **1.1** and **1.2**) contain procedures and syntheses (e.g., 1.1.1 and 1.1.2) as specified at the beginning of the section and in the *Table of Contents* (cf. p. II). Each synthesis is organized as follows:

1. In the general part (a), the *structural formula* of the target molecule and the *topics* of the presented synthesis (important for rapid information!) are given, which is followed by *introductory information* on the target molecule, *retrosynthesis* [7], and *planning of the synthesis* (possibilities, strategies, and synthetic alternatives; considerations on practicability for laboratory use).
2. In part (b), the *synthesis of the target molecule* and the *synthetic steps* performed in the experimental part are described. This is accompanied by information about the mechanism(s), the stereochemical outcome, and the selectivity of the transformations (specific reaction principles). Finally, the number of steps performed and the yields obtained are summarized. In general, Section (b) contains a complete *scheme of the synthesis* performed.
3. In Section (c), individual *experimental procedures* are described. Each procedure has the following structure:
    a. An identification number, which characterizes the prepared compound according to chapter, section, and synthesis (e.g., **1.1.1.1** and **1.1.1.2**); the identification number carries one or more asterisks (*, **, ***) according to the degree of difficulty of the procedure.
    b. Literature reference(s) for the prepared compound.
    c. A formula equation, which gives structures of reactants and products, and their relative molecular masses. In general, apparatus is not discussed in detail; however, in special cases, information about specialized

equipment (photochemical, high-pressure, microwave, etc.) is given.

d. Throughout, the procedures are presented in two parts. The first, describing the reaction, often includes additional notes about purification and characteristics of the substrates, such as toxicity and safety aspects. The second describes the work-up, isolation, and purification of the product, along with criteria of purity (mp, bp, n_D, TLC/R_f, $[\alpha]_D$), notes about characteristics of the product, and other crucial experimental details.

e. Characterization of the product by spectral data (IR, UV–vis, ^1H and ^{13}C NMR, MS). In selected cases, the preparation of derivatives together with their instrumental and chemical analysis is given.

4. The presentation of each synthesis is concluded by a compilation of the *literature references* cited in Sections (a–c). They cover the primary literature on the synthesis, its steps, and its topics, and refer to important collective articles, reviews, and textbooks of advanced organic chemistry [8].

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Preface to the Second Edition

Since the appearance of the first edition of the book *Reaction and Syntheses* in 2007, new facets in synthesis have arisen. The synthesis of chemical compounds is still a key issue in chemistry not only in academia but also in industry, but besides the chemo, region, diastereo, and enantioselectivity, new aspects in synthesis have gained importance: efficiency, reduction of waste, conservation of our resources, protecting of our environment, and finally also economic advantages by reducing the transformation time and the amount of the needed chemicals. Therefore, we have added a fifth chapter, which deals with domino reactions to meet all these requirements. A domino reaction is defined as a process of two or more bond-forming reactions under identical reaction conditions, in which the latter transformations take place on the functionalities obtained in the former bond-forming reactions [1]. In the process, one, two, three, and more substrates can be involved. Thus, multicomponent transformations are domino reactions per definition. The quality and the usefulness of domino reactions are related to the increase in complexity and diversity in the final product compared to the starting material.

In addition, besides the Heck, the Suzuki–Miyaura, and Songashira reactions, we have also added novel transition-metal-catalyzed reactions such as the alkene as well as the alkyne ring-closing metathesis and an enantioselective Wacker oxidation; furthermore, novel Ru catalysts are prepared, and organocatalytic reactions have been introduced. Moreover, examples of CH activation in organic synthesis are included and also novel interesting classes of new materials as molecular switches.

Finally, some procedures, which did not meet our expectations in reproducibility, have been removed or modified.

On the other hand, we did not change the concept with the retrosynthetic analysis of the products and discussing the mechanism of the different steps, because this approach has been highly successful and proven its value.

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Göttingen and Saarbrücken, Germany Summer 2014

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About the Authors

Lutz F. Tietze obtained his Ph.D. in 1968 in Kiel. He then worked as a research associate with Prof. G. Büchi at MIT, Cambridge, USA, as well as with Prof. A. Battersby in Cambridge, UK. Since 1978 he has been Professor and Head of the Institute of Organic and Biomolecular Chemistry at the Georg-August-University in Göttingen. His research focuses on the development of efficient synthetic methods as domino reactions, the total synthesis of natural products, and the design of new selective anticancer agents. Professor Tietze has received many prizes, inter alia the highly prestigious Emil Fischer Medal of the GDCh. He was speaker of a Sonderforschungsbereich, delegate of the DFG Fachkollegium and obtained several guest professorships. He is member of the Göttingen Academy of Sciences and Humanities, Dr. h.c. of the University of Szeged, Chairman of the DZfCh, member of the DHKZ, and has been awarded in 2012 with the position of a Distinguished Research Professor. He has over 460 papers, 34 patents and five books to his name.

Theophil Eicher studied chemistry at the University of Heidelberg, Germany,

and obtained his Ph.D. under Georg Wittig in 1960. After postdoctoral work at Columbia University, New York, USA, in the laboratories of Ronald Breslow, he habilitated 1967 at the University of Würzburg, Germany, under Siegfried Hünig. In 1974 he was appointed as Associate Professor at the University of Hamburg, Germany, in 1976 as Full Professor of Organic Chemistry at the University of Dortmund, Germany. Since 1982, he worked as Full Professor at Saarland University, Germany, and was retired in 2000. His research interests concerned the synthetic chemistry of cyclopropenones and triafulvenes, as well as natural product synthesis in the field of bryophyte constituents. He is co-author of several books. Jointly with L. F. Tietze, he was awarded the literature prize of the ``Fonds der chemischen Industrie". He is Dr. h. c. and Prof. a. h. of the Facultad de Quimica of the Universidad de la Republica, Montevideo/Uruguay.

Ulf Diederichsen studied Chemistry in Freiburg, Germany, with a diploma work in organic synthesis and completed his Ph.D. in 1993 under the supervision of Albert Eschenmoser at the ETH Zürich working on homo-and glucose-DNA. After postdoctoral work on radical chemistry at the University of Pittsburgh, USA, in the group of Dennis Curran, he gained his habilitation at the Technical University Munich, Germany. In 1999, he was appointed professor of Organic Chemistry at the University Würzburg, Germany, until joining the Georg-August-University in Göttingen, Germany, in 2001 as full professor of Organic Chemistry. He was visiting professor at the LMU Munich and Goering Visiting Professor at the University of Wisconsin, USA. He got the Karl Winnacker stipend and Hellmut-Bredereck award and is member of Göttingen Academy of Sciences and Humanities.

Andreas Speicher studied chemistry at Saarland University, Germany. He obtained his Ph.D. in 1994 under Theophil Eicher and was honored with the Eduard-Martin-Award of his university. He started his independent scientific career and completed habilitation in 2003. He is head of a research group and university lecturer for organic chemistry at the Saarland University and was appointed extraordinary professor in 2011. He is temporarily holding a guest professorship at the University of Strasbourg/France since 2006 and is co-author of several books. His research interests are directed to synthesis and characterization of chemically and biologically relevant natural products, especially to axially chiral macrocyclic compounds.

Nina Schützenmeister studied chemistry at the Georg-August-University in Göttingen. After finishing her diploma thesis at the ETH Zürich in the group of Peter H. Seeberger she completed her Ph.D. in 2012 under supervision of Lutz F. Tietze at the Georg-August-University in Göttingen. She then worked as a postdoctoral fellow with Christian Griesinger at the Max-Planck-Institute for Biophysical Chemistry in Göttingen and is currently a Marie-Curie fellow in the group of Varinder K. Aggarwal F.R.S. at the University of Bristol, United Kingdom.

Abbreviations and Symbols

General Abbreviations and Symbols

g	gram
mg	milligram
l	liter
ml	milliliter
mol	mole
mmol	millimole
min	minute(s)
h	hour(s)
d	day(s)
°C	degrees Celsius
%	percent
mp	melting point
bp	boiling point
n^{20}_{D}	refractive index at Na D line (at 20 °C)
$[\alpha]_{D}$	specific rotation
M_r	relative mass
ee	enantiomeric excess
dr	diastereomeric ratio
ds	diastereoselectivity
TLC	thin-layer chromatography
HPLC	high-performance liquid chromatography
ca.	approximately
cf.	compare
dec.	decomposition
ed.	edition
Ed(s).	editor(s)

eq	equivalent
equiv	equivalent
et al.	and others (lat. *et alii*)
i.e.	that means (lat. *id est*)
p.	page
ref.	literature reference
rt	room temperature
)))	sonification
vs.	as opposed to (lat. versus)

Spectroscopic Abbreviations

IR	infrared spectrum
$\tilde{\nu}$	wave number (cm^{-1})
^{1}H NMR	proton nuclear magnetic resonance spectrum
^{13}C NMR	^{13}C nuclear magnetic resonance spectrum
δ (ppm)	chemical shift relative to tetramethylsilane ($\delta_{TMS} = 0$)
s	singlet
d	doublet
dd	doublet of doublets
t	triplet
dt	doublet of triplets
q	quartet
quint	quintet
sext	sextet
sept	septet
m	multiplet
br	broad
Hz	hertz
J	coupling constant
UV–vis	ultraviolet–visible spectrum
nm	nanometer

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λ_{max} (log ϵ)	wavelength of the absorption maximum (molar extinction coefficient)

Abbreviations for Substituents…

Ac	$-COCH_3$ acetyl
All	$-CH=CH_2CH_2$ allyl
Ar	aryl
Me	$-CH_3$ methyl
Et	$-CH_2CH_3$ ethyl
Pr	$-CH_2CH_2CH_3$ propyl
*i*Pr	$-CH(CH_3)_2$ *iso*-propyl
*n*Bu	$-(CH_2)_3CH_3$ *n*-butyl
*i*Bu	$-CH_2CH(CH_3)_2$ *iso*-butyl
*s*Bu	$-CH(CH_3)CH_2CH_3$ *sec*-butyl
*t*Bu	$-C(CH_3)_3$ *tert*-butyl
Mes	$-SO_2CH_3$ methanesulfonyl
Ph	$-C_6H_5$ phenyl
Tf	$-SO_2CF_3$ trifluoromethanesulfonyl
Tos	$-SO_2C_6H_4CH_3$ *p*-toluenesulfonyl
Bn	benzyl
Bu	butyl
Boc	*tert*-butoxycarbonyl
Bz	benzoyl
Cbz	carbonylbenzyloxy
Cp	cyclopentadienyl
Cy	cyclohexyl
Fmoc	9-fluorenylmethoxy-carbonyl
MEM	(2-methoxyethoxy)-methyl
MOM	methoxymethyl

MTM	methylthiomethyl
Piv	pivalate
PMB	*p*-methoxybenzyl
TBDMS or TBS	*tert*-butyldimethylsilyl
TBDPS or TBPS	*tert*-butyldiphenylsilyl
TES	triethylsilyl
TMS	trimethylsilyl
TIPS	triisopropylsilyl
Tol	tolyl

…and Commonly Used Compounds and Special Expressions…

acac	acetylacetone
ACCN	1,1′-azobis(cyclohexanecarbonitrile)
Ac_2O	acetic anhydride
AcOH	acetic acid
AIBN	2,2′-azobisisobutyronitrile
ARC	anionic relay chemistry
ASG	anion stabilizing group
ATBT	allyltri-*n*-butyltin
atm	standard atmosphere
BAIB	(diacetoxyiodo)benzene
BER	borohydride exchange resin
$BF_3{\cdot}OEt_2$	boron trifluoride–diethyl ether complex
BHT	butylhydroxytoluene
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthalene
BINAPO	2-diphenylphosphino-2′-diphenylphosphinyl-1,1′-binaphthalene
BINOL	1,1′-bi-2-naphthol
Biphep	1,1′-biphenyl-2,2′-diphenylphosphine
[Bmim]	1-butyl-3-methylimidazolium

borsm	based on recovered starting material
bpz	2,2′-bipyrazine
CA	cycloaddition
CAN	ceric ammonium nitrate
CD	circular dichroism
CM	cross-metathesis
cod	1,5-cyclooctadiene
coe	cyclooctene
CR	cycloreversion
CSA	camphorsulfonic acid
DA	Diels–Alder reactions
DABCO	1,4-diazabicyclo[2.2.2]octane
DAIB	(diacetoxy)iodobenzene
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCB	1,2-dichloroisobutane
DCE	1,2-dichloroethane
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DFT	density functional theory
DHQ	hydroquinine
DHQD	dihydroquinidine
DIB	(diacetoxyiodo)benzene
DIBAL	diisobutylaluminum hydride
DIOP	4,5-bis(diphenylphosphinomethyl)-2,2-dimethyl-1,3-dioxolane
DIPEA	diisopropylethylamine
DKP	diketopiperazine
DLP	1,2-dichloroethane with lauroyl peroxide
DMA	*N*,*N*-dimethylacetamide
DMAD	dimethyl acetylenedicarboxylate
DME	dimethoxyethane

DMF	*N*,*N*-dimethylformamide
DMP	Dess–Martin-periodinane
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
DMPU	*N*,*N*-dimethyl propylene urea
DMSO	dimethyl sulfoxide
DOS	diversity-oriented synthesis
dpm	dipivaloylmethane
dppe	1,2-bis(diphenylphosphino)ethane
dppf	1,2-bis(diphenylphosphino)ferrocene
dppp	1,3-bis(diphenylphosphino)propane
DTBP	2,6-di-*tert*-butylpyridine
E	electrophile
EC	electrocyclization
ERO	electrocyclic ring-opening
EWG	electron-withdrawing group
fod	1,1,1,2,2,3,3,3-heptafluoro-7,7-dimethyl-4,6-octanedionate
GAP	group-assisted purification
HAT	hydrogen atom transfer
HFIP	hexafluoroisopropanol
HIV	human immunodeficiency virus
HMPA	hexamethylphosphortriamide
HOMO	highest occupied molecular orbital
IBX	2-iodoxybenzoic acid
IMDA	intramolecular Diels–Alder reaction
L	ligand
LDA	lithium diisopropylamide
LG	leaving group
LiHMDS	lithium hexamethyldisilazide
LUMO	lowest unoccupied molecular orbital
MAOS	microwave-assisted organic synthesis
MBH	Morita–Baylis–Hillman

MDRs	multicomponent domino reactions
(*S*,*S*)-MeDuPhos	(+)-1,2-bis[(2*S*,5*S*)-2,5-dimethylphospholano]benzene
MeCN	acetonitrile
MEK	methyl ethyl ketone
MW	microwave
NADH	nicotinamide adenine dinucleotide
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NMM	*N*-methyl morpholine
NMO	*N*-methylmorpholine-*N*-oxide
NMP	*N*-methyl-2-pyrrolidinone
NP	natural product
Ns	*p*-nitrobenzenesulfonyl
Nu	nucleophile
o-DCB	*ortho*-dichlorobenzene
PCC	pyridinium chlorochromate
PET	photochemical electron transfer
PEG	polyethylene glycol
PFBA	pentafluorobenzoic acid
PG	protecting group
Phen	9,10-phenanthroline
PhMe	toluene
PIDA	phenyliodine diacetate
PNO	pyridine-*N*-oxide
PPh_3	triphenylphosphine
PPTS	pyridinium *p*-toluenesulfonate
PS-BEMP	polystyrene-(2-*tert*-butylimino-2-diethylamino-1,-dimethyl-perhydro-1,3,2-diazaphosphorine)
PS-DMAP	polystyrene-dimethylaminopyridine
p-TsOH or	*p*-tolylsulfinic acid

p-TSA	
PVE	propargyl vinyl ether
Py	pyridine
R	rest
rac	racemic
RCM	ring-closing metathesis
ROM	ring-opening metathesis
RRM	ring-rearrangement metathesis
SEM	2-trimethylsilylethoxymethoxy
SET	single electron transfer
sigR	sigmatropic rearrangement
S_N	nucleophilic substitution
S_N1	substitution nucleophilic unimolecular
S_N2	substitution nucleophilic bimolecular
SolFC	solvent free condition
SOMO	singly occupied molecular orbital
SPPS	solid-phase peptide synthesis
t	*tert*
TADDOL	(−)-(4*R*,5*R*)- or (+)(4*S*,5*S*)-2,2-dimethyl-α,α,α′,α′-tetraphenyl-1,3-dioxolane-4,5-dimethanol
TBA	tetra-*n*-butylammonium
TBA	tribromoacetic acid
TBAB	tetra-*n*-butylammonium bromide
TBAF	tetra-*n*-butylammonium fluoride
TBAI	tetra-*n*-butylammonium iodide
TBCHD	2,4,4,6-tetrabromo-2,5-cyclohexadienone
TBD	1,5,7-triazabicyclo[4.4.0]dec-5-ene
TBPA	[tris(4-bromophenyl)aminium hexachloroantimonate]
TBPS	*tert*-butyldiphenylsilyl
t-BuOH	*tert*-butyl alcohol
t-BuOK	*tert*-butylate potassium

TC	thiophene-2-carboxylate
TEA	triethylamine
TEBA	benzyltriethylammonium chloride
TEMPO	tetramethylpiperidinyl-1-oxy
TESOTf	triethylsilyltrifluoromethanesulfonate
TFA	trifluoroacetic acid
TFE	2,2,2-trifluorethanol
TfO	trifluoromethanesulfonate
TFP	tri-(2-furyl)phosphine
THF	tetrahydrofuran
$(TMS)_2NH$	hexamethyldisilazane or bis(trimethylsilyl)amine
TMSOTf	trimethylsilyl trifluromethanesulfonate
Thio	thiophene
TMEDA	tetramethylethylenediamine
TMSI	trimethylsilyl iodide or iodotrimethylsilane
TS	transition state
TsOH	*p*-tolunesulfonic acid
TTMSS	tris(trimethylsilyl)silane
VAPOL	2,2′-diphenyl-(4-biphenanthrol)
XPhos	2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl

…and Retrosynthesis

disc	bond disconnection
FGI	functional group interconversion
FGA	functional group addition

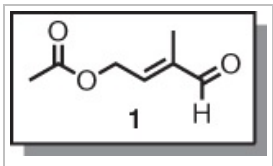
Chapter 1
C–C Bond Formation

C–C bond formations are essential for the construction of the backbone of any organic compound, and their mechanistic description can be used as a general tool for their classification. Thus, in Sections 1.1–1.8, the focus is on transformations in which nucleophilic, electrophilic, radical, and pericyclic reactions as well as reactions mediated by organometallics and transition-metal compounds play the decisive role.

In Section 1.1, examples are given of nucleophilic additions to the carbonyl group of aldehydes, ketones, and derivatives of carboxylic acids (esters, anhydrides, etc.) as well as addition to acceptor-substituted olefins (Michael addition) and carbonyl olefination. In Section 1.2, alkylation reactions of aldehydes, ketones, carboxylic acids, and β-dicarbonyl compounds at their α-and γ-positions are described. In Section 1.3, reactions of the aldol and Mannich type and in Section 1.4, electrophilic and nucleophilic acylation reactions are depicted. Section 1.5 deals with reactions of alkenes proceeding via carbenium ions and Section 1.6 with transition-metal-catalyzed reactions such as the Heck reaction and Suzuki–Miyaura, Sonogashira, and metathesis reactions. In Section 1.7, pericyclic reactions such as cycloadditions, electrocyclic transformations, and sigmatropic reactions, and, finally, in Section 1.8 some basic radical reactions are described. Further transition-metal-catalyzed transformations such as the Wacker oxidation are described in Chapters 2 and 5.

1.1 Nucleophilic Addition to Aldehydes, Ketones, Carboxylic Acid Derivatives (Esters, Anhydrides), and α,β-Unsaturated Carbonyl Compounds; Carbonyl Olefination

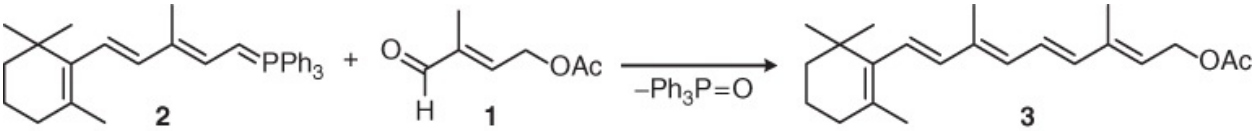
1.1.1 (*E*)-4-Acetoxy-2-methyl-2-butenal

 1	***Topics:***	• Preparation of a C_5-building block for vitamin A

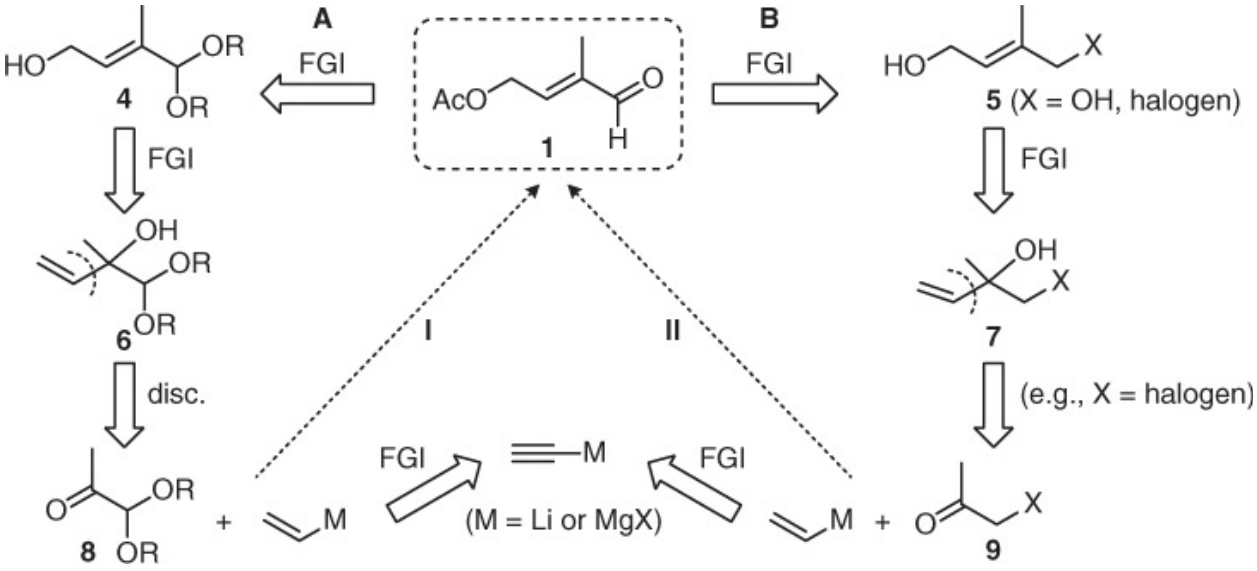
		synthesis • Allylic alcohols from ketones and vinyl Grignard compounds • Acetylation of an allyl alcohol with allylic inversion • Kornblum oxidation R–CH_2–X → R–CH=O

(a) General

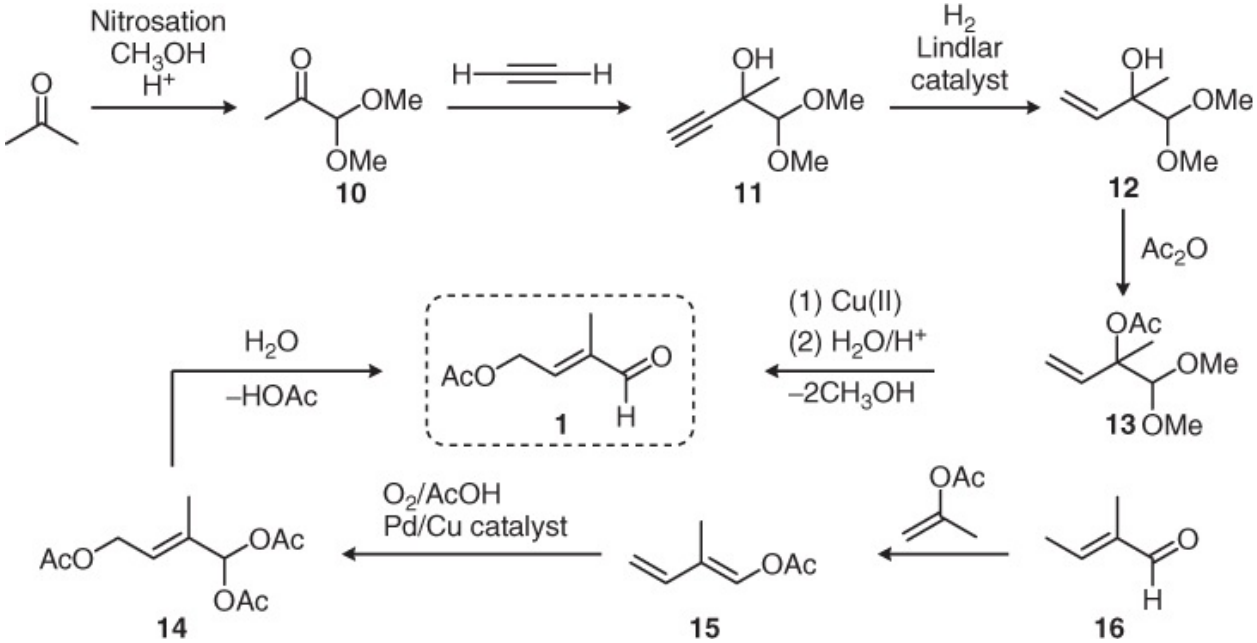
(*E*)-2-Methyl-2-butenal bearing an acetoxy group at the 4-position can be regarded as a functional isoprene unit and is used as a C_5-building block for the synthesis of terpenes by carbonyl olefination [1]. Thus, in the classical industrial vitamin A synthesis of BASF (cf. Section 4.1.5), (*E*)-4-acetoxy-2-methyl-2-butenal (**1**) is combined with the C_{15}-ylide **2** in a Wittig reaction to give vitamin A acetate **3**:



Retrosynthesis of the target molecule **1** can be conducted in two directions (**A**/**B**) via the intermediates **4**/**5** and further by allylic inversions to allyl alcohols **6**/**7**. These should result from the acetone derivatives **8**/**9** either by addition of allyl metals or by ethynylation followed by partial hydrogenation of the primarily formed acetylenic alcohols (approaches **I**/**II**). Both approaches **I** and **II** have been described in Refs [2, 3].

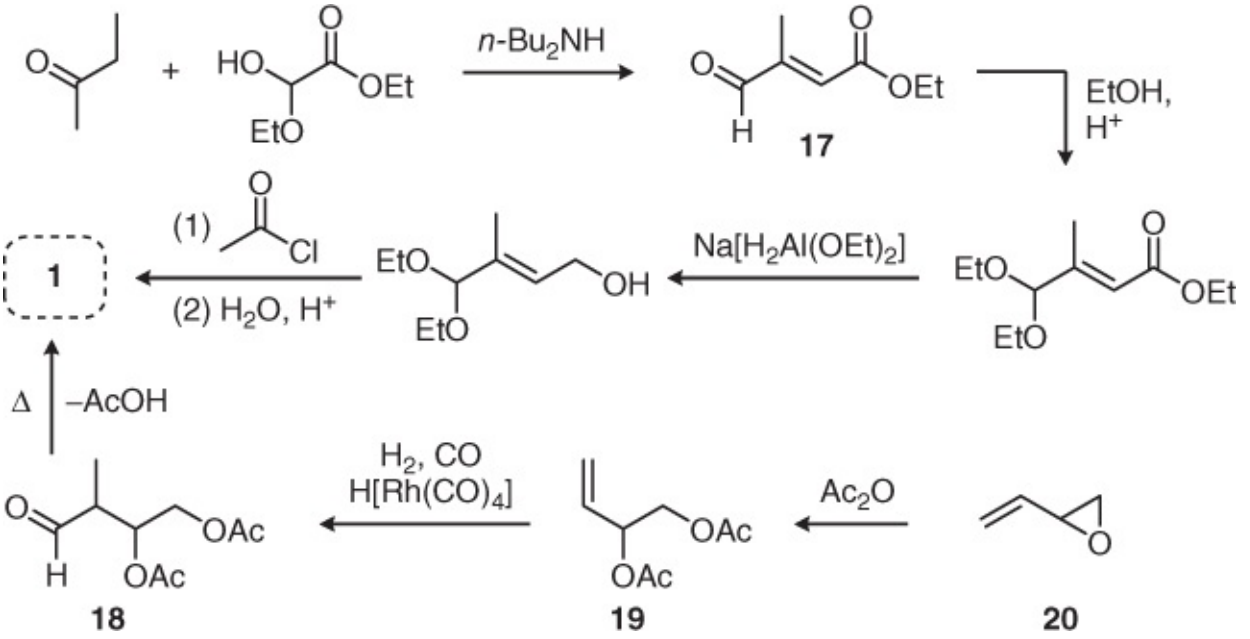


Approach **I** corresponds to a former industrial synthesis of **1** by BASF [2], starting with oxidation (nitrosation in the presence of methanol) of acetone to give methylglyoxal dimethyl acetal (**10**). This is followed by ethynylation with acetylene, partial hydrogenation, and acetylation (**10** → **11** → **12** → **13**). The synthesis is completed by a Cu(II)-catalyzed allylic inversion and acid hydrolysis of the acetal function (**13** → **1**). Alternatively, oxygenation of the dienol acetate **15** with O_2 in glacial acetic acid in the presence of a Pd/Cu catalyst leads to the allyl-inverted acylal **14**. Hydrolysis of the latter gives **1** [4, 5]; **15** can be obtained from the readily available tiglic aldehyde (**16**) and isopropenyl acetate:

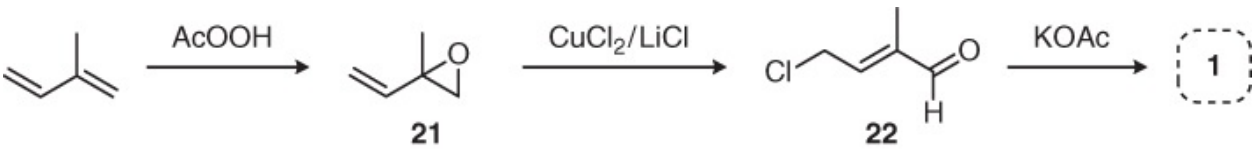


Approach **II** is the basis of a laboratory synthesis of **1** [3], which is described in detail in Section (b).

More recently, two other processes have been introduced for the industrial syntheses of **1** [6], starting from (i) 3-formyl crotonate **17** and (ii) 3,4-epoxy-1-butene (**20**), respectively. In (ii), the key step is a regioselective Rh-catalyzed hydrocarbonylation (→**18**) of the diacetate **19**, obtained by ring opening of **20** with acetic anhydride.

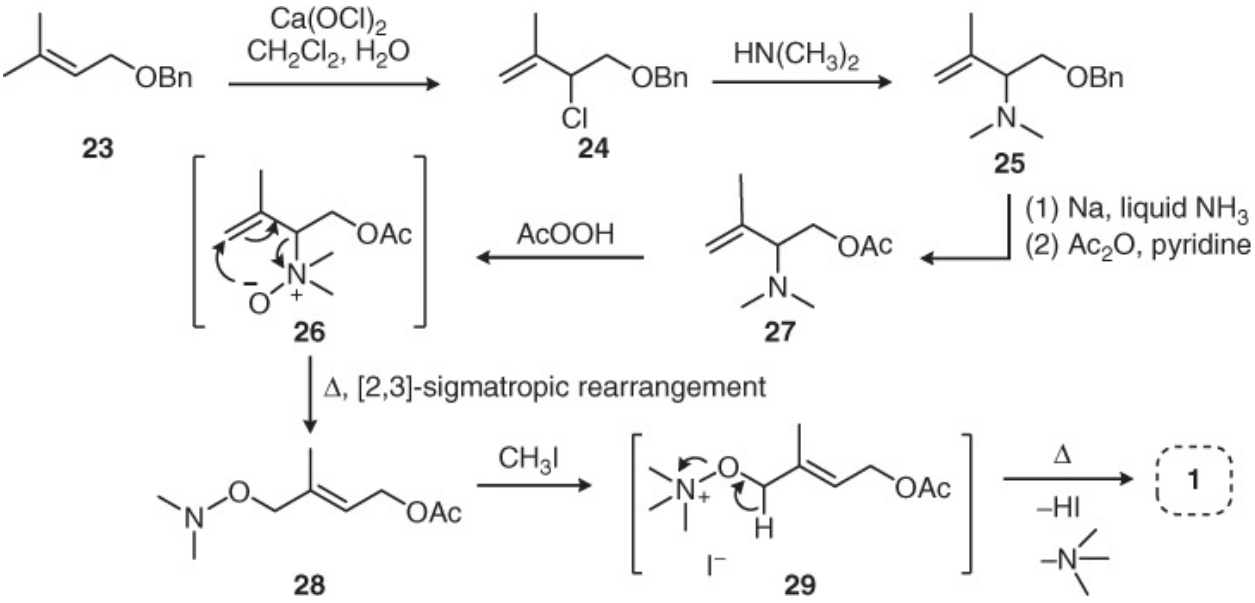


Likewise, isoprene monoepoxide (**21**) undergoes ring opening with subsequent oxidative chlorination upon reaction with $CuCl_2$/LiCl. The product is (*E*)-4-chloro-2-methyl-2-butenal (**22**), which yields **1** upon substitution of chlorine by acetate [7]:



A more complex synthesis of **1** [8] is initiated by ene-type chlorination [9] of prenyl benzyl ether (**23**) with hypochlorite. In this reaction, the double bond is regioselectively transposed to the *gem*-dimethyl position to give **24**, in which the allylic chlorine can be substituted by dimethylamine (→**25**). The benzyl ether moiety is replaced by acetate, and the formed allylamine **27** is oxidized with peracetic acid to afford exclusively the (*Z*)-configured allyloxyamine **28**. This transformation involves a [2,3]-sigmatropic rearrangement of the primarily formed *N*-oxide **26**. N-Alkylation of **28** with CH_3I followed by a thermal

Hofmann-like elimination of $(CH_3)_3N$ finally provides **1** via **29**:

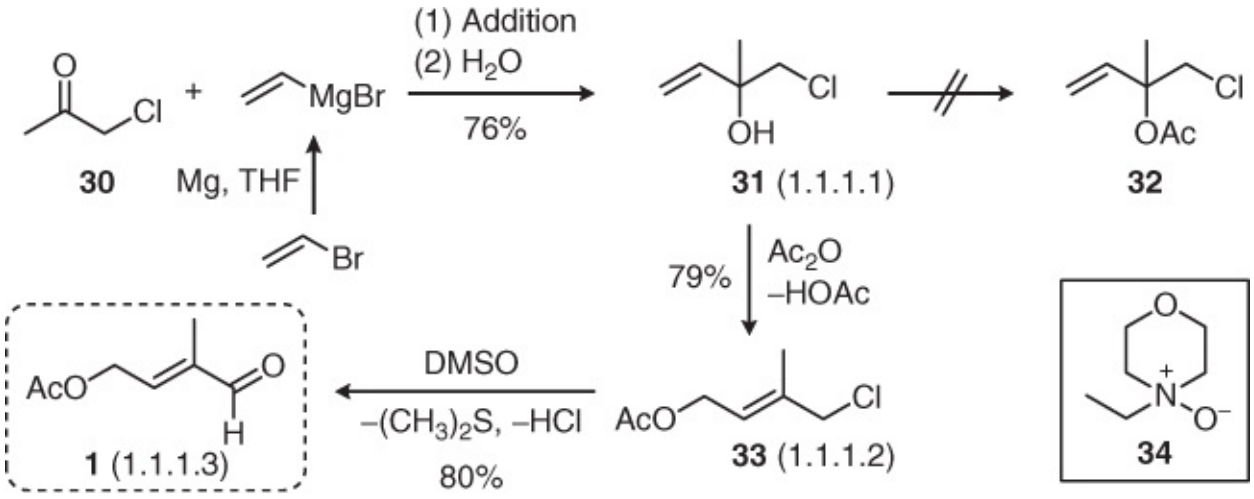


(b) Synthesis of 1

The synthesis of **1** starts with the addition of vinyl magnesium bromide to chloroacetone (**30**) to afford the isoprene chlorohydrin (**31**). For the formation and handling of vinyl Grignard compounds, the use of tetrahydrofuran (THF) as solvent is crucial [10]. When the tertiary alcohol **31** is treated with acetic anhydride in the presence of *p*-toluenesulfonic acid, the product is not the tertiary acetate **32** but the thermodynamically more stable primary acetate **33**, resulting from an allylic inversion involving an allylic cation formed from **31** or a Cope rearrangement of **32**.

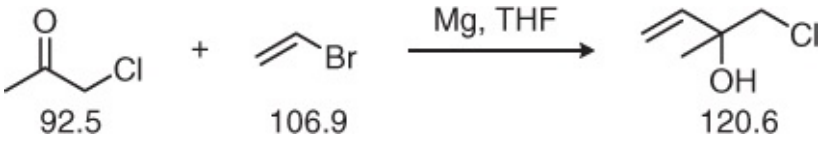
For the final step of the synthesis, the primary chloride in **33** is converted into the aldehyde group of **1** by means of Kornblum oxidation with dimethyl sulfoxide (DMSO). The disadvantage of the Kornblum oxidation (in particular, odor of $(CH_3)_2S$!) can be avoided by the use of *N*-ethylmorpholine *N*-oxide (**34**), which cleanly oxidizes primary allyl chlorides to the corresponding aldehydes [11, 12].

Thus, the target molecule **1** is obtained in a three-step sequence in an overall yield of 48% (based on **30**).



(c) Experimental Procedures for the Synthesis of 1

1.1.1.1	****	**1-Chloro-2-methyl-3-buten-2-ol (isoprene chlorohydrin)** [3]



Magnesium turnings (7.30 g, 300 mmol) are added to anhydrous THF (70 ml) under nitrogen atmosphere, and a small amount of ethyl bromide (~1 g, 0.7 ml) is added to start the reaction. Vinyl bromide (300 mmol, 1 M solution in THF, 0.30 ml) is then added dropwise with stirring at such a rate that the temperature never exceeds 40 °C (approximately 90 min). Stirring is continued for 30 min, the dark-gray solution is cooled to 0 °C, and a solution of chloroacetone (18.5 g, 0.20 mol) (note) in anhydrous THF (70 ml) is added dropwise over 45 min. Stirring is continued at room temperature for 1 h.

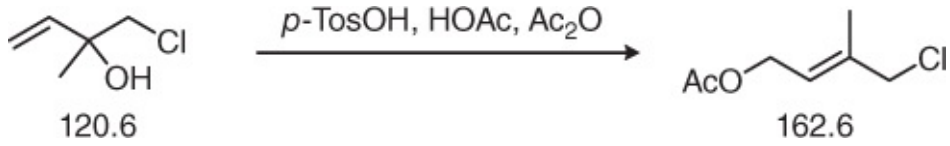
The adduct is hydrolyzed by the dropwise addition of ice-cold saturated aqueous NH_4Cl solution (100 ml) at 0 °C. The phases are separated, and the aqueous phase is extracted with Et_2O (2 × 100 ml). The combined organic phases are washed with 2% aqueous $NaHCO_3$ solution (100 ml) and H_2O (100 ml), dried over Na_2SO_4, and filtered. The solvent is removed *in vacuo* and the residue is fractionally distilled to give a colorless oil. The yield is 18.3 g (76%), bp_{17} 48–49 °C, n^{20}_D = 1.4608.

IR (film): $\tilde{\nu}$ (cm^{-1}) = 3420, 3080, 1640.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 5.89 (dd, 15.0, 9.0 Hz, 1H, 3-H), 5.35 (dd, 15.0, 3.0 Hz, 1H, 4-H_a), 5.18 (dd, 9.0, 3.0 Hz, 1H, 4-H_b), 3.46 (s, 2H, 1-H_2), 2.37 (s_{br}, 1H, OH), 1.38 (s, 3H, CH_3).

Note: Chloroacetone (lachrymator!) is distilled (bp_{760} 118–119 °C) through a short packed column before use.

1.1.1.2 * (*E*)-1-Acetoxy-4-chloro-3-methyl-2-butene [3]



120.6 → 162.6

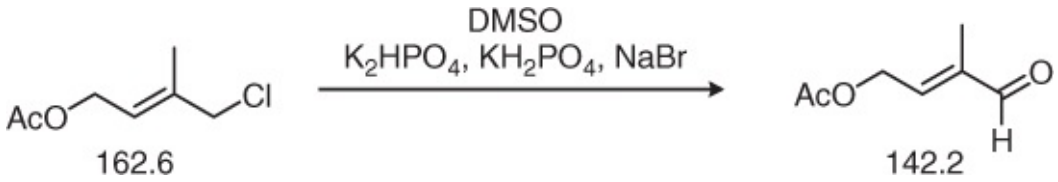
A solution of *p*-toluenesulfonic acid monohydrate (2.54 g, 13.4 mmol) in glacial acetic acid (60.0 ml) is added dropwise to a stirred solution of isoprene chlorohydrin **1.1.1.1** (15.3 g, 127 mmol) in acetic anhydride (20.0 ml) and glacial acetic acid (60.0 ml) at 15 °C over a period of 15 min. The temperature of the bath is raised to 55 °C and stirring is continued for 24 h.

The solution is cooled and carefully poured into a mixture of 10% aqueous NaOH (800 ml) and ice (200 g). The resulting mixture is extracted with Et_2O (3 × 100 ml), and the combined organic phases are dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue is fractionally distilled to give the product as a colorless oil; 16.3 g (79%), bp_{10} 91–93 °C, n^{20}_D = 1.4658; 6 : 1 mixture of the *E*/*Z* stereoisomers.

IR (film): $\tilde{\nu}$ (cm^{-1}) = 1740, 1235, 1025, 685.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 5.65 (t, *J* = 9.0 Hz, 1H, 2-H), 4.59 (d, *J* = 9.0 Hz, 2H, 1-H_2), 4.06, 3.98 (2 × s, 2 × 2H, ratio 1 : 6, *Z*/*E*-CH_2Cl), 2.02 (s, 3H, $OCOCH_3$), 1.79 (s_{br}, 3H, 3-CH_3).

1.1.1.3 * (*E*)-Acetoxy-2-methyl-2-butenal [3]



162.6 → 142.2

K_2HPO_4 (19.9 g, 114 mmol), KH_2PO_4 (4.14 g, 30.0 mmol), and NaBr (1.20 g, 11.6 mmol) are suspended in a stirred solution of allyl chloride **1.1.1.2** (16.1 g, 99.0 mmol) in anhydrous DMSO (120 ml). The mixture is heated to 80 °C and stirred for 24 h (Hood! formation of dimethyl sulfide!).

The mixture is then cooled and poured into H_2O (400 ml) and CH_2Cl_2 (200 ml). The phases are separated, the aqueous phase is extracted with CH_2Cl_2 (100 ml), the combined organic layers are dried over Na_2SO_4, and filtered. The solvent is removed *in vacuo*, and the yellow residue is fractionally distilled to give the acetoxy aldehyde as a colorless oil; 11.2 g (80%), bp_2 66–72 °C, n^{20}_D = 1.4647 (note).

IR (film): $\tilde{\nu}$ (cm^{-1}) = 2720, 1735, 1690, 1645.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 9.55 (s, 1H, CHO; *Z*-isomer: δ = 10.23), 6.52 (tq, *J* = 6.0, 1.0 Hz, 1H, 3-H), 4.93 (dq, *J* = 6.0, 1.0 Hz, 2H, 4-H_2), 2.12 (s, 3H, $OCOCH_3$), 1.81 (dt, *J* = 1.0, 1.0 Hz, 3H, C2-CH_3).

Note: If smaller amounts of starting material are used, column chromatography (silica gel, *n*-hexane/Et_2O, 9 : 1) is recommended as the purification procedure.

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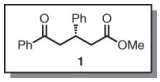
11. Suzuki, S., Onishi, T., Fujita, Y., Misawa, M., and Otera, J. (1986) *Bull. Chem. Soc. Jpn.*, **59**, 3287–3288; for **1**, a yield of 88% is reported.

12. Sulfoxides anchored on ionic liquids are reported to represent nonvolatile and odorless reagents for Swern oxidation: He, X. and Chan, T.H. (2006) *Tetrahedron*, **62**, 3389–3394.

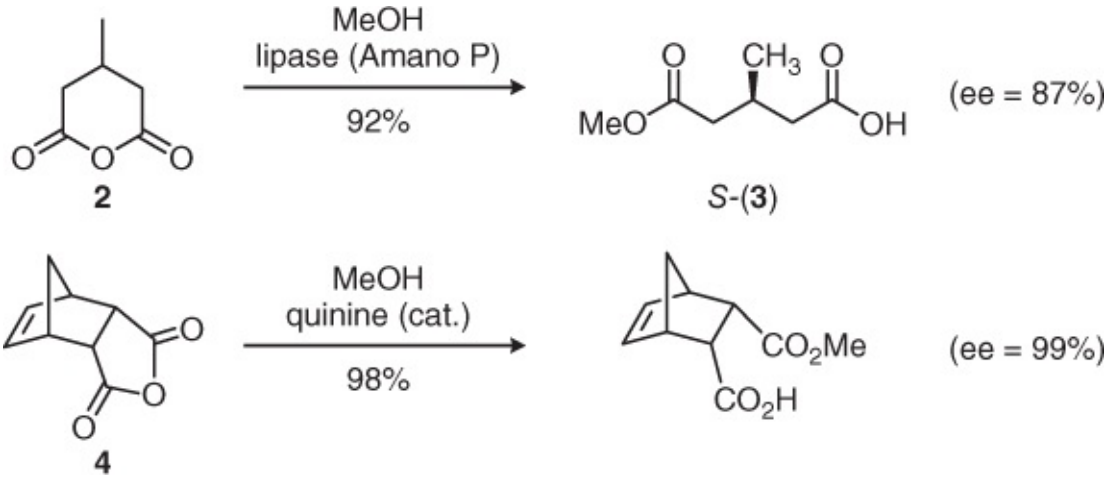
1.1.2 Methyl (*S*)-5-oxo-3,5-diphenylpentanoate

	***Topics:***	• Knoevenagel condensation, Michael addition • “Acid cleavage” of acetoacetate, anhydride formation • Enantioselective asymmetric desymmetrization of a cyclic *meso*-anhydride by a Grignard compound in the presence of (−)-sparteine as a stereocontrolling agent • Determination of enantiomeric excess by high-performance liquid chromatography (HPLC) on a chiral phase

(a) General

The desymmetrization of meso and other prochiral compounds represents an important approach in asymmetric synthesis [1]. The desymmetrization of five- and six-membered cyclic anhydrides of the meso type (such as **2** and **4**) by ring-opening attack of nucleophiles at one of the enantiotopic carbonyl groups is broadly possible (i) by chiral alcohols or amines and (ii) by achiral alcohols in combination with enzymes or other organocatalysts [2]. Clearly, the catalytic variant is by far the more attractive route for reasons of atom economy and

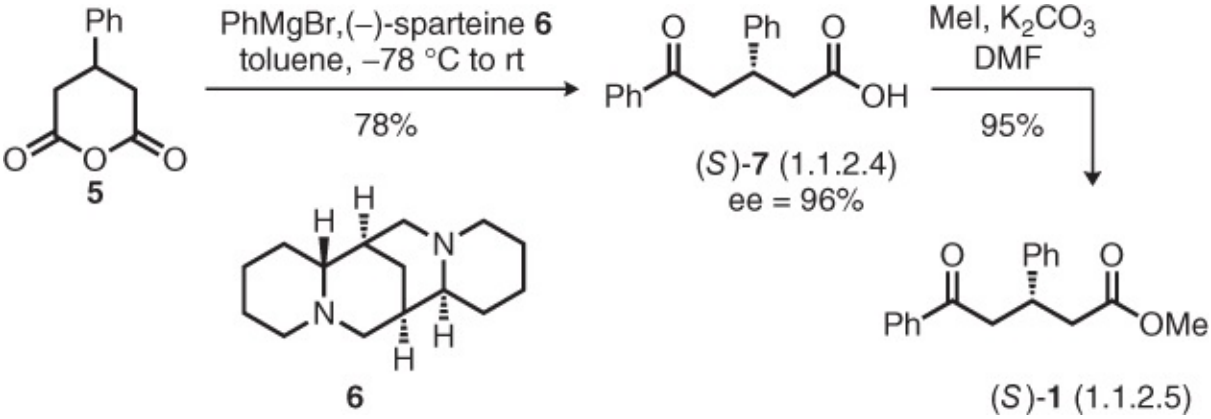
preparative efficiency,[1] for example:



Only a few examples of the desymmetrization of cyclic anhydrides with carbon nucleophiles have been described [2]. Recently, asymmetric ring-opening reactions of 3-substituted glutaric anhydrides (such as **2**) were found [3] to occur with Grignard compounds in the presence of (−)-sparteine as a chiral complexing ligand system, which has been shown [4] to be a very versatile organocatalyst [5] for asymmetric stereocontrol in reactions of organolithium compounds.

As described in Section (b), a simple synthesis of the chiral target molecule **1** [6] can be achieved by the application of the above protocol.

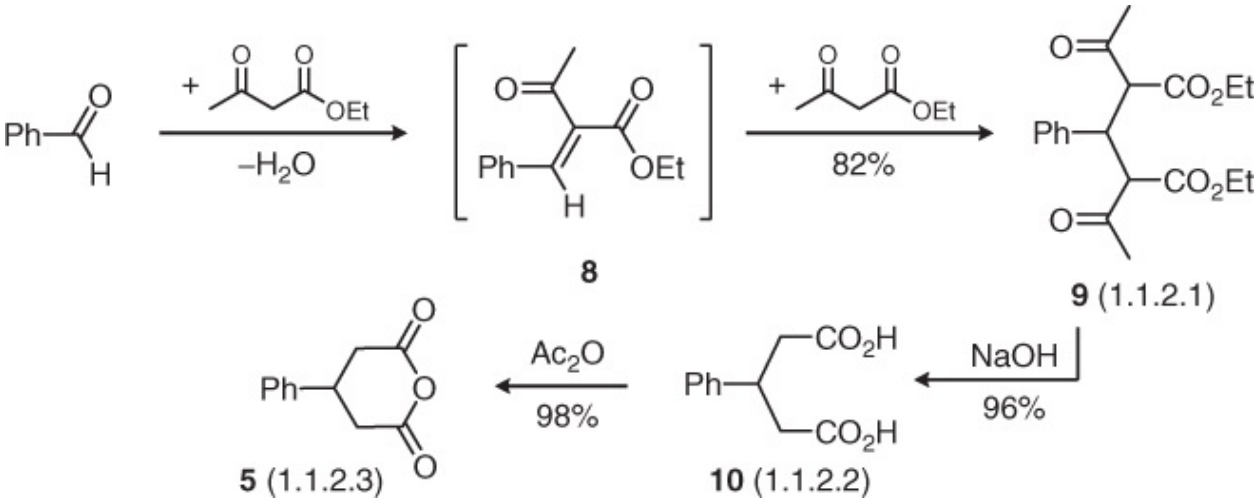
(b) Synthesis of 1



3-Phenylglutaric anhydride (**5**) is reacted with phenylmagnesium bromide in toluene at −78 °C in the presence of 1.3 equiv of (−)-sparteine (**6**) as a stereocontrolling agent to give the δ-keto acid **7** in 78% yield and with high enantioselectivity (ee = 96%) [3]. The enantiomeric purity of **7** may be determined by HPLC on a chiral phase of the methyl ester **1**, easily accessible

from the acid **7** by Oalkylation of its potassium salt with methyl iodide.

The *meso*-anhydride **5** is conventionally prepared [7] starting from benzaldehyde and 2 equivalents of ethyl acetoacetate. The product **9** of this base-catalyzed, three-component reaction results from a domino process involving Knoevenagel condensation of the first molecule of acetoacetate with benzaldehyde followed by Michael addition of the second acetoacetate to the primary condensation product **8** in the presence of piperidine:

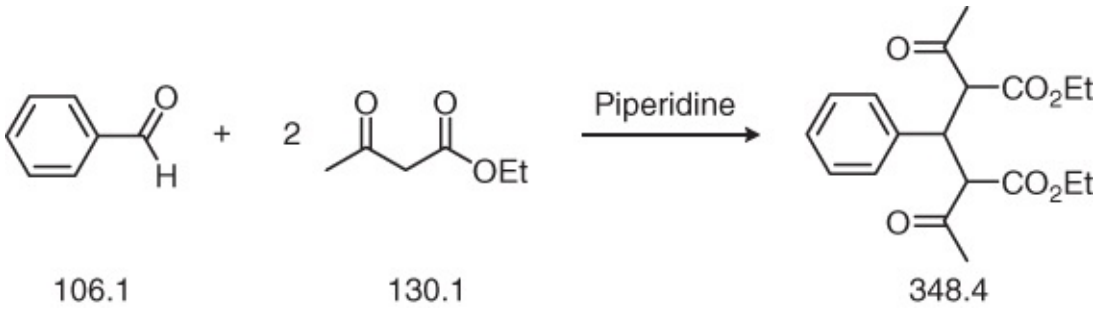


The diester **9** undergoes a twofold "acid cleavage" of the acetoacetate moieties upon treatment with NaOH in EtOH, which results in the loss of two molecules of acetate and saponification of the carboxylic acid ester moieties to give 3-phenylglutaric acid (**10**). Finally, the diacid **10** is transformed to the cyclic anhydride **5** using acetic anhydride.

Thus, the target molecule **1** is obtained in a four-step sequence with an overall yield of 60% (based on benzaldehyde).

(c) Experimental Procedures for the Synthesis of 1

1.1.2.1	*	**Diethyl 2,4-diacetyl-3-phenylpentanedioate** [7]



Ethyl acetoacetate (75.5 g, 580 mmol, note 1) and benzaldehyde (28.5 g, 269

Ethyl acetoacetate (75.5 g, 580 mmol, note 1) and benzaldehyde (28.5 g, 269 mmol) are dissolved in anhydrous EtOH (160 ml). Piperidine (4.0 ml) is added, and the solution is heated to reflux for 10 min and then stirred for 12 h at room temperature. The product begins to crystallize after 2–3 h (note 2).

The slurry is cooled to −20 °C (MeOH/dry ice), and the product is collected by filtration and washed with cold EtOH (−20 °C) until the washings remain colorless. The residue is dried *in vacuo*. The product is obtained as colorless crystal; 77.2 g (82%), mp 150–152 °C (note 3).

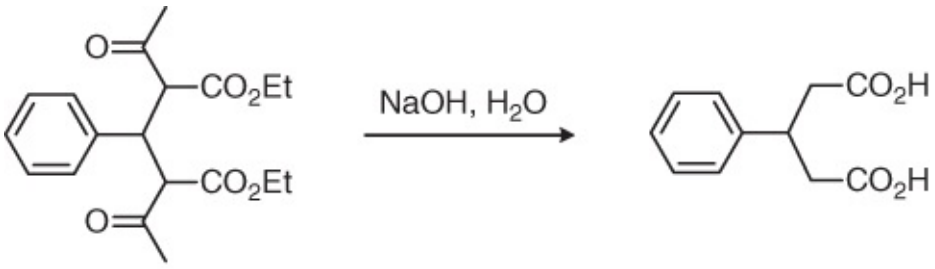
IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3515, 2980, 1740, 1720, 1500, 1470, 1380, 1190, 830.

^{1}H NMR (300 MHz, $CDCl_3$): very complex because of enolization and different *E*/*Z* geometries.

Notes:

1. Ethyl acetoacetate is freshly distilled prior to use (bp_{15} 76–77 °C).
2. If the slurry becomes too viscous for stirring, it is diluted with additional EtOH (50–100 ml).
3. The product is sufficiently pure according to thin-layer chromatography (TLC) (SiO_2/Et_2O). It may be recrystallized from EtOH, which increases the mp to 154–155 °C.

1.1.2.2 * **3-Phenylglutaric acid** [7]



348.4 208.2

The diester **1.1.2.1** (69.7 g, 194 mmol) is added to a mixture of 50% aqueous NaOH (200 ml) and EtOH (200 ml), and the resulting mixture is heated to reflux for 3 h.

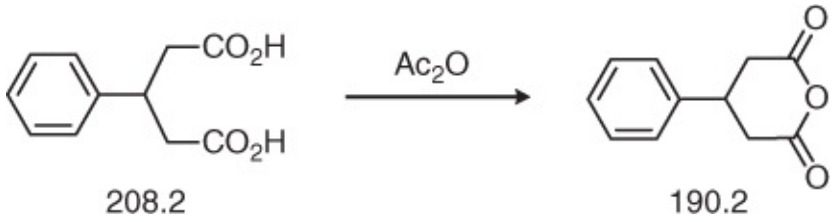
The slurry is diluted with H_2O (200 ml), concentrated to dryness *in vacuo*, and the residue is taken up in H_2O (400 ml). The resulting solution is acidified to pH

2 using concentrated HCl, and the phenylglutaric acid is extracted with Et_2O (3 × 150 ml). The combined extracts are dried over Na_2SO_4, filtered, and concentrated to a volume of 100–120 ml. Cooling to −20 °C results in crystallization of the product, which is collected by filtration, washed with a small amount of cold Et_2O (−20 °C), and dried *in vacuo*. The acid is obtained as colorless crystals; 40.0 g (96%), mp 145–147 °C; the product is sufficiently pure for further use.

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3200–2500, 1720, 1705, 1495, 1450, 1420, 820.

^{1}H NMR (300 MHz, [D_6]acetone): δ (ppm) = 10.88 (s_{br}, 2H, 2 × CO_2H), 7.25 (m_c, 5 H), 3.66 (quintet, *J* = 6.7 Hz, 1H, 3-H), 2.72 (d, *J* = 6.7 Hz, 4H, 2-H_2, 4-H_2).

1.1.2.3 * 3-Phenylglutaric anhydride [7]



The dicarboxylic acid **1.1.2.2** (26.0 g, 125 mmol) in acetic anhydride (140 ml) is heated under reflux for 2 h.

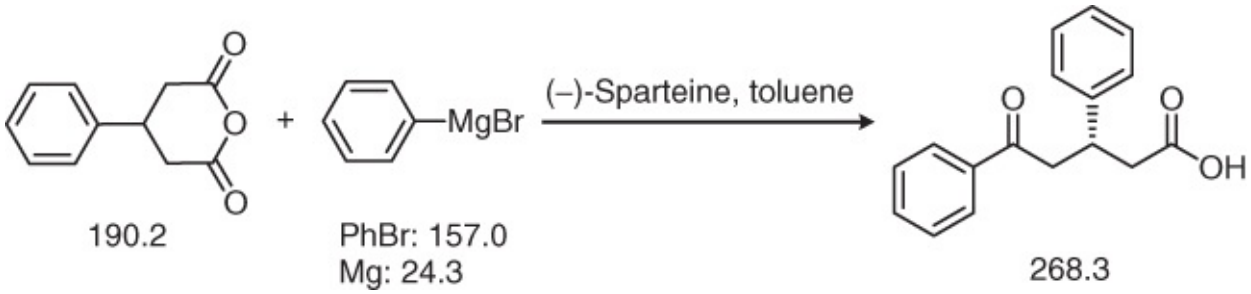
The reaction mixture is then concentrated to dryness. The residue is suspended in Et_2O (100 ml), filtered off, washed with Et_2O, and dried *in vacuo*. The yield is 23.3 g (98%) as colorless crystals, mp 103–105 °C; the product is sufficiently pure for further use.

IR (solid): $\tilde{\nu}$ (cm^{-1}) = 3034, 2980, 1809, 1751, 1243, 1172, 1066, 953, 763, 702, 605, 591.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.40 (t, *J* = 7.4 Hz, 2H), 7.34 (t, *J* = 7.6 Hz, 1H), 7.20 (d, *J* = 7.25 Hz, 2H, 2 × Ar–H), 3.42 (m_c, 1H, 3-H), 3.11 (dd, *J* = 17.3, 4.4 Hz, 2H, 2-H_A, 4-H_A), 2.89 (dd, *J* = 17.3, 11.4 Hz, 2H, 2-H_B, 4-H_B).

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 165.8 (C-1, C-5), 139.1, 129.4, 128.2, 126.3 (6 × Ph–C), 37.2 (C-3), 34.1 (C-2, C-3).

1.1.2.4	***	**(*S*)-5-Oxo-3,5-diphenylpentanoic acid** [3]



Approximately one-fifth of a solution of bromobenzene (1.02 g, 6.50 mmol) in anhydrous Et_2O (10 ml) is added to magnesium turnings (158.0 mg, 6.50 mmol) under a nitrogen atmosphere. Once the Grignard reaction has started, the remaining bromobenzene solution is added dropwise. The solution is then heated to reflux until all of the magnesium turnings have reacted.

The Grignard solution is added dropwise to a solution of (−)-sparteine (1.52 g, 6.50 mmol) in anhydrous toluene (25 ml) at room temperature under nitrogen atmosphere. The solution is stirred for 3 h and then cooled to −78 °C. A solution of 3-phenylglutaric anhydride **1.1.2.3** (951 mg, 5.00 mmol) in toluene (10 ml) is added dropwise to the Grignard/(−)-sparteine solution at −78 °C. The mixture is stirred at this temperature for an additional 3 h before being allowed to warm to room temperature.

The solution is quenched with 2 M NaOH (50 ml), stirred thoroughly, and extracted with Et_2O (3 × 20 ml). The aqueous layer is separated and acidified with concentrated HCl under ice cooling. The carboxylic acid precipitates and is collected by suction filtration, washed with H_2O (2 × 20 ml), and air-dried to give the acid as colorless crystals; 1.05 g (78%), mp 126–127 °C.

IR (solid): $\tilde{\nu}$ (cm^{-1}) = 3030, 1734, 1698, 1682, 1595, 1578.

^{1}H NMR (300 MHz, [D_6]DMSO): δ (ppm) = 12.06 (s_{br}, 1H, CO_2H), 7.91 (d, *J* = 7.3 Hz, 2H, 2 × ArH), 7.60 (t, *J* = 7.6 Hz, 1H, ArH), 7.48 (t, *J* = 7.6 Hz, 2H, 2 × ArH), 7.26 (d, *J* = 7.0 Hz, 2H, 2 × ArH), 7.23 (t, *J* = 7.6 Hz, 2H, 2 × ArH), 7.13 (t, *J* = 7.3 Hz, 1H, ArH), 3.66 (quintet, *J* = 7.9 Hz, 1H, 3-H),

3.44 (dd, *J* = 17.1, 7.9 Hz, 1H, 2-H_a), 3.37 (dd, *J* = 17.1, 6.3 Hz, 1H, 2-H_b), 2.69 (dd, *J* = 15.8, 6.3 Hz, 1H, 4-H_a), 2.56 (dd, *J* = 15.8, 8.5 Hz, 1H, 4-H_b).

^{13}C NMR (76 MHz, [D_6]DMSO): δ (ppm) = 198.4 (C-5), 172.9 (C-1), 143.8, 136.7, 133.1, 128.6, 128.1, 127.8, 127.5, 126.2 (12 × Ar–C), 44.0, 40.4, 37.2 (C-2. C-3, C-4).

1.1.2.5	*	**Methyl (*S*)-5-oxo-3,5-diphenylpentanoate** [3]

Methyl iodide (2.84 g, 20.0 mmol; Caution: carcinogenic!) is added dropwise with stirring to a solution of the carboxylic acid **1.1.2.4** (268 mg, 1.00 mmol), anhydrous K_2CO_3 (207 mg, 1.50 mmol), and *N*,*N*-dimethylformamide (DMF) (5 ml). The resulting mixture is stirred overnight at room temperature.

It is then quenched with 10% aqueous K_2CO_3 solution (10 ml). The product is extracted with Et_2O (5 × 10 ml), and the combined ethereal extracts are washed with brine (3 × 10 ml), dried over Na_2SO_4, and filtered. The solvent is removed *in vacuo*, and the product is allowed to crystallize; one obtains 268 mg (96%) as colorless crystals, mp 82 °C, $[\alpha]^{20}_D$ = +1.8 (*c* = 0.85, $CHCl_3$), 96% ee.

IR (solid): $\tilde{\nu}$ (cm^{-1}) = 2970, 2870, 1735, 1680, 1596, 1578, 1496.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.91 (d, *J* = 6.9 Hz, 2H, ArH), 7.53 (t, *J* = 7.6 Hz, 1H, ArH), 7.43 (t, *J* = 7.9 Hz, 2H, ArH), 7.26 (m, 3H, ArH), 7.19 (m, 2H, ArH), 3.88 (quintet, *J* = 7.3 Hz, 1H, PhC<u>H</u>), 3.58 (s, 3H, OCH_3), 3.39 (dd, *J* = 16.7, 6.9 Hz, 1H) and 3.33 (dd, *J* = 16.7, 6.9 Hz, 1H, C<u>H_2</u>CO_2Me), 2.82 (dd, *J* = 15.3, 7.3 Hz, 1H), and 2.69 (dd, *J* = 15.3, 7.3 Hz, 1H, PhCOC<u>H_2</u>).

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 198.13, 172.29, 143.36, 136.95, 133.09, 128.62, 128.07, 127.33, 127.18, 126.82, 51.55, 44.55, 40.58, 37.53.

The enantiomeric ratio of 98 : 2 (96% ee) was determined by HPLC on a Daicel Chiralcel® OD-H column (4.6 × 250 mm; isopropanol/*n*-hexane (20 : 80), 0.5 ml min^{-1}; UV 254 nm, baseline separation). A reference sample of racemic 5-oxo-3,5-diphenylpentanoic acid methyl ester may be obtained by performing the reaction **1.1.2.4** in the absence of sparteine and then generating the methyl ester according to the procedure described above.

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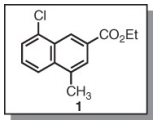
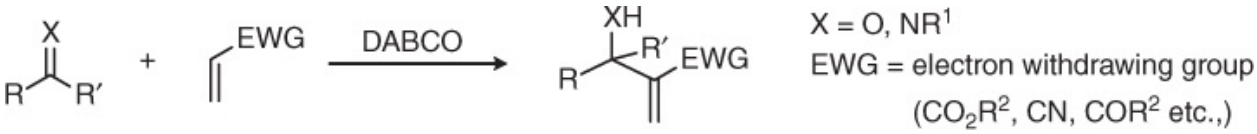
1.1.3 Ethyl 8-chloro-4-methylnaphthalene-2-carboxylate

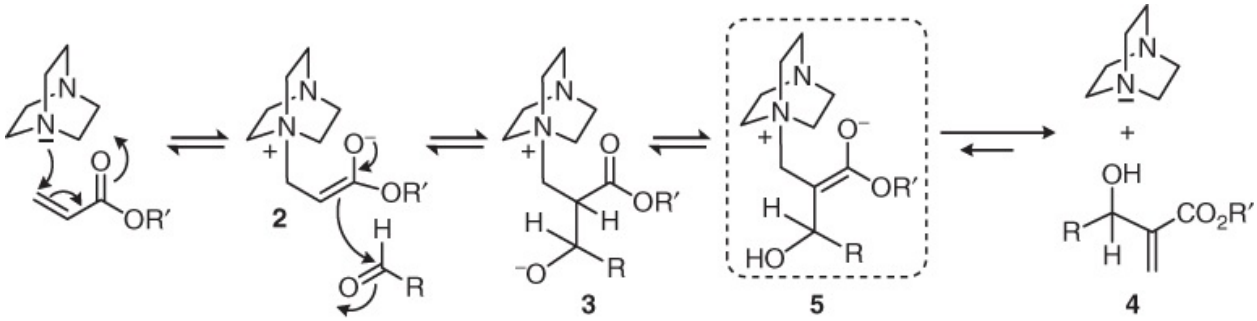
 **1**	***Topics:***	• Baylis–Hillman reaction of an aryl aldehyde with an acrylate in the presence of DABCO • Acetylation of an OH functionality • Transformation of an acetylated Baylis–Hillman adduct to a functionalized naphthalene system by reaction with nitroalkane/base (domino process)

(a) General

The addition of carbonyl compounds, mainly aldehydes or aldimines, to acceptor-substituted alkenes (e.g., acrylates, acrylonitrile, enones, etc.) induced by tertiary amines (or phosphines), preferentially 1,4-diazabicyclo[2.2.2]octane (DABCO), is known as the ***Baylis–Hillman reaction*** [1, 2]:



The generally accepted mechanism for the Baylis–Hillman process is illustrated by the reaction of an aldehyde with acrylate under the catalytic influence of DABCO:



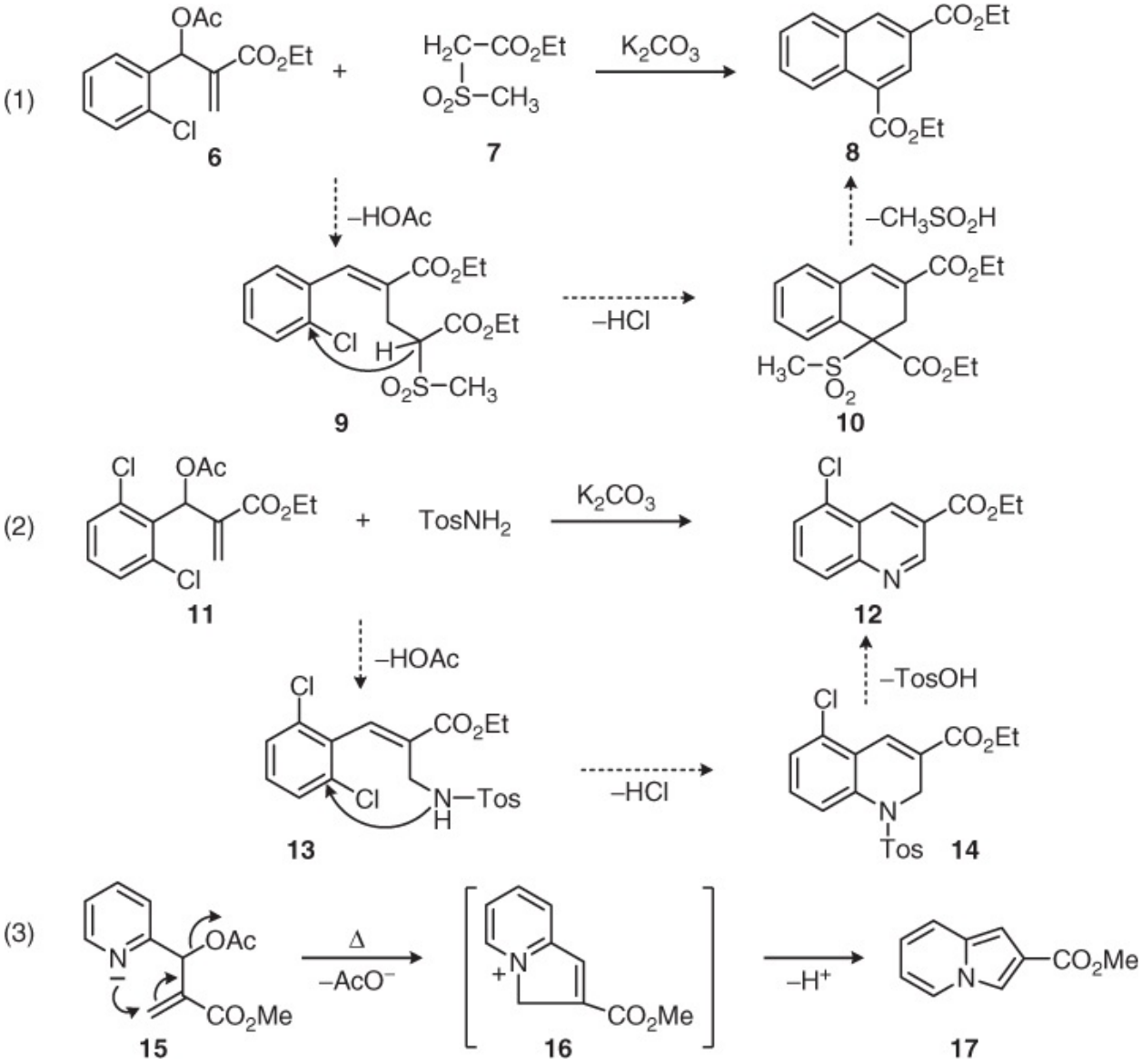
The first step involves a Michael-type addition of DABCO to the acrylate to produce the zwitterionic enolate betaine **2**, which then adds as a nucleophile to the aldehyde carbonyl group in an aldol-like manner to give the zwitterion **3**. Subsequent proton transfer (**3** → **5**) and release of the tertiary amine complete the catalytic cycle and provide the Baylis–Hillman adduct **4**.

The product **4** contains three different functionalities and is therefore capable of undergoing several different transformations [2]. Moreover, if the electrophilic component in the Baylis–Hillman reaction carries additional functionalities, domino reactions [3] can be induced, which lead to the formation of carbocyclic and heterocyclic compounds [4], as illustrated by the following examples (1)–(3).

In (1), the acetylated Baylis–Hillman adduct **6** (obtained from 2-chlorobenzaldehyde and ethyl acrylate with subsequent acetylation) reacts with the sulfone **7** in the presence of a base. The product is the naphthalene derivative **8**, which is formed via S_N' attack (→**9**), intramolecular S_NAr reaction (→**10**), and finally elimination of sulfinic acid [5].

In (2), the acetylated Baylis–Hillman adduct **11** (obtained as above from 2,6-dichlorobenzaldehyde) is reacted with *p*-toluenesulfonamide/base to give the quinoline derivative **12** in a sequence analogous to (1) (**11** → **13** → **14** → **12**) [6].

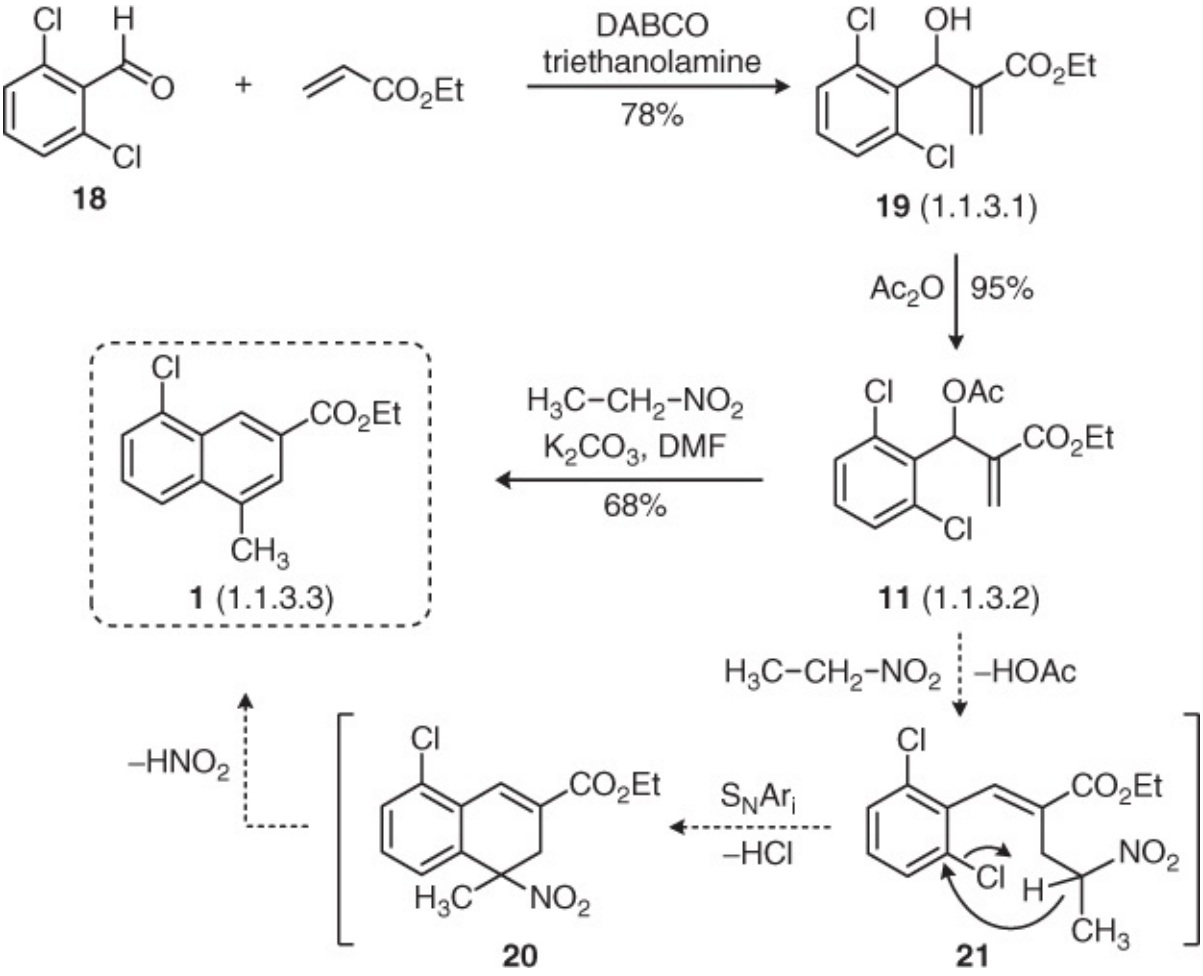
In (3), the acetylated Baylis–Hillman adduct **15** (obtained from pyridine-2-aldehyde and methyl acrylate with subsequent acetylation) is transformed into the indolizine derivative **17** by thermolysis. The process involves an S_N' substitution of the allylic acetate moiety in **15** to give the indolizinium ion **16** followed by deprotonation [7].



As a further example, the synthesis of **1** is described in detail in Section (b)[2] [8].

(b) Synthesis of 1

The synthesis of **1** [8] starts with the reaction of 2,6-dichlorobenzaldehyde (**18**) and ethyl acrylate in the presence of DABCO, which provides the Baylis–Hillman adduct **19**. As in most cases, this DABCO-initiated Baylis–Hillman process requires a long reaction time of 5 days for completion, probably in this case due to steric hindrance in the o,o′-disubstituted benzaldehyde **18**. In other cases, the reaction time may be decreased to approximately 12 h by the use of a catalytic system consisting of DABCO, triethanolamine, and the Lewis acid $La(OTf)_3$ [9]. Such acceleration, however, could not be observed for the transformation **18** → **19**. Nevertheless, triethanolamine was used as solvent, which proved to be more effective even than octanol [9c]. In the next step, the adduct **19** is acetylated using acetic anhydride to give the acetate **11**:



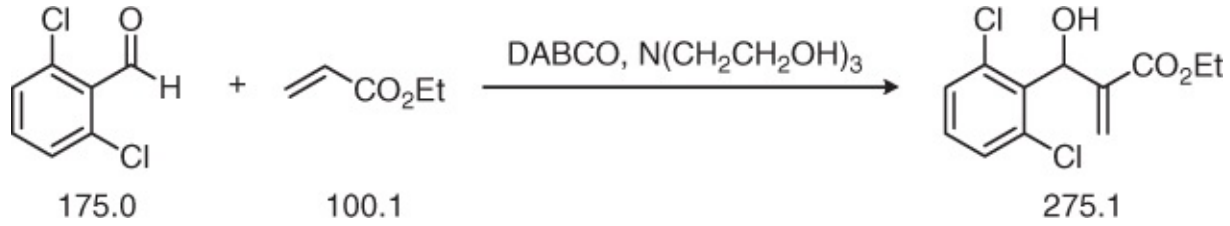
The acetate **11** reacts smoothly with nitroethane in DMF in the presence of K_2CO_3 as a base to provide the target molecule **1** in good yield (68%). Again, the functionalized naphthalene system is formed by way of a three-step domino

process. First, the nitronate anion from nitroethane displaces acetate in **11** in an S_N'-like mechanism to give the cinnamic ester **21**; second, one of the arene *ortho*-halogens (activated by the α,β-unsaturated ester moiety) is substituted by the nitronate in **21** in an intramolecular S_NAr reaction to afford **20**; third, aromatization of the 1,2-dihydronaphthalene intermediate **20** takes place by base-induced elimination of HNO_2.

Thus, the naphthalene-2-carboxylic ester **1** is obtained in a three-step sequence with an overall yield of 50% (based on aldehyde **18**).

(c) Experimental Procedures for the Synthesis of 1

1.1.3.1	*	**2-[(2,6-Dichlorophenyl)hydroxymethyl]-acrylic acid ethyl ester** [9]



To a stirred mixture of ethyl acrylate (4.51 g, 45.0 mmol) and 2,6-dichlorobenzaldehyde (5.25 g, 30.0 mmol) at room temperature under inert gas are added DABCO (3.37 g, 30.0 mmol) and triethanolamine (1.99 ml, 15.0 mmol).

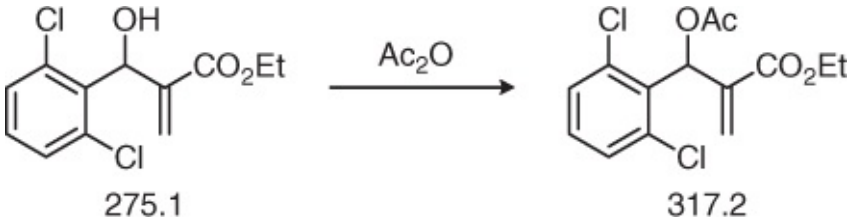
After 5–7 days, the reaction is quenched by dilution with Et_2O (150 ml), and the mixture is washed sequentially with 2% aqueous HCl (100 ml) and H_2O (100 ml). After drying over $MgSO_4$ and filtration, the solvent is removed *in vacuo*. The crude product is purified by column chromatography (SiO_2; petroleum ether/Et_2O, 2 : 1); yield 6.44 g (78%); colorless crystalline solid, mp 67–68 °C.

IR (solid): $\tilde{\nu}$ (cm^{-1}) = 3492, 1694, 1288, 1191, 1047, 964, 762.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.31 (d, *J* = 7.8 Hz, 2H, Ar–H), 7.17 (t, *J* = 7.8 Hz, 1H, Ar–H), 6.41 (d, *J* = 1.6 Hz, 1H, = CH_a), 6.34 (dt, *J* = 9.0, 1.9 Hz, 1H, C<u>H</u>OH), 5.79 (d, *J* = 1.9 Hz, 1H, = CH_b), 4.18 (m, 2H, $C\underline{H}_2CH_3$), 3.37 (d, *J* = 9.0 Hz, 1H, OH), 1.23 (t, *J* = 7.3 Hz, 3H, CH_2CH_3).

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 166.0, 139.8, 135.6, 135.5, 129.5, 129.4, 126.1, 70.1, 61.0, 14.0.

1.1.3.2	*	**2-[Acetoxy-(2,6-dichlorophenyl)methyl]acrylic acid ethyl ester** [10]



275.1 317.2

To a mixture of the benzyl alcohol **1.1.3.1** (4.13 g, 15.0 mmol) in acetic anhydride (50 ml) (note) is added one drop of concentrated H_2SO_4. After stirring for 30 min, the mixture is diluted with cold 2 M NaOH (100 ml) and then stirred for 1 h at room temperature.

The mixture is then extracted with chloroform (3 × 30 ml). The combined extracts are washed with 10% aqueous $NaHCO_3$, dried over $MgSO_4$, and filtered, and the solvent is removed *in vacuo* to give 4.54 g (95%) of a colorless, viscous oil.

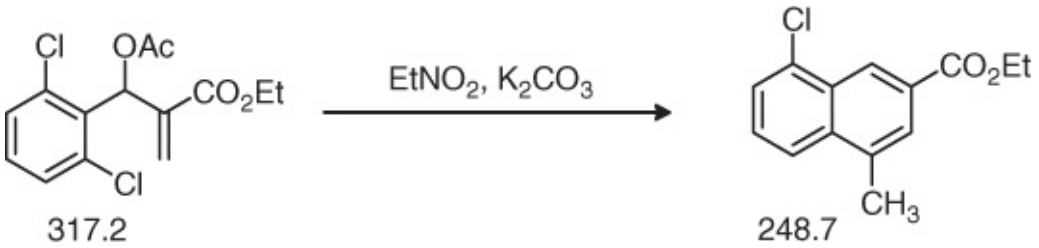
IR (film): $\tilde{\nu}$ (cm^{-1}) = 1747, 1436, 1370, 1228, 1027.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.33 (t, *J* = 1.9 Hz, 1H, C<u>H</u>OAc), 7.31 (d, *J* = 8.2 Hz, 2H, 2 × Ar–H), 7.17 (t, *J* = 7.6 Hz, 1H, Ar–H), 6.48 (d, *J* = 1.3 Hz, 1H, = CH_2), 5.69 (d, *J* = 1.9 Hz, 1H, = CH_2), 4.20 (m, 2H, C<u>H</u>$_2$CH$_3$), 2.12 (s, 3H, C(O)C<u>H</u>$_3$), 1.24 (t, *J* = 7.3 Hz, 3H, CH$_2$C<u>H</u>$_3$).

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 169.4, 166.0, 136.2, 136.1, 132.5, 129.9, 129.4, 127.9, 70.3, 61.1, 20.7, 14.0.

Note: Acetic anhydride has to be distilled before use, bp_{760} 140–141 °C.

1.1.3.3	*	**Ethyl 8-chloro-4-methylnaphthalene-2-carboxylate** [8]



Nitroethane (1.44 ml, 20.0 mmol) is added to a stirred solution of well-ground K_2CO_3 (4.14 g, 30.0 mmol) (note) in DMF (30 ml) at room temperature. After stirring for 10 min, a solution of the acrylic ester **1.1.3.2** (3.17 g, 10.0 mmol) in DMF (10 ml) is added dropwise over a period of 20 min at the same temperature. The reaction mixture is stirred for 17 h at 50–60 °C.

The yellow reaction mixture is then poured into dilute HCl (150 ml) (Caution: foaming!). The aqueous mixture is extracted with Et_2O (3 × 50 ml), and the combined extracts are washed with H_2O (50 ml), dried over $MgSO_4$, and filtered, and the solvent is removed *in vacuo* to give the crude product as a brown oil. It is purified by column chromatography (SiO_2, *n*-hexane/CH_2Cl_2, 1 : 1) to give 1.70 g (68%) of a yellow crystalline solid; mp 52–53 °C.

IR (solid): $\tilde{\nu}$ (cm^{-1}) = 1708, 1269, 1236, 1186, 765.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.88 (s, 1H, Ar–H), 7.95 (s, 1H, Ar–H), 7.92–7.48 (m, 3H, Ar–H), 4.46 (q, *J* = 7.1 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 2.72 (s, 3H, Ar–CH_3), 1.46 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2C\underline{H}_3$).

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 166.6, 135.9, 135.3, 134.0, 130.4, 128.3, 127.7, 126.7, 125.7, 123.3, 61.3, 19.7, 14.4.

Note: It is recommended that K_2CO_3 is dried for 24 h at 80 °C before use.

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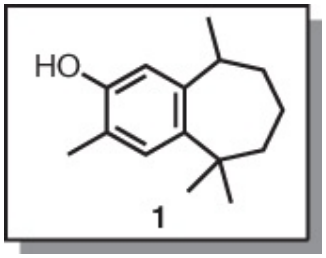
1.1.4 (±)-4-Hydroxy-*ar*-himachalan



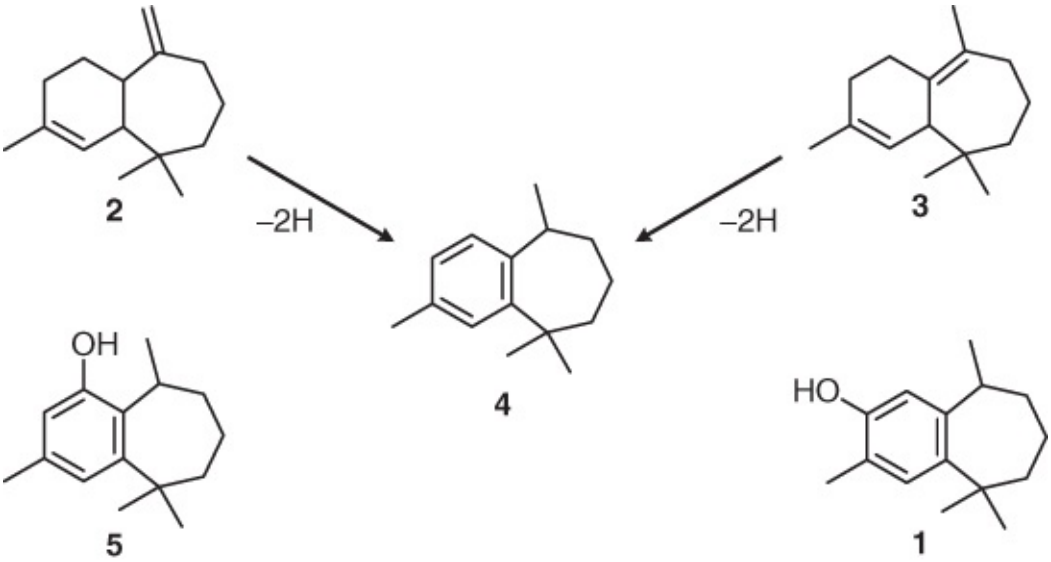
Topics:

- Synthesis of a phenolic sesquiterpene
- Intramolecular Friedel–Crafts acylation
- Wittig reaction

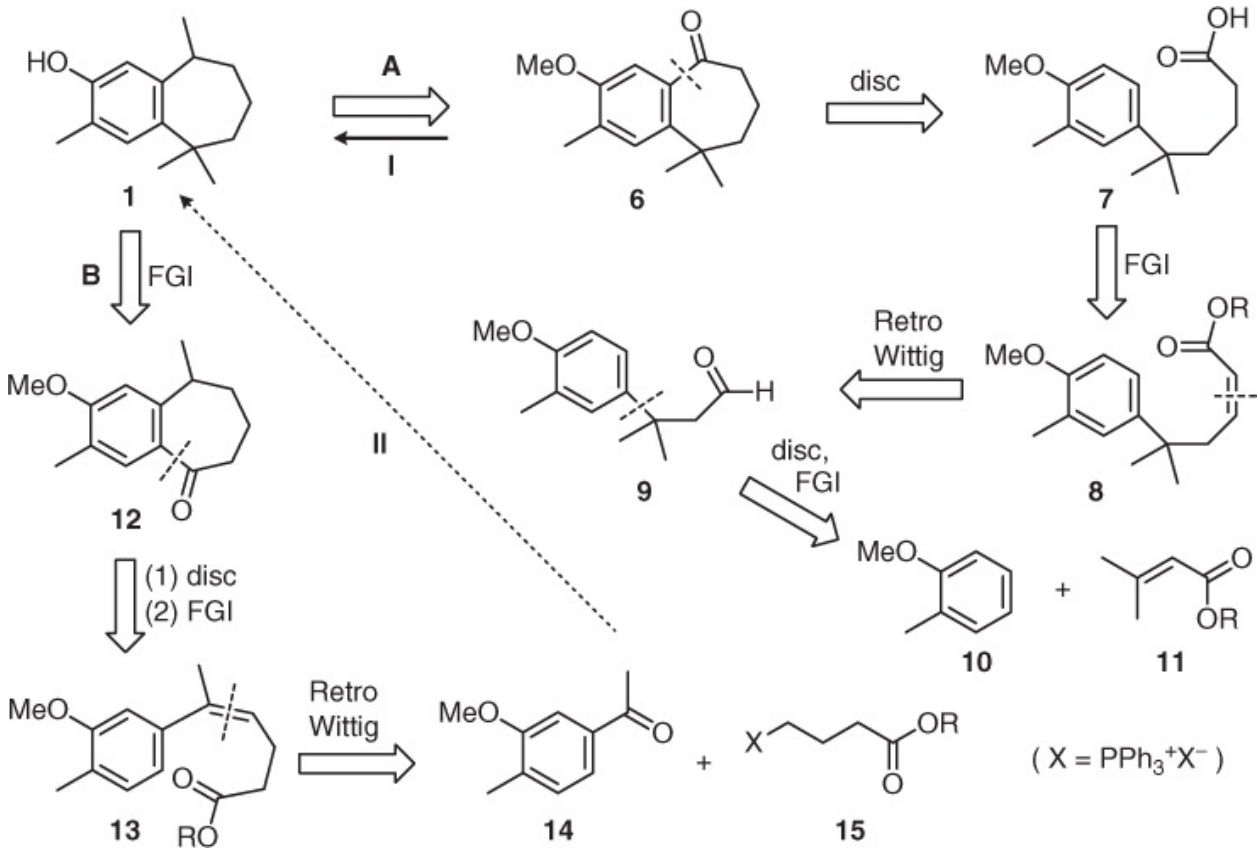
		• Transformation Ar–NO_2 → Ar–NH_2 → Ar–OH • Demethylation of Ar–O–CH_3 • Ti-induced geminal dialkylation of a ketone

(a) General

Himachalans constitute a long-known but rather rare family of sesquiterpenes possessing a methyl-substituted seven-membered ring system. α-and β-Himachalens (**2**/**3**) can be dehydrogenated to *ar*-himachalan **4**, the structure of which has been proven by independent synthesis [1]. More recently, phenolic derivatives of **4** have been isolated from the plant *Lasianthaea podocephala* (**5** [2]) and from the liverwort *Lepidozia incurvata* (**1**) [3]. Himachalans are ingredients of precious perfumes.

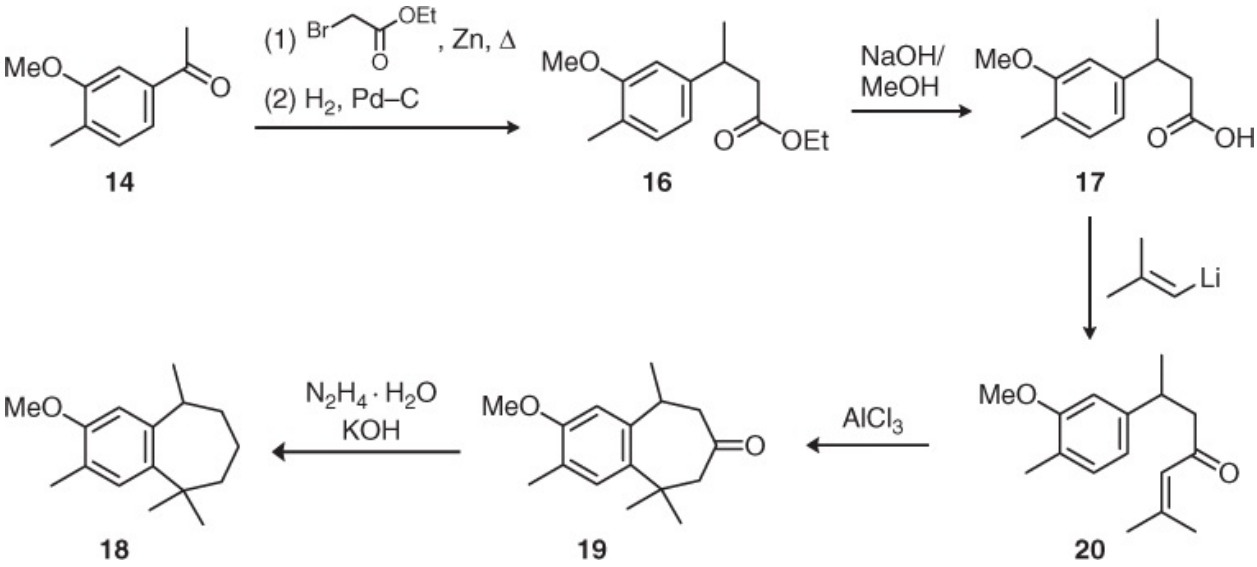


Two retrosynthetic pathways (**A** and **B**) can be considered for **1**. The first one leads to the benzosuberone **6**, which is further cleaved to the substrate *o*-methylanisole **10** and the 3-methyl-2-butenoic acid derivative **11** via **7**, **8**, and **9**. The second one leads to the differently substituted benzosuberone **12** and further on to **14** and **15** via **13**.



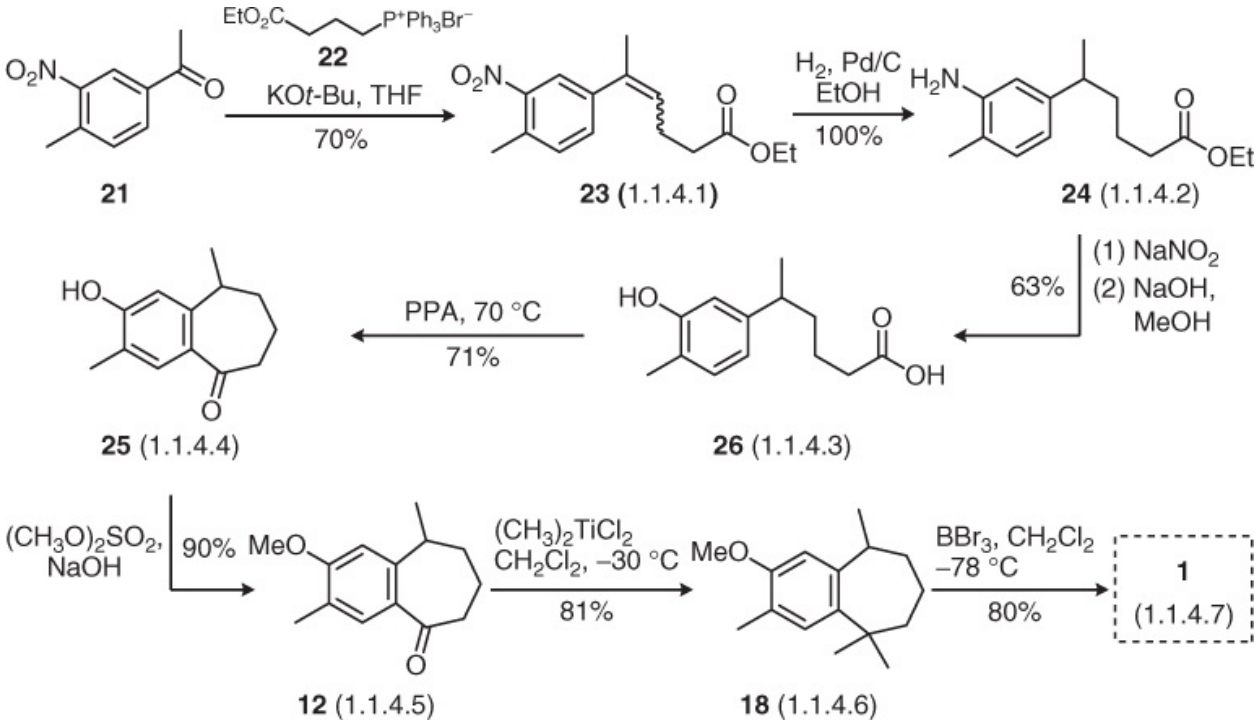
(b) Synthesis of 1

The synthesis of the methyl ether of **1** (**18**) has been reported in the Ref. [4]; the strategy deviates from approaches **I**/**II** suggested by the retrosynthesis patterns **A**/**B**. This synthesis begins with a Reformatsky reaction of the acetophenone **14** and bromoacetate followed by catalytic hydrogenation to give the ester **16**. Reaction of the corresponding acid **17** with β,β-dimethylvinyllithium leads to the vinyl ketone **20**, which, after a Friedel–Crafts-analogous ring closure (→ **19**) and removal of the keto function (in **19**) by a Huang–Minlon procedure, affords **18**. The moderate outcome of the final steps (**17** → → → **18**) is responsible for the modest overall yield of 4% (based on **14**).

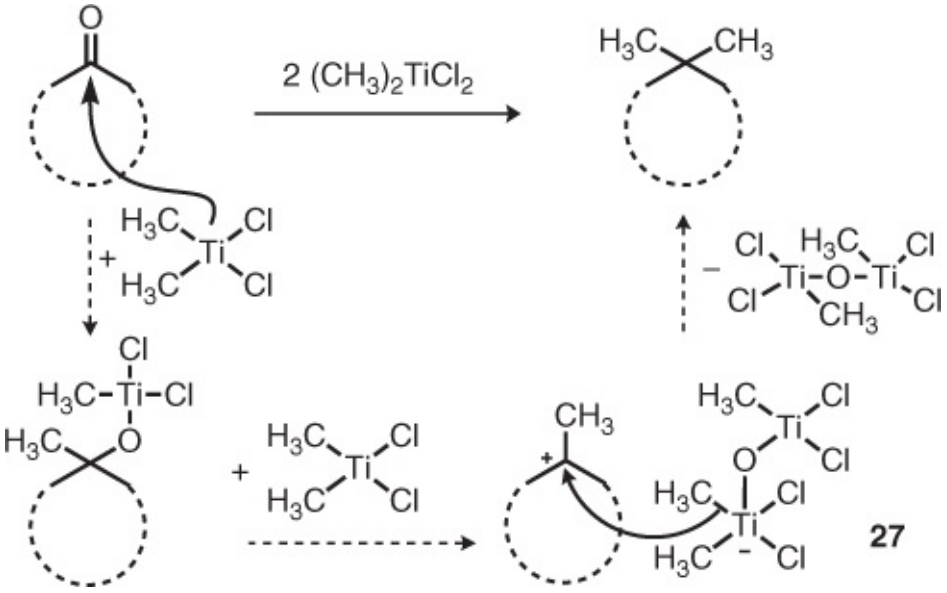


In contrast, the synthesis of **1** according to approach **II** (from retrosynthesis according to **B**) was found to be superior to all other alternatives [5] and is described in the following section with experimental details. This access via benzosuberone **12** requires the construction of the *gem*-dimethyl moiety from a carbonyl group, a transformation elegantly accomplished by use of the titanium reagent $(CH_3)_2TiCl_2$ [6].

4-Methyl-3-nitroacetophenone (**21**) is subjected to a Wittig reaction with the commercially available C_4-phosphonium salt **22** in the presence of KO*t*Bu as base. The carbonyl olefination results in the formation of the unsaturated ester **23** (obtained as a mixture of *E*/*Z* isomers). Hydrogenation of the C=C double bond and the nitro group in **23** using Pd/C in ethanol provides the amino ester **24**. The primary aromatic amine function in **24** is then transformed into a phenolic OH group by the classical two-step process of diazotization with aqueous HNO_2 and nucleophilic substitution of the diazonium group by hydroxide in methanol. In this process, the ester function is also hydrolyzed to give the carboxylic acid **26**. Ring closure to the benzosuberone **25** by intramolecular Friedel–Crafts acylation is then achieved by treatment with polyphosphoric acid. After methylation of the phenolic OH group using dimethyl sulfate/NaOH (**25** → **12**), geminal dimethylation at the C=O group of **12** is accomplished with $(CH_3)_2TiCl_2$ at −30 °C to give the benzocycloheptene **18**. Finally, the methyl ether function in **18** is cleaved with BBr_3 to give the *ar*-himachalan **1** in a linear seven-step sequence with an overall yield of 18% (based on **21**).

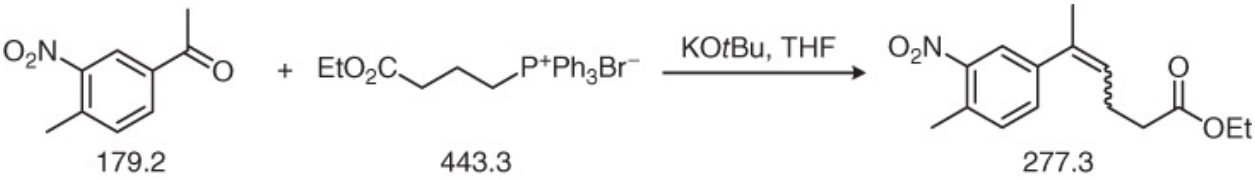


For the geminal dimethylation of **12**, 2 equiv of $(CH_3)_2TiCl_2$ per carbonyl group are required. This leads to the following mechanism: (i) methyl transfer from titanium to the carbonyl carbon atom by nucleophilic addition of Ti–CH_3 to C=O and (ii) methyl migration within the ion-pair ate-complex **27**. As the driving force, the large difference in Δ_H Ti–O versus Δ_H Ti–C (480 vs. 250 kJ mol^{-1}) can be assumed [6, 7].



(c) Experimental Procedures for the Synthesis of 1

1.1.4.1	*	**Ethyl 5-(4-methyl-3-nitrophenyl)-4-hexenoate** [5]



(3-Carbethoxypropyl)triphenylphosphonium bromide (42.8 g, 94.0 mmol) (note) is added to a stirred solution of KO*t*Bu (10.0 g, 90.0 mmol) in anhydrous THF (100 ml), and stirring is continued for 1.5 h. A solution of 4-methyl-3-nitroacetophenone (11.2 g, 72.0 mmol) in anhydrous THF (100 ml) is then added dropwise with stirring. When the addition is complete, the dark mixture is heated to reflux for 12 h (TLC control).

The reaction mixture is cooled to room temperature, poured into H_2O (500 ml), and extracted with Et_2O (4 × 250 ml). The combined ethereal phases are washed with H_2O (5 × 200 ml), dried over $MgSO_4$, and filtered. The solvent is removed *in vacuo*, the crude oily product is dissolved in the minimum volume of CH_2Cl_2, and purified (i) by rapid filtration through SiO_2 (CH_2Cl_2) and (ii) by chromatography on SiO_2 (Et_2O/petroleum ether, 1 : 6). The product (14.0 g, 70% 2 : 1 mixture of *E*/*Z* stereoisomers, R_f = 0.28 (Et_2O/petroleum ether 1 : 6)) is used directly in the next step.

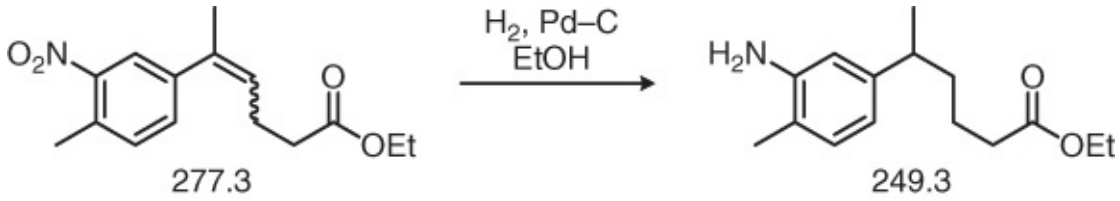
IR (film): $\tilde{\nu}$ (cm^{-1}) = 1770, 1655.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.95 (d, *J* = 1.8 Hz, 1H, Ar–H, *Z*), 7.79 (d, *J* = 1.3 Hz, 1H, Ar–H, *E*), 7.50 (dd, *J* = 8.0, 1.8 Hz, 1H, Ar–H, *Z*), 7.35–7.29 (m, 2H, Ar–H, *E*), 7.26 (d, *J* = 8.0 Hz, 1H, Ar–H, *Z*), 5.82 (m_c, 1H, = CH, *Z*), 5.52 (m_c, 1H, = CH, *E*), 4.15 (q, *J* = 7.1 Hz, 2H, $OC\underline{H}_2CH_3$, *Z*), 4.10 (q, *J* = 7.1 Hz, 2H, $OC\underline{H}_2CH_3$, *E*), 2.59 (s, 3H, Ar–CH_3, *E*), 2.57 (s, 3H, Ar–CH_3, *Z*), 2.55–2.44 and 2.36–2.25 (m, 4H, CH_2–CH_2, *E* and *Z*), 2.06 (d, *J* = 1.3 Hz, 3H, = C–CH_3, *Z*), 2.03 (d, *J* = 1.3 Hz, 3H, = C–CH_3, *E*), 1.28 (t, *J* = 7.1 Hz, 3H, $OCH_2C\underline{H}_3$, *Z*), 1.23 (t, *J* = 7.1 Hz, 3H, $OCH_2C\underline{H}_3$, *E*).

MS (CI, 120 eV): *m*/*z* (%) = 277 (76) $[M]^+$.

Note: The phosphonium salt is commercially available but rather expensive. However, it can be prepared according to Ref. [8].

1.1.4.2	*	**Ethyl 5-(3-amino-4-methylphenyl)hexanoate** [5]



5% Pd/C catalyst (approximately 0.5 g) is added to a solution of the unsaturated ester **1.1.4.1** (10.0 g, 36.0 mmol) in EtOH (200 ml). Hydrogenation is carried out in a hydrogenation apparatus for 12 h under a hydrogen pressure of 2.5 bar (TLC control).

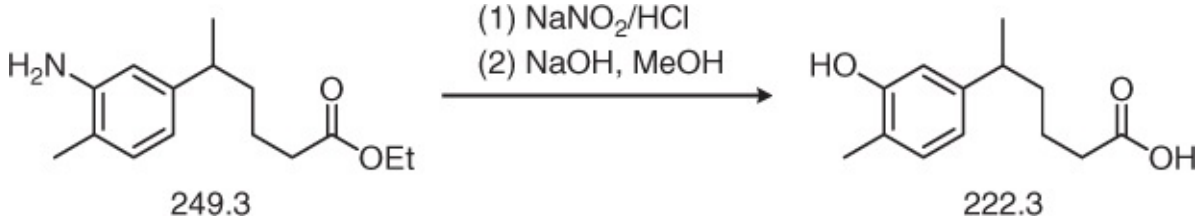
The catalyst is then filtered through Celite®, and the filter cake is rinsed with EtOH. The EtOH solution is concentrated *in vacuo*. The product (9.00 g, 100%) is obtained as a faintly yellow oil, which is homogeneous according to TLC and is used in the next step without further purification.

IR (film): $\tilde{\nu}$ (cm^{-1}) = 3455, 3370, 1740.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 6.95 (d, *J* = 7.5 Hz, 1H, Ar–H), 6.52 (d, *J* = 7.5 Hz, 1H, Ar–H), 6.49 (s_{br}, 1H, Ar–H), 4.09 (q, *J* = 7.1 Hz, 2H, OCh_2CH_3), 3.57 (s_{br}, 2H, NH_2), 2.59–2.54 (m, 1H, C<u>H</u>–CH_3), 2.26–2.22 (m, 2H, CH_2), 2.12 (s, 3H, Ar–CH_3), 1.59–1.48 (m, 4H, $(CH_2)_2$), 1.24 (t, *J* = 7.1 Hz, 3H, CH_3), 1.19 (d, *J* = 6.6 Hz, 3H, CH–C<u>H</u>$_3$).

MS (CI, 120 eV): *m*/*z* (%) = 249 (3) $[M]^+$.

1.1.4.3	*	**5-(3-Hydroxy-4-methylphenyl)hexanoic acid** [5]



The amino ester **1.1.4.2** (8.00 g, 32.0 mmol) is stirred with HCl (5 M, 20 ml). When most of the ester has dissolved, the reaction mixture is cooled in an ice bath and a solution of $NaNO_2$ (2.5 M, 13 ml, 32.5 mmol) is added with stirring

at such a rate that the internal temperature does not exceed 5 °C. More $NaNO_2$ solution is added until the I_2/starch test for free HNO_2 is positive (approximately 15 min after the last addition); the excess of HNO_2 is then destroyed by the addition of urea. The solution of the diazonium salt thus obtained is heated to 100 °C until evolution of N_2 ceases.

After cooling to room temperature, the resulting two-phase system is extracted with Et_2O (3 × 50 ml), the combined extracts are dried over $MgSO_4$, and filtered, and the solvent is removed *in vacuo*. The residue (ester of **1.1.4.3**) is dissolved in a solution of NaOH (5.12 g, 128 mmol) in MeOH (100 ml) and stirred at room temperature for 12 h.

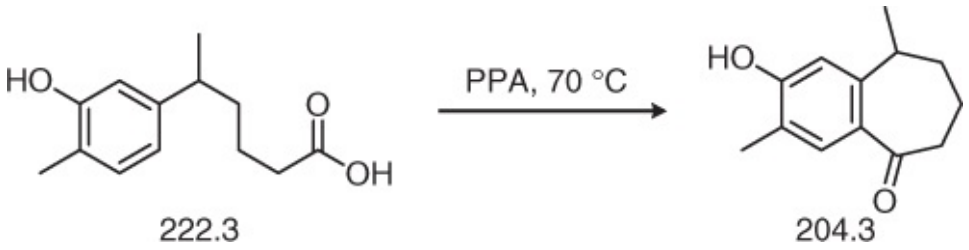
The solvent is then removed *in vacuo*, the residue is dissolved in H_2O (100 ml), and the (alkaline) solution is washed with Et_2O (3 × 50 ml). The organic extracts are discarded (check by TLC), and the aqueous phase is brought to pH 1 by the addition of concentrated HCl (stirring!) and extracted with Et_2O (3 × 50 ml). The combined ethereal extracts are dried over $MgSO_4$ and filtered, and the solvent is removed *in vacuo*. The residue is purified by chromatography (SiO_2, Et_2O/petroleum ether, 3 : 2). The product is obtained as orange solid; 4.50 g (63%), mp 96–97 °C.

IR (film): $\tilde{\nu}$ (cm^{-1}) = 3450, 1720.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.01 (d, *J* = 7.5 Hz, 1H, Ar–H), 6.65 (d, *J* = 7.5 Hz, 1H, Ar–H), 6.58 (s, 1H, Ar–H), 2.61–2.56 (m, 1H, C<u>H</u>–CH_3), 2.31–2.28 (m, 2H, CH_2), 2.19 (s, 3H, Ar–CH_3), 1.57–1.49 (m, 4H, $(CH_2)_2$), 1.19 (d, *J* = 6.6 Hz, 3H, CH–C<u>H</u>$_3$).

MS (CI, 120 eV): *m*/*z* (%) = 222 (76) $[M]^+$.

1.1.4.4	*	**2-Hydroxy-3,9-dimethyl-6,7,8,9-tetrahydro-5*H*-benzo[*a*]cyclohepten-**
		5-one [5]



The finely powdered carboxylic acid **1.1.4.3** (2.00 g, 9.00 mmol) is suspended in polyphosphoric acid (20 ml, 85% P_4O_{10}). The resulting orange suspension is heated to 70 °C for 2 h with intense stirring.

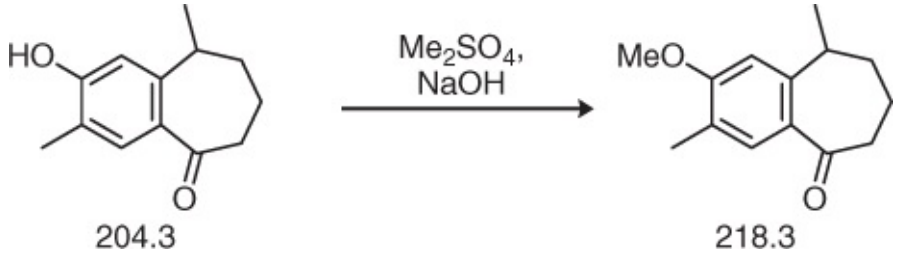
The dark-red reaction mixture is then poured into H_2O (50 ml) and extracted with Et_2O (3 × 25 ml). The combined ethereal extracts are dried over $MgSO_4$ and filtered, and the solvent is removed *in vacuo*. The residue is purified by column chromatography (SiO_2; Et_2O/petroleum ether, 1 : 2). The product is obtained in the form of colorless crystals; 1.30 g (71%), mp 142–143 °C.

IR (film): $\tilde{\nu}$ (cm^{-1}) = 3115, 1670.

^{1}H NMR (400 MHz, [D_6]DMSO): δ (ppm) = 9.90 (s, 1H, OH), 7.29, 6.74 (2 × s, 2 × 1H, 2 × Ar–H), 3.09–3.02 (m_c, 1H, C<u>H</u>–CH_3), 2.58–2.51 (m, 2H, CH_2), 2.11 (s, 3H, Ar–CH_3), 1.92–1.76 (m, 2H, CH_2), 1.48–1.34 (m, 2H, CH_2), 1.28 (d, *J* = 6.6 Hz, 3H, CH–C<u>H</u>$_3$).

MS (EI, 70 eV): *m*/*z* (%) = 204 $[M]^+$.

1.1.4.5	*	**2-Methoxy-3,9-dimethyl-6,7,8,9-tetrahydro-5*H*-benzo[*a*]cyclohepten-**
		5-one [5]



The hydroxybenzosuberone **1.1.4.4** (1.00 g, 5.0 mmol) is added over a period of 5 min to a stirred solution of NaOH (200 mg, 5.00 mmol) in H_2O (2.0 ml). Dimethyl sulfate (0.63 g, 5.0 mmol, 500 µl; Caution: carcinogenic!) is then

added, and stirring is continued for 30 min at room temperature; more $(CH_3O)_2SO_2$ (0.63 g, 5.0 mmol, 500 µl) is then added, and stirring is continued for 1 h at room temperature and for 30 min at 100 °C (water bath).

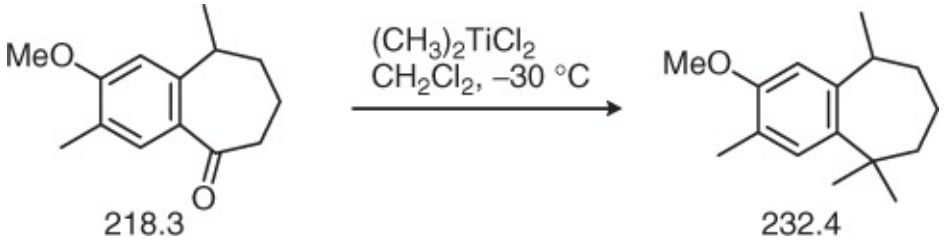
The reaction mixture is then cooled to room temperature, diluted with H_2O (10 ml), and extracted with Et_2O (3 × 20 ml). The combined extracts are dried over $MgSO_4$ and filtered, and the solvent is removed *in vacuo*. The oily residue is purified by chromatography (SiO_2; CH_2Cl_2). The product is obtained as a faintly yellow solid; 0.96 g (90%), mp 61–62 °C.

IR (film): $\tilde{\nu}$ (cm^{-1}) = 1690.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.44, 6.69 (2 × s, 2 × 1H, Ar–H), 3.88 (s, 3H, OCH_3), 3.13 (m_c, 1H, C<u>H</u>–CH_3), 2.74–2.68, 2.61–2.53 (2 × m, 2 × 1H, CH_2), 2.19 (s, 3H, Ar–CH_3), 1.98–1.83, 1.66–1.49 (2 × m, 2 × 2H, CH_2), 1.39 (d, *J* = 7.0 Hz, 3H, CH–C<u>H</u>$_3$).

MS (EI, 70 eV): *m*/*z* (%) = 218 (77) $[M]^+$.

1.1.4.6	**	**2-Methoxy-3,5,5,9-tetramethyl-6,7,8,9-tetrahydro-5*H*-benzo[*a*]cycloheptene** [5]



Under a nitrogen atmosphere, a solution of dimethylzinc in toluene (2 M, 2.5 ml, 5.00 mmol) is added dropwise to a stirred solution of titanium tetrachloride (0.96 g, 5.00 mmol) in anhydrous CH_2Cl_2 (25 ml) at such a rate that an internal temperature of −30 °C is maintained. After 15 min, a solution of the ketone **1.1.4.5** (0.50 g, 2.30 mmol) in CH_2Cl_2 (1.0 ml) is added dropwise at −30 °C. During the addition, the brown color of the reaction mixture changes to an intense dark brown. The mixture is allowed to warm to room temperature and is then heated under reflux for 12 h.

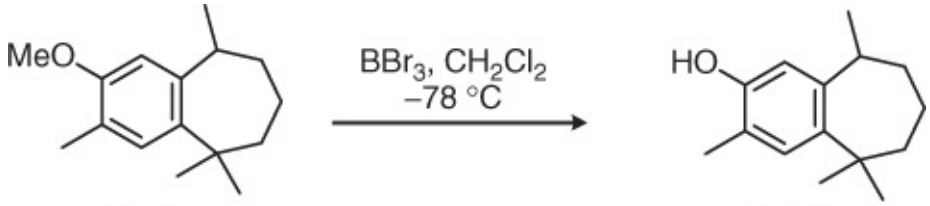
The reaction mixture is poured into H_2O (50 ml) and extracted with CH_2Cl_2 (3 ×

20 ml). The extracts are combined, washed successively with H_2O (100 ml) and saturated aqueous $NaHCO_3$ solution (100 ml), dried over $MgSO_4$, and filtered. The solvent is removed *in vacuo*, and the residue is purified by rapid filtration through silica gel (CH_2Cl_2). The product is obtained as a colorless oil; 0.43 g (81%), which is homogeneous according to TLC.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.12, 6.71 (2 × s, 2 × 1H, Ar–H), 3.81 (s, 3H, OCH_3), 3.27 (m_c, 1H, C<u>H</u>–CH_3), 2.18 (s, 3H, Ar–CH_3), 1.79–1.74, 1.65–1.52 (2 × m, 2 × 3H, 3 × CH_2), 1.39, 1.31 (2 × s, 2 × 3H, $C(CH_3)_2$), 1.36 (d, *J* = 7.1 Hz, 3H, CH–C<u>H</u>$_3$).

MS (CI, 120 eV): *m*/*z* (%) = 232 (66) $[M]^+$.

1.1.4.7	*	**2-Hydroxy-3,5,5,9-tetramethyl-6,7,8,9-tetrahydro-5*H*-benzo[*a*]cycloheptene** [5]



A 1.0 M solution of boron tribromide (4.0 ml, 8.0 mmol) in CH_2Cl_2 is added to a stirred solution of the methoxy compound **1.1.4.6** (0.42 g, 1.48 mmol) in anhydrous CH_2Cl_2 (40 ml) at −78 °C. The reaction mixture is allowed to warm to room temperature over 12 h.

H_2O (50 ml) is then added, the organic phase is separated, the aqueous phase is extracted with CH_2Cl_2 (3 × 20 ml), and the combined organic phases are dried over $MgSO_4$ and filtered. The solvent is removed *in vacuo*, and the crude product is purified by column chromatography (SiO_2; CH_2Cl_2) to give 0.25 g (80%) of the hydroxy-*ar*-himachalan as a yellowish oil, which is pure according to TLC.

IR (film): $\tilde{\nu}$ (cm^{-1}) = 3370.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.10, 6.65 (2 × s, 2 × 1H, Ar–H), 4.57 (s_{br}, 1H, OH), 3.22 (m_c, 1H, C<u>H</u>–CH_3), 2.21 (s, 3H, Ar–CH_3), 1.83–1.49 (m, 6H, $(CH_2)_3$), 1.39 and 1.30 (2 × s, 2 × 3H, $C(CH_3)_2$), 1.29 (d, *J* = 7.1 Hz, 3H, CH–C<u>H</u>$_3$).

MS (CI, 120 eV): *m*/*z* (%) = 218 (478) $[M]^+$.

Note: The ^{1}H NMR spectrum is identical to that of the natural product according to Ref. [4].

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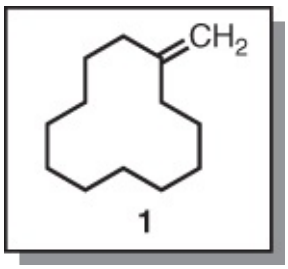
6. Krause, N. (1996) *Metallorganische Chemie*, Spektrum Akademischer Verlag, Heidelberg, p. 166; for an alternative Al-organic method for the conversion of a carbonyl group to a geminal dimethyl functionality, see: Kim, C.U., Misco, P.F., Luh, B.Y. and Mansouri, M.M. (1994**)** *Tetrahedron Lett.*, **35**, 3017–3020.

7. For the use of titanium complexes with chiral ligands as valuable tools in enantioselective synthesis, see: Ramon, D.J. and Yus, M. (2006) *Chem. Rev.*, **106**, 2126–2208.

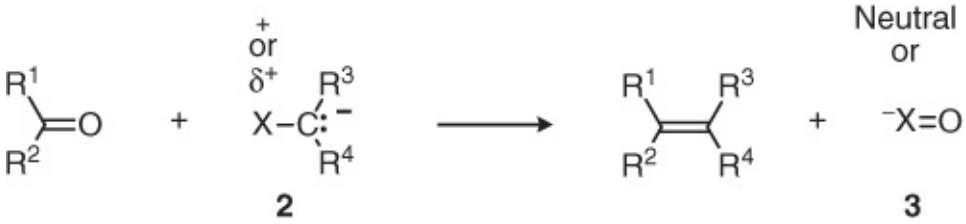
8. For synthesis of the phosphonium salt **22**, see: Perlmutter, P., Selajerem, W., and Vounatsos, F. (2004) *Org. Biomol. Chem.*, **2**, 2220–2228.

1.1.5 Methylenecyclododecane

 1	***Topics:***	• Carbonyl olefination by the Lombardo reaction

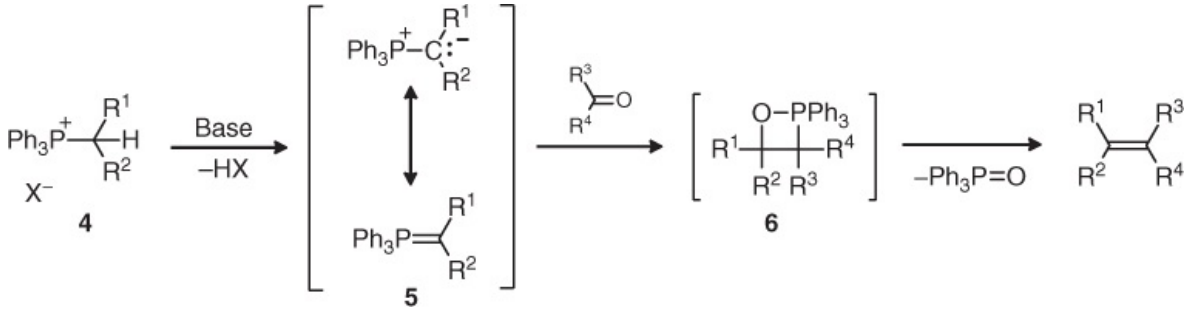
(a) General

The term ***carbonyl olefination*** covers a series of C–C bond-forming reactions, which allow the chemo-and stereoselective formation of an olefinic double bond at carbonyl groups of aldehydes, ketones, esters, amides, and so on, according to the following general scheme:



As reactants for carbonyl olefinations, α-carbanionic species of type **2** are required, which attack as nucleophiles at the carbonyl C atom. They also exhibit electrophilic properties at the structural unit X for attack at the carbonyl oxygen, which is removed as an X=O moiety **3** in the olefination process. If X carries a positive charge, **2** represents a betaine or ylide. Several types of reactants **2** containing P, Si, and metal centers in the X part have been developed as carbonyl olefinating reagents.

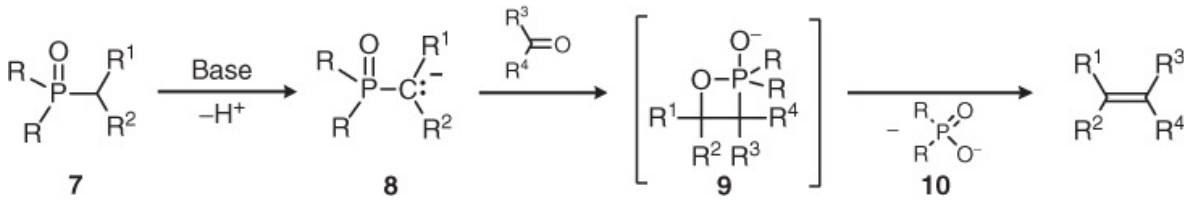
1. The classical procedure for carbonyl olefination is the Wittig reaction [1], using phosphoranes **5**. The phosphoranes **5** (easily obtainable by deprotonation of the corresponding α-CH phosphonium salts **4**) react with aldehydes or ketones to give alkenes and phosphine oxide:



The mechanism and stereochemistry of the Wittig reaction have been

thoroughly investigated [2, 3]. The intermediates are the oxaphosphetanes **6** (from nonstabilized P-ylides), which collapse thermally by elimination of phosphine oxide. As a simplified rule, resonance-stabilized P-ylides give rise to (*E*)-alkenes, while nonstabilized P-ylides preferentially lead to (*Z*)-alkenes. The high value of the Wittig reaction is documented by a very large number of applications in the synthesis of alkenes (cf. Sections 1.1.4 and 4.1.6).

2. The Wittig–Horner reaction is a prominent example of the principle of "PO-activated olefination" [1], in which α-carbanions **8** (R = OR′) from phosphonates react with aldehydes and ketones; phosphonamides and phosphine oxides behave analogously:

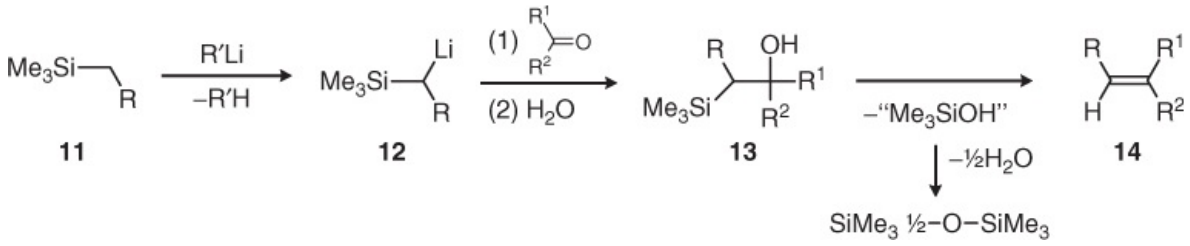


The mechanism of the Wittig–Horner reaction is comparable to that of the Wittig reaction [2, 3]. Oxaphosphetanes **9** can be assumed as primary intermediates, which are cleaved by olefin formation and elimination of phosphate **10** (R = OR′). The main advantages of the Wittig–Horner reaction lie in the facts that:

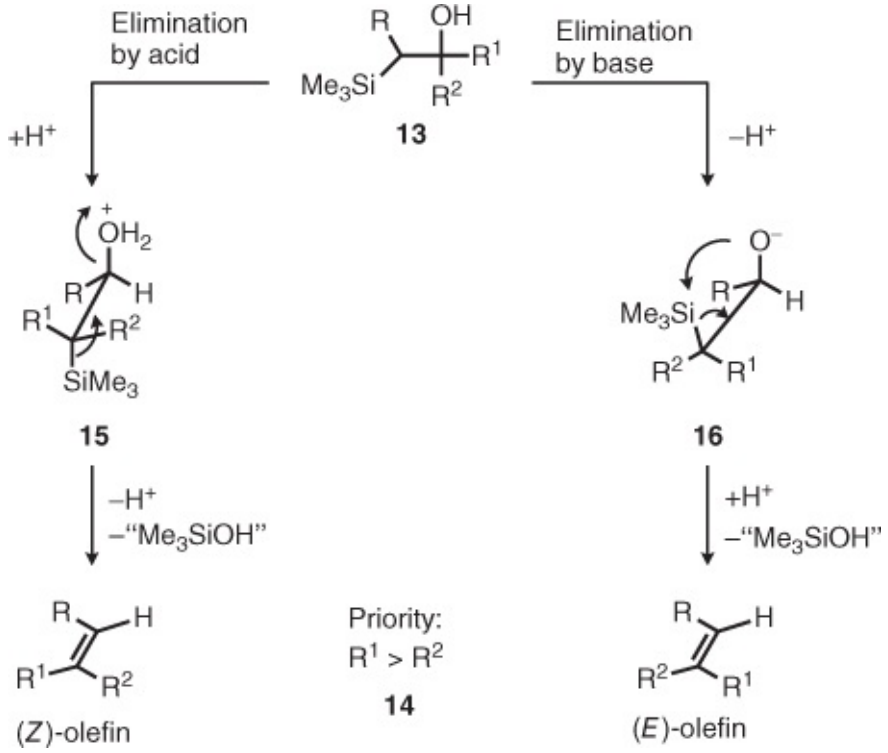
- the reactivity of the α-carbanions **8** often proves to be superior to that of the corresponding P-ylides **5**, thus allowing olefination of carbonyl substrates not or less susceptible to the Wittig method, for example, cyclohexanone, and
- the phosphates **10** (R = OR′) formed in the olefination process are water soluble, thus considerably improving the isolation and purification procedures for the olefinic products.

Phosphonates **7** (R = OR′) are obtained from phosphites and halogenoalkanes by the Arbusov reaction.

3. In the Peterson olefination (sometimes called the *sila-Wittig reaction*) [4], α-lithiated trialkylsilanes **12**, obtained from tetraalkylsilanes of type **11** by metallation with lithium diisopropylamide (LDA) or *n*BuLi, react with aldehydes or ketones:

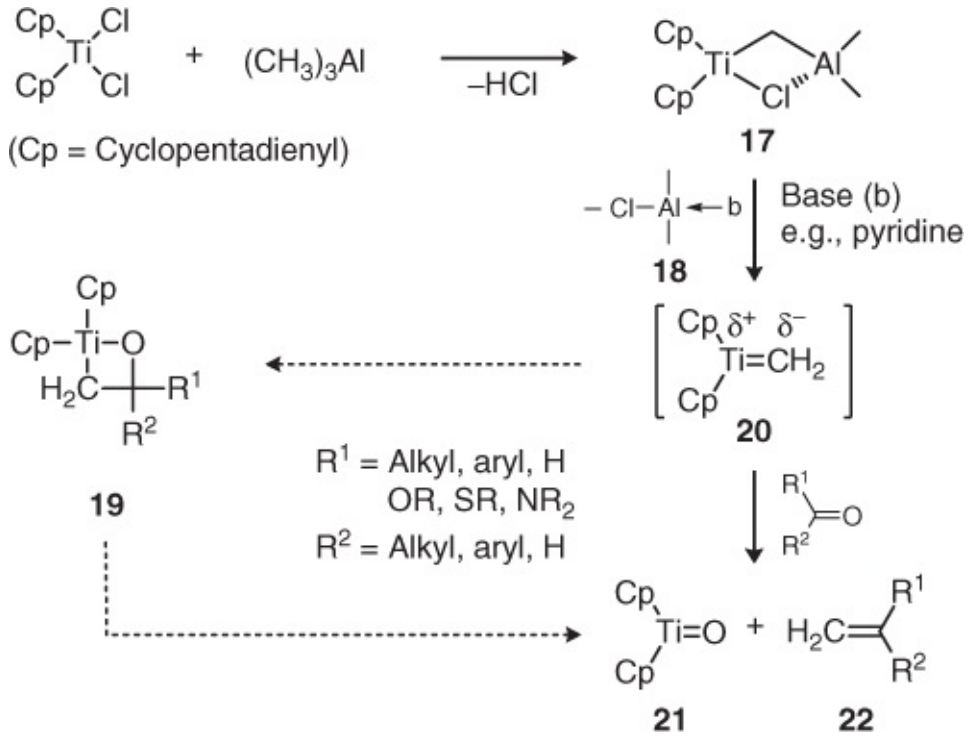


Initially, a β-hydroxysilane **13** is obtained, which is transformed into the olefin **14** by elimination of a silanol $Me_3Si–OH$ (finally appearing as $Me_3Si–O–SiMe_3$). The stereochemistry of olefin formation **13** → **14** can often be controlled by whether an acid or a base is used for the silanol elimination. Use of an acid generally leads to an anti-elimination (transition state **15**), whereas use of base leads to a syn-elimination (transition state **16**); in this way, the stereoselective formation of either (*Z*)- or (*E*)-alkenes **14** can be achieved.



4. Olefin formation using the Wittig, Horner, or Peterson procedures is, with only a few exceptions, restricted to aldehydes and ketones. However, by the application of a series of titanium-based reagents, a broad variety of carbonyl-containing substrates, not only aldehydes and ketones but also esters, lactones, amides, and so on, become amenable to olefination reactions, predominantly methylenations.

a. The Tebbe reagent **17**, obtained from bis(cyclopentadienyl)titanium dichloride and trimethylaluminum, can react with practically all kinds of carbonyl-containing substrates [5, 6] in the presence of a Lewis base (e.g., pyridine) to give methylenation products **22** (alkenes, enol ethers, enamines, etc.):

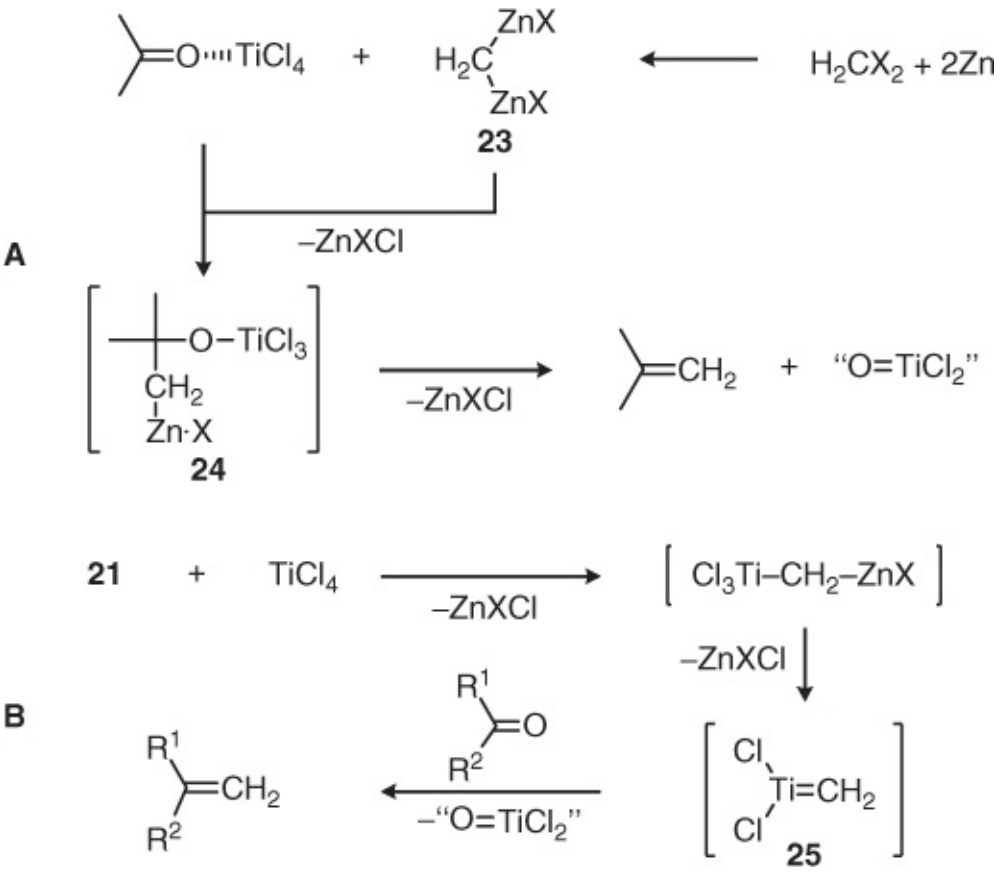


The Tebbe reaction is likely to proceed via a titanium ylide **20** (generated from the bridged reagent **17** by a Lewis base-induced removal of the chlorodimethylaluminum moiety **18**), its (formal) [2 + 2]-cycloaddition to the carbonyl group, and eliminative cycloreversion of the intermediate **19** to give the methylenation product **22**. In addition, **21** is formed by an oxygen transfer to titanium.

b. Reagent combinations of dihalogenomethanes, zinc, and titanium tetrachloride (H_2CX_2/Zn/$TiCl_4$, Lombardo and Takai reagents), which are easier to handle and less expensive than the Tebbe reagent, may also allow the methylenation of aldehydes and ketones; in general, however, ester functionalities are not affected [5].

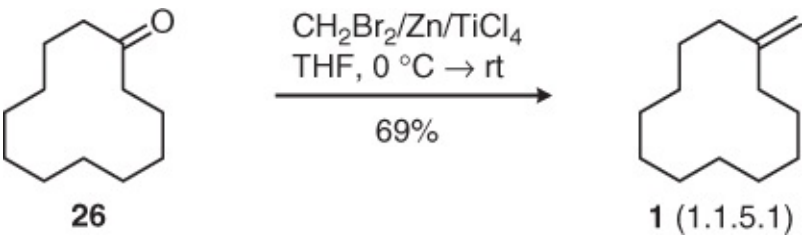
The structures of the titanium species responsible for the Lombardo/Takai olefination are unknown. It is assumed that a “dimetallic” Zn species **23** is formed initially, which can lead to methylenation products via two alternative routes: (i) by reaction with the carbonyl group activated by $TiCl_4$ as a Lewis acid

(via **24**) or (ii) by transmetallation with $TiCl_4$ leading to a Ti ylide **25**, which reacts with the carbonyl group in analogy with the Tebbe reaction:



(b) Synthesis of 1

Methylenecyclododecane (**1**) is prepared from cyclododecanone (**26**) in a one-pot procedure [7] by means of methylenation using the Lombardo reagent prepared *in situ* from dibromomethane, titanium tetrachloride, and zinc dust (in the ratio 1.5 : 1.1 : 4.5). The reaction proceeds smoothly at 0 °C to room temperature in anhydrous THF to give the macrocycle **1** in 69% yield after the usual work-up and purification by chromatography on silica gel.

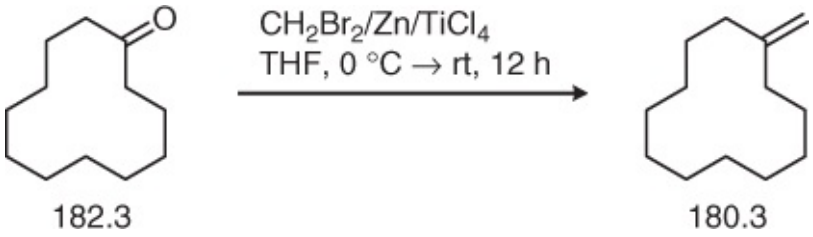


26 **1** (1.1.5.1)

It should be noted that **1** is also accessible by a Wittig reaction starting from ketone **26** [8].

(c) Experimental Procedure for the Synthesis of 1

1.1.5.1	**	**Methylenecyclododecane** [7]



182.3 180.3

Dibromomethane (13.0 g, 74.8 mmol, 5.94 ml) and titanium tetrachloride (10.4 g, 55.0 mmol, 6.07 ml) are added sequentially to a vigorously stirred suspension of zinc dust (14.8 g, 226 mmol) in anhydrous THF (250 ml). After stirring the mixture for 15 min at 0 °C, a solution of cyclododecanone (9.10 g, 49.9 mmol) in anhydrous THF (50 ml) is added dropwise, and stirring is continued for 12 h at room temperature.

The mixture is then diluted with Et_2O (200 ml) and filtered, and the filtrate is washed with 1 M aqueous HCl (250 ml) and brine (250 ml). The organic layer is dried over $MgSO_4$ and filtered, and the solvent is removed *in vacuo*. The residue is dissolved in *n*-pentane and purified by column chromatography (SiO_2, *n*-pentane) to give the product as a colorless liquid; 6.24 g (69%), R_f = 0.76 (*n*-pentane).

UV (CH_3CN): λ_{max} (nm) (log ϵ) = 192.0 (3.854).

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 2930, 1643, 887, 469.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 4.79 (m_c, 2H, 1-CH_2), 2.06 (m, 4H, 2-H_2, 12-H_2), 1.55–1.47 (m, 4H, 4-H_2, 10-H_2), 1.31 (m_c, 14H, 3-H_2, 5-H_2, 6-H_2, 7-H_2, 8-H_2, 9-H_2, 11-H_2).

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 147.5 (C-1), 110.3 (1-CH_2), 33.04 (C-2, C-12), 24.43, 24.11, 23.69, 23.24 (C-3, C-4, C-5, C-6, C-8, C-9, C-10, C-11), 22.59 (C-7).

MS (EI, 70 eV): *m*/*z* (%) = 180 (46) $[M]^+$, 96 (100) $[M-C_6H_{12}]^+$.

Note: The product can be distilled *in vacuo*, $bp_{0.8}$ 76–77 °C.

References

1. (a) Smith, M.B. (2013) *March's Advanced Organic Chemistry*, 7th edn, John Wiley & Sons, Inc., New York, p. 1165;(b) For a review on olefination of carbonyl compounds, see: Korotchenko, V.N., Nenajdenko, V.G., Balenkova, E.S., and Shastin, A.V. (2004) *Russ. Chem. Rev. (Engl. Transl.)*, **73**, 957–989.

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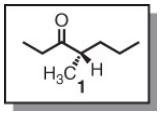
1.2 Alkylation of Aldehydes/Ketones, Carboxylic Acids, and β-Dicarbonyl Compounds

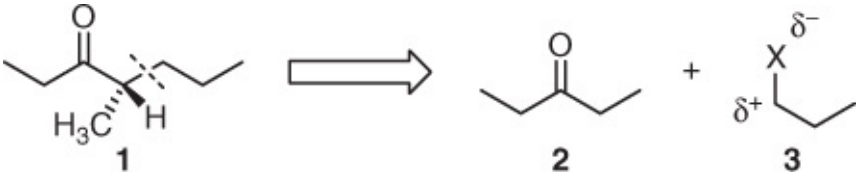
1.2.1 (+)-(*S*)-4-Methylheptan-3-one

	***Topics:***	• Synthesis of an enantiopure pheromone by application of the Enders SAMP method • Formation of the SAMP hydrazone of a methylene ketone • Diastereoselective α-alkylation of a SAMP hydrazone, hydrolytic cleavage of the alkylated SAMP hydrazone

(a) General

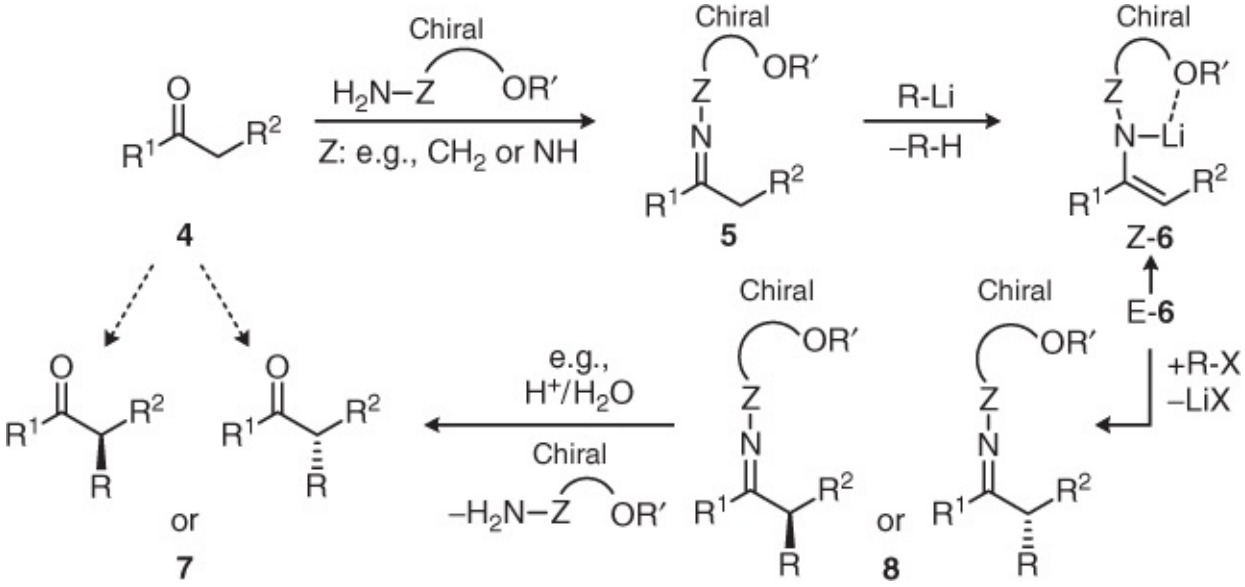
(+)-(*S*)-4-Methylheptan-3-one (**1**) is the main alarm pheromone of the leafcutter ant *Atta texana*; it is 400 times more active than its enantiomer.

Retrosynthetic analysis leads directly to pentan-2-one (**2**) and an alkylation reagent **3** representing the α-side chain.



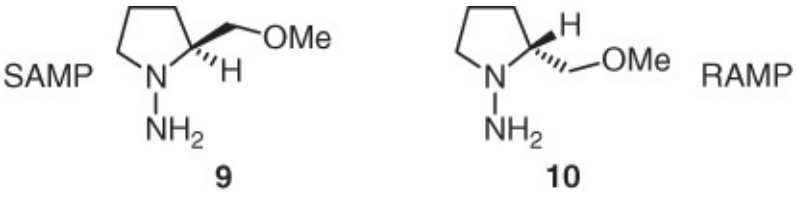
The main objective in the synthesis of **1** is therefore the stereoselective monoalkylation of a dialkyl ketone **4** possessing an α-CH_2 group. This requires the transformation of the C=O group into a C=N–R moiety carrying a chiral group R, which provides stereochemical control for the alkylation process. Since an additional binding, for example, by chelate formation, is necessary, β-alkoxyamines and alkoxyhydrazines are interesting candidates; they can be easily prepared from "chiral pool" amino acids.

For a stereoselective alkylation, the following steps have to be considered. Derivatization of the ketone (**4** → **5**), α-deprotonation at CH_2 and formation of a chelated azaenolate **6** with a rigid backbone, diastereoselective reaction of **6** with an electrophile (here: R–X, **6** → **8**), and finally removal of the auxiliary to give one pure enantiomer of the desired α-alkylated ketone (**8** → **7**):



This concept has been verified in several modifications [1]. Particularly successful outcomes have been achieved with the enantiomers of the hydrazine derived from (*S*)- or (*R*)-prolinol methyl ether (SAMP/RAMP, **9**/**10**), both of

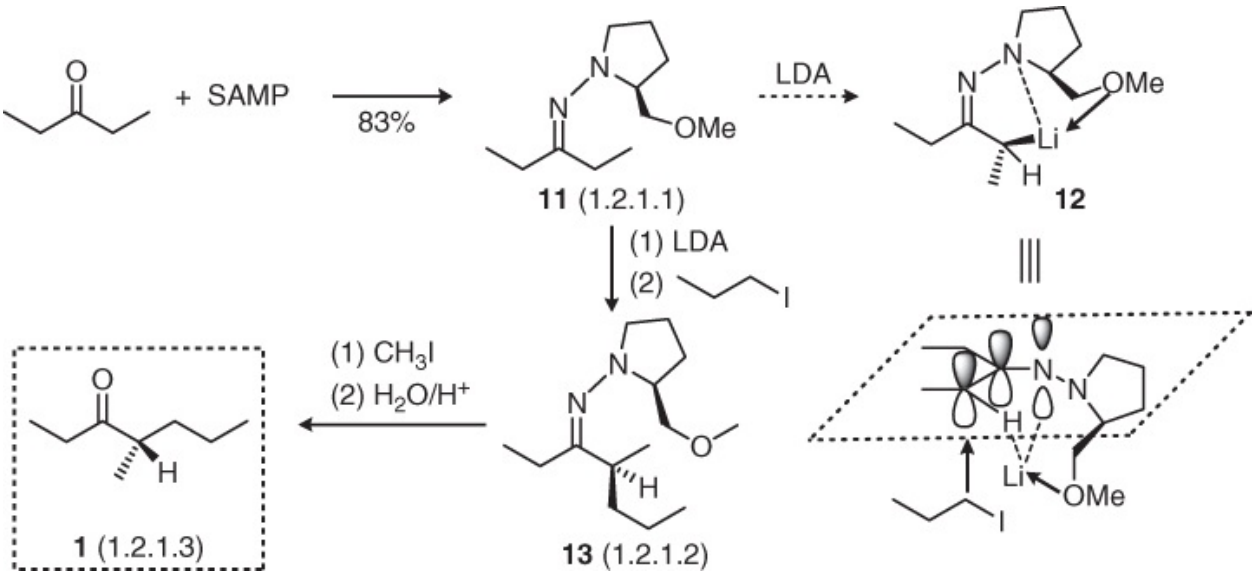
which are readily available [2] and thus allow the preparation of both enantiomers of an α-alkyl ketone [3].



Here, the SAMP method (Enders method) is used to prepare the ketone **1** with high enantiopurity [4].[3]

(b) Synthesis of 1

First, the SAMP auxiliary is condensed with diethyl ketone (**2**) to give the chiral hydrazone **11**:



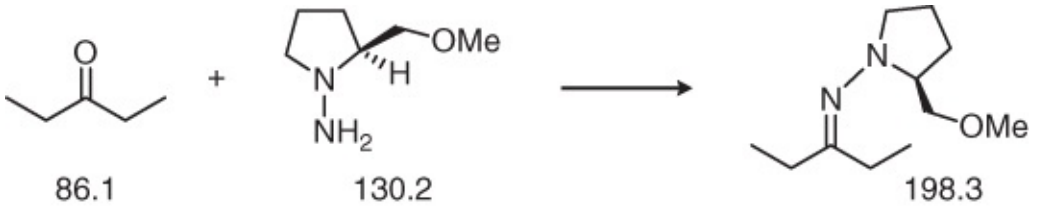
The hydrazone **11** is metallated with LDA, and the formed azaenolate **12** is reacted with *n*-propyl iodide to provide the α-alkylated hydrazone **13** as a single diastereomer. The alkylation process presumably follows an S_E2 mechanism with retention of configuration, as visualized in the transition state **12**. Li chelation of the methoxy group is obviously responsible for the high degree of diastereoselection observed.

The hydrazone **13** is cleaved by alkylation with CH_3I to give the corresponding hydrazonium salt, which is cleaved by acid hydrolysis in an aqueous two-phase system to give the α-alkylated ketone **1** with 99% ee. This mild method of hydrazone cleavage has the drawback that the chiral auxiliary cannot be recovered ("sacrificial" vs. "regenerative" use of a chiral auxiliary [5]).

Ozonolysis is another method that has been introduced for the cleavage of SAMP hydrazones; it leads directly to the α-alkylated carbonyl source and a SAMP-derived nitrosamine [6].

(c) Experimental Procedures for the Synthesis of 1

1.2.1.1	**	**Preparation of the Chiral Hydrazone** [4][3)]

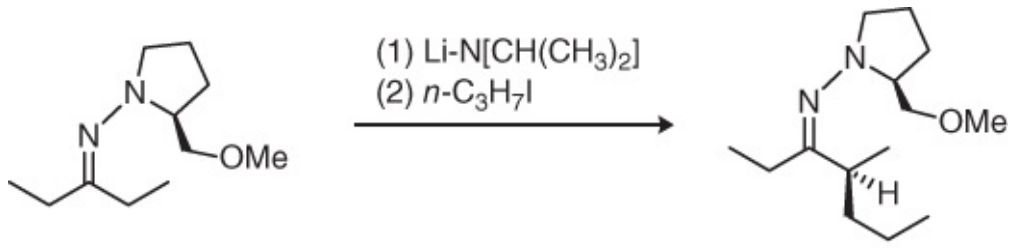


86.1 130.2 198.3

(−)-(*S*)-1-Amino-2-(methoxymethyl)pyrrolidine [2] (2.60 g, 20.0 mmol) and 3-pentanone (distilled, bp_{760} 101–102 °C; 1.89 g, 22.0 mmol, ≈2.32 ml) are stirred at 60 °C for 20 h in a 25-ml single-necked flask.

The reaction mixture is then diluted with anhydrous CH_2Cl_2 (20 ml) and dried over Na_2SO_4. The solvent is evaporated, and the residue is distilled from a deactivated Kugelrohr (trimethylchlorosilane is distilled from the apparatus at atmospheric pressure). Any remaining solvent in the distillate is evaporated *in vacuo* to leave a colorless oil; 3.29 g (83%), $bp_{0.04}$ 46 °C (oven temperature 50–55 °C).

1.2.1.2	***	**Diastereoselective Alkylation of the Chiral Hydrazone** [4]



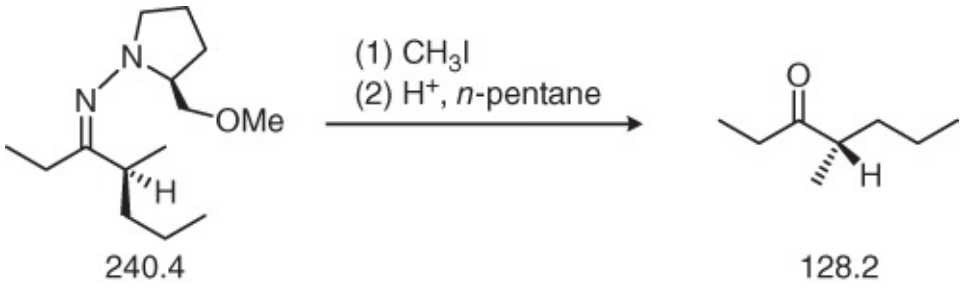
198.3 240.4

A solution of diisopropylamine (distilled from CaH_2, bp_{760} 84 °C; 0.84 g, 8.30 mmol, ≈1.17 ml) in anhydrous diethyl ether (40 ml) is prepared under nitrogen at −78 °C in an oven-dried, 100-ml, two-necked flask fitted with a septum. *n*-Butyllithium in *n*-hexane (1.6 M, 5.2 ml) is added by means of a syringe (cannula), and the solution is stirred for 10 min at −78 °C. The solution is then warmed to 0 °C over approximately 30 min, and the hydrazone prepared in **1.2.1.1** (1.52 g, 7.70 mmol) is slowly added dropwise from a syringe. Stirring is

continued at 0 °C for 10 h. The solution is then cooled to −110 °C (petroleum ether/N_2), propyl iodide (distilled, bp_{760} 102 °C; 1.47 g, 8.65 mmol, ∼0.84 ml) is added dropwise over 10 min through a cannula (the cannula is cooled during the addition), and stirring is continued for 1 h.

The mixture is warmed to room temperature, diluted with CH_2Cl_2 (40 ml), and filtered, and the solvent is evaporated. The residue is used immediately for the next step.

1.2.1.3	***	**Cleavage of the alkylated hydrazone** [4]



The crude product prepared in **1.2.1.2** and methyl iodide (3.54 g, 25.0 mmol, ∼1.56 ml; Caution: carcinogenic!) are heated under reflux. Excess methyl iodide is evaporated *in vacuo*. The formed hydrazonium iodide (green-brown oil) is stirred vigorously with *n*-pentane (60 ml)/aqueous HCl (6 M, 40 ml) for 60 min.

The organic phase is separated, and the aqueous phase is extracted with *n*-pentane (2 × 50 ml). The combined organic layers are washed with brine, dried over Na_2SO_4, and filtered. The solvent is removed *in vacuo* and the green residue is distilled from a Kugelrohr (pretreated with trimethylchlorosilane). The ketone is obtained as colorless liquid; 475 mg (48% based on SAMP), bp_{110} 140 °C (oven temperature), $[\alpha]^{20}_D$ = +16.5 (*c* = 1.2, *n*-hexane) (note).

IR (film): $\tilde{\nu}$ (cm^{-1}) = 1710, 740.

^{1}H NMR ($CDCl_3$): δ (ppm) = 2.45 (m, 3H, CH_2CO, CHCO), 1.84–0.71 (m, 13H, CH_2 + CH_3).

Note: Observed ee = 87% (*S*); reported [3]: $[\alpha]^{20}_D$ = +22.1 (*c* = 1.0, *n*-hexane), ee = 99.5% (*S*).

References

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3. (a) A simple example is the enantioselective preparation of both enantiomers of the defense substance of the “daddy longleg” cranefly: Enders, D. and Braus, U. (1983) *Liebigs Ann. Chem.*, 1439–1445;For other applications of the SAMP methodology, see: (b) Enders, D. and Klatt, M. (1996) *Synthesis*, 1403–1418;(c) Vicario, J.L., Job, A., Wolberg, M., Mueller, M., and Enders, D. (2002) *Org. Lett.*, **4**, 1023–1026;(d) Enders, D. and Voith, M. (2002) *Synlett*, 29–32;(e) Enders, D., Boudou, M., and Gries, J. (2005) *New Methods Asymm. Synth. Nitrogen Heterocycl.*, 1.

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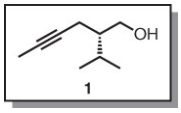
1.2.2 (*S*)-2-Isopropylhex-4-yn-1-ol



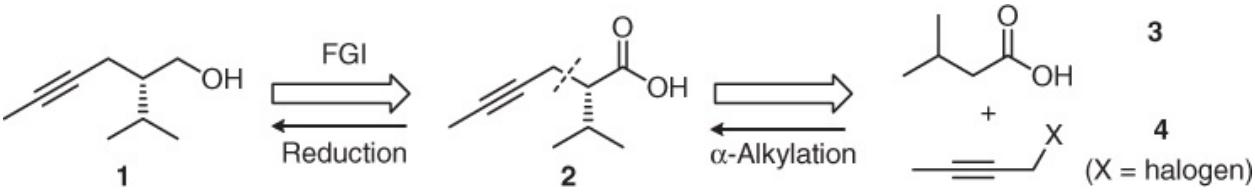
Topics:

- Enantioselective α-alkylation of an alkanoic acid by application of the Evans methodology
- Synthesis of a chiral oxazolidinone (Evans auxiliary) from L-valine
- Synthesis of 1-bromobut-2-yne (alkylating reagent)
- N-Acylation and enantioselective α-alkylation of a chiral *N*-acyloxazolidinone
- Reductive removal of the Evans auxiliary, transformation of the *N*-acyl moiety into the

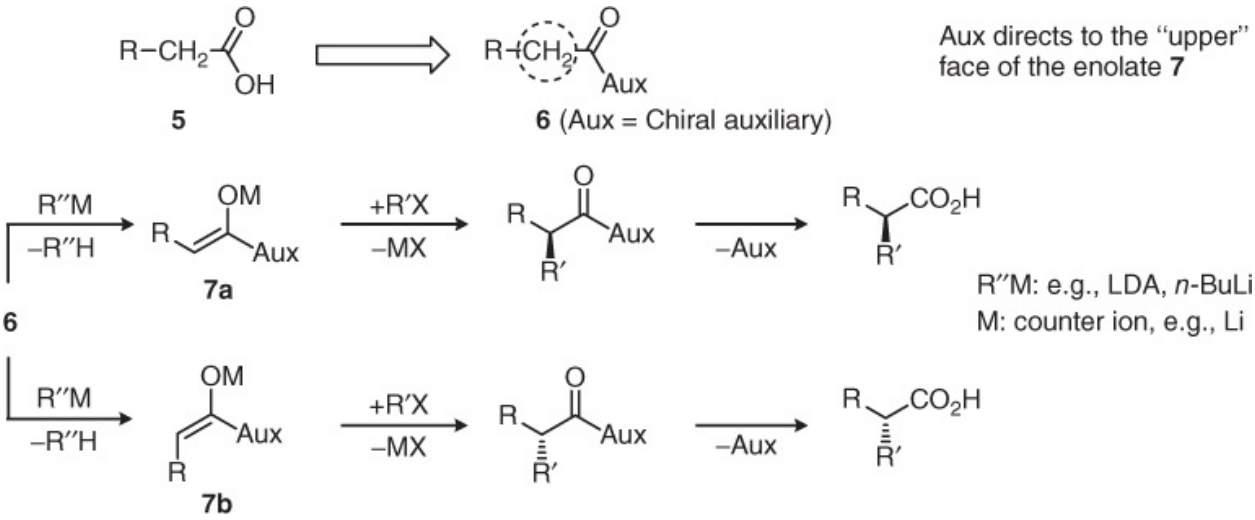
		corresponding primary alcohol

(a) General

The target molecule **1** was required as a building block in the context of a multistep natural product synthesis (L.F. Tietze *et al.*, unpublished results). Retrosynthesis of **1** leads to **2** and, furthermore, to isovaleric acid (**3**) and the propargylic halide **4** as substrates.



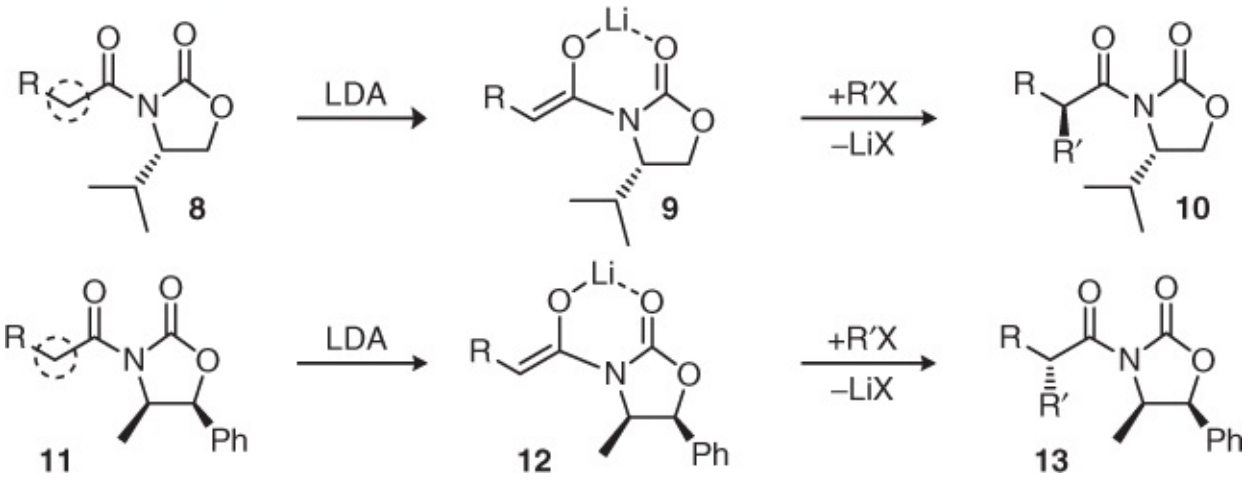
Accordingly, the synthesis consists of an α-alkylation of the acid **3** followed by reduction of the carboxyl group of the formed product **2** to provide the primary alcohol **1**. The main objective for a stereochemically concise synthesis of **1** is stereoselective α-alkylation of an alkanoic acid R–CH_2–CO_2H (**5**). For stereodifferentiation in the alkylation process, carboxylic acid derivatives **6** can be employed, in which a chiral auxiliary is introduced at the acyl C-atom (cf. Section 1.2.1) [1]. The chiral auxiliary influences the configuration of the enolates **7a**/**7b** (*Z* or *E*, formed by deprotonation of **6**) and the facial selectivity of the alkylation (*re* or *si*) according to the following scheme:



For high stereoselectivity in the enolate formation and the alkylation, formation of a chelate by coordination of the metal ion to an appropriate functionality of the chiral auxiliary is necessary. Widely used chiral carboxylic acid derivatives are **8** and **11**, containing an oxazolidinone as the chiral auxiliary (Evans

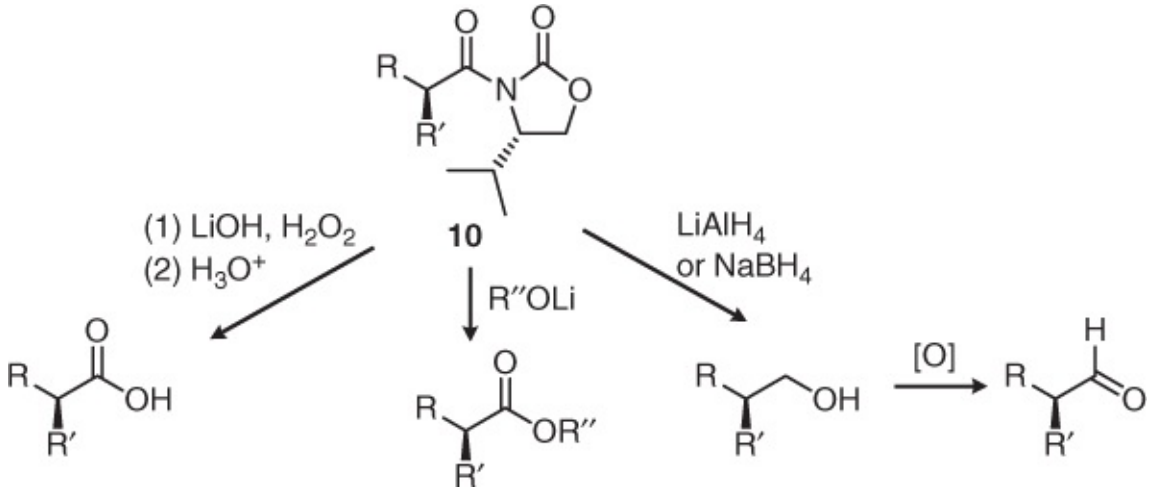
auxiliaries) [2].

Deprotonation of **8** and **11** with LDA produces the chelated enolates **9** and **12**, respectively, with a *Z*-selectivity of >99 : 1, which can then be α-alkylated with alkyl halides (only reactive alkyl halides such as methyl, benzyl, allyl, and propargyl can be used) with very high levels of diastereoselectivity to give the products **10** and **13**:



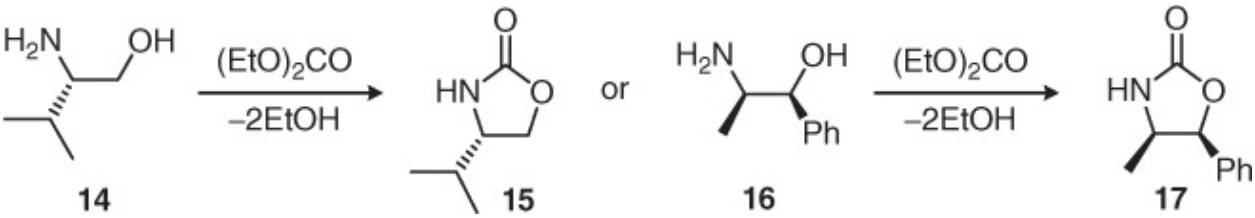
It should be noted that the enolates **9** and **12** can also be used in aldol reactions. In these transformations, using a (*Z*)-enolate, a syn product is obtained via a closed transition state, whereas with an (*E*)-enolate the anti product is formed predominately. By adding 1 mol of a Lewis acid, the stereochemical outcome is reversed, because under these conditions an open transition structure is preferred.

Removal of the chiral auxiliary from the α-alkylated *N*-acyl oxazolidinones **10** and **13** may be achieved by hydrolysis, alcoholysis, or reduction, as illustrated for **10**.



In this way, almost enantiopure α-alkylated carboxylic acids, esters, primary alcohols, and aldehydes can be obtained.

The chiral oxazolidinones **15** and **17**, as parts of the chiral *N*-acyl derivatives **8** and **11**, are prepared from readily available 1,2-amino alcohols such as L-valinol (**14**), formed from L-valine, and norephedrine (**16**) by reaction with diethyl carbonate. The acylation of **15** and **17** to give **8** and **11**, respectively, is accomplished by deprotonation with *n*-BuLi or LDA followed by reaction of the anion with an acid chloride:



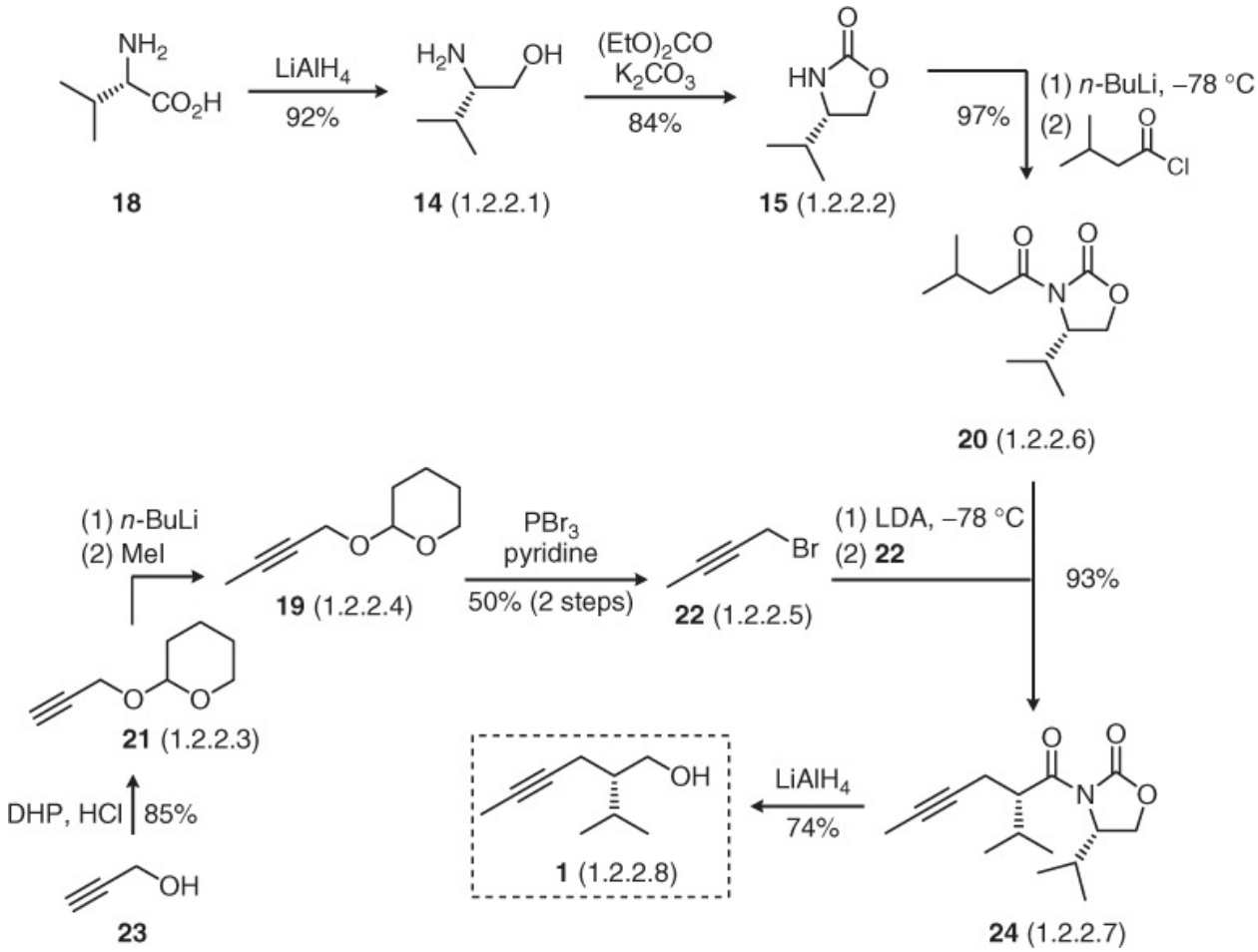
14 **15** **16** **17**

Because of the complementary outcomes of their α-alkylations, the systems **8** and **11** allow the preparation of both enantiomers of an (α-alkyl)alkanoic acid R–CHR′–CO_2H.

In Section (b), the synthesis of the target molecule **1** from a chiral α-alkylated isovaleric acid (**2**) is presented, which is accessible by application of the auxiliary **15** and the Evans methodology.

(b) Synthesis of 1

The synthesis of **1** is convergent and is divided into three parts. First, the auxiliary **15** is prepared from (*S*)-valine; second, the propargylic halide **22** is synthesized from propargyl alcohol (**23**); third, the auxiliary **15** is acylated, then the diastereoselective α-alkylation with **22** is performed, and finally the auxiliary is removed reductively.



1. L-Valine (**18**) is reduced with $LiAlH_4$ in THF to give L-valinol (**14**), which is transformed into the chiral oxazolidinone **15** by cyclocondensation with diethyl carbonate in the presence of K_2CO_3 [3, 4].

2. Propargylic alcohol (**23**) is converted to its tetrahydropyranyl ether **21** by reaction with dihydropyran in the presence of concentrated HCl. The THP ether **21** is deprotonated at the terminal acetylene function, and the formed acetylide is methylated *in situ* with CH_3I to give **19**. The THP ether in **19** is cleaved by treatment with phosphorus tribromide in the presence of pyridine in diethyl ether, thereby generating 1-bromo-2-butyne (**22**) required as the alkylating agent [5, 6].

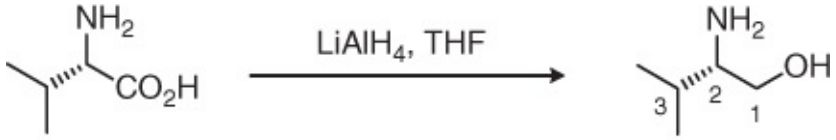
3. The oxazolidinone **15** is N-deprotonated using *n*-BuLi in THF and acylated with isovaleroyl chloride (both at −78 °C) to give the *N*-isovaleroyloxazolidinone **20** in almost quantitative yield. α-Alkylation of **20** is achieved in THF by deprotonation at the CH_2 group with LDA to yield the enolate **9** (R = $(CH_3)_2CH$), and subsequent reaction with the propargylic

halide **22** in the presence of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) at −78 °C cleanly affords the alkylation product **24** as a single diastereomer (93% yield, ds = 150 : 1).

Finally, treatment of **24** with $LiAlH_4$ in THF at −78 °C leads to reductive removal of the auxiliary with the formation of the chiral acetylenic alcohol **1** [5, 6].

(c) Experimental Procedures for the Synthesis of 1

1.2.2.1	**	**(2*S*)-2-Amino-3-methylbutan-1-ol (**L-**valinol)** [4]



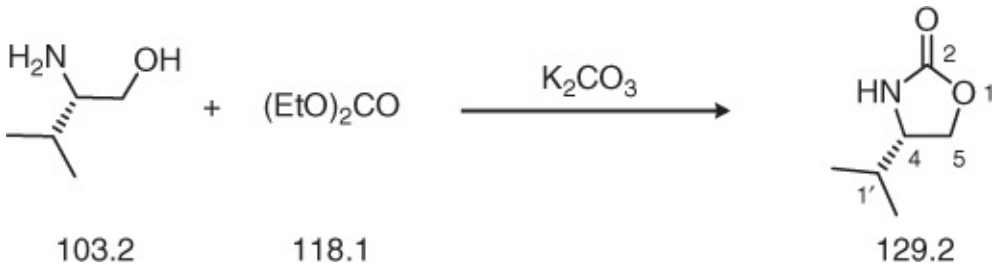
117.1 103.2

In a flame-dried, three-necked, round-bottomed flask equipped with a reflux condenser and a mechanical stirrer, $LiAlH_4$ (25.8 g, 0.68 mol) is suspended in anhydrous THF (300 ml) and cooled to 0 °C (nitrogen atmosphere). L-Valine (40.0 g, 0.34 mol) is carefully added in 1 g portions under vigorous stirring (Caution: reaction starts slowly!), and after addition the reaction mixture is heated to reflux for 15 h.

It is then cooled to 0 °C, and ice-cold water (40 ml) is carefully added (dropwise at the beginning). The gray-white aluminum salts are filtered off, suspended in a THF/H_2O mixture (4 : 1, 200 ml), stirred for 30 min, and then this mixture is also filtered. The process is repeated once more. The combined filtrates are concentrated *in vacuo*, the residue is dissolved in $CHCl_3$ (200 ml), and the mixture is refluxed in a Dean–Stark apparatus. The solvent is removed *in vacuo*, and the residue is distilled under reduced pressure to afford L-valinol as a colorless liquid; 32.2 g (92%), mp 55–56 °C, bp_{16} 85–86 °C, $[\alpha]^{20}_D$ = +25.7 (*c* = 1.0, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.62 (dd, *J* = 12.0, 3.5 Hz, 1H, 1-H_b), 3.31 (dd, *J* = 8.0, 12.0 Hz, 1H, 1-H_a), 2.60 (ddd, *J* = 8.0, 6.5, 3.5 Hz, 1H, 2-H), 2.34 (s_{br}, 3H, NH_2, OH), 0.99 (dsept, *J* = 7.0, 6.5 Hz, 1H, 3-H), 0.92 (d, *J* = 7.0 Hz, 6H, 2 × CH_3).

1.2.2.2	**	**(4*S*)-Isopropyloxazolidin-2-one** [4]

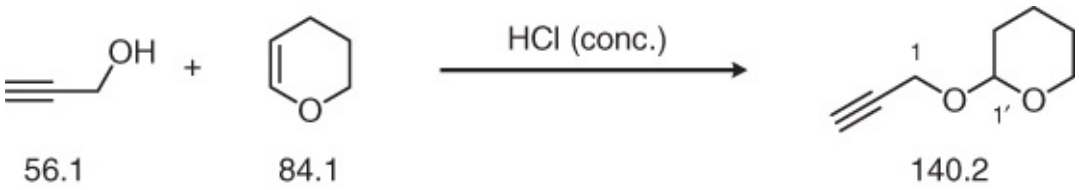


In a micro distillation apparatus equipped with a Vigreux column (30 cm) and an internal thermometer, a mixture of L-valinol **1.2.2.1** (31.0 g, 0.30 mol), diethyl carbonate (76.8 g, 0.65 mol), and anhydrous K_2CO_3 (4.13 g, 0.03 mol) is slowly heated to 130–140 °C. EtOH is distilled off in the course of the reaction (internal temperature should not exceed 100 °C, temperature at the top of the Vigreux column should not exceed 85 °C). After EtOH formation has ceased, the mixture is heated for another 30 min.

It is then cooled to room temperature, diluted with CH_2Cl_2 (200 ml), and filtered. The filtrate is washed with saturated aqueous $NaHCO_3$ solution (2 × 50 ml), dried over $MgSO_4$, filtered, and concentrated *in vacuo*, and the residue is crystallized from EtOAc/*n*-pentane to afford the oxazolidinone; 32.7 g (84%), mp 74–75 °C, $[\alpha]^{20}_D = -19.2$ (*c* = 1.24, EtOH).

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.14 (s_{br}, 1H, NH), 4.47 (dd, *J* = 9.0, 8.5 Hz, 1H, 5-H_b), 4.12 (dd, *J* = 9.0, 6.0 Hz, 1H, 5-H_a), 3.64 (ddd, *J* = 8.5, 6.5, 6.0 Hz, 1H, 4-H), 1.76 (dsept, *J* = 7.0, 6.5 Hz, 1H, 1′-H), 0.97 (d, *J* = 7.0 Hz, 3H, CH_3), 0.90 (d, *J* = 7.0 Hz, 3H, CH_3).

1.2.2.3	*	**2-(2-Propynyloxy)tetrahydropyran** [5, 6]

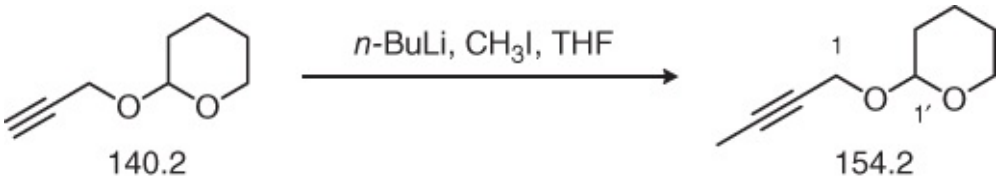


Concentrated HCl (1 µl) is added to a stirred mixture of propargyl alcohol (28.1 g, 500 mmol) and 3,4-dihydro-2*H*-pyran (DHP) (43.7 g, 520 mmol) at 0 °C. Stirring is continued for 24 h at room temperature.

KOH (900 mg) is then added and the mixture is stirred for another 15 min. Fractional distillation using a Vigreux column affords the tetrahydropyran as a colorless liquid; 59.6 g (85%), bp_{20} 72–80 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 4.78 (t, *J* = 3.2 Hz, 1H, 1′-H), 4.26 (dq, *J* = 15.2, 2.3 Hz, 1H, 1-H_b), 4.09 (dq, *J* = 15.2, 2.3 Hz, 1H, 1-H_a), 3.90–3.75 (m, 1H, 5′-H_b), 3.52–3.43 (m, 1H, 5′-H_a), 2.02 (t, *J* = 2.5 Hz, 1H, 3-H), 1.88–1.40 (m, 6H, 2′-H_2, 3′-H_2, 4′-H_2).

1.2.2.4	**	**2-(2-Butynyloxy)tetrahydropyran** [5, 6]

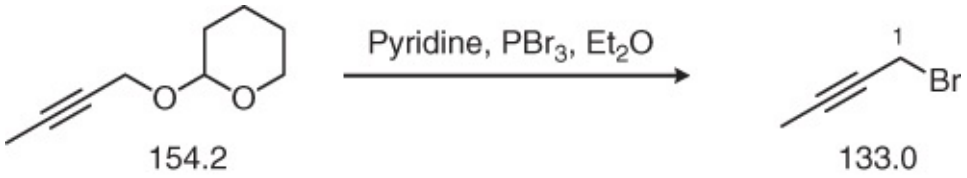


n-Butyllithium in *n*-hexane (2.5 M, 172 ml, 429 mmol) is added dropwise over 1 h to a stirred solution of the tetrahydropyran **1.2.2.3** (50.0 g, 357 mmol) in THF (600 ml) at −78 °C. Stirring is continued at −78 °C for 5 h; then methyl iodide (152 g, 1.07 mol, 66.9 ml; Caution: carcinogenic!) is added and the solution is allowed to warm to room temperature over 14 h.

The reaction is quenched by the addition of H_2O (20 ml) and the solvent is removed *in vacuo*. The brown, oily crude product is dissolved in benzene (150 ml; Caution: carcinogenic!) and this solution is concentrated *in vacuo* to remove the remaining H_2O by azeotropic distillation. The residue is fractionally distilled to afford the product as a colorless oil; 50.4 g (91%), bp_{10} 75–80 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 4.76 (t, *J* = 3.2 Hz, 1H, 1′-H), 4.27 (dq, *J* = 15.2, 2.3 Hz, 1H, 1-H_b), 4.14 (dq, *J* = 15.2, 2.3 Hz, 1H, 1-H_a), 3.86–3.73 (m, 1H, 5′-H_b), 3.54–3.42 (m, 1H, 5′-H_a), 1.90–1.42 (m, 6H, 2′-H_2, 3′-H_2, 4′-H_2), 1.81 (t, *J* = 2.3 Hz, 3H, 4-H_3).

1.2.2.5	**	**1-Bromo-2-butyne** [5, 6]



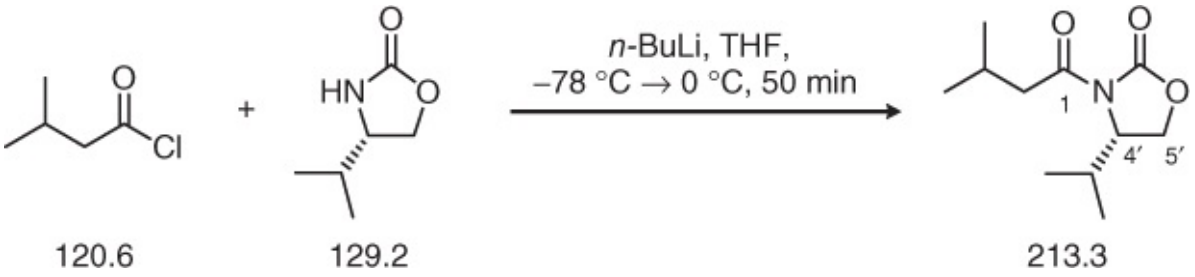
Phosphorus tribromide (37.6 g, 139 mmol, 13.1 ml) is added dropwise to a solution of the tetrahydropyran **1.2.2.4** (42.9 g, 278 mmol) and pyridine (0.2 ml) in Et_2O (25 ml), and the mixture is heated under reflux for 3 h.

The reaction is quenched with H_2O (50 ml), the organic layer is separated, and the aqueous layer is extracted with Et_2O (2 × 150 ml). The combined organic layers are washed with saturated $NaHCO_3$ solution (2 × 150 ml), dried over Na_2SO_4, and filtered, and the solvent is removed *in vacuo*. The residue is fractionally distilled with a Vigreux column to afford 1-bromo-2-butyne as a colorless liquid; 21.6 g (58%), bp_{43} 38–43 °C, R_f = 0.72 (*n*-pentane/MeO*t*Bu = 5 : 1).

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.91 (q, *J* = 2.5 Hz, 2H, 1-H_2), 1.89 (t, *J* = 2.5 Hz, 3H, 4-H_3).

MS (EI): *m*/*z* (%) = 135 (60) $[M+2H]^+$, 133 (60) $[M]^+$.

1.2.2.6	**	**(*S*)-4-Isopropyl-3-isovaleroyl-oxazolidin-2-one** [5, 6]



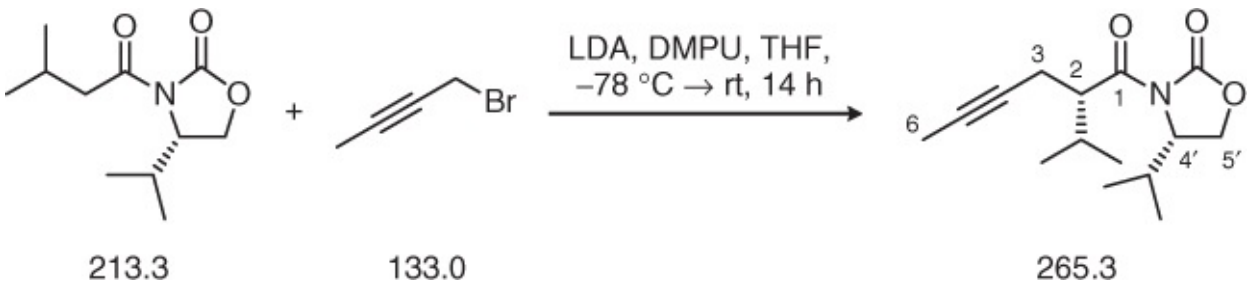
n-Butyllithium in *n*-hexane (2.6 M, 78.2 ml, 203 mmol) is added dropwise with stirring to a solution of the oxazolidinone **1.2.2.2** (25.0 g, 194 mmol) in anhydrous THF (800 ml) at −78 °C and stirring is continued for 30 min. Isovaleroyl chloride (25.7 g, 213 mmol, 26.2 ml) is then added dropwise and the reaction mixture is stirred at −78 °C for 20 min and at 0 °C for 30 min.

The reaction is quenched by the addition of K_2CO_3 solution (1 M, 150 ml), and the solvents are removed *in vacuo*. After the addition of H_2O (500 ml), the layers

are separated and the aqueous layer is extracted with MeO*t*Bu (4 × 400 ml). The combined organic layers are washed with brine (2 × 100 ml), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue is fractionally distilled to afford the product as a colorless liquid; 41.3 g (100%), $bp_{0.008}$ 70–85 °C, R_f = 0.47 (*n*-pentane/Et_2O, 1 : 1).

^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) = 4.38 (m_c, 1H, 4′-H), 4.26–4.08 (m, 2H, 5′-H_2), 2.88 (dd, *J* = 15.9, 7.2 Hz, 1H, 2-H_b), 2.64 (dd, *J* = 15.9, 7.2 Hz, 1H, 2-H_a), 2.32 (dsept, *J* = 7.3, 4.0 Hz, 1H, *i*Pr-CH), 2.13 (non, *J* = 7.2 Hz, 1H, 3-H), 1.00–0.76 (m, 12H, 4 × CH_3).

1.2.2.7	***	**(*S*,*S*)-4-Isopropyl-3-(2-isopropyl-hex-4-ynoyl)-oxazolidin-2-one** [5, 6]



n-Butyllithium in *n*-hexane (2.8 M, 41.5 ml, 116 mmol) is added dropwise to a stirred solution of diisopropylamine (12.8 g, 126 mmol, 17.8 ml) in anhydrous THF (250 ml) at −78 °C. Stirring is continued at 0 °C for 45 min, and then the mixture is again cooled to −78 °C. A solution of the oxazolidinone **1.2.2.6** (22.5 g, 105 mmol) in THF (25 ml) is added dropwise with stirring over 1 h at −78 °C, and the resulting mixture is stirred for a further 2 h. DMPU (32 ml) and the freshly prepared bromide **1.2.2.5** (20.0 g, 150 mmol) are then added over 1 h. The reaction mixture is allowed to slowly warm to room temperature and stirred for a further 14 h.

Saturated aqueous NH_4Cl solution (100 ml) is then added, the organic layer is separated, and the aqueous layer is extracted with Et_2O (3 × 150 ml). The combined organic layers are successively washed with ice-cold aqueous HCl (1 M, 100 ml), saturated aqueous $NaHCO_3$ solution (100 ml), and brine (100 ml), dried over Na_2SO_4, and filtered. The solvents are removed *in vacuo*, and the residue is purified by column chromatography (SiO_2, *n*-pentane/MeO*t*Bu, 20 : 1

→ *n*-pentane/MeO*t*Bu, 3 : 1) to afford the alkylation product as a colorless oil; 26.0 g (93%), ds = 150 : 1, $[\alpha]^{20}_{D}$ = +63.6 (*c* = 0.5, $CHCl_3$), R_f = 0.41 (*n*-pentane/MeO*t*Bu, 5 : 1).

IR (NaCl): $\tilde{\nu}$ (cm^{-1}) = 3376, 2964, 2924, 2876, 1780, 1698, 1468, 1432, 1388.

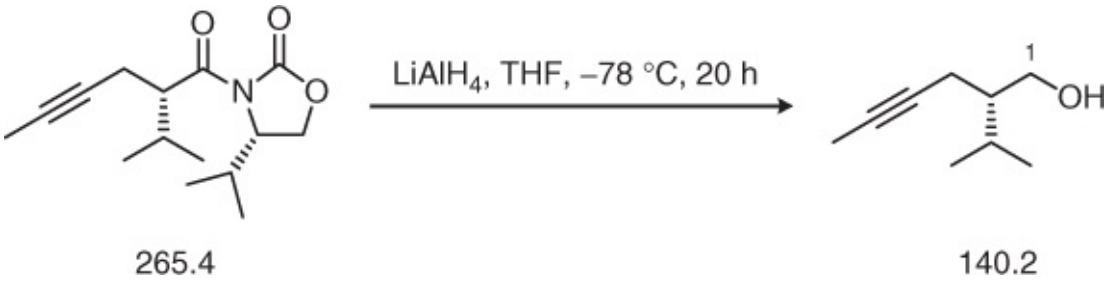
UV (CH_3CN): λ_{max} (nm) (log ε) = 206.0 (3.5222).

^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) = 4.52 (ddd, *J* = 7.6, 3.8, 3.8 Hz, 1H, 2-H), 4.34–4.16 (m, 2H, 5′-H_2), 3.93 (ddd, *J* = 9.5, 7.0, 5.0 Hz, 1H, 4′-H), 2.61–2.32 (m, 3H, 3-H_2, 2-C<u>H</u>Me_2), 1.98 (oct, *J* = 7.0 Hz, 1H, 4′-C<u>H</u>Me_2), 1.71 (t, *J* = 2.8 Hz, 3H, 6-H_3), 0.95 (d, *J* = 6.8 Hz, 3H, *i*Pr-CH_3), 0.94 (d, *J* = 7.0 Hz, 6H, 2 × *i*Pr-CH_3), 0.92 (d, *J* = 7.0 Hz, 3H, *i*Pr-CH_3).

^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) = 174.8 (C-1), 153.6 (C-2′), 76.4 (C-4), 76.2 (C-5), 62.9 (C-5′), 58.5 (C-4′), 48.2 (C-2), 29.8 (4′-*i*Pr-*C*H), 28.3 (2-*i*Pr-*C*H), 20.6 (2-*i*Pr-*C*H_3), 19.0 (C-3), 18.9 (2-*i*Pr-*C*H_3), 17.8 (4′-*i*Pr-*C*H_3), 14.4 (4′-*i*Pr-*C*H_3), 3.4 (C-6).

MS (DCI, 200 eV): *m*/*z* (%) = 549 (40) $[2M+NH_4]^+$, 283 (100) $[M+NH_4]^+$.

1.2.2.8 ** (***S***)-2-Isopropylhex-4-yn-1-ol** [5, 6]



A suspension of $LiAlH_4$ (5.74 g, 151 mmol) in THF (66 ml) is added dropwise to a stirred solution of the oxazolidinone **1.2.2.7** (20.0 g, 75.4 mmol) in anhydrous THF (300 ml) at −78 °C, and stirring is continued for 20 h.

The reaction is then quenched by the dropwise addition of H_2O (6 ml), and the mixture is allowed to warm to room temperature, whereupon 15% NaOH solution (6 ml) and H_2O (20 ml) are added. The precipitate formed is filtered off,

washed with THF, and extracted with Et_2O using a Soxhlet apparatus for 14 h. The solvent is then evaporated under reduced pressure, the residue is redissolved in benzene (Caution: carcinogenic!), and this solution is concentrated once more *in vacuo* to remove small amounts of H_2O by azeotropic distillation. The residue is fractionally distilled with a Vigreux column to afford the alcohol as a colorless liquid; 7.8 g (74%), $bp_{0.5}$ 48–49 °C, $[\alpha]^{20}_D = -3.0$ (*c* = 0.5, $CHCl_3$), $R_f = 0.27$ (*n*-pentane/MeO*t*Bu, 5 : 1).

IR (NaCl): $\tilde{\nu}$ (cm^{-1}) = 3346, 2960, 2922, 2876, 1388, 1368, 1072, 1040.

^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) = 3.79–3.59 (m, 2H, 1-H_2), 2.37–2.07 (m, 2H, 3-H_2), 1.89 (s, 1H, OH), 1.78 (m_c, 1H, C<u>H</u>Me_2), 1.75 (t, *J* = 2.6 Hz, 3H, 6-H_3), 1.45 (m_c, 1H, 2-H), 0.91 (d, *J* = 6.5 Hz, 3H, CH(C<u>H</u>$_3$)$_2$), 0.88 (d, *J* = 6.5 Hz, 3H, CH(C<u>H</u>$_3$)$_2$).

^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) = 77.7 (C-4), 76.8 (C-5), 63.8 (C-1), 46.1 (C-2), 27.8 (*i*Pr-*C*H), 19.9 (*i*Pr-*C*H_3), 19.7 (*i*Pr-*C*H_3), 18.2 (C-3), 3.4 (C-6).

MS (EI, 70 eV): *m*/*z* (%) = 140 (2) $[M]^+$, 125 (31) $[M-CH_3]^+$, 97 (100) $[M-i\text{Pr}]^+$, 53 (20) $[CH_3CCCH_2]^+$.

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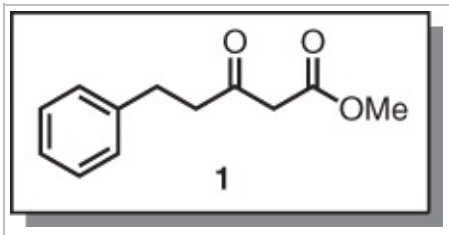
1.2.3 Methyl 3-oxo-5-phenylpentanoate



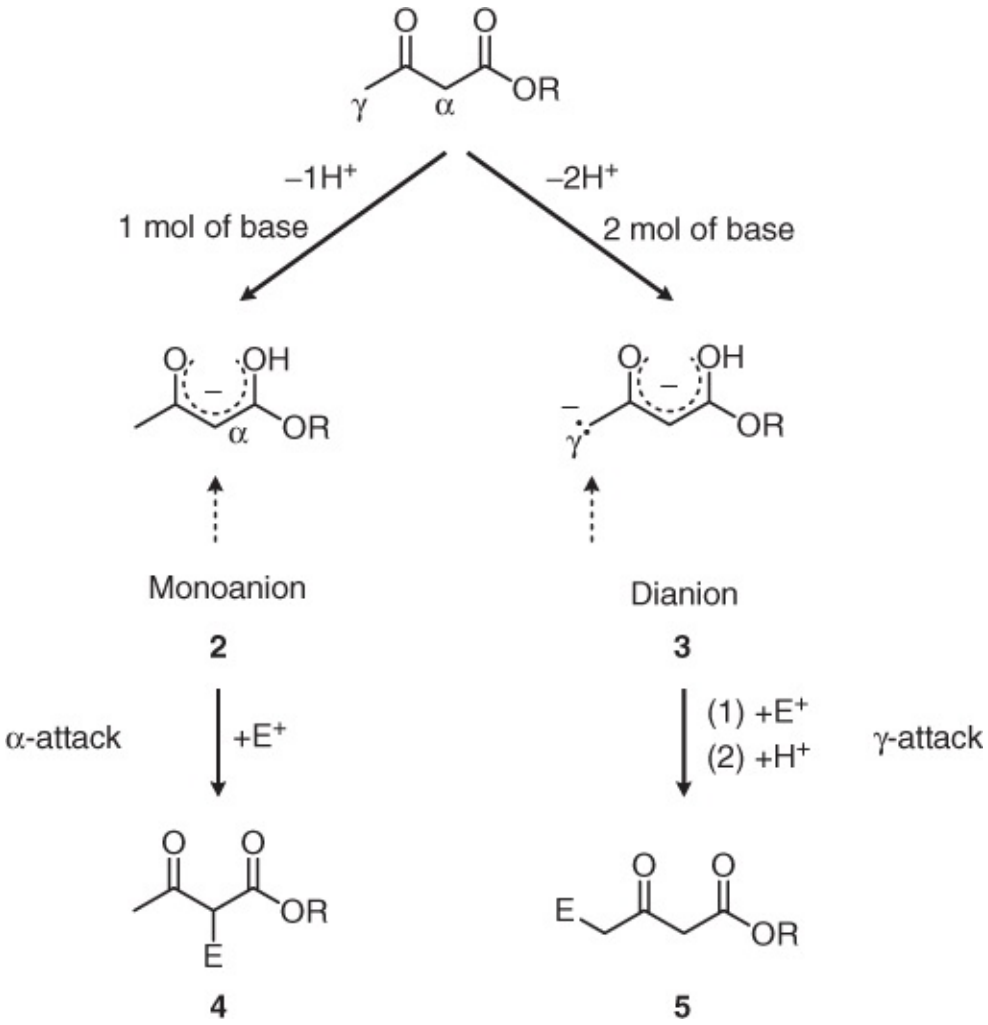
Topic:

- γ-Alkylation of acetoacetate

(a) General

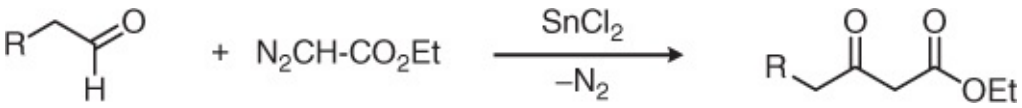
Among the numerous methods for the synthesis of β-ketoesters [1], the elongation of acetoacetate by γ-alkylation is the most relevant for β-ketoesters of structural type **1**.

In acetoacetate, the α-CH_2 group shows far stronger C–H acidity than the γ-CH_3 group (ΔpK_a (α vs. γ) approximately 10). As a consequence, attack of electrophiles can be regioselectively directed either to the α-position through formation of the monoanion **2** or to the γ-position through the formation of the (ambident) dianion **3**.



Accordingly, with an alkyl halide as attacking electrophile, acetoacetate is transformed to the product **4** of α-alkylation using 1 equiv of base, whereas with 2 equiv of a sufficiently strong base, product **5** is obtained, since the γ-CH_2 group in the dianion is of higher electron density than the (delocalized) α-CH group [2].

A useful and preparatively versatile alternative for the synthesis of γ-substituted acetoacetates such as **1** is the C_2-chain elongation of aldehydes with ethyl diazoacetate catalyzed by tin(II) chloride [3]:

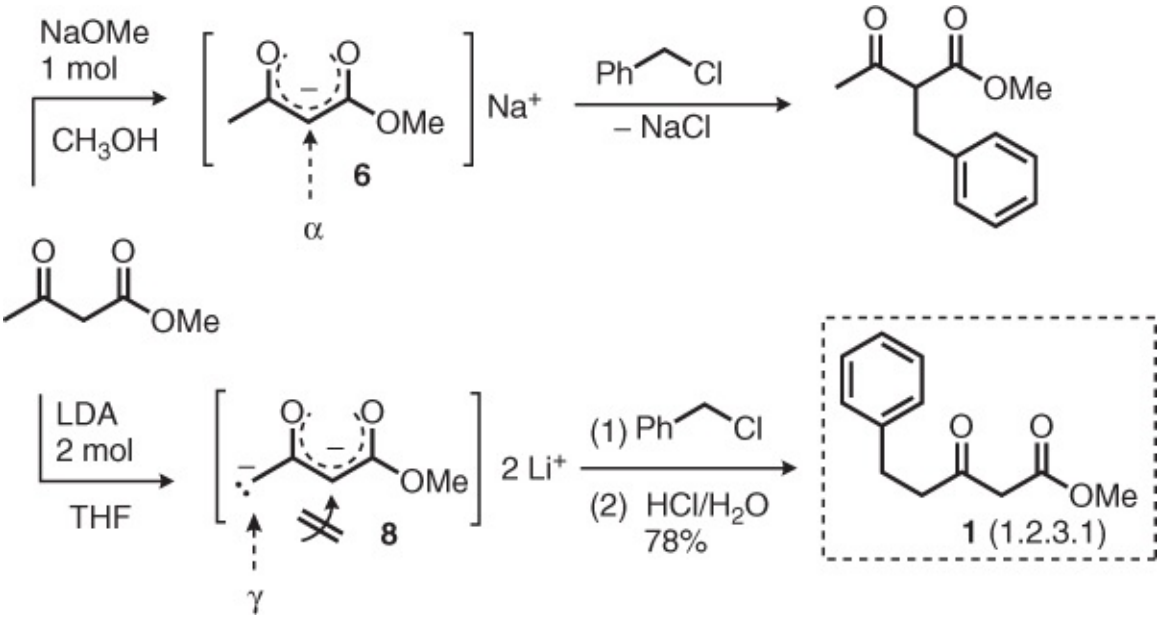


(b) Synthesis of 1

If methyl acetoacetate is reacted with benzyl chloride in the presence of

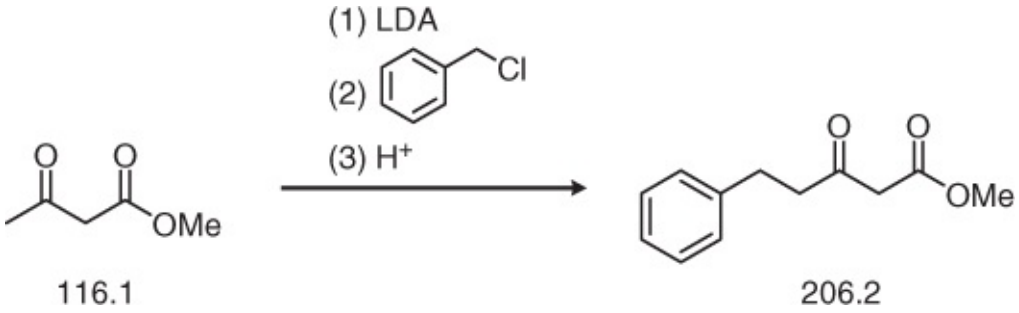
$NaOCH_3$ in anhydrous methanol, the "classical" α-alkylation of acetoacetate occurs via the formation of the α-monoanion **6** and its nucleophilic attack at the benzyl halide to give methyl 2-benzyl-3-oxobutanoate (**7**) in 80% yield [4]:

If methyl acetoacetate is reacted with 2 equiv of LDA in THF at 0 °C and subsequently with benzyl chloride, **1** is obtained after work-up with aqueous HCl in 78% yield. Initially, the acetoacetate dianion **8** is formed, which undergoes regioselective γ-alkylation with the benzyl halide in an S_N process [5].



(c) Experimental Procedure for the Synthesis of 1

1.2.3.1	**	**Methyl 3-oxo-5-phenylpentanoate** [5]



In a 250-ml two-necked flask, fitted with a septum, an inert gas attachment (N_2), and a magnetic stirrer, diisopropylamine (5.15 g, 50.0 mmol, approximately 7.13 ml) (note 1) is added by means of a syringe to anhydrous THF (100 ml). *n*-Butyllithium in *n*-hexane (1.6 M, 32.5 ml, 52.0 mmol) is slowly added dropwise with stirring at 0 °C. After 20 min, methyl acetoacetate (2.80 g, 24.0 mmol,

approximately 2.60 ml) is added dropwise, and stirring is continued for 20 min at 0 °C (formation of the dianion). Finally, benzyl chloride (3.04 g, 24.0 mmol, approximately 2.76 ml) is added dropwise, and stirring is continued for an additional 20 min at 0 °C.

A mixture of concentrated HCl (10 ml), H_2O (25 ml), and Et_2O (75 ml) is added to the reaction mixture. The organic phase is separated, and the aqueous phase is extracted with Et_2O (2 × 50 ml). The combined organic phases are washed with saturated $NaHCO_3$ solution and brine, dried over $MgSO_4$, and filtered, and the solvent is removed *in vacuo*. The residue is distilled *in vacuo* to give the product as a colorless oil; 3.67 g (78%), $bp_{0.2}$ 116–117 °C; n^{20}_D = 1.5293.

IR (film): $\tilde{\nu}$ (cm^{-1}) = 3080, 3060, 3030, 1745, 1715, 1600, 1495.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.22 (s, 5H, Ar–H), 3.67 (s, 3H, CO_2CH_3), 3.39 (s, 2H, 2-CH_2), 2.86 (s, 4H, 4-and 5-CH_2) (note 2).

Notes:

1. Diisopropylamine is distilled over CaH_2 before use; bp_{760} 83–84 °C.
2. In the ^{1}H NMR spectrum, the 4-and 5-CH_2 signals happen to coincide and thus appear as a singlet. In addition, small peaks due to the enol form of **1** are observed.

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3. Holmquist, C.R. and Roskamp, E.J. (1989) *J. Org. Chem.*, **54**, 3258. By application of this method to hydrocinnamic aldehyde, the ethyl ester of **1** is formed in 86% yield; for the mechanism, see ref. [2], p. 1407.

4. In analogy to *Organikum* (2001), 21st edn, Wiley-VCH Verlag GmbH, Weinheim, p. 608.

5. (a) Harris, T.M. and Harris, C.M. (1969) *Org. React.*, **17**, 155;(b) Harris, T.M.

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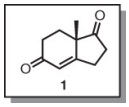
1.3 Reactions of the Aldol and Mannich Type

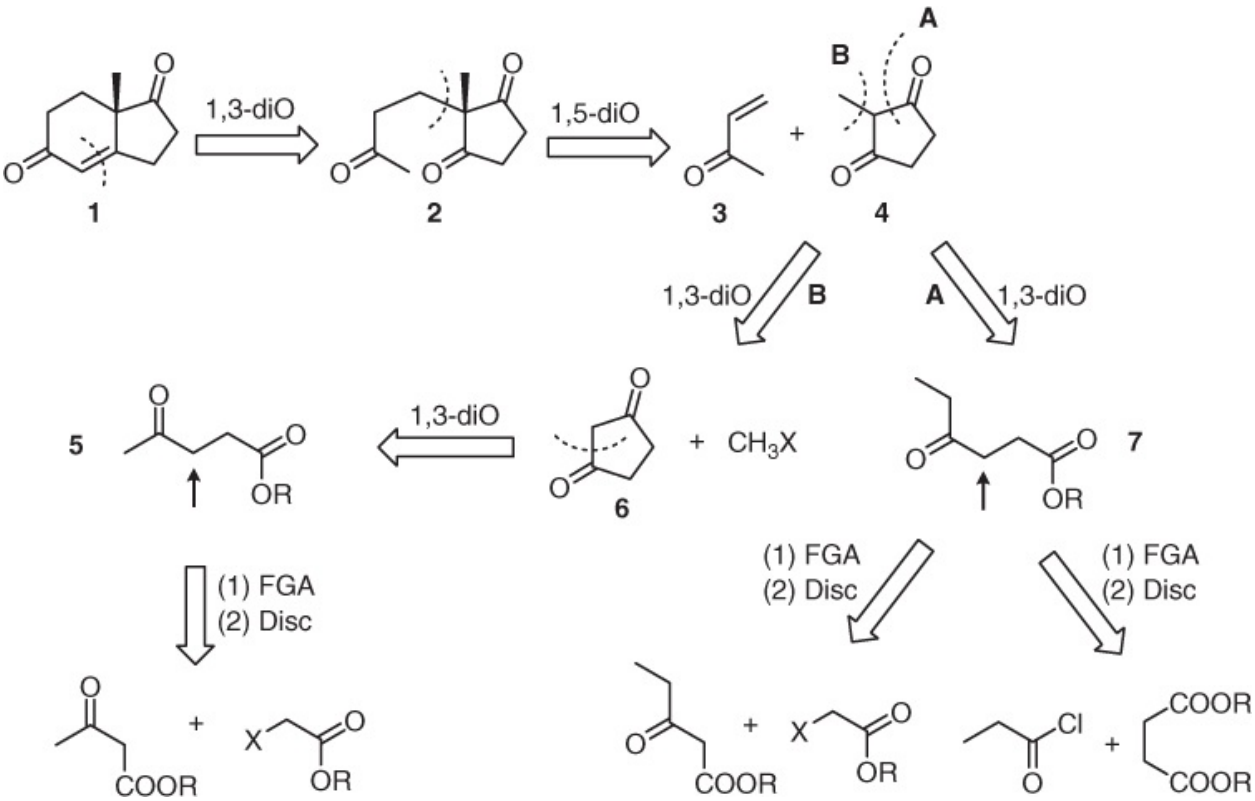
1.3.1 (+)-(7a*S*)-7,7a-Dihydro-7a-Methyl-1,5(6*H*)-Indanedione

	***Topics:***	• Acylation of succinic acid • Michael addition • Asymmetric intramolecular aldol condensation with a chiral catalyst, enantioselective organocatalysis, Eder–Sauer–Wiechert–Hajos–Parrish reaction • Asymmetric Robinson annulation

(a) General

The hydrindene **1** is an important building block in numerous syntheses of steroids and of other natural products [1]. Its preparation is one of the first outstanding examples of the importance of enantioselective organocatalysis, which has gained general acceptance in recent years.

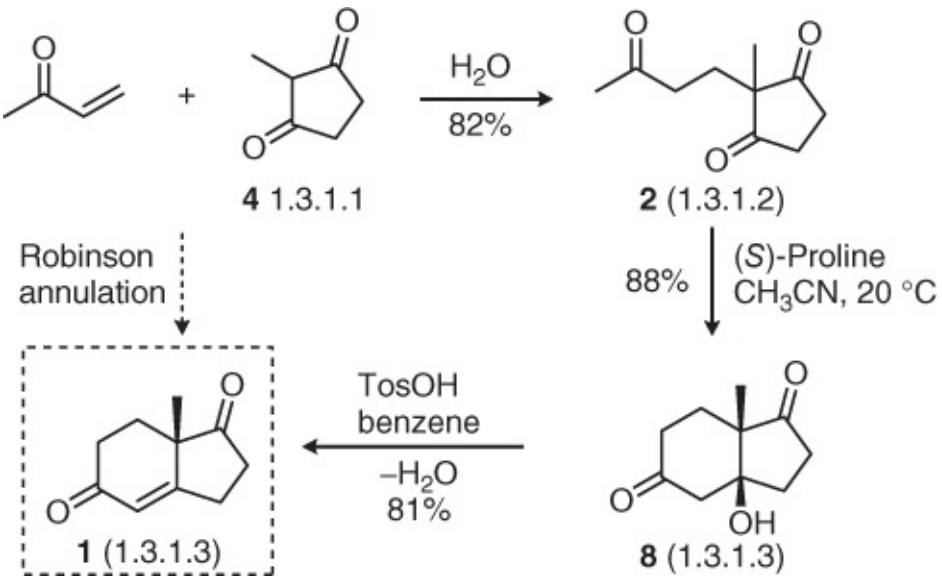
The retrosynthesis of **1** follows a retro-Robinson annulation, which consists of a retro-aldol reaction and a retro-Michael addition to give 2-methyl-cyclopentane-1,3-dione (**4**) and methyl vinyl ketone (**3**) as starting materials.



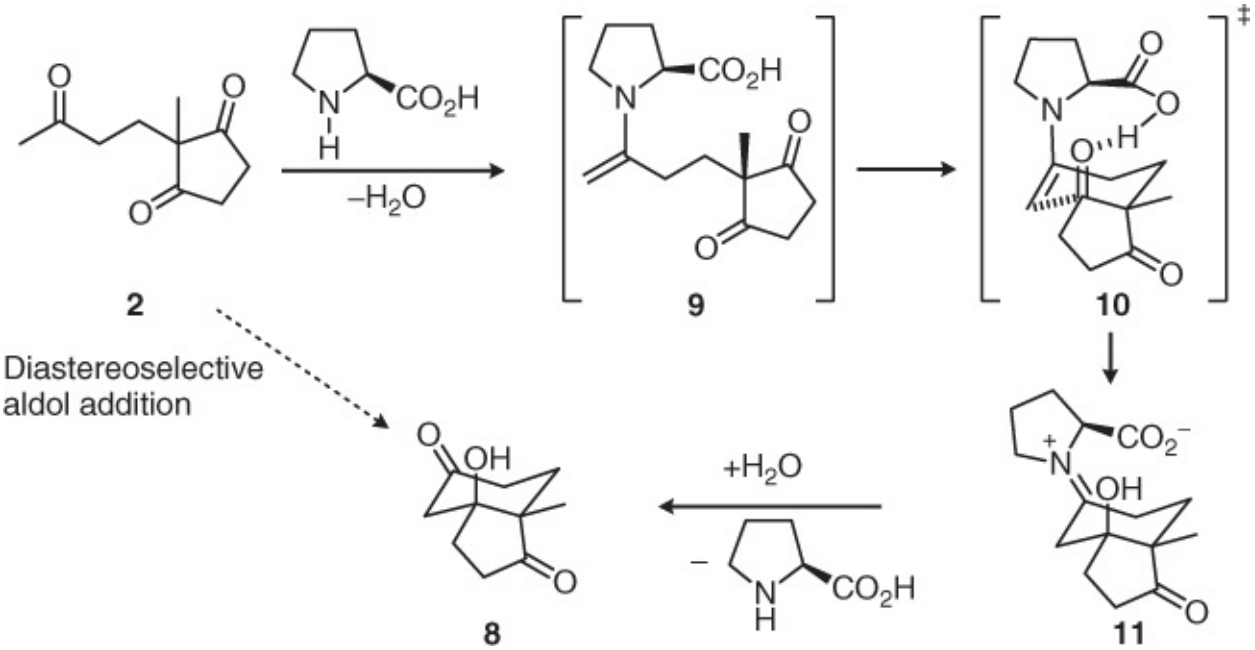
The dione **4** can be obtained either from acetoacetate and haloacetate via a γ-ketoester and cyclopenta-1,3-dione (**6**) according to pathway **B**, or from the γ-ketoester **7** according to pathway **A**. For the preparation of **7**, again two different approaches could be used. According to the proposed retrosynthetic analysis, the synthesis of **1** has been achieved in an enantioselective way by 1,4-addition of 2-methylcyclopentane-1,3-dione (**4**) to methyl vinyl ketone to give the Michael adduct **2** and subsequent asymmetric intramolecular aldol condensation of **2** in the presence of (*S*)-proline as organocatalyst to give **1** in high chemical yield and excellent enantiopurity [2].

(b) Synthesis of 1

The procedure presented here was developed by Eder *et al*. [3], as well as by Hajos and Parrish [4]. Cyclization of the Michael adduct **2** initially provides the *cis*-aldol adduct **8** as a single diastereomer in 88% yield and with 84% ee; subsequently, **8** is subjected to acid-catalyzed H_2O elimination with TosOH in benzene to give the desired product **1** in 81% yield:



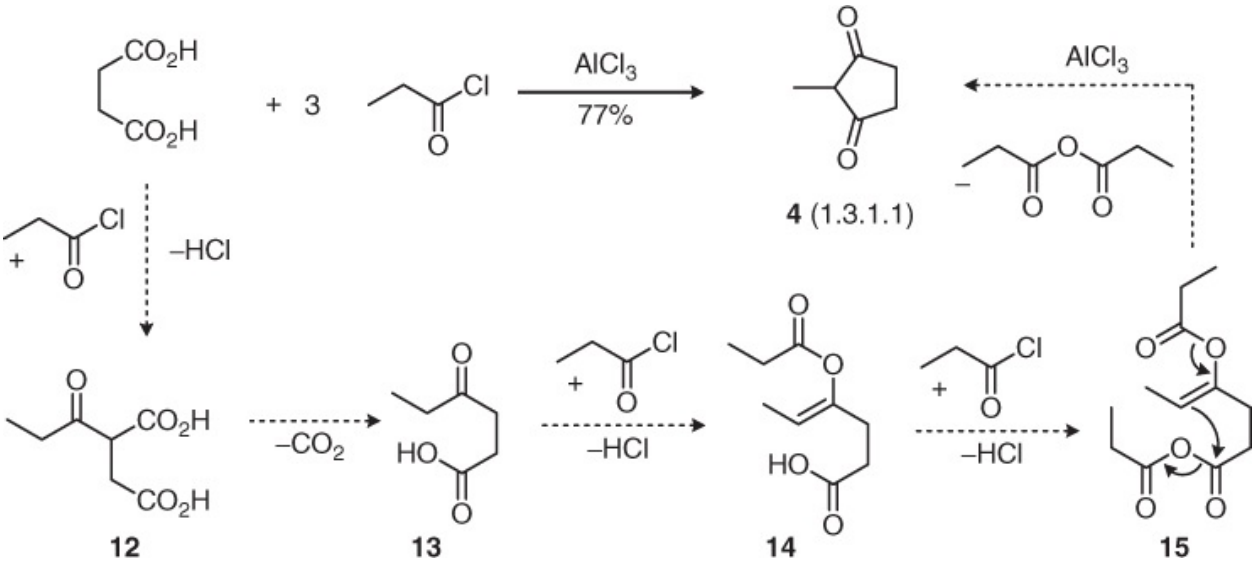
The role of proline as chiral organocatalyst can be interpreted in terms of a mechanism [5] based on initial enamine formation between (*S*)-proline and the carbonyl group in the side chain of **2**. Subsequent ring closure of the enamine **9** by addition to one of the remaining C=O groups leads to the iminium carboxylate betaine **11**. A transition state **10** with hydrogen-bond differentiation between the two diastereotopic C=O groups may account for the high stereoselectivity of the ring-closure reaction (**9** → **11**). The catalytic cycle is terminated by hydrolysis of **11** to yield the aldol adduct **8** with the regeneration of the catalyst:



(*S*)-Proline can also be used for other enantioselective intermolecular aldol and

Mannich reactions [5, 6]. Moreover, analogs of proline have been used as organocatalysts for a multitude of different reactions [7].

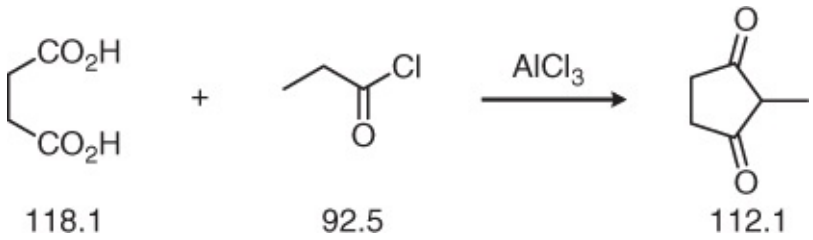
For the synthesis of 2-methyl-cyclopentane-1,3-dione (**4**), an efficient one-step procedure [8] is used, which consists of the acylation of succinic acid with propionyl chloride in the presence of $AlCl_3$ according to the retrosynthetic pathway **A** [9].



Since 3 equiv of the acid chloride are required, a domino process is likely to occur, which involves α-acylation of succinic acid (→ **12**), decarboxylation of the β-keto acid **12** (→ **13**), and acylation of its enol (→ **14**); finally, activation of the remaining carboxyl function by formation of a mixed anhydride (or chloride) (→ **15**) and Claisen-like cyclization of the acylenol functionality in **15** lead to the dione **4**.

(c) Experimental Procedures for the Synthesis of 1

1.3.1.1	*	**2-Methylcyclopentane-1,3-dione** [8]



Finely powdered succinic acid (5.90 g, 0.50 mol) is added in small portions to a solution of anhydrous aluminum chloride (200 g, 1.50 mol) in anhydrous nitromethane (200 ml), causing vigorous gas evolution (HCl Hood). When HCl

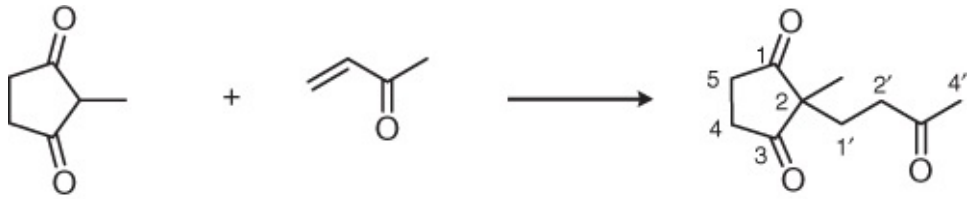
evolution has ceased, propionyl chloride (139 g, 1.50 mol) is added and the mixture is heated to 80 °C for 3 h. A red solution results.

The solution is cooled and poured onto ice (400 g). The mixture is maintained at −10 °C for 15 h, allowing the product to crystallize. The solid is collected by filtration, washed with a 10% aqueous NaCl solution (200 ml) and toluene (200 ml), and recrystallized from H_2O (heating with activated charcoal and filtration) to give colorless prisms; 43.0 g (77%), mp 214–216 °C.

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3200–2600, 1590.

^{1}H NMR (300 MHz, [D_4]MeOH): δ (ppm) = 4.84 (s, OH), 2.44 [s, CH_2–CH_2; keto form], 2.90–2.25 [m, CH_2–CH_2; enol form], 1.54 (s, CH_3); keto–enol tautomeric mixture.

1.3.1.2	*	**2-Methyl-2-(3-oxobutyl)-cyclopentane-1,3-dione** [3, 4]



Methyl vinyl ketone (14.0 g, 200 mmol, ∼16.2 ml) is added in one portion to a suspension of 2-methyl-1,3-cyclopentanedione **1.3.1.1** (11.2 g, 100 mmol) in H_2O (25 ml), and the mixture is stirred for 5 days at room temperature under a nitrogen atmosphere.

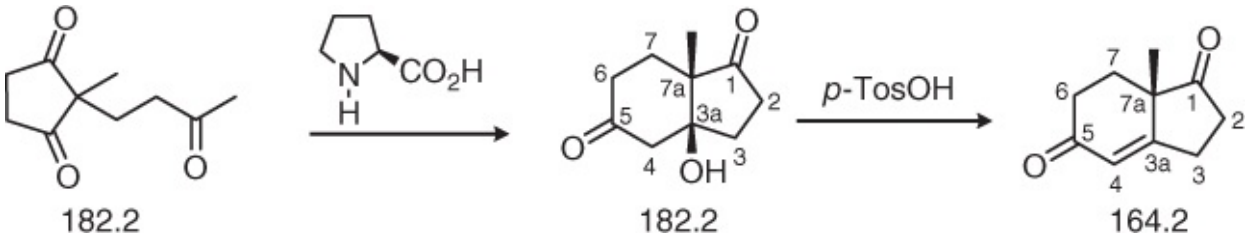
The clear, red-brown solution is then extracted with toluene (3 × 25 ml). The combined extracts are dried over $MgSO_4$, filtered, and stirred for 2 h at room temperature with activated charcoal. The charcoal is removed by filtration and washed with hot toluene (50 ml). The combined filtrates are concentrated, and the residue is fractionally distilled *in vacuo* to give a colorless oil; 15.0 g (82%), $bp_{0.1}$ 108–110 °C.

IR (film): $\tilde{\nu}$ (cm^{-1}) = 2970, 2930, 2875, 1765, 1720, 1450, 1420, 1370, 1170.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.79 (s, 4H, 4-H_2, 5-H_2), 2.60–1.65

(m, 4H, 1′-H_2, 2′-H_2), 2.09 (s, 3H, 4′-H_3), 1.10 (s, 3H, CH_3).

1.3.1.3 * **(+)-(7a*S*)-7,7a-Dihydro-7a-methyl-1,5(6*H*)-indanedione** [3, 4]



182.2 182.2 164.2

1. **(+)-(3a*S*,7a*S*)-3a,4,7,7a-Tetrahydro-3a-hydroxy-7a-methyl-1,5(6*H*)-indanedione**

   A solution of the triketone **1.3.1.2** (5.60 g, 30.7 mmol) and (−)-(*S*)-proline (3.54 g, 30.7 mmol) in acetonitrile (40 ml) is stirred at room temperature for 6 days under a nitrogen atmosphere (balloon). The initially light-yellow solution becomes dark brown to black.

   Proline is collected by filtration and washed with a small amount of acetonitrile. The filtrate is concentrated *in vacuo*, the dark-brown residue is dissolved in EtOAc (100 ml), and this solution is filtered through silica gel (10 g). The silica gel is rinsed with additional EtOAc (150 ml), and the combined filtrates are concentrated *in vacuo*. A light-brown residue is obtained, which solidifies after 14 h at −20 °C. Recrystallization from Et_2O gives light-yellow crystals. The yield is 4.90 g (88%), mp 119–120 °C, $[\alpha]_D^{20}$ = +60 (*c* = 0.5, $CHCl_3$).

   IR (film): $\tilde{\nu}$ (cm^{-1}) = 3470 (OH), 1740, 1710 (6-ring C=O), 1305, 1270, 1065.

   ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.84 (s, 1H, OH), 2.63 (s, 2H, 4-H_2), 2.61–1.65 (m, 8H, 2-H_2, 3-H_2, 6-H_2, 7-H_2), 1.21 (s, 3H, CH_3).

2. **(+)-(7a*S*)-7,7a-Dihydro-7a-methyl-1,5(6*H*)-indanedione**

   A mixture of the hydroxy ketone prepared in step (1) (3.64 g, 20.0 mmol), anhydrous *p*-toluenesulfonic acid (25 mg, 0.15 mmol), and molecular sieves (4 Å, 5 g) in anhydrous benzene (30 ml; Caution: carcinogenic!) is heated under reflux for 30 min.

The mixture is then cooled, aqueous $NaHCO_3$ solution (1 M, 2 ml) is added, and the phases are separated. The organic phase is dried over $MgSO_4$ and filtered, and the solvent is removed *in vacuo*. The residue is a yellow oil, which solidifies in 14 h at −20 °C. The product is washed with ice-cold Et_2O and recrystallized from Et_2O/*n*-pentane; 2.66 g (81%), mp 64–65 °C, $[\alpha]^{20}_D$ = +362 (*c* = 0.1, benzene). The compound is almost enantiopure with >98% ee.

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3045, 1745, 1660, 1455, 1355, 1235, 1150, 1065.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 5.95 (m, 1H, 4-H), 2.95–1.75 (m, 8H, 2-H_2, 3-H_2, 6-H_2, 7-H_2), 1.30 (s, 3H, CH_3).

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L.-F., Mi, A.-Q., Jiang, Y.-Z., and Gong, L.-Z. (2005) *J. Am. Chem. Soc.*, **127**, 9285–9289;(e) Cordova, A., Zou, W., Ibrahem, I., Reyes, E., Engqvist, M., and Liao, W.-W. (2005) *Chem. Commun.*, 3586–3588.

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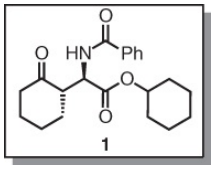
1.3.2 Cyclohexyl 2-benzoylamino-2-(2-oxocyclohexyl) acetate

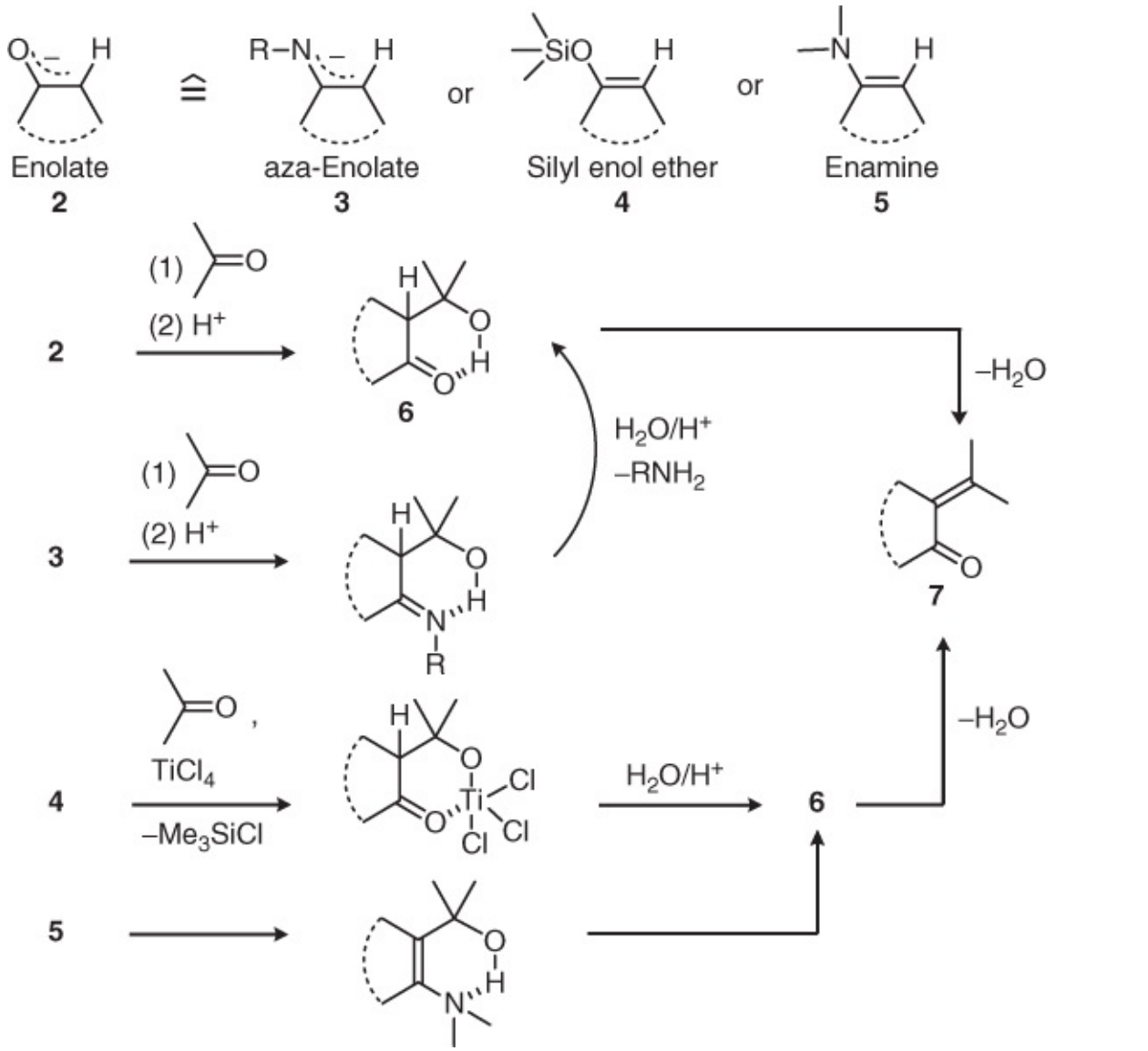


Topics:

- Diastereoselective aminoalkylation of an enamine by an *N*-acyl imino ester (modified aldol reaction)
- Esterification of an *N*-acyl-α-amino acid
- Formation of an *N*-acyl imino ester by α-halogenation/dehydrohalogenation

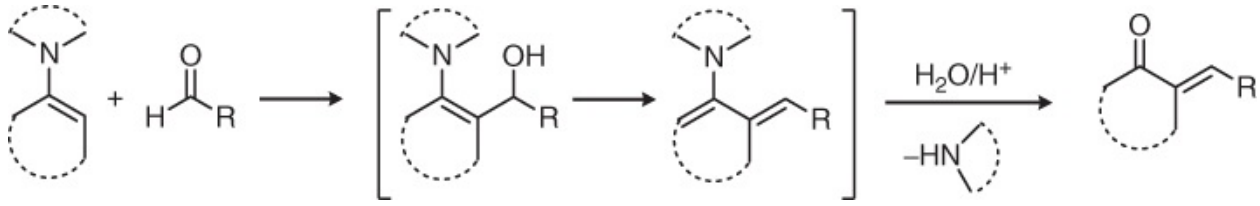
(a) General

In the directed aldol reaction [1], equivalents of enolates **2** for example, α-lithiated imines **3** (Wittig aldol reaction), silyl enol ethers **4** (Mukaiyama aldol reaction, cf.



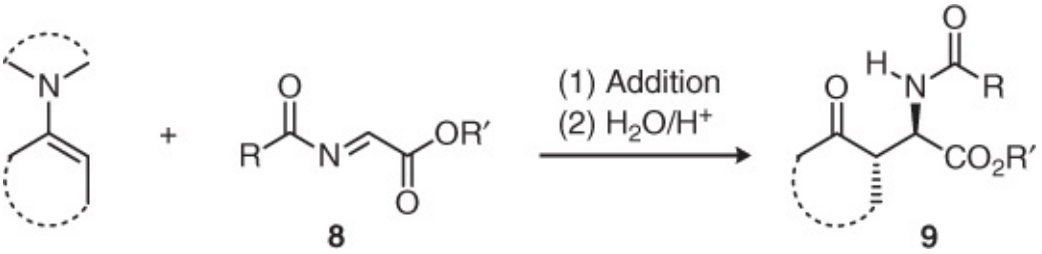
Section 1.3.4), or enamines **5** react with aldehydes or ketones to give the product **6** by an aldol addition and/or **7** by an aldol condensation:

Enamines of cycloalkanones are easily accessible and can undergo aldol condensation with aldehydes under equilibrium conditions with azeotropic removal of H_2O and subsequent acid hydrolysis [2]:

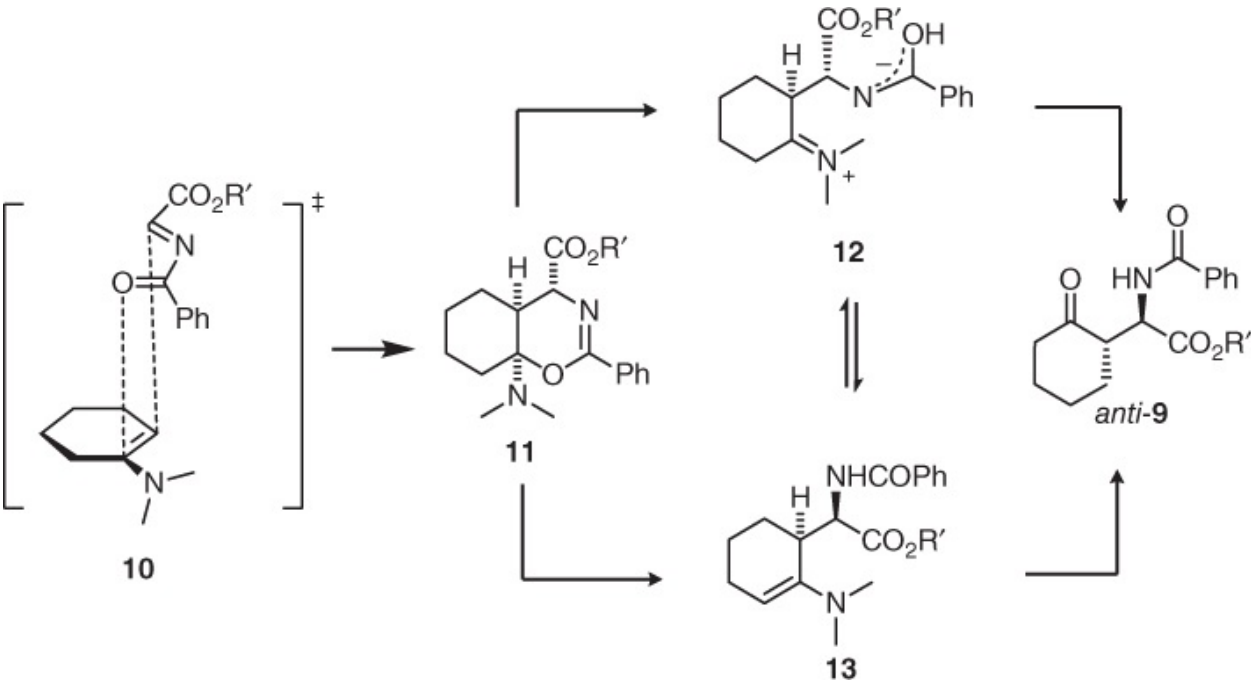


When enamines of this type are reacted with acyl iminoacetates **8** as electrophilic substrates, an aza-analogous aldol addition takes place to give *N*-

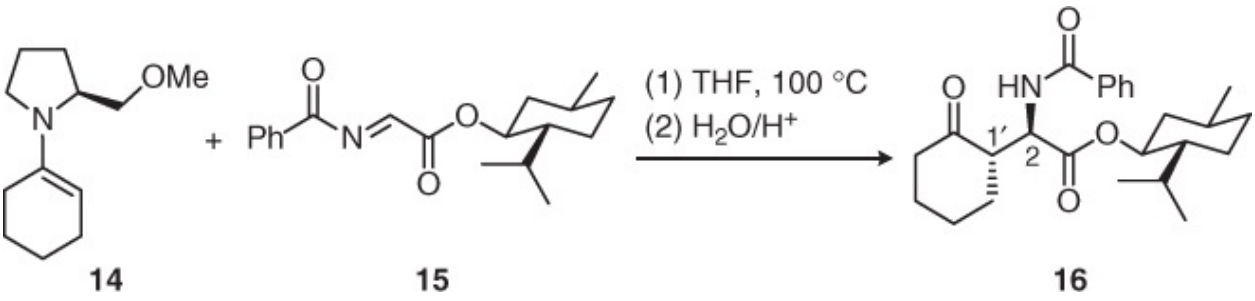
acyl-γ-keto-α-aminoesters **9** [3], as exemplified in Section (b).



The relative configuration of the products **9** is anti (X-ray). The high diastereoselectivity (>96% de) in this aza-modified aldol process is consistent with a hetero-Diels–Alder-like transition state **10** for the formation of an intermediate **11**, which may undergo ring opening either to the zwitterion **12** or the enamine **13**. After acid hydrolysis, the anti product **9** is obtained [3]:

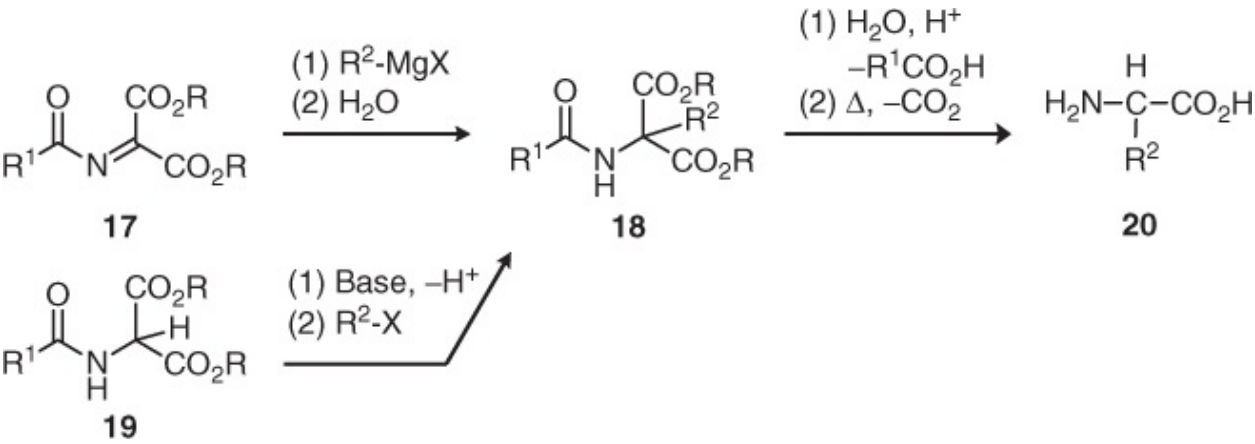


For the formation of enantioenriched products, chiral esters and chiral enamines can be used. Following the concept of double stereodifferentiation [4], the (+) and (−)-menthyl esters of **8** (R = Ph) are reacted with the chiral enamine **14** derived from (*S*)-proline. Using the (+)-menthyl ester **15**, reaction proceeds in quantitative yield and with complete diastereo and enantioselectivity (de = ee > 99%) and gives the pure compound **16** with (1′*S*,2*R*)-configuration at the newly formed stereogenic centers (“matched” case), while the (−)-menthyl ester (**8**, R = Ph) leads to a product of type **9** with de > 98% and ee = 45% (“mismatched” case [5]).



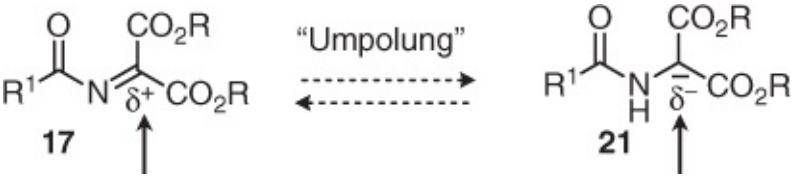
14 15 16

It should be noted that acyl iminomalonates **17** represent interesting electrophilic building blocks and can be used for the synthesis of α-amino acids [6] by reaction with Grignard compounds followed by hydrolysis and decarboxylation:



17 18 20 19

This mode of formation of α-amino acids is an alternative to a method [7] in which acyl aminomalonates **19** are alkylated in the presence of a base to give **18**. Acyl iminomalonates **17** represent the “umpoled” version [8] of the acyl amidomalonate anion **21**:



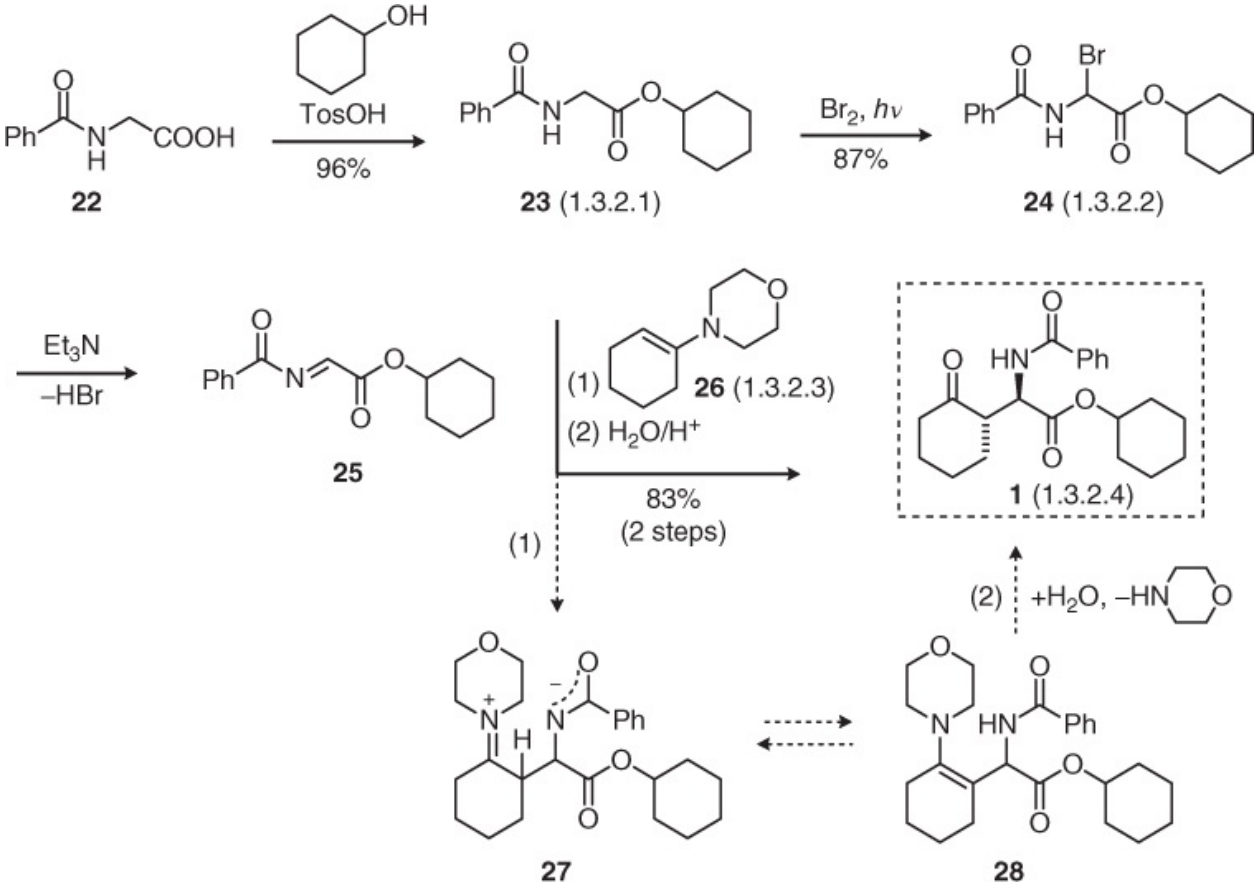
17 21

(b) Synthesis of 1

Commercially available hippuric acid (**22**) is subjected to azeotropic esterification with cyclohexanol in the presence of TosOH in toluene. Photobromination of the cyclohexyl ester **23** with Br_2 in CCl_4 occurs at the α-position to the COOR group and affords the bromo ester **24**. In the concluding steps, the bromo ester **24** is transformed into the benzoyl iminoacetate **25**, which, without isolation, leads to **1** by reaction with the enamine **26** followed by hydrolysis. For this reaction, a solution of the bromo ester **24** in THF is treated at

−78 °C first with triethylamine and then with the enamine morpholinocyclohexene (**26**) [9]. The reaction presumably proceeds via the intermediates **27** and **28**. After hydrolysis of the reaction mixture at pH 4–5, **1** is isolated in 79% yield and with ds > 98 : 2, thus documenting the high level of stereoselectivity of the aza-modified aldol process. In the described process, **1** is obtained as a racemic mixture because neither a chiral enamine nor a chiral ester is used.

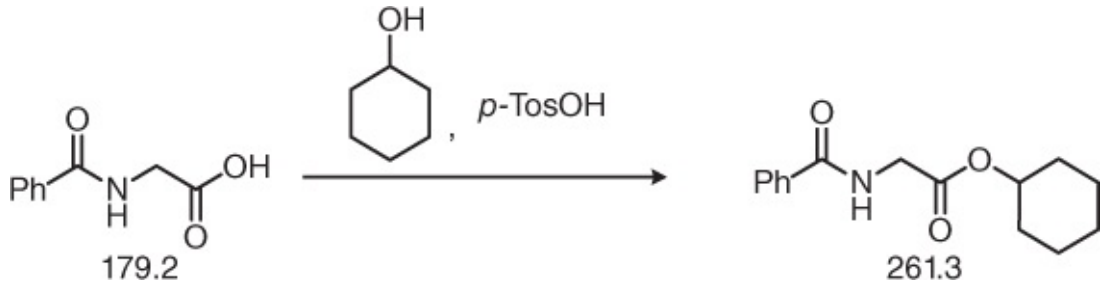
Interestingly, the diastereoselectivity seen with the corresponding methyl or ethyl esters is significantly more temperature-dependent compared to that with the larger cyclohexyl ester **23** used here. The methyl and ethyl esters give high diastereoselectivity in the reaction with the enamine **26** only at −100 °C (ds > 98 : 2), whereas only around 85 : 15 ds is achieved at −78 °C [3].



The target molecule **1** is obtained in a three-step sequence in an overall yield of 67% (based on hippuric acid (**22**)).

(c) Experimental Procedures for the Synthesis of 1

1.3.2.1	*	**Cyclohexyl 2-benzoylaminoacetate** [3]



Hippuric acid (35.8 g, 0.20 mol) and cyclohexanol (20.0 g, 0.20 mol) are heated under reflux with *p*-toluenesulfonic acid (1.0 g) in toluene (200 ml) under azeotropic removal of H_2O in a Dean–Stark trap, until the theoretical amount of H_2O is formed.

After cooling to 35–40 °C and diluting with additional EtOAc (200 ml), the organic layer is washed twice with H_2O, dried over $MgSO_4$, and filtered. The solvent is removed *in vacuo*, and the crude product is recrystallized from EtOAc/*n*-hexane (1 : 1) to give a colorless solid; 50.3 g (96%); mp 102–103 °C; TLC (SiO_2, EtOAc/*n*-hexane, 1 : 2): R_f = 0.57.

UV: λ_{max} (nm) = 224, 194.

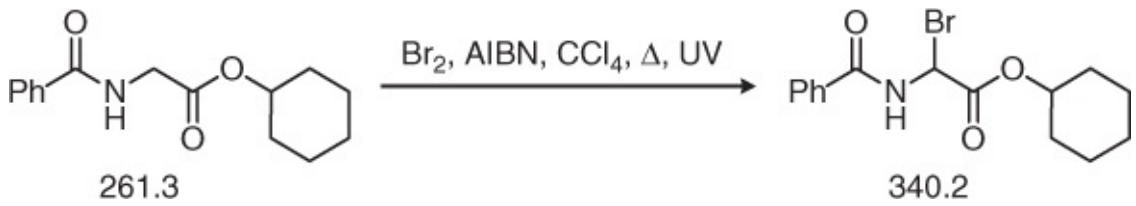
IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3326, 2955, 2939, 2854, 1748, 1650, 1550, 1494, 1450, 1401, 1380, 1360, 1312, 1251, 1201, 1081, 1013, 949, 733, 692.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.82–7.79 (m, 2H, Ar–H), 7.54–7.42 (m, 3H, Ar–H), 6.70 (s, 1H, NH), 4.84 (m, 1H, hex-H_1), 4.20 (d, *J* = 3.3 Hz, 2H, α-H_2), 1.93–1.83 (m, 2H, c-hex-H_2), 1.79–1.68 (m, 2H, c-hex-H_2), 1.60–1.20 (m, 6H, c-hex-H_2).

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 169.5, 167.3, 133.8, 131.7, 128.6, 127.0, 74.3, 42.1, 31.5, 25.2, 23.6.

EI HRMS: *m*/*z* = 261.1364 (calcd. 261.1365).

1.3.2.2	**	**Cyclohexyl 2-benzoylamino-2-bromoacetate** [9]



A solution of bromine (3.51 g, 22.0 mmol) in anhydrous carbon tetrachloride (30 ml; Caution: resorption through the skin!) is added dropwise over 2 h under UV irradiation (500 W) to a refluxing solution of the acetate **1.3.2.1** (5.22 g, 20.0 mmol) and azobisisobutyronitrile (50 mg) in carbon tetrachloride (40 ml) to give a light-brown solution. After completion of the addition of bromine, irradiation and refluxing are continued for 3 h.

The solvent is removed *in vacuo*, and the product is crystallized from EtOAc/petroleum ether (50–80 °C) (1 : 1). The water-sensitive product is kept under argon at 4 °C. The product is obtained as a colorless solid; 5.92 g (87%); mp 107–109 °C; TLC (SiO_2, EtOAc/*n*-hexane, 1 : 2): R_f = 0.27.

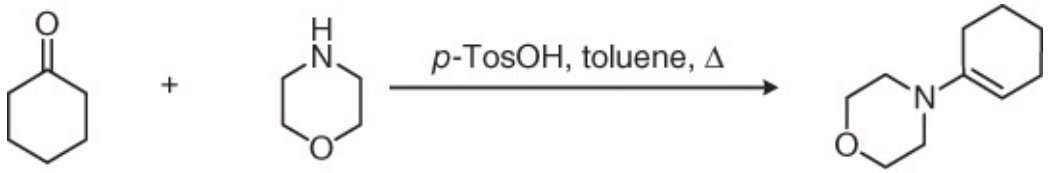
UV: λ_{max} (nm) = 231.5, 194.5.

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3298, 3038, 2940, 2861, 1733, 1660, 1602, 1581, 1519, 1490, 1453, 1379, 1358, 1340, 1285, 1240, 1194, 1133, 1009, 934, 719, 691, 530.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.80–7.40 (m, 6H, Ar–H, NH), 6.60 (d, *J* = 9.9 Hz, 1H, CH), 4.90 (m, 1H, c-hex-H), 1.20–1.90 (m, 10H, c-hex-H_2).

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 166.3, 165.6, 132.8, 132.4, 128.8, 127.4, 75.9, 50.5, 31.1, 30.6, 25.1, 23.3, 23.2.

1.3.2.3 * 1-Morpholine-1-cyclohexene [10]



98.1 87.1 167.2

Cyclohexanone (11.8 g, 0.12 mol) and morpholine (12.5 g, 0.14 mol) are heated under reflux with *p*-toluenesulfonic acid (20 mg) in toluene (25 ml) for 10 h with azeotropic removal of H_2O in a Dean–Stark trap.

After cooling to room temperature, the organic layer is washed twice with H_2O until pH 7 is reached, then dried over $MgSO_4$, and filtered. The solvent is removed, and the residue is distilled *in vacuo* to give the enamine as a colorless

liquid; 17.5 g (87%), bp_{93} 74–75 °C; TLC (SiO_2, EtOAc/*n*-hexane, 1 : 2): R_f = 0.58.

UV: λ_{max} (nm) = 220.

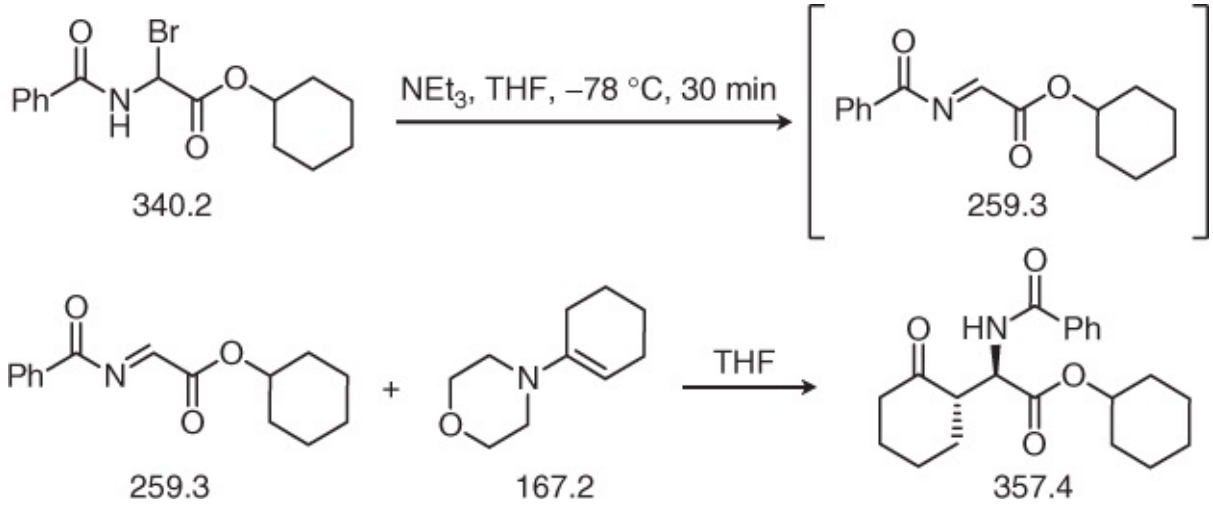
IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 2926, 2893, 1647, 1450, 1385, 1358, 1264, 1204, 1123, 899, 789.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 4.62 (t, *J* = 1.7 Hz, 1H, 12-H_1), 3.76–3.54 (m, 2H, 2-H_2, 6-H_2), 2.92–2.64 (m, 4H, 3-H_2, 5-H_2), 2.07–1.84 (m, 4H, 9-H_2, 12-H_2), 1.60 (m, 4H, 10-H_2, 11-H_2).

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 145.4, 100.4, 66.9, 48.4, 26.8, 24.3, 23.3, 22.7.

EI-HRMS: *m*/*z* = 167.1306 (calcd. 167.1310).

1.3.2.4	**	**Cyclohexyl 2-benzoylamino-2-(2-oxocyclohexyl) acetate** [3]



Triethylamine (697 µl, 0.50 g, 5.0 mmol) is added to a solution of the bromoacetate **1.3.2.2** (5.0 mmol) in anhydrous THF (35 ml) under an argon atmosphere at −78 °C. After stirring for 30 min, the solution is cooled to −95 °C, and a precooled (−78 °C) solution of the enamine **1.3.2.3** (0.92 g, 5.5 mmol) in anhydrous THF (10 ml) is carefully added. The temperature is maintained at −95 °C for 6 h and at −78 °C for 6 h thereafter. After warming to room temperature, the mixture is hydrolyzed by the addition of a dilute citric acid solution until the pH reaches 4–5, and stirring is continued for 5 h.

The solvent is then removed *in vacuo*, the residue is extracted with EtOAc (3 × 35 ml), and the organic layer is washed with H_2O (20 ml), dried over $MgSO_4$, and filtered. After removal of the solvent, the product is purified by column chromatography (SiO_2, *n*-hexane/EtOAc, 2 : 1) and the resulting oil is dissolved in *n*-hexane and treated in a sonicator for 20 min. Recrystallization yields a colorless solid; 1.49 g (83%); mp 106–108 °C; TLC (EtOAc/*n*-hexane, 2 : 1): R_f = 0.52; de > 98% based on HPLC (RP C18, H_2O/0.1% TFA (trifluoroacetic acid), CH_3CN/H_2O, 8 : 2/0.1% TFA; 60–90% in 30 min, t_R = 14.6 min).

UV: λ_{max} (nm) = 224.0, 192.5.

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3320, 2936, 2860, 1712, 1654, 1546, 1517, 1488, 1447, 1316, 1281, 1268, 1240, 1208, 1011, 719, 693.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.78–7.40 (m, 5H, Ar–H), 7.00 (d, *J* = 9.65 Hz, 1H, NH), 4.90 (dd, *J* = 3.22, 9.59 Hz, 1H, α-H), 4.80 (td, 1H, c-hexane), 3.39–3.31 (m, 1H, c-hexanone), 2.42–2.34 (m, 4H, 2 CH_2, c-hexanone), 2.29–2.26 (m, 2H, CH_2, c-hexanone), 2.10 (m, 2H, CH_2, c-hexanone) 1.90–1.20 (m, 10H, c-hexane).

EI HRMS: *m*/*z* = 358.20131 (calcd. 358.20128).

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1. Smith, M.B. (2013) *March's Advanced Organic Chemistry*, 7th edn, John Wiley & Sons, Inc., New York, p. 1141.

2. For an example, see: Tietze, L.F. and Eicher, Th. (1991) *Reaktionen und Synthesen im organisch-chemischen Praktikum und Forschungslaboratorium*, 2nd edn, Georg Thieme Verlag, Stuttgart, p. 186.

3. (a) Kober, R., Papadopoulos, K., Miltz, W., Enders, D., and Steglich, W. (1985) *Tetrahedron*, **41**, 1693–1702;(b) For the direct organocatalyzed enantioselective α-aminomethylation of ketones, see: Ibrahem, I., Casas, J., and Cordova, A. (2004) *Angew. Chem.*, **116**, 6690–6693; *Angew. Chem. Int. Ed.*, (2004), **43**, 6528–6531.

4. (a) Heathcock, C.H. (1984) in *Asymmetric Synthesis*, (ed. J.P. Morrison), vol. 3, Academic Press, New York, p. 111;(b) see also: Hauptmann, S. and Mann, G.

(1996) *Stereochemie*, Spektrum Akademischer Verlag, Heidelberg, p. 216.

5. Masamune, S., Choy, W., Petersen, J.S., and Sita, L.R. (1985) *Angew. Chem.*, **97**, 1–31; *Angew. Chem., Int. Ed. Engl.*, (1985), **24**, 1–30.

6. Kober, R., Hammes, W., and Steglich, W. (1982) *Angew. Chem.*, **94**, 213–214; *Angew. Chem., Int. Ed. Engl.*, (1982), **21**, 203.

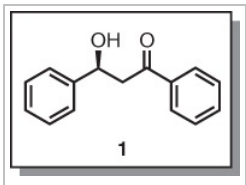
7. (a) *Methoden der Organischen Chemie (Houben-Weyl)*, vol. XI/2 (1958), Georg Thieme Verlag, Stuttgart, p. 309;(b) *Organikum* (2001), 21st edn, Wiley-VCH Verlag GmbH, Weinheim, p. 492.

8. (a)See ref. [1], p. 553;(b) for a monograph, see: Hase, T.A. (1987) *Umpoled Synthons*, John Wiley & Sons, Inc., New York.

9. Kober, R. and Steglich, W. (1983) *Liebigs Ann. Chem.*, 599–604.

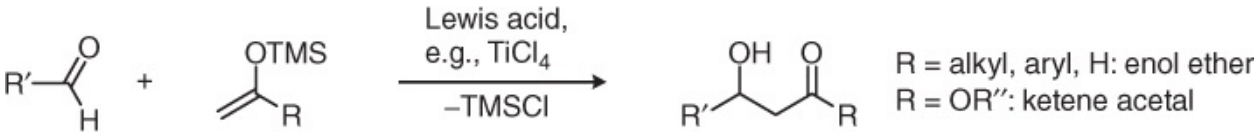
10. Eicher, Th. and Tietze, L.F. (1995) *Organisch-Chemisches Grundpraktikum*, 2nd edn, Georg Thieme Verlag, Stuttgart, p. 204.

1.3.3 (*S*)-1-Hydroxy-1,3-diphenyl-3-propanone

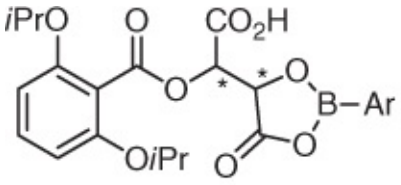
	***Topics:***	• Chiral (acyloxy)borane catalyzed asymmetric Mukaiyama aldol reaction • Synthesis of chiral β-hydroxy ketones • Preparation of the CAB ligand from 2,6-dihydroxybenzoic acid and (*S*,*S*)-(−)-tartaric acid • Ester and aryl ether formation, cleavage of benzyl esters

(a) General

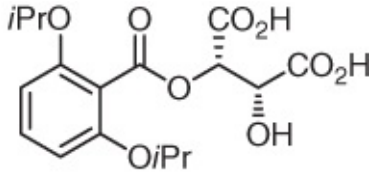
Aldol reactions are among the most powerful and efficient synthetic methods for the formation of carbon–carbon bonds [1]. In the Mukaiyama aldol reaction (cf. Section 1.3.3), silyl enol ethers or silyl ketene acetals are combined with aldehydes in the presence of a Lewis acid (e.g., $TiCl_4$) to give β-hydroxy ketones (aldols) or β-hydroxy esters, respectively:



By using a chiral Lewis acid, an asymmetric Mukaiyama aldol reaction can be performed. For this purpose, Ishihara and Yamamoto [2] developed the chiral (acyloxy)borane (CAB) complexes **2**, which are based on a chiral ligand derived from tartaric acid and aryl boronic acids. They proved to be efficient chiral catalysts for aldol reactions [3] and have also been successfully applied for a variety of other asymmetric transformations such as Diels–Alder reactions [4], hetero-Diels–Alder reactions [5], and allylations [6].



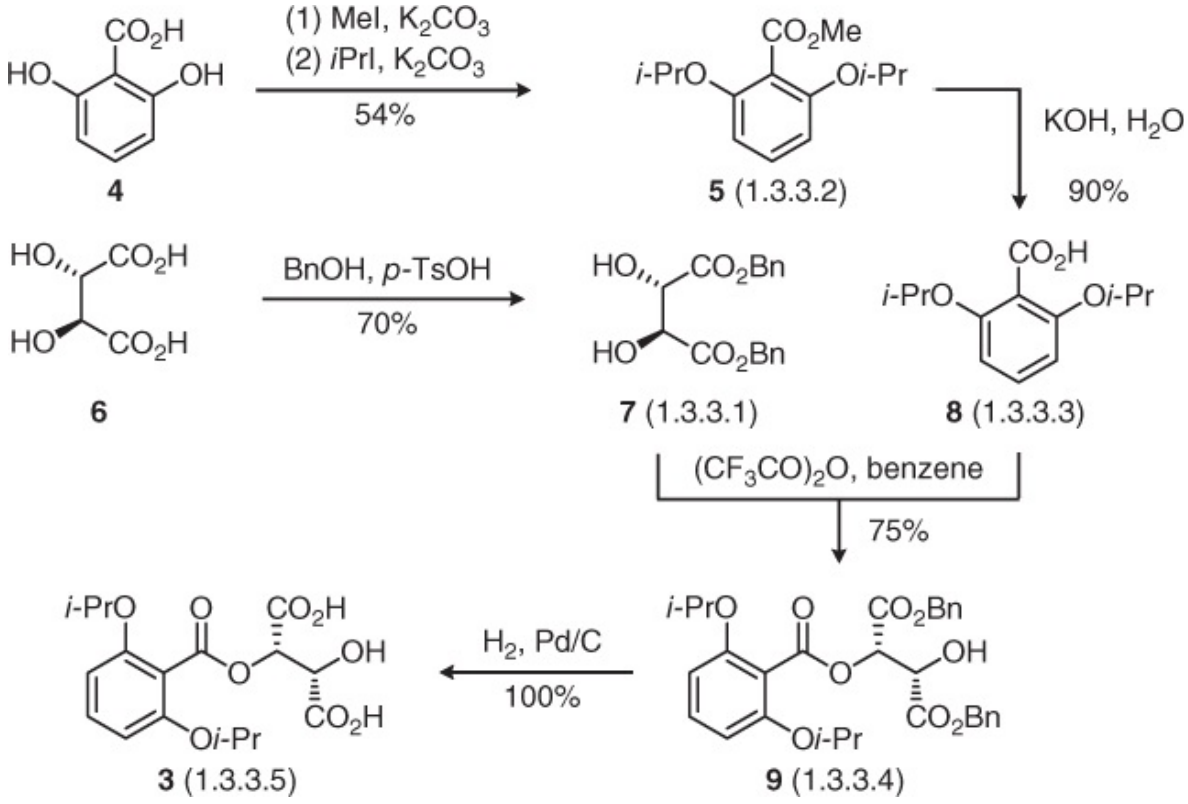
2



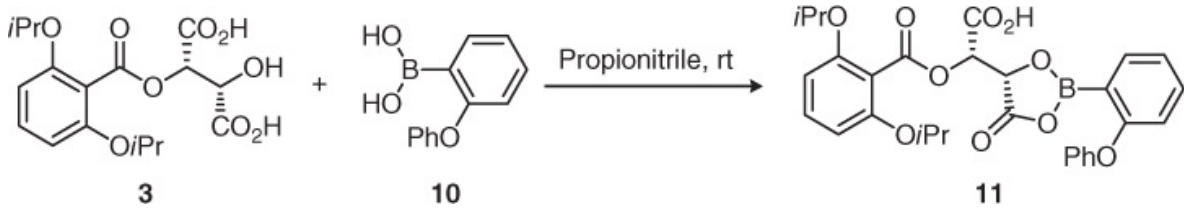
3

(b) Synthesis of 1

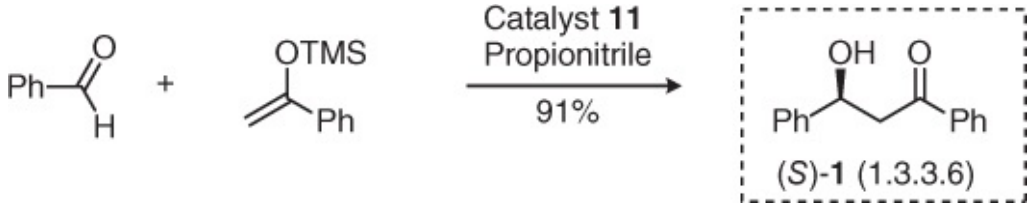
1. For the synthesis of the catalyst of type **2**, the chiral CAB ligand **3** is prepared in a five-step sequence starting from 2,6-dihydroxybenzoic acid (**4**) and (*S*,*S*)-(−)-tartaric acid (**6**). First, the Oalkylated carboxylic acid **8** is synthesized in a three-step sequence consisting of the formation of the methyl ester, its Oalkylation to give the bis-isopropyl ether **5**, and saponification of the methyl ester moiety (**5** → **8**) [5c]. Second, (*S*,*S*)-(−)-tartaric acid (**6**) is transformed into the dibenzyl ester **7** by reaction with benzyl alcohol in the presence of a catalytic amount of *p*-toluenesulfonic acid with azeotropic removal of H_2O [7]. Mono-esterification of the 1,2-diol functionality in the dibenzyl ester **7** with the carboxylic acid **8** is accomplished with trifluoroacetic anhydride, probably via the intermediate formation of a mixed anhydride. The final step of the synthesis is cleavage of the dibenzyl ester moieties in **9** by hydrogenation to give the desired CAB ligand **3** [6b].



The active CAB species **11** is prepared *in situ* from (2*S*,3*S*)-2-*O*-(2,6-diisopropoxybenzoyl)tartaric acid (**3**) and commercially available 2-phenoxyphenylboronic acid (**10**) in propionitrile [3c]:

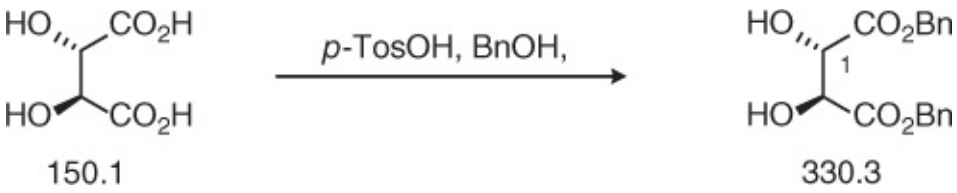


2. The asymmetric Mukaiyama aldol reaction of benzaldehyde and 1-phenyl-1-(trimethylsilyloxy)ethylene is performed in propionitrile at −78 °C under promotion by 20 mol% of the catalyst **11** and leads to the (*S*)-enantiomer of 1-hydroxy-1,3-diphenyl-3-propanone (**1**) in 91% chemical yield and 90% ee.



(c) Experimental Procedures for the Syntheses of 3 and 1

1.3.3.1 * (*S*,*S*)-Dibenzyl tartrate [5]



150.1 330.3

A stirred solution of (*S*,*S*)-(−)-tartaric acid (15.0 g, 100 mmol), benzyl alcohol (20.7 ml, 21.6 g, 200 mmol), and *p*-toluenesulfonic acid monohydrate (476 mg, 2.50 mmol, 2.5 mol%) in toluene (200 ml) is refluxed for 48 h in a 500-ml round-bottomed flask equipped with a Dean–Stark trap and an argon bubbler.

It is then cooled to room temperature, diluted with EtOAc (120 ml), and washed with saturated aqueous $NaHCO_3$ solution (2 × 30 ml) and brine (2 × 30 ml). The organic layer is dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue is dissolved in toluene (80 ml) and the desired product is obtained by precipitation upon addition of isooctane (80 ml). After filtration and drying the residue under high vacuum, the tartrate is obtained as white fibers; 23.2 g (70%), mp 54–55 °C, $[\alpha]^{20}_{D}$ = +10.0 (*c* = 1.0, $CHCl_3$).

UV (CH_3CN): λ_{max} (nm) (log ϵ) = 267.0 (2.200), 262.5 (2.439), 251.5 (2.376), 257.0 (2.515), 207.0 (4.207).

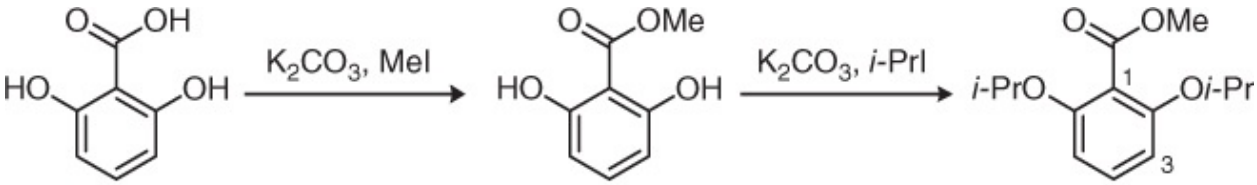
IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3464, 3280, 3034, 2946, 1747, 1498, 1455, 1378, 1275, 1218, 1192, 1126, 1093, 1029, 1003, 978, 736, 695, 608, 507, 457.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.34 (m_c, 10H, Ph–H), 5.25 (d, *J* = 2.0 Hz, 4H, C<u>H</u>$_2$Ph), 4.59 (d, *J* = 7.3 Hz, 2H, 1-H), 3.17 (d, *J* = 7.3 Hz, 2H, OH).

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 171.3 (*C*O_2Bn), 134.7 (Ph–*C*$_{quart}$), 128.7 (Ph–*C*H), 128.4 (Ph–*C*H), 72.1 (C-1), 68.1 (*C*H_2Ph).

MS (ESI): *m*/*z* (%) = 683 (100) $[2M+Na]^+$, 353 (22) $[M+Na]^+$.

1.3.3.2 ** Methyl 2,6-diisopropoxybenzoate [5]



154.1 168.1 252.3

Iodomethane (Caution: carcinogenic!) (17.8 ml, 40.6 g, 286 mmol) is added to a mixture of 2,6-dihydroxybenzoic acid (20.0 g, 130 mmol), anhydrous K_2CO_3 (19.8 g, 143 mmol), and anhydrous DMF (300 ml) in a 1000-ml round-bottomed flask equipped with a dropping funnel. The mixture is stirred at room temperature for 20 h, then poured into ice-cold aqueous HCl (1 M, 300 ml), and extracted with Et_2O (3 × 250 ml). The combined organic layers are washed with brine (150 ml), dried over Na_2SO_4, filtered, and concentrated *in vacuo*.

The oily residue (crude 2,6-dihydroxybenzoic acid methyl ester, max. 130 mmol) is dissolved in DMF (300 ml) in a 1000-ml round-bottomed flask equipped with a dropping funnel. First, anhydrous K_2CO_3 (44.9 g, 325 mmol) is added in one batch; then 2-iodopropane (36.4 ml, 61.9 g, 364 mmol) is added dropwise under continuous stirring at room temperature. Stirring is continued for 2 days, and then the mixture is poured into ice-cold aqueous HCl (1 M, 300 ml) and extracted with Et_2O (2 × 250 ml). The combined organic layers are washed with brine (3 × 150 ml), dried over Na_2SO_4, filtered, and concentrated *in vacuo*.

Purification of the residue by column chromatography on silica gel (400 g, *n*-pentane/EtOAc, 20 : 1) leads to the methyl ester as colorless cuboids; 17.7 g (54% for two steps), mp 57–59 °C, R_f = 0.30 (*n*-pentane/EtOAc, 20 : 1).

UV (CH_3CN): λ_{max} (nm) (log ϵ) = 280.5 (3.353), 203.0 (4.585).

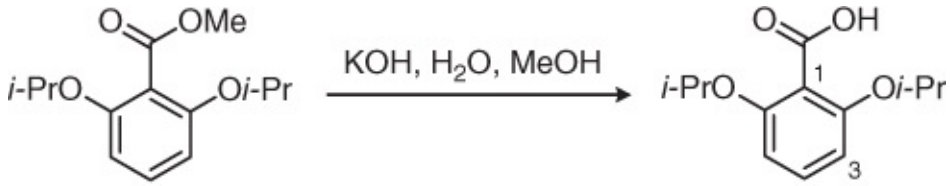
IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 2981, 1735, 1595, 1467, 1386, 1295, 1255, 1112, 1071, 959, 902, 823, 783, 739, 665.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.18 (t, *J* = 8.4 Hz, 1H, H-4), 6.50 (d, *J* = 8.4 Hz, 2H, 2 × H-3), 4.49 (sept, *J* = 6.2 Hz, 2H, 2 × OC<u>H</u>$(CH_3)_2$), 3.86 (s, 3H, CO_2CH_3), 1.28 (d, *J* = 6.2 Hz, 12H, 2 × OCH(C<u>H</u>$_3)_2$).

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 167.3 (CO_2CH_3), 155.9 (C-2), 130.5 (C-4), 116.2 (C-1), 106.5 (2 × C-3), 71.4 (2 × O*C*H$(CH_3)_2$), 52.1 (CO_2CH_3), 22.1 (2 × OCH($CH_3)_2$).

MS (EI, 70 eV): *m*/*z* (%) = 252 (15) $[M]^+$, 221 (10), 168 (39) $[M-2C_3H_6]^+$, 136 (100) $[M-2C_3H_6CH_3OH]^+$, 108 (12), 43 (9) $[C_3H_7]^+$.

1.3.3.3	**	**2,6-Diisopropoxybenzoic acid** [5]



252.3 238.3

The benzoate **1.3.3.2** (15.6 g, 61.9 mmol) is added to a solution of KOH (28.2 g, 681 mmol) in MeOH (170 ml) and H_2O (19 ml). The mixture is heated to 80 °C and stirred for 15 h at this temperature.

After the addition of H_2O (200 ml), the MeOH is evaporated under reduced pressure. The aqueous solution is added dropwise to a stirred aqueous HCl solution (2 M, 400 ml) at 0 °C to give a white precipitate, which is collected by filtration, washed with ice-cold H_2O (3 × 30 ml), and dried *in vacuo*. The benzoic acid is isolated as a colorless amorphous solid; 13.3 g (90%), mp 106–107 °C, R_f = 0.05 (*n*-pentane/EtOAc, 10 : 1).

UV (CH_3CN): λ_{max} (nm) (log ϵ) = 280.5 (3.343), 204.0 (4.581).

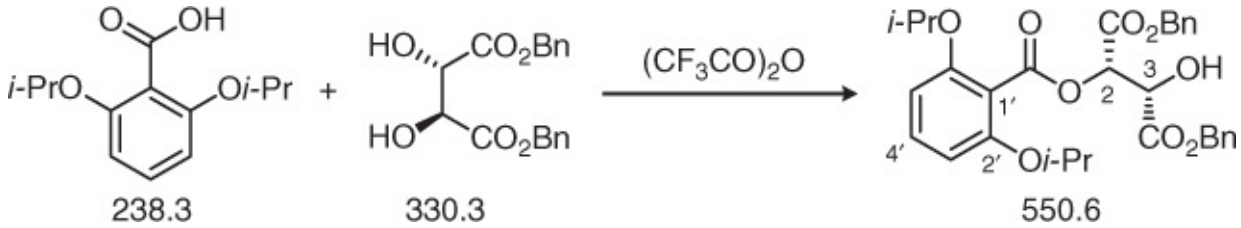
IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 2982, 2934, 2662, 1702, 1597, 1467, 1387, 1340, 1302, 1258, 1173, 1112, 1072, 904, 804, 782, 742, 655, 445.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.24 (t, *J* = 8.4 Hz, 1H, 4-H), 6.56 (d, *J* = 8.4 Hz, 2H, 3-H), 4.56 (sept, *J* = 5.9 Hz, 2H, OC<u>H</u>$(CH_3)_2$), 1.33 (d, *J* = 5.9 Hz, 12H, OCH(C<u>H</u>$_3)_2$).

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 168.8 (CO_2H), 156.7 (C-2), 131.4 (C-4), 114.4 (C-1), 106.9 (2 × C-3), 72.0 (2 × O*C*H$(CH_3)_2$), 22.0 (2 × OCH(*C*H$_3)_2$).

MS (EI, 70 eV): *m*/*z* (%) = 238 (8) $[M]^+$, 154 (27) $[M-2C_3H_6]^+$, 136 (100) $[M-OCH(CH_3)_2-C_3H_7]^+$, 108 (12), 43 (7) $[C_3H_7]^+$.

1.3.3.4	**	**Dibenzyl (2*S*,3*S*)-2-*O*-(2,6-diisopropoxybenzoyl) tartrate** [5]



238.3 330.3 550.6

Trifluoroacetic anhydride (1.96 ml, 2.91 g, 13.9 mmol) is added by means of a syringe over a period of 20 min to a stirred suspension of the acid **1.3.3.3** (3.00 g, 12.6 mmol) and the tartrate **1.3.3.1** (4.16 g, 12.6 mmol) in anhydrous benzene (65 ml; Caution: carcinogenic!) at room temperature. Stirring is continued for 90 min.

The pale-yellow solution is then poured into saturated aqueous $NaHCO_3$ solution (100 ml), and the mixture is extracted with Et_2O (3 × 50 ml). The combined organic layers are dried over Na_2SO_4 and filtered. The solvent is removed *in vacuo*, and the residue is purified by column chromatography (SiO_2, CH_2Cl_2). The tartaric acid dibenzyl ester is obtained as a colorless sticky oil; 5.23 g (75%), $[\alpha]^{20}_D$ = +33.4 (*c* = 1.0, $CHCl_3$), R_f = 0.19 (CH_2Cl_2).

UV (CH_3CN): λ_{max} (nm) (log ϵ) = 282.5 (3.382), 203.0 (4.711).

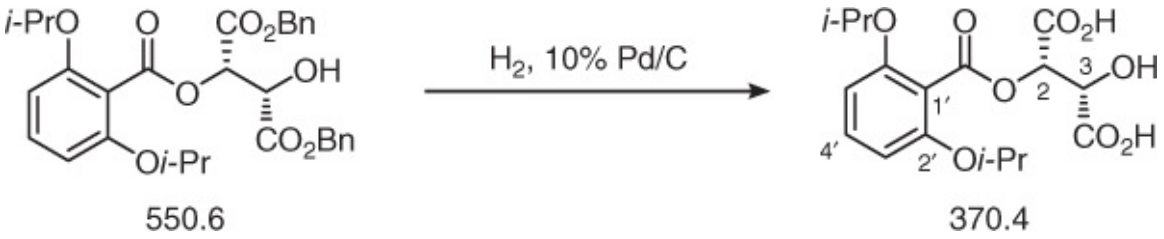
IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3522, 3034, 2979, 2935, 1748, 1595, 1499, 1465, 1385, 1334, 1255, 1114, 1071, 967, 905, 789, 736.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.38–7.31 (m, 10H, Ph–H), 7.25 (t, *J* = 8.3 Hz, 1H, 4′-H), 6.53 (d, *J* = 8.3 Hz, 2H, 3′-H), 5.85 (d, *J* = 2.4 Hz, 1H, 2-H), 5.33 (d, *J* = 12.0 Hz, 1H, C$\underline{H}_2$Ph), 5.26 (d, *J* = 1.8 Hz, 2H, C$\underline{H}_2$Ph), 5.10 (d, *J* = 12.0 Hz, 1H, C$\underline{H}_2$Ph), 4.82 (dd, *J* = 9.0, 2.4 Hz, 1H, 3-H), 4.55 (sept, *J* = 6.0 Hz, 2H, OC$\underline{H}$(CH_3)$_2$), 3.18 (d, *J* = 9.0 Hz, 1H, OH), 1.30 (d, *J* = 6.0 Hz, 6H, OCH(C$\underline{H}_3$)$_2$), 1.28 (d, *J* = 6.0 Hz, 6H, OCH(C$\underline{H}_3$)$_2$).

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 170.2 (CO_2Bn), 166.4 (CO_2Bn), 165.1 (CO_2Ar), 156.4 (2 × C-2′), 135.2 (Ph–C_{quart}), 134.7 (Ph–C_{quart}), 131.2 (C-4′), 128.6, 128.5, 128.3, 128.2 (Ph–*C*H), 114.0 (C-1′), 105.9 (2 × C-3′), 73.0 (C-2), 71.1 (2 × O*C*H(CH_3)$_2$), 71.0 (C-3), 67.9 (*C*H_2Ph), 67.3 (*C*H_2Ph), 21.9 (OCH(*C*H_3)$_2$), 21.8 (OCH(*C*H_3)$_2$).

MS (ESI): *m*/*z* (%) = 1124 (100) $[2M+Na]^+$, 573 (25) $[M+Na]^+$.

1.3.3.5	**	**(2*S*,3*S*)-2-*O*-(2,6-Diisopropoxybenzoyl)tartaric acid** [5]



550.6 370.4

Palladium on charcoal (10%, 240 mg) is added to a solution of the dibenzyl ester **1.3.3.4** (3.00 g, 5.45 mmol) in EtOAc (25 ml) under an argon atmosphere. The balloon filled with argon is then replaced by a balloon filled with hydrogen, and the reaction mixture is stirred at room temperature for 14 h.

The mixture is then filtered through a Celite® pad, and the solvent is removed *in vacuo* to afford the monoacylated tartaric acid in quantitative yield, which is dried *in vacuo* to become a colorless crystalline solid; 2.02 g (100%), mp 76–78 °C, $[\alpha]^{20}_D$ = +27.8 (*c* = 1.0, EtOH).

UV (CH_3CN): λ_{max} (nm) (log ϵ) = 282.0 (3.376), 202.5 (4.539).

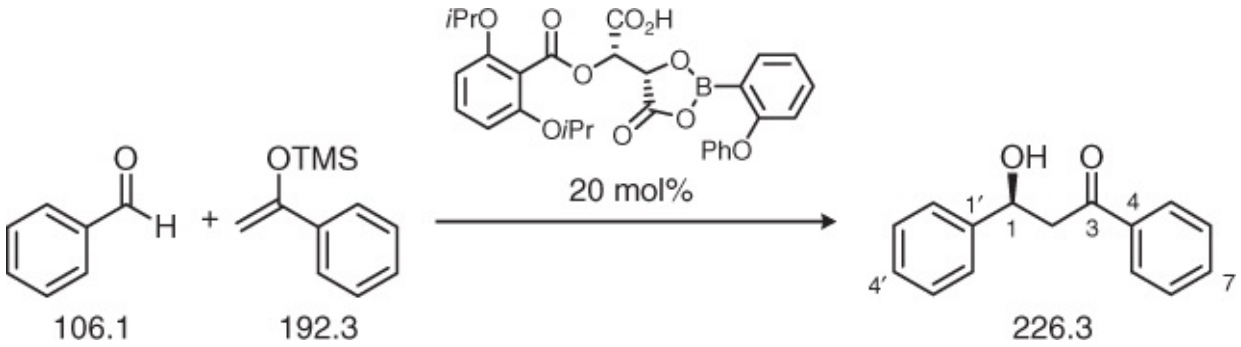
IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3495, 2982, 1743, 1596, 1467, 1387, 1254, 1112, 903, 733, 662.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.25 (t, *J* = 8.4 Hz, 1H, 4′-H), 6.53 (d, *J* = 8.4 Hz, 2H, 3′-H), 5.84 (d, *J* = 1.5 Hz, 1H, 2-H), 4.87 (d, *J* = 1.5 Hz, 1H, 3-H), 4.54 (sept, *J* = 6.1 Hz, 2H, OC<u>H</u>$(CH_3)_2$), 1.30 (d, *J* = 6.1 Hz, 6H, OCH(C<u>H</u>$_3)_2$), 1.25 (d, *J* = 6.1 Hz, 6H, OCH(C<u>H</u>$_3)_2$).

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 173.1 (CO_2H), 170.0 (CO_2H), 164.4 (CO_2Ar), 156.2 (2 × C-2′), 131.8 (C-4′), 114.0 (C-1′), 113.6 (2 × C-3′), 72.6 (C-2), 72.1 (2 × O*C*H$(CH_3)_2$), 70.5 (C-3), 21.9 (OCH(*C*H$_3)_2$), 21.8 (OCH(*C*H$_3)_2$).

MS (ESI): *m*/*z* (%) = 763 (87) $[2M+Na]^+$, 393 (100) $[M+Na]^+$.

1.3.3.6	**	**(*S*)-1-Hydroxy-1,3-diphenyl-3-propanone** [4]



The monoacylated tartaric acid **1.3.3.5** (74.1 mg, 0.20 mmol) and 2-phenoxyphenylboronic acid (42.8 mg, 0.20 mmol) are dissolved in anhydrous propionitrile (1.0 ml) and stirred at room temperature for 30 min. The reaction mixture is then cooled to −78 °C, and benzaldehyde (101 µl, 106 mg, 1.00 mmol) is added by means of a syringe, followed by 1-phenyl-1-(trimethylsiloxy)ethylene (349 µl, 327 mg, 1.70 mmol). The reaction mixture is stirred at −78 °C for 4 h, then an aqueous HCl solution (0.25 M, 4.0 ml) is added, and the mixture is allowed to warm to room temperature.

The mixture is poured into Et_2O (40 ml) and H_2O (20 ml), the phases are separated, and the aqueous layer is extracted with Et_2O (2 × 20 ml). The combined organic layers are washed with H_2O (20 ml) and saturated aqueous $NaHCO_3$ solution (20 ml), dried over Na_2SO_4, and filtered. The solvent is removed *in vacuo* and purified by column chromatography on deactivated silica gel (30 g + 0.3 ml NEt_3, *n*-pentane/Et_2O, 5 : 1) to give the aldol adduct as a light-yellow sticky oil; 206 mg (91%), ee = 90%, $[\alpha]^{20}_D = -67.0$ (*c* = 1.0, $CHCl_3$), $R_f = 0.14$ (*n*-pentane/Et_2O, 5 : 1).

The enantiomeric excess value of the aldol **1.3.3.6** is determined by HPLC analysis of the corresponding (+)-MTPA ester, which is obtained by small-scale reaction of **1.3.3.6** with (+)-α-methoxy-α-trifluoromethylphenyl acetyl chloride and anhydrous pyridine in CCl_4 according to Mosher's method [8]. (*S*)-1-Hydroxy-1,3-diphenyl-3-propanone (25.0 mg, 0.11 mmol) and (+)-α-methoxy-α-trifluoromethylphenyl acetyl chloride (20.7 µl, 27.8 mg, 0.11 mmol) are mixed with CCl_4 (0.1 ml; Caution: resorption through the skin!) and pyridine (0.1 ml). The reaction mixture is stirred at room temperature for 12 h and poured into Et_2O (10 ml) and H_2O (10 ml), and after extraction the phases are separated. The organic layer is dried over Na_2SO_4, filtered, and concentrated, and the residue obtained is dissolved in EtOAc for HPLC analysis.

UV (CH_3CN): λ_{max} (nm) (log ϵ) = 279.0 (3.178), 241.0 (4.103).

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3469, 3057, 1670, 1597, 1447, 1393, 1215, 1055, 1020, 916, 872, 747.

^{1}H NMR (300 MHz, [D_6]benzene): δ (ppm) = 7.61 (dd, *J* = 8.1, 1.5 Hz, 2H, 2 × 5-H), 7.35 (dd, *J* = 7.5, 1.8 Hz, 2H, 2 × 2′-H), 7.20 (t, *J* = 7.5 Hz, 2H, 2 × 3′-H), 7.13–7.05 (m, 2H, 7-H, 4′-H), 6.96 (t, *J* = 8.1 Hz, 2H, 2 × 6-H), 5.23 (dd, *J* = 9.3, 2.9 Hz, 1H, 1-H), 3.53 (s_{br}, 1H, OH), 2.94 (dd, *J* = 17.7, 9.3 Hz, 1H, 2-H_b), 2.80 (dd, *J* = 17.7, 2.9 Hz, 1H, 2-H_a).

^{13}C NMR (76 MHz, [D_6]benzene): δ (ppm) = 199.7 (C-3), 144.1 (C-1′), 137.0 (C-4), 133.2 (C-7), 128.5 (2 × C-5, 2 × C-6, C-4′), 127.5 (2 × C-3′), 126.1 (2 × C-2′), 70.0 (C-1), 48.0 (C-2).

MS (EI, 70 eV): *m*/*z* (%) = 226 (48) $[M]^+$, 208 (58) $[M-H_2O]^+$, 186 (47), 131 (11) $[M-H_2O-C_6H_5]^+$, 120 (48), 105 (100) $[C_6H_5CHCH_3]^+$, 77 (96) $[C_6H_5]^+$, 51 (33).

HPLC: Chiralcel OD (Daicel); 250 × 4.6 mm ID

eluent: *n*-hexane/EtOAc, 40 : 1; isocratic

retention time: t_{R1} = 12.8 min (*S*)-isomer; t_{R2} = 15.1 min (*R*)-isomer.

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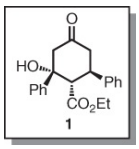
8. (a) Dale, J.A. and Mosher, H.S. (1973) *J. Am. Chem. Soc.*, **95**, 512–519;(b) Dale, J.A., Dull, D.L., and Mosher, H.S. (1969) *J. Org. Chem.*, **34**, 2543–2549.

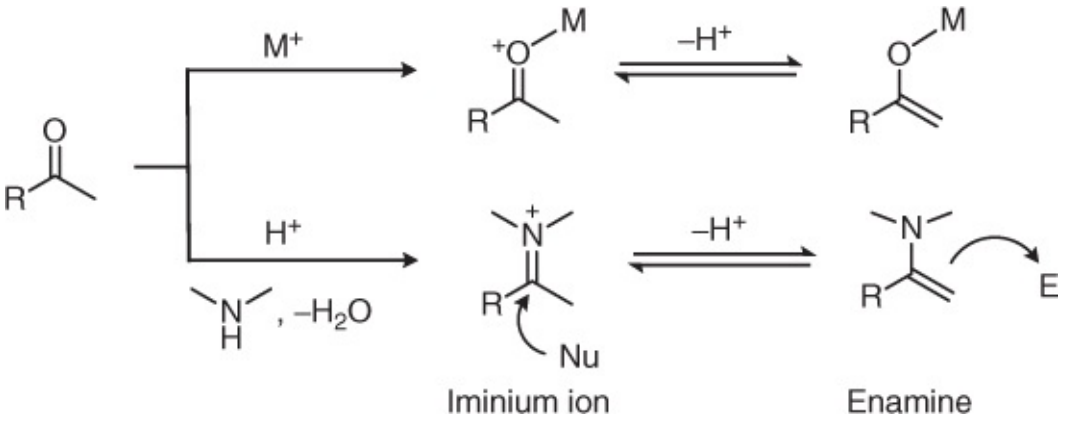
1.3.4 Ethyl (1*S*,2*R*,6*R*)-2-hydroxy-4-oxo-2,6-diphenylcyclohexane-1-carboxylate

	***Topics:***	• Organocatalysis • Enantioselective synthesis of an oxocyclohexane carboxylic ester (Michael addition, intramolecular aldol reaction) • Synthesis of Jørgensen's catalyst from L-phenylalanine (amide formation, amines by reduction of amides, imidazolidine formation)

(a) General

Enantioselective catalysis is an important topic in organic synthesis. In the past, this was mainly accomplished by the use of transition-metal catalysts containing metals such as Pd [1], Ru, or Rh in the presence of chiral ligands. However, on the basis of the enantioselective synthesis of hydrindens by Wiechert, Eder, Sauer, Hajos, and Parrish [2] over 30 years ago, using L-proline as chiral catalyst (cf. Section 1.3.1), it has been demonstrated that enantioselective catalysis can also be effected by a wide range of small, metal-free chiral molecules, such as amino acids and their derivatives.

In the meantime, extensive studies have been carried out with regard to the use of such organocatalysts in various reactions [3], such as the aldol [4], Michael [5], Mannich [6], and Diels–Alder reactions [7], as well as hydrogenations [8], with high stereoselectivity. The concept of organocatalysis (or aminocatalysis) is mainly based on electronic similarities between a Lewis-acid-activated carbonyl group and an iminium ion. Thus, an iminium ion is more reactive than a carbonyl moiety because of a lower energy of its lowest unoccupied molecular orbital (LUMO), which is manifested in an increase of its electrophilicity and its α-C–H acidity. In this way, organocatalysis exploits both the higher reactivity of iminium ions and their easy deprotonation to give enamines, which can either react with electrophiles or be used in pericyclic processes.

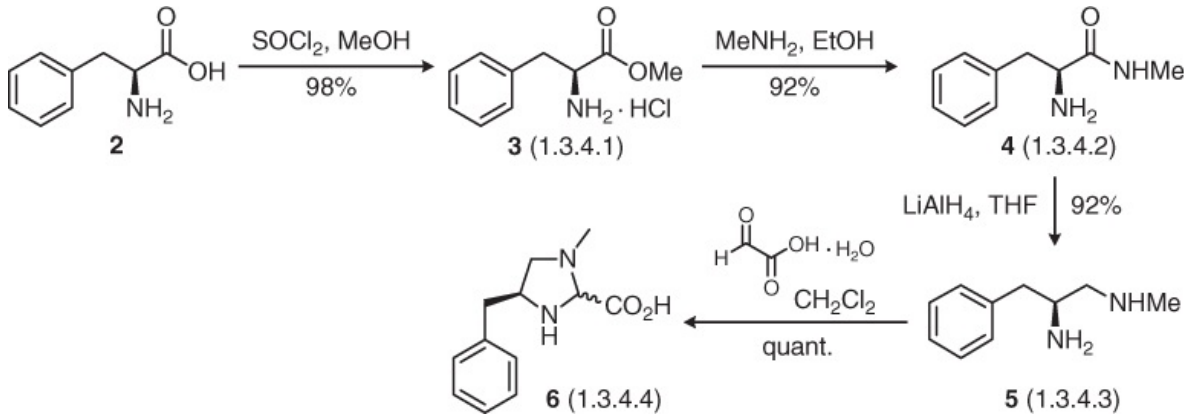


Among the various asymmetric C–C bond-forming reactions that may be exploited for the formation of chiral building blocks, enantioselective domino reactions [9] are of particular importance as multiple stereogenic centers can be formed during a single transformation. Jørgensen and coworkers [10][4] recently published a highly diastereo and enantioselective domino-Michael–aldol reaction of acyclic β-keto esters and α,β-unsaturated ketones in the presence of a chiral organocatalyst easily accessible in a few steps from L-phenylalanine. An example of this organocatalyzed domino process, yielding cyclohexanone-4-carboxylates with several stereogenic centers, is presented in Section (b), together with the synthesis of the required organocatalyst.

(b) Synthesis of 1

1. Jørgensen's catalyst **6** is prepared in a four-step sequence, starting from L-phenylalanine (**2**), which is transformed into the methyl ester hydrochloride **3** by reaction with $SOCl_2$ in MeOH. Aminolysis of **3** leads to the corresponding methyl amide **4**, which is reduced with lithium aluminum hydride. The 1,2-diamine **5** thus obtained is subjected to cyclocondensation

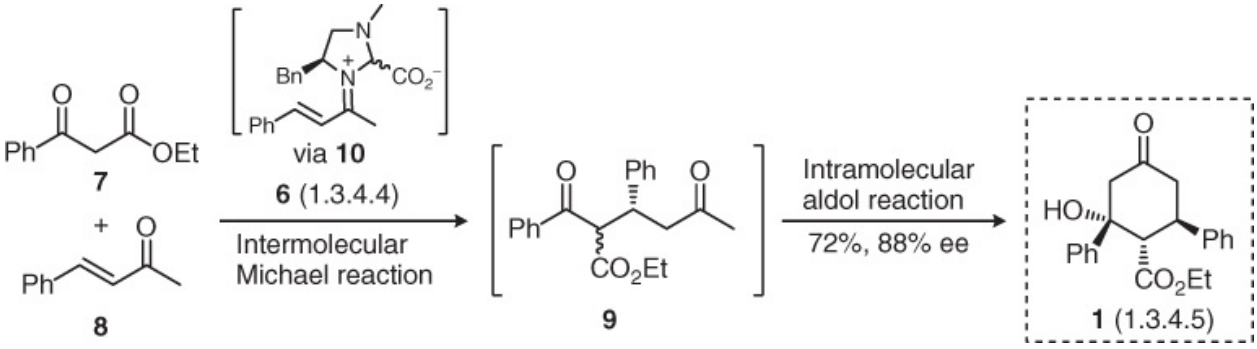
with glyoxylic acid monohydrate to give the desired organocatalyst imidazolidine-2-carboxylic acid **6**.



2. The synthesis of the oxocyclohexanecarboxylic acid ethyl ester **1** in a single process is achieved by a highly diastereo and enantioselective domino-Michael–aldol reaction of ethyl benzoylacetate (**7**) and benzylidene acetone (**8**) in the presence of the organocatalyst **6**.

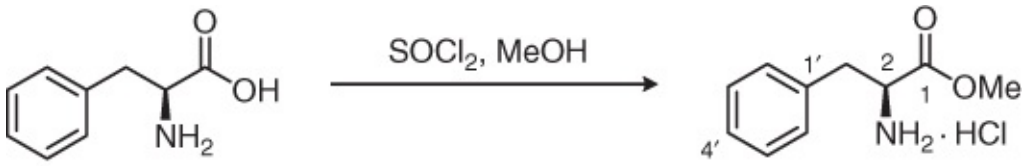
Initially, the β-keto ester (**7**) and the enone (**8**) undergo an intermolecular Michael reaction to form the adduct **9**, which subsequently undergoes an intramolecular aldol reaction to give the target molecule **1** with three defined stereogenic centers in a chemical yield of 72% and 88% ee.

The catalyst plays a threefold role in this domino process: (i) it activates the Michael acceptor by the formation of an iminium ion (**10**); (ii) it generates the active Michael donor by deprotonation of the β-keto ester (**7**); and (iii) it acts as a base in the intramolecular aldol reaction.



(c) Experimental Procedures for the Synthesis of 1

1.3.4.1	**	**Methyl (2*S*)-2-amino-3-phenylpropionate hydrochloride** [11]



165.2 215.7

Thionyl chloride (18.8 g, 158 mmol, 11.5 ml) is slowly added to a stirred suspension of L-phenylalanine (20.1 g, 122 mmol) in MeOH (120 ml) under an argon atmosphere at 0 °C, and stirring is continued at room temperature for 22 h.

After removal of the solvent *in vacuo*, H_2O (30 ml) is added and evaporated *in vacuo*. This process is repeated three times. After drying *in vacuo*, the hydrochloride is obtained as a colorless solid; 25.7 g (98%), mp 160–161 °C.

UV (CH_3CN): λ_{max} (nm) (log ϵ) = 263.5 (2.197), 257.0 (2.298), 252.0 (2.214), 192.5 (4.435).

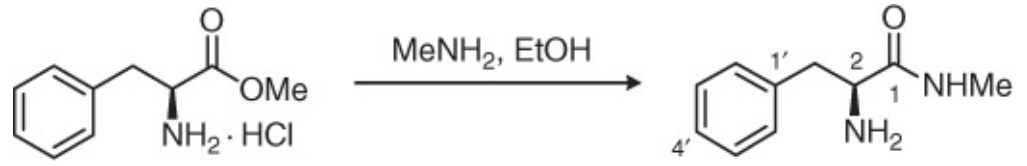
IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 2845, 1747, 1584, 1496, 1242, 1146, 1084, 935, 741, 702.

^{1}H NMR (300 MHz, D_2O): δ (ppm) = 7.88–7.33 (m, 5H, Ph–H), 4.70 (s_{br}, NH_2), 4.50 (t, *J* = 5.9 Hz, 1H, 2-H), 3.91 (s, 3H, CO_2CH_3), 3.42 (dd, *J* = 14.6, 5.9 Hz, 1H, 3-H), 3.32 (dd, *J* = 14.3, 7.5 Hz, 1H, 3-H).

^{13}C NMR (76 MHz, D_2O): δ (ppm) = 171.0 (C-1), 134.7 (C-4′), 130.4 (C-2′, C-6′), 130.2 (C-3′, C-5′), 129.1 (C-1′), 55.1 (C-2), 54.6 (CO_2CH_3), 36.6 (C-3).

MS (EI, 70 eV): *m*/*z* (%) = 179 (2) $[M-HCl]^+$.

1.3.4.2 * (2*S*)-2-Amino-3-phenylpropionic acid methyl amide [7c]



215.7 178.2

A solution of the hydrochloride **1.3.4.1** (25.6 g, 119 mmol) in EtOH (200 ml) is added to a stirred solution of methylamine (8 M, 59.4 ml, 475 mmol) in EtOH under an argon atmosphere at 0 °C, and stirring is continued for 20 h at room

temperature.

The solvent is then removed *in vacuo*, the residue is suspended in Et_2O (30 ml), and the solvent is again evaporated to remove the excess methylamine. This procedure is repeated twice to give the hydrochloride of the desired product as a white solid. The amide is obtained from the hydrochloride by treating the residue with saturated aqueous $NaHCO_3$ solution (100 ml) and extracting with $CHCl_3$ (4 × 100 ml).

The combined organic layers are washed with brine, dried over Na_2SO_4, and filtered, and the solvent is removed *in vacuo* to afford the amide as colorless crystals; 19.6 g (92%), mp 55–56 °C, $[\alpha]^{20}_D = -100.5$ (*c* = 1.0, $CHCl_3$), $R_f = 0.39$ (EtOAc/MeOH, 1 : 1).

UV (CH_3CN): λ_{max} (nm) (log ϵ) = 268 (2.096), 264 (2.190), 258.0 (2.307), 253.0 (2.237), 248.0 (2.130), 192.5 (4.515).

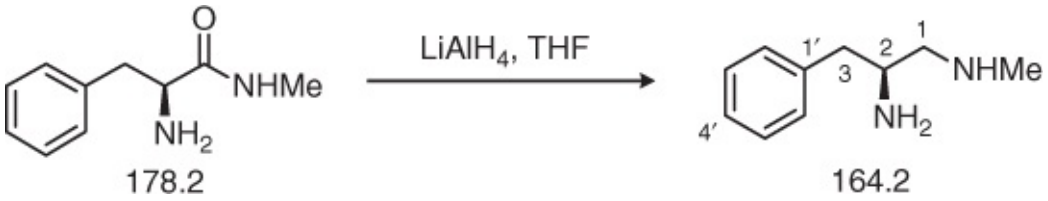
IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3372, 2939, 1646, 1527, 1399, 1109, 927, 857, 747, 701, 482.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.35–7.17 (m, 5H, Ph–H), 3.60 (dd, *J* = 9.4, 3.8 Hz, 1H, 3-H_A), 3.28 (dd, 1H, *J* = 13.8, 4.0 Hz, 3-H_B), 2.81 (d, *J* = 4.9 Hz, 3H, CH_3), 2.67 (dd, *J* = 13.8, 9.6 Hz, 1H, 2-H), 1.33 (s_{br}, 2H, NH_2).

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 174.7 (C-1), 137.9 (C-1′), 129.2 (C-2′,C-6′), 128.6 (C-3′, C-5′), 126.7 (C-4′), 56.4 (C-2), 40.9 (C-3), 25.7 (NH*C*H_3).

MS (DCI, 200 eV): *m*/*z* (%) = 179 (100) $[M+H]^+$, 196 (45) $[M+NH_4]^+$.

1.3.4.3	**	**(2*S*)-1*N*-Methyl-3-phenylpropane-1,2-diamine**



178.2 164.2

A solution of the amide **1.3.4.2** (3.79 g, 21.3 mmol) in THF (80 ml) is added

dropwise to a stirred suspension of $LiAlH_4$ (2.96 g, 78.0 mmol) in THF (60 ml) under an argon atmosphere, and stirring is continued at reflux for 20 h.

After cooling to 0 °C, saturated Na_2SO_4 solution is added dropwise, and the mixture is stirred for 30 min. The white solid is then filtered off and washed with EtOAc. The filtrate is washed with brine, dried over Na_2SO_4, and filtered, and the solvent is removed *in vacuo*. Finally, the residue is purified by distillation to yield the diamine as a colorless oil; 3.40 g (97%), $bp_{0.4}$ 120–121 °C, n^{20}_D = 1.528, $[\alpha]^{20}_D$ = −6.0 (*c* = 1.0, $CHCl_3$), R_f = 0.33 ($CHCl_3$/MeOH, 1 : 1 + 10% NEt_3).

UV (CH_3CN): λ_{max} (nm) (log ϵ) = 268.0 (2.138), 261.0 (2.268), 192.0 (4.491).

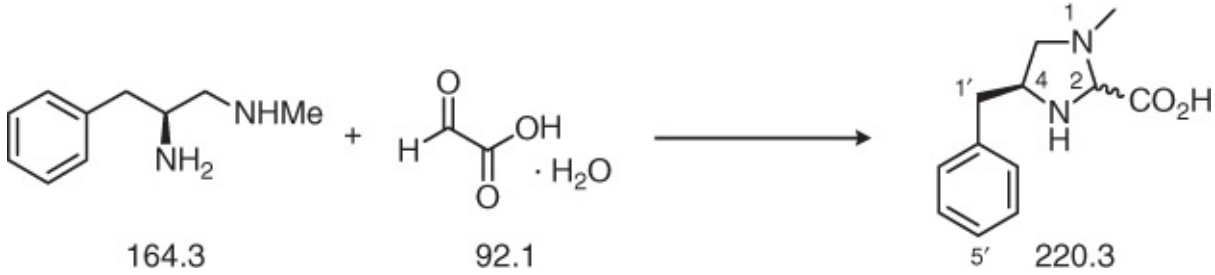
IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3372, 2939, 1646, 1527, 1399, 1109, 928, 747, 701.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.30–7.13 (m, 5H, Ph–H), 2.75 (dd, *J* = 15.5, 5.0 Hz, 1H, 3-H_A), 2.62 (dd, 1H, *J* = 11.4, 3.8 Hz, 3-H_B), 2.51–2.41 (m, 2H, 1-H), 2.40 (s, 3H, NHC$\underline{H}_3$), 1.23 (s_{br}, 3H, NH_2, N*H*CH_3).

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 139.1 (C-1′), 129.1 (C-2′, C-6′), 128.3 (C-3′, C-5′), 126.1 (C-4′), 58.3 (C-1), 52.2 (C-2), 42.7 (C-3), 36.5 ($NHCH_3$).

MS (DCI, 200 eV): *m*/*z* (%) = 165 (100) $[M+H]^+$.

1.3.4.4	*	**(4*S*,2*R*/*S*)-4-Benzyl-1-methylimidazolidine-2-carboxylic acid**
		(Jørgensen's catalyst) [5b]



The diamine **1.3.4.3** (2.96 g, 18.05 mmol) is suspended in CH_2Cl_2 (180 ml) under an argon atmosphere. Glyoxylic acid monohydrate (1.66 g, 18.05 mmol) is

added, and the resulting suspension is stirred at room temperature for 16 h.

Evaporation of the solvent under reduced pressure affords the carboxylic acid in quantitative yield as a colorless solid as a 2 : 1 mixture of diastereomers; mp 122–123 °C, $[\alpha]^{20}_{D}$ = +10.3 (*c* = 1.0, MeOH), R_f = 0.47 ($CHCl_3$/MeOH, 1 : 1 [+10% NEt_3]).

UV (CH_3CN): λ_{max} (nm) (log ϵ) = 267.0 (2.104), 258.0 (2.359), 252.0 (2.330), 248.0 (2.270), 205.0 (3.949).

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3483, 2951, 2786, 1664, 1629, 1573, 1435, 1301, 1205, 1176, 1025, 943, 781, 755, 704, 607.

^{1}H NMR (300 MHz, $CDCl_3$): major diastereomer: δ (ppm) = 8.10–7.40 (2 × s_{br}, 2H, CO_2H, NH), 7.32–7.20 (m, 5H, Ph–H), 4.19 (s, 1H, 2-H), 3.74 (quintet, *J* = 6.8 Hz, 1H, 4-H), 3.48–3.41 (m, 1H, 5-H_A), 3.21 (dd, *J* = 13.4, 5.8 Hz, 1H, 5-H_B), 2.93–2.52 (m, 2H, 1′-H), 2.89 (s, 3H, N–CH_3).

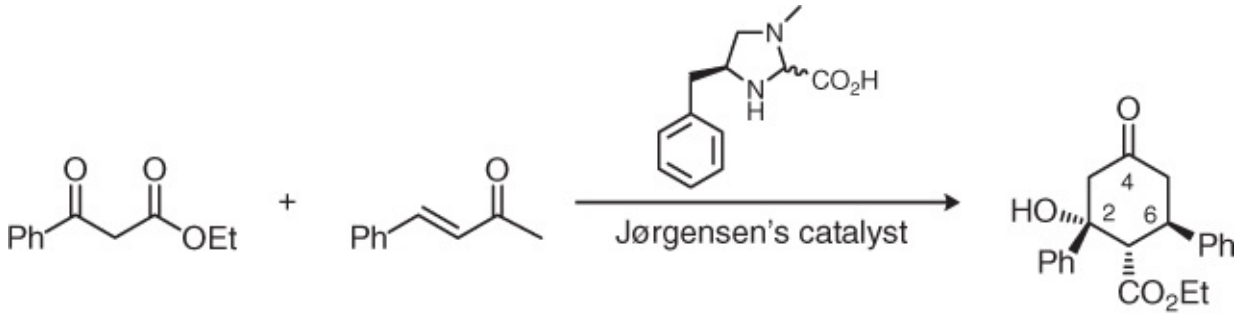
Minor diastereomer*:* δ (ppm) = 8.10–7.40 (2 × s_{br}, 2H, CO_2H, NH), 7.32–7.20 (m, 5H, Ph–H), 4.12 (s, 1H, 2-H), 4.01 (quintet, *J* = 6.7 Hz, 1H, 4-H), 3.71–3.64 (m, 1H, 5-H_A), 3.01 (dd, *J* = 13.4, 6.3 Hz, 1H, 5-H_B), 2.93–2.52 (m, 2H, 1′-H), 2.84 (s, 3H, NCH_3).

^{13}C NMR (76 MHz, $CDCl_3$): major diastereomer: δ (ppm) = 168.9 (CO_2H), 137.4 (C-2′), 128.8 (2 × C-3′), 128.7 (2 × C-4′), 126.8 (C-5′), 84.9 (C-2), 58.4 (C-4), 58.1 (C-5), 40.4 (N–CH_3), 38.3 (C-1′).

Minor diastereomer*:* δ (ppm) = 169.4 (CO_2H), 137.3 (C-2′), 129.1 (2 × C-3′), 128.6 (2 × C-4′), 126.7 (C-5′), 81.9 (C-2), 58.9 (C-5), 57.3 (C-4), 39.8 (C-1′), 39.2 (NCH_3).

MS (ESI): *m*/*z* (%) = 243 (40) $[M+Na]^+$.

1.3.4.5	**	**Ethyl (1*S*,2*R*,6*R*)-2-hydroxy-4-oxo-2,6-diphenylcyclohexane-**
		1-carboxylate [10][4]



To a stirred solution of benzylidene acetone (77.1 mg, 527 µmol) in CH_3CN (1 ml) are added ethyl benzoylacetate (203 mg, 1.06 mmol) and Jørgensen's catalyst **1.3.4.4** (11.6 mg, 52.7 µmol, 10 mol%), and the resulting solution is stirred for 93 h at room temperature.

The reaction mixture is then diluted with Et_2O (2 ml). After filtration and washing the filter cake with Et_2O (2 ml), the solvent is removed *in vacuo* to afford the ethyl ester as a colorless solid; 127 mg (72%), ee = 88%, $[\alpha]^{20}_D = -7.6$ (*c* = 1.0, $CHCl_3$).

UV (CH_3CN): λ_{max} (nm) (log ϵ) = 256.5 (0.074), 251.0 (0.022), 201.0 (1.340).

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3348, 1713, 1374, 1225, 1145, 1029, 749, 698.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.55 (d, *J* = 7.5 Hz, 2H, Ph–H), 7.39–7.22 (m, 7H, Ph–H), 4.45 (d, *J* = 2.5 Hz, 1H, OH), 3.86–3.74 (m, 1H, 5-H), 3.61–3.49 (m, 3H, 1-H, OCH_2), 2.79–2.70 (m, 4H, 3-H, 5-H), 0.53 (t, *J* = 7.2 Hz, 3H, CH_3).

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 206.0 (C-4), 174.2 (-*C*O_2R), 144.1 (Ph–C_{quat}), 140.2 (Ph–C_{quat}), 128.4 (2 × Ph–C), 127.6 (2 × Ph–C), 127.6 (2 × Ph–C), 127.5 (2 × Ph–C), 124.6 (2 × Ph–C), 60.6 (C-2), 56.6 (C-1), 54.0 (C-3), 47.4 (C-5), 43.3 (C-6), 13.2 (CH_3).

MS (EI, 70 eV): *m*/*z* (%) = 338 (12) $[M]^+$.

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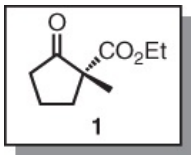
1.4 Electrophilic and Nucleophilic Acylation

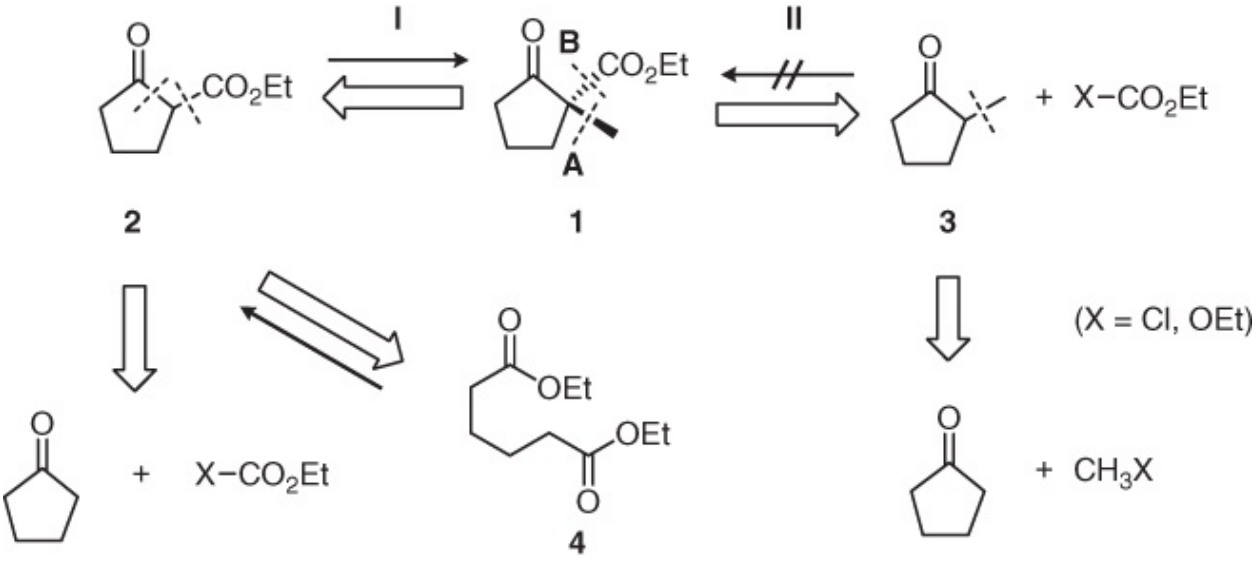
1.4.1 (−)-Ethyl (1*R*)-1-methyl-2-oxocyclopentane-1-carboxylate

	***Topics:***	• Dieckmann cyclization • Stereoselective enzymatic reduction of a β-keto ester to a β-hydroxy ester • Stereoselective α-alkylation of a β-hydroxy ester (Frater–Seebach alkylation) • Oxidation of a secondary hydroxy group to a keto group

(a) General

The chiral β-keto ester **1** is the starting material for a synthesis of the pheromone frontalin [1]. In general, cyclopentane derivatives are valuable building blocks in the total synthesis of natural products, since many of them, for example, steroids and iridoids, contain a five-membered ring system.

Retrosynthesis of **1** according to **A** and **B** immediately leads to cyclopentanone or diethyl adipate and two routes **I**/**II** for the synthesis of **1**:

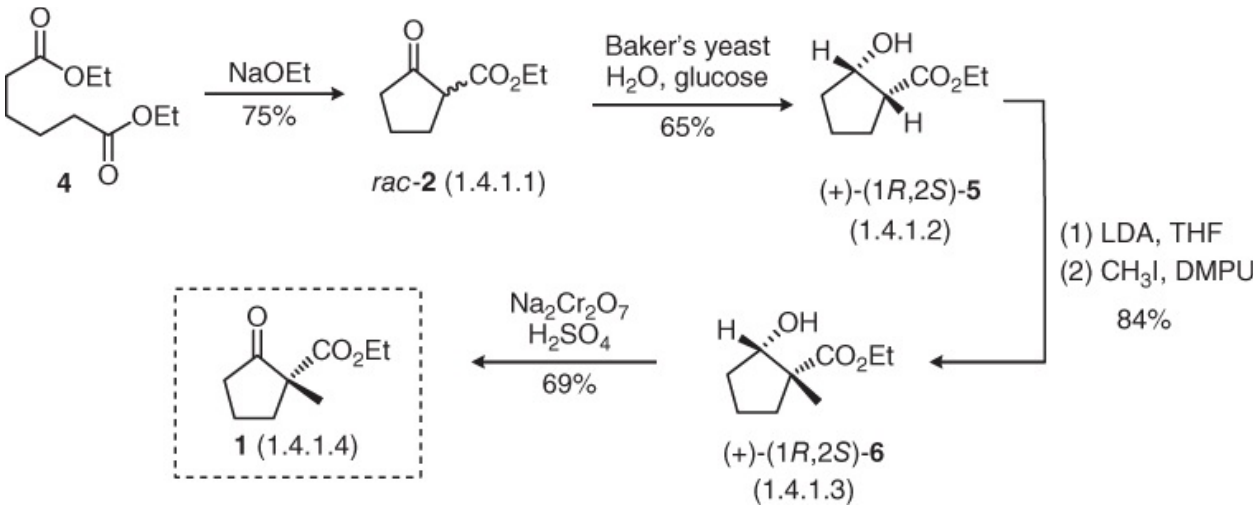


Route **I** represents a 2-methylation of cyclopentanone-2-carboxylate (**2**), which is easily accessible either from diethyl adipate or from α-acylation of cyclopentanone with dialkyl carbonate. Route **II** requires a 2-acylation of 2-methylcyclopentanone (**3**) with dialkyl carbonate; however, the disadvantage arises that Claisen condensations of **3** are reported to take place preferentially at the less hindered C-5 [2]. Therefore, route **I** is favorable and, as the central problem of the synthesis of **1**, there remains the enantioselective formation of its stereogenic center.

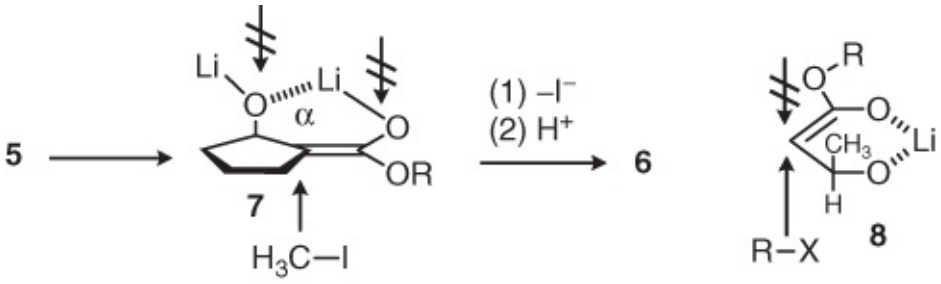
(b) Synthesis of 1

The starting material of choice for the synthesis of **1** is cyclopentanone carboxylate *rac*-**2**, which is readily prepared from diethyl adipate (**4**) by Dieckmann cyclization in the presence of NaOEt [3]. Since direct enantioselective methylation of *rac*-**2** at the 2-position by application of the SAMP methodology (cf. Section 1.2.1) proceeds only with modest stereoselection [4], an indirect approach to **1** is applied [5].

In the first step, the well-established [6] enzymatic reduction of the racemic β-keto ester **2** with Baker's yeast in fermenting aqueous glucose solution is performed, which produces the 2-cyclopentanol-1-carboxylate **5** with (1*R*,2*S*)-configuration in 99% ee as a single diastereomer. In the second step, the chiral β-hydroxy ester **5** is deprotonated with 2 equiv of LDA and then reacted with methyl iodide in the presence of DMPU. In this process, known as ***Frater–Seebach alkylation*** [7], exclusive α-C-alkylation of the β-hydroxy ester is observed to give the product **6** with high stereoselectivity (>98% de).



Intermediates in the Frater–Seebach alkylation are dianions (here: **7**), which exist as rigid Li-chelated structures. These are thought to be responsible for the stereodifferentiation in the alkylation **5** → **6**, as also described for analogous reactions of open-chain systems (e.g., **8**, "acyclic stereoselection") [8].

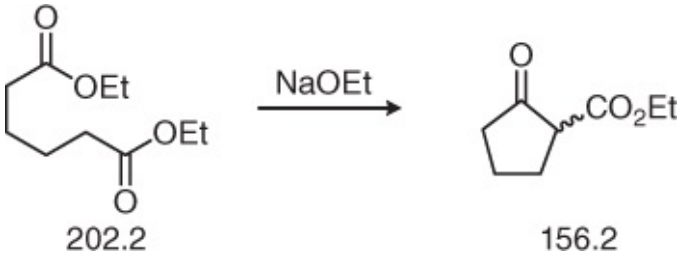


In the last step, the hydroxy ester **6** is oxidized using $Na_2Cr_2O_7/H_2SO_4$ to provide the chiral β-keto ester **1**.

Thus, the target molecule is obtained in practically enantiopure form (>98% ee) in a four-step procedure with an overall yield of 28% (based on **4**).

(c) Experimental Procedures for the Synthesis of 1

1.4.1.1	*	**Ethyl 2-oxo cyclopentane-1-carboxylate** [3]



Sodium ethoxide is prepared by reacting metallic sodium (11.5 g, 0.50 mol) with

anhydrous EtOH (150 ml) and distilling off the excess EtOH *in vacuo*. Anhydrous toluene (100 ml) and diethyl adipate (101 g, 0.50 mol) are added, and the resulting suspension is heated under reflux with stirring for 8 h.

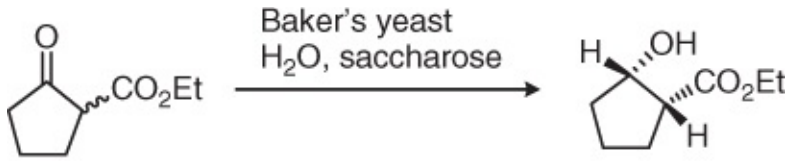
The mixture is then cooled to room temperature, aqueous HCl (2 M) is added until a clear two-phase system is obtained (approximately 250 ml), and the phases are separated. The organic phase is washed with saturated aqueous $NaHCO_3$ and brine (each 100 ml), dried over Na_2SO_4, and filtered. The solution is distilled *in vacuo* (20 mbar), and the fraction obtained in the range 100–140 °C is again distilled *in vacuo* (2 mbar, Vigreux column) to give a colorless oil; 58.2 g (75%), bp_2 88–89 °C, n^{20}_D = 1.4519.

IR (film): $\tilde{\nu}$ (cm^{-1}) = 1740, 1715.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 4.01 (q, *J* = 7.1 Hz, 2H, OCH_2), 3.15 (dd, *J* = 9.3, 8.7 Hz, 1H, 1-H), 2.13–2.04 (m, 4H, CH_2), 1.98–1.88 (m, 1H, CH_2), 1.77–1.61 (m, 1H, CH_2), 1.08 (t, *J* = 7.1 Hz, 3H, CH_3).

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 211.8 (C-2), 168.9 (CO_2Et), 60.5, 54.2, 37.5, 26.9, 20.5, 13.7.

1.4.1.2 * (+)-Ethyl (1*R*,2*S*)-2-hydroxycyclopentane-1-carboxylate [5]



156.2 158.2

In a 3-l Erlenmeyer flask with a stirring or shaking apparatus, Baker's yeast (225 g; *Pleser*, *Darmstadt*) is suspended in H_2O (tap, 1.5 l), and saccharose (225 g) is added. After 0.5 h, ethyl 2-oxocyclopentane-1-carboxylate **1.4.1.1** (22.5 g, 143 mmol) and Triton® X 114 (450 mg, *Fluka*) are added, and the mixture is stirred for 48 h at room temperature.

Hyflow Super Cel® (80 g, Fluka) is added in portions with stirring, and then the mixture is filtered through a G2-frit, saturated with NaCl, and extracted with Et_2O (4 × 300 ml). The ethereal extracts are dried over $MgSO_4$ and filtered. The extracts of four such experiments are combined, the solvent is removed under normal pressure, and the residue is purified by distillation. The product is

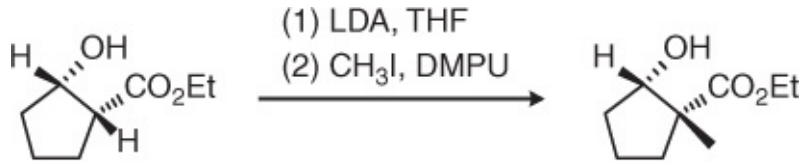
obtained as a colorless oil; 62.6 g (65%), bp_{10} 95–96 °C. $[\alpha]^{20}_D$ = +15.1 (*c* = 2.25, $CHCl_3$), Ref. [9]: +14.7 (*c* = 2.08, $CHCl_3$).

IR (film): $\tilde{\nu}$ (cm^{-1}) = 3660, 3450, 2985, 1765.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 4.38 (dt, *J* = 4.3, 3.5 Hz, 1H, 2-H), 4.13 (q, *J* = 7.1 Hz, 2H, OCH_2), 3.14 (s_{br}, 1H, OH), 2.62 (ddd, *J* = 9.9, 8.8, 4.4 Hz, 1H, 1-H), 2.00–1.80 (m, 3H, CH_2), 1.75–1.69 (m, 2H, CH_2), 1.63–1.54 (m, 1H, CH_2), 1.22 (t, *J* = 7.1 Hz, 3H, CH_3).

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 174.5, 73.5, 60.3, 49.4, 33.8, 26.0, 21.8, 14.0.

1.4.1.3	**	**(+)-Ethyl (1*R*,2*S*)-2-hydroxy-1-methylcyclopentane-1-carboxylate** [5]



A solution of LDA is prepared by adding *n*-butyllithium (375 ml, 0.60 mol, 1.6 M in *n*-hexane) to *N*,*N*-diisopropylamine (60.7 g, 0.60 mol) in anhydrous THF (225 ml) at −78 °C, and then the mixture is kept at 0 °C for 1 h. A solution of the carboxylate **1.4.1.2** (40.1 g, 0.25 mol) in anhydrous THF (60 ml) is then added in one portion to this LDA solution at −50 °C. The temperature rises to −10 °C, and stirring is continued for 0.5 h at this temperature. Iodomethane (49.7 g, 0.35 mol; Caution: carcinogenic!) in DMPU (125 ml) is added, whereupon the temperature rises to 40 °C. Stirring is continued for 20 h at room temperature.

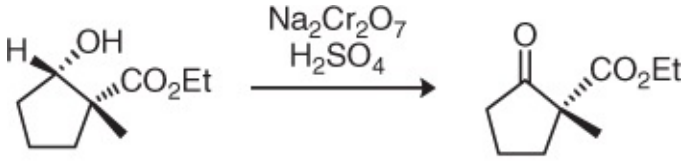
The mixture is then poured into saturated aqueous NH_4Cl solution (1000 ml) and extracted with Et_2O (4 × 200 ml). The combined organic layers are washed with brine, dried over $MgSO_4$, and filtered, and the solvent is removed *in vacuo*. The crude product is purified by distillation; 36.1 g (84%), colorless oil, bp_{10} 99–100 °C; $[\alpha]^{20}_D$ = +28.4 (*c* = 1.61, $CHCl_3$).

IR (film): $\tilde{\nu}$ (cm^{-1}) = 3455 (OH), 1730, 1720, 1705.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 4.09 (q, *J* = 7.3 Hz, 2H, OCH_2), 3.90 (dd, *J* = 5.6, 3.3 Hz, 1H, 2-H), 3.09 (s_{br}, 1H, OH), 2.19–2.09 (m, 1H, CH_2), 1.96–1.70 (m, 2H, CH_2), 1.66–1.43 (m, 3H, CH_2), 1.19 (t, *J* = 7.3 Hz, 3H, $CH_2C\underline{H}_3$), 1.09 (s, 3H, 1-CH_3).

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 177.0 (C=O), 79.8 (C-2), 60.4 ($O\text{-}CH_2$), 53.9 (C-1), 33.0 (CH_2), 31.8 (CH_2), 22.2 (CH_2), 20.3 (CH_2), 17.1 (CH_3), 14.0 (CH_3).

1.4.1.4	*	**(−)-Ethyl (1*R*)-1-methyl-2-oxocyclopentane-1-carboxylate** [5]



172.2 170.2

A chromic acid solution prepared from $Na_2Cr_2O_7{\cdot}2H_2O$ (89.4 g, 0.30 mol) and concentrated H_2SO_4 (75 g) in H_2O (200 ml) is added dropwise to a solution of (+)-(1*R*,2*S*)-**1.4.1.3** (34.4 g, 0.20 mol) in Et_2O (200 ml) at 0–5 °C, and stirring is continued for 20 h at room temperature (note).

H_2O (220 ml) is then added, and the mixture is extracted with Et_2O (4 × 200 ml). The combined organic layers are washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and filtered, and the solvent is removed *in vacuo*. The crude product is purified by distillation; 23.5 g (69%), colorless oil, bp_{10} 96 °C; $[\alpha]^{20}_D$ = −13.3 (*c* = 1.09, $CHCl_3$).

IR (film): $\tilde{\nu}$ (cm^{-1}) = 1750, 1735.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 4.10 (q, *J* = 7.1 Hz, 2H, OCH_2), 2.50–2.20 (m, 3H, CH_2), 2.07–1.76 (m, 3H, CH_2), 1.25 (s, 3H, 1-CH_3), 1.19 (t, *J* = 7.1 Hz, 3H, $CH_2C\underline{H}_3$).

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 215.8 (C-2), 172.3 (CO_2Et), 61.2, 55.8, 37.6 (3 × CH_2), 36.1 (CH_2), 19.5 (CH_2), 19.3 (CH_3), 14.0 (CH_3).

Note: The alcohol can be also oxidized with Dess–Martin-periodinane

(DMP) following the procedure described in **2.3.2.4**.

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7. (a) Frater, G. (1979) *Helv. Chim. Acta*, **62**, 2825–2828;(b) Seebach, D. and Wasmuth, D. (1980) *Helv. Chim. Acta*, **63**, 197–200.

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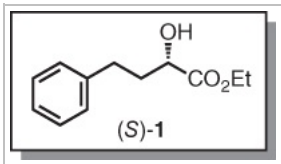
1.4.2 Ethyl (*S*)- and (*R*)-2-hydroxy-4-phenylbutanoate

	***Topics:***	• Ex-chiral pool synthesis of both enantiomers of an α-hydroxy-alkanoic ester

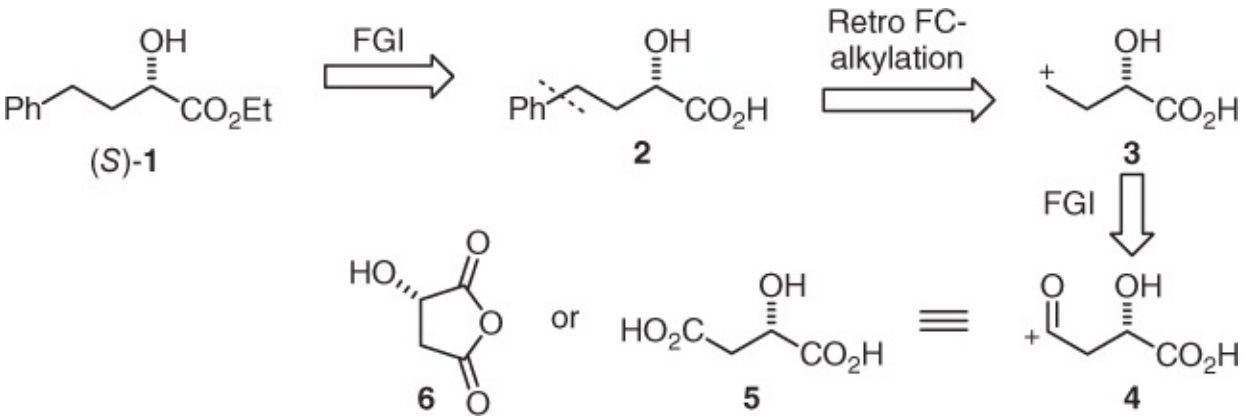
		• Friedel–Crafts acylation of an arene (succinoylation) • Catalytic reduction Ph–C=O → Ph–CH_2 • Mesylation of an OH function • Inversion of configuration of a secondary alcohol

(a) General

Syntheses of enantiopure compounds can be performed following two principal strategies:

1. The construction of the target molecule is conducted in a stereoselective manner with respect to the required operations, either in an enantioselective way using chiral catalysts or in a diastereoselective way using chiral auxiliaries, which are subsequently removed (*asymmetric synthesis*) [1].
2. The stereogenic elements required, for example, one (or several) stereogenic center(s), are introduced by using natural products or other readily available enantiopure compounds as chiral starting materials, which are transformed to the target molecule by stereocontrolled reactions (*ex-chiral pool synthesis*, *ECP synthesis*) [2].

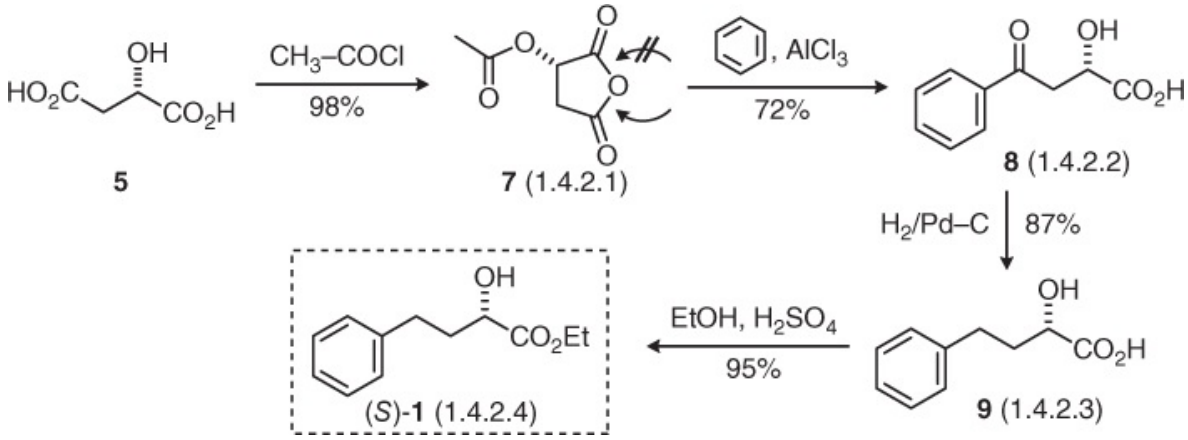
ECP syntheses have been performed using a multitude of stereodefined natural products, for example, hydroxy-and amino acids, terpenoids, and carbohydrates. For an appropriate choice of a suitable candidate from the chiral pool, the functionalities as well as the number of stereogenic elements and their absolute configuration in the natural product and in the target molecule should correspond. This is demonstrated by the synthesis [3] of (*S*)-**1** containing one stereogenic center.



Functional group interconversion (FGI) and arene bond disconnection at the benzylic carbon (**1** → **2**) leads to a C_4-synthon **3**, which is represented by the acylium ion **4** derived from (*S*)-malic acid (**5**). This chiral (*S*)-configured hydroxyC_4-dicarboxylic acid is a readily available natural product (i.e., from the "chiral pool") that contains the complete carbon side chain of the target molecule together with the "correct" terminal functionalization and stereochemistry. Therefore, (*S*)-malic acid (**5**), or preferably its anhydride **6**, are excellent substrates for an ECP synthesis of (*S*)-**1** [4].[5]

(b) Synthesis of 1

1. Reaction of (*S*)-malic acid (**5**) with acetyl chloride gives *O*-acetyl malic anhydride (**7**) by acetylation of the hydroxy group in **5** and elimination of H_2O. Chemoselective Friedel–Crafts acylation (succinoylation) of benzene with the unsymmetrical anhydride **7** in the presence of $AlCl_3$ at the more sterically accessible C=O group affords (*S*)-2-hydroxy-4-oxo-4-phenylbutanoic acid (**8**) in good yield [5]. The acetate in **7** is also cleaved in this process to give a free hydroxy group.

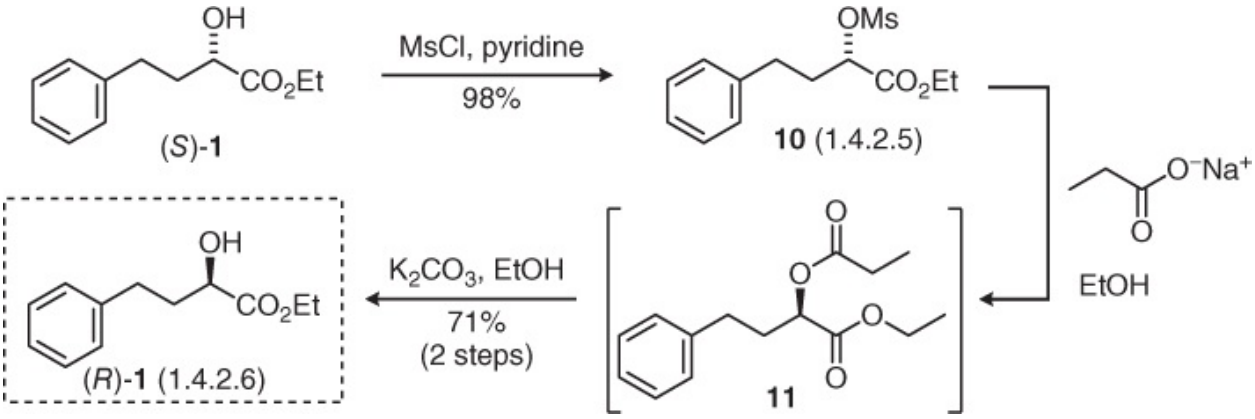


On hydrogenation of the α-oxo acid **8**, the benzylic carbonyl group is readily reduced to a CH_2 unit to yield the α-hydroxy acid **9** in almost quantitative yield and 99% ee. Esterification of the acid **9** according to the Fischer method (EtOH/H_2SO_4) yields the ethyl ester (*S*)-**1** in practically enantiopure form (ee = 99%).

2. The simplest way to obtain (*R*)-**1** would be direct inversion of the 2-OH group in the (*S*)-2-hydroxy ester prepared in (1). However, the Mitsunobu reaction (cf. Section 3.4.4) as the method of choice gives unsatisfactory results. Thus, even under modified conditions with $EtO_2C–N=N–$

$CO_2Et/Ph_3P/ClCH_2CO_2H$, followed by hydrolysis with K_2CO_3/H_2O, the acid *ent*-**9** is obtained only in moderate yield [6].

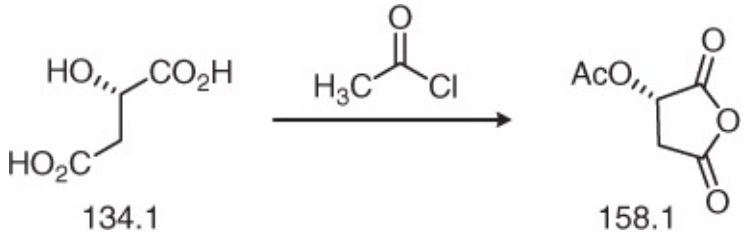
Therefore, the OH group inversion of the stereogenic center in (*S*)-**1** is performed by converting the hydroxy group into a good leaving group by mesylation with CH_3SO_2Cl in pyridine. The mesylate **10**, which is obtained quantitatively, is subjected to an S_N2 displacement (Walden inversion) with sodium propionate in ethanol. The diester **11** is selectively cleaved by alcoholysis with K_2CO_3 in EtOH (due to equilibrium formation of ethanolate) to give the enantiomeric ethyl ester (*R*)-**1** in almost enantiopure form (ee = 97%).



Thus, the target molecule (*S*)-**1** is obtained in a four-step sequence from (*S*)-malic acid in an overall yield of 63%, and the target molecule (*R*)-**1** is obtained from (*S*)-**1** in a three-step sequence in an overall yield of 83% (or from **5** in a seven-step sequence in an overall yield of 52%).

(c) Experimental Procedures for the Synthesis of 1 (both enantiomers)

1.4.2.1	*	**(*S*)-α-Acetoxybutanedioic anhydride** [7]



A solution of (*S*)-malic acid (10.0 g, 75.0 mmol) in acetyl chloride (350 ml) is heated to reflux with stirring for 5 h.

The solvent is then removed under reduced pressure and co-evaporated with

toluene (2 × 30 ml) to yield (*S*)-α-acetoxybutanedioic anhydride as a light-yellow solid; 11.6 g (98%); mp 50–52 °C; $[\alpha]^{20}_{D}$ = −23.1 (*c* = 5.0, $CHCl_3$); TLC (SiO_2, $CHCl_3$/MeOH/H_2O/AcOH = 50 : 50 : 3 : 0.3): R_f = 0.88.

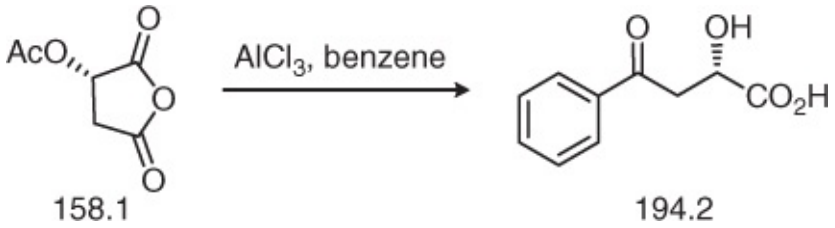
UV (MeOH): λ_{max} (nm) = 209.

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3012, 2962, 1806, 1743, 1405, 1375, 1293, 1216, 1099, 1032, 966, 917, 722, 663, 572.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 5.51 (dd, *J* = 9.6, 6.3 Hz, 1H, CH), 3.36 (dd, *J* = 19.0, 9.4 Hz, 1H, CH_2), 3.01 (dd, *J* = 19.0, 6.3 Hz, 1H, CH_2), 2.18 (s, 3H, CH_3).

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 170.5, 169.9, 169.5, 137.1, 68.4, 37.7.

1.4.2.2 * (*S*)-2-Hydroxy-4-oxo-4-phenylbutanoic acid [7]



Anhydrous $AlCl_3$ (30.0 g, 225 mmol) is added in one portion to a solution of (*S*)-anhydride **1.4.2.1** (9.50 g, 60.1 mmol) in anhydrous benzene (100 ml; Caution: carcinogenic!) at 0 °C. The mixture is heated under reflux with vigorous stirring for 4 h.

It is then poured onto a mixture of crushed ice (100 g) and acidified with aqueous HCl (1 N, ∼100 ml) to give a solution of pH ∼ 1. The mixture is stirred for 2 h and extracted with EtOAc (3 × 100 ml). The combined organic phases are washed with brine, dried over Na_2SO_4, and filtered, and the solvent is removed *in vacuo*. The crude product is crystallized from EtOAc by the addition of petroleum ether to yield the (*S*)-2-hydroxy acid as a colorless powder; 8.4 g (72%); mp 136–138 °C; $[\alpha]^{20}_{D}$ = −8.75 (*c* = 4.0, EtOH); TLC (SiO_2; $CHCl_3$/MeOH/H_2O/AcOH = 70 : 30 : 3 : 0.3): R_f = 0.58.

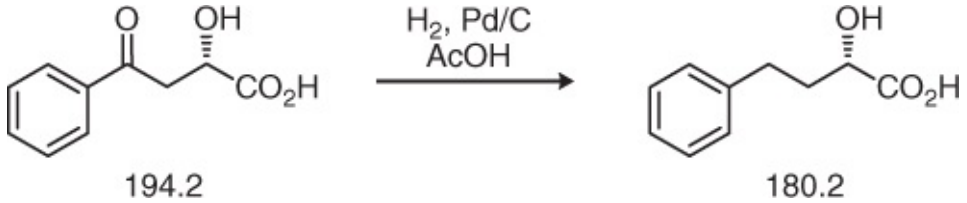
UV (CH_3OH): λ_{max} (nm) = 278, 241, 201.

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3476, 3083, 3061, 2928, 1734, 1677, 1595, 1451, 1364, 1222, 1194, 1105, 811, 761, 689, 580.

^{1}H NMR (300 MHz, [D_6]DMSO): δ (ppm) = 12.0 (s_{br}, 1H, CO_2H), 7.95 (d, *J* = 7.2 Hz, 2H, Ar–H), 7.64 (dd, *J* = 7.5, 7.2 Hz, 1H, Ar–H), 7.53 (t, *J* = 7.5 Hz, 2H, Ar–H), 5.50 (s_{br}, 1H, OH), 4.50 (t, *J* = 6.0 Hz, 1H, CH), 3.32 (d, *J* = 6.0 Hz, 2H, CH_2).

^{13}C NMR (76 MHz, [D_6]DMSO): δ (ppm) = 197.4, 174.8, 136.7, 128.5, 127.9, 66.6, 42.6.

1.4.2.3 ** (*S*)-2-Hydroxy-4-phenylbutanoic acid [3]



A solution of the hydroxy acid **1.4.2.2** (5.4 g, 0.028 mol) in AcOH (80 ml) is hydrogenated (1 bar) over 10% palladium on carbon (0.7 g) at room temperature for ∼2 days.

After complete conversion, indicated by TLC, the solution is filtered and the solvent is removed *in vacuo*. The crude product is recrystallized from toluene to give (*S*)-2-hydroxy-4-phenylbutanoic acid as a colorless powder; 4.40 g (87%); mp 65–67 °C; $[\alpha]^{20}_D$ = +13.4 (*c* = 2.5, EtOH); TLC (SiO_2; $CHCl_3$/MeOH/H_2O/AcOH = 70 : 30 : 3 : 0.3): R_f = 0.65.

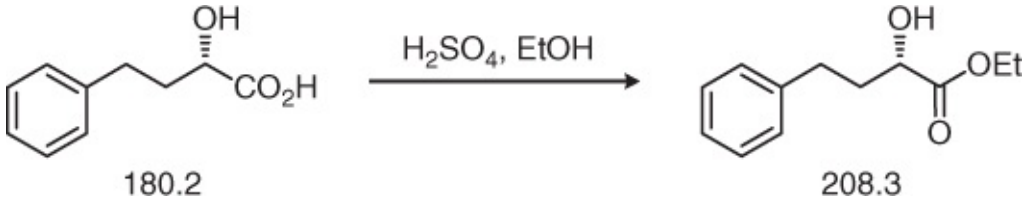
UV (CH_3OH): λ_{max} (nm) = 267, 258, 242, 207.

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3461, 3027, 2957, 2926, 2861, 2589, 1733, 1497, 1454, 1290, 1270, 1242, 1175, 1097, 1077, 866, 767, 742, 696.

^{1}H NMR (300 MHz, [D_6]DMSO): δ (ppm) = 7.27 (m, 2H, Ar–H), 7.17 (m, 3H, Ar–H), 3.93 (dd, *J* = 8.1, 4.5 Hz, 1H, CH), 2.67 (t, *J* = 7.8 Hz, 2H, CH_2), 1.86–1.99 (m, 1H, CH_2), 1.74–1.85 (m, 1H, CH_2).

^{13}C NMR (76 MHz, [D_6]DMSO): δ (ppm) = 175.5, 141.5, 128.3 (2 Ar–C), 126.0, 69.0, 35.7, 30.6.

1.4.2.4	*	**Ethyl (*S*)-2-hydroxy-4-phenylbutanoate** [3]



180.2 208.3

Concentrated H_2SO_4 (2 ml) is added to a solution of the hydroxy acid **1.4.2.3** (3.06 g, 0.017 mol) in anhydrous EtOH (200 ml). The mixture is heated under reflux with stirring for 2 h (TLC control).

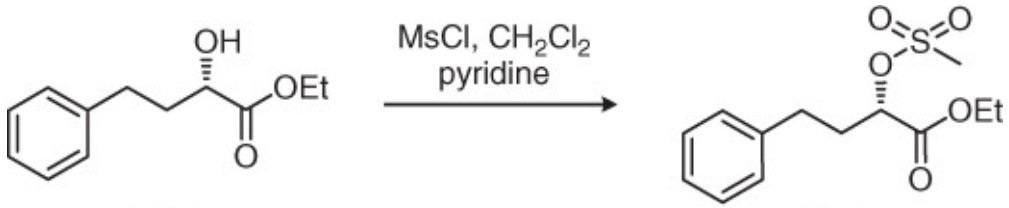
The solvent is removed *in vacuo*, and a mixture of H_2O (50 ml) and EtOAc (200 ml) is added. The organic phase is separated, washed with saturated aqueous $NaHCO_3$ (80 ml) and brine (90 ml), dried over Na_2SO_4, and filtered. The solvent is removed *in vacuo* to provide the ester as a light-yellow oil; 3.36 g (95%); $[\alpha]_D^{20}$ = +19.8 (*c* = 2.5, $CHCl_3$); TLC (SiO_2; $CHCl_3$, 0.1% AcOH): R_f = 0.67.

UV (CH_3OH): λ_{max} (nm) = 267, 247, 205.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.33–7.15 (m, 5H, Ar–H), 4.23–4.16 (m, 2H, C<u>H</u>$_2$-CH_3, 1H, CH), 2.94 (s_{br}, 1H, OH), 2.84–2.69 (m, 2H, Ph–C<u>H</u>$_2$–CH_2), 2.17–2.06 (m, 2H, Ph–CH_2–C<u>H</u>$_2$), 2.01–1.88 (m, 2H, Ph–CH_2–C<u>H</u>$_2$), 1.27 (t, *J* = 7.1 Hz, 3H, CH_3).

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 175.1, 141.1, 128.5, 128.3, 125.9, 69.6, 61.6, 35.9, 30.9, 14.1.

1.4.2.5	*	**Ethyl (*S*)-2-methanesulfonyloxy-4-phenylbutanoate** [3]



208.3 286.3

Methanesulfonyl chloride (3 ml) is added dropwise to a solution of the hydroxy ester **1.4.2.4** (3.13 g, 0.015 mol) in anhydrous CH_2Cl_2 (10 ml) and anhydrous pyridine (10 ml) at 0 °C. The resulting mixture is stirred at room temperature overnight.

The reaction mixture is then diluted with EtOAc (200 ml), the resulting solution is washed with ice-cold H_2O (3 × 200 ml), ice-cold 2 M aqueous HCl (200 ml), saturated aqueous $NaHCO_3$ (200 ml), and brine (200 ml), then dried over Na_2SO_4, and filtered. The solvent is removed *in vacuo* to give the mesylated hydroxy ester as a light-yellow oil; 4.21 g (98%), TLC (SiO_2; $CHCl_3$/MeOH/H_2O/AcOH = 50 : 50 : 3 : 0.3): R_f = 0.88.

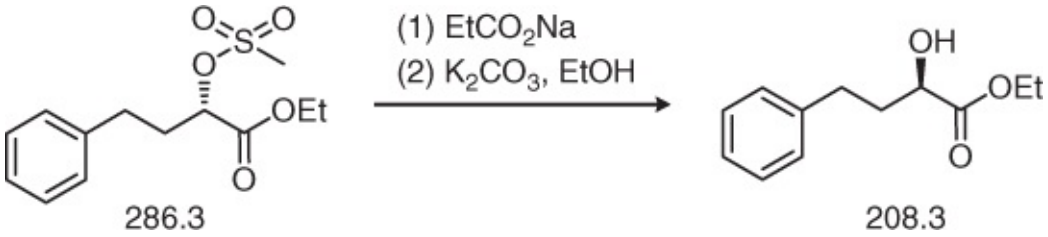
UV (CH_3OH): λ_{max} (nm) = 267, 242, 202.

IR (film): $\tilde{\nu}$ (cm^{-1}) = 3062, 3029, 2983, 2939, 2869, 1751, 1497, 1455, 1362, 1300, 1252, 1211, 1174, 1039, 964, 864, 844, 820, 747, 701.

^{1}H NMR (300 MHz, [D_6]DMSO): δ (ppm) = 7.30 (m, 2H, Ar–H), 7.18–7.24 (m, 3H, Ar–H), 5.08 (dd, *J* = 7.5, 5.1 Hz, 1H, CH), 4.17 (q, *J* = 7.2 Hz, 2H, $C\underline{H}_2CH_3$), 3.27 (s, 3H, SCH_3), 2.71 (t, *J* = 7.5 Hz, 2H, CH_2), 2.07–2.17 (m, 2H, CH_2), 1.21 (t, *J* = 7.2 Hz, 3H, CH_3).

^{13}C NMR (76 MHz, [D_6]DMSO): δ (ppm) = 168.5, 140.1, 128.3, 128.1, 126.1, 76.8, 61.34, 37.9, 33.2, 30.0, 13.8.

1.4.2.6	**	**Ethyl (*R*)-2-hydroxy-4-phenylbutanoate (*ent*-1)** [3]



Sodium propionate (4.57 g, 0.016 mol) is added to a solution of the mesylated hydroxy ester **1.4.2.5** (3.92 g, 0.013 mol) in EtOH (130 ml). The resulting mixture is heated under reflux with stirring for 48 h.

The reaction mixture is then cooled to room temperature and filtered; the filtrate is concentrated under reduced pressure. The residue is dissolved in EtOAc (100

ml), and the resulting solution is washed twice with brine, dried over anhydrous Na_2SO_4, and filtered, and the solvent is removed *in vacuo*. The residue (crude diester **11**) is dissolved in EtOH (250 ml), K_2CO_3 (5.88 g, 0.043 mol) is added, and the resulting mixture is stirred at room temperature overnight.

It is then filtered, and the filtrate is neutralized with aqueous HCl (6 M) and concentrated *in vacuo*. The product is dissolved in EtOAc (150 ml) and washed with H_2O (50 ml), and brine (50 mL), dried over anhydrous Na_2SO_4, and filtered. The solvent is removed *in vacuo* to give the alcohol as an colorless oil; 1.92 g (71%), TLC (SiO_2; $CHCl_3$, 0.1% AcOH): R_f = 0.67, $[\alpha]^{20}_D$ = −18.8 (*c* = 2.4 in $CHCl_3$).

UV (CH_3OH): λ_{max} (nm) = 267, 258, 242, 205.

IR (film): $\tilde{\nu}$ (cm^{-1}) = 3429, 3063, 3028, 2980, 2961, 2930, 2865, 1732, 1497, 1454, 1370, 1299, 1247, 1178, 1077, 864, 747, 701.

^{1}H NMR (300 MHz, [D_6]DMSO): δ (ppm) = 7.28 (m, 2H, Ar–H), 7.14–7.20 (m, 3H, Ar–H), 5.41 (s_{br}, 1H, OH), 4.08 (q, *J* = 7.4 Hz, 2H, $C\underline{H}_2CH_3$), 4.00 (m_{br}, 1H, CH), 2.66 (t, *J* = 8.1 Hz, 2H, CH_2), 1.77–1.86 (m, 1H, CH_2), 1.18 (t, *J* = 7.4 Hz, 3H, CH_3).

^{13}C NMR (76 MHz, [D_6]DMSO): δ (ppm) = 174.0, 141.5, 128.3, 128.2, 126.8, 68.9, 59.7, 35.7, 30.6, 13.7.

References

1. For monographs, see: (a) Procter, G. (1999) *Asymmetric Synthesis*, Oxford University Press, Oxford;(b) Atkinson, R.S. (1997) *Stereoselective Synthesis*, John Wiley & Sons, Inc., New York;(c) Christmann, M. and Bräse, S. (eds) (2007) *Asymmetric Synthesis–The Essentials*, Wiley-VCH Verlag GmbH, Weinheim.

2. (a) For a monograph, see: Hanessian, S. (1983) *The Chiron Approach*, Pergamon Press, New York;(b) for chiral pool reagents (“chirons”), see: Fuhrhop, J.-H. and Li, G. (2003) *Organic Synthesis*, 3rd edn, Wiley-VCH Verlag GmbH, Weinheim;(c) for a compilation of commercially available enantiopure products, see: Breuer, M., Ditrich, K., Habicher, T., Hauer, B., Keßeler, M.,

Stürmer, R., and Zelinsky, T. (2004) *Angew. Chem.*, **116**, 806–843; *Angew. Chem. Int. Ed.*, (2004), **43**, 788–824.

3. Lin, W.-Q., He, Z., Jing, Y., Cui, X., Liu, H., and Mi, A.-Q. (2001) *Tetrahedron: Asymmetry*, **12**, 1583–1588.

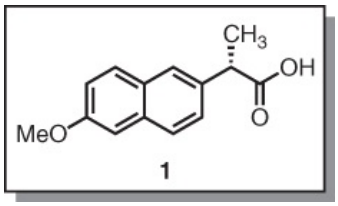
4. Conventional retrosynthesis of the α-hydroxy acid **2** leads to hydrocinnammic aldehyde by retro-cyanohydrin transformation. For the problem of asymmetric cyanohydrin synthesis, see: Brunel, J.-M. and Holmes, I.P. (2004) *Angew. Chem.*, **116**, 2807–2810; *Angew. Chem. Int. Ed.*, (2004), **43**, 2752–2778.

5. Compound **9** has also been prepared by chemo and enantioselective enzymatic reduction of 4-phenyl-2,4-dioxobutanoic acid: Casy, G. (1992) *Tetrahedron Lett.*, **33**, 8159–8162.

6. Mitsunobu, O. (1981) *Synthesis*, 1–28.

7. Henrot, S., Larcheveque, M., and Petit, Y. (1986) *Synth. Commun.*, **16**, 183–190.

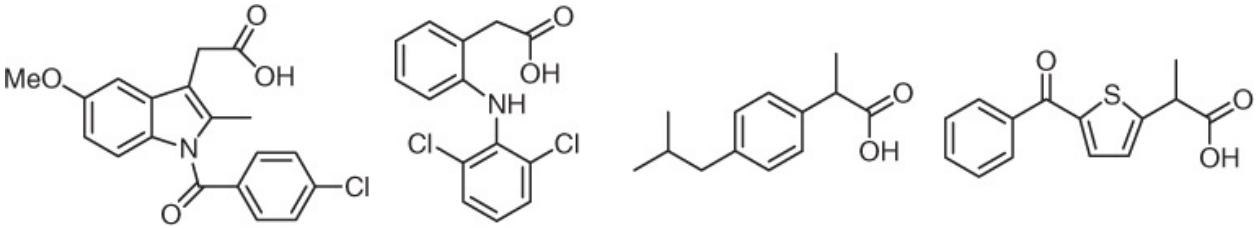
1.4.3 Naproxen

 1	***Topics:***	• Enantioselective synthesis of a drug • Friedel–Crafts acylation • Chemoselective α-halogenation of an alkyl aryl ketone • Acetalization using an orthoester • Lewis acid-induced rearrangement of an α-halogeno acetal • Kinetic resolution by enantioselective enzymatic ester hydrolysis • Resolution by formation of diastereomeric salts

(a) General

(a) General

Naproxen (**1**, (*S*)-(+)-2-(6′-methoxy-2-naphthyl)propionic acid) is a prominent member of the drugs derived from aryl-and hetaryl-substituted acetic and propionic acids, which exhibit anti-inflammatory, analgetic, and antirheumatic properties [1]. Other important examples are indomethacin (**2**), diclofenac (**3**), ibuprofen (**4**), and tiaprofenic acid (**5**).



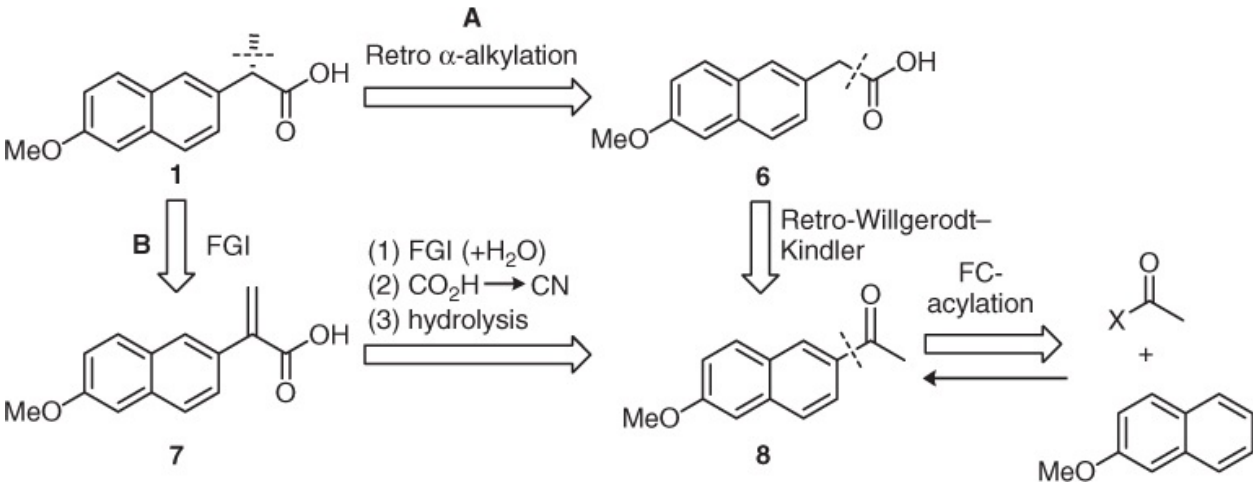
2 **3** **4** **5**

Derivatives of acetic acid — Derivatives of α-substituted propionic acid

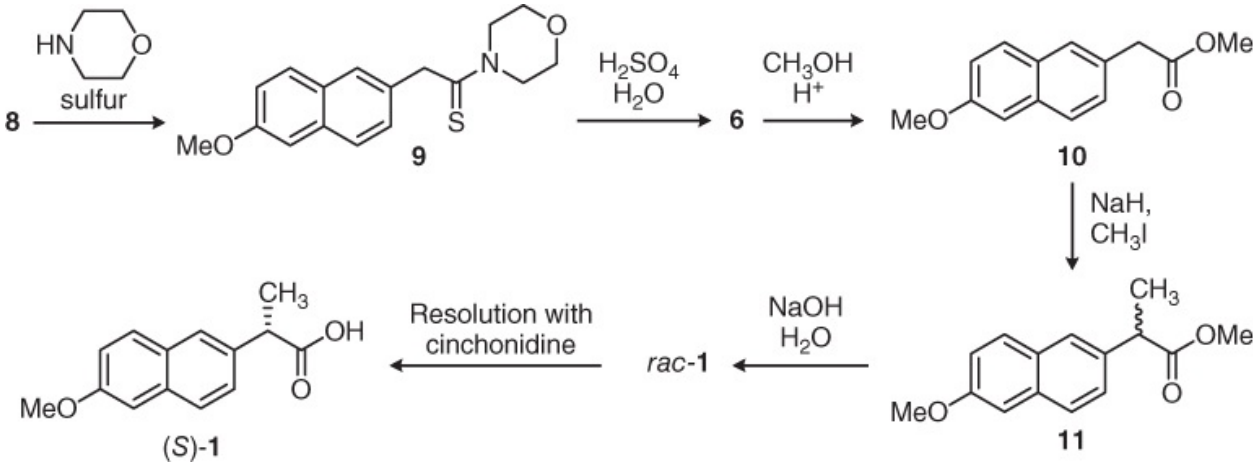
These nonsteroidal anti-inflammatory compounds act as effective inhibitors of prostaglandin biosynthesis [2].

The α-aryl and α-hetaryl propionic acids (e.g., **4** and **5**) are used therapeutically as racemic mixtures. An exception is naproxen, which is marketed and applied as the (+)-(*S*)-enantiomer.

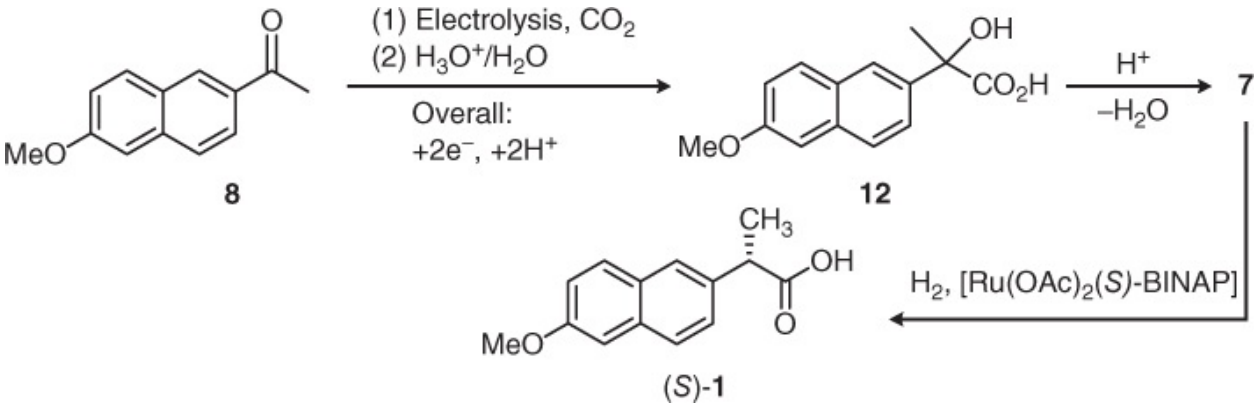
The retrosynthesis of **1** according to pathway **A** leads to 2-methoxynaphthalene via **6** and **8**. Similarly, according to pathway **B**, **1** can be traced back to **7**, which again would be accessible from 2-methoxynaphthalene via **8**. Selective formation of the stereogenic center in **1** could be achieved either by a facially selective alkylation of **6** using the Evans procedure or by enantioselective hydrogenation of **7**. Compounds **6** and **7** should be easily accessible from **8** by classical routes, such as Willgerodt–Kindler or Tl(III)-induced redox transformations (→**6**) or a cyanohydrin reaction/CN → CO_2H hydrolysis/H_2O elimination sequence (→**7**).



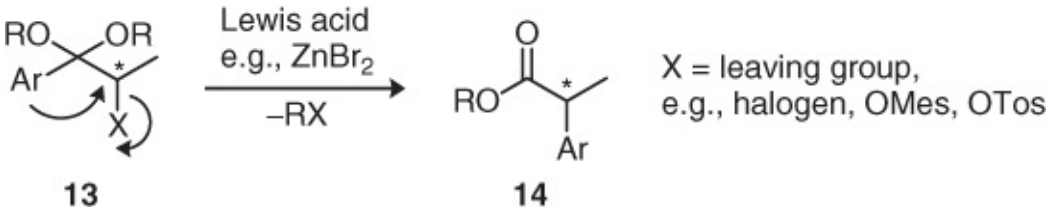
In fact, the first industrial synthesis of naproxen (Syntex) [3] used a Willgerodt–Kindler reaction of 2-acetyl-6-methoxynaphthalene (**8**) to give the morpholide **9**; subsequent hydrolysis led to the arylacetic acid **6**. Its methyl ester **10** was alkylated with CH_3I/NaH (**10** → **11**); saponification of the alkylated ester **11** provided the racemic acid (*rac*-**1**), which was resolved using cinchonidine or other chiral bases to give (*S*)-naproxen (**1**).



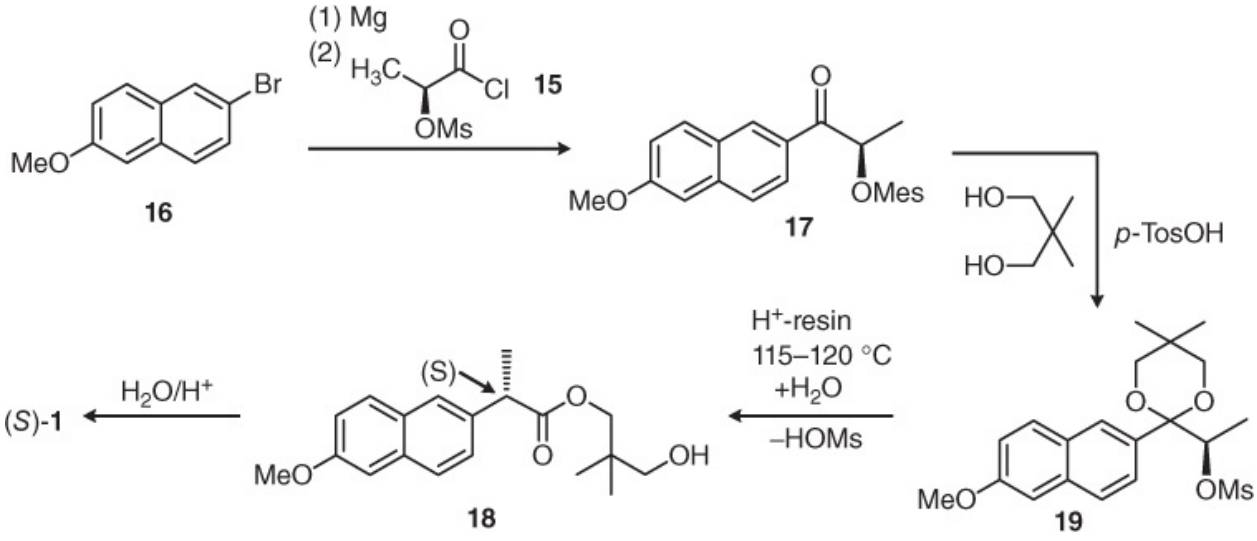
According to the retrosynthetic analysis, (β-naphthyl)acrylic acid **7** is a suitable substrate for the enantioselective formation of **1**, which is readily formed from **7** by homogeneous catalytic hydrogenation in the presence of a chiral Ru complex (Ru(II)-(*S*)-BINAP (2,2′-bis(diphenylphosphino)-1,1′-binaphthalene)) [4]. The acrylic acid **7** may be obtained from 2-acetyl-6-methoxynaphthalene (**8**) via the already mentioned cyanohydrin route or more elegantly by an electrocarboxylation. Thus, $2e^-$ cathodic reduction of the carbonyl group in **8** in the presence of CO_2 gives the hydroxy acid **12**, whose subsequent acid-catalyzed dehydration leads to **7** [5].



In a strategy that differs from the above retroanalytical considerations, the α-arylpropionate side chain in **1** can also be established by Lewis acid-induced 1,2-migration of the aryl moiety in aryl ethyl ketals **13** bearing a leaving group at C-2. The reaction leads to esters **14** [6]:



If the leaving group X in **13** assumes a stereodefined position, the 1,2-aryl shift proceeds with preservation of the stereochemical information. This was accomplished in an ECP synthesis of naproxen (**1**) starting with the acid chloride **15** of (*S*)-*O*-mesyl lactic acid [3]:



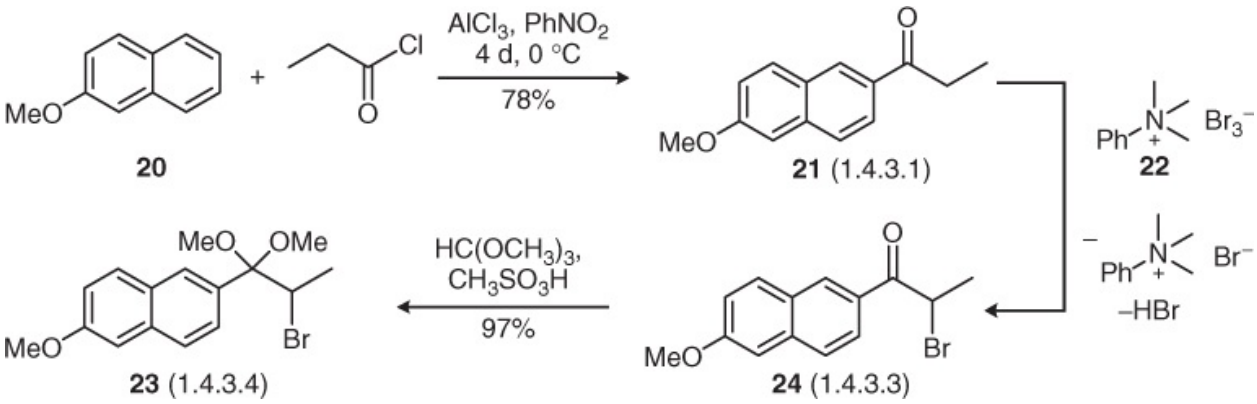
In the first step, the Grignard compound from 2-bromo-6-methoxynaphthalene (**16**) is acylated with the acid chloride **15** to give the naphthyl ketone **17**, the C=O group of which is protected as a 1,3-dioxane with the formation of **19**. On

treatment with an acidic ion-exchange resin, the *O*-mesyl acetal moiety in **19** rearranges to give the ester **18**, acid hydrolysis of which provides (*S*)-naproxen (**1**) in enantiomerically pure form and in 75% overall yield. Remarkably, in the rearrangement step **19** → **18**, migration of the β-naphthyl residue occurs stereoselectively with complete inversion of configuration at the propionate side chain [7].

For reasons of practicability in the laboratory, a synthesis is presented here that is based on the Lewis acid-promoted rearrangement of an α-bromo ketal to a racemic naproxen ester. This racemic ester is transformed to the chiral target molecule (i) by enantioselective enzymatic hydrolysis, and (ii) by saponification to give the racemic acid and its resolution by cinchonidine salt formation.

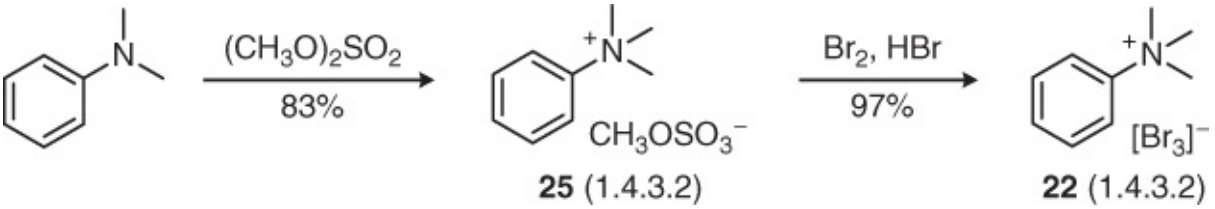
(b) Synthesis of 1

The synthesis starts with Friedel–Crafts acylation of 2-methoxynaphthalene (**20**) with propionyl chloride in the presence of $AlCl_3$. The reaction conditions (nitrobenzene as solvent, 4 days at 0 °C) favor thermodynamic product control in the S_EAr process and direct substitution at the desired β-(2)-position (**20** → **21**) [8]:



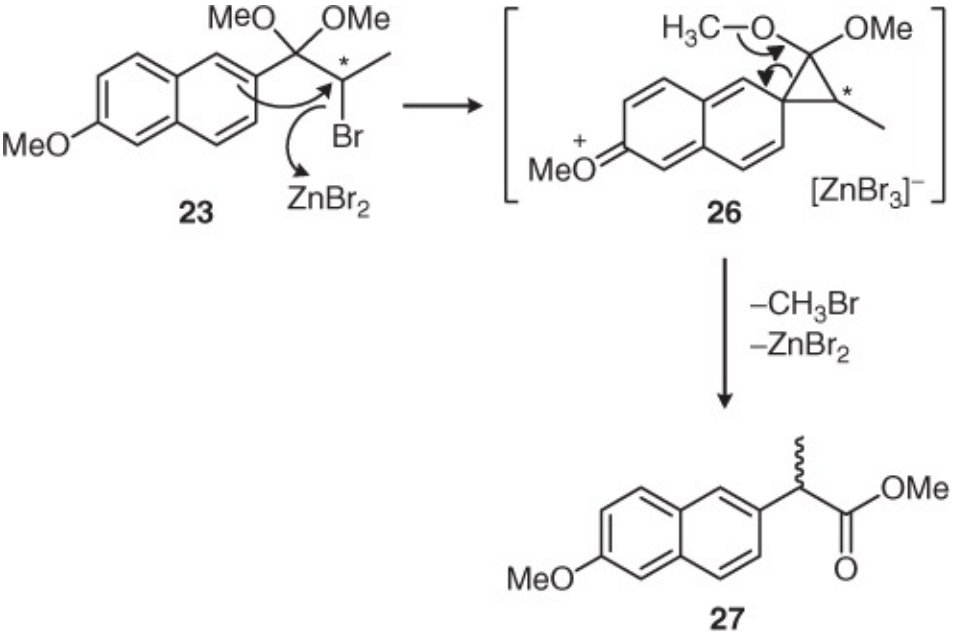
Next, 6-methoxy-2-propionylnaphthalene (**21**) has to be brominated chemoselectively at the aliphatic side chain. Since treatment with elemental bromine would lead to additional bromination at the 5-position of the aromatic nucleus [9], trimethylphenylammonium perbromide (**22**) is used as a specific reagent, which leads exclusively to the α-bromo ketone **24** [10].

The perbromide **22** is prepared in two steps from *N*,*N*-dimethylaniline via the methanesulfate **25** [11]:



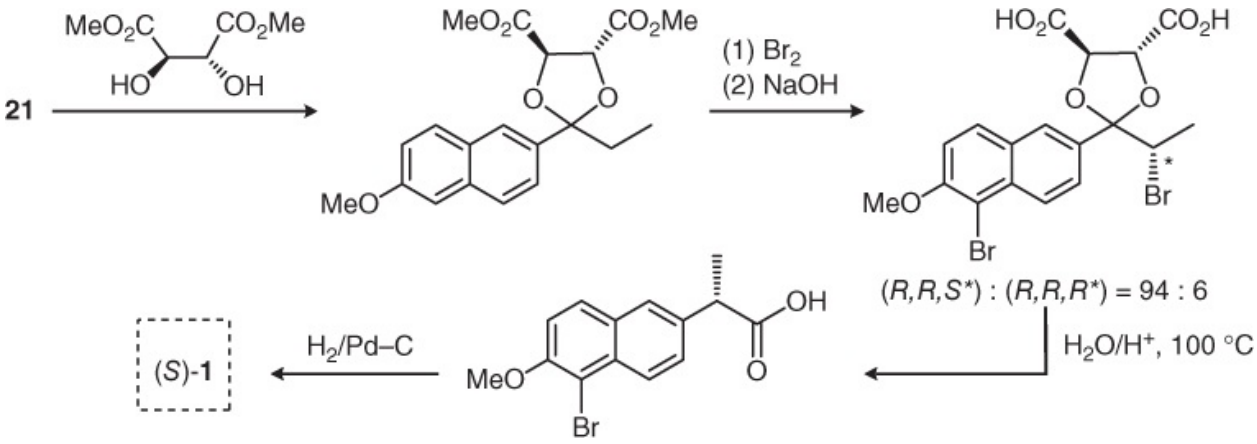
25 (1.4.3.2) **22** (1.4.3.2)

Bromo ketone **24** is transformed to the dimethyl ketal **23** by reaction with trimethyl orthoformate in the presence of CH_3SO_3H. On heating with anhydrous $ZnBr_2$ in toluene, the α-bromo acetal **23** rearranges to the methyl ester **27** of racemic naproxen. For the Lewis acid-induced 1,2-aryl shift, an arenium ion **26** [12] can be postulated as intermediate, which rearomatizes upon dealkylation with a bromide ion to give CH_3Br and the methyl ester **27** [10, 13].

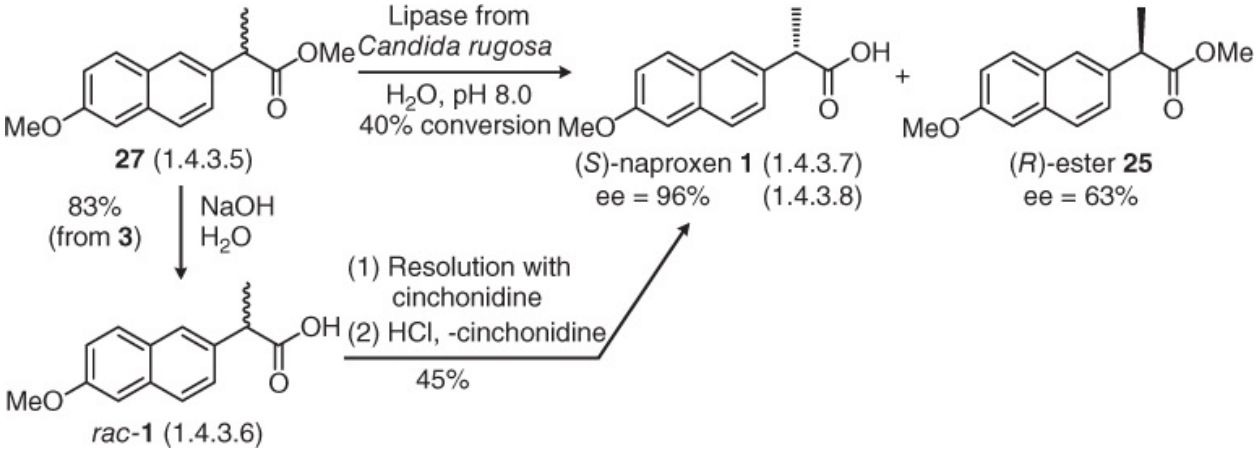


23 **26** **27**

It should be noted that the procedure can be slightly modified by first transforming the ketone **21** into its acetal, which is then brominated using bromine. If one uses a chiral alcohol such as dimethyl tartrate for the acetalization, the subsequent bromination and rearrangement proceed with high induced stereoselectivity [14].



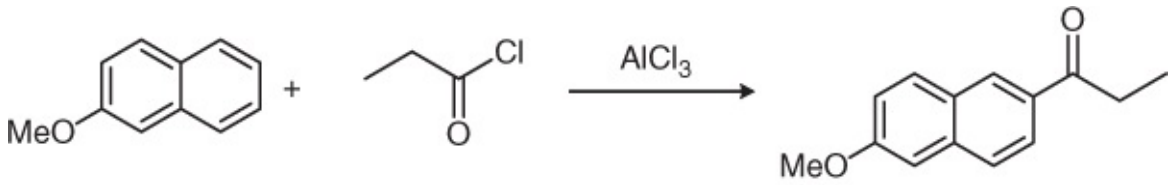
In the final step of the described synthesis of **1**, the racemic methyl ester **27** is subjected to kinetic resolution by enzymatic hydrolytic ester cleavage, using the lipase from *Candida rugosa*. This transformation is conducted up to 40% conversion and gives (*S*)-naproxen (**1**) with 96% ee and the (*R*)-ester with 63% ee [15]:



Alternatively, the racemic methyl ester **27** may be saponified with aqueous NaOH to give racemic naproxen (*rac*-**1**). This is resolved by the formation of diastereomeric salts with the chiral base cinchonidine, which are separated by fractional crystallization. The cinchonidine salt of the (+)-enantiomer is isolated, purified, and cleaved with aqueous HCl to give optically pure (+)-(*S*)-naproxen in 45% yield with $[\alpha]^{20}_{D}$ = +68 (*c* = 0.84, CH_2Cl_2); for the isolation of the (−)-(*R*)-enantiomer, see Ref. [16].

(c) Experimental Procedures for the Synthesis of 1

1.4.3.1	*	**6-Methoxy-2-propionylnaphthalene** [8]



158.2 92.5 214.3

Anhydrous aluminum trichloride (112 g, 0.84 mol) is dissolved in anhydrous nitrobenzene (1300 ml), and the solution is cooled to 0 to −2 °C under an argon atmosphere. With vigorous stirring, a solution of 2-methoxynaphthalene (106 g, 0.67 mol) in anhydrous nitrobenzene (340 ml) is added dropwise over 2 h. After stirring for 1 h at 0 °C, propionyl chloride (71.6 g, 0.77 mol, note) is added at such a rate that the internal temperature is kept at −3 °C. When the addition is complete, the dark reaction mixture is stirred for 96 h at 0 °C.

It is then poured onto a mixture of crushed ice (approximately 2 kg) and concentrated HCl (225 ml). CH_2Cl_2 is added to provide a clean phase separation, and the aqueous phase is extracted with CH_2Cl_2 (500 ml). The CH_2Cl_2 is distilled off from the combined organic phases, and the remaining solution is steam-distilled (to remove the nitrobenzene). The solid residue is dissolved in CH_2Cl_2, the solution is dried over Na_2SO_4 and filtered, and the solvent is removed *in vacuo*. The brownish residue is distilled *in vacuo* ($bp_{0.2}$ 154–156 °C), and the distillation product is recrystallized from MeOH. The acylation product is obtained as colorless needles; 112 g (78%), mp 111–112 °C, TLC (SiO_2; benzene): R_f = 0.55.

IR (film): $\tilde{\nu}$ (cm^{-1}) = 1680, 1625, 1600.

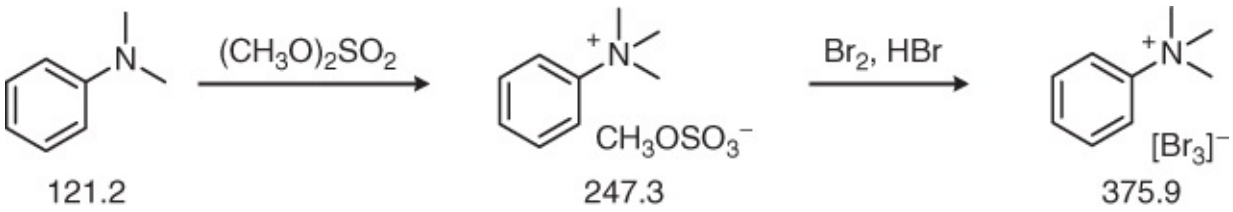
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.38 (d, *J* = 3.0 Hz, 1H, Ar–H), 7.99 (dd, *J* = 9.0, 3.0 Hz, 1H, Ar–H), 7.82 (d, *J* = 9.0 Hz, 1H, Ar–H), 7.74 (d, *J* = 9.0 Hz, 1H, Ar–H), 7.17 (d, *J* = 9.0, 3.0 Hz, 1H, Ar–H), 7.13 (d, *J* = 3.0 Hz, 1H, Ar–H), 3.92 (s, 3H, OCH_3), 3.05 (q, *J* = 8.0 Hz, 2H, $COCH_2$), 1.26 (t, *J* = 8.0 Hz, 3H, CH_3).

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 200.1 (C=O), 159.4, 137.4, 131.3, 129.6, 128.1, 127.3, 124.9, 119.9, 55.6 (OCH_3), 31.9 (CH_2), 8.7 (CH_3).

MS (EI): *m*/*z* = 214.1 $[M]^+$, 185.0 $[M-C_2H_5]^+$, 158.0 $[M-C_3H_5O]^+$.

Note: It is recommended that the reaction is performed under N_2.

1.4.3.2	*	**Trimethylphenylammonium perbromide** [11]



1. Dimethyl sulfate (63.0 g, 0.50 mol, ~48.0 ml; Caution: carcinogenic!) is added dropwise to a vigorously stirred solution of *N*,*N*-dimethylaniline (63.0 ml, 0.50 mol) in benzene (120 ml; Caution: carcinogenic!) at 5 °C. During the addition, the temperature of the reaction mixture rises to approximately 75 °C. After stirring for 1 h, the mixture is cooled to 3 °C; the crystalline salt is collected by suction filtration, washed with benzene, and air-dried (Hood!). Trimethylphenylammonium methanesulfate is obtained as colorless crystals; 103 g (83%), mp 108–110 °C.

   ^{1}H NMR (300 MHz, [D_6]DMSO): δ (ppm) = 7.86 (m, 2H, 2-H, 6-H), 7.59 (m, 3H, 3-H, 4-H, 5-H), 3.82 (s, 9H, $^{+}N(CH_3)_3$), 3.72 (s, 3H, $CH_3OSO_3^{-}$).

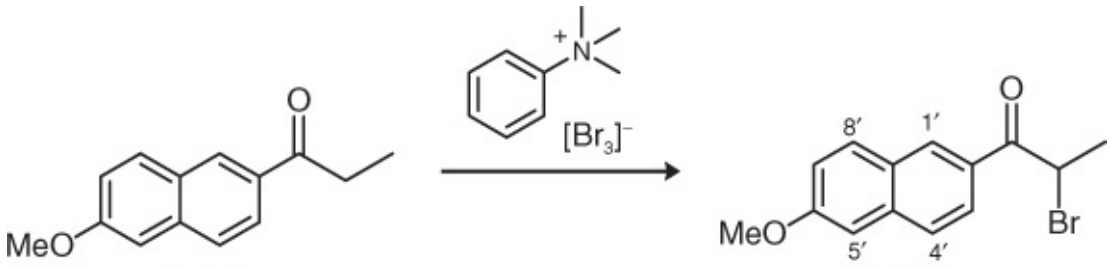
2. The methanesulfate from (1) (80.0 g, 0.32 mol) is dissolved in 24% aqueous HBr (320 ml, 1.41 mol), and bromine (74.9 g, 0.47 mol, ~24.0 ml) is added dropwise with intense stirring over 30 min. The precipitated perbromide is collected by suction filtration and recrystallized from acetic acid; yellow needles, 117 g (97%), mp 113–115 °C.

   IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 1600, 1490, 1460, 960.

   ^{1}H NMR (300 MHz, [D_6]DMSO): δ (ppm) = 7.96 (m, 2H, 2-H, 6-H), 7.61 (m, 3H, 3-H, 4-H, 5-H), 3.61 (s, 9H, $^{+}N(CH_3)_3$).

   ^{13}C NMR (76 MHz, [D_6]DMSO): δ (ppm) = 147.1 (C-1), 129.9 (C-3, C-4, C-5), 120.2 (C-2, C-6) 56.3 (CH_3).

1.4.3.3	*	**2-Bromo-1-(6-methoxy-2-naphthyl)propan-1-one** [9]



The perbromide **1.4.3.2** (75.2 g, 0.20 mol) is added in one portion to a stirred solution of 6-methoxy-2-propionylnaphthalene (**1.4.3.1**) (42.8 g, 0.20 mol) in THF (420 ml). A clear orange-red solution results, from which a colorless salt precipitates (note 1) after some minutes; the supernatant solution becomes colorless. Stirring is continued for 30 min at room temperature.

The reaction mixture is diluted with H_2O (1200 ml) and extracted with petroleum ether (2 × 150 ml), and the combined organic extracts are dried over Na_2SO_4 and filtered. The solvent is removed *in vacuo*, and the oily residue is triturated with EtOH (400 ml). The bromo ketone crystallizes in fine colorless needles (note 2), which is collected by suction filtration, washed with pre-cooled EtOH, and dried *in vacuo*; 56.0 g (96%), mp 78–79 °C, TLC (SiO_2; benzene): R_f = 0.65.

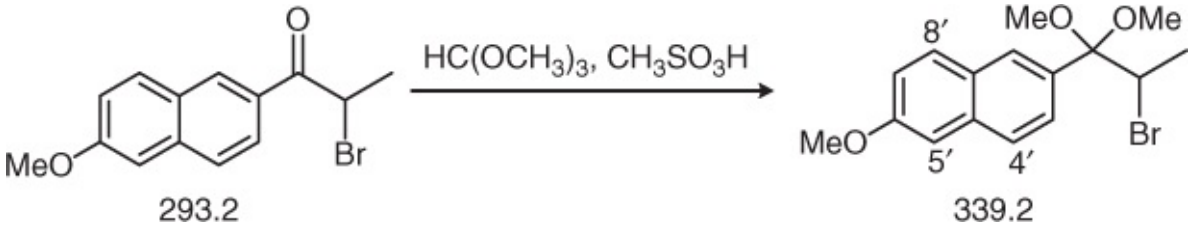
IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 1685, 1620, 1600.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.46 (d, *J* = 1.7 Hz, 1H, 1′-H), 8.01 (dd, *J* = 8.7, 1.9 Hz, 1H, 3′-H), 7.84 (d, *J* = 9.0 Hz, 1H, 8′-H), 7.76 (d, *J* = 8.8 Hz, 1H, 4′-H), 7.19 (dd, *J* = 8.9, 2.5 Hz, 1H, 7′-H), 7.14 (d, *J* = 2.5 Hz, 1H, 5′-H), 5.42 (q, *J* = 6.7 Hz, 1H, 2-H), 3.93 (s, 3H, OCH_3), 1.93 (d, *J* = 6.7 Hz, 3H, 3-H_3).

Notes:

1. Trimethylphenylammonium bromide, mp 210–212 °C.
2. Crystallization is complete after 12 h in a refrigerator.

1.4.3.4	*	**2-Bromo-1-(6-methoxy-2-naphthyl)propan-1-one dimethyl acetal** [10]



293.2 339.2

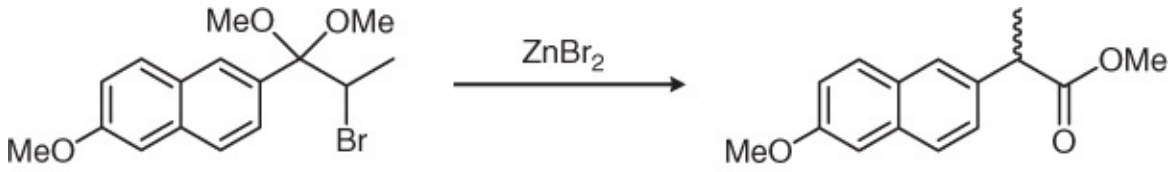
A suspension of the bromo ketone **1.4.3.3** (41.4 g, 0.14 mol), trimethyl orthoformate (43.5 g, 0.41 mol), and methanesulfonic acid (2.72 g) in anhydrous MeOH (150 ml) is heated to 45 °C for 24 h; a clear solution results.

The reaction mixture is then poured into 2% aqueous Na_2CO_3 solution (1000 ml) and is extracted with Et_2O (3 × 250 ml). The combined extracts are dried over Na_2CO_3 and filtered, and the solvent is removed *in vacuo*. The resulting almost colorless oil is dissolved in MeOH (300 ml), and the solution is cooled (refrigerator, 12 h). The crystallized dimethyl acetal is collected by suction filtration, washed with MeOH at −10 °C, and dried *in vacuo*; fine colorless needles, 46.0 g (97%), mp 87–88 °C, TLC (SiO_2; benzene): R_f = 0.75.

IR (KBr): $\tilde{\nu}$ (cm^{-1}) 2990, 2970, 2940, 2830 (CH), 1630, 1610.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.93 (d, *J* = 1.8 Hz, 1H, 1′-H), 7.76 (d, *J* = 9.8 Hz, 1H, 8′-H), 7.69 (d, *J* = 8.7 Hz, 1H, 4′-H), 7.57 (dd, *J* = 8.6, 1.8 Hz, 1H, 3′-H), 7.14 (m, 2H, 5′-H, 7′-H), 4.54 (q, *J* = 6.0 Hz, 1H, 2-H), 3.91, 3.39, 3.23 (3 × s, 9H, 3 × OCH_3), 1.54 (d, *J* = 6.3 Hz, 3H, 3-H_3).

1.4.3.5 * (*R*,*S*)-Methyl 2-(6-methoxy-2-naphthyl)propionate [13]



339.2 244.3

A suspension of the dimethyl acetal **1.4.3.4** (33.9 g, 0.10 mol) and anhydrous zinc bromide (2.25 g, 10.0 mmol) in anhydrous toluene (100 ml) is heated to reflux with stirring under a N_2 atmosphere for 1 h.

After cooling to room temperature, the reaction mixture is poured into H_2O (1000 ml) and extracted with Et_2O (3 × 300 ml). The combined extracts are dried

over Na_2SO_4 and filtered, and the solvent is removed *in vacuo*.

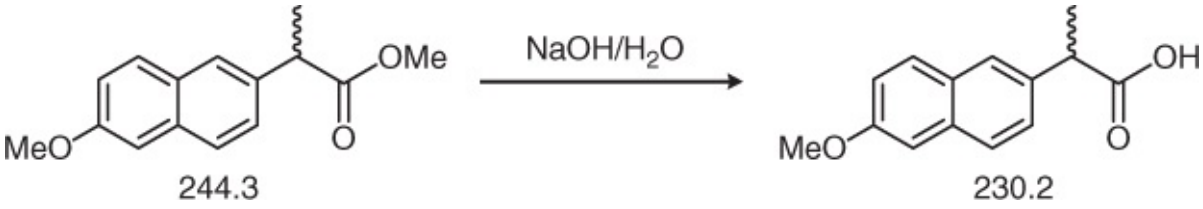
For enzymatic resolution, a pure sample of the racemic methyl ester **1.4.3.5** is obtained by column chromatography (SiO_2; *n*-hexane/EtOAc, 85 : 15), mp 89–90 °C.

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3005, 2974, 2932, 1731, 1602.

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.70 (d, *J* = 8.5 Hz, 2H, 4′-H, 8′-H), 7.66 (d, *J* = 1.6 Hz, 1H, 1′-H), 7.40 (dd, *J* = 8.5, 1.9 Hz, 1H, 3′-H), 7.14 (dd, *J* = 8.8, 2.5 Hz, 1H, Ar–H), 7.11 (d, *J* = 2.2 Hz, 1H, Ar–H), 3.90 (s, 3H, $ArOCH_3$), 3.85 (q, *J* = 7.3 Hz, 1H, 2-H), 3.66 (s, 3H, CO_2CH_3), 1.57 (d, *J* = 7.3 Hz, 3H, 3-H_3).

^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) = 175.1, 157.7, 135.7, 133.7, 129.3, 129.0, 127.2, 126.2, 126.0, 119.0, 105.7, 55.3, 52.0, 45.4, 18.6.

1.4.3.6	*	**(*R*,*S*)-2-(6-Methoxy-2-naphthyl)propionic acid (*rac*-naproxen)** [13]



244.3 230.2

The crude methyl ester **1.4.3.5** is dissolved in MeOH (500 ml), 30% aqueous NaOH (150 ml) is added, and the mixture is heated to reflux for 4 h.

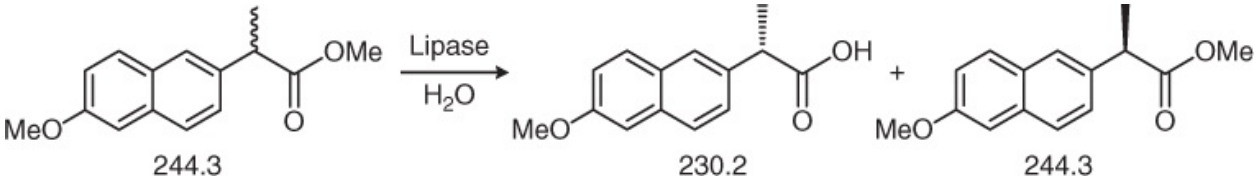
The MeOH is distilled off *in vacuo*, the residue is dissolved in H_2O (approximately 1200 ml), and the alkaline solution is extracted with Et_2O (2 × 400 ml). The organic phase is discarded. The aqueous phase is acidified with concentrated HCl (pH ∼ 1), and the precipitated acid is extracted with Et_2O (2 × 400 ml). The combined extracts are dried over Na_2SO_4 and filtered, and the solvent is removed *in vacuo*. The remaining solid is recrystallized from acetic acid, and a second crop is obtained by (careful) dilution of the mother liquor with H_2O. The racemic acid is obtained as fine colorless needles; 19.0 g (83%), mp 152–153 °C, TLC (SiO_2; Et_2O): R_f = 0.80.

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3200–2800, 1710, 1605.

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 10.6 (s_{br}, 1H, CO_2H), 7.75–7.65 (m, 3H, 1′-H, 4′-H, 8′-H), 7.40 (dd, *J* = 8.5, 1.8 Hz, 1H, 3′-H), 7.13 (d, *J* = 8.8 Hz, 1H, 7′-H), 7.10 (d, *J* = 2.4 Hz, 1H, 5′-H), 3.90 (s, 3H, OCH_3), 3.86 (q, *J* = 7.0 Hz, 1H, 2-H), 1.58 (d, *J* = 7.0 Hz, 3H, 3-H_3).

^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) = 180.5, 157.7, 134.9, 133.8, 129.3, 128.9, 127.2, 126.2, 126.1, 119.0, 105.6, 55.3, 45.2, 18.1.

1.4.3.7	**	**(*S*)-2-(6-Methoxy-2-naphthyl)propionic acid** [(*S*)-**naproxen]**
		(by kinetic enzymatic resolution, [15])



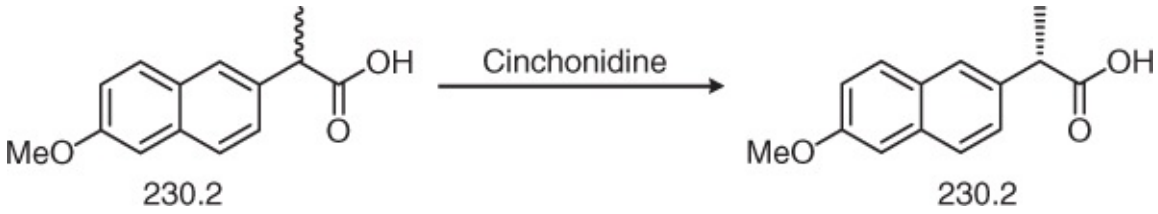
Finely powdered racemic naproxen methyl ester **1.4.3.5** (150 mg, 0.65 mmol), mercaptoethanol (1 drop), and polyvinyl alcohol (5 mg) are added to crude *C. rugosa* lipase (EC 3.1.1.3, Type VII, Sigma L-1754, 50 mg, 600 µg of protein) in a 0.2 M phosphate buffer solution at pH 8.0 (1 ml). The suspension is stirred at 30 °C for 120 h. Both the progress of the conversion and the enantiomeric purity can be monitored simultaneously by HPLC analysis (chiral HPLC Lichro Cart 250-4 (*S*,*S*)-Whelk-01, 5 µm; hexane/isopropanol/acetic acid, 90 : 9.5 : 0.5, 1.2 ml min^{-1}, 254 nm).

The pH of the reaction mixture is adjusted to 2–3 with concentrated HCl, and the mixture is extracted with Et_2O (5 × 10 ml). The combined ethereal extracts are extracted with saturated aqueous Na_2CO_3 solution (5 × 10 ml), and the combined aqueous layers are re-extracted with Et_2O (3 × 10 ml). The combined ethereal extracts are washed with brine, dried over $MgSO_4$, and filtered, and the solvent is removed *in vacuo* to give the unreacted naproxen methyl ester as a white solid.

The Na_2CO_3 extracts are acidified with aqueous HCl (6 N), saturated with NaCl, and extracted with Et_2O (5 × 10 ml). The ethereal phase is washed with brine, dried over $MgSO_4$, and filtered, and the solvent is removed *in vacuo* to give (*S*)-

naproxen as a white solid; 53 mg (35% isolated yield); $[\alpha]^{20}_{D}$ = +65 (*c* = 1.00, $CHCl_3$); ee = 96% [15].

1.4.3.8	**	**(*S*)-2-(6-Methoxy-2-naphthyl)propionic acid** [(*S*)-**naproxen]**
		(by resolution with cinchonidine, [16])



Racemic naproxen **1.4.3.6** (11.5 g, 50.0 mmol) is dissolved in a hot mixture of MeOH (200 ml) and acetone (50 ml). A warm solution of cinchonidine (15.0 g, 51.0 mmol) in MeOH (150 ml)/acetone (100 ml) is added, and the mixture is allowed to cool and crystallize over 12 h. The precipitate is filtered off and recrystallized twice from MeOH (350 ml)/acetone (150 ml), allowing a 12 h crystallization time; cinchonidine salt of (*S*)-naproxen, mp 178–179 °C.

The salt is suspended in benzene (160 ml; Caution: carcinogenic!)/6.5 N aqueous HCl (160 ml), and the stirred mixture is heated at 30–40 °C until two clear phases are formed (approximately 30 min). The organic layer is separated, dried over Na_2SO_4, and filtered, and the solvent is removed *in vacuo*. The residue is recrystallized from acetone/petroleum ether (40–65 °C); yield 2.60 g (45%) of (*S*)-naproxen, colorless needles, mp 156–157 °C, $[\alpha]^{20}_{D}$ = +68 (*c* = 0.84, $CHCl_3$).

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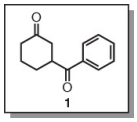
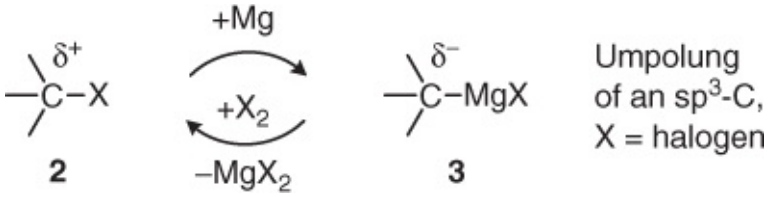
1.4.4 3-Benzoylcyclohexanone

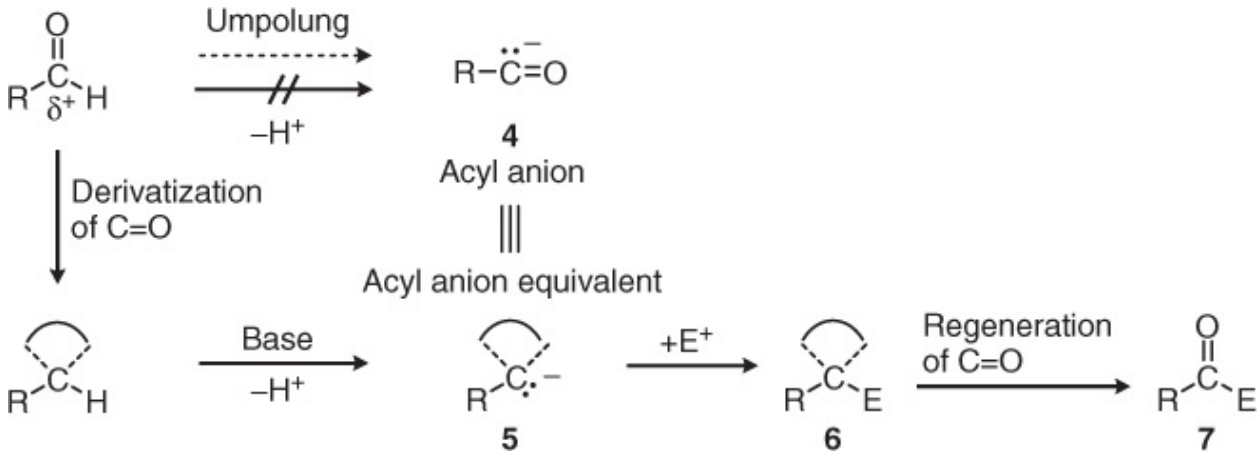
	***Topics:***	• (*O*-Trimethylsilyl)cyanohydrin anions as acyl anion equivalents, umpolung of carbonyl groups, nucleophilic acylation according to the Hünig methodology • Formation of an (*O*-trimethylsilyl)cyanohydrin • 1,4-Addition of an α-metallated (*O*-trimethylsilyl) cyanohydrin to an enone

(a) General

The concept of “umpolung” [1] has been developed on the basis of reactions in which the polarity of an atom (mainly carbon) in a functional group is reversed through chemical transformation. A simple example is provided by the formation of a Grignard compound from a halide R–X through insertion of Mg into the C–X bond (**2** → **3**). Another example is the reaction of a Grignard compound with an elemental halogen (**3** → **2**). In these two processes, an sp^3 C atom changes its polarity from δ^+ to δ^-, and vice versa:

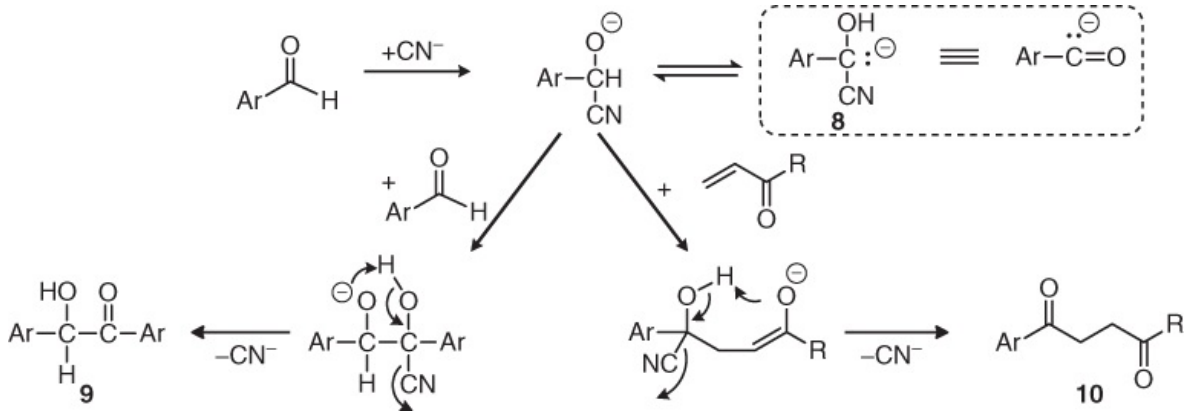


Attractive for synthesis are umpolung reactions at the carbonyl group of aldehydes, in which the polarity of the electrophilic carbon atom of the C=O group is switched to that of an acyl anion **4**:



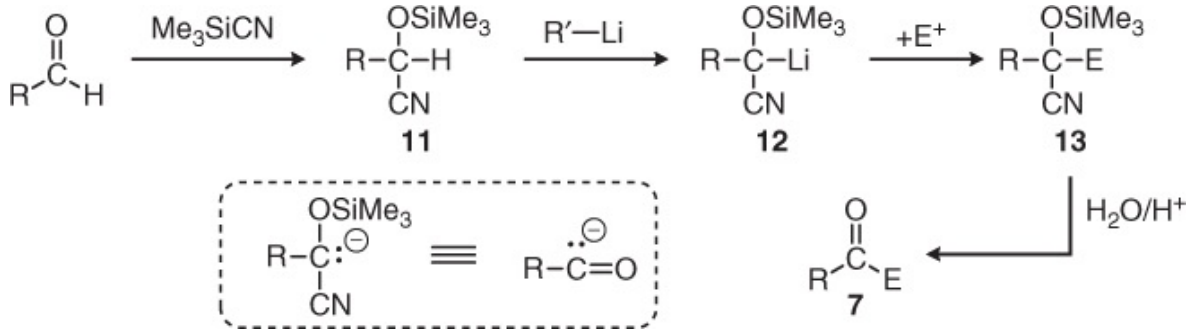
Direct deprotonation at the aldehyde CH=O group is not possible because the pK_a of the hydrogen is about 54. However, by derivatization of the C=O group, the acidity of the C–H can be increased to allow the generation of a carbanion **5** as an equivalent of the acyl anion **4**, which is capable of reacting with electrophiles (simplified as E^+, **5** → **6**). Regeneration of the carbonyl group (**6** → **7**) affords a product of type **7** resulting from combination of E^+ with an aldehyde; thus, the process represents a (formal) nucleophilic acylation of an electrophilic system, as illustrated by the following examples.

1. The acyl anion equivalent **8** formed by the addition of cyanide to the carbonyl group of aryl aldehydes is the central intermediate in the combination of two aryl aldehydes to give benzoins **9** (benzoin reaction [2]) or the 1,4-addition of aryl aldehydes to α,β-unsaturated ketones to give 1,4-diones **10** (Stetter reaction [3]), both of which are catalyzed by cyanide:

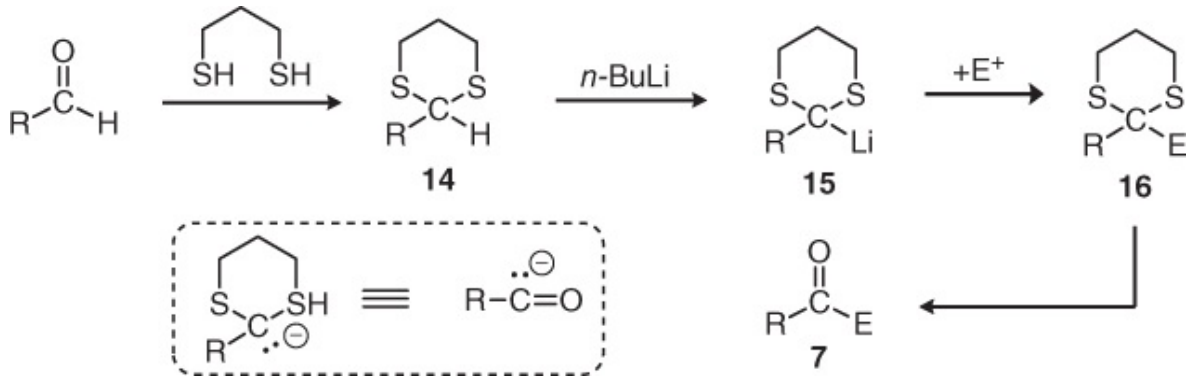


2. Similar acyl anion equivalents are represented by the α-lithiated *O*-silylcyanohydrins **12**, which result from metalation of *O*-silylcyanohydrins **11** (accessible by addition of trimethylsilyl cyanide to aldehydes) with R–Li (Hünig procedure for nucleophilic acylation [4]). Their reactions with

electrophilic systems – for example, alkylation, addition to aldehydes or ketones, 1,4-addition to enones – lead to **13**, which can easily be transformed into products of type **7** by subsequent desilylation and loss of HCN, as exemplified in Section (b):

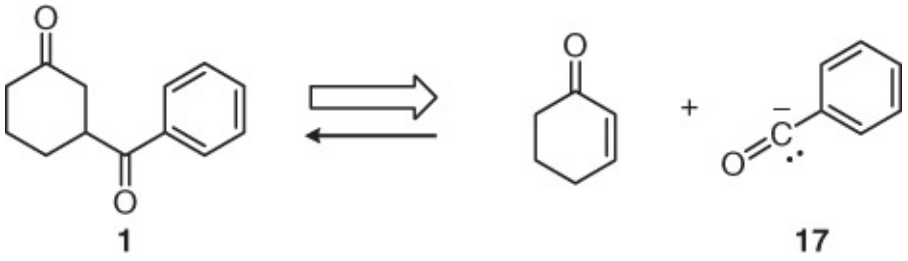


3. 2-Substituted 1,3-dithianes **14** (cyclic dithioacetals, accessible from aldehydes and propane-1,3-dithiol) can be deprotonated with *n*-BuLi to give 2-lithio-1,3-dithianes **15**, which also represent acyl anion equivalents (Corey–Seebach procedure for nucleophilic acylation [5]). As expected, the lithiodithianes **15** are again susceptible to reactions with electrophilic systems: for example, alkylation, addition to aldehydes or ketones, conjugate addition to enones, ring-opening addition to oxiranes. In the products **16** thus formed, the carbonyl moiety can be regenerated (**16** → **7**) by dethioacetalization, which is preferably carried out by means of an oxidative procedure:



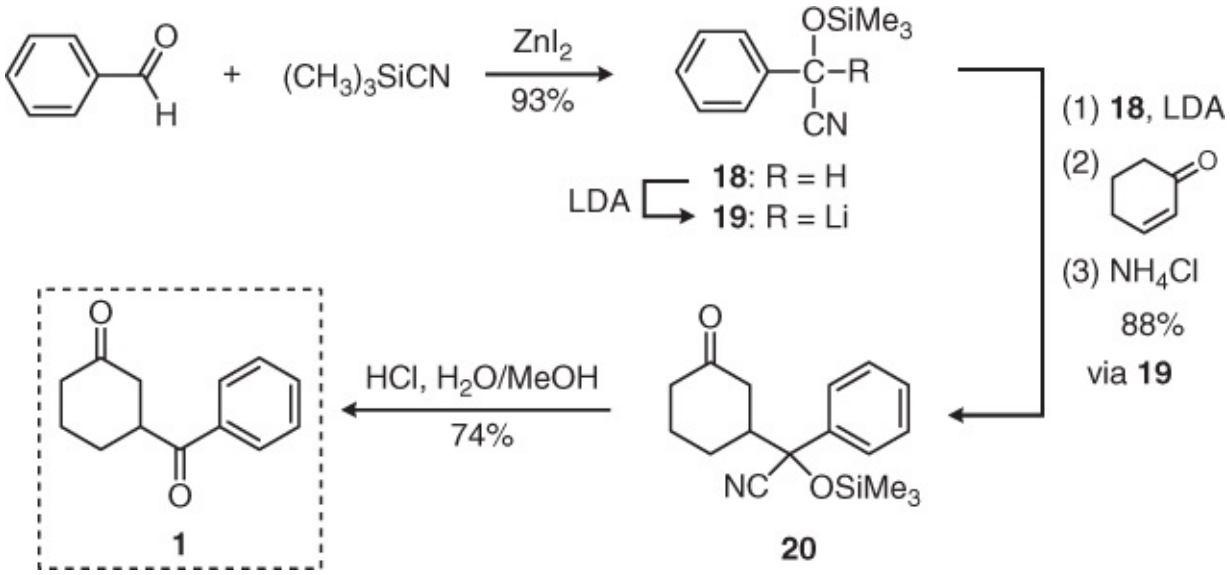
Since 1,3-dithiane chemistry often suffers from the disadvantages of unpleasant odor produced by the sulfur compounds involved and problems in cleaving the thioacetal moiety, the Hünig protocol is often preferred for nucleophilic acylations.

As the result of a simple retrosynthetic analysis, the target molecule **1** should be accessible from cyclohexenone by 1,4-addition of a benzoyl carbanion (**17**) or an equivalent thereof.



(b) Synthesis of 1

The requisite *O*-trimethylsilylated cyanohydrin **18** is prepared by Lewis acid-catalyzed addition (ZnI_2) of trimethylsilyl cyanide to benzaldehyde [6, 7]:



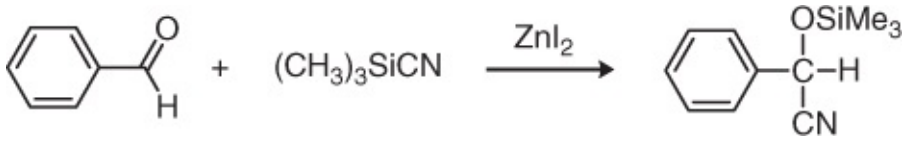
Compound **18** is then subjected to metalation with LDA in THF at −78 °C to give the lithiated cyanohydrin **19**, which is reacted *in situ* with cyclohexenone at −78 to −20 °C. 1,4-Addition of the benzoyl anion equivalent **19** to the enone occurs smoothly, leading to the product **20** after work-up with aqueous NH_4Cl solution.

On hydrolysis with a strong acid (HCl in H_2O/methanol), the cyanohydrin *O*-silyl ether functionality in **20** is cleaved with loss of cyanide to yield the 3-benzoylcyclohexanone (**1**).

Thus, the target molecule **1** is obtained in a three-step sequence in an overall yield of 61% (based on benzaldehyde).

(c) Experimental Procedures for the Synthesis of 1

1.4.4.1	***	**Phenyl(trimethylsilyloxy)acetonitrile** [8]



Under nitrogen and with exclusion of moisture, benzaldehyde (7.64 g, 72.0 mmol, note 1) is added dropwise over a period of 20 min to trimethylsilyl cyanide (7.94 g, 80.0 mmol, note 2) and a few milligrams of anhydrous zinc iodide (note 3) with stirring. The solution is then heated to 80–100 °C for 2 h; the progress of the reaction may be followed by IR.

The product is isolated by fractionating distillation *in vacuo* and is obtained as a colorless oil; 13.7 g (93%), bp_1 62–63 °C, n^{20}_D = 1.4840 (note 4).

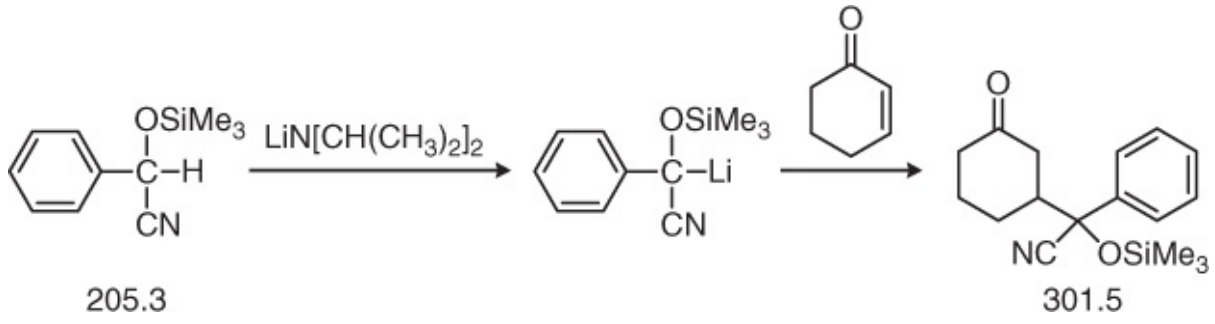
IR (film): $\tilde{\nu}$ (cm^{-1}) = 3070, 3040, 1260, 875, 850, 750.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.40–7.24 (m, 5H, Ph–H), 5.48 (s, 1H, C–H), 0.21 (s, 9H, $Si(CH_3)_3$).

Notes:

1. Benzaldehyde has to be freshly distilled, bp_{10} 62–63 °C.
2. Trimethylsilyl cyanide has to be distilled prior to use, bp 118–119 °C.
   nicht kursiv $(CH_3)_3SiCN$ is a toxic compound!
3. ZnI_2 should be dried *in vacuo* at 100 °C for 5 h before use.
4. The cyanohydrin is easily hydrolyzed to give HCN. Caution: Hood!

1.4.4.2	***	**(3-Oxocyclohexyl)phenyl(trimethylsilyloxy)acetonitrile** [9]



n-Butyllithium (1.6 M in *n*-hexane, 19.4 ml, 31.0 mmol) is added to a stirred solution of diisopropylamine (3.12 g, 31.0 mmol, note 1) in anhydrous THF (20 ml) at −78 °C under nitrogen and with exclusion of moisture, and the mixture is

stirred for 15 min. The silylated cyanohydrin **1.4.4.1** (6.15 g, 30.0 mmol) is added dropwise at the same temperature, which leads to the deposition of a yellow precipitate. Finally, 2-cyclohexen-1-one (2.88 g, 30.0 mmol, note 2) is added dropwise, and the temperature of the reaction mixture is slowly increased to −20 °C over a period of 4 h (note 3).

Saturated aqueous NH_4Cl solution (30 ml) is added, and the mixture is stirred for 3 min at room temperature. It is then extracted with Et_2O (3 × 30 ml), and the combined organic extracts are washed with saturated aqueous NH_4Cl (30 ml) solution and brine (30 ml), dried over Na_2SO_4, and filtered. The solvents are removed *in vacuo*, and the residue is distilled *in vacuo* in a Kugelrohr apparatus to give the product as a colorless liquid; 8.00 g (88%), $bp_{0.05}$ 140 °C (oven temperature 145 °C), n^{20}_D = 1.5125 (note 4).

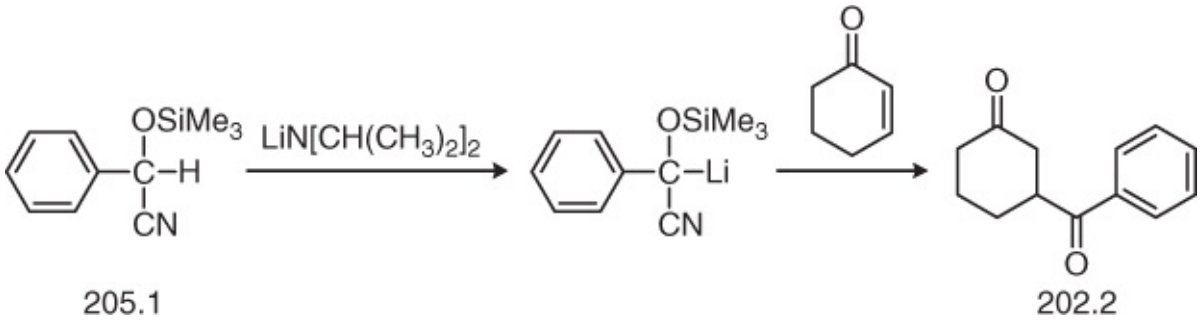
IR (film): $\tilde{\nu}$ (cm^{-1}) = 3080, 3060, 3030, 2960, 2900, 2870, 1720, 1260.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.41–7.21 (m, 5H, Ph–H), 2.65–1.25 (m, 9H, c-hexane-H), 0.12 (s, 9H, $(CH_3)_3Si$).

Notes:

1. Diisopropylamine is distilled from CaH_2 before use, bp 84–85 °C.
2. Cyclohexenone is distilled before use, bp 168–169 °C.
3. For the preparation of 3-benzoylcyclohexanone, hydrolysis of the reaction mixture is conducted with HCl in H_2O/CH_3OH as described in the preparation of **1.4.4.3**.
4. The product is easily hydrolyzed forming HCN. Caution: Hood!

1.4.4.3	***	**3-Benzoylcyclohexanone** [9]



205.1 202.2

Aqueous HCl (2 N, 30 ml) and MeOH (15 ml) are added to the reaction mixture (cf. **1.4.4.2**) and stirring is continued for 14 h at room temperature (note).

The mixture is then diluted with water (approximately 100 ml) and extracted with Et_2O (3 × 50 ml). The combined ethereal extracts are washed with aqueous NaOH (1 M, 50 ml) and brine, dried over Na_2SO_4, and filtered. The solvents are removed *in vacuo*, and the residue is fractionally distilled *in vacuo* to give the product as a colorless oil; 4.48 g (74%), $bp_{0.01}$ 130–131 °C, n^{20}_D = 1.5574.

IR (film): $\tilde{\nu}$ (cm^{-1}) = 3080, 3070, 3030, 2960, 2880, 1710, 1680.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.05–7.15 (m, 5H, Ph–H), 4.10–3.53 (m, 1H, CH–CO), 2.75–1.45 (m, 8H, CH_2).

Note: HCN is formed during the hydrolysis. Caution: Hood!

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3. (a) Stetter, H. (1976) *Angew. Chem.*, **88**, 695–704; *Angew. Chem., Int. Ed. Engl.*, (1976), **15**, 639–647.

4. Hünig, S. and Reichelt, H. (1986) *Chem. Ber.*, **119**, 1772–1800.

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6. For new efficient catalysts for the cyanotrialkylsilylation of aldehydes and ketones, see: (a) Fetterly, B.M. and Verkade, J.G. (2005) *Tetrahedron Lett.*, **46**, 8061–8066;(b) Kano, T., Sasaki, K., Konishi, T., Mii, H., and Maruoka, K. (2006) *Tetrahedron Lett.*, **47**, 4615–4618.

7. For catalytic enantioselective cyanotrialkylsilylation of ketones, see: (a) Fuerst, D.E. and Jacobsen, E.N. (2005) *J. Am. Chem. Soc.*, **127**, 8964–8965;(b) Kim, S.S. and Kwak, J.M. (2006) *Tetrahedron*, **62**, 49–53.

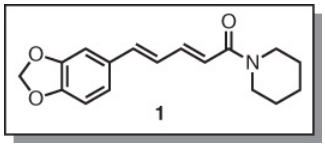
8. Deuchert, K., Hertenstein, U., Hünig, S., and Wehner, G. (1979) *Chem. Ber.*,

112, 2045–2061.

9. Hünig, S. and Wehner, G. (1979) *Chem. Ber.*, **112**, 2062–2064; *Chem. Ber.*, (1980), **113**, 302, 324–332.

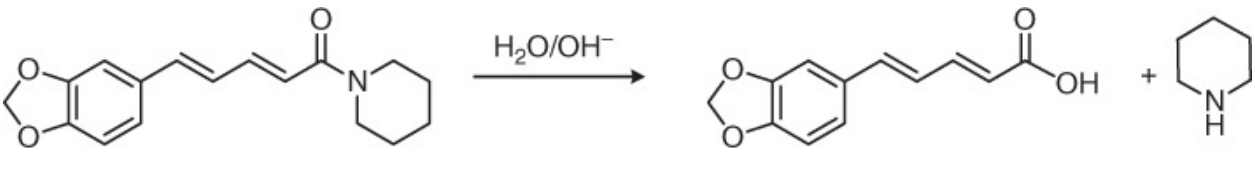
1.5 Reactions of Alkenes Via Carbenium Ions

1.5.1 Piperine

 1	***Topics:***	• Synthesis of a natural product of the arylpolyene type • Acetal formation by the orthoester method • Lewis acid-induced C–C bond formation by addition of an acetal to an enol ether • Acid-catalyzed ROH elimination; acetal hydrolysis • Knoevenagel condensation/decarboxylation • Transformation of a carboxylic acid into a carboxylic acid amide

(a) General

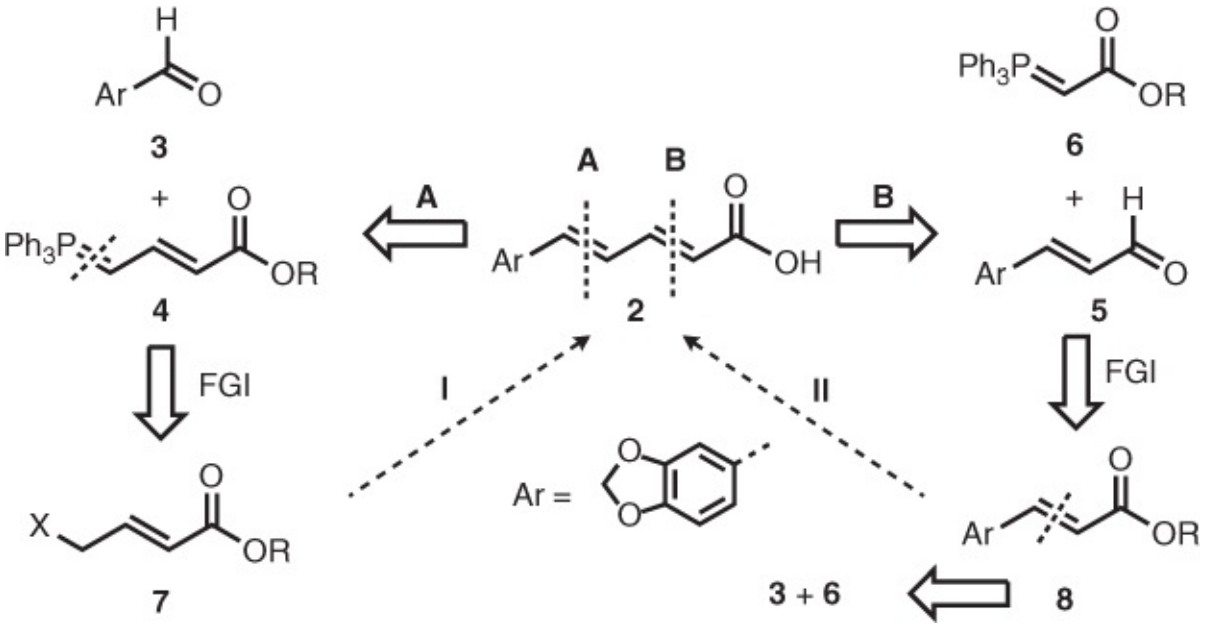
Piperine (**1**, 4-(3,4-methylenedioxyphenyl)-1,3-butadiene-1-carboxypiperidide) is a constituent of several pepper species (piperaceae), especially of black pepper (*Piper nigrum* L.), as the pungent component. Like many piper alkaloids, piperine also exhibits antimicrobial properties [1]. Hydrolysis of **1** in a basic medium leads to piperinic acid (**2**) and piperidine, whose name is derived from its natural origin:



1 2

Piperinic acid (**2**) can be regarded as an intermediate for the synthesis of **1**. The

retrosynthesis of **2** can be performed in two directions (**A**/**B**) by disconnections at the double bonds according to a retro-Wittig transformation:



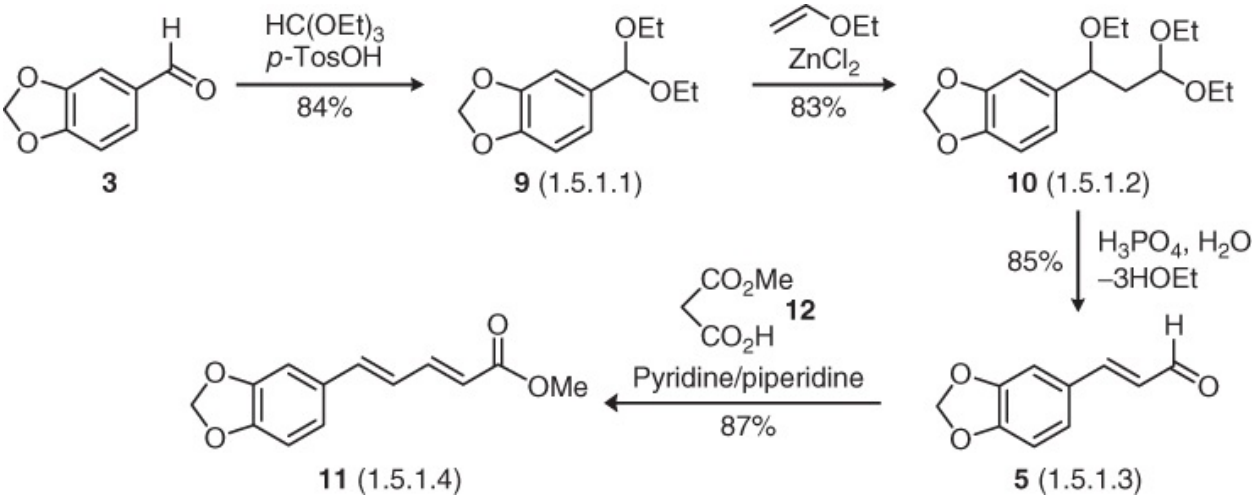
Retrosynthesis according to A leads to the aldehyde piperonal (**3**) and a C_4-ylide **4**, which is derived from γ-halogeno crotonate **7**, in turn available from crotonate by allylic halogenation (e.g., with NBS (*N*-bromosuccinimide)).

Retrosynthesis according to **B** leads to the C_2-ylide **6** (derived from haloacetate) and 3-arylacrolein **5**, which should be accessible from cinnamate **8** by reduction (e.g., with DIBAL (diisobutylaluminum hydride)).

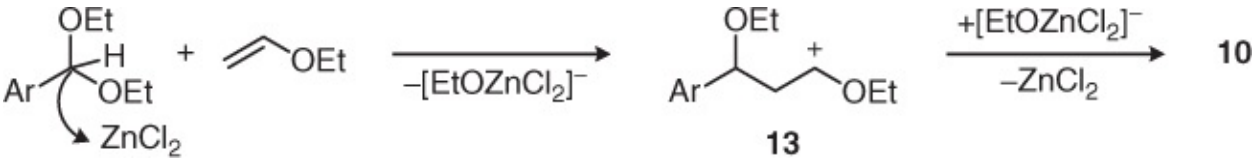
Both approaches toward **2** have been described in the literature. However, the carbonyl olefination of **3** and **4** to give **2** (route **I**) suffers from preparative disadvantages [2]; the same is true for the construction of **2** by two consecutive carbonyl olefinations via **5** (route **II**) (R. Pick and Th. Eicher, unpublished results). Therefore, an alternative method is used for the synthesis of **2** [3], which has been effectively applied in the synthesis of polyolefinic systems ([4], cf. Section 4.1.5) and which relies on carbenium ion-based C–C bond formation.

(b) Synthesis of 1

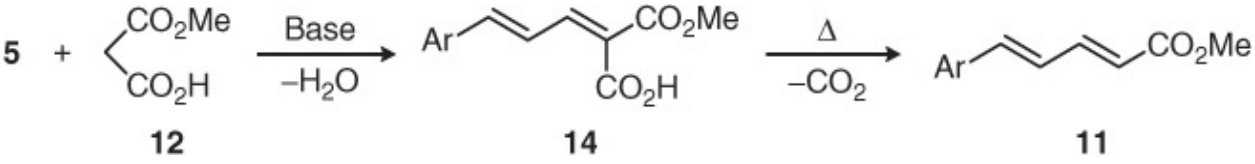
In the first part of the synthesis of **1**, piperonal (**3**) is transformed to its diethyl acetal **9** by reaction with triethyl orthoformate in the presence of TosOH. The acetal **9** adds to the C=C double bond of ethyl vinyl ether in the presence of a Lewis acid, for example, $ZnCl_2$, to give rise to the 3-aryl-1,1,3-triethoxypropane derivative **10**:



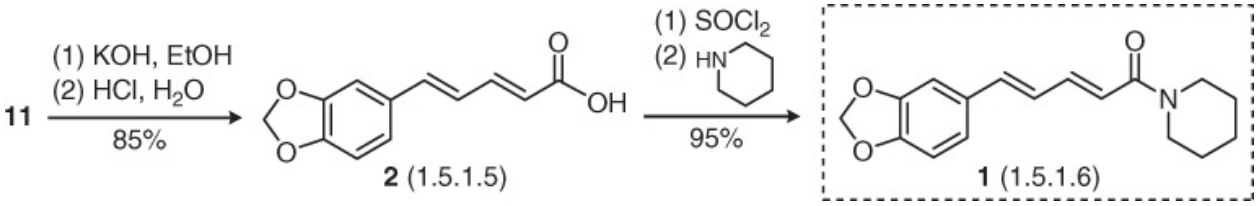
The transformation **9** → **10** can be rationalized by (i) the formation of a carbenium ion from the acetal **9** induced by the Lewis acid, (ii) its electrophilic Markownikov-oriented addition to the electron-rich C=C double bond of the vinyl ether, and (iii) termination by transfer of OEt to the cationic intermediate **13**:



Compound **10** is transformed into the α,β-unsaturated aldehyde by acid-catalyzed hydrolysis of the acetal followed by elimination of EtOH. Finally, the C_5-1,3-diene side chain in **1** is completed by Knoevenagel condensation of **5** with monomethyl malonate (**12**) to give the methyl ester **11** as a result of concomitant decarboxylation of the initial condensation product **14** under the reaction conditions [5]:



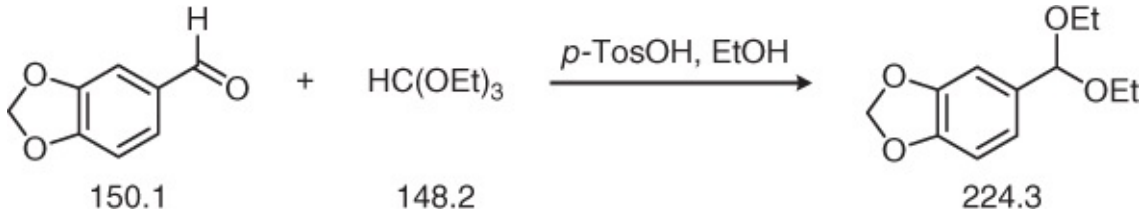
As the last step in the synthesis of **1**, the methyl ester **11** is saponified using KOH in ethanol to give piperinic acid (**2**), and the amide is formed in the conventional manner by reacting **2** with $SOCl_2$ followed by Schotten–Baumann reaction of the intermediate acid chloride with piperidine:



Thus, the target molecule **1** is obtained in a six-step sequence in an overall yield of 42% (based on piperonal).

(c) Experimental Procedures for the Synthesis of 1

1.5.1.1 * **Piperonal diethyl acetal** [3]



A stirred solution of piperonal (50.0 g, 0.33 mol), triethyl orthoformate (97.8 g, 0.66 mol), and TosOH·H_2O (10 mg) in anhydrous EtOH (330 ml) is heated to 80 °C for 1 h (TLC control) with exclusion of moisture.

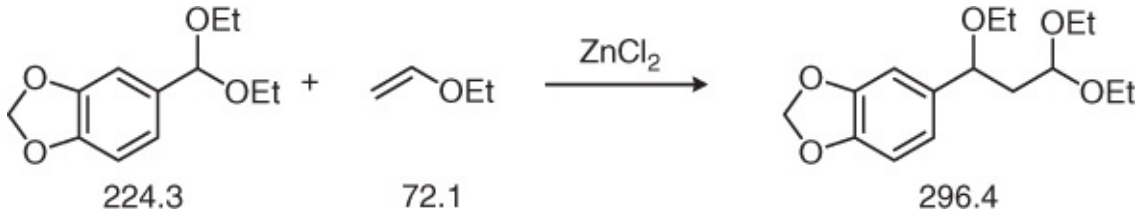
The excess EtOH is then distilled off, the residue is dissolved in Et_2O (200 ml), and the solution is washed several times with H_2O (100 ml). The ethereal solution is dried over K_2CO_3 and filtered, and the solvent is removed *in vacuo*. The residue is fractionated *in vacuo* on a 20-cm Vigreux column. The acetal is obtained as a colorless oil; 62.1 g (84%), $bp_{0.1}$ 84–86 °C, R_f = 0.55 (*n*-pentane/Et_2O 1 : 1).

IR (film): $\tilde{\nu}$ (cm^{-1}) = 2974, 2880, 1504.

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 6.98 (d, *J* = 1.3 Hz, 1H, ArH), 6.93 (dd, *J* = 7.9, 1.3 Hz, 1H, ArH), 6.78 (d, *J* = 7.9 Hz, 1H, ArH), 5.94 (s, 2H, OCH_2O), 5.39 (s, 1H, OCHO), 3.60 (dq, *J* = 9.4, 6.9 Hz, 2H, $OC\underline{H}_2CH_3$), 3.50 (dq, *J* = 9.4, 6.9 Hz, 2H, $OC\underline{H}_2CH_3$), 1.24 (t, *J* = 6.9 Hz, 6H, $OCH_2C\underline{H}_3$).

^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) = 147.7, 147.5, 133.4, 120.3, 107.8, 107.0, 101.4, 101.0, 61.1, 15.2.

1.5.1.2	*	**1,1,3-Triethyl-3-(3,4-methylenedioxyphenyl)propane** [3]



A suspension of anhydrous zinc chloride (0.70 g, note 1) in anhydrous EtOAc (5 ml) is added to the diethyl acetal **1.5.1.1** (56.0 g, 250 mmol) with stirring and under exclusion of moisture. The mixture is heated to 40 °C, and ethyl vinyl ether (19.5 g, 270 mmol) is added at such a rate that the temperature is maintained between 40 and 45 °C. When the addition is complete, stirring is continued at 40–45 °C for 1 h.

The reaction mixture is then allowed to cool to room temperature and is diluted with Et_2O (130 ml). The ethereal solution is washed with aqueous NaOH (2 N, 25 ml), dried over Na_2SO_4, and filtered. After removal of the solvent, the residue is fractionated *in vacuo* (20-cm Vigreux column). The product is obtained as a colorless oil; 62.7 g (83%), $bp_{0.1}$ 97–99 °C.

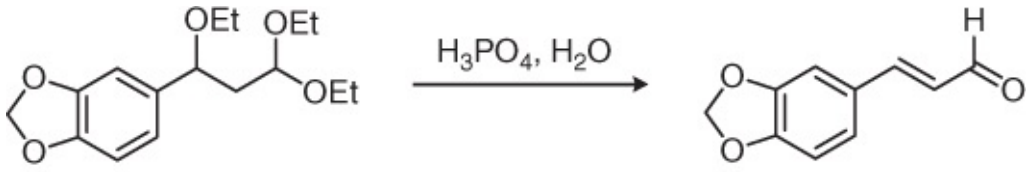
IR (film): $\tilde{\nu}$ (cm^{-1}) = 2973, 2875, 1503.

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 6.83 (s_{br}, 1H, ArH), 6.75 (s_{br}, 2H, ArH), 5.95 (s, 2H, OCH_2O), 4.58 (dd, *J* = 6.9, 4.7 Hz, 1H, OCHO), 4.28 (dd, *J* = 8.8, 5.4 Hz, 1H, Ar–CH–O), 3.22–3.75 (m, 6H, 3 × OCH_2), 2.08 (ddd, *J* = 13.9, 6.9, 5.4 Hz, 1H, C–CH_2–C), 1.84 (ddd, *J* = 13.6, 8.8, 4.7 Hz, 1H, C–CH_2–C), 1.21, 1.20, 1.15 (3 × t, *J* = 6.9 Hz, 3 × 3H, $OCH_2C\underline{H}_3$).

^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) = 147.9, 146.9, 136.7, 120.1, 108.0, 106.7, 100.9, 100.4, 78.3, 63.8, 61.3, 42.4, 18.5, 15.4.

Note: Commercially available anhydrous zinc chloride is dried *in vacuo* over P_4O_{10}.

1.5.1.3	*	**3-(3,4-Methylenedioxyphenyl)acrolein** [3]



296.4 176.2

A stirred mixture of the triethoxypropane **1.5.1.2** (60.4 g, 204 mmol), 1,4-dioxane (400 ml), H_2O (140 ml), 90% phosphoric acid (20 ml), and hydroquinone (0.2 g) is heated under reflux for 8 h under a N_2 atmosphere.

After cooling to room temperature, the reaction mixture is poured into ice-cold H_2O (1000 ml). After stirring for 1 h, the precipitated product is collected by suction filtration, and washed with diluted aqueous $NaHCO_3$ solution and with H_2O until the washings are neutral. The crude aldehyde is recrystallized from EtOH; 30.0 g (83%), yellow crystals, mp 84–85 °C.

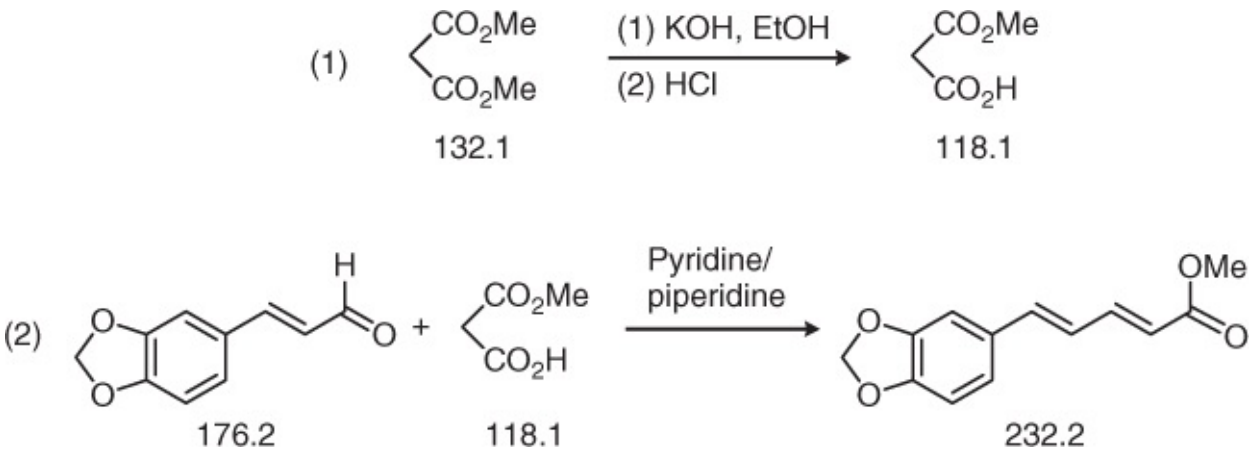
UV (EtOH): λ_{max} (log ϵ) = 338 nm (4.29), 297 (4.06), 248 (4.07), 220 (4.06).

IR (solid): $\tilde{\nu}$ (cm^{-1}) = 3048, 2992, 2916, 2823, 2729, 2701, 1666, 1620, 1597.

^{1}H NMR (500 MHz, [D_6]DMSO): δ (ppm) = 9.59 (d, *J* = 7.9 Hz, 1H, CHO), 7.62 (d, *J* = 15.8 Hz, 1H, Ar–C<u>H</u>=CH), 7.42 (d, *J* = 1.6 Hz, 1H, ArH), 7.23 (dd, *J* = 7.9, 1.6 Hz, 1H, ArH), 7.00 (d, *J* = 7.9 Hz, 1H, ArH), 6.74 (dd, *J* = 15.8, 7.9 Hz, 1H, =C<u>H</u>CHO), 6.09 (s, 2H, OCH_2O).

^{13}C NMR (126 MHz, [D_6]DMSO): δ (ppm) = 194.0 (CHO), 153.1, 150.0, 148.1, 128.5, 126, 125.7, 108.6, 106.8, 101.7 (OCH_2O).

1.5.1.4	**	**Methyl 4-(3,4-methylenedioxyphenyl)-1,3-butadiene-1-carboxylate** [3]



1. Monomethyl malonate: A solution of KOH (16.8 g, 0.30 mol) in anhydrous MeOH (170 ml) is added dropwise to a stirred solution of dimethyl malonate (40.0 g, 0.30 mol) in anhydrous MeOH (170 ml) at room temperature. Stirring is continued for 24 h, and the precipitated potassium salt is collected by suction filtration, washed with Et_2O (50 ml), and dried *in vacuo*.

   The salt is dissolved in H_2O (30 ml), and concentrated HCl (58 ml) is added dropwise at 0 °C with stirring. The mixture is then extracted with Et_2O (4 × 50 ml), the combined ethereal extracts are dried over Na_2SO_4, and filtered, and the solvent is removed *in vacuo*. The residue is distilled *in vacuo*, and the product is obtained as a colorless oil; 33.6 g (95%), $bp_{0.18}$ 84–85 °C.

   ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 10.90 (s, 1H, CO_2H), 3.78 (s, 3H, CH_3), 3.46 (s, 2H, CH_2).

   ^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 171.8 (*C*O_2H), 167.1 (*C*O_2CH_3), 52.8 (CH_2), 40.7 (CH_3).

2. A mixture of the aldehyde **1.5.1.3** (17.6 g, 0.10 mol), monomethyl malonate (17.7 g, 0.10 mol), anhydrous piperidine (1 ml), and anhydrous pyridine (40 ml) is heated at 80 °C for 2 h and at 130 °C for 1 h.

   The reaction mixture is then diluted with Et_2O (150 ml), and the ethereal solution is washed several times with H_2O (100 ml). Thereafter, it is washed with aqueous HCl (2 N, 100 ml), and then with further H_2O until the washings are neutral. The ethereal solution is dried over $MgSO_4$ and filtered, the solvent is removed *in vacuo*, and the residue is recrystallized

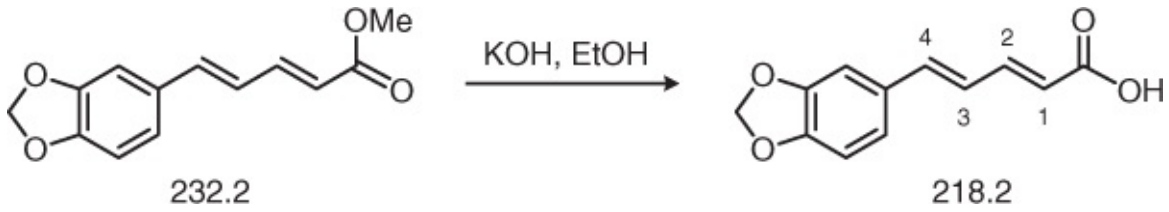
from MeOH. The diene ester is obtained as yellow crystals; 20.1 g (87%), mp 142–143 °C.

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 2947, 1706, 1616, 1607, 1505.

^{1}H NMR (500 MHz, [D_6]DMSO): δ (ppm) = 7.37 (ddd, *J* = 15.1, 8.5, 1.9 Hz, 1H, C<u>H</u>=CHCO$_2$), 7.22 (d, *J* = 1.3 Hz, 1H, ArH), 7.10–7.05 (combined signals, 3H, ArH, Ar–C<u>H</u>=C<u>H</u>), 6.92 (d, *J* = 7.9 Hz, 1H, ArH), 6.04 (s, 2H, OCH$_2$O), 6.00 (d, *J* = 15.1 Hz, 1H, =CHCO$_2$), 3.67 (s, 3H, OCH$_3$).

^{13}C NMR (126 MHz, [D_6]DMSO): δ (ppm) = 166.6, 148.2, 148.0, 145.2, 140.5, 130.4, 124.6, 123.2, 119.4, 108.5, 105.7, 101.3, 51.2.

1.5.1.5	*	**4-(3,4-Methylenedioxyphenyl)-1,3-butadiene-1-carboxylic acid** [3]



A solution of the methyl ester **1.5.1.4** (18.6 g, 80.0 mmol) in 20% KOH in EtOH (100 ml) is heated under reflux for 3 h.

The solvent is then removed *in vacuo*, and the residue is dissolved in the minimum amount of hot H_2O (approximately 50 ml). The solution is cooled to 0 °C and acidified by the dropwise addition of concentrated HCl with stirring. The precipitated acid is collected by suction filtration, washed with ice-cold water, dried over $MgSO_4$, and filtered, and the solvent is removed *in vacuo*. The residue is recrystallized from EtOH; 14.5 g (83%), yellow crystals, mp 217–218 °C; TLC (SiO_2/Et_2O): R_f = 0.60.

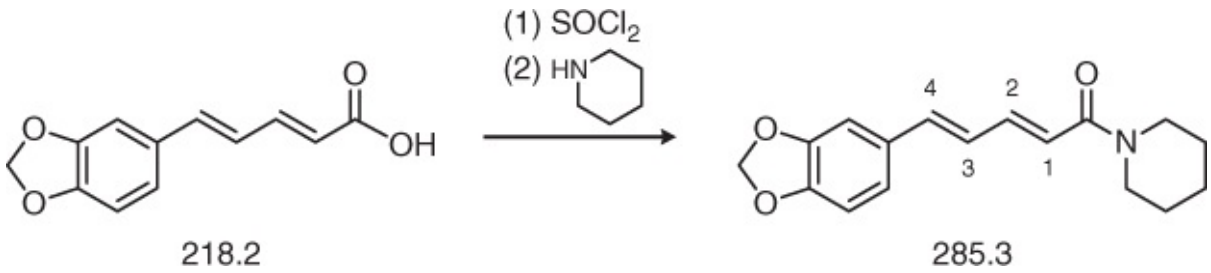
IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3100–2400, 1680.

UV (EtOH): λ_{max} (log ϵ) = 343 nm (4.42), 308 (4.21), 262 (4.07).

^{1}H NMR ([D_6]DMSO): δ = 7.54–7.16 (m, 1H, vinyl-H-2), 7.21–6.68 (m, 5H, Ar–H, H-3, H-4), 6.01 (s, 2H, OCH$_2$), 5.93 (d, *J* = 14 Hz, 1H, vinyl-H-

1).

1.5.1.6	*	4-(3,4-Methylenedioxyphenyl)-1,3-butadiene carboxypiperidide
		(piperine), [2]



1. The acid **1.5.1.5** (8.72 g, 40.0 mmol) is suspended in anhydrous benzene (180 ml; Caution: “Leerzeichen einfügen” carcinogenic!), and then thionyl chloride (10 ml, distilled before use, bp_{760} 78–79 °C) and anhydrous DMF (1.2 ml) are added. The mixture is heated to reflux with stirring for 2 h (N_2 atmosphere, Hood, evolution of HCl and SO_2!). The solvents are removed *in vacuo*, and the solid residue (crude acid chloride) is used directly in the next step.
2. The acid chloride from the previous step is dissolved in anhydrous benzene (40 ml), and the solution is cooled to 0 °C. A solution of anhydrous piperidine (14.8 g, 0.17 mol, 16.0 ml) in benzene (40 ml) is then added dropwise with stirring over 20 min; when the addition is complete, stirring is continued for 2 h at room temperature.

H_2O (200 ml) is then added, the aqueous phase is extracted with benzene (3 × 50 ml; Caution: carcinogenic!), and the combined organic extracts are dried over Na_2SO_4 and filtered. The solvent is removed *in vacuo*, and the residue (dark oil) is dissolved in hot 4 : 1 cyclohexane/benzene (80 ml). On cooling to room temperature, the product crystallizes in well-shaped yellowish needles, which are collected by suction filtration, washed with cyclohexane, and dried; 11.0 g (95%), mp 130–132 °C, TLC (SiO_2; Et_2O): R_f = 0.40.

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 1640, 1615, 1590.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.61–7.28 (m, 1H, vinyl-H-2), 6.98–6.64 (m, 5H, Ar–H, 3-H, 4-H), 6.46 (d, *J* = 13.9 Hz (trans coupling), 1H, H-1), 6.00 (s, 2H, OCH_2), 3.69–3.51 (m, 4H, NCH_2), 1.82–1.42 (m, 6H, β-and γ-

piperidine-CH_2).

References

1. (a) Steglich, W., Fugmann, B., and Lang-Fugmann, S. (eds) (1997) *Römpp, Lexikon "Naturstoffe"*, Georg Thieme Verlag, Stuttgart, p. 500;(b) For the isolation of piperine from black pepper, see: Becker, H. and Adam, K.P. (eds) (2000) *Analytik biogener Arzneistoffe*, Pharmazeutische Biologie, vol. 4, Wissenschaftliche Verlagsgesellschaft mbH, Stuttgart, p. 333.

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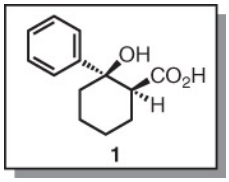
4. Isler, J., Lindlar, H., Montavon, M., Rüegg, R., and Zeller, P. (1956) *Helv. Chim. Acta*, **39**, 249–259.

5. Compare the analogous behavior of malonic acid in the formation of cinnamic acid by decarboxylative Knoevenagel condensation with benzaldehyde: *Organikum* (2001), 21st edn, Wiley-VCH Verlag GmbH, Weinheim, p. 529.

1.5.2 Cicloxilic Acid



1

Topics:

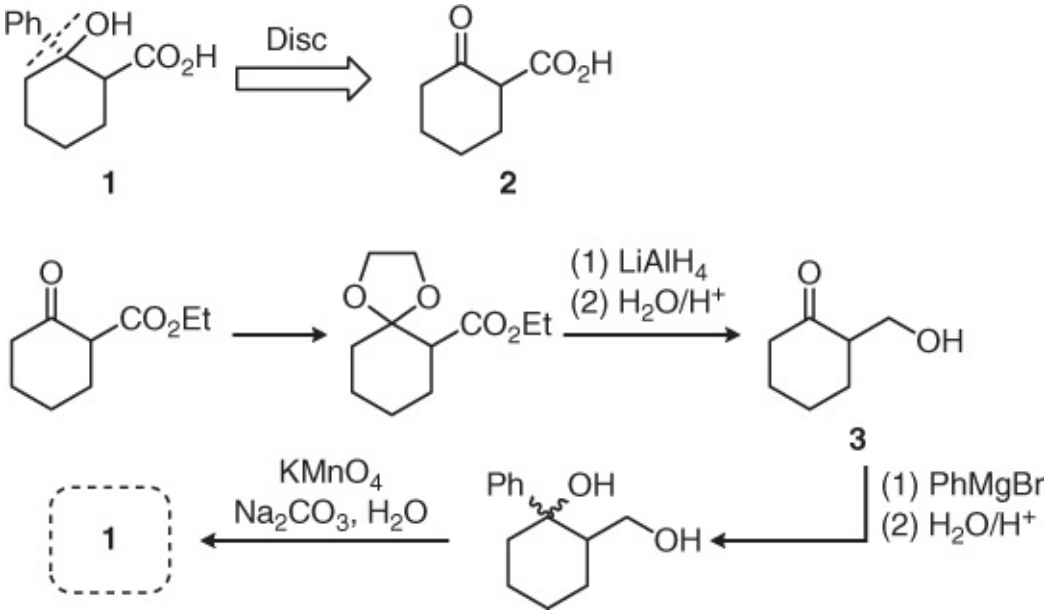
- Synthesis of a drug
- Formation of a tertiary alcohol by addition of RMgX to a ketone
- Acid-catalyzed dehydration of a tertiary alcohol
- Stereoselective Prins reaction (acid-catalyzed addition of formaldehyde to an alkene)
- Oxidation of a primary alcohol to a carboxylic acid

(a) General

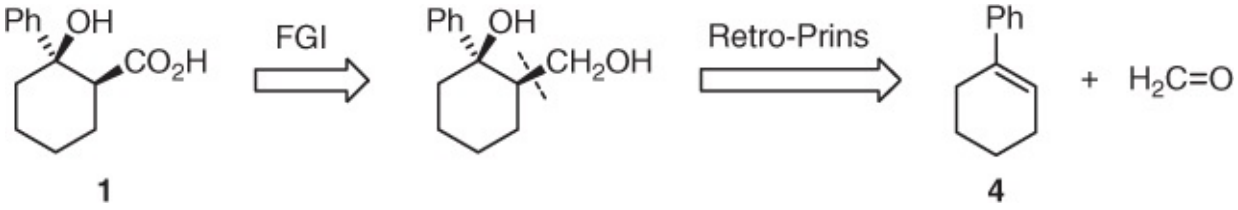
Cicloxilic acid (**1**, *rac-cis*-2-hydroxy-2-phenylcyclohexane-1-carboxylic acid) is

used medicinally as a choleretic and hepatic protectant [1]. Its stereochemistry, with a cis relationship of the OH and CO_2H groups, was established by ^1H NMR spectroscopic investigation [2].

A straightforward retrosynthesis of **1** leads to cyclohexanone-2-carboxylic acid (**2**) as starting material, from which **1** might have been considered accessible by a simple Grignard reaction with PhMgBr. However, since this did not work, a somewhat lengthy transformation of the keto ester into **3** was necessary [3], which was then transformed into **1** by Grignard reaction (PhMgBr) followed by oxidation. Further negative aspects of this synthesis are its low yield and its lack of stereoselectivity, giving a mixture of the cis and trans diastereomers.



A second, less conventional retrosynthetic analysis leads to 1-phenylcyclohexene and formaldehyde:



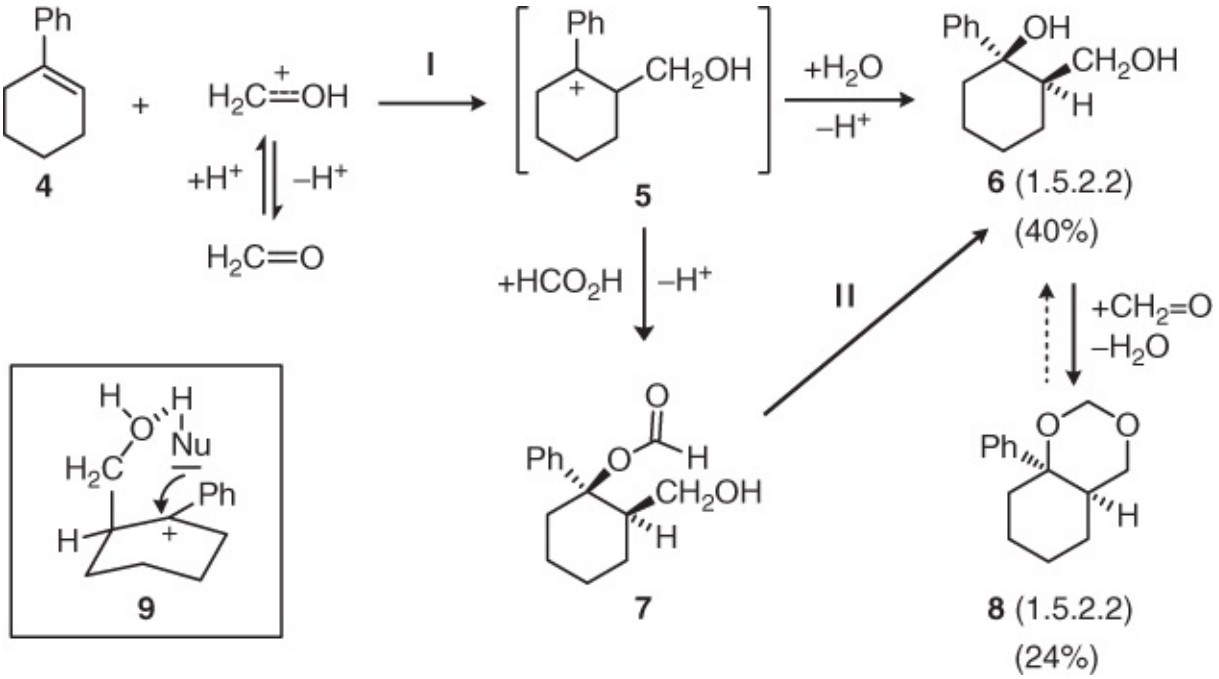
This approach was used in the described synthesis of **1**, with the advantage that it proceeds with high diastereoselectivity.

The acid-catalyzed addition of aldehydes, mainly formaldehyde, to alkenes is known as the ***Prins reaction***. In this process, the carbenium ion derived from the addition of the protonated carbonyl source to the alkene C=C bond is the central intermediate; it is intercepted by addition of a nucleophile, preferentially the

solvent used (H_2O, formic acid, etc.), to give as products a 1,3-diol and/or its monoester [4, 5].

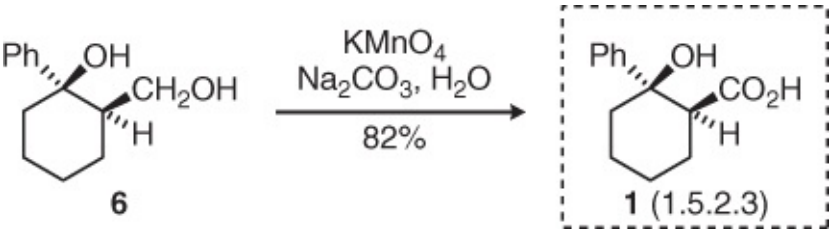
(b) Synthesis of 1

For the synthesis of **1**, 1-phenylcyclohex-1-ene (**4**) is reacted with formaldehyde in aqueous formic acid (5 : 95) to give **6** and **7** as the main products, accompanied by a side product **8**, which contains an acetal moiety formed by the reaction of **6** with a second molecule of formaldehyde. The formate **7** can easily be transformed into **6** by saponification with NaOH.

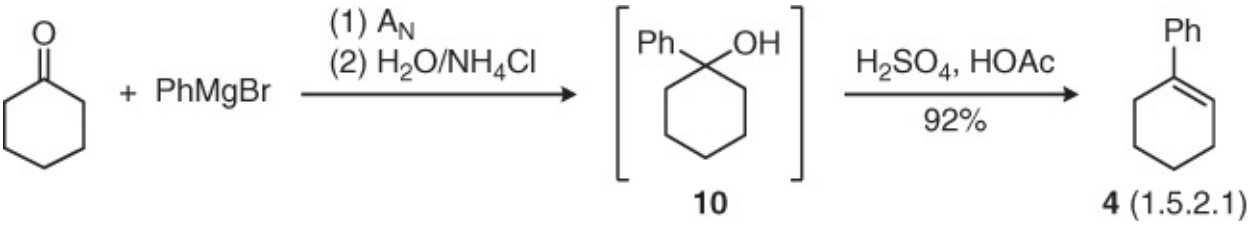


The high stereoselectivity of the Prins reaction, giving the cis diastereomers **6** and **7**, can be explained in terms of a pre-orientation through hydrogen bonding between the incoming nucleophile and the hydroxymethyl group in the cation **5** in the transition state [2].

In the final step of the synthesis, the diol **6** is oxidized with $KMnO_4$ in aqueous Na_2CO_3 solution to give cicloxilic acid **1**:



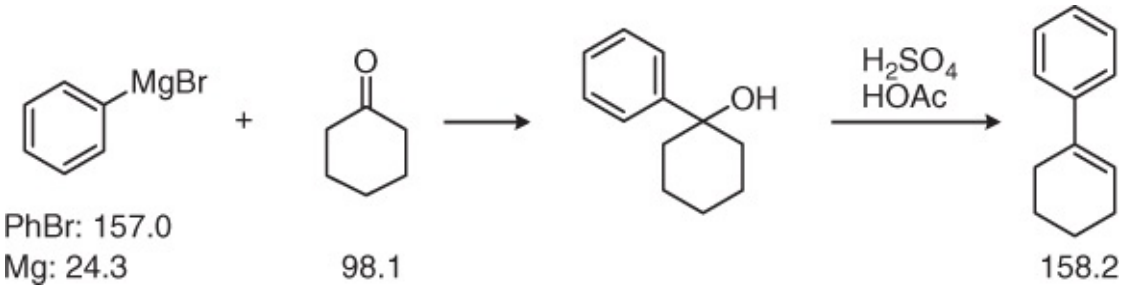
The required substrate, 1-phenylcyclohex-1-ene (**4**), is prepared from cyclohexanone by addition of phenylmagnesium bromide and subsequent acid-catalyzed elimination of H_2O (E1 process) from the formed tertiary benzyl alcohol [6]:



In this way, the target molecule **1** is obtained in a stereoselective three-step sequence in an overall yield of 47% (based on cyclohexanone).[6]

(c) Experimental Procedures for the Synthesis of 1

1.5.2.1	*	**1-Phenylcyclohex-1-ene** [6]



The first 20 ml of a solution of bromobenzene (94.5 g, 0.50 mol; note 1) in anhydrous Et_2O (200 ml) and methyl iodide (4–6 drops; Caution: carcinogenic!) are added to magnesium turnings (14.5 g, 0.50 mol) in anhydrous Et_2O (20 ml). When the reaction has started, the rest of the bromobenzene solution is added dropwise with efficient stirring at such a rate that gentle boiling of the reaction mixture is maintained. When the addition is complete, heating under reflux is continued for 2 h.

A solution of cyclohexanone (49.1 g, 0.50 mol; note 2) in anhydrous Et_2O (40 ml) is then added dropwise with efficient stirring to the solution of phenylmagnesium bromide prepared as described above, again at such a rate that gentle boiling of the reaction mixture is maintained. When the addition is complete, heating at reflux is continued for 30 min.

The mixture is then cooled in an ice bath, and an ice-cold saturated aqueous NH_4Cl solution (400 ml) is added dropwise with vigorous stirring. The organic

phase is separated, and the aqueous phase is extracted with Et_2O (150 ml). The ethereal phases are combined, dried over Na_2SO_4, and filtered. The solvent is removed *in vacuo*, and the yellowish residue (note 3) is stirred for 30 s with a mixture of concentrated H_2SO_4 (20 ml) and acetic acid (80 ml) at 50 °C. The mixture is then poured into a two-phase system of H_2O (500 ml) and Et_2O (300 ml) and shaken. The ethereal phase is separated, washed repeatedly with saturated aqueous $NaHCO_3$ solution (4 × 100 ml), dried over Na_2SO_4, and filtered. The solvent is removed, and the residue is distilled *in vacuo*. The product is obtained as a colorless liquid; 72.5 g (92%), $bp_{4.5}$ 90–91 °C, n^{20}_D = 1.5665.

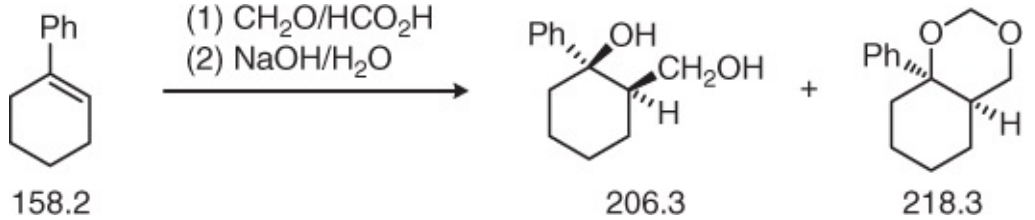
IR (film): $\tilde{\nu}$ (cm^{-1}) = 3010, 2910–2835, 1660, 1495, 1445.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.50–7.05 (m, 5H, Ph–H), 6.20–5.91 (m, 1H, vinyl-H), 2.61–2.00 (m, 4H, CH_2), 2.00–1.43 (m, 4H, CH_2).

Notes:

1. Bromobenzene is purified by distillation *in vacuo*, bp_{15} 48–49 °C.
2. Cyclohexanone has to be distilled before use; bp_{760} 155–156 °C, $[\alpha]^{20}_D$ = 1.4500.
3. This residue consists of 1-phenylcyclohexan-1-ol as the crude product and is subjected *in situ* to acid-catalyzed dehydration.

1.5.2.2 ** *cis*-2-Hydroxymethyl-1-phenylcyclohexan-1-ol [4]



Phenylcyclohexene (**1.5.2.1**) (66.5 g, 0.42 mol) is suspended in a mixture of formic acid (420 ml) and H_2O (15 ml). A 40% formaldehyde solution (44.1 ml, 0.59 mol) is added dropwise over 30 min with stirring. When the addition is complete, the suspension is stirred for 3 h at room temperature.

The solvent is then removed *in vacuo* at an external temperature of 30 °C. A

colorless oil is obtained, which is treated with a solution of NaOH (28.0 g) in EtOH (210 ml) with efficient stirring for 12 h at room temperature. The reaction mixture is then diluted with an equal volume of H_2O (approximately 250 ml) and extracted with chloroform (2 × 150 ml); the combined extracts are dried over Na_2SO_4, and filtered, and the solvent is removed *in vacuo*. The oily residue is dissolved in petroleum ether (300 ml) with heating, and the solution is cooled to room temperature and kept in a freezer for 24 h. The crystallized diol is filtered off, retaining also the filtrate (see below), and the purification procedure is repeated. The product is obtained as colorless crystals; 34.5 g (40%), mp 82–83 °C, TLC (SiO_2; Et_2O): R_f = 0.80.

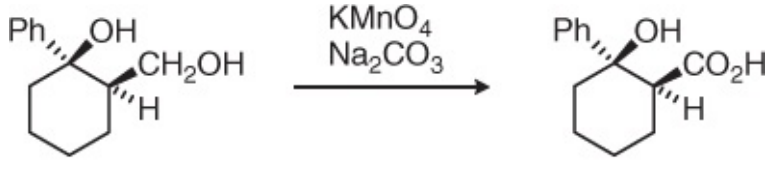
IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3500–3180, 2930–2840.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.62–7.21 (m, 5H, phenyl-H), 3.73, 2.45 (s, 1H, OH; exchangeable with D_2O), 3.65–3.25 (m, 2H, OCH_2), 2.25–1.25 (m, 9H, cyclohexyl-H).

The solvent is removed *in vacuo* from the petroleum ether solution of the first crystallization of the diol, the residue is dissolved in the minimum amount of EtOH, and the solution is kept in a freezer for 12 h. The dioxane is obtained as colorless crystals; 22.5 g (24%), mp 62–63 °C, TLC (SiO_2; Et_2O): R_f = 0.80.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.41–7.25 (m, 5H, phenyl-H), 4.87–4.75 (m, 2H, OCH_2O), 3.85, 3.53 (d, J = 11.2 Hz, 2 × 1H, OCH_2), 2.54–1.08 (m, 9H, cyclohexyl-H).

1.5.2.3	*	***cis*-2-Hydroxy-2-phenylcyclohexane carboxylic acid (cicloxilic acid)** [4]



206.3 220.3

A solution of the diol **1.5.2.2** (29.0 g, 141 mmol) in H_2O (1500 ml) is heated to 85 °C (internal temperature). At this temperature, a mixture of finely powdered

$KMnO_4$ (57.5 g, 364 mmol) and anhydrous Na_2CO_3 (29.0 g, 274 mmol) is added in small portions with vigorous stirring. When the addition is complete, stirring at 85 °C is continued for 30 min (note).

The MnO_2 formed is removed by suction filtration, and the filter cake is washed with H_2O (3 × 100 ml). Concentrated HCl is added dropwise to the filtrate with stirring until a pH of approximately 1 is reached. The colorless precipitate is collected by suction filtration, washed with a small amount of iced water, and dried over P_4O_{10} *in vacuo*. Recrystallization from cyclohexane yields 25.5 g (82%) of cicloxilic acid; mp 139–140 °C, TLC (SiO_2; Et_2O): R_f = 0.75.

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3530, 3200–2600, 1680.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.57–7.15 (m, 5H, Ph–H), 3.10–2.91 (m, 1H, 1-H), 2.15–1.20 (m, 8H, 4 × CH_2).

Note: If the reaction mixture still contains an excess of permanganate, MeOH is added until decolorization occurs.

References

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3. Brit. (1969), GB 1167386 19691015.

4. Ger. Offen. (1977), DE 2607967 A1 19770526. *Chem. Abstr.*, (1977), **87**, 84688.

5. (a) Adams, D.R. and Bhatnagar, S.P. (1977) *Synthesis*, 661;(b) Thiem, J. (1980) *Houben-Weyl*, *Methoden der Organischen Chemie*, vol. 6/1a, p. 793;(c) For the use of Prins cyclizations in natural product synthesis, see: Overman, L.E. and Pennington, L.D. (2003) *Chem. Soc. Rev.*, **32**, 381–383.

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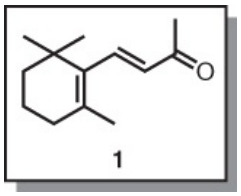
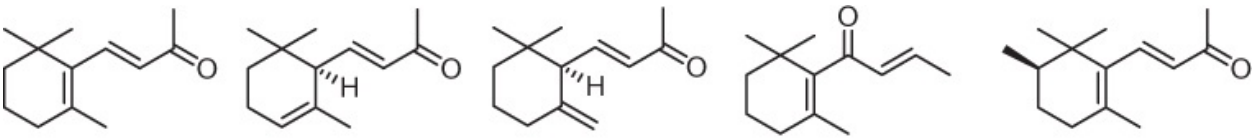
1.5.3 β-Ionone

 1	***Topics:***	• Synthesis of a terpene-derived C_{13}-dienone • α-Alkylation of acetoacetate • Ethynylation of a carbonyl compound • Acetoacetylation of an alcohol with diketene • Carroll reaction of allyl acetoacetates ([3,3]-sigmatropic rearrangement) • Cationic cyclization of a 1,5-diene to a cyclohexene derivative

(a) General

Ionones are a group of natural fragrances, which are formed by oxidative degradation of tetraterpenoids (carotins) [1]. α-Ionone **2** is the main component of violet oil, while β-and γ-ionones (**1** and **3**) are found in several essential oils. Structurally related to the ionones are the damascones (e.g., β-damascone **4**, a constituent of rose oil) and irones (e.g., β-irone **5** (2-methyl-β-ionone), a fragrant compound from the oil of iris roots) [2].



β-Ionone **1** | (*R*)-(+)-α-Ionone **2** | (*R*)-(+)-γ-Ionone **3** | β-Damascone **4** | (*R*)-(+)-β-Irone **5**

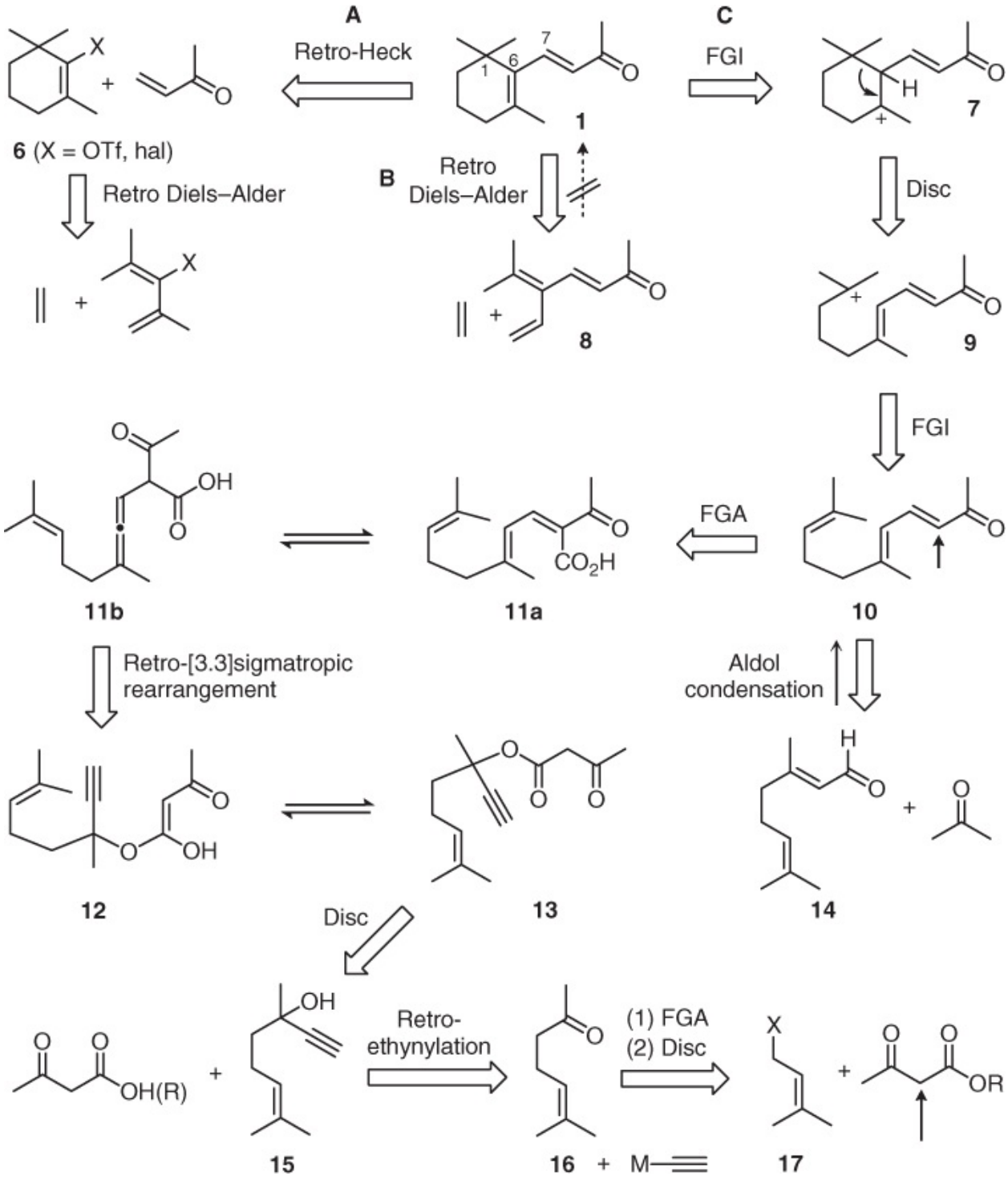
β-Ionone is one of the most potent odorous organic compounds (perceptible in concentrations <0.1 ppb); it is an important ingredient of perfumes and is used as a substrate in natural product syntheses, for example, of damascone [3] and of vitamin A (cf. Section 4.1.5).

Three retrosynthetic pathways for β-ionone (**1**) are discussed here.

In A, disconnection of the C-6/C-7 bond according to a retro-Heck transformation leads to the cyclohexene **6**, which could formally be obtained by a Diels–Alder reaction. However, this would be an electronically disfavored transformation.

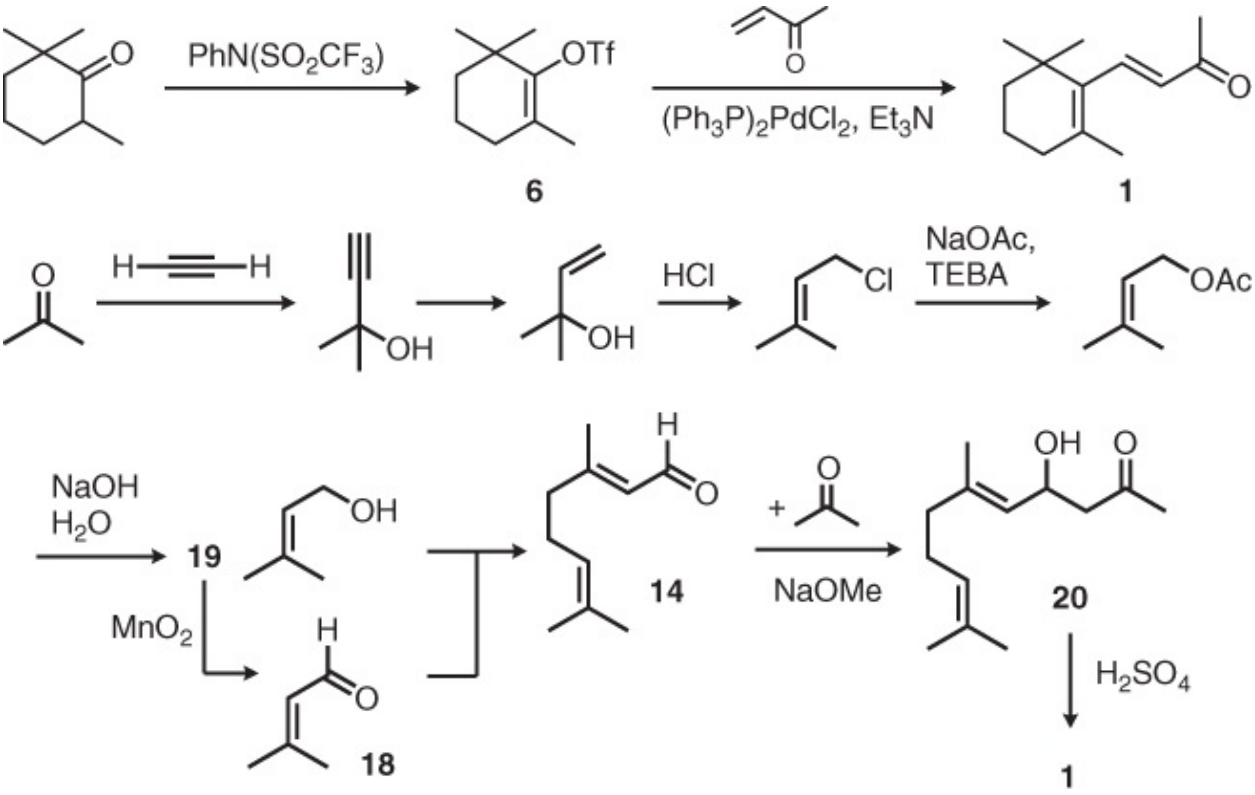
In B, the cyclohexene ring is disconnected by a retro-Diels–Alder reaction to give ethylene as dienophile and the 1,3-diene system **8**. However, as discussed before, their [4 + 2]-cycloaddition is not a favorable process, again because of electronic reasons (no activated dienophile) as well as a lack of regioselectivity (different 1,3-diene moieties exist in **8**).

In C, a protonation/deprotonation sequence initiates a ring opening (**1** → **7** → **9**) to pseudoionone (**10**), which could be obtained by an aldol condensation of geranial (**14**) with acetone. Another possible retrosynthesis of **10** includes a retro-Claisen protocol (**10** → **11a** → **11b**) leading to dehydrolinalool (**15**) and acetoacetate via dehydrolinalool acetoacetate (**12**/**13**). **15** may be obtained from methylheptenone **16**, which is accessible from **17** and acetoacetate.

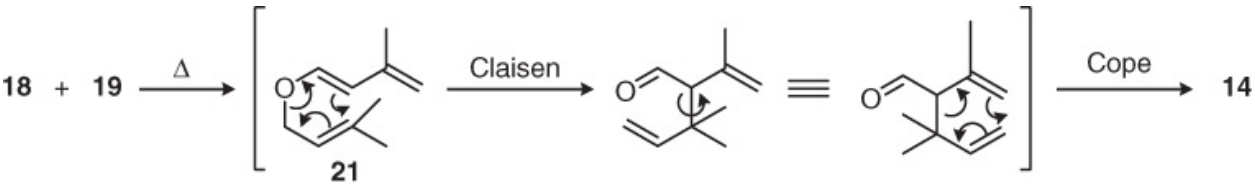


Realizations of the retroanalytical pathways A–C for the synthesis of **1** have been reported in the literature.

Thus, a short and efficient approach to **1** utilizes the Heck reaction of the trifluoromethanesulfonate **6** (X = OSO_2CF_3) of 2,6,6-trimethylcyclohexanone with methyl vinyl ketone [4]:



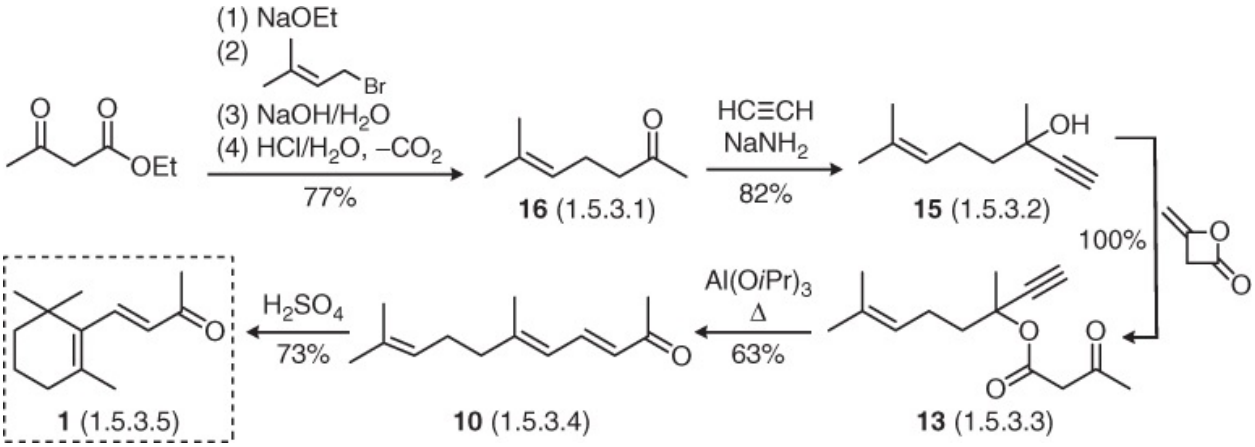
In the second approach toward **1**, acetone is condensed with geranial (**14**) [5], which is obtained by a pericyclic domino process of two [3,3]-sigmatropic reactions between the allylic alcohol **19** and the aldehyde **18** via the vinyl allyl ether **21**:



The third approach to the target molecule **1**, according to retrosynthesis C, uses elements of the industrial β-ionone synthesis of BASF and is described in detail [6].

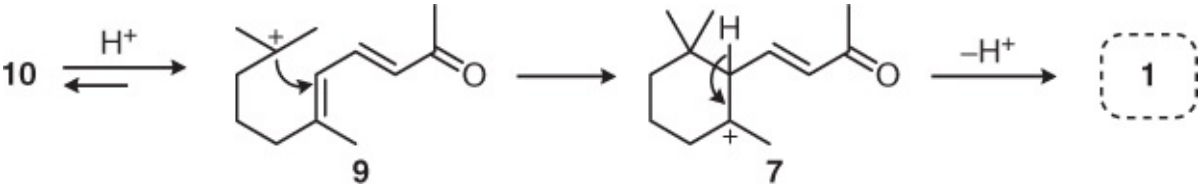
(b) Synthesis of 1

First, 6-methylhept-5-ene-2-one (**16**) is prepared from acetoacetate by α-alkylation with prenyl bromide (cf. Section 4.1.3), ester hydrolysis, and decarboxylation of the intermediately formed β-keto acid. Ethynylation of methylheptenone **16** with sodium acetylide [7] gives the tertiary alcohol dehydrolinalool (**15**), which is esterified with diketene.



The propargylic acetoacetate **13** is subjected to a thermal [3,3]-sigmatropic rearrangement in the presence of $Al(O\textit{i}Pr)_3$ with concomitant decarboxylation of the resulting β-allenic acid (**11b**) to give the unsaturated ketone **10** (pseudoionone). The Claisen (oxa-Cope) rearrangement of allylic or propargylic acetoacetates (Carroll reaction) is often used in terpene synthesis (also industrially [8]) as a C_3 chain elongation process (here: $C_{10} \rightarrow C_{13}$).

The final step of the synthesis of β-ionone (**1**) is the acid-catalyzed cycloisomerization of pseudoionone (**10**). Mechanistically, a cationic cyclization of the 1,5-diene through carbenium ion formation (by protonation of the terminal C=C double bond) and its addition to an internal olefinic C=C bond resulting in the formation of a cyclohexene can be assumed.

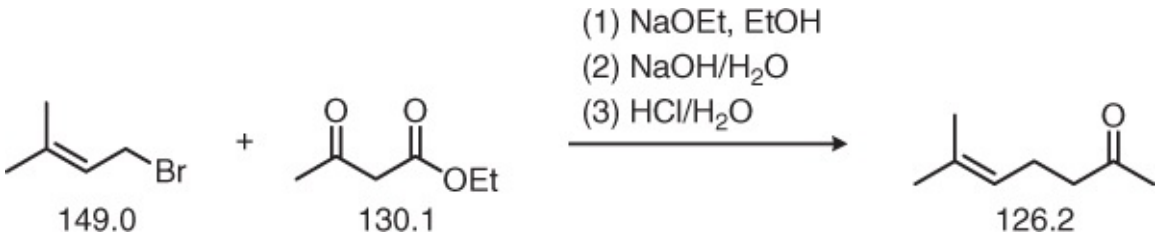


Cyclizations of this type occur with a high degree of stereoselectivity (stereoelectronic control in **9** → **7** as a result of a chair-like transition state) and are involved in the biosynthesis of steroids and other polycycles [9].

Using the described approach, the target molecule **1** is obtained in a five-step sequence with an overall yield of 29% (based on acetoacetate).

(c) Experimental Procedures for the Synthesis of 1

1.5.3.1	*	**6-Methylhept-5-en-2-one** [10]



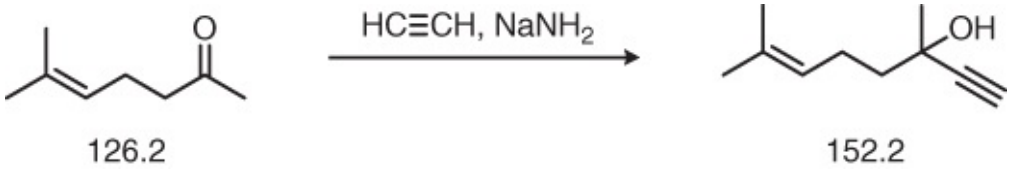
Sodium (12.6 g, 0.55 mol) is added to a stirred solution of ethyl acetoacetate (87.8 g, 0.67 mol) and anhydrous EtOH (150 ml) (formation of H_2). The mixture is cooled to 0 °C, and 1-bromo-3-methyl-2-butene (**4.2.2.2**) (74.5 g, 0.50 mol) is added dropwise over 20 min. Stirring is continued at room temperature for 3 h and at 60 °C for 4 h. During this time, a fine crystalline precipitate of sodium bromide is formed.

The mixture is then filtered, the filtrate is concentrated *in vacuo*, and the residue is treated with 10% aqueous NaOH solution (200 ml). The resulting mixture is stirred at room temperature for 2 h and at 60 °C for 3 h, cooled, and acidified to pH 4 with concentrated HCl. The solution is extracted with Et_2O (3 × 100 ml), and the combined organic phases are washed with saturated aqueous $NaHCO_3$ solution (150 ml) and H_2O, dried over $MgSO_4$, and filtered. The solvent is removed *in vacuo*, and the residue is fractionally distilled through a Vigreux column to give a colorless oil with a fruity odor; 51.7 g (77%), bp_{12} 64–65 °C, n^{20}_D = 1.4404.

IR (film): $\tilde{\nu}$ (cm^{-1}) = 1720, 1360, 1160.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 5.00 (m, 1H, 5-H), 2.4–2.1 (m, 4H, 3-H_2, 4-H_2), 2.04 (s, 3H, 1-H_3), 1.63 (m, 6H, 7-H_3, 6-CH_3).

1.5.3.2	**	**Dehydrolinalool (3,7-dimethyl-1-octyn-6-en-3-ol)** [11]



Finely powdered sodium amide (18.0 g, 0.46 mol, note 1) is added in portions to a stirred solution of methylheptenone **1.5.3.1** (30.0 g, 0.24 mol) in anhydrous Et_2O (150 ml) at −15 °C. After stirring the mixture for 3 h, a rapid stream of acetylene is passed through it for 4 h. The temperature is then held at −20 °C for

15 h. Thereafter, a rapid stream of acetylene is again passed through the mixture at −15 °C for 4 h.

The brown-yellow mixture is poured into well-stirred iced water (500 ml). The ethereal phase is separated, and the aqueous phase is extracted with Et_2O (150 ml). The combined organic phases are dried over $MgSO_4$ and filtered, and the solvent is removed *in vacuo*. The yellow residue is fractionally distilled *in vacuo* to give a colorless oil with an odor similar to that of geranial; 29.7 g (82%), bp_{10} 85–88 °C. n^{20}_D = 1.4632 (note 2).

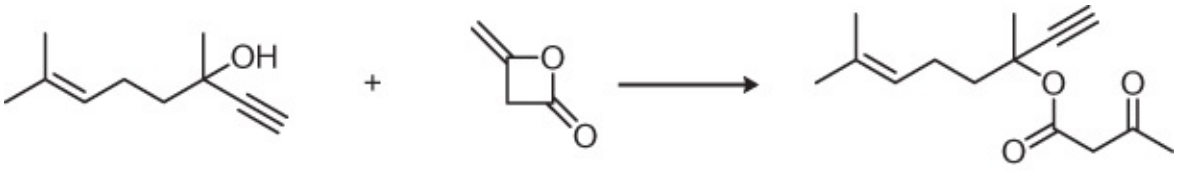
IR (film): $\tilde{\nu}$ (cm^{-1}) = 3400, 3300, 2970, 2920, 2860, 1450, 1120.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 5.15 (t, *J* = 6.5 Hz, 1H, 6-H), 2.52 [s, 1H, OH (exchangeable with D_2O)], 2.49 (s, 1H, 1-H), 2.35–1.9 (m, 2H, 5-H_2), 1.66 (s, 6H, 2 × 7-CH_2), 1.64 (t, *J* = 7 Hz, 2H, 4-H_2), 1.50 (s, 3H, 3-CH_3).

Notes:

1. $NaNH_2$ is obtained by filtering a suspension in toluene (sintered glass filter) and washing twice with Et_2O.
2. If the product still contains methylheptenone (determined by GC), it is shaken for 15 h with sodium bisulfite solution and redistilled.

1.5.3.3	**	**Dehydrolinalool acetoacetate** [12]



Sodium methoxide (0.20 g; freshly prepared and dried at 100 °C/0.1 mbar) is added to a solution of dehydrolinalool (**1.5.3.2**) (26.6 g, 175 mmol) in anhydrous toluene (40 ml). Diketene (16.4 g, 195 mmol) is added dropwise to the stirred solution over a period of 2 h, keeping the temperature under 30 °C with occasional cooling if necessary. Stirring is continued at 30 °C for 5 h and at room temperature for 15 h.

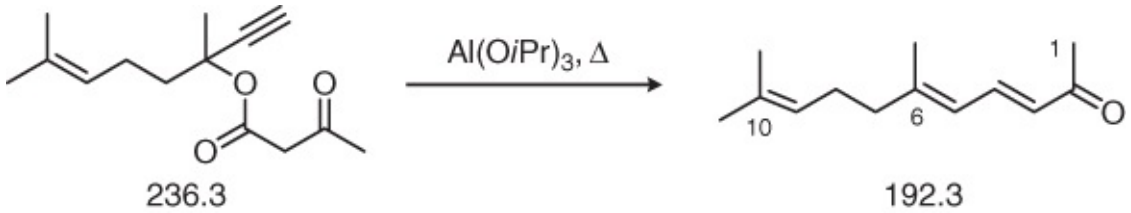
The light-brown mixture is then washed with aqueous H_2SO_4 (1 M, 50 ml),

saturated aqueous $NaHCO_3$ solution (50 ml), and H_2O (2 × 50 ml). The organic phase is dried over Na_2SO_4 and filtered, and the solvent is removed *in vacuo*. The residual yellow oil is sufficiently pure for further use; yield 41.3 g (100%). Distillation *in vacuo* gives a colorless oil, $bp_{0.005}$ 43–44 °C, n^{20}_D = 1.4652.

IR (film): $\tilde{\nu}$ (cm^{-1}) = 3290, 2060, 1755, 1725.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 5.25–4.80 (m, vinyl-H + enol-H), 3.34 (s, including previous signal 3H, CO–CH_2), 2.56 (s, 1H, ≡CH), 2.22 (s, 3H, CO–CH_3), 2.1–1.8 (m, 2H, allyl-CH_2), 1.70 [s, 6H, =$C(CH_3)_2$], 1.60 (s, 3H, CH_3), 1.75–1.5 (m, 2H, CH_2).

1.5.3.4	**	**Pseudoionone (6,10-dimethylundeca-3,5,9-trien-2-one)** [12]



A stirred mixture of the crude dehydrolinalool acetoacetate (**1.5.3.3**) (41.3 g, 175 mmol), decalin (50 ml), glacial acetic acid (0.5 ml), and aluminum isopropoxide (40 mg) is heated to 175–190 °C for 2 h with evolution of CO_2 (bubble trap).

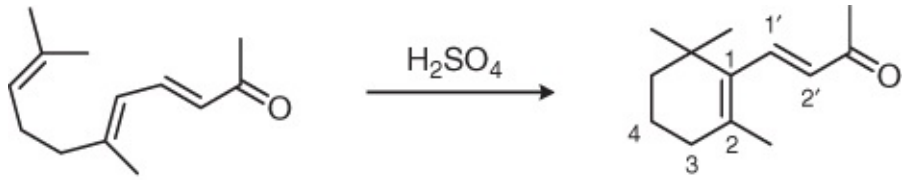
The mixture is then cooled, washed with aqueous H_2SO_4 (1 M, 50 ml), saturated aqueous $NaHCO_3$ solution (3 × 50 ml), and H_2O (2 × 50 ml), dried over $CaSO_4$, and filtered. The decalin is distilled off at 10 mbar (bp_{10} 70–71 °C). The yellow residue is fractionally distilled to give a pale-yellow oil; 21.2 g (63%), $bp_{0.5}$ 92–95 °C, n^{20}_D = 1.5272. The purity of the product is determined by GC.

UV (CH_3CN): λ_{max} (log ϵ) = 284 (4.51), 212 nm (4.14).

IR (film): $\tilde{\nu}$ (cm^{-1}) = 1685, 1665, 1630, 1590, 1250, 975.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.41 (dd, *J* = 11.0, 3.0 Hz, 1H, 4-H), 6.20–5.81 (m, 2H, 3-H, 5-H), 5.05 (m, 1H, 9-H), 2.40–2.05 (m, 4H, 7-H_2, 8-H_2), 2.27 (s, 3H, 1-H_3), 1.90 (s, 3H, 6-CH_3), 1.67, 1.61 (s, 6H, 2 × 10-CH_3).

1.5.3.5	**	**β-Ionone [4-(2,6,6-trimethylcyclohex-1-en-1-yl)but-3-en-2-one]** [13]



192.3 192.3

Pseudoionone (**1.5.3.4**) (50.0 g, 0.26 mol) is added to a well-stirred mixture of concentrated sulfuric acid (175 g) and glacial acetic acid (75 g) at 5 °C over 40 min, keeping the temperature below 10 °C. Stirring is continued at 10–15 °C for 10 min.

The mixture is then poured into a well-stirred mixture of iced water (1000 ml) and Et_2O (250 ml). The organic phase is separated, and the aqueous phase is extracted with Et_2O (250 ml). The combined organic phases are washed with H_2O (250 ml), 1% aqueous Na_2CO_3 solution (250 ml), and further H_2O (250 ml). The solvent is evaporated *in vacuo* and the residue is steam-distilled. The β-ionone is taken up in Et_2O (2 × 250 ml), the ethereal solution is dried over Na_2SO_4 and filtered, and the solvent is removed *in vacuo*. The residue is distilled through a 20 cm packed column (Raschig–rings) to give a light-yellow oil with a characteristic, pleasant odor; 36.5 g (73%), $bp_{0.7}$ 91–93 °C, n^{20}_D = 1.5198.

IR (film): $\tilde{\nu}$ (cm^{-1}) = 1700, 1675, 1615, 1590, 1260.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.13, 5.99 (d, *J* = 16.1 Hz, 1H, 4-H, 3-CH), 2.19 (s, 3H, 4′-H_3), 2.07 (m, 2H, 3-H_2), 1.75 (s, 3H, 2-CH_3), 1.80–1.20 (m, 4H, 4-H_2, 5-H_2), 1.07 (s, 6H, 6-$(CH_3)_2$).

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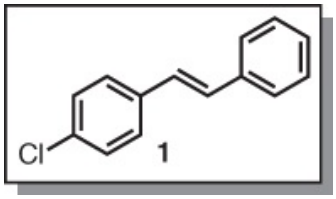
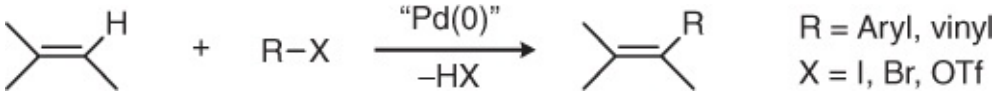
1.6 Transition-Metal-Catalyzed Reactions

1.6.1 (*E*)-4-Chlorostilbene

	***Topic:***	• Pd-catalyzed arylation of an alkene by a Heck reaction

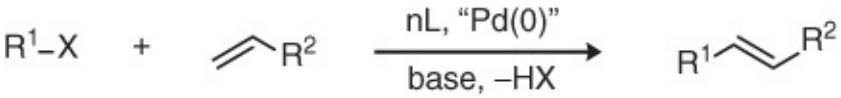
(a) General

The palladium-catalyzed arylation and alkenylation of alkenes is known as the ***Heck reaction*** [1]:



This coupling reaction of two sp^2-hybridized carbon centers usually requires the presence of (i) a mono-or bidentate phosphine as complexing ligand, and (ii) a base, often a tertiary amine such as triethylamine or diisopropylethylamine (Hünig base) or an inorganic base such as K_2CO_3 and NaOAc.

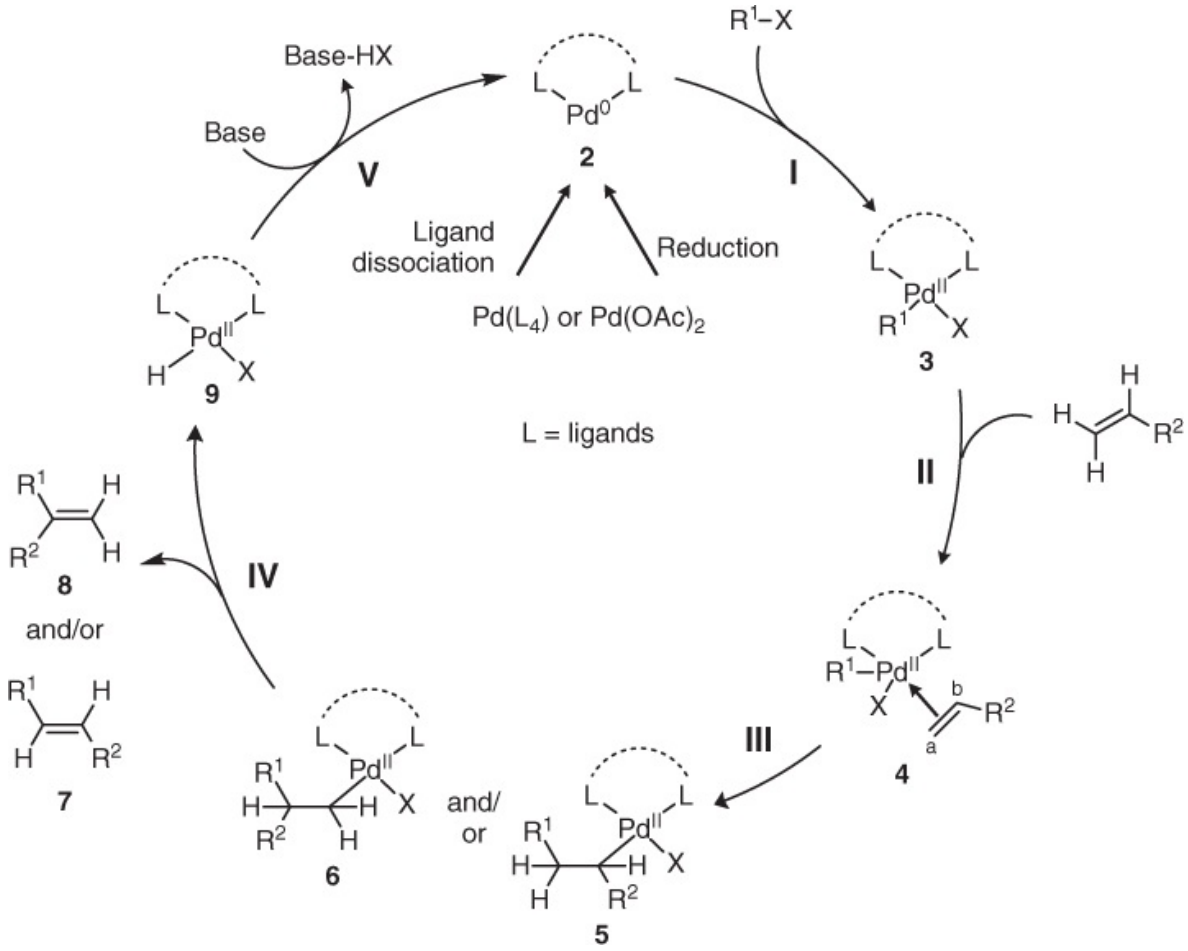
The generally accepted mechanism for the Heck reaction [2] consists of a catalytic cycle of five consecutive partial steps **I–V**, as formulated for the reaction of a monosubstituted alkene R^2–CH=CH_2 with an aryl or alkenyl halide R^1–X:



In step **I**, an oxidative addition of a 14-electron complex, Pd(0)L_2 (**2**), takes place by insertion into the C(sp^2)–X bond of R^1–X to give a tetracoordinated 16-electron Pd(II) complex **3**. Complex **2** is formed *in situ* either by reduction of a Pd(II) source such as Pd(OAc)$_2$ by, for example, a tertiary amine [1e, 2b] or a phosphine, or by dissociation of two ligands of a Pd(0)L_4 species such as Pd(PPh_3)$_4$.

In steps **II** and **III**, the alkene coordinates to the Pd(II) species **3** (π-complex

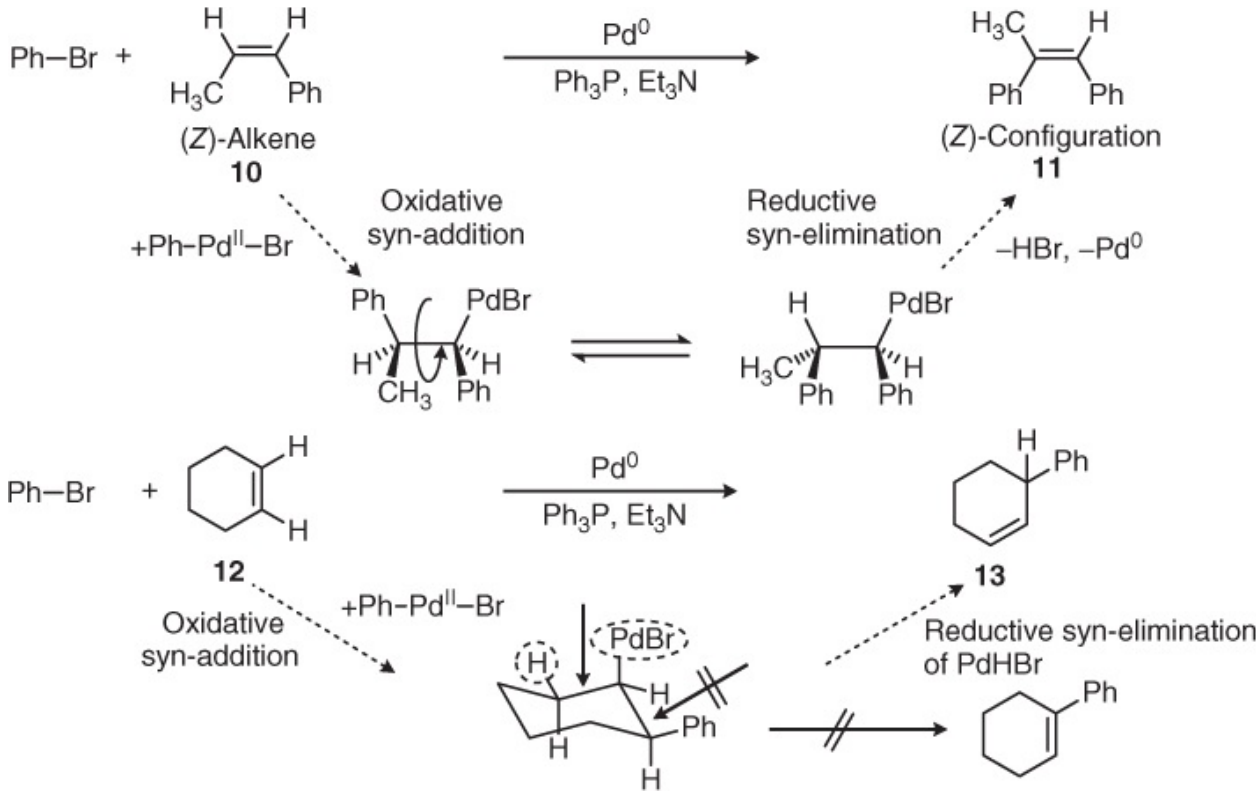
4) and is inserted into the Pd(II)–R^1 bond. The insertion process **III** is stereoselective and proceeds in a syn manner. Since the alkene R^2–CH=CH_2 is unsymmetrical, C_a or C_b may be involved in the insertion and two regioisomeric σ-alkyl-Pd(II) species **5** and/or **6** may be formed.



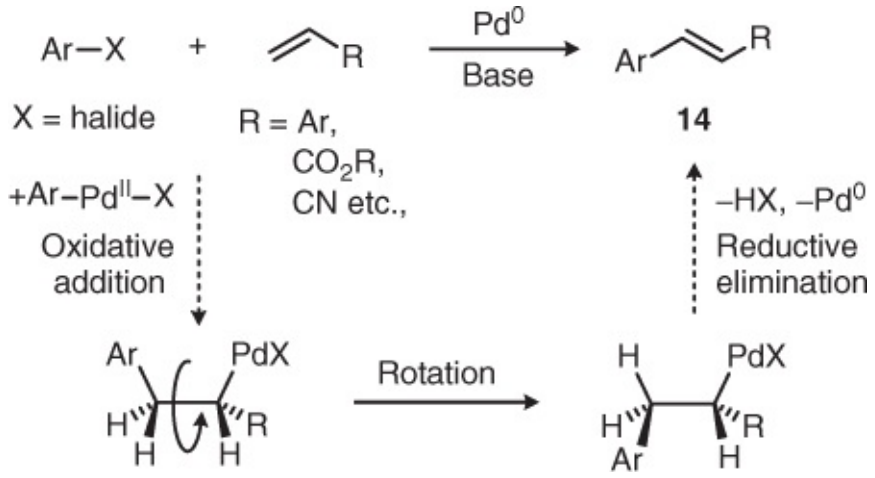
In step **IV**, a syn Pd-β-hydride elimination leads to the formation of the products **7**/**8** and the Pd(II) hydrido complex **9**.

In step **V**, the catalytic cycle is completed by regeneration of the catalytic Pd(0)L_2 species (**2**) from **9** by reaction with a base. Steps **IV** and **V** are regarded as reductive elimination.

The syn-stereoselectivity of the insertion into the C=C double bond and the reductive elimination has been shown in Heck reactions of stereodefined alkenes such as **10** and **12**, from which the products **11** and **13** are obtained [3]:

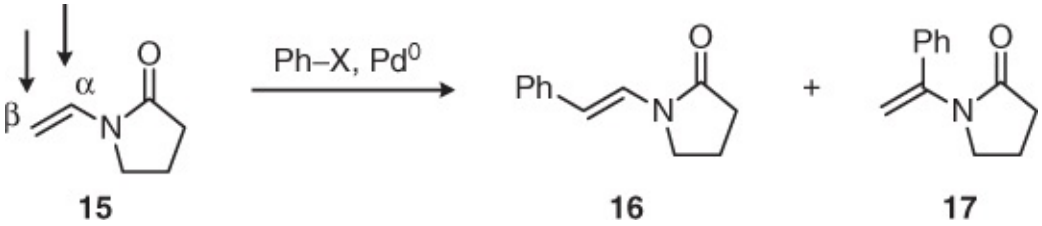


The regioselectivity (steps (**III**)/(**IV**)) of Heck reactions of unsymmetrical alkenes R–CH=CH_2 with Ar–X [2a] has been investigated using acryl derivatives and styrenes. Substitution usually occurs practically exclusively at the β-CH_2 site of the olefinic substrate to give products **14**, which are predominantly of (*E*)-configuration:



However, in some cases, the regioselectivity has been shown to be influenced (*inter alia*) by the nature of the leaving group X in Ar–X. Thus, from the enamide **15** with X = halide, a mixture of regioisomers **16**/**17** is produced, in which the β-product **16** predominates (3 : 2). However, with X = *O*-triflate, the

α-substitution product **17** is formed exclusively:



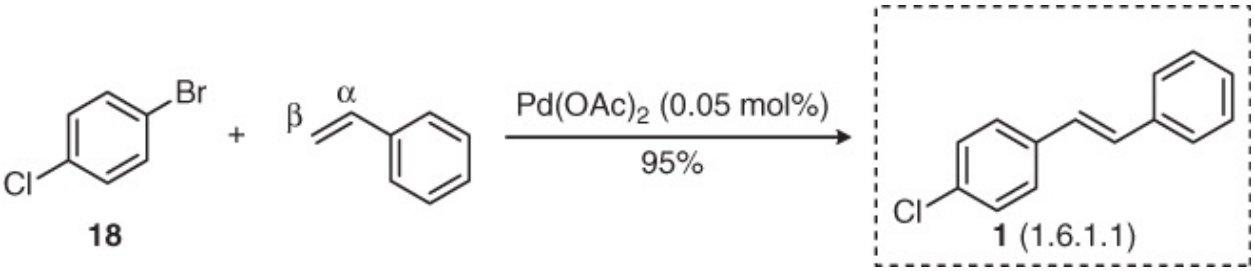
15 **16** **17**

A similar result is obtained if one performs the reaction of Ar–X (X = Hal) in the presence of Ag^+ salts. It is assumed that in this case, as well as using ArOTf, a Pd^+ intermediate is formed. It should be noted that acrylates react at the β-position under both conditions. The Heck reaction is of great synthetic value (cf. Section 3.3.5 and Ref. [4]). It can be performed in inter-and intramolecular modes [5]. Using chiral ligands, enantioselective transformations can be performed with >98% ee [6]. Increasingly, palladacycles are finding application as catalysts in phosphine-free Heck reactions [7, 8], even in polymer-supported form [9]. Likewise, as presented in Section (b), ligand-free Pd sources can be used [10]; for a conventional example, see Section 3.3.5.

Ligand-free Pd catalysts are effective for Heck reactions of aryl iodides [11], for Heck reactions in water [12], and for Heck reactions of substrates with less common leaving groups such as diazonium salts and carboxylic acid derivatives [13]. For the preparatively preferred aryl bromides, however, a convenient ligand-free method has only recently been devised [10].

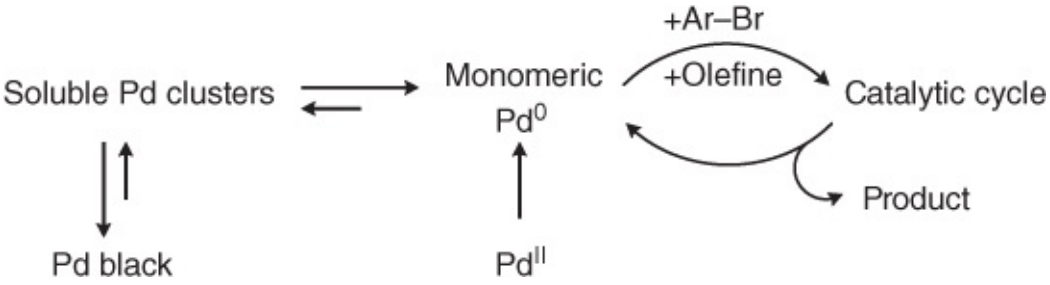
(b) Synthesis of 1

Heck reactions of donor-and acceptor-monosubstituted alkenes (preferentially acrylates and styrenes) can be performed with ligand-free palladium acetate as long as the amount of Pd catalyst is kept between 0.01 and 0.1 mol%. This is exemplified by the reaction of 4-(chloro)bromobenzene (**18**) with styrene in the presence of 0.05 mol% $Pd(OAc)_2$ in *N*-methyl-2-pyrrolidinone (NMP) at 135 °C, which proceeds chemoselectively to give the 4-chloro-substituted *trans*-stilbene **1** in a yield of 94%; the overall conversion is 99%, the trans selectivity is 99 : 1, and the regioselectivity (i.e., α-attack vs. β-attack, cf. Section (a)) is >95 : 5:



At higher catalyst concentrations, palladium black precipitates and the reaction stops before full conversion is obtained.

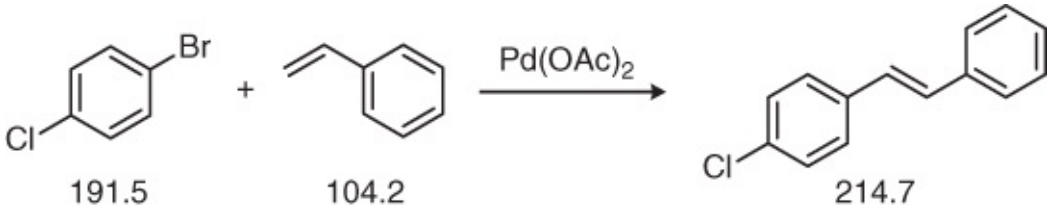
The following proposed mechanism for the arylation [10] explains the effect of low catalyst concentration:



With aryl bromides, the rate-determining step of a Heck reaction is usually the oxidative addition of a monomeric Pd(0) species to the sp^2C–Br bond.[7] Thus, if one uses a higher concentration of Pd(0), in a side reaction this can also aggregate to form soluble Pd clusters, which will turn into insoluble palladium black. Since the latter process is autocatalyzed, it rapidly leads to a lack of soluble Pd(0) species and thus to a termination of product formation.

(c) Experimental Procedure for the Synthesis of 1

1.6.1.1	**	**(*E*)-4-Chlorostilbene** [10]



Under an inert atmosphere, a two-necked flask is charged with NaOAc (0.90 g, 11.0 mmol), 1-bromo-4-chlorobenzene (1.91 g, 10.0 mmol) in NMP (14.0 ml). In a separate flask, $Pd(OAc)_2$ (5.0 mg) is dissolved in NMP (100 ml) to give a stock solution. An aliquot (9.00 ml) of this solution (0.02 mol% Pd with respect to 1-bromo-4-chlorobenzene) is added to the flask containing the

bromochlorobenzene by means of a syringe. The stirred mixture is heated to 120 °C, styrene (1.46 g, 14.0 mmol) is added, and stirring is continued at 135 °C for 15 h.

The mixture is then cooled to room temperature, poured into H_2O (75 ml), and extracted with toluene (2 × 75 ml). The combined organic layers are washed with H_2O (3 × 50 ml) and brine (50 ml), dried over Na_2SO_4, and filtered. The solution is filtered through a small plug of Celite® to remove the catalyst, the Celite® is washed with toluene (50 ml), and the solvent is removed *in vacuo* to give a white solid; yield 2.01 g (94%, note), R_f = 0.33 (SiO_2; petroleum ether).

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.03 (d, *J* = 16.4 Hz, 1H, CH=CH) and 7.07 (d, *J* = 16.4 Hz, 1H, CH=CH), 7.20–7.53 (m, 9H, 9 × Ar–H).

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 126.6, 127.4, 127.7, 127.9, 128.7, 128.9, 129.3, 133.2, 135.9, 137.0.

Note: The product contains 5% of 4-chloro-(1-phenylethenyl)benzene (determined by ^{1}H NMR), R_f = 0.49 (SiO_2; petroleum ether).

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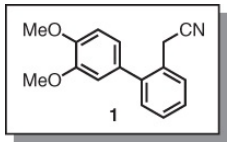
1.6.2 2-Cyanomethyl-3′,4′-dimethoxybiphenyl



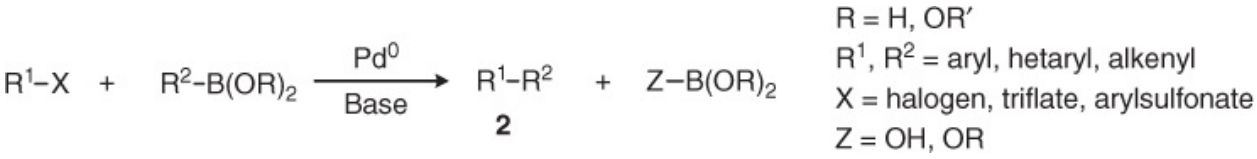
Topic:

- Synthesis of biaryls by Suzuki–Miyaura cross-coupling reaction of arylboronic acids with

		haloarenes

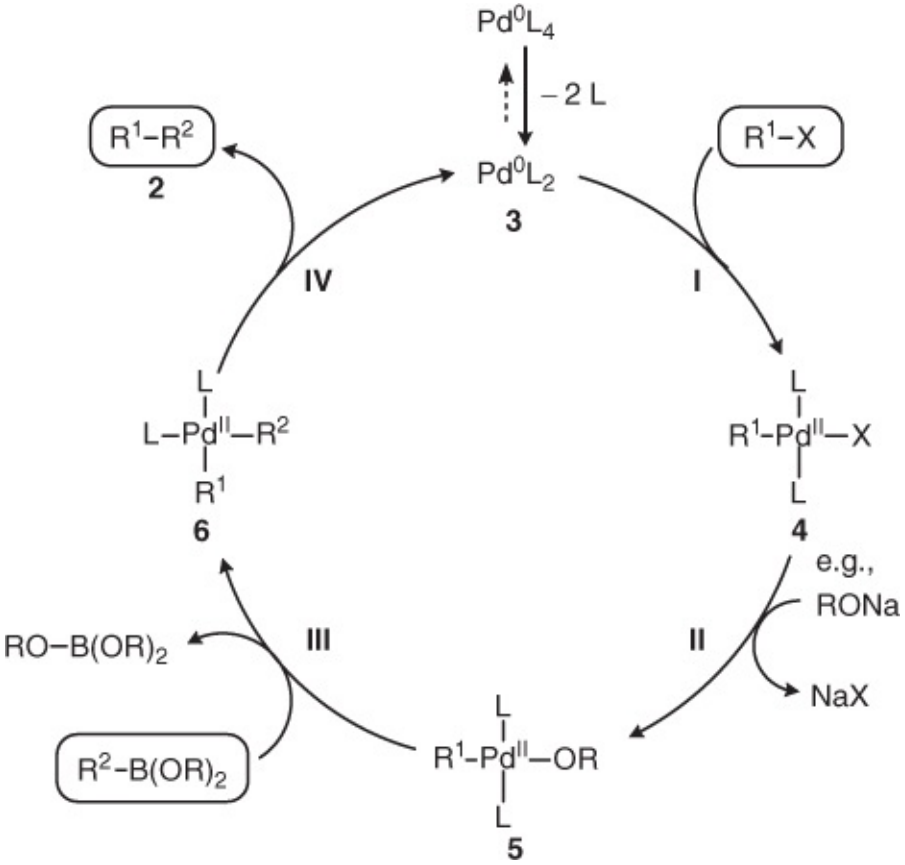
(a) General

The Suzuki–Miyaura cross-coupling reaction [1] allows C–C bond formation between aryl or alkenyl boronic acids/esters and arenes, hetarenes, or alkenes bearing a leaving group (halides, triflates, arylsulfonates) to afford products of type **2**:



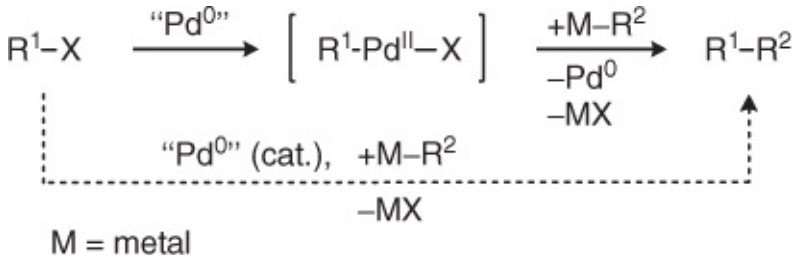
This C(sp^2)–C(sp^2) bond-forming process [2] is catalyzed by Pd(0) complexes, mostly $Pd(PPh_3)_4$, and requires the presence of an inorganic base such as an alkali metal hydroxide, alcoholate, or carbonate to form an ate-complex as an intermediate.

The proposed mechanism of the Suzuki–Miyaura reaction [3] is represented by a catalytic cycle that, in principle, is similar to that operating in the Heck and Sonogashira reactions (cf. Sections 1.6.1 and 1.6.3):

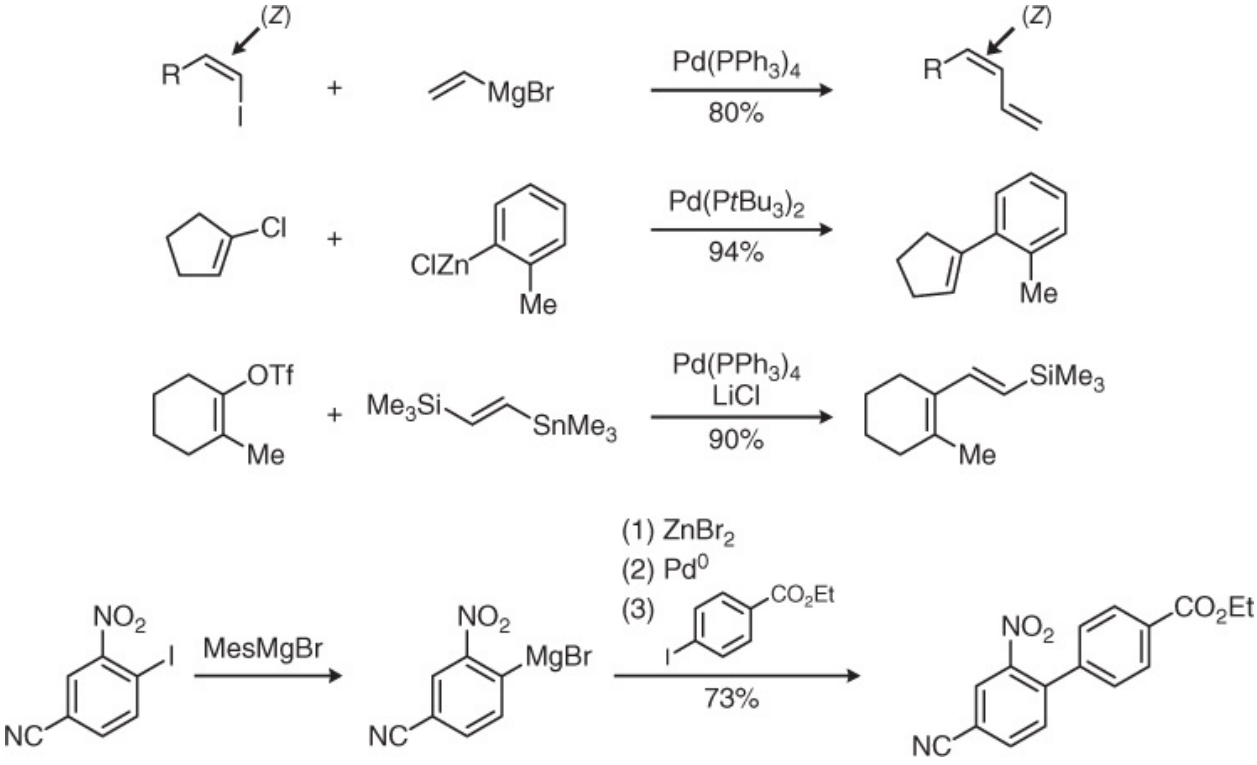


The catalytically active Pd species is again a 14 e $Pd(0)L_2$ complex (**3**) (produced from $Pd(0)L_4$ by ligand dissociation), which starts the catalytic cycle by oxidative addition to R^1–X (step **I**). The resulting tetracoordinated Pd(II) complex **4** is attacked by the base, for example, RONa, the ligand X is exchanged by alcoholate, and a new complex **5** is formed (step **II**). In a second exchange reaction, the boronic acid/ester substitutes the alkoxy ligand (**5** → **6**) by transfer of its organic residue R^2 to the Pd coordination sphere (presumably via ate-complex formation at boron, step **III**). Finally, the Pd(II) complex **6** undergoes a reductive elimination to afford the C–C coupled product **2** (most likely from a complex with a cis orientation of R^1 and R^2 in **6**) and the Pd(0) species **3**, which reenters the catalytic cycle (step **IV**).

Similarly, other organometallics M–R^2 can also be used in this Pd(0)-catalyzed “transmetallation” process:



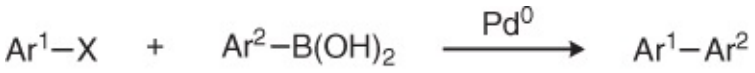
Thus, Pd(0)-mediated transmetallation allows numerous synthetically useful $C(sp^2)$–$C(sp^2)$ coupling reactions of alkenes and arenes substituted with halogen or triflate. In this respect, Grignard compounds [4], organozinc halides (Negishi cross-coupling [5]), organotin compounds (Stille cross-coupling [6]), and organosilanes have been used, as shown by the following examples:



Besides the Suzuki cross-coupling reactions, the Stille reaction is also widely used, with the advantage that the addition of a base is not necessary. On the other hand, tin is highly toxic. The Negishi protocol also seems to be quite flexible, since the required organozinc halides can be generated by transmetallation from Grignard compounds [5]. Using the commercially available stable catalyst $HPd(PtBu_3)_3 \cdot BF_4$, even aryl and alkenyl chlorides undergo coupling reactions with aryl, vinyl, and alkyl zinc bromides [7]; numerous functional groups (NO_2, CO_2R, CN, COR) are tolerated.

The Suzuki reaction is widely used for the formation of 1,3-butadienes and

unsymmetrical biaryls, which are challenging targets in natural product and pharmaceutical chemistry [8–12]:



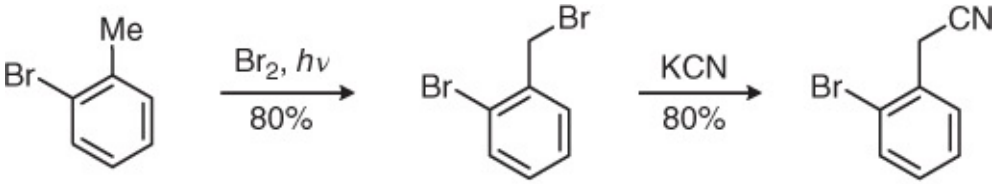
X = Br, I, triflate, arylsulfonate
Ar^1 = Functionalized aryl (CO_2R, CN, NO_2, etc.)
Ar^2 = Functionalized aryl (ether, acetal, etc.)

As Ar^1–X species, mainly bromides, iodides, triflates, and arylsulfonates [13] are used; chlorides can also be coupled in the presence of highly active Pd catalysts such as $HPd(PtBu_3)_3 \cdot BF_4$ [14]. Moreover, diazonium salts and aromatic carboxylic acids can also be employed [15]. Phosphine-free and palladacycle-based modifications of the Suzuki reaction have also been developed [16]. Generally, in Ar^1–X, functional groups such as NO_2, CN, and CO_2R, are tolerated, whereas the boronic acids Ar^2–$B(OH)_2$ may contain ether or acetal functions.

In Section (b), a Suzuki reaction is used for the preparation of **1**, which serves as a substrate for the synthesis of a simple alkaloid (cf. Section 5.2.3 Buflavine) containing an unsymmetrical functionalized biaryl unit [17].

(b) Synthesis of 1

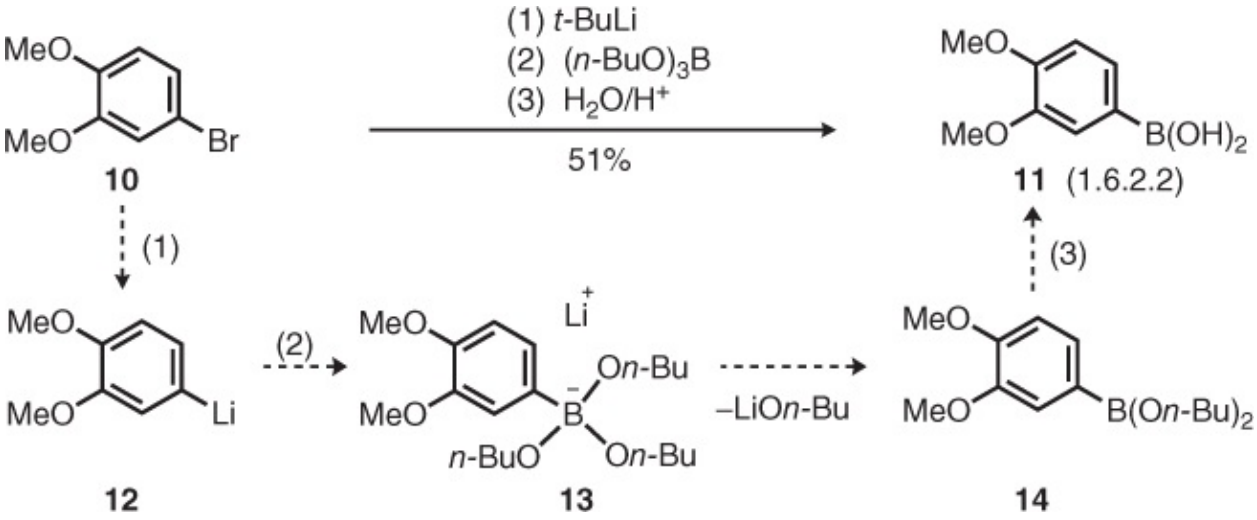
First, the substrate for the Suzuki reaction, (2-bromophenyl)acetonitrile (**9**) is prepared by way of a conventional two-step procedure [18] by photobromination of 2-bromotoluene (**7**) to give **8** and S_N displacement of the benzylic bromide by cyanide:



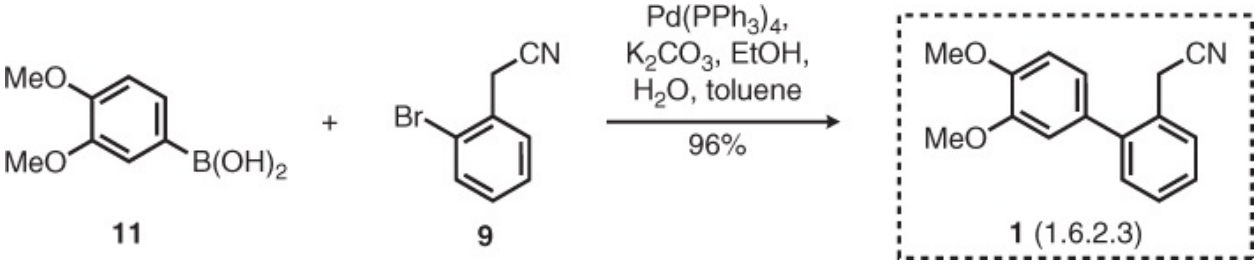
7 **8** **9** (1.6.2.1)

The second building block is (3,4-dimethoxyphenyl)boronic acid (**11**), which is obtained [19] from 4-bromoveratrole (**10**) by halogen–metal exchange with *t*-BuLi (**10** → **12**; with the usually employed *n*BuLi partial o-lithiation is observed). Reaction of the formed lithio compound **12** with tri-*n*-butyl borate and subsequent acid hydrolysis of the thus obtained boronate **14** leads to **11**. The formation of **14** probably proceeds via the ate-complex **13** and cleavage thereof

with loss of *n*-BuOLi:

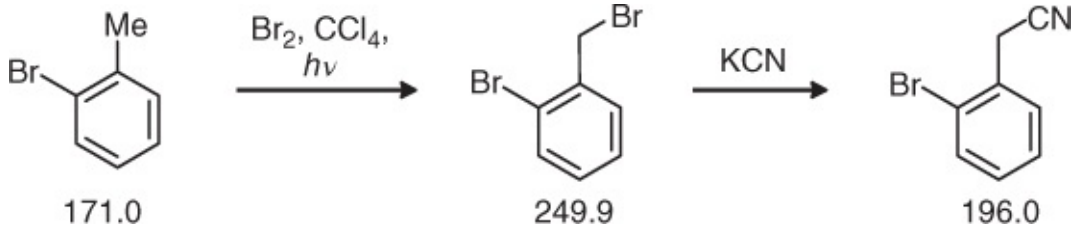


The building blocks **9** and **11** are combined in a Suzuki–Miyaura cross-coupling reaction using $Pd(PPh_3)_4$ as catalyst and K_2CO_3 as base in a solvent mixture. After standard work-up, the biaryl system **1** is isolated in almost quantitative yield.



(c) Experimental Procedures for the Synthesis of 1

1.6.2.1	**	**(2-Bromophenyl)acetonitrile** [18]



2-Bromotoluene (8.55 g, 50.0 mmol) is dissolved in CCl_4 (250 ml; Caution: resorption through the skin!), and the solution is stirred and heated to reflux under irradiation (daylight lamp 500 W). Bromine (8.19 g, 51.3 mmol) is slowly added from a dropping funnel at such a rate that the refluxing CCl_4 remains almost colorless. After completion of the reaction, the irradiation is stopped and

the solution is cooled to room temperature. The mixture is then rapidly washed with iced water (150 ml), ice-cold saturated aqueous $NaHCO_3$ solution (150 ml), and further iced water (150 ml). The organic layer is dried over $MgSO_4$ and filtered, and the solvent is removed *in vacuo*. The residue is distilled *in vacuo* (bp_{16} 130–131 °C) to yield the bromide as colorless liquid; yield 10.0 g (80%).

2-Bromobenzyl bromide (10.0 g, 40 mmol), sodium cyanide (2.45 g, 50.0 mmol, Caution!), and triethylene glycol (20 ml) are carefully heated to 100 °C with vigorous stirring. The mixture is stirred at this temperature for a further 30 min, then poured into water, and extracted with $CHCl_3$ (4 × 20 ml). The isocyanide (formed as a side-product) is removed from the combined organic layers by shaking with 5% aqueous H_2SO_4 (15 ml) for 5 min, and the organic layer is separated and washed sequentially with dilute aqueous $NaHCO_3$ solution (30 ml) and water. The organic layer is dried over $CaCl_2$ and filtered, and the solvent is removed *in vacuo*. The residue is purified by distillation (bp_{17} 146–147 °C) to yield a colorless liquid; yield 6.27 g (80%).

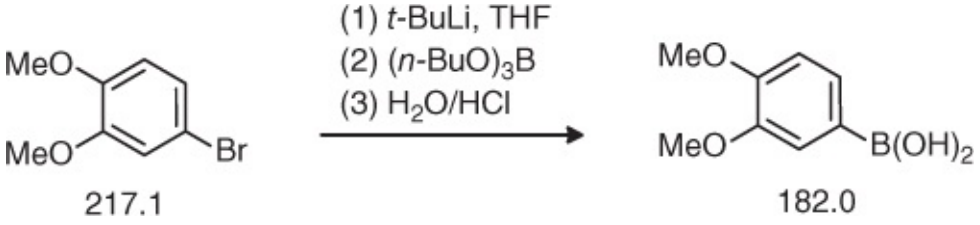
IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3060, 2260, 1565, 1475, 1020, 740.

^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) = 7.57 (dd, *J* = 7.8, 1.7 Hz, 1H, Ar–H), 7.49 (dd, *J* = 7.8, 1.7 Hz, 1H, Ar–H), 7.33 (dt, *J* = 7.8, 1.7 Hz, 1H, Ar–H), 7.18 (dt, *J* = 7.8, 1.7 Hz, 1H, Ar–H), 3.80 (s, 2H, CH_2).

^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) = 132.8, 129.7, 129.6, 129.5, 127.9, 123.3, 116.7, 24.60.

MS (EI, 70 eV): *m*/*z* (%) = 197 (34) $[M+H]^+$, 195 (35) $[M-H]^+$, 171 (8), 169 (9), 116 (100), 89 (36).

1.6.2.2	**	**3,4-Dimethoxyphenylboronic acid** [19]



217.1 182.0

tert-Butyllithium (1.5 M in CH_2Cl_2, 13.5 ml, 20.2 mmol) is slowly added to a

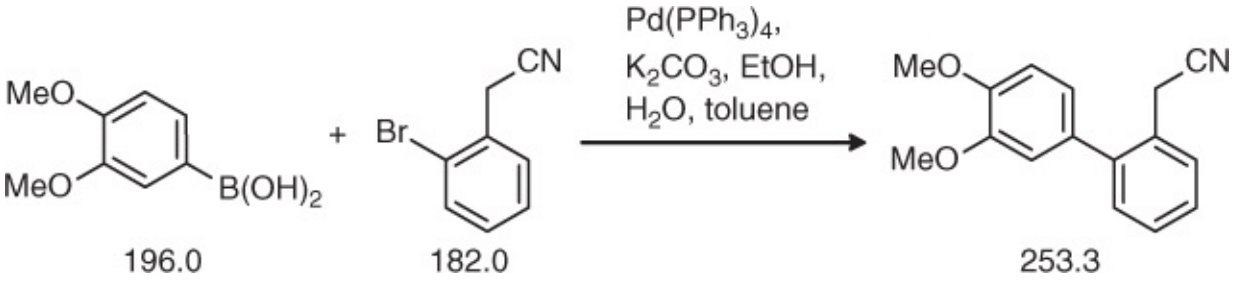
stirred solution of 4-bromoveratrole (4.00 g, 18.4 mmol) in THF (50 ml) at −78 °C over 4 h (the temperature must not exceed −70 °C), followed by trimethyl borate (2.87 g, 27.6 mmol). The mixture is then allowed to warm to room temperature overnight.

HCl (2 M, 25 ml) is added, and the aqueous phase is extracted with Et_2O (2 × 50 ml). The combined organic layers are extracted with aqueous NaOH (2 M, 2 × 50 ml), and then the combined aqueous extracts are acidified with concentrated HCl to pH 1. The aqueous layer is extracted with Et_2O (3 × 50 ml), and the combined organic layers are dried over $MgSO_4$, filtered, and concentrated to give the boronic acid as colorless solid; 1.72 g (51%), mp 238–240 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.85 (dd, *J* = 8.2, 1.3 Hz, 1H, Ar–H), 7.68 (d, *J* = 1.3 Hz, 1H, Ar–H), 7.01 (d, *J* = 8.2 Hz, 1H, Ar–H), 4.01 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3).

^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) = 153.0, 148.6, 129.9, 117.5, 110.8, 55.9, 55.9.

1.6.2.3	**	**2-Cyanomethyl-3′,4′-dimethoxybiphenyl** [17]



A solution 3,4-dimethoxyphenylboronic acid **1.6.2.2** (2.00 g, 11.0 mmol) in EtOH (60 ml) is added to a mixture of (2-bromophenyl)acetonitrile **1.6.2.1** (1.96 g, 10.0 mmol), toluene (60 ml), $Pd(PPh_3)_4$ (348 mg, 0.30 mmol), K_2CO_3 (4.15 g, 30.0 mmol), and water (40 ml). The mixture is degassed and heated to reflux for 24 h under inert gas atmosphere.

After cooling to room temperature, water (50 ml) is added and the mixture is extracted with Et_2O (3 × 80 ml). The combined organic layers are dried over $MgSO_4$, filtered, and concentrated. The residue is purified by column chromatography (SiO_2; CH_2Cl_2) to give 2.43 g (96%) of a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.56–7.46 (m, 1H, Ar–H), 7.44–7.26 (comb. m, 3H, Ar–H), 6.95 (d, *J* = 8.5 Hz, 1H, Ar–H), 6.85 (s_{br}, 2H, Ar–H), 3.93 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 3.63 (s, 2H, CH_2–CN).

^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) = 149.1, 148.7, 141.9, 132.6, 130.6, 129.1, 128.2, 128.1, 121.2, 118.5, 112.3, 111.4, 56.0, 56.0, 22.1.

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(1999), **38**, 2096–2152;(b) Nicolaou, K.C. and Snyder, S.A. (2003) *Classics in Total Synthesis II*, Wiley-VCH Verlag GmbH, Weinheim, p. 239.

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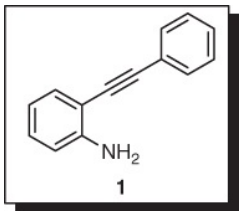
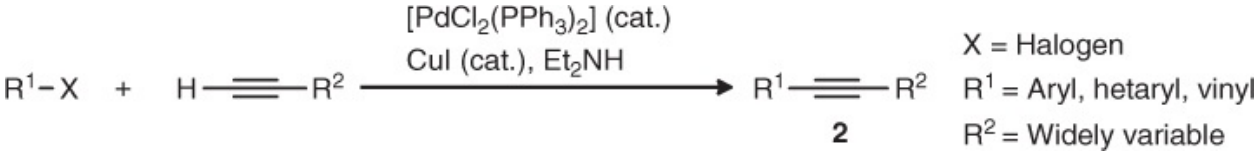
1.6.3 (2-Phenylethynyl)aniline

 1	***Topic:***	• Sonogashira cross-coupling reaction of terminal acetylenes with aryl and vinyl halides

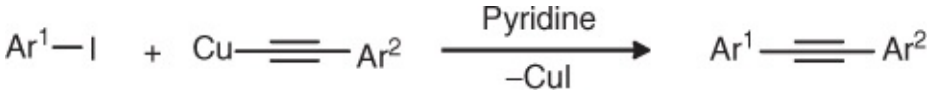
(a) General

The Sonogashira cross-coupling reaction [1] allows C–C bond formation between C(sp) and C(sp^2) centers by a Pd(0)-catalyzed reaction of haloarenes, halohetarenes, and haloalkenes with alkynes to give the coupled products **2**. The reaction is co-catalyzed by Cu(I) iodide and requires the presence of a base, preferably diethylamine:

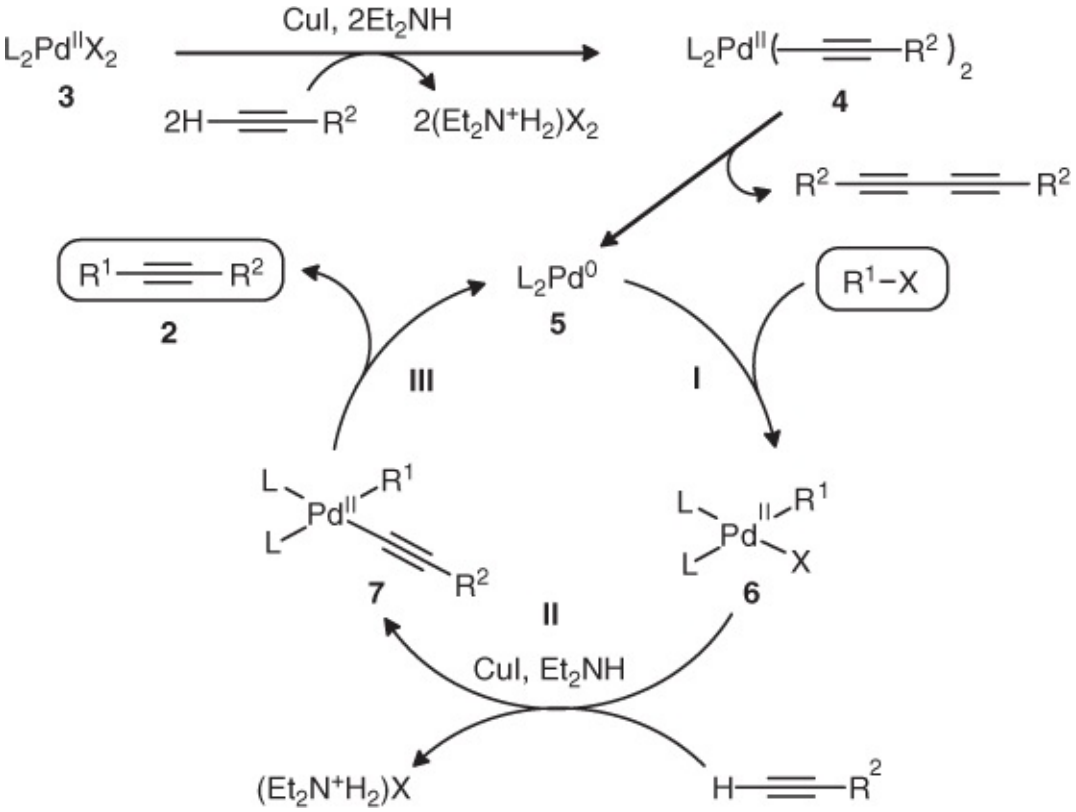


The Sonogashira coupling is related to the Stephens–Castro reaction [2], the

The Sonogashira coupling is related to the Stephens–Castro reaction [2], the coupling of iodoarenes with copper(I) aryl acetylides:



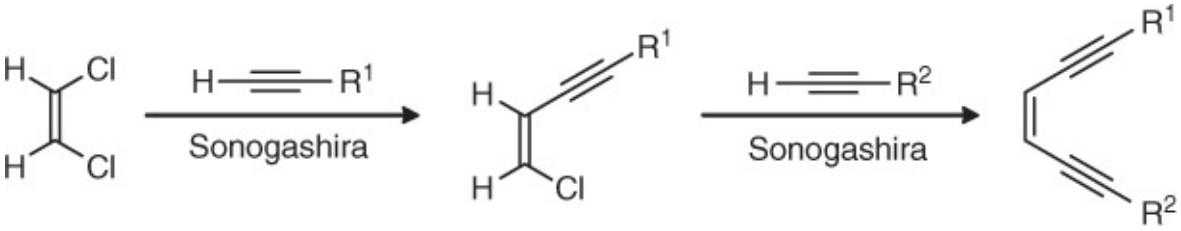
The mechanism of the Sonogashira cross-coupling reaction [2] resembles that of the Heck and Suzuki–Miyaura reactions by providing C–C bond formation in the coordination sphere of Pd complexes (L = ligand, e.g., Ph_3P).



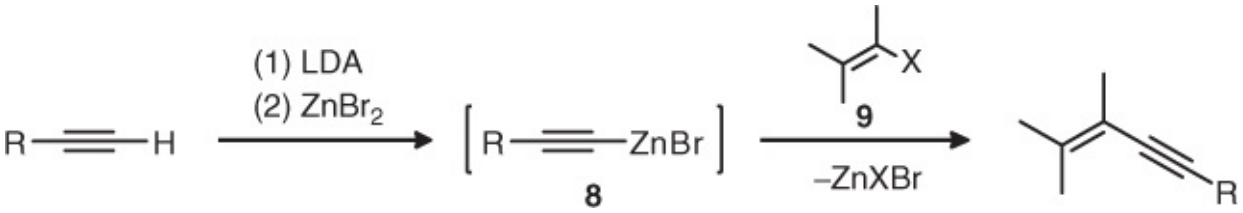
The catalytic cycle is initiated by a $Pd(0)L_2$ species **5**, which is generated, for example, in a preceding sequence from a Pd(II) complex **3** by base-induced exchange of the ligands X with acetylide and subsequent disproportionation of the acetylide Pd(II) complex **4** leading to the formation of $Pd(0)L_2$ (**5**) and, as a side product, a diyne. This can be avoided by using a Pd(0) complex such as $Pd(PPh_3)_4$ as catalyst. The Pd(0) species **5** undergoes an oxidative addition to R^1–X (step **I**), which is followed by base-induced substitution of X by acetylide in the Pd(II) complex **6** catalyzed by Cu(I) iodide (step **II**). Finally, a reductive elimination process of the formed Pd(II) complex **7**, most likely from a syn arrangement (step **III**), leads to the disubstituted acetylene **2** and $Pd(0)L_2$, which again enters into the catalytic cycle.

Usually, iodo compounds are used in the Sonogashira reaction because these are

Usually, iodo compounds are used in the Sonogashira reaction because these are more reactive than the bromo and chloro compounds [3]. This allows the chemoselective reaction of haloarenes bearing different halogens as substituents. Moreover, the consecutive introduction of two different acetylenic moieties in dihaloalkenes is also possible, which is used in the syntheses of analogs of enediyne antibiotics [2]:



As an alternative to the Sonogashira reaction, alkynylation of haloalkenes **9** can be efficiently accomplished by Pd(0)-catalyzed reaction with *in situ* generated alkynyl zinc bromides **8**, which are easily accessible from acetylides and $ZnBr_2$ [4]:

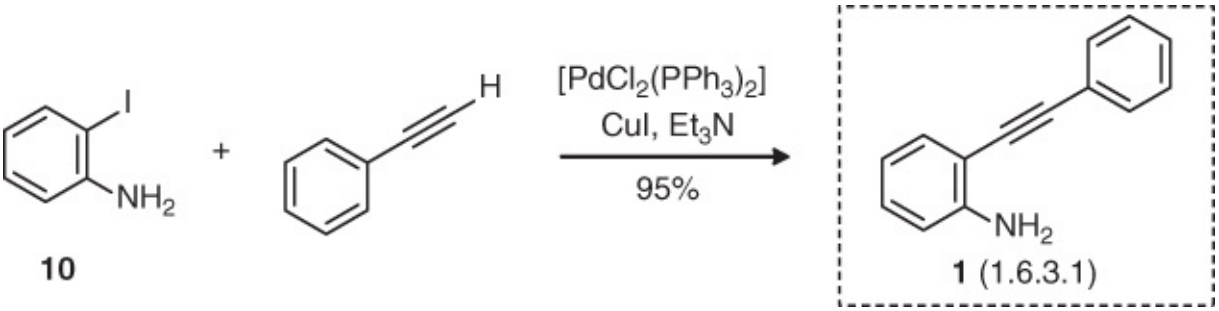


The great synthetic value of the Sonogashira reaction, above all, stems from the fact that further transformations of the alkyne moiety may be performed. This is documented, for example, in a series of syntheses of heterocyclic systems [5].

Thus, in Section (b), the preparation of substrate **1** for a Pd-catalyzed indole synthesis (cf. Section 3.2.4) by means of a Sonogashira cross-coupling [6] is described.

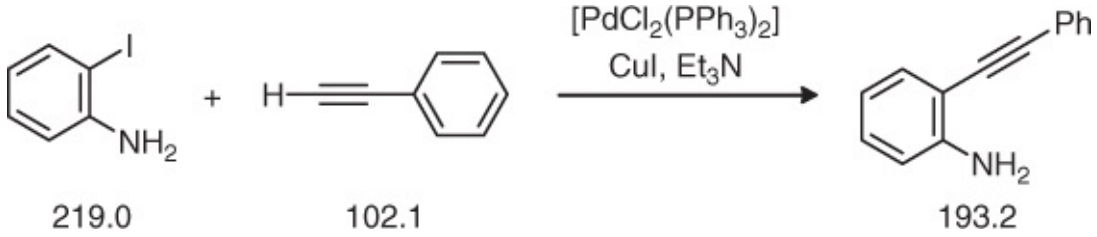
(b) Synthesis of 1

The synthesis of **1** starts from 2-iodoaniline (**10**), which is commercially available but can also be easily prepared by ortho-lithiation of aniline and subsequent quenching with iodine [7]. The Sonogashira cross-coupling reaction of **10** with phenylacetylene in the presence of $[PdCl_2(PPh_3)_2]$ as catalyst, Cu(I) iodide as co-catalyst, and triethylamine as base provides (2-phenylethynyl)aniline (**1**) in almost quantitative yield:



(c) Experimental Procedure for the Synthesis of 1

1.6.3.1	**	**2-(Phenylethynyl)aniline** [6]



A mixture of 2-iodoaniline (2.19 g, 10.0 mmol), phenylacetylene (1.12 g, 11.0 mmol), CuI (190 mg, 1.00 mmol), $[PdCl_2(PPh_3)_2]$ (210 mg, 0.30 mmol), and Et_3N (20 ml) is stirred for 1 h at 60 °C.

The reaction mixture is then diluted with H_2O (20 ml) and extracted with $CHCl_3$ (3 × 20 ml). The combined extracts are dried over $MgSO_4$ and filtered, and the solvent is removed *in vacuo*. The crude product is purified by column chromatography (SiO_2; *n*-hexane/EtOAc, 3 : 1) and recrystallized from *n*-hexane/EtOAc (20 : 1) to give pale-yellow prisms; 1.84 g (95%); mp 86–87 °C; R_f = 0.60 (*n*-hexane/EtOAc, 3 : 1).

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3500, 2250, 1620.

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.56–7.51 (m, 2H, Ph–H), 7.39–7.32 (m, 4H, Ph–H), 7.14 (dt, *J* = 7.9, 1.4 Hz, 1H), 6.79 (t, *J* = 7.7 Hz, 2H), 4.29 (s_{br}, 2H, NH_2).

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Diederich, F. (eds) (2004) *Metal-Catalyzed Cross-Coupling Reactions*, 2nd edn, **2** vols., Wiley-VCH Verlag GmbH, Weinheim;Instead of Pd complexes, nanosized Pd(0) ((c) Li, P., Wang, L., and Li, H. (2005) *Tetrahedron*, **61**, 8633–8640), ultrafine Ni(0) (Wang, L., Li, P., and Zhang, Y. (2004**)** *Chem. Commun.*, 514–515), or Pd immobilized on organic–inorganic hybrid materials (Li, P.-M. and Wang, L. (2006**)** *Adv. Synth. Catal.*, **348** 681–685) has also been applied in the Sonogashira process.

2. Nicolaou, K.C. and Sorensen, E.J. (1996) *Classics in Total Synthesis*, Wiley-VCH Verlag GmbH, Weinheim, p. 582.

3. (a) Krause, N. (1996) *Metallorganische Chemie*, Spektrum Akademischer Verlag, Heidelberg, p. 216;Efficient catalysts have also been developed for the Sonogashira coupling of chloroarenes: (b) Köllhofer, A., Pullmann, T., and Plenio, H. (2003) *Angew. Chem.*, **115**, 1086–1088; *Angew. Chem. Int. Ed.*, **(**2001**)**, **40**, 1056–1058.

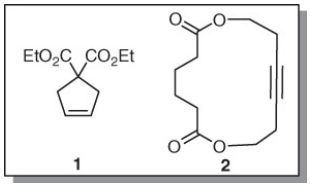
4. (a) Negishi, E.-i., Qian, M., Zeng, F., Anastasia, L., and Babinski, D. (2003) *Org. Lett.*, **5**, 1597–1600;(b) Anastasia, L. and Negishi, E.-I. (2001) *Org. Lett.*, **3**, 3111–3113.

5. See: Eicher, Th., Hauptmann, S., and Speicher, A. (2012) *The Chemistry of Heterocycles*, 3rd edn, Wiley-VCH Verlag GmbH, Weinheim, p. 83, 140.

6. Yasuhara, A., Kanamori, Y., Kaneko, M., Numata, A., Kondo, Y., and Sakamoto, T. (1999) *J. Chem. Soc., Perkin Trans. 1*, 529–534.

7. Snieckus, V. (1990) *Chem. Rev.*, **90**, 879–933.

1.6.4 Diethyl cyclopent-3-ene-1,1-dicarboxylate and 1,8-Dioxacyclotetradec-11-yne- 2,7-dione

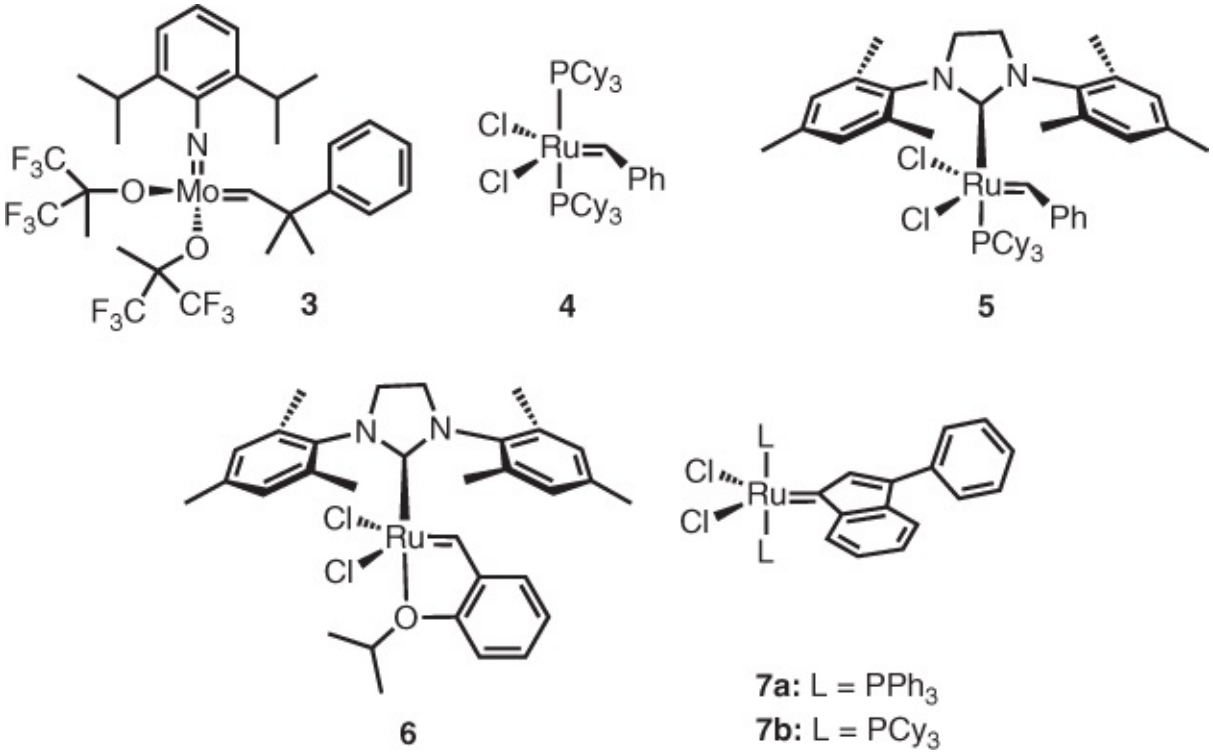
	***Topics:***	• Ring-closing alkene metathesis • Synthesis of Ru complexes • Ligand exchange • Ring-closing alkyne metathesis with an air-

		stable molybdenum alkylidene phenanthroline catalyst • Synthesis of a cyclopentene • Synthesis of an acyclic dialkyne • Synthesis of a cyclic alkyne

(a) General

The alkene metathesis is a very important method for the formation of C=C-double bonds. The most useful procedures from the synthetic standpoint are the ring-closing metathesis (RCM), the ring-opening metathesis (ROM), and the cross metathesis (CM) of alkenes. Further important variants are the ring-opening metathesis polymerization (ROMP), the acyclic diene metathesis (ADMET), and the alkyne metathesis mostly in the ring-closing mode (RCAM (ring-closing alkene metathesis)) [1].

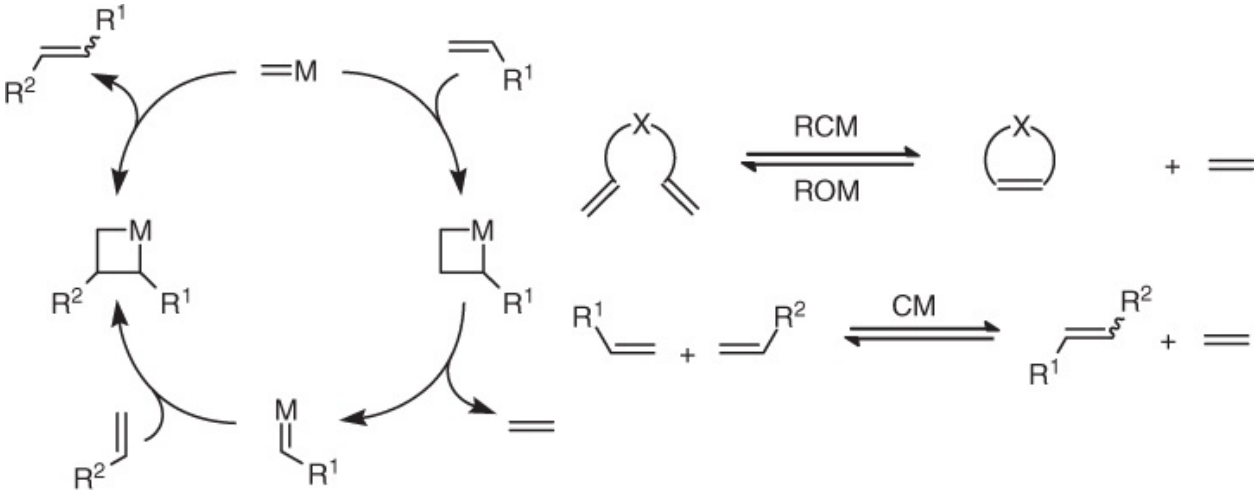
As catalysts for these transformations, organometallic compounds of the Schrock type **3** containing molybdenum or tungsten and of the Grubbs type **4**, **5**, and **6** containing ruthenium are used. Another useful catalyst for the alkene metathesis are the Ru-phenylindenylidene complexes **7a** and **7b**.



The alkene metathesis proceeds via a [2 + 2]-cycloaddition of an alkene and the

The alkene metathesis proceeds via a [2 + 2] cycloaddition of an alkene and the alkylidene unit of the catalyst to form a metallacyclobutane. In a cycloreversion, the reaction could go backwards or form another alkylidene unit which reacts with another alkene to give the product and the catalyst. It is important to know that metatheses are thermodynamically controlled. In this respect, CMs and RCMs are favored by an entropic effect because of the formation of ethene or other gases.

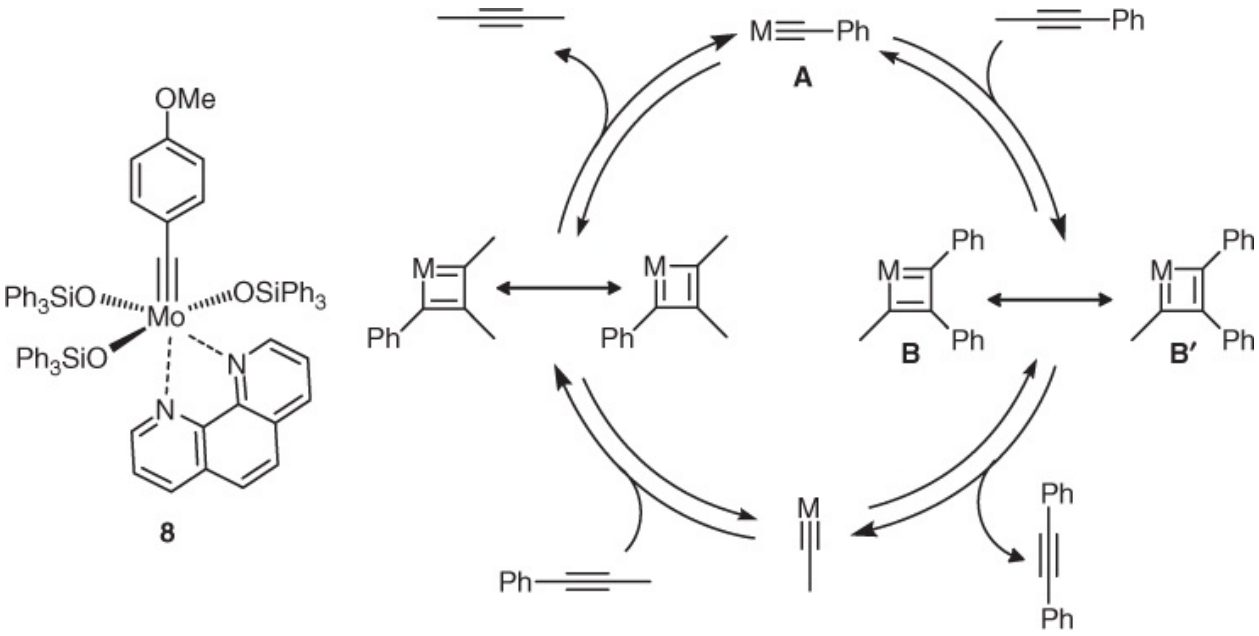
CMs are nowadays often used as a replacement for the Wittig reaction and the RCMs leading to cyclohexenes as a replacement for the Diels–Alder reaction.



However, one of the major drawbacks is the usually low *E*/*Z*-selectivity, though novel developments by Schrock *et al.* [2] seem to solve the problem. But another possibility to prepare selectively *E*- or *Z*-cycloalkenes of larger rings is the use of the alkyne RCM. Fürstner [3] has recently developed novel air-stable Mo complexes **8** which can be employed for this purpose.

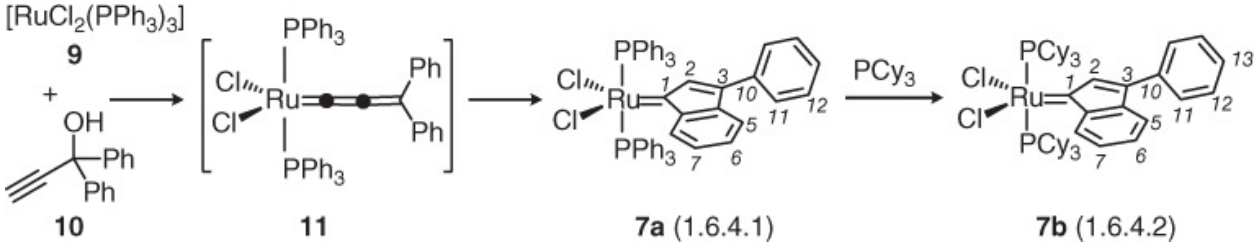
The cyclic alkynes obtained can then be hydrogenated using a Lindlar-type catalyst to give (*Z*)-cycloalkenes. On the other hand, Birch reduction or some novel methods [4] lead to the corresponding (*E*)-compounds.

The alkyne metathesis follows a similar mechanism as the alkene metathesis with a metallayclobutadiene as an intermediate:

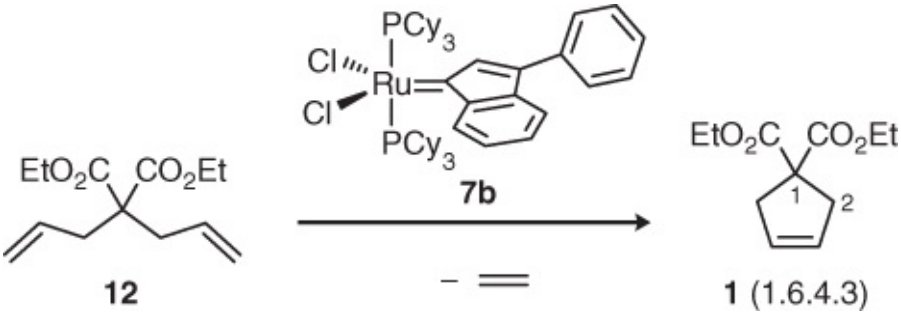


(b) Synthesis of 1 and 2

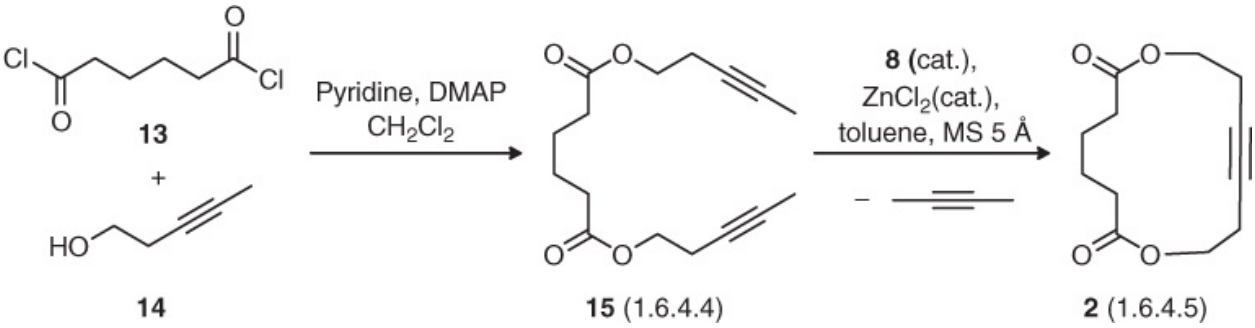
For the synthesis of the cyclopentene **1** by an RCM of the α,ω-diene **12**, the Ru-phenylindenylidene complex **7b** is used as catalyst [5]. Though catalysts **4** and **5** would also be suitable, the ruthenium-phenyliden complexes **7a** and **7b** developed by Fürstner [3] are very good alternatives to the first-generation Grubbs catalyst **4**. The main advantage of these catalysts is their ease of preparation using the Ru complex **9** and the inexpensive and nontoxic diphenylpropargylic alcohol **10** as the carbene source. In contrast, for the synthesis of the Grubbs catalysts, phenyldiazomethane has to be employed. The preparation of **7a** proceeds via **11** by heating a mixture of **9** and **10** under reflux for 90 min in THF. The complex **7a** can then be transformed into the complex **7b** by heating **7a** in the presence of tricyclohexylphosphane.



For the synthesis of **1**, the commercially available 1,6-diene **12** is used in the presence of 1.5 mol% of **7b** in dichloromethane.

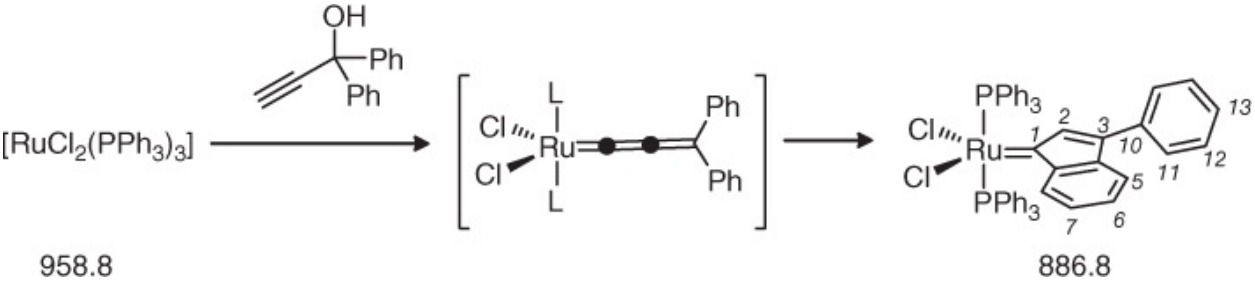


For the ring-closure alkyne metathesis, the novel air-stable Mo complex **8**, which is commercially available, can be employed [3], and as a substrate for the metathesis, the adipic ester **15** containing two alkyne moieties is used in the example described here. It can be obtained from adipyl dichloride **13** with 3-pentynol **14**.



(c) Experimental Procedures for the Synthesis of 1 and 2

1.6.4.1	***	**Ruthenium-phenylindenylidene complex 7a** [5]



A two-necked flask equipped with a reflux condenser, a magnetic stirring bar, and an argon or nitrogen supply is evacuated, dried with a heat gun, and flushed with argon or nitrogen. The flask is charged with $[RuCl_2(PPh_3)_3]$ (10.4 g, 10.8 mmol), THF (600 ml), and 1,1-diphenylpropargyl alcohol (3.37 g, 16.2 mmol), and the resulting mixture is refluxed under inert gas for 2.5 h. During this period, the mixture turns dark-red.

For work-up, the solvent is evaporated *in vacuo* (12 mbar), the residue is

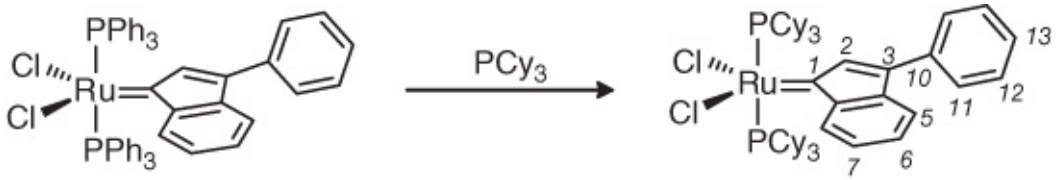
suspended in *n*-hexane (400 ml), and the suspension is stirred for approximately 3 h until the solid is thoroughly ground and has a homogeneous appearance. The powdered solid is filtered off and dried *in vacuo* to give 9.60 g (quant.) of the complex **1.6.4.1** as an orange powder.

^{1}H NMR (600 MHz, CD_2Cl_2): δ (ppm) = 7.54 (1H, 13-H), 7.54 (12H, Ph), 7.50 (2H, 11-H, 12-H), 7.46 (6H, Ph), 7.34 (2H, 12-H), 7.33 (12H, Ph), 7.31 (td, *J* = 7.5, 1.5 Hz, 1H, 6-H), 7.25 (dd, *J* = 7.5, 1.5 Hz, 1H, 5-H), 7.08 (dd, *J* = 7.3, 1.0 Hz, 1H, 8-H), 6.67 (td, *J* = 7.4, 1.0 Hz, 1H, 7-H), 6.38 (s, 1H, 2-H).

^{13}C NMR (150 MHz, CD_2Cl_2): δ (ppm) = 301.0 (s, *J* = 12.9 Hz (t), C-1), 145.4 (s, C-3), 141.8 (s, *J* = 2.7 Hz (t), C-9), 139.8 (s, C-4), 139.4 (d, *J* = 5.2 Hz (t), 175.4 Hz, C-2), 135.6 (s, C-10), 130.1 (d, C-6), 130.1 (d, C-7), 129.41 (2C, d, C-12), 129.36 (d, C-13), 129.33 (d, 165 Hz, C-8), 127.1 (2C, d, C-11), 118.6 (d, 160 Hz, C-5). Phenyl signals: X part of ABX spin systems (A, B = ^{31}P, X = ^{13}C), δ = 135.2 (d, [*J*(P,C) + *J*(P′,C)] = 11.2 Hz, C-*ortho*), 131.2 (s, [*J*(P,C) + *J*(P′,C)] = 42.8 Hz, C-*ipso*) 130.6 (d, C-*para*), 128.4 (d, [*J*(P,C) + *J*(P′,C)] = 9.6 Hz, C-*meta*).

^{31}P NMR (243 MHz, CD_2Cl_2, rel. ext. H_3PO_4): δ (ppm) = 28.7.

1.6.4.2	***	**Ruthenium-phenylindenylidene complex (7b)** [5]



886.8 923.1

PCy_3 (9.39 g, 33.5 mmol) is added to a solution of the complex **1.6.4.1** in CH_2Cl_2 (250 ml), and the resulting mixture is stirred for 2 h at ambient temperature under argon.

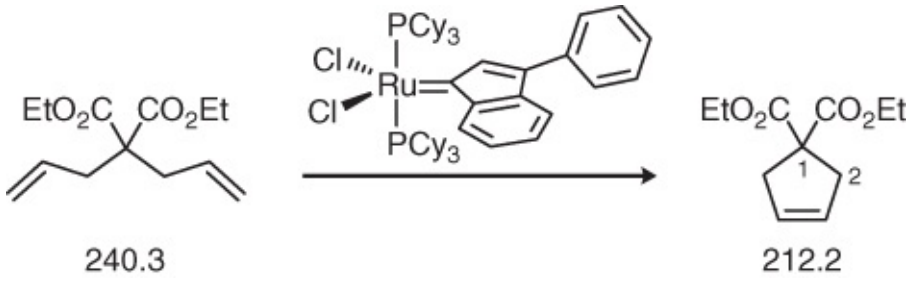
The solvent is evaporated, and the crude product is suspended in *n*-hexane (400 ml) and stirred for approximately 3 h at ambient temperature. The thoroughly powdered complex is filtered off and is carefully washed with *n*-hexane (100 ml) in several portions. Drying of the product *in vacuo* affords 7.90 g (80%) of complex **1.6.4.2** as an analytically pure orange powder.

^{1}H NMR (600 MHz, CD_2Cl_2): δ (ppm) = 8.67 (dd, *J* = 7.5 Hz, 1H, 8-H), 7.75 (2H, 11-H), 7.52 (1H, 13-H), 7.40 (2H, 12-H), 7.39 (s, 1H, 2-H), 7.38 (td, 1H, *J* = 7.3 Hz, 6-H), 7.29 (td, *J* = 7.5 Hz, 1H, 7-H), 7.27 (dd, *J* = 7.3 Hz, 1H, 5-H). Cyclohexyl signals: δ = 2.60, 1.77, 1.73, 1.66, 1.65, 1.52, 1.50, 1.47, 1.21, 1.19, 1.18.

^{13}C NMR (150 MHz, CD_2Cl_2): δ (ppm) = 293.9 (s, *J* = 8.1 Hz (t), C-1), 145.0 (s, C-9), 141.4 (s, C-4), 139.8 (s, C-3), 139.1 (d, ^{1}J(C,H) = 175 Hz, C-2), 136.8 (s, C-10), 129.4 (d, ^{1}J(C,H) = 163 Hz, C-8), 129.4 (2C, d, C-12), 129.2 (d, C-7), 128.7 (d, C-6), 128.4 (d, C-13), 126.6 (2C, d, C-11), 117.6 (d, ^{1}J(C,H) = 157 Hz, C-5). Cyclohexyl signals: δ (ppm) = 33.1 (CH), 30.21, 30.16, 28.3, 28.1, 26.9 (all CH_2).

^{31}P NMR (243 MHz, CD_2Cl_2, rel. ext. H_3PO_4) δ (ppm) = 32.6.

1.6.4.3	**	**Diethyl cyclopent-3-ene-1,1-dicarboxylate** [5]



To a stirred solution of the ruthenium-indenyliden complex **1.6.4.2** (32.5 mg, 1.5 mol%) in dichloromethane (5.0 ml) in a dry two-neck round-bottom flask equipped with a gas inlet and a glass stopper, diethyl 2,2-diallylmalonate (577 mg, 2.40 mmol) is added under argon or nitrogen atmosphere (note) at room temperature, and stirring is continued for 90 min at this temperature.

The solvent is removed *in vacuo*, and the residue is purified by column chromatography on silica gel (*n*-pentane/diethyl ether = 20 : 1) to give 459 mg (90%) of the cyclopentene derivative **1.6.4.3** as a colorless oil.

IR (film) $\tilde{\nu}$ (cm^{-1}) = 3063, 2983, 1733, 1625, 1256, 1182, 1072, 697.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 5.62–5.60 (m, 2H, 2 × 3-H), 4.20 (q, *J* = 7.1 Hz, 4H, $C\underline{H}_2CH_3$), 3.01 (s, 4H, 2 × 2-H_2), 1.25 (t, *J* = 7.1 Hz,

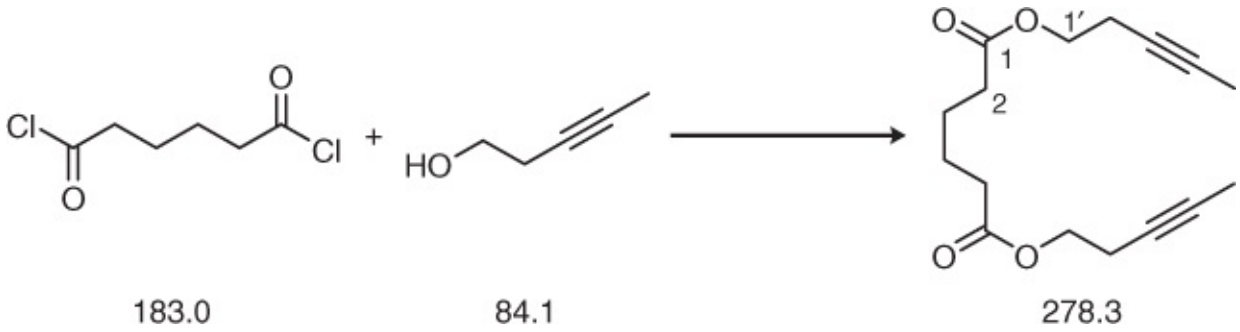
6H,$CH_2C\underline{H}_3$).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 172.2 ($\mathit{C}OCH_2CH_3$), 127.7 (2 × C-3), 61.4 ($CO\mathit{C}H_2CH_3$), 58.8 (C-1), 40.8 (C-2), 14.0 ($COCH_2\mathit{C}H_3$).

MS: *m*/*z* (rel. intensity): 212 (M^+, 23), 166 (52), 138 (89), 123 (2), 111 (52), 93 (44), 79 (63), 66 (84), 55 (8), 39 (20), 29 (100).

Note: Strict exclusion of oxygen is necessary for high yields.

1.6.4.4	*	**Di(pent-3-yn-1-yl) adipate** [6, 7]



To a stirred solution of 3-pentynyl-1-ol (5.04 g, 59.9 mmol) and dimethyl-aminopyridine (DMAP) (cat., ∼40 mg) in anhydrous pyridine (5.0 ml) and anhydrous dichloromethane (50 ml) in a dry two-neck round-bottom flask equipped with a dropping funnel and a glass stopper, a solution of adipyl dichloride (5.48 g, 29.9 mmol) in dichloromethane (20 ml) is added dropwise at 0 °C. Stirring is continued for 12 h at room temperature.

For work-up, aqueous HCl (1 M, 80 ml) is added slowly with stirring. The organic phase is separated and washed consecutively with aqueous HCl (1 M, 30 ml) and saturated aqueous $NaHCO_3$ solution (30 ml). The combined aqueous phases are extracted with ethyl acetate (50 ml), and the combined organic layers are washed with brine (50 ml), dried over Na_2SO_4, and filtered. The solvent is removed *in vacuo*, and the residue is co-evaporated twice with a small amount of toluene (15 ml) to remove remaining pyridine by azeotropic distillation. After drying of the residue *in vacuo*, the adipic acid dialkynylester **1.6.4.4** is obtained as a colorless solid, which is used in the next step without further purification; 7.49 g (90%); mp = 63–64 °C.

IR (film) $\tilde{\nu}$ (cm^{-1}) = 2962, 2918, 2856, 1735, 1698, 1468, 1453, 1427, 1412,

1394, 1371, 1302, 1250, 1136, 1070, 1051, 981, 924, 913, 750, 734, 707.

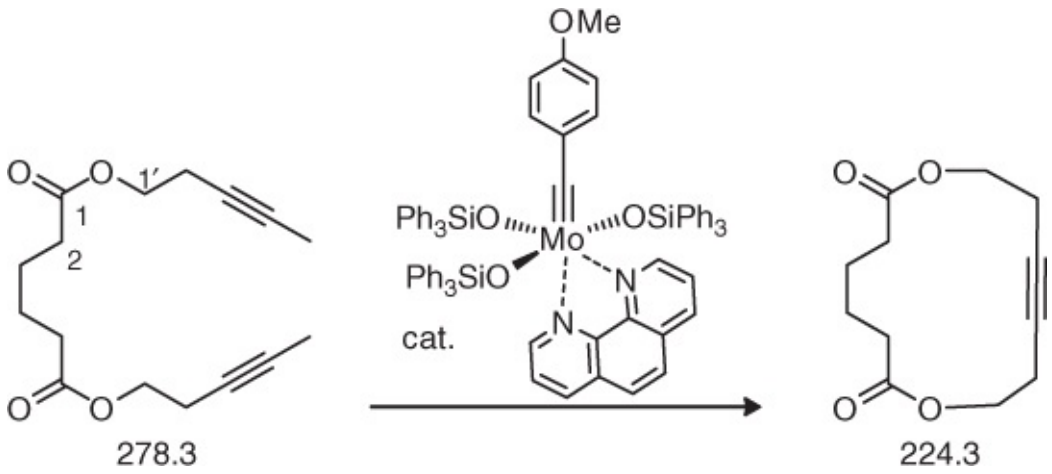
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 4.11 (t, *J* = 7.0 Hz, 4H, 2 × 1′-H_2), 2.44 (tq, *J* = 7.0, 2.5 Hz, 4H, 2 × CH_2), 2.36–2.31 (m, 4H, 2 × CH_2), 1.76 (t, *J* = 2.5 Hz, 6H, 2 × CH_3), 1.69–1.63 (m, 4H, 2 × CH_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 173.0 (C-1), 77.2, 74.7 (C-3′, C-4′), 62.7 (C-1′), 33.8, 24.3, 19.2 (C-2, C-3, C-2′), 3.4 (C-5′).

MS: *m*/*z* (EI) (rel. intensity): 278 (2) $[M]^+$, 213 (22), 196 (11), 195 (92), 177 (12), 153 (12), 150 (16), 149 (26), 135 (27), 133 (10), 132 (76), 131 (22), 129 (35), 126 (13), 125 (12), 117 (78), 111 (64), 107 (20), 101 (17), 97 (13), 83 (19), 67 (100), 66 (76), 65 (21), 55 (24), 41 (19).

HRMS: (ESI+): *m*/*z*: calc. for $[C_{16}H_{22}O_4 + Na]^+$: 301.1410; found: 301.1409.

1.6.4.5	**	**1,8-Dioxacyclotetradec-11-yne-2,7-dione** [6, 7]



A two-necked flask with a magnetic stirring bar, an argon or nitrogen supply, and a glass stopper is evacuated, dried with a heat gun, and flushed with argon or nitrogen. Then it is charged with $ZnCl_2$ (12.7 mg, 5 mol%) and molecular sieves (5 Å, about 4 g, activated at 180 °C *in vacuo*). Anhydrous toluene (90 ml) is added, and the suspension is stirred for 1 h at room temperature. Afterwards, [Mo(≡CAr)($OSiPh_3$)$_3$(phen)] (Ar = 4-methoxyphenyl, phen = 1,10-phenanthroline) (114 mg, 5 mol%) and 1,6-bis(pent-3-yne-1-yl)hexanedioate **1.6.4.4** (519 mg, 1.87 mmol) are added in solid form and the mixture stirred for 18 h at room temperature.

For work-up, a frit (diameter about 4.5 cm) is filled with silica gel (∼19 g) with the help of *n*-hexane/ethyl acetate (5 : 1). Then the reaction mixture is filtered through this pad of silica gel with *n*-hexane/ethyl acetate (5 : 1, ∼140 ml) as eluent, and the filtrate is discarded (TLC control). Then the pad is eluted again with *n*-hexane/ethyl acetate (5 : 1, ∼120 ml), and the filtrate is collected and evaporated *in vacuo* to give analytically pure **1.6.4.5** as colorless solid; 350 mg (84%); mp = 109–110 °C.

IR (film) $\tilde{\nu}$ (cm^{-1}) = 2995, 2954, 2937, 2918, 2901, 2872, 1721, 1458, 1425, 1384, 1341, 1272, 1236, 1167, 1140, 1080, 1065, 1021, 981, 931, 843, 824, 699.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 4.13–4.06 (m, 4H, 2 × CH_2), 2.53–2.47 (m, 4H, 2 × CH_2), 2.39–2.30 (m, 4H, 2 × CH_2), 1.76–1.67 (m, 4H, 2 × CH_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 173.2 (2 × CH_2*C*$O_2$$CH_2$), 78.2 (2 × C≡C), 62.8 (2 × CH_2), 35.2 (2 × CH_2), 25.4 (2 × CH_2), 19.4 (2 × CH_2).

MS: *m*/*z* (EI) (rel. intensity): 129 (3), 111 (8), 78 (100), 66 (20), 55 (15), 41 (8).

HRMS: (ESI+): *m*/*z*: calc. for $[C_{12}H_{16}O_4 + Na]^+$: 247.0941; found: 247.0938.

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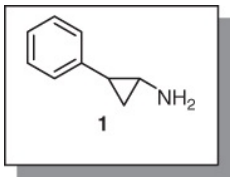
1.7 Pericyclic Reactions

1.7.1 Tranylcypromine

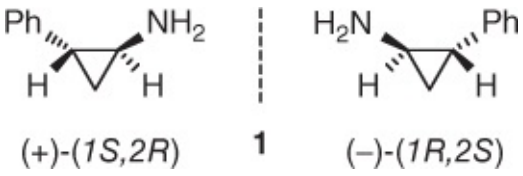


Topics:

- Synthesis of an aminocyclopropane-based drug
- [1 + 2]-Cycloaddition of carbethoxycarbene to styrene, cyclopropanation of an alkene
- Ester saponification
- Separation of stereoisomers by fractional crystallization
- Thermal Curtius degradation

(a) General

Tranylcypromine (**1**) is the racemic mixture of *trans*-(*E*)-2-phenylcyclopropyl-1-amine and is used pharmaceutically as a psychoanaleptic and antidepressant [1]. Tranylcypromine acts as an inhibitor of monoamine oxidase A, thus retarding the metabolic degradation of serotonin, noradrenaline, adrenaline, and other amines [2].



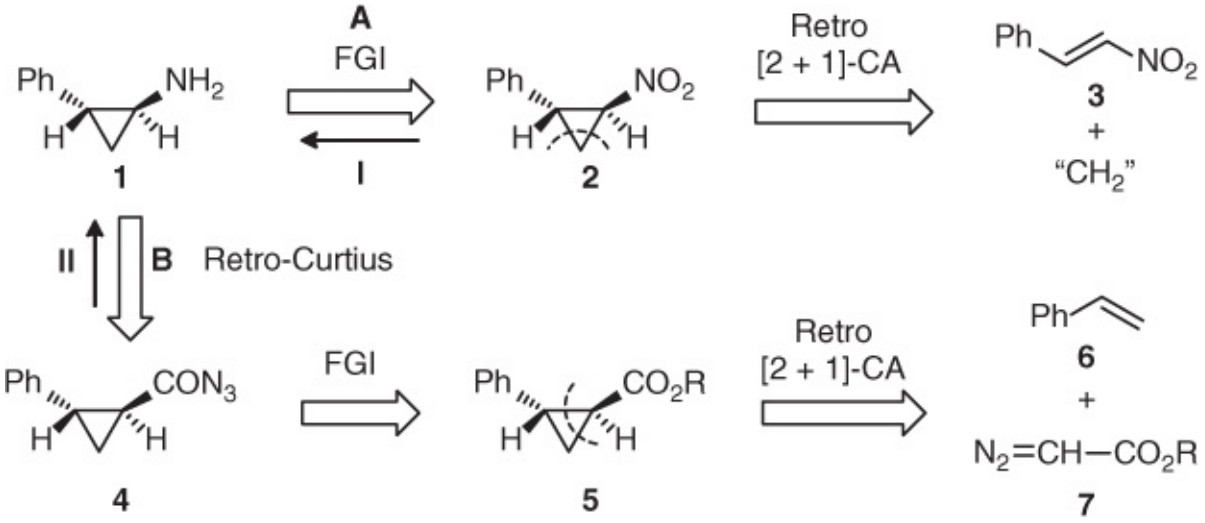
Both enantiomers of **1** are known, and their structure–activity relationships have been investigated; the (1*S*,2*R*)-compound shows a 10 times higher inhibitory

activity than its enantiomer.

For the retrosynthesis of cyclopropanes, the most appropriate bond disconnections generally result from retro-[1 + 2]-cycloadditions. Thus, the target molecule **1** offers two retroanalytical pathways (**A**/**B**).

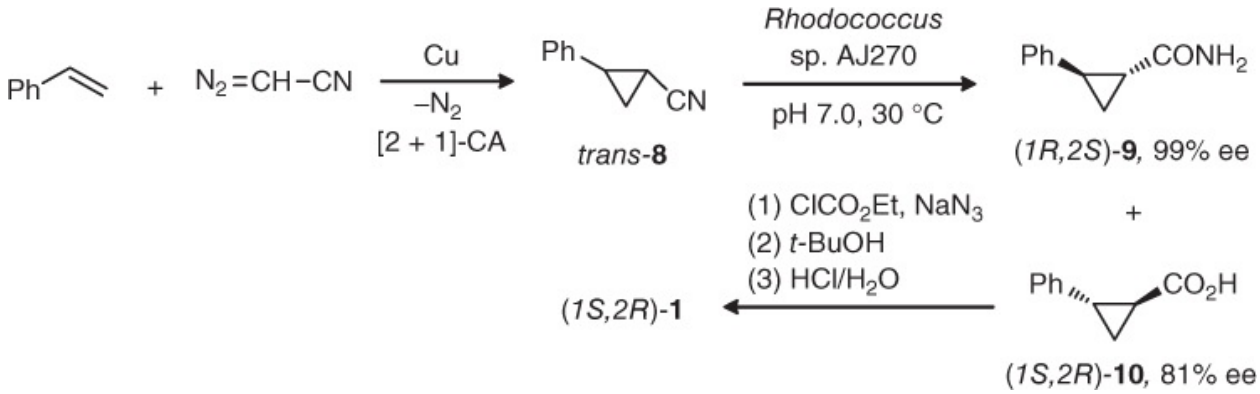
In **A**, after FGI (NH_2 → NO_2), the resulting phenylnitrocyclopropane **2** should result from [1 + 2]-cycloaddition of a methylene (CH_2) source to (*E*)-2-phenyl-1-nitroethene (**3**), which is easily accessible by nitroaldol condensation (Henry reaction) of benzaldehyde and nitromethane.

In **B**, after FGI of the primary amine function to an acyl azide **4** (retro-Curtius rearrangement) and further on to (*E*)-2-phenylcyclopropane carboxylate **5**, retro-[1 + 2]-cycloaddition would lead to a carbalkoxycarbene (easily accessible from diazoacetate **7**) and styrene (**6**).



In fact, phenylnitrocyclopropane **2** can be prepared from phenylnitroethene **3** by cyclopropanation with trimethyloxosulfonium iodide/NaH according to the Corey–Chaykovsky method [3]. Unfortunately, its reduction to tranylcypromine is not described in the literature, thus eliminating this short and straightforward possibility (**I**) for the synthesis for **1**.

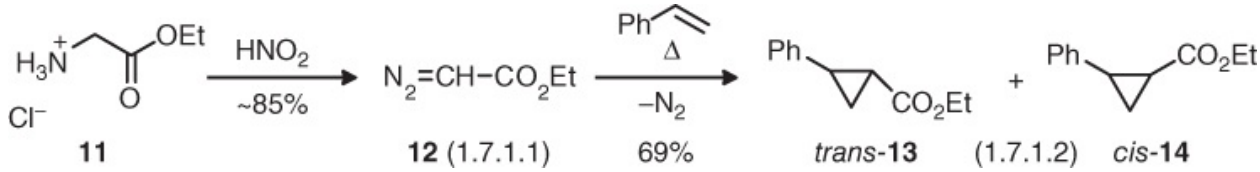
However, approach **II** based on retrosynthesis **B** is documented [4] and is described in detail in Section (b).



It should be noted that enantiopure (1*R*,2*S*)-**1** can be obtained by way of a chemoenzymatic transformation of (*E*)-2-phenylcyclopropanecarbonitrile (**8**) [5]. *Rhodococcus* sp. AJ 270, a versatile nitrile hydratase/amidase, catalyzes the enantioselective hydrolysis of **8** to afford the corresponding amide **9** and the acid **10** in high enantiomeric excess. The acid **10** is transformed to (+)-(1*S*,2*R*)-tranylcypromine by a modified Curtius rearrangement.

(b) Synthesis of 1

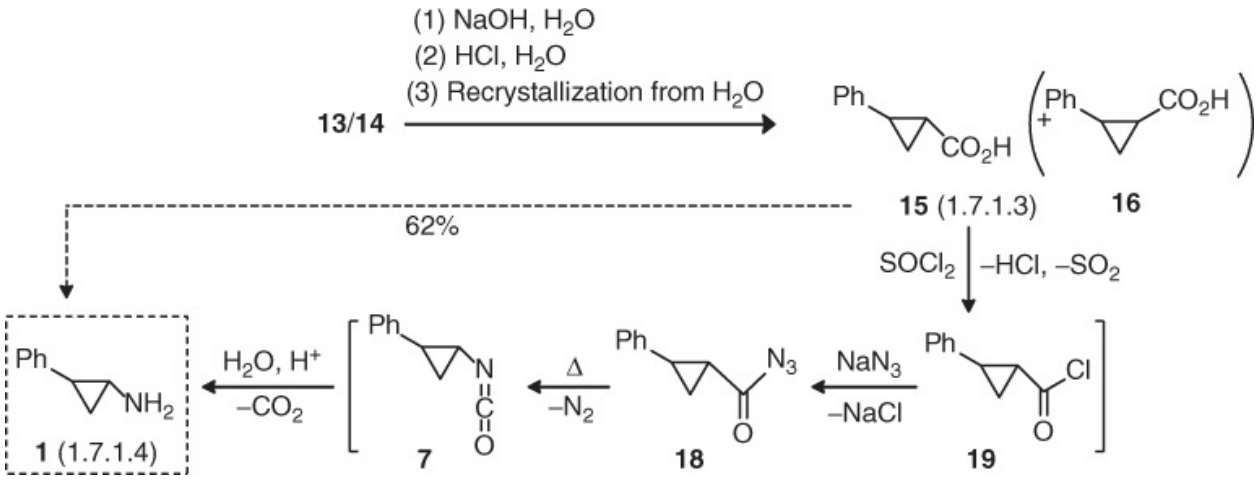
The synthesis of **1** [4] starts with cyclopropanation of styrene with carbethoxycarbene generated by thermolysis of ethyl diazoacetate (**12**). The diazoacetate **12** is prepared from glycine ethyl ester hydrochloride (**11**) by nitrosation with HNO_2 [6]:



The cyclopropanation leads to a mixture of the diastereomers of ethyl 1-phenylcyclopropane-1-carboxylate (**13** and **14**) as a racemic mixture with a trans/cis ratio of approximately 21. The cis/trans mixture **13**/**14** is saponified using aqueous NaOH, and the resulting isomeric acids **15**/**16** are separated by fractional crystallization from H_2O to obtain the pure *trans*-acid **15** required for the further synthesis.

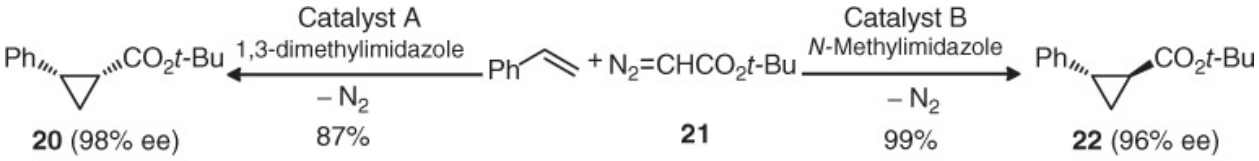
The *trans*-1-phenylcyclopropane-2-carboxylic acid (**15**) is transformed to **1** by Curtius degradation of the corresponding acyl azide. This is achieved by conversion of **15** to the acid chloride (**19**), reaction with NaN_3 to give the azide (**18**), and thermolysis of the azide to afford the isocyanate (**17**) via 1,2-*N*-sextet rearrangement. Finally, the isocyanate is transformed in acidic medium (via the corresponding carbamic acid and decarboxylation thereof) to the primary amine

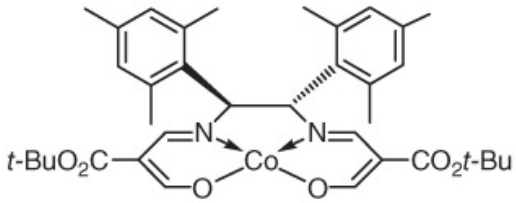
1:



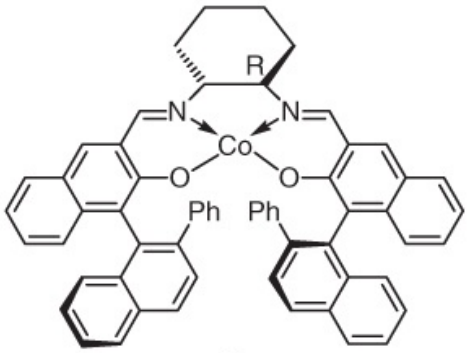
The four-step transformation **15** → **1** is executed in a one-pot procedure with spectroscopic detection of the intermediates **17–19**. Tranylcypromine is thus obtained in four separate steps with an overall yield of 19% (based on **11**).

Another possibility is the enantio and diastereoselective cyclopropanation of styrene with diazoacetates in the presence chiral Co(II) chelate complexes:





A

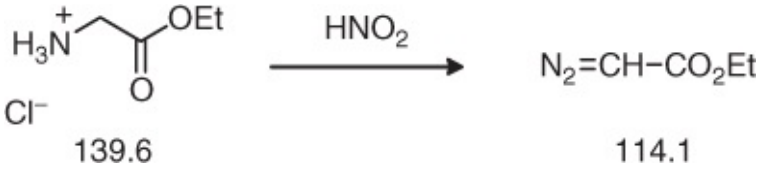


B

Thus, reaction of styrene with *tert*-butyl diazoacetate (**21**) using the β-ketoimidato-Co(II) complex **A** leads to the cis-disubstituted cyclopropane **20** [7], whereas using the salen-type Co(II) complex **B** leads to the trans-disubstituted cyclopropane **22**, both with >96% ee [8].

(c) Experimental Procedures for the Synthesis of 1

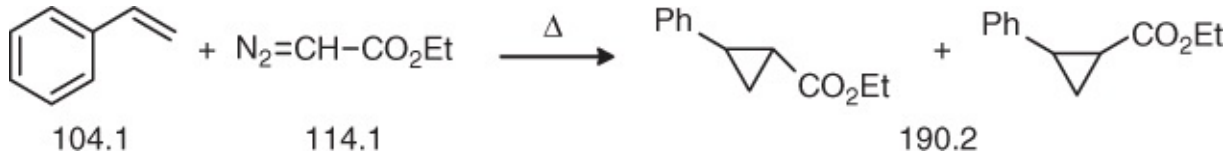
1.7.1.1 ** Ethyl diazoacetate [6]



A solution of sodium nitrite (32.8 g, 0.48 mol) in H_2O (100 ml) at −5 °C is added to a well-stirred mixture of glycine ethyl ester hydrochloride (56.0 g, 0.40 mol) in H_2O (100 ml) and CH_2Cl_2 (240 ml) also at −5 °C. The mixture is cooled to −9 °C, and 5% aqueous sulfuric acid (cold, 38.0 g) is added dropwise over approximately 3 min, keeping the reaction temperature below 1 °C; after the addition, stirring is continued for 15 min.

The mixture is transferred to a cold separatory funnel, the phases are separated, and the aqueous phase is extracted with CH_2Cl_2 (30 ml). The combined organic phases are neutralized with 5% aqueous $NaHCO_3$ solution (400 ml in total) until the gas formation (CO_2) ends. The organic layer is dried over $CaCl_2$, filtered, and used directly for the next step without further purification; approximately 280 ml containing 36.0–40.0 g (79–88%) of ethyl diazoacetate.

1.7.1.2 ** Ethyl 2-phenylcyclopropane-1-carboxylate [4]



In a three-necked flask fitted with a dropping funnel, a stirrer, a thermometer, and a distillation unit (note 1), styrene (17.7 g, 0.17 mol; note 2) and hydroquinone (0.4 g) are heated to 125 °C. Then, the solution of ethyl diazoacetate prepared in **1.7.1.1**, in which additional styrene (34.4 g, 0.33 mol) and hydroquinone (0.4 g) are dissolved, is added dropwise with vigorous stirring at such a rate that the internal temperature stays at 125–135 °C (external temperature approximately 160 °C). The addition is complete after approximately 3 h.

The CH_2Cl_2 solution (faintly yellow) which distilled off is concentrated *in vacuo* at room temperature to a volume of approximately 40 ml and added dropwise to the reaction mixture (same conditions as above).

For work-up, the CH_2Cl_2 is removed at normal pressure, and the excess styrene

is distilled off at 15 mbar (18.7 g, 0.18 mol). Distillation is continued at 1 mbar to yield 41.8 g (69% based on reacted styrene) of a colorless liquid, bp_1 106–108 °C, which consists of a mixture of the cis and trans products (as indicated by ^1H NMR).

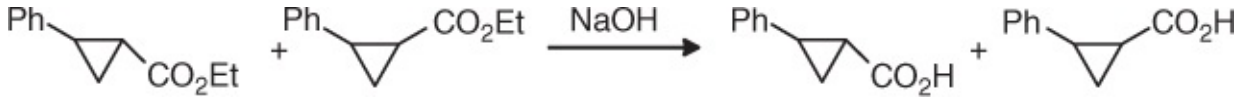
IR (film): $\tilde{\nu}$ (cm^{-1}) = 1725, 760, 700.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.4–7.0 (m, 5H, Ph–H), 4.16, 3.86 (q, *J* = 7.0 Hz, together 2H, OCH_2), 2.7–2.4 (m, 1H, 2-H), 2.2–1.4 (m, 3H, 3-H_2, 1-H), 1.26, 0.96 (t, *J* = 7.0 Hz, 3H, CH_3; relative intensity 1 : 2, ratio of the cis/trans stereoisomers).

Notes:

1. A reaction flask of volume at least 500 ml should be used because (especially at the beginning) the production of N_2 during the thermolysis of the diazoacetate causes strong foaming.
2. Styrene has to be distilled over hydroquinone before use; bp_{12} 33–34 °C.

1.7.1.3 ** *trans*-2-Phenylcyclopropane-1-carboxylic acid [4]



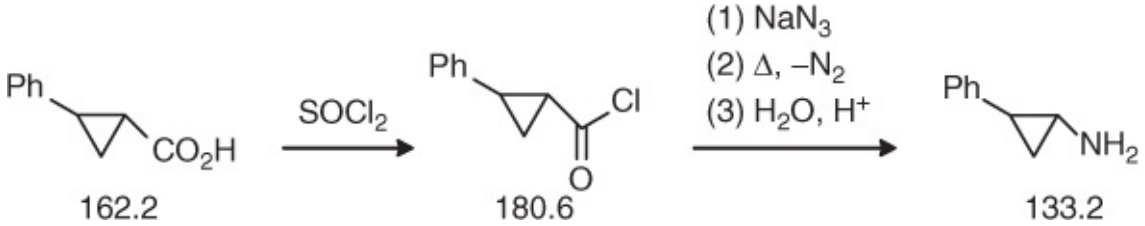
A solution of the *cis*/*trans*-ester mixture from **1.7.1.2** (38.0 g, 0.20 mol) and NaOH (11.8 g, 0.30 mol) in EtOH/H_2O (110 ml/15 ml) is heated under reflux for 9 h.

The reddish mixture is then concentrated *in vacuo*, the residue is dissolved in H_2O (50 ml), and the solution is cooled in an ice bath. With efficient stirring, concentrated HCl is added; the precipitated acid is collected by suction filtration, washed with H_2O, and recrystallized from H_2O (approximately 2.5 l) with the addition of charcoal. After a second recrystallization from H_2O, the pure *trans*-acid is obtained; 11.4 g (35%), colorless crystals, mp 92.5–93.5 °C. Concentration of the combined mother liquors from both recrystallizations to a volume of approximately 500 ml yields a second crop; 5.20 g (16%), mp 91–92 °C; total yield of the *trans*-acid 51%, TLC (SiO_2; Et_2O): $R_f \approx 0.75$.

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3500–2300, 1695, 1245.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.4–6.9 (m, 5H, Ph–H), 2.7–2.4 (m, 1H, 2-H), 2.9–1.2 (m, 3H, 1-H, 3-H_2); CO_2H is not observed.

1.7.1.4	**	**(±)-*trans*-2-Phenylcyclopropyl-1-amine (tranylcypromine)** [4]



1. *trans*-2-Phenylcyclopropane-1-carboxylic chloride: A solution of the *trans*-acid **1.7.1.3** (13.0 g, 0.08 mol) and thionyl chloride (20.3 g, 0.17 mol) in anhydrous benzene (45 ml; Caution: carcinogenic!) is heated under reflux for 5 h (Caution: Hood! Evolution of HCl and SO_2!). The reaction mixture is then concentrated *in vacuo*, benzene (30 ml) is added, and distillation *in vacuo* is repeated to remove the excess $SOCl_2$. The yellowish crude acid chloride (IR (film): $\tilde{\nu}$ = 1780 cm^{-1} (C=O), 13.5 g, (93%)) is used in the next step without further purification.
2. A solution of the acid chloride from (1) in toluene (70 ml) is added dropwise over 1 h to a well-stirred suspension of sodium azide (21.0 g, 0.32 mol, Caution: Hood! Shield!) in anhydrous toluene at 70 °C (external temperature). The temperature is then slowly increased, whereupon N_2 evolution occurs at 70–80 °C. When the addition is complete, the reaction mixture is heated to reflux until the evolution of N_2 ceases (approximately 4 h).

After cooling to room temperature, the inorganic salts are filtered off by suction and washed with toluene; the solvent is removed from the filtrate *in vacuo*, leaving the isocyanate as the residue (IR (film): ν = 2280 cm^{-1} (N=C=O), 11.9 g). After cooling to 10 °C, concentrated HCl (135 ml) is added dropwise over 45 min and the solution is heated to reflux for 2 h. The mixture is then cooled to room temperature, and ice cold H_2O (50 ml) is added. After extraction with Et_2O (100 ml), the acidic aqueous phase is concentrated to dryness *in vacuo*. The residue is suspended in Et_2O (100 ml) and, with cooling in an ice bath, a 50%

aqueous KOH solution (50 ml) is added. The liberated amine is taken up in Et_2O, the aqueous (alkaline) phase is washed twice with Et_2O (50 ml), and the ethereal extracts are combined and dried over $MgSO_4$ and filtered. The solvent is removed *in vacuo*, and the oily, faintly yellow residue is fractionated *in vacuo* (microdistillation apparatus). Tranylcypromine is obtained as a colorless liquid; 6.60 g (62% based on *trans*-acid **1.7.1.3**), $bp_{0.4}$ 43–45 °C.

IR (film): $\tilde{\nu}$ (cm^{-1}) = 3370, 3300, 1605, 1500, 1460, 745, 700.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.4–6.9 (m, 5H, Ph–H), 2.7–2.4 (m, 1H, 2-H), 2.1–1.7 (m, 1H, 1-H), 1.55 (s, 2H, NH_2), 1.2–0.7 (m, 2H, 3-H_2).

Derivatives:

1. Tranylcypromine hydrochloride: The hydrochloride is obtained by passing anhydrous HCl into a solution of the amine in anhydrous Et_2O; colorless crystals, mp 155–157 °C (from MeOH by addition of EtOAc/Et_2O, 1 : 1).
2. *N*-Benzoyl-2-phenyl-1-cyclopropylamine: Tranylcypromine benzoate is obtained by Schotten–Baumann acylation of the amine (1,4-dioxane as solvent, 1 h at +20 °C) with an equimolar amount of benzoyl chloride; colorless needles, mp 120–121 °C (from MeOH).

References

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3. (a) Asunksis, J. and Shechter, H. (1968) *J. Org. Chem.*, **33**, 1164–1168;Cyclopropane α-aminocarboxylates have been obtained by reduction of the corresponding nitrocarboxylates resulting from cycloaddition of nitrodiazoacetates to alkenes: (b) Wurz, R.P. and Charette, A.B. (2004) *J. Org. Chem.*, **69**, 1262–1269.

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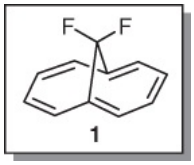
8. (a) Ikeno, T., Sato, M., and Yamada, T. (1999) *Chem. Lett.*, 1345–1346;For other catalyst types and their stereoselectivities, see: (b) Yamada, T., Ikeno, T., Sekino, H., and Sato, M. (1999) *Chem. Lett.*, 719–720;(c) Loeffler, F., Hagen, M., and Luening, U. (1999) *Synlett*, 1826–1828.

1.7.2 11,11-Difluoro-1,6-methano[10]annulene

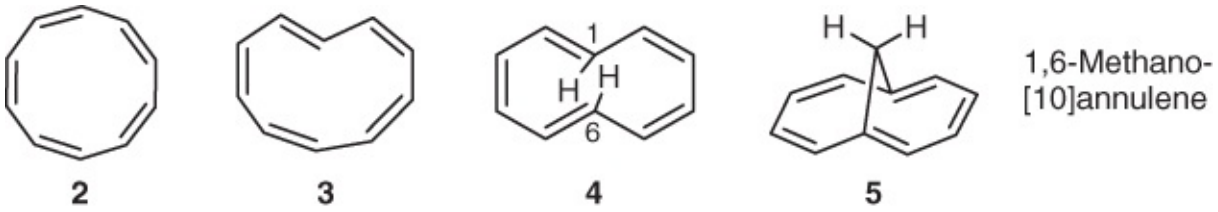


Topics:

- Vogel synthesis of a 1,6-methano-bridged [10]annulene
- Birch reduction of naphthalene
- Chemoselective cyclopropanation ([1 + 2]-cycloaddition) of a polyolefinic system
- Base-induced dehydrohalogenation
- Norcaradiene–cycloheptatriene rearrangement

(a) General

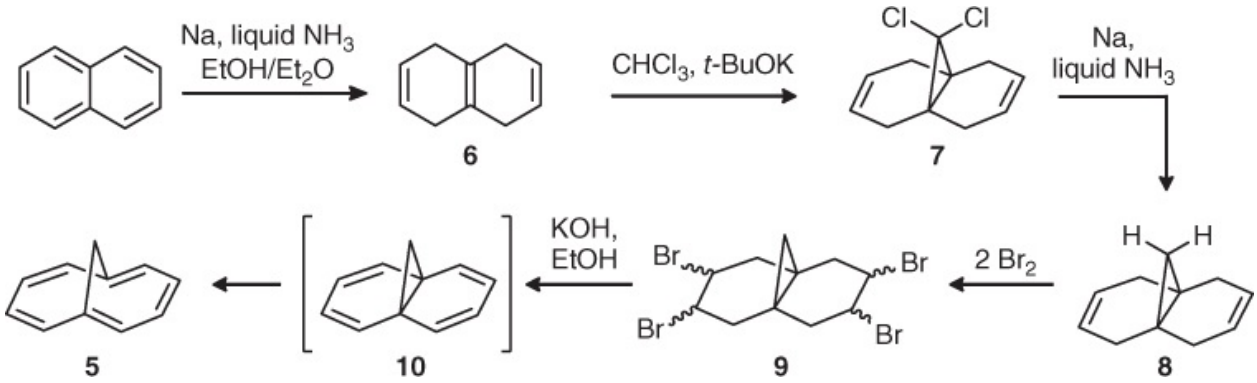
[10]Annulene is a problematic member of the family of aromatic [*n*]annulenes [1]. Containing 10π-electrons, it formally fulfills the criteria of the Hückel rule for aromatic compounds with $n = 2$. However, in all of its possible double-bond stereoisomers, either high sp^2-bond-angle deformations (as in **2**) or severe steric interactions of hydrogens (as in **4**) exist, which prohibit an approximately planar 10π perimeter geometry required for “aromatic” stabilization.



2 3 4 5

In fact, the diastereomeric all-*cis*- and mono-*trans*-[10]annulenes (**2** and **3**) have been prepared and proved to be unstable, nonplanar, and therefore non-aromatic polyenes. As conceived and realized by Vogel [2], removal of the hydrogen interference in the di-trans-form **4** by replacement of the inner hydrogens by a methylene group led to the 1,6-bridged [10]annulene **5**, the spectroscopic data of which correspond to an aromatic 10π-system.

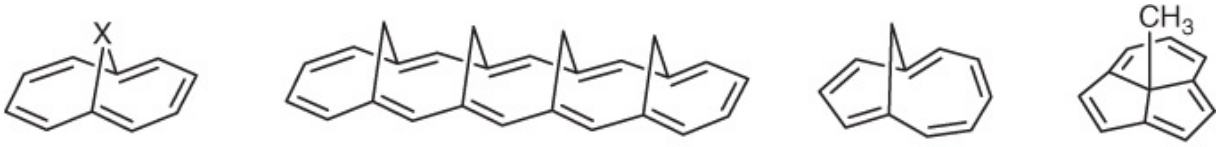
The ^{1}H NMR spectrum of **5** shows it to be a diatropic hydrocarbon (ring protons giving rise to an AA′BB′ multiplet at δ = 7.27 and 6.95 ppm; CH_2 positioned above the π-plane and giving a signal at δ = −0.52 ppm). According to X-ray structural analysis, the sp^2-C perimeter lacks overall planarity, but the average sp^2C–sp^2C distance is of the order seen in benzenoid compounds (137.3–141.9 pm vs. 139.8 pm in benzene) and indicates significant delocalization of the π-system. Chemically, **5** is stable toward oxygen and thermally stable up to 220 °C; it undergoes S_EAr reactions (e.g., bromination, nitration, acylation), as expected for a benzenoid aromatic.



Vogel's synthesis [2] of 1,6-methano[10]annulene (**5**) starts with isotetralin **6**, which is readily available by Birch reduction of naphthalene. Reaction with dichlorocarbene, generated from $CHCl_3$ and *tert*-BuOK, takes place chemoselectively at the internal double bond of **6** to give **7** by cyclopropanation. Dehalogenation of **7** by treatment with Na/liquid NH_3 leads to the propellane **8**, which is converted to **5** either (i) by addition of bromine to the double bonds followed by dehydrohalogenation with KOH (via **9**) or (ii) by dehydrogenation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). In both

transformations (i) and (ii), the intermediate norcaradiene derivative **10** undergoes thermal electrocyclic ring opening to afford the [10]annulene system.

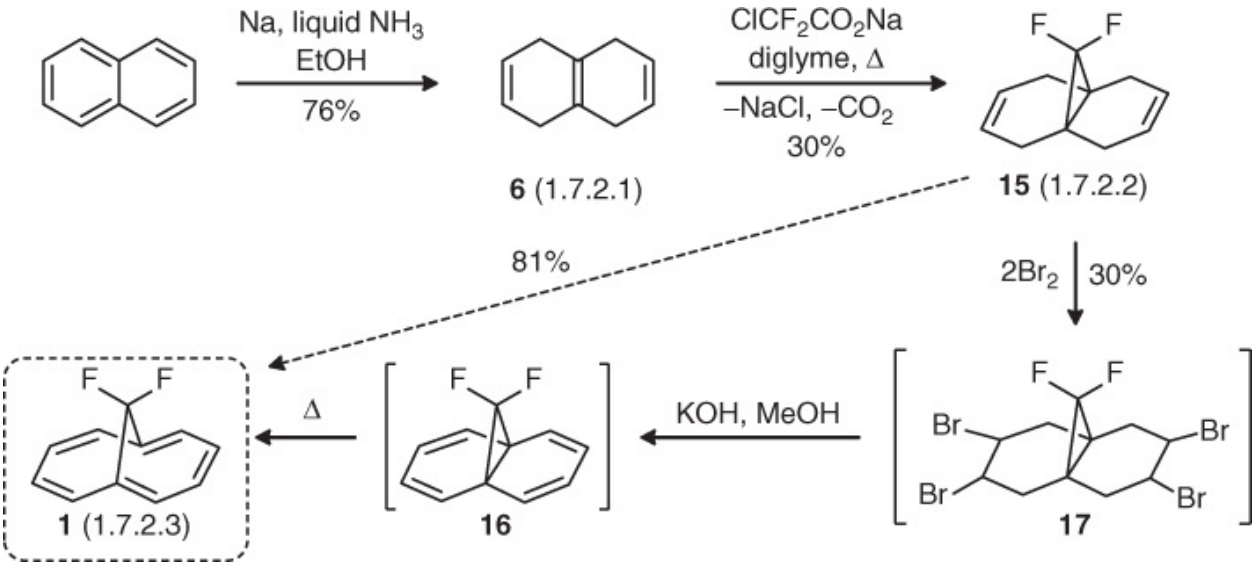
The Vogel concept has also been realized for [10]annulenes with other bridging groups (**11**, X = O, NH, CF_2) and – using a different synthetic strategy from that used to obtain **5** [3] – for a series of multibridged [14]-, [18]-, and [22]annulenes (e.g., **12**).[8] Other types of bridging in [10]annulene are present in the 1,5-methano species **13**, which shows strong structural similarity to the isoelectronic azulene (cf. Section 1.7.3), and in the tricyclic hydrocarbon **14**, a triply short-circuited derivative of tris-*trans*-di-*cis*-[10]annulene:



11 (X = CF_2, O, NH) **12** **13** **14**

(b) Synthesis of 1

The synthesis of **1** follows the basic concept developed for the 1,6-methano species **5** [4]. First, naphthalene is subjected to Birch reduction using Na in liquid NH_3 (with EtOH as proton source). As already mentioned, a twofold 1,4-reduction of the condensed aromatic system takes place to give the 1,4,5,8-tetrahydronaphthalene (**6**, isotetralin). Compound **6** is then reacted in diglyme at 165 °C with sodium chlorodifluoroacetate, from which difluorocarbene is generated ($F_2ClCCO_2N \rightarrow CF_2 + CO_2 + NaCl$), which adds chemoselectively to the internal double bond (more electron-rich by virtue of its tetraalkyl substitution than the peripheral disubstituted C=C bonds) to yield the carbene monoadduct **15**:

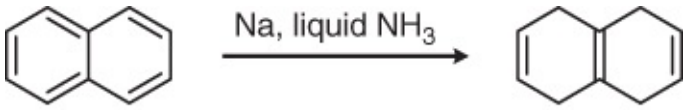


The transformation of the difluoropropellane **15** to 11,11-difluoro-1,6-methano[10]annulene (**1**) follows the already established protocol: addition of 2 mol of bromine to **15** gives the tetrabromide **17** (not isolated), which is followed by a fourfold dehydrobromination by KOH in MeOH to afford the norcaradiene system **16**. Under the reaction conditions, the central 1,6-bond in **16** is cleaved in a norcaradiene–cycloheptatriene rearrangement to provide the target molecule.

The [10]annulene **1** is thus synthesized in a three-step sequence with an overall yield of 18% (based on naphthalene).

(c) Experimental Procedures for the Synthesis of 1

1.7.2.1	**	**1,4,5,8-Tetrahydronaphthalene** [4]



Ammonia (1.0 l) is condensed into a flask in a dry ice/acetone bath (Hood!). The drying tube is removed, and sodium (64.1 g, 1.80 mol) is added in small pieces with vigorous stirring over 1 h. A solution of naphthalene (64.1 g, 0.50 mol) in anhydrous diethyl ether (250 ml) and anhydrous ethanol (200 ml) is then added over a period of 3 h and stirring is continued for 6 h at −78 °C.

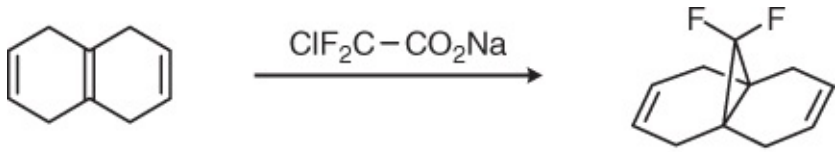
The cooling bath is removed, and the ammonia is allowed to evaporate over 12 h. The residue is then taken up in MeOH (40 ml) with stirring under nitrogen to destroy the excess sodium. Ice water (1.5 l) is added, and the mixture is

extracted with Et_2O (3 × 100 ml). The combined organic phases are dried over Na_2SO_4 and concentrated under reduced pressure at 20 °C. The residue is washed several times with H_2O using a glass frit and is recrystallized from MeOH (approximately 530 ml). The yield is 60.5 g (76%), mp 52–53 °C (approximately 98% pure). Recrystallization from MeOH raises the mp to 57–58 °C.

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3020, 2870, 2840, 2810, 1660.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 5.67 (s, 4H, vinyl-H), 2.50 (s, 8H, allyl-H).

1.7.2.2	**	**11,11-Difluorotricyclo[4.4.1.0^{1,6}]undeca-2,8-diene** [4]



132.2 182.2

1. Sodium chlorodifluoroacetate: A solution of chlorodifluoroacetic acid (71.7 g, 0.55 mol) in methanol (110 ml) is added dropwise to a stirred solution of NaOH (22.0 g, 0.55 mol) in MeOH (250 ml). The temperature is held at 40 °C by occasional cooling with an ice bath. The solvent is evaporated *in vacuo* and the salt is dried over P_4O_{10} at 1 mbar. The yield is 83.7 g (100%).

2. A solution of sodium chlorodifluoroacetate prepared in (1) (76.1 g, 0.50 mol) in anhydrous diglyme (100 ml) is added to a refluxing, vigorously stirred solution of isotetralin **1.7.2.1** (46.2 g, 0.35 mol) in diglyme (140 ml) at such a rate that the temperature of the reaction mixture does not fall below 165 °C. After the addition, stirring is continued for 15 min at 165 °C until carbon dioxide evolution ceases.

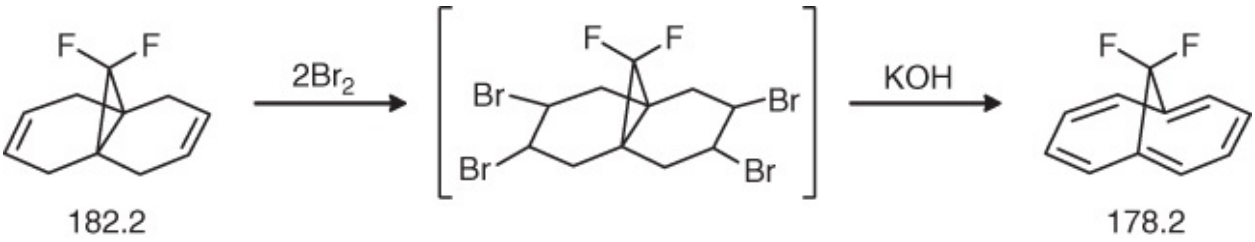
The solution is cooled to room temperature, poured into H_2O (1 l), and extracted with *n*-pentane (1 × 300 ml, 4 × 100 ml). The combined extracts are washed with H_2O (300 ml), dried over $MgSO_4$, and filtered. The solvent is removed *in vacuo* at room temperature, and the residue is distilled over a 30-cm packed column (Raschig rings). The column is heated during the distillation with a heating gun or infrared lamp to prevent solidification of the product in the column. The first

fraction (bp_{12} 89–91 °C) is discarded. The next fractions (bp_{12} 91–103 °C) are collected and recrystallized from MeOH to give 19.0 g (29%) of colorless, square plates; mp 58–60 °C, 98% pure (GC).

IR (KBr): $\tilde{\nu}$ = 3040, 2980, 2890, 2830, 1670 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 5.59 (s, 4H, vinyl-H), 2.8–1.8 (m, 8H, allyl-H).

1.7.2.3	**	**11,11-Difluoro-1,6-methano[10]annulene** [4]



The carbene adduct **1.7.2.2** (10.9 g, 60.0 mmol) is dissolved in anhydrous dichloromethane (120 ml), and the solution is cooled to −60 °C. A solution of bromine (19.2 g, 0.12 mol) in CH_2Cl_2 (60 ml) is added with stirring at such a rate that no brown color from excess bromine remains (approximately 15 min).

The solvent is evaporated *in vacuo* at room temperature, and the colorless crystalline residue is dried under high vacuum (oil pump) for approximately 15 min and then dissolved in THF (60 ml). This solution is dropped into a stirred, refluxing solution of potassium hydroxide (28.0 g, 0.50 mol) in MeOH (160 ml) over a period of 20 min and refluxing is continued for 2 h. The solution is then cooled to 40 °C, aqueous HCl (6 N, 120 ml) is carefully added, and the mixture is heated under reflux for 1 h.

The reaction mixture is cooled to room temperature, poured into H_2O (800 ml), and extracted with *n*-pentane (5 × 150 ml). The combined organic extracts are washed with saturated aqueous $NaHCO_3$ solution (300 ml), dried over $MgSO_4$, and filtered. Al_2O_3 (20 g, basic, activity grade I) is added, and the solvent is evaporated *in vacuo*. The product is eluted from the alumina in a Soxhlet extractor with *n*-pentane, which crystallizes on cooling the extract to give long, pale-yellow needles, and are recrystallized from MeOH. The yield is 7.20 g, mp 116–118 °C. Concentration of the mother liquor gives an additional 1.20 g. Chromatography of the residue on silica gel (120 × 1.5 cm column; *n*-pentane)

affords about 0.40 g of additional product. The total yield is 8.80 g (81%).

UV (cyclohexane): λ_{max} (log ϵ) = 409 (2.73), 398 (2.93), 389 (2.90), 380 (2.77), 293 (3.77), 253 nm (4.81).

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3030, 1375, 1100, 790.

^{1}H NMR ($CDCl_3$): δ (ppm) = 7.4–6.8 (m, AA′BB′ system of eight aromatic protons [4]).

References

1. For an instructive and detailed discussion of the [10]annulene problem, see Hopf, H. (2000) *Classics in Hydrocarbon Chemistry*, Wiley-VCH Verlag GmbH, Weinheim, p. 218 and 227.

2. Vogel, E. and Roth, H.D. (1964) *Angew. Chem.*, **76**, 145.

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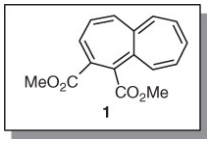
4. (a) Rautenstrauch, V., Scholl, H.-J., and Vogel, E. (1968) *Angew. Chem.*, **80**, 278–279;(b) Vogel, E., Klug, W., and Breuer, A. (1974) *Org. Synth.*, **54**, 11; original contribution from Vogel, E., 1981.

1.7.3 Dimethyl heptalene-1,2-dicarboxylate



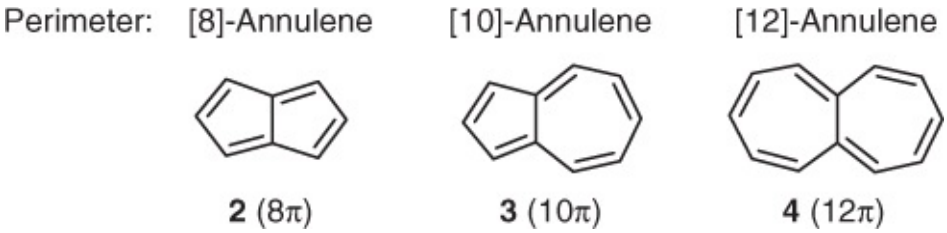
Topics:

- Hafner–Ziegler azulene synthesis
- S_NAr of activated haloarenes
- Zincke reaction (pentamethine cyanines from nucleophilic ring-opening of N-acceptor-substituted pyridinium ions)
- Formation of a vinylogous 6-aminofulvene and its electrocyclization to azulene
- Dipolar [2 + 2]-cycloaddition to azulene, ring

		expansion azulene → heptalene

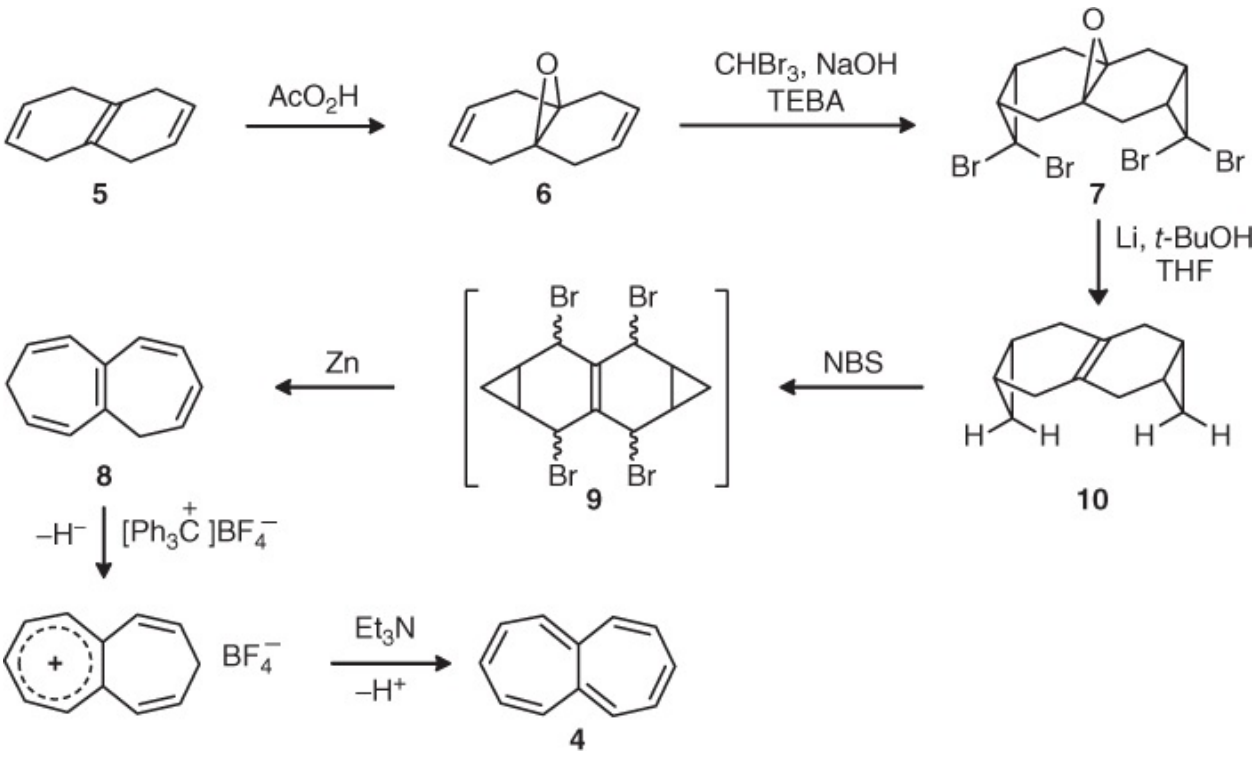
(a) General

Heptalene (**4**) belongs to the first members of the group of zero-bridged annulenes (cf. Section 1.7.2) [1], the π-electron systems of which formally contain a pentafulvene unit (as in pentalene (**2**) and azulene (**3**)) or a heptafulvene unit (as in heptalene (**4**)) [1]:



Heptalene (**4**) itself is a very reactive, oxygen-sensitive, nonplanar cyclopolyolefin, temperature-dependent ^{1}H NMR spectroscopic analysis of which is indicative of dynamic interconversions between different conformers. The nonplanar structure of the heptalene skeleton has been confirmed by X-ray analysis of stable derivatives such as the dicarboxylate **1**, the two rings of which preferentially adopt a boat-like structure in the crystalline state [2].

Most syntheses of **4** start from 1,4,5,8-tetrahydronaphthalene (**5**), the educt of Vogel's classical methano[10]annulene synthesis (cf. Section 1.7.2):

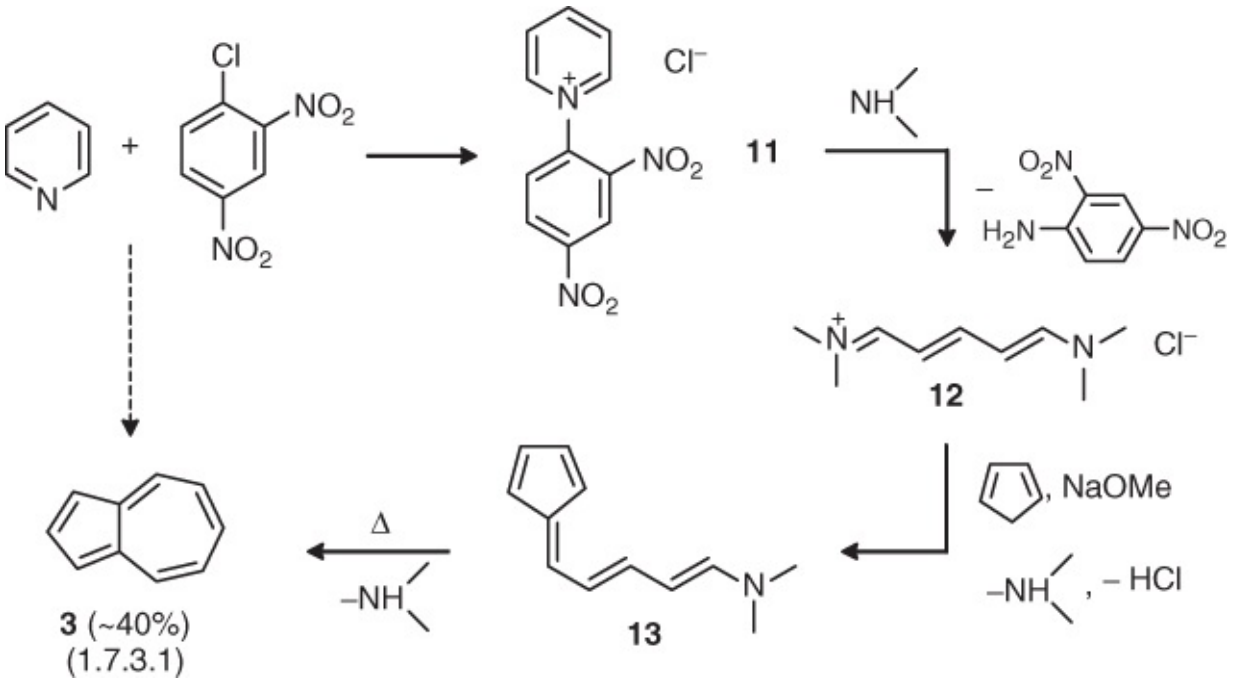


Isotetralin **5** can be epoxidized chemoselectively at the central double bond to give **6**, and subsequent dibromocarbene addition under phase-transfer conditions provides the antibis-adduct **7**, which is readily dehalogenated and deoxygenated by Li in *tert*-BuOH/THF (→ **10**). NBS bromination of **10** furnishes a mixture of tetrabromides (**9**), reduction of which with zinc gives 3,8-dihydroheptalene (**8**). Dehydrogenation, first by hydride abstraction ($Ph_3C^+ \cdot BF_4^-$) and then by deprotonation (Et_3N) (**8** → **4**), completes the synthesis of **4** [3].

(b) Synthesis of 1

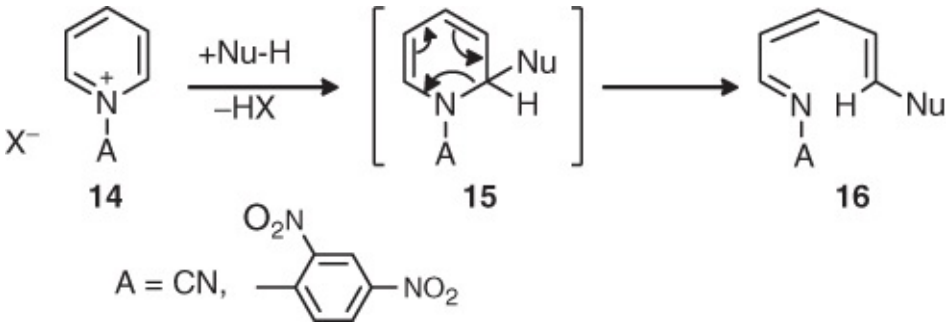
For the synthesis of the stable heptalene derivative **1**, a straightforward approach has been reported [4], which is based on the ring expansion of azulene (**3**) by a [2 + 2]-cycloaddition with dimethyl acetylene dicarboxylate.

Thus, first the synthesis of azulene (**3**) is described [5]. The method of choice is the one-pot, multistep procedure submitted by Hafner [6] starting from 1-(2,4-dinitrophenyl)pyridinium chloride (**11**), which is prepared *in situ* by S_NAr reaction of 2,4-dinitrochlorobenzene with pyridine.

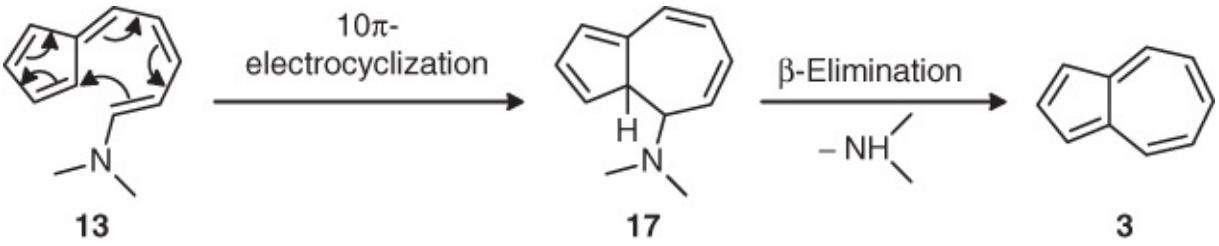


On reaction with dimethylamine, the salt **11** undergoes ring-opening of the pyridine nucleus with amine exchange, resulting in the formation of the (symmetrical) pentamethine cyanine **12** as the key intermediate. Condensation of **12** with cyclopentadiene in the presence of NaOMe leads to the bisvinylogous 6-aminofulvene **13**, which, on heating to 125 °C, cyclizes to afford azulene (**3**) with concomitant elimination of $HN(CH_3)_2$.

The ring-opening process **11** → **12** is an example of the Zincke reaction, which is generally observed when N-acceptor-substituted pyridinium salts **14** interact with *O*- or *N*-nucleophiles through initial attack at C-2 (→**15**) and opening of the N–C-2 bond to furnish 1-azatrienals **16** [7]:

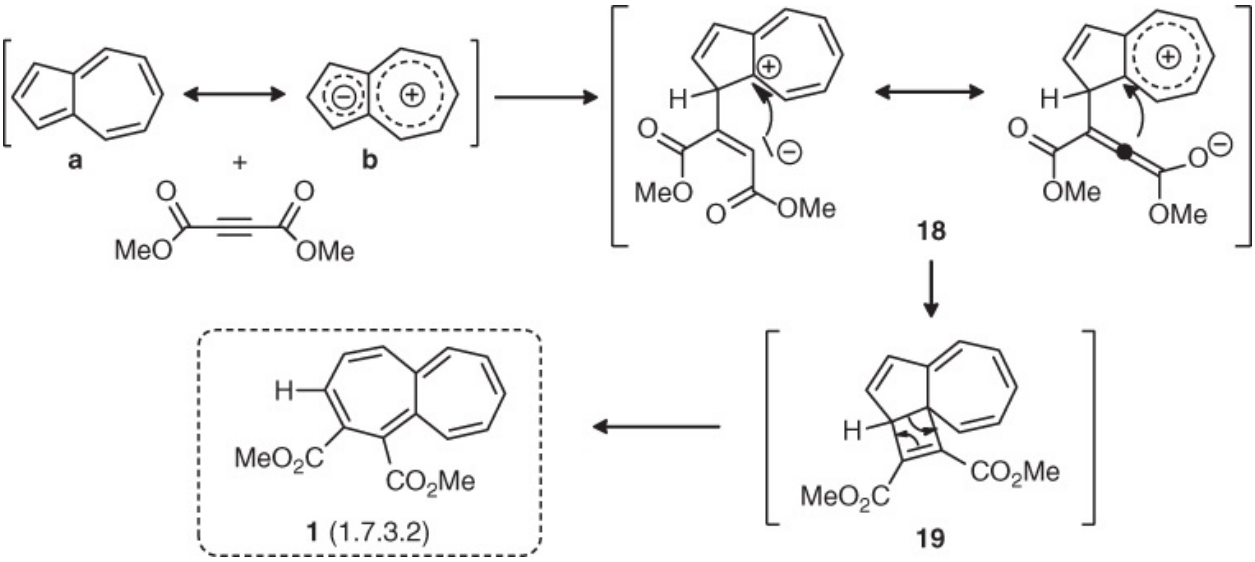


The cyclization of the bisvinylogous 6-aminofulvene **13** to azulene is mechanistically interpreted as an electrocyclic 10π process leading to **17**, which subsequently undergoes loss of the amine moiety in a (thermal) β-elimination (**17** → **3**) [5]:

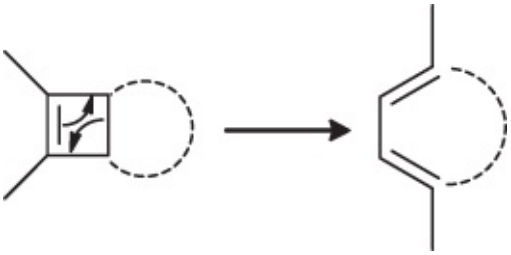


The ring expansion of azulene with dimethyl acetylene dicarboxylate proceeds as a thermal reaction in boiling tetralin. After purification by chromatography (separation from unreacted azulene), the heptalene diester **1** is obtained as air-stable, brown-red crystals.

The formation of **1** from azulene (**3**) can be understood as a two-step dipolar [2 + 2]-cycloaddition [8], since the electron distribution (**b**) in azulene (**3**) leads to exclusive attack of electrophiles at the five-membered ring with formation of a stabilized tropylium ion in the dipolar intermediate **18**:

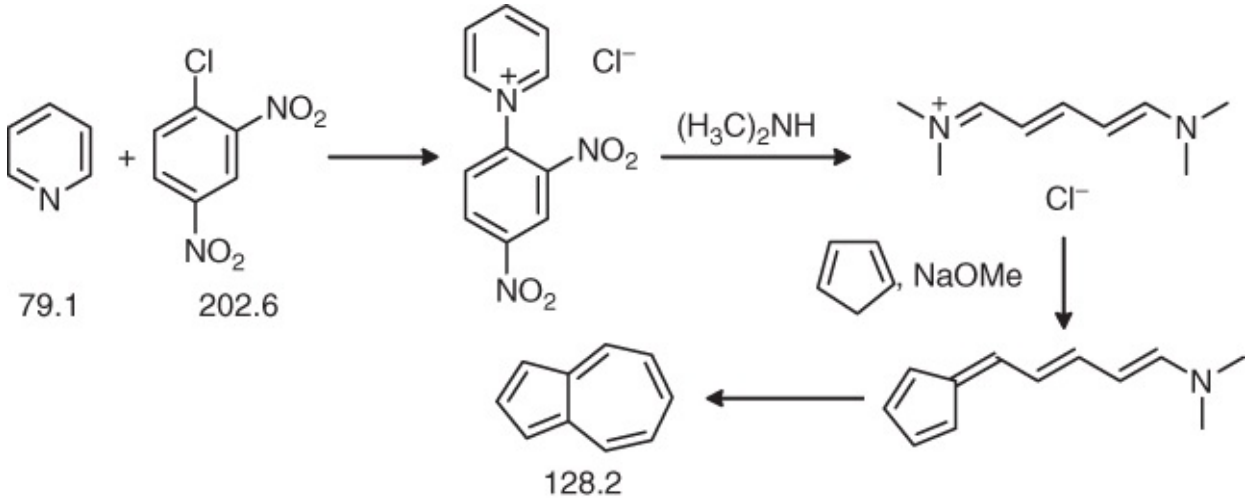


Finally, the formed [2 + 2]-cycloadduct **19** expands to the heptalene system by 4π-cycloreversion of the cyclobutene subunit to a 1,3-diene.



(c) Experimental Procedures for the Synthesis of 1

1.7.3.1 ** Azulene [6]



2,4-Dinitrochlorobenzene (40.5 g, 0.20 mol, Caution: Caustic!) and anhydrous pyridine (240 ml) are stirred and heated at 85–90 °C (steam bath) for 4 h. *N*-(2,4-Dinitrophenyl)pyridinium chloride begins to precipitate as a yellow-brown solid after approximately 30 min. The mixture is cooled to 0 °C in an ice–salt bath, and then a solution of dimethylamine (20.0 g, 0.44 mol, see note) in anhydrous pyridine (60 ml) is added dropwise over 30 min. The temperature of the reaction mixture rises to 4 °C. After the addition, the red-brown solution is slowly warmed to room temperature and stirred for 12 h. The drying tube is then replaced with a gas inlet tube and the system is flushed with nitrogen.

Cyclopentadiene (prepared by distillation of the dimer [9]; 14.0 g, 0.21 mol) is added under a nitrogen atmosphere. Sodium methoxide (2.5 M; sodium (4.60 g) in anhydrous MeOH (80 ml)) is added dropwise with stirring over a period of 30 min. The solution warms to 26 °C and is left at room temperature for 15 h. The dropping funnel is then replaced by a distillation head, and the reaction mixture is carefully heated (Hood! $(H_3C)_2NH$ is evolved!). Pyridine and MeOH are distilled off until the temperature reaches 105 °C (approximately 150 ml of distillate). The distillation head is removed, anhydrous pyridine (200 ml) is added, and the mixture is heated for 4 days at 125 °C under nitrogen.

The mixture is then cooled to 60 °C, and pyridine is distilled off under reduced pressure. The blue-black crystalline residue is extracted with *n*-hexane (400 ml) in a Soxhlet extractor for 4 h. Traces of pyridine are removed from the blue *n*-hexane solution by washing it with 10% aqueous HCl (3 × 30 ml) and H_2O (30 ml). The organic phase is dried over Na_2SO_4, and the volume is reduced by half by distillation using a 50 cm Vigreux column. The concentrated solution is

filtered through a column (30 × 4 cm, 200 g of basic Al_2O_3, activity grade II, *n*-hexane as eluent). The solvent is evaporated from the eluate to give dark-blue leaflets, 9.10 g (36%, mp 97–98 °C). Further purification can be achieved by sublimation at 90 °C and 10 mbar (mp 99–100 °C).

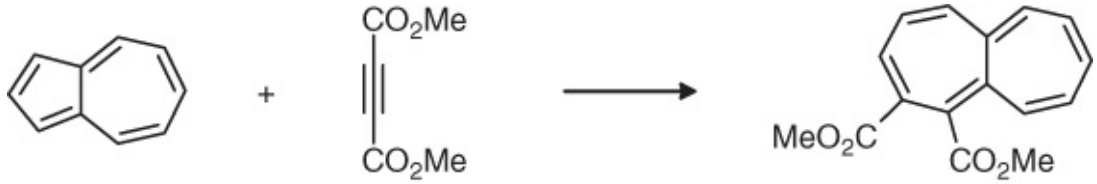
UV (*n*-hexane): λ_{max} (log ϵ) = 580 (2.46), 352 (2.87), 339 (3.60), 326 (3.48), 315 (3.26), 294 (3.53), 279 (4.66), 274 (4.70), 269 (4.63), 238 (4.24), 222 nm (4.06).

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 1580, 1450, 1395, 1210, 960, 760.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.4–6.8 (m).

Note: The solution of dimethylamine in pyridine is prepared by adding dimethylamine gas (dried over KOH) to anhydrous pyridine under water-free conditions.

1.7.3.2	**	**Dimethyl heptalene-1,2-dicarboxylate** [6]



128.2 142.1 270.3

Azulene **1.7.3.1** (1.28 g, 10.0 mmol) and dimethyl acetylene dicarboxylate (2.13 g, 15.0 mmol) are heated under reflux in freshly distilled tetralin (20 ml) for 20 min. The solution is cooled, diluted with *n*-hexane (150 ml), and chromatographed on alumina (basic, activity grade IV, 100 g) with *n*-hexane as eluent (fraction 1). Absorbed material is eluted with CH_2Cl_2 until no more product appears in the eluate (TLC) (fraction 2).

The fractions are treated as follows:

Fraction 1: The blue eluate is concentrated *in vacuo*, and the residue is chromatographed on alumina (basic, activity grade I, 200 g) eluting with *n*-hexane. Tetralin elutes first, followed by a blue solution containing unreacted azulene. The azulene crystallizes on evaporating the solvent to give a recovered yield of 0.78 g (61%).

Fraction 2: The solvent is evaporated, and the residue is chromatographed on

an alumina column (basic Al_2O_3, activity grade IV, 500 g) eluting with *n*-hexane/Et_2O (5 : 3). Purple (1), dark blue (2), blue-green (3), yellow-brown (4), violet (5), and blue (6) fractions are obtained. The product is isolated from fraction 4 by evaporating the solvents *in vacuo* and recrystallizing the residue from *n*-hexane/Et_2O. The yield is 0.26 g (9.6%; 25% based on recovered azulene), mp 112–113 °C.

UV (*n*-hexane): λ_{max} (log ϵ) = 337 (3.63), 266 (4.29), 204 nm (4.36).

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 1720, 1570, 1440, 1260, 1230.

^{1}H NMR (300 MHz, [D_6]acetone): δ (ppm) = 7.27 (d, *J* = 7.0 Hz, 1H, 3-H), 6.7–5.7 (m, 7H, vinyl-H), 3.71, 3.64 (s, 2 × 3H, 2 × OCH_3).

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5. (a) For a review on azulene syntheses, see ref. [1], p. 281, and Zeller, K.-P. (1985) Houben-Weyl, *Methoden der Organischen Chemie*, vol. 5/2c, Thieme Verlag, Stuttgart, p. 127;Recently, a highly flexible route to azulenes was reported, starting with cycloaddition of dichloroketene to cycloheptatriene and ring expansion with diazomethane: (b) Carret, S., Blanc, A., Coquerel, Y., Berthod, M., Greene, A.E., and Deprés, J.-P. (2005) *Angew. Chem.*, **117**, 5260–5263; *Angew. Chem. Int. Ed.*, (2005), **44**, 5130–5133.

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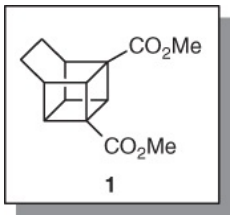
1.7.4 Dimethyl 1,8-bishomocubane-4,6-dicarboxylate



1

Topics:

- Halogenation of a phenol (S_EAr)
- Dehydrogenation of a hydroquinone to a 1,4-benzoquinone
- Use of 1,4-quinones as electron-deficient dienophiles in a Diels–Alder reaction
- Photochemical intramolecular [2 + 2]-cycloaddition with cyclobutane formation
- Favorskii rearrangement
- Methyl esters from carboxylic acids and diazomethane

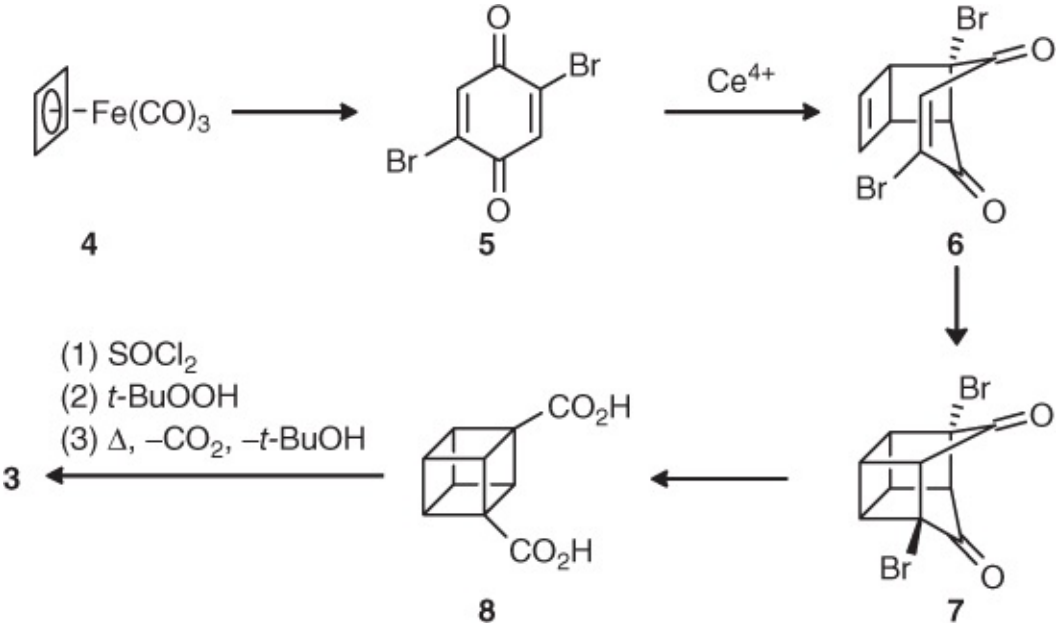
(a) General

1,8-Bishomocubane (**2**) is structurally derived from cubane (**3**) by replacement of one cube-edge C–C bond by an ethano (CH_2–CH_2) bridge. For this basket-shaped cage hydrocarbon, the trivial name “basketane” is used.


2


3

The synthesis of **2** is based on an elegant approach to cubane [1], developed by Pettit [2], as outlined in the following scheme:

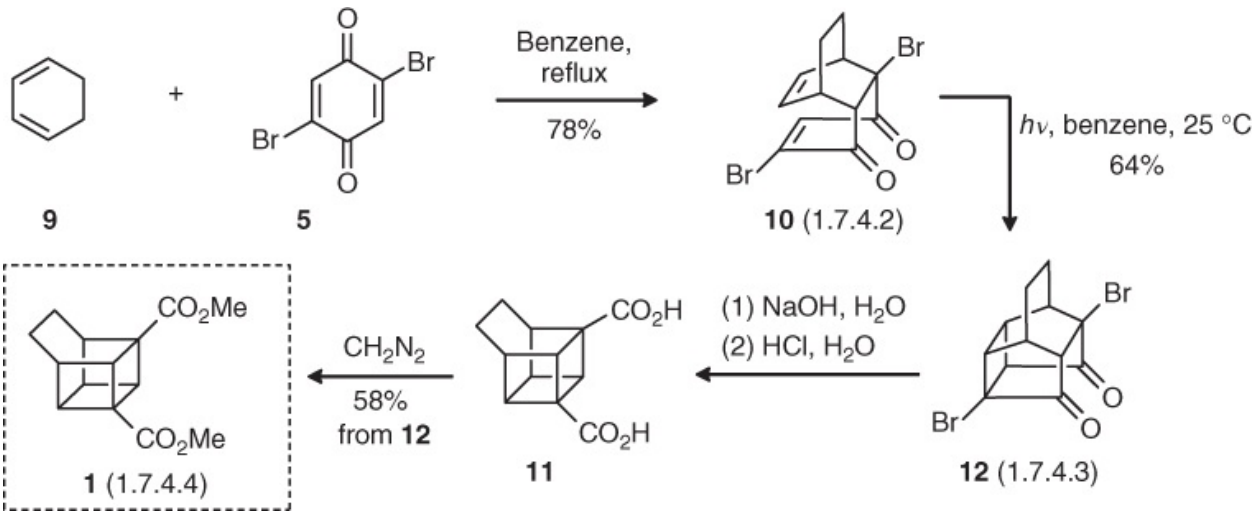


Cyclobutadiene (liberated from its iron complex **4** by oxidation with Ce(IV)) reacts with the dibromoquinone **5** to give the [2 + 2]-cycloadduct **6**. The two double bonds in **6** are in a syn-arrangement, making them suitably predisposed for an intramolecular [2 + 2]-cycloaddition, which occurs readily upon irradiation and provides the dibromodiketone **8**. This is converted to the cubane-1,3-diacid by ring contraction through twofold Favorskii rearrangement (→**7**) and further to cubane (**3**) by decarboxylation of its bis-*tert*-butyl perester.

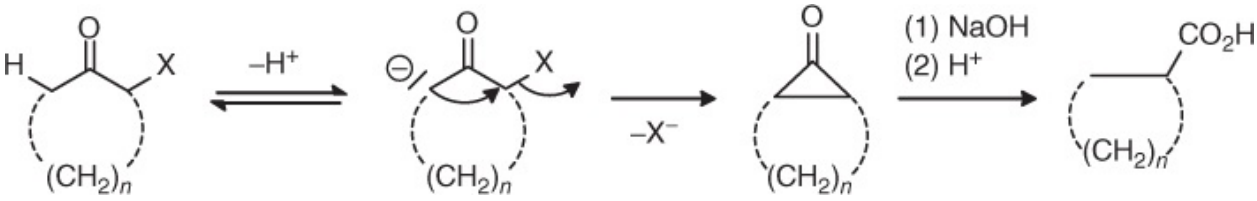
Consequently, the synthesis of **2** includes the essential features of the foregoing strategy, namely (i) an intramolecular [2 + 2]-photocyclization of an appropriate precursor containing the handle of the basketane system and (ii) Favorskii ring contraction to transform an α-bromocyclopentanone to a cyclobutane dicarboxylic acid.

(b) Synthesis of 1

The synthesis of **1** starts with the Diels–Alder reaction of cyclohexa-1,3-diene (**9**) with 2,5-dibromo-1,4-benzoquinone (**5**) utilizing the well-established ability of 1,4-quinones to act as electron-deficient dienophiles in [4 + 2]-cycloadditions [3] (**9** + **5** → **10**):

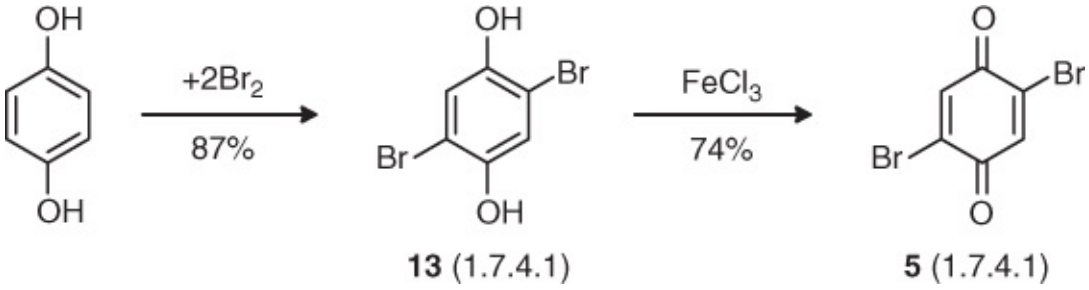


On irradiation of the Diels–Alder adduct **10** in benzene at 25 °C, a photochemically allowed intramolecular [2 + 2]-cycloaddition of the two syn-oriented C=C double bonds occurs with the formation of the dibromodione **12**. Treatment of **12** with NaOH leads to the bishomocubane 1,3-dicarboxylic acid **11** by ring contraction via a cyclopropanone [4].



Finally, the diacid **11** is esterified with diazomethane to give the dimethyl ester **1**. The sequence **12** → **11** → **1** is performed as a one-pot procedure.

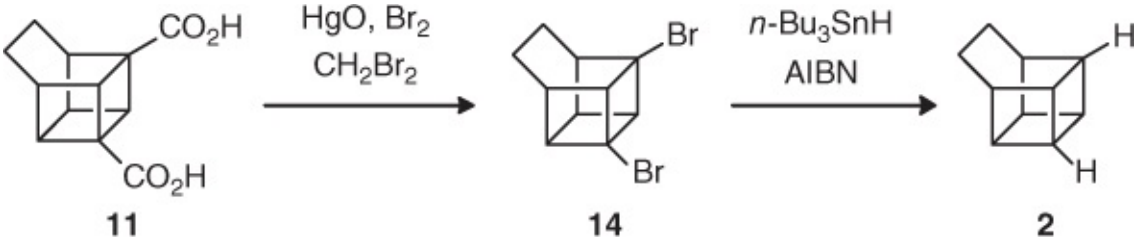
The requisite dibromo-1,4-benzoquinone **5** is prepared by bromination of hydroquinone, which as an activated arene undergoes symmetrical disubstitution to give **13**. This is oxidized using $FeCl_3$ to afford the dibromoquinone **5**.



Thus, the basketane diester **1** is obtained in a five-step sequence with an overall yield of 19% (based on hydroquinone).

It should be noted that the hydrocarbon **2** may be obtained from the diacid **11** by

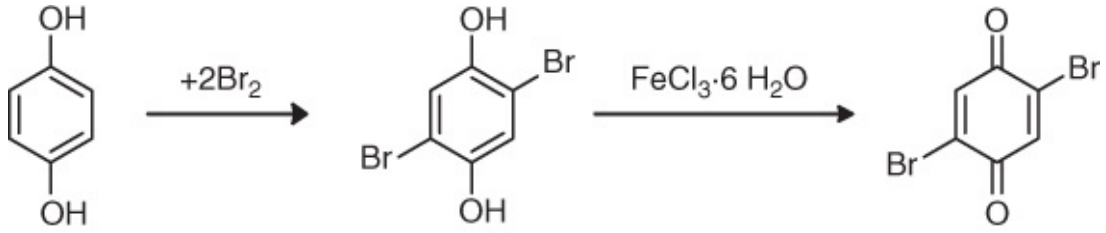
a modified Hunsdiecker reaction to give the dibromide **14** followed by reductive debromination with *n*Bu_3SnH (**14** → **2**) [5]. This two-step sequence corresponds to an overall decarboxylation of **11**:



11 **14** **2**

(c) Experimental Procedures for the Synthesis of 1

1.7.4.1	*	**2,5-Dibromo-1,4-benzoquinone** [6]



110.1 267.9 265.9

1. A solution of bromine (64.0 g, 0.40 mol, ~20.5 ml) in glacial acetic acid (20 ml) is added dropwise to a stirred suspension of hydroquinone (22.0 g, 0.20 mol) in glacial acetic acid (200 ml) at room temperature. The temperature rises to about 30 °C, with the initial formation of a clear solution, followed, after 5–10 min, by the deposition of a colorless precipitate. Stirring is continued for 1 h.

   The mixture is then filtered, and the solid is washed with a small amount of glacial acetic acid. The mother liquor is concentrated *in vacuo* to around half of its original volume and is allowed to stand for 12 h. The formed crystals are collected, and the procedure is repeated to give a third crop. The total yield of crude product is 46.4 g (87%), mp 180–187 °C. Recrystallization from glacial acetic acid gives crystals with mp 188–189 °C. However, the crude product can be used without purification for the next step.

2. A solution of $FeCl_3 \cdot 6H_2O$ (65.4 g, 242 mmol) in H_2O (140 ml) is added dropwise to a stirred, refluxing solution of 2,5-dibromohydroquinone prepared in step (1) (27.4 g, 102 mmol) in H_2O (800 ml) over a period of 15

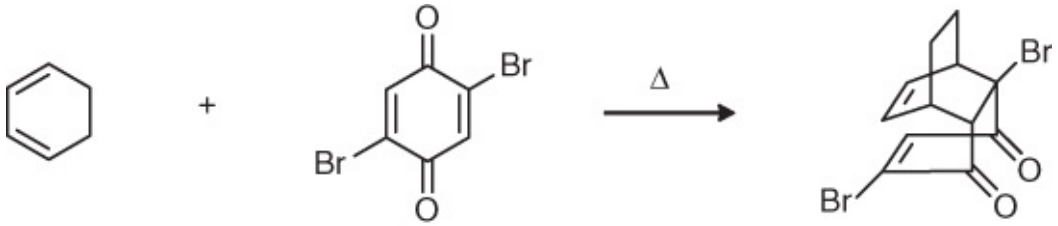
min. The desired *p*-quinone immediately crystallizes from the mixture.

It is collected by filtration after cooling to room temperature, washed with H_2O, and recrystallized from EtOH (800 ml) to give yellow needles; 20.0 g (74%), mp 188–190 °C.

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 1770, 1760.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.12 (s, 2H, 3-H, 6-H).

1.7.4.2	*	**2,5-Dibromotricyclo[6.2.2.0^{2,7}]dodeca-4,9-dien-3,6-dione** [5]



80.1 265.9 346.0

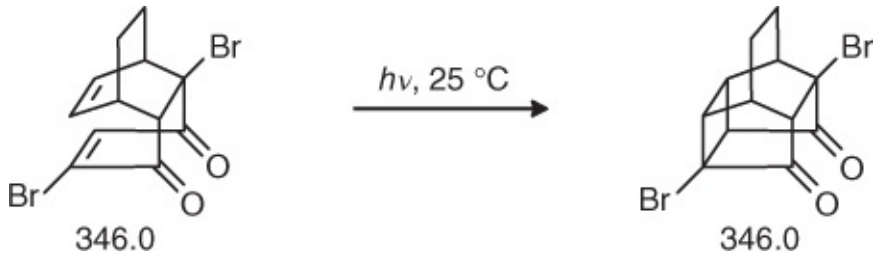
A solution of 2,5-dibromo-*p*-benzoquinone **1.7.4.1** (10.0 g, 37.5 mmol) and cyclohexa-1,3-diene (6.40 g, 80.0 mmol) in anhydrous benzene (20 ml, Caution: Carcinogenic!) is heated under reflux for 3 h.

The solvent and excess cyclohexa-1,3-diene are then distilled off to leave a thick oil, which crystallizes on scratching. The solid is treated with hot petroleum ether (40–60 °C, 2 × 100 ml). The filtrates are combined and cooled to −10 °C. The product crystallizes as colorless crystals. Concentration of the mother liquor gives a small second crop. The total yield is 10.3 g (78%), mp 116–118 °C.

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 1690, 1670, 1600.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.39 (s, 1H, vinyl-H), 6.3–6.2 (m, 2H, vinyl-H), 3.7–3.1 (m, 3H, bridgehead-H and CO–CH), 2.6–1.2 (m, 4H, CH_2–CH_2).

1.7.4.3	**	**1,6-Dibromopentacyclo[6.4.0$^{3.6}$.0$^{4.12}$.0$^{5..9}$]dodeca-2,7-dione** [5]



346.0 346.0

Apparatus: Photolysis apparatus with quartz filter and high-pressure mercury vapor lamp (Philips HPK-125 W or Hanau TQ-150 W).

Dibromodione **1.7.4.2** (10.0 g, 29.9 mmol) in anhydrous benzene (260 ml; Caution: carcinogenic!) (note) is flushed with nitrogen for approximately 15 min and irradiated at room temperature for 5 h, during which partial crystallization of the product occurs.

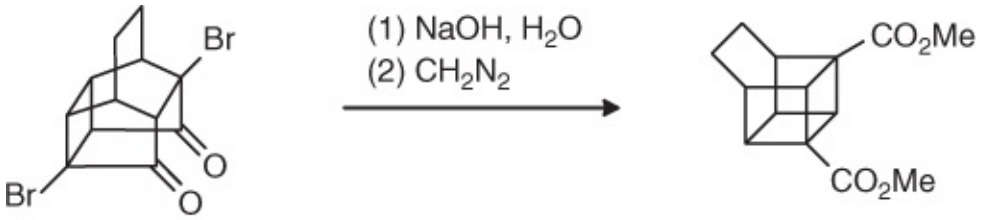
The crystals are filtered off, and the mother liquor is concentrated *in vacuo* to a volume of approximately 30 ml, which leads to the deposition of a second crop of yellowish crystals; total yield 6.40 g (64%), mp 206–208 °C, pure by TLC (silica gel; CH_2Cl_2).

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 1780.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.41 (s_{br}, 3H), 3.15–3.0 (m, 1H, CH adjacent to CO and CBr; assignment unclear), 2.5–1.6 (m, 6H, CH + CH_2).

Note: Irradiation in toluene (under otherwise identical conditions) gives a lower yield (41%).

1.7.4.4	**	**Dimethyl 1,8-bishomocubane-4,6-dicarboxylate** [5]



346.0 248.3

A stirred mixture of product **1.7.4.3** (6.30 g, 18.2 mmol) and 25% aqueous sodium hydroxide (65 ml) is heated under reflux for 2 h. The cooled solution is acidified with concentrated hydrochloric acid, keeping the temperature below 5 °C. The colorless precipitate is collected by filtration, washed with H_2O, and

dried *in vacuo*. The yield is 5.4 g.

The solid is added in small portions to an ethereal solution of diazomethane (prepared from 6.20 g, ∼60.0 mmol of nitroso methyl urea [7] at 0 °C). Complete dissolution occurs with nitrogen evolution. The mixture is stirred for 5 min, and excess diazomethane is destroyed by slow addition of 2 M acetic acid until N_2 evolution stops.

The organic layer is separated, washed with H_2O, saturated aqueous $NaHCO_3$, and brine (30 ml each), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The dark residue is chromatographed on silica gel (0.06–0.02 mm, 150 g) eluting with *n*-hexane/Et_2O (1 : 1). The first fraction contains the product, which is obtained as a colorless oil after evaporation of the solvents; it crystallizes from *n*-pentane on cooling to −15 °C. The yield is 2.60 g (58%), mp 54–56 °C (pure by TLC).

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 1725.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.73, 3.70 (s, 3H, CO_2Me), 3.5–2.85 (m, 6H, cyclobutane CH), 1.54 (s_{br}, 4H, CH_2–CH_2).

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cations: (c) Ryu, D.H., Zhou, G., and Corey, E.J. (2004) *J. Am. Chem. Soc.*, **126**, 4800–4802;(d) Hu, Q.-Y., Zhou, G., and Corey, E.J. (2004) *J. Am. Chem. Soc.*, **126**, 13708–13713.

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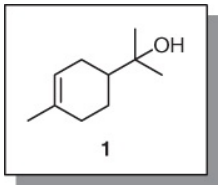
7. *Organikum* (2001), 21st edn, Wiley-VCH Verlag GmbH, Weinheim, p. 647.

1.7.5 α-Terpineol

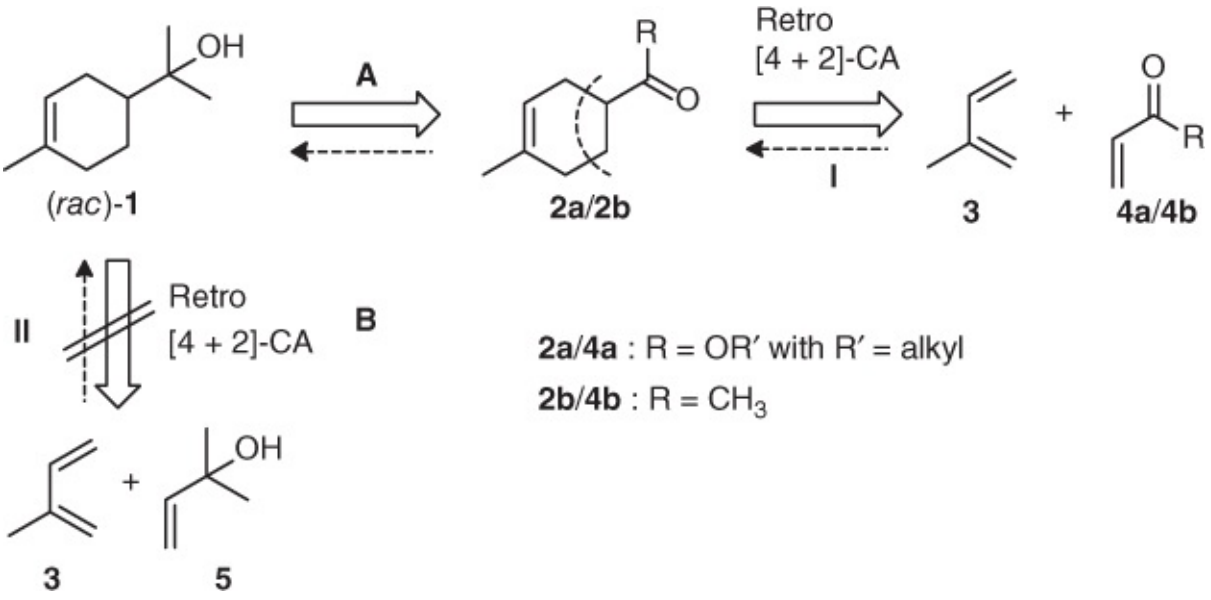
 1	***Topics:***	• Synthesis of a cyclic monoterpene alcohol: (i) in racemic form, (ii) in enantiopure form • Lewis acid-catalyzed regioselective Diels–Alder reaction • Diastereoselective Diels–Alder reaction by use of a chiral auxiliary (Evans auxiliary) • Tertiary alcohols from esters and Grignard compounds • Synthesis and application of an (*S*)-phenylalanine-based Evans auxiliary

(a) General

α-Terpineol (**1**, *p*-menthenol) belongs to the class of cyclic monoterpenes, which are biogenetically derived from two isoprene units via the mevalonate pathway. α-Terpineol is widespread in Nature; its (+)- and (−)-enantiomers have been found in pine oil (etheric oil from *Pinus palustris* (Pinaceae)). Because of its odor, which is reminiscent of that of lavender, it is used in perfumery as a fragrance. α-Terpineol is obtained industrially from α-pinene [1].

Retrosynthetic analysis of **1** according to pathway A leads to isoprene (**3**) and

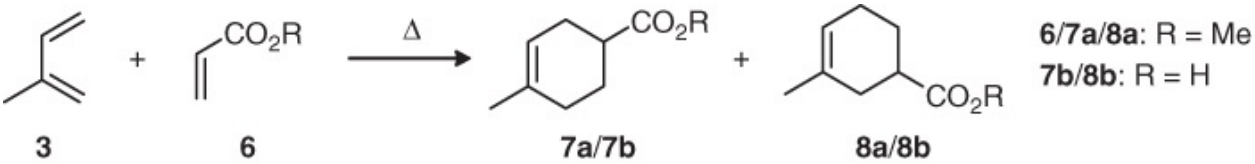
acrylate (**4a**) or methyl vinyl ketone (**4b**) via the cyclohexene **2**.



The formation of **2** from **3** and **4** by a Diels–Alder reaction is a favored process because of favorable electronic interaction (electron-rich diene and electron-poor dienophile). The tertiary alcohol function in **1** can be introduced by reaction of cycloadduct **2a** with 2 mol of CH_3MgX (see the synthesis in Section (b)) or by treating **2b** with 1 mol of CH_3MgX.

Retrosynthesis according to pathway **B** by direct retro-Diels–Alder disconnection of **1** leads to isoprene (**3**) and the allylic alcohol **5** as dienophile. However, their combination in a thermal [4 + 2]-cycloaddition (**II**) is a less favorable process according to frontier orbital interaction considerations since the highest occupied molecular orbital (HOMO) (diene)/LUMO (dienophile) energy difference is significantly higher in the case of **5** than it is with **4a** [2].

The [4 + 2]-cycloaddition of isoprene (**3**) to an acrylic ester **4a** has served as a model reaction in investigating the regioselectivity and stereoselectivity of Diels–Alder reactions.



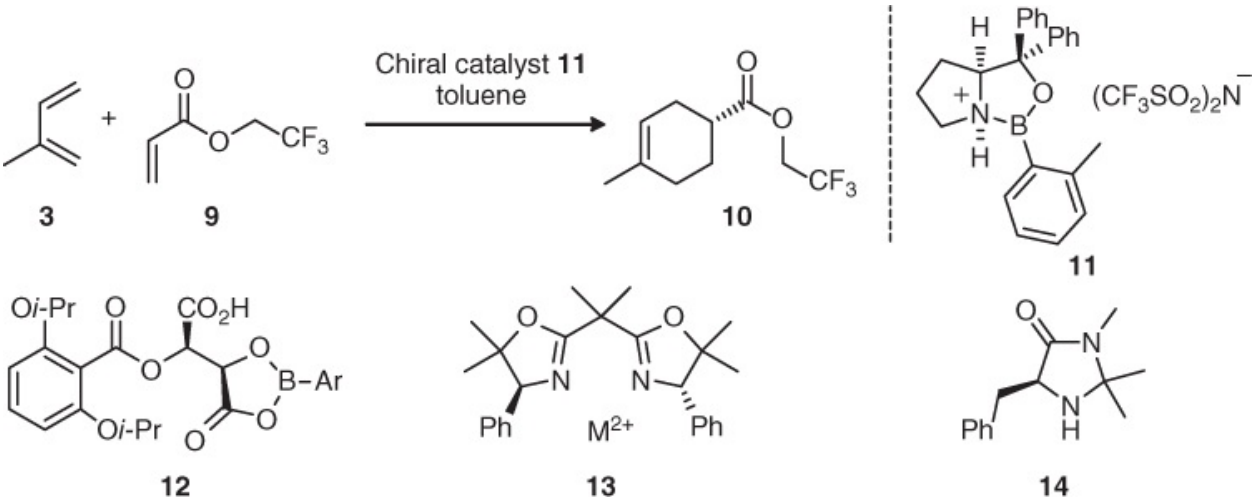
1. When isoprene (**3**) and methyl acrylate (**6**) are reacted thermally at 80 °C, a 70 : 30 mixture of the regioisomeric cycloadducts **7a** and **8a** is obtained in 80% yield. The regioselectivity is significantly improved by the addition of a Lewis acid; thus, in the presence of $AlCl_3$, a 95 : 5 mixture of **7a** and **8a**

(77% yield, see Section (b)) results [3, 4]. Separation is possible by fractional crystallization of the regioisomeric acids **7b** and **8b** after saponification; the ester **7a** may then be obtained free of its regioisomer by re-esterification of the purified acid **7b** with CH_2N_2.

2. Asymmetric Diels–Alder reactions have been performed (i) by use of a dienophile connected to a chiral auxiliary and (ii) by use of a chiral Lewis acid as catalyst [5].

Concerning (i), an example is presented in Section (b), in which an acrylic acid attached to an Evans auxiliary (cf. Section 1.2.2) is utilized for [4 + 2]-cycloaddition to isoprene [6]. After removal of the auxiliary, an enantiopure ester of type **7a** is produced, which allows the preparation of (*R*)-**1**.

Concerning (ii), a catalytic asymmetric version of the Diels–Alder reaction of isoprene with acrylate has been developed [7], which involves the use of the trifluoroethyl ester **9** and a chiral proline-derived cationic oxazaborolidine derivative **11** (as its triflimide) and gives the cycloadduct **10** in excellent yield (99%) and with high enantioselectivity (ee = 98%). Ester **10** could also be used as a substrate for the synthesis of (*R*)-**1**.



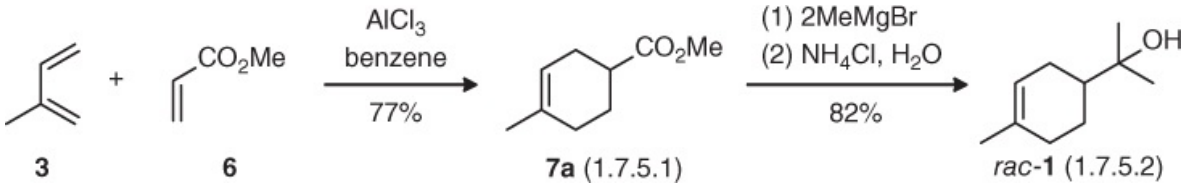
Catalysts of type **11** have been shown to have a broad spectrum of applications in enantioselective [4 + 2]-cycloadditions [7, 8]. CAB [9] (**12**, cf. Section 1.3.3) and chiral bisoxazoline ligands [10] (BOX, **13**) have also proved to be successful catalysts for asymmetric Diels–Alder reactions [11] because they form rigid metal–substrate complexes and provide excellent stereoselectivities. Likewise, for hetero-Diels–Alder reactions with inverse electron demand, efficient catalysts based on Cr, Zr, or Sc complexes are known [12]. Furthermore, enantioselective Diels–Alder reactions [13] using α,β-unsaturated aldehydes as

dienophiles and chiral amines as organo catalysts can be performed by employing, for example, imidazolidinone **14**. The formation of an iminium ion by reaction of the carbonyl moiety of the dienophile with the amine functionality of the organo catalyst lowers the LUMO energy of the dienophile, leading to an acceleration of the Diels–Alder reaction.

(b) Synthesis of 1

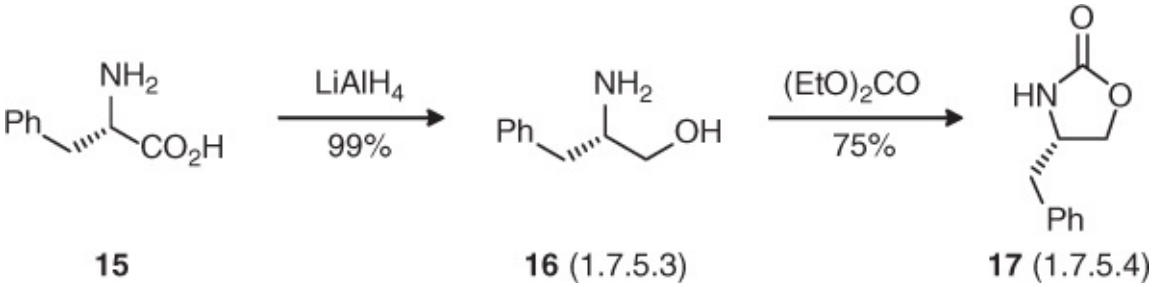
1. Synthesis of (*rac*)-α-terpineol [3, 14]

   The Diels–Alder reaction of isoprene with methyl acrylate (**6**) is performed in benzene solution at room temperature in the presence of $AlCl_3$ as Lewis acid. The cycloadduct **7a** (containing a 5% impurity of the regioisomeric ester **8a**; for separation, see Section (a)) is reacted with 2 mol of methylmagnesium iodide. This classical transformation of an ester to a tertiary carbinol containing two equal α-substituents leads to the racemic α-terpineol (*rac*-**1**) after the usual work-up with NH_4Cl solution.



2. Synthesis of (+)-(*R*)-α-terpineol [6]

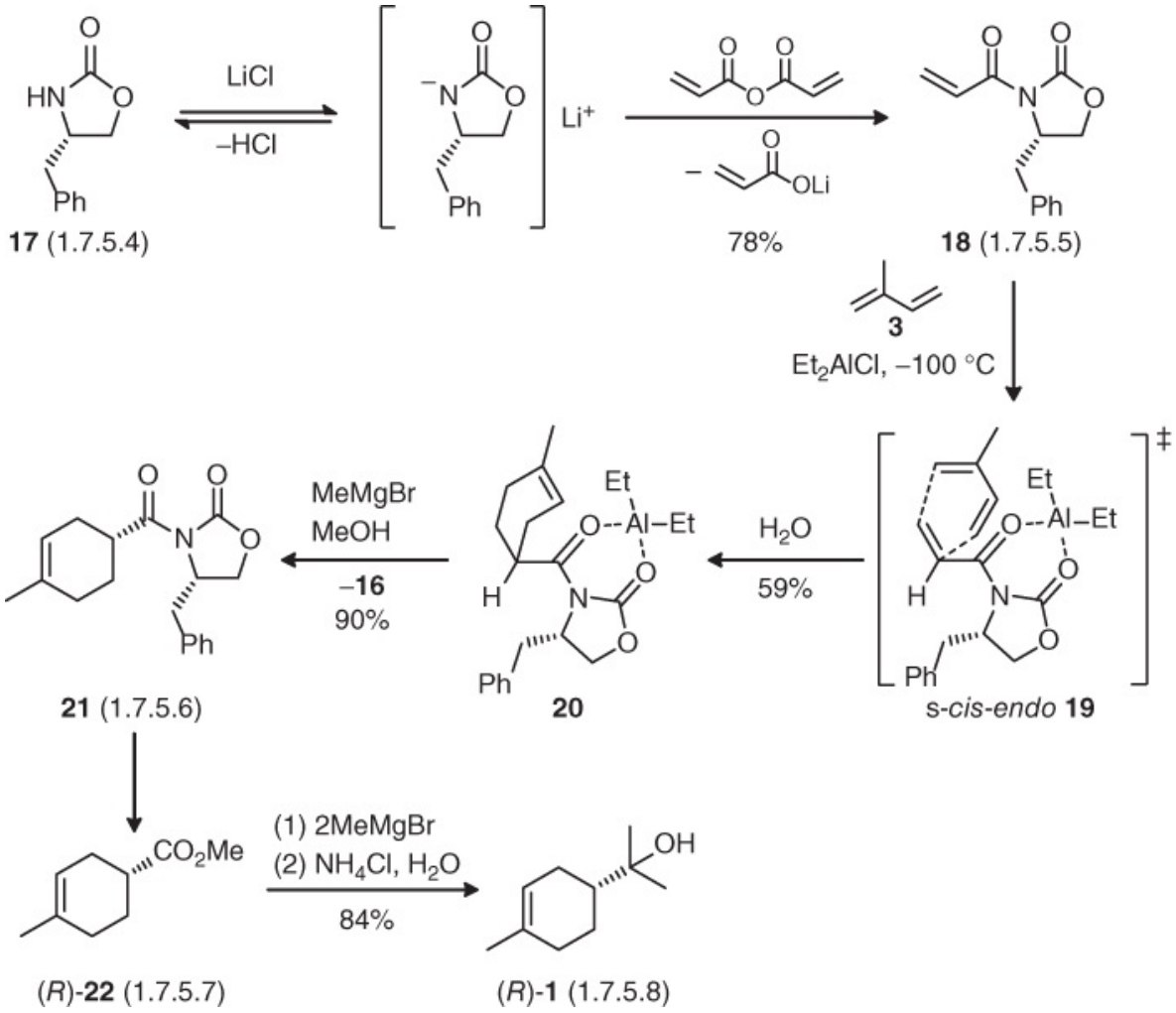
   As chiral auxiliary, an oxazolidin-2-one **17** of the Evans type (cf. Section 1.2.2) is used. It is readily prepared from (*S*)-phenylalanine (**15**) by reduction with $LiAlH_4$ and cyclocondensation of the resulting (*S*)-phenylalaninol (**16**) with diethyl carbonate.



   To introduce an acrylic moiety, the chiral auxiliary **17** is equilibrium-deprotonated using LiCl in THF and acylated with acryloyl anhydride prepared *in situ* from acryloyl chloride and acrylic acid in the presence of triethylamine [15] to give the chiral acrylic amide **18**.

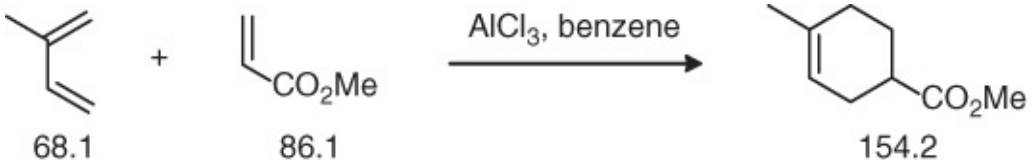
Diels–Alder reaction of **18** with isoprene (**3**) proceeds readily at −100 °C in the presence of diethylaluminum chloride in CH_2Cl_2/toluene as solvent to give (after hydrolytic work-up) the cycloadduct **21** with a diastereoselectivity of de = 90% via an s-cis-endo transition state **19**. The efficient stereodiscrimination can be explained (i) by the Lewis acid Et_2AlCl, which provides for rigid chelation of the dienophile moiety by coordinative interaction with both C=O groups of the *N*-acyloxazolidin-2-one system **20**, and by (ii) π-stacking, which causes a stereoelectronic stabilization of the transition state [6]. Thus, improved diastereoselectivity is observed with the benzyl-substituted auxiliary **17** as compared to that seen with auxiliaries with aliphatic residues, for example, the valinol-derived analog.

The diastereomeric purity of the cycloadduct **21** can be raised up to >98% de by recrystallization. Compound **21** is cleaved by treatment with CH_3OMgBr (prepared *in situ* by reaction of CH_3MgBr with CH_3OH) to give the chiral methyl ester (*R*)-**22** with >99% ee. The chiral auxiliary **17** can be recovered from the reaction mixture, allowing its regenerative use. Finally, the methyl ester (*R*)-**22** is transformed into (+)-(*R*)-α-terpineol ((*R*)-**1**) by reaction with 2 mol of MeMgI; the chiral monoterpene alcohol (*R*)-**1** is obtained in almost enantiopure form with >98% ee.



(c) Experimental Procedures for the Synthesis of 1

1.7.5.1	**	**Methyl 4-methylcyclohex-3-ene-1-carboxylate** [14]



A solution of methyl acrylate (26.1 g, 303 mmol) (note 1) in anhydrous benzene (30 ml; Caution: carcinogenic!) is added dropwise to a well-stirred suspension of anhydrous $AlCl_3$ (4.30 g, 32.0 mmol) in anhydrous benzene (250 ml) over 15 min. The temperature rises to 25 °C and the $AlCl_3$ dissolves. A solution of isoprene (20.9 g, 307 mmol) in benzene (50 ml) is then added dropwise over a period of 60 min. The temperature is held at 15–20 °C with occasional cooling during this period. Stirring is continued at room temperature for 3 h.

The solution is poured into aqueous HCl (2 M) saturated with NaCl (500 ml), the phases are separated, and the organic phase is washed with H_2O (250 ml), dried over Na_2SO_4, and filtered. The solvent is evaporated under slightly reduced pressure at 70 °C and the residue is fractionally distilled *in vacuo*. The product is obtained as a colorless oil; 35.7 g (77%), bp_{17} 80–82 °C, n^{20}_D = 1.4630 (note 2).

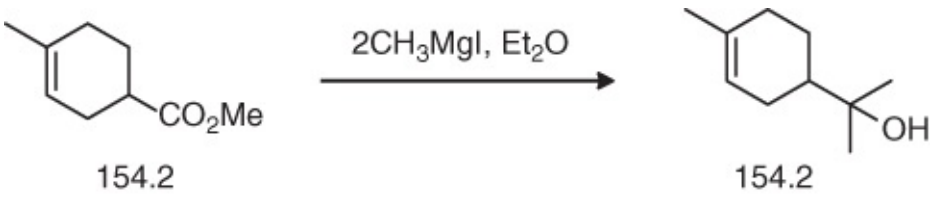
IR (NaCl): $\tilde{\nu}$ (cm^{-1}) = 1745, 1440, 1175.

^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) = 5.28 (s_{br}, 1H, 3-H), 3.60 (s, 3H, CO_2CH_3), 2.70–1.65 (m, 7H, 1-H, 2-H_2, 5-H_2, 6-H_2), 1.63 (s, 3H, CH_3).

Notes:

1. Methyl acrylate should be freshly distilled over hydroquinone before use, bp_{760} 80–81 °C.
2. The product is a 95 : 5 mixture with the regioisomeric 3-methylcyclohex-3-ene-1-carboxylic methyl ester [4] (see Section (a)). This mixture is used in the next step.

1.7.5.2 * ***rac*-α-Terpineol** [3]



An iodine crystal is added to magnesium turnings (7.20 g, 300 mmol) covered with anhydrous Et_2O (30 ml), followed by a few milliliters of a solution of methyl iodide (42.6 g, 300 mmol; Caution: carcinogenic!) in anhydrous Et_2O (50 ml). The formation of the Grignard reagent starts immediately, and the remaining methyl iodide solution is added dropwise at such a rate that the Et_2O refluxes gently (approximately 1 h). After the addition is complete, the solution is heated under reflux for 30 min. Then, a solution of the ester **1.7.5.1** (20.0 g, 130 mmol) in Et_2O (50 ml) is added dropwise with stirring over 40 min. The mixture boils vigorously during the addition, and a gray precipitate forms. Heating under reflux is continued for 2 h.

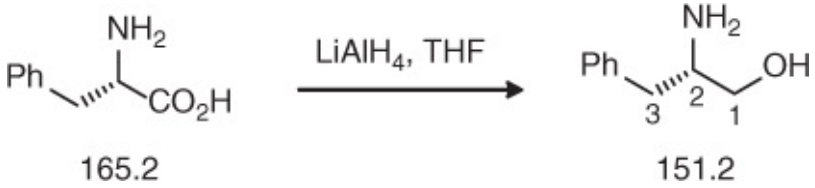
The mixture is then cooled in an ice bath, and a pre-cooled solution of NH_4Cl

(60 g) in H_2O (300 ml) is added. The organic layer is separated, and the aqueous layer is extracted with Et_2O (2 × 50 ml). The combined organic layers are dried over Na_2SO_4 and filtered, and the solvent is removed *in vacuo*. The residue is fractionally distilled to give the product as a colorless oil with a turpentine-like odor; 16.4 g (82%), bp_{15} 94–95 °C, n^{20}_D = 1.4790.

IR (NaCl): $\tilde{\nu}$ (cm^{-1}) = 3600–3200, 2980, 2940, 2850, 1450, 1390, 1375.

^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) = 5.30 (s_{br}, 1H, 3-H), 2.41 (s, 1H, OH), 2.20–1.50 (m, 7H, 1-H, 2-H_2, 5-H_2, 6-H_2), 1.60 (s, 3H, 4-CH_3), 1.13 (s, 6H, $C(CH_3)_2$).

1.7.5.3	**	**(2*S*)-2-Amino-3-phenylpropan-1-ol** [15]



165.2 151.2

L-Phenylalanine (54.5 g, 330 mmol) is added with caution to a stirred suspension of $LiAlH_4$ (25.0 g, 660 mmol) in anhydrous THF (400 ml) over 30 min at 0 °C under a N_2 atmosphere (note). The mixture is warmed to room temperature and then heated under reflux with stirring for 15 h.

The solution is then cooled in an ice bath, and H_2O (135 ml) is carefully added dropwise. After filtration, the filtrate is concentrated under reduced pressure, and the residue is recrystallized from THF/H_2O (4 : 1, 200 ml) to yield the L-phenylalaninol as light-yellow needles; 49.2 g (99%), mp 91–92 °C, $[\alpha]^{20}_D$ = −17.4 (*c* = 1.0, $CHCl_3$), R_f = 0.14 (EtOAc/MeOH, 10 : 1).

UV (CH_3CN): λ_{max} (nm) (log ϵ) = 268.0 (2.229), 258.5 (2.363), 254.0 (2.304), 192.5 (4.473).

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3356, 2876, 1577, 1492, 1338, 1122, 1065, 754, 698, 621, 592.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.32–7.17 (m, 5H, Ph–H), 3.58 (dd,

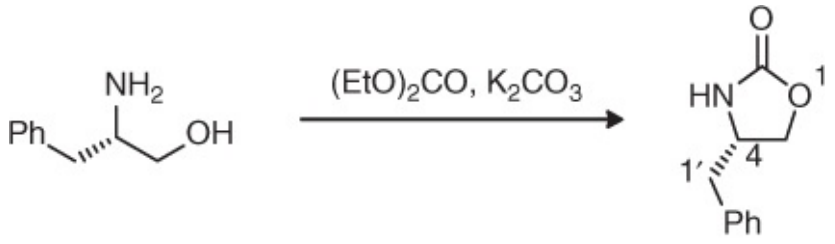
J = 10.6, 4.2 Hz, 1H, 1-H_b), 3.35 (dd, J = 10.6, 7.3 Hz, 1H, 1-H_a), 3.05 (m_c, 1H, 2-H), 2.75 (dd, J = 13.5, 5.4 Hz, 1H, 3-H_b), 2.48 (s_{br}, 3H, NH_2, OH), 2.46 (dd, J = 13.5, 8.8 Hz, 1H, 3-H_a).

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 138.6, 129.1, 128.5, 126.3 (6 × Ph–C), 65.9 (C-1), 54.1 (C-2), 40.5 (C-3).

MS (DCI, 200 eV): *m*/*z* (%) = 152 (100) $[M+H]^+$, 169 (37) $[M+NH_4]^+$.

Note: The reaction starts with delay, but then vigorously.

1.7.5.4	**	**(4*S*)-4-Benzyloxazolidin-2-one** [15]



151.2 177.2

A dry, three-necked, round-bottomed flask equipped with a thermometer, a Vigreux column, and a magnetic stirring bar is charged with the amino alcohol **1.7.5.3** (15.1 g, 100 mmol), K_2CO_3 (1.38 g, 10.0 mmol), and diethyl carbonate (29.5 g, 250 mmol). The mixture is carefully heated to 135–140 °C, and EtOH is allowed to distil as it is formed. After 2 h, 15 ml of distillate would have been collected.

The reaction mixture is then diluted with CH_2Cl_2 (250 ml) and filtered. The solution is washed with saturated aqueous $NaHCO_3$ solution (100 ml), dried over $MgSO_4$, and filtered, and the solvent is removed *in vacuo*. Recrystallization from EtOAc/*n*-pentane gives the oxazolidinone as colorless needles; 13.3 g (75%), mp 88–89 °C, $[\alpha]^{20}_D$ = −62.5 (*c* = 1.0, $CHCl_3$), R_f = 0.47 (EtOAc).

UV (CH_3CN): λ_{max} (nm) (log ϵ) = 263.5 (2.191), 258.0 (2.302), 252.5 (2.218), 206.0 (3.939).

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 1751, 1404, 1244, 1096, 1021, 942, 757, 708.

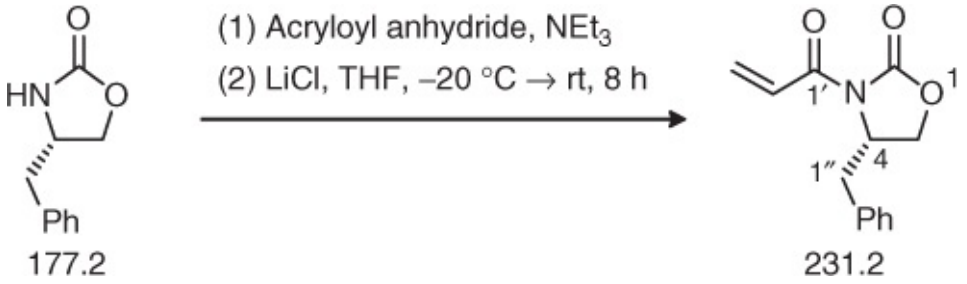
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.37–7.17 (m, 5H, Ph–H), 6.01 (s_{br},

1H, NH), 4.43 (m_c, 1H, 5-H_b), 4.17–4.05 (m, 2H, 4-H, 5-H_a), 2.88 (m_{cr}, 2H, 1′-H_2).

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 159.5 (C-2), 135.9, 129.0, 128.9 (6 × Ph–C), 69.52 (C-5), 53.72 (C-4), 41.33 (C-1′).

MS (EI, 70 eV): *m*/*z* (%) = 177 (7) $[M]^+$, 86 (86) $[M-C_7H_7]^+$.

1.7.5.5	**	**(4*S*)-3-(1-Acryloyl)-4-benzyl-oxazolidin-2-one** [6]



Triethylamine (13.4 g, 132 mmol, 18.4 ml) and acryloyl chloride (5.98 g, 66.0 mmol, 5.34 ml) are added to a stirred solution of acrylic acid (5.13 g, 71.2 mmol, 4.88 ml) in anhydrous THF (300 ml) at −20 °C under a N_2 atmosphere, and stirring is continued at this temperature for 2 h. LiCl (2.58 g, 61.0 mmol) is added, followed by the oxazolidinone **1.7.5.4** (9.00 g, 50.8 mmol). The mixture is allowed to warm to room temperature and then stirred for 8 h.

The reaction is quenched by the addition of aqueous HCl (0.2 M, 70 ml), and the THF is removed *in vacuo*. After addition of EtOAc (100 ml), the mixture is washed with half-saturated aqueous $NaHCO_3$ solution (80 ml) and brine (80 ml), dried over Na_2SO_4, and filtered, and the solvent is removed *in vacuo*. Column chromatography of the residue on silica gel (*n*-pentane/EtOAc, 4 : 1) yields the acryloyloxazolidinone as colorless crystals; 9.21 g (78%), mp 74–75 °C, R_f = 0.42 (*n*-pentane/EtOAc, 4 : 1), $[\alpha]^{20}_D$ = +79.0 (*c* = 1.0, $CHCl_3$).

UV (CH_3CN): λ_{max} (nm) (log ϵ) = 207.5 (4.316), 191.5 (4.658).

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 1784, 1682, 1389, 1352, 1313, 1245, 1216, 989, 696.

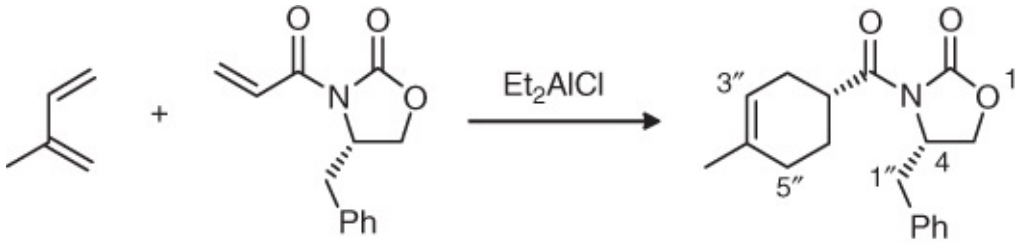
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.47 (dd, *J* = 17.0, 10.5 Hz, 1H, 2′-H), 7.37–7.21 (m, 5H, 5 × Ph–H), 6.58 (dd, *J* = 17.0, 1.7 Hz, 1H, 3′-H_b),

5.92 (dd, J = 10.5, 1.7 Hz, 1H, 3′-H_a), 4.70 (m_c, 1H, 4-H), 4.17 (m_c, 2H, 5-H_2), 3.33 (dd, J = 13.3, 3.3 Hz, 1H, 1″-H_b), 2.78 (dd, J = 13.3, 9.4 Hz, 1H, 1″-H_a).

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 164.8 (C-1′), 153.3 (C-2), 135.2 (C-2″), 131.9 (C-3′), 129.4 (C-2′), 128.9, 127.3 (5 × Ph–C′), 66.20 (C-5), 55.22 (C-4), 37.70 (C-1″).

MS (EI, 70 eV): m/z (%) = 231 (27) $[M]^+$, 140 (18) $[M-CH_2Ph]^+$, 55 (100) $[M-C_{10}H_{10}NO_2]^+$.

1.7.5.6	***	**(4*S*,1″*R*)-4-Benzyl-3-(4-methylcyclohex-3-enecarbonyl)oxazolidin-**
		2-one [6]



68.1 231.2 299.4

A solution of the acryloyloxazolidinone **1.7.5.5** (6.89 g, 29.8 mmol) and isoprene (70 ml) in anhydrous dichloromethane (70 ml) is cooled to −100 °C. Diethylaluminum chloride (41.7 ml, 1 M in *n*-hexane, 41.7 mmol), cooled to −78 °C, is added via a coolable dropping funnel over a period of 10 min, whereupon the mixture turns yellow. The mixture is stirred at −100 °C for 30 min.

It is then poured into aqueous HCl (1 M, 600 ml). After the addition of CH_2Cl_2 (100 ml), the layers are separated and the aqueous phase is extracted with CH_2Cl_2 (2 × 200 ml). The combined organic layers are dried over $MgSO_4$ and filtered, and the solvent is removed *in vacuo*. Purification of the residue by column chromatography on silica gel (*n*-pentane/EtOAc, 4 : 1) gives the product as white needles; 5.30 g (59%), mp 87–88 °C, $[\alpha]^{20}_D$ = +92.8 (c = 1.0, $CHCl_3$), R_f = 0.39 (*n*-pentane/EtOAc, 4 : 1).

UV (CH_3CN): λ_{max} (nm) (log ϵ) = 263.5 (2.239), 257.5 (2.392), 252.0

(2.392), 247.0 (2.367).

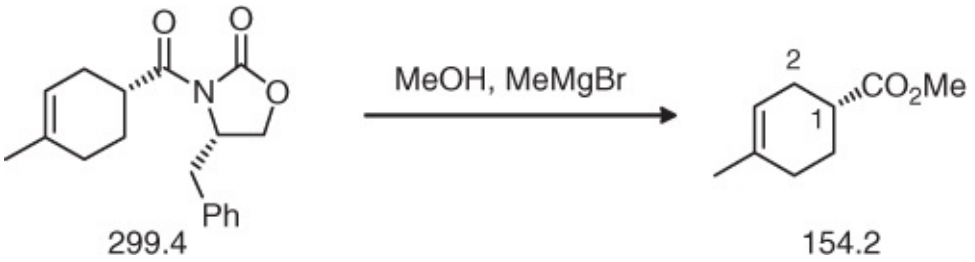
IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3026, 2963, 2835, 1700, 1387, 1238, 1219, 1202.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.36–7.15 (m, 5H, 5 × Ph–H), 5.40 (m, 1H, 3″-H), 4.66 (m, 1H, 4-H), 4.23–4.10 (m, 2H, 5-H_2), 3.72–3.59 (m, 1H, 1″-H), 3.24 (dd, *J* = 13.4, 3.2 Hz, 1H, 1′-H_b), 2.75 (dd, *J* = 13.4, 9.5 Hz, 1H, 1′-H_a), 2.35–1.68 (m, 6H, 2″-H_2, 5″-H_2, 6″-H_2), 1.65 (s, 3H, 4″-CH_3).

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 176.5 (1″-(CO)N), 153.0 (C-2), 135.3, 133.7, 129.4, 128.9, 127.3 (5 × Ph–C, C-4″), 119.0 (C-3″), 66.00 (C-5), 55.24 (C-4), 38.41 (C-1″), 37.88 (Ph–*C*H_2), 29.42 (C-5″), 27.71 (C-2″), 25.68 (C-6″), 23.38 (4″-CH_3).

MS (ESI, 70 eV): *m*/*z* (%) = 622 (6) $[2M+Na]^+$, 354 (100) $[M-H+2Na]^+$, 322 (25) $[M+Na]^+$.

1.7.5.7	**	**Methyl (*R*)-4-methylcyclohex-3-enecarboxylate** [6]



299.4 154.2

Methylmagnesium bromide (3 M in Et_2O, 2.3 ml, 4.68 mmol) is added dropwise to anhydrous methanol (20 ml) at 0 °C, and the solution is stirred at this temperature for 5 min. A solution of the Diels–Alder adduct **1.7.5.6** (0.70 g, 2.34 mmol) in MeOH (20 ml) is then added dropwise and the mixture is stirred for 90 min.

The reaction is quenched by the addition of aqueous pH 7 phosphate buffer solution (20 ml), and stirring is continued for a further 30 min at room temperature. The mixture is diluted with half-saturated aqueous NH_4Cl (40 ml) and brine (40 ml), and CH_2Cl_2 (40 ml) is added. The layers are separated and the aqueous layer is extracted with CH_2Cl_2 (3 × 40 ml). The combined organic layers are dried over $MgSO_4$ and filtered, and the solvent is removed at room temperature under reduced pressure. The crude product is purified by column

chromatography on silica gel (*n*-pentane/Et_2O, 14 : 1) to give the methyl ester as a colorless liquid; 324 mg (90%), n^{20}_D = 1.4624, $[\alpha]^{20}_D$ = +52.2 (*c* = 2.1, CH_2Cl_2), R_f = 0.46 (*n*-pentane/EtOAc, 20 : 1).

UV (CH_3CN): λ_{max} (nm) (log ϵ) = 267.0 (1.934), 263.0 (2.159), 251.5 (2.155), 257.0 (2.269), 191.5 (4.576).

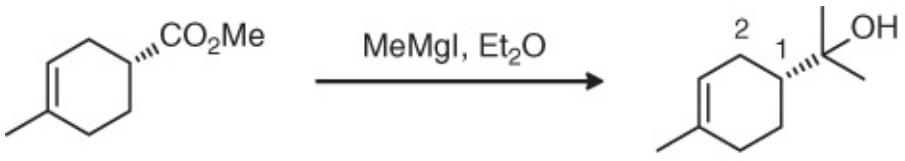
IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 2961, 2928, 1734, 1455, 1442, 1163, 697.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 5.41–5.34 (2 × m, 1H, 3-H), 3.68 (s, 3H, OCH_3), 2.56–2.43 (m, 1H, 1-H), 1.62–1.78, 1.94–2.05, 2.17–2.26 (3 m, 9H, 2-H_2, 3-H_2, 4-CH_3, 5-H_2).

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 23.43 (4-CH_3), 25.43 (C-6), 27.62 (C-2), 29.24 (C-5), 39.03 (C-1), 51.56 (O-CH_3), 119.15 (C-3), 133.69 (C-4), 176.47 (C=O).

MS (EI, 70 eV): *m*/*z* (%) = 154 (32) $[M]^+$, 95 (46) $[M-CH_3-CO_2]^+$, 94 (100) $[M-CH_3-CO_2-H]^+$.

1.7.5.8	**	**(+)-(*R*)-α-Terpineol** [6]



230.3 154.3

A solution of the methyl ester **1.7.5.7** (209 mg, 1.36 mmol) in anhydrous Et_2O (10 ml) is added dropwise to a solution of methylmagnesium iodide (3 M in Et_2O, 1.62 ml, 4.86 mmol) in Et_2O (15 ml) at room temperature. The mixture is stirred for 4.5 h at this temperature (TLC control).

The mixture is then poured into saturated aqueous NH_4Cl solution (30 ml). The layers are separated, and the aqueous layer is extracted with Et_2O (5 × 20 ml). The combined organic phases are washed with H_2O (20 ml) and brine (20 ml), dried over $MgSO_4$, and filtered, and the solvent is removed *in vacuo*. The residue is purified by column chromatography on silica gel (*n*-pentane/Et_2O, 7 :

3) to give (+)-(*R*)-α-terpineol as a colorless oil, which crystallizes upon refrigeration; 177 mg (84%), ee = 90%, mp 25–26 °C, $[\alpha]^{20}_D$ = +91.1 (*c* = 1.0, $CHCl_3$), R_f = 0.27 (*n*-pentane/Et_2O, 7 : 3).

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3600–3100, 2970, 2924, 2889, 2836, 1438, 1377, 1366, 1158, 1133.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 5.42–5.36 (m, 1H, 3-H), 1.67–1.64 (m, 3H, 4-CH_3), 1.50 (m, 1H, 1-H), 2.13–1.72, 1.33–1.20 (2 × m, 7H, 2-H_2, 5-H_2, 6-H_2, OH), 1.91, 1.17 (2 × s, 2 × 3H, C(OH)(C$\underline{H}_3$)$_2$).

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 133.99 (C-4), 120.51 (C-3), 72.71 (COH), 44.95 (C-1), 30.96 (C-5), 26.85 (C-2), 27.42*, 26.22* (COH(*C*H_3)$_2$), 23.93 (C-6), 23.33 (4-CH_3).

MS (EI, 70 eV): *m*/*z* (%) = 154 (14) $[M]^+$, 136 (69) $[M-CH_3]^+$, 121 (55) $[M-2CH_3]^+$.

GC: column: WCOT fused silica CP-Chiralsil-DEX CB (25 m × 0.25 mm)

carrier: H_2; temperature: 100 °C

retention time: t_{R1} = 9.14 min (minor enantiomer); t_{R2} = 9.34 min (major enantiomer).

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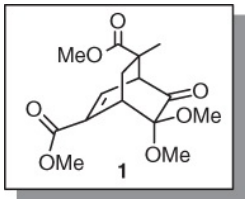
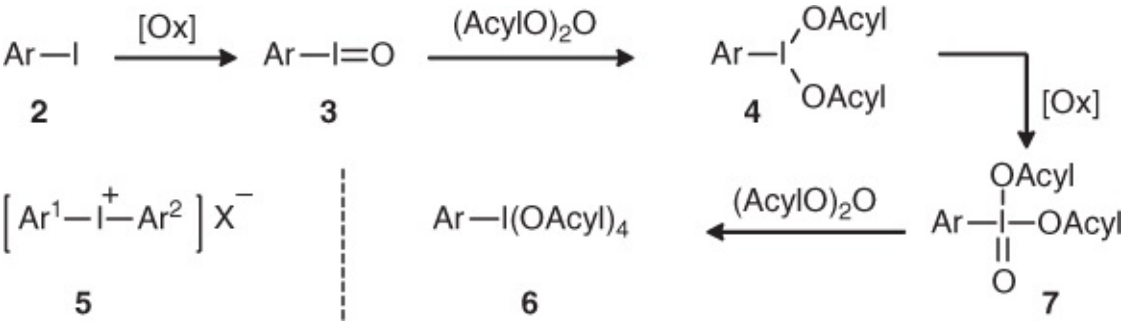
1.7.6 Bicyclo[2.2.2]octene Derivative

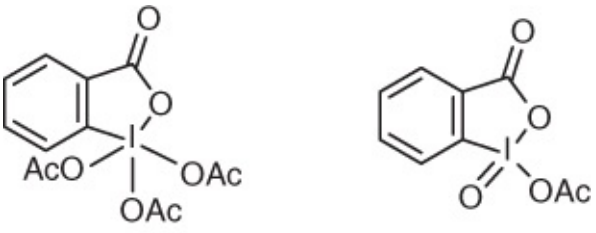
	***Topics:***	• Oxidation of an *o*-methoxy-substituted phenol with a hypervalent iodine compound • Diels–Alder reaction of a cyclohexa-1,3-dienone with methacrylate

(a) General

In general, hypervalent organoiodine compounds [1–3] are derived from aryl iodides **2** (oxidation level of I: +1) by oxidation at the iodine atom. Thus, **2** can be oxidized to iodoxyarenes **3** and diacylated to give (diacyloxy)iodoarenes **4** (oxidation level of I: +3):



Hypervalent iodine(III) compounds such as **4** can be further oxidized to iodine(V) compounds of types **6**/**7** represented, for example, by Dess–Martin periodinane (**8**, DMP) and *ortho*-iodoxybenzoic acid (**9**, IBX), which are important reagents for the oxidation of primary and secondary alcohols to give aldehydes and ketones, respectively (cf. Section 2.3.2).

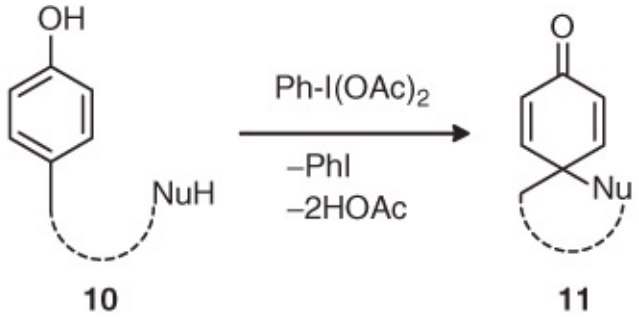


Diaryliodonium compounds **5** are another type of hypervalent iodine compounds used in synthetic chemistry [4].

The trivalent (diacyloxy)iodoarenes **4** (most frequently Ar = Ph, acyl = acetyl or

trifluoroacetyl) are often applied for oxidative transformations of organic substrates, leading to the formation of C–C bonds or C–heteroatom bonds of various types [1].

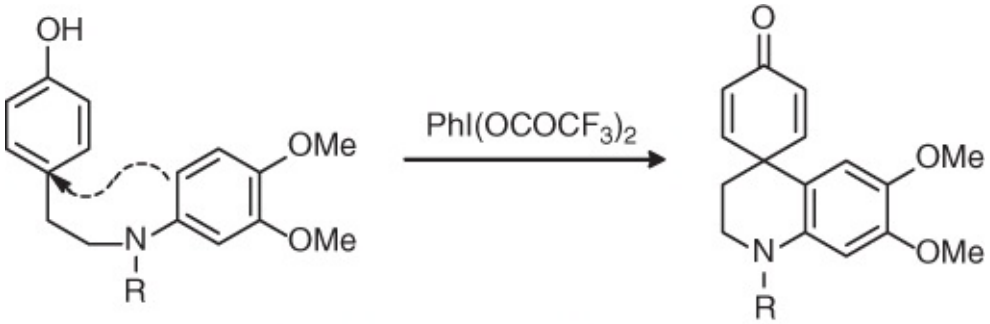
In particular, the oxidation of phenols with **4** leads to a variety of synthetically useful products [2]. Ortho-substituted phenols and *o*- or *p*-hydroquinones afford the corresponding benzoquinones, whereas para-substituted phenols **10** in the presence of an external or internal nucleophile lead to the corresponding 4,4-disubstituted cyclohexa-2,5-dienones (or spirodienones) **11**:



10 **11**

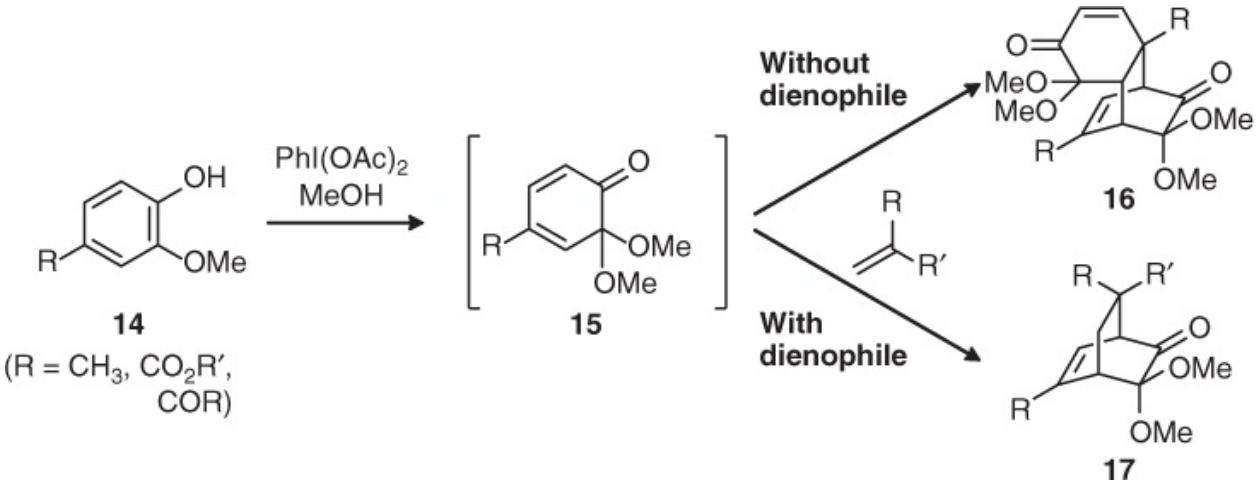
Nu = RO, halogenide anions, electron-rich arenes

Intramolecular phenol oxidations have been widely exploited for the construction of a spirodienone fragment in polycyclic systems [1], especially for the oxidative coupling of two phenolic arene units [5], as illustrated by the following example (**12** → **13**) [6]:



12 (R = H, CH_3, acyl, CO_2R) **13**

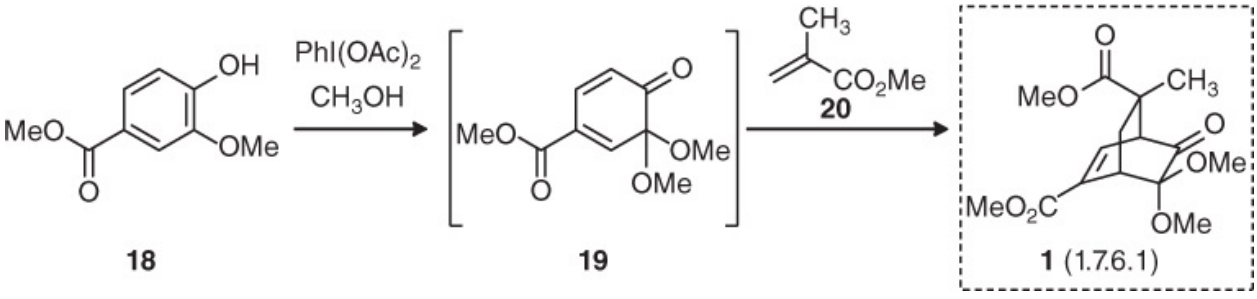
An analogous type of reaction is observed when phenols **14** with a methoxy substituent in an ortho-position to the OH function are oxidized with $PhI(OAc)_2$ in methanol as solvent [7, 8]:



The initial products are the acetal-masked *o*-quinonoid systems **15**, which are of limited stability but, as potential cyclohexa-1,3-dienes, can be readily trapped by electron-deficient dienophiles in a Diels–Alder reaction to give cycloadducts **17** of the bicyclo[2.2.2]octenone type. In the absence of dienophiles, compounds **15** dimerize to polycycles **16**. As shown in Section (b), this remarkable phenol oxidation mediated by a hypervalent iodine source can be conducted as an efficient one-pot synthesis of highly functionalized bicyclo[2.2.2]octane derivatives [8] that are otherwise difficult to obtain.

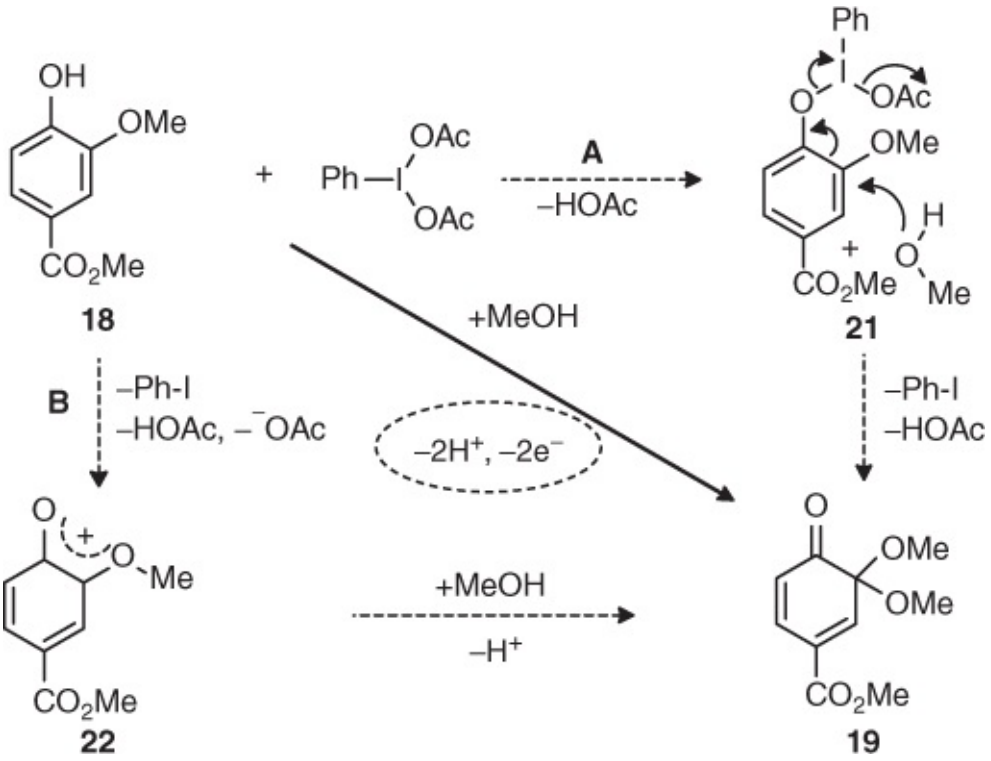
(b) Synthesis of 1

Methyl vanillate (**18**) is oxidized with (diacetoxy)iodobenzene in the presence of an excess of methyl methacrylate (**20**) in methanol at room temperature. The bicyclo[2.2.2]octen-2-one **1** is obtained (54% overall yield) in a clean, regio and stereoselective [4 + 2]-cycloaddition of the dienophile to cyclohexa-2,4-dienone **19** formed *in situ* by oxidation of the electron-rich phenolic substrate **18**.



The observed regio and stereoselectivity of the Diels–Alder reaction **19** + **20** → **1** can be explained in terms of frontier molecular orbital theory [8].

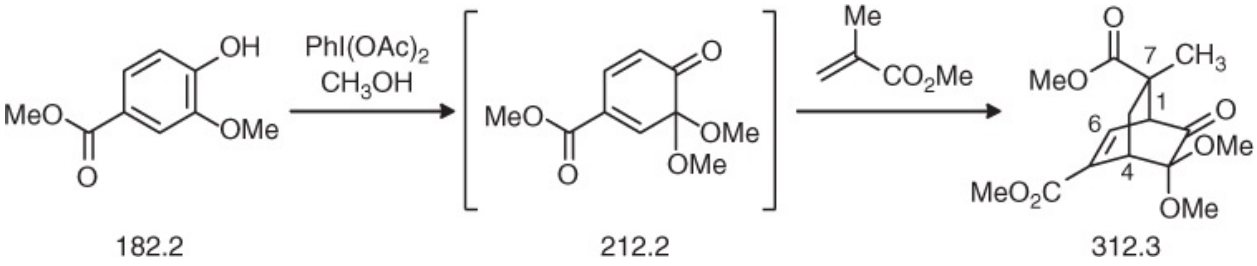
For the oxidative transformation **18** → **19**, two mechanistic alternatives are reasonable [2]. In mechanism A, the phenol **18** is attached to the iodine(III) of



$PhI(OAc)_2$ by ligand exchange with extrusion of HOAc to give an intermediate **21**. This undergoes redox disproportionation in an addition/elimination process by attack of CH_3OH, resulting in the formation of the cyclohexa-2,4-dienone **19**, iodobenzene, and HOAc. In mechanism **B**, the phenol **18** is oxidized in a two-electron/one-proton transfer – presumably via a phenoxy radical – to give the (resonance-stabilized) carboxenium ion **22**, which is trapped by addition of CH_3OH and loss of a second proton to afford the product **19**. Concomitantly, $PhI(OAc)_2$ is reduced to iodobenzene with formation of two molecules of acetate.

(c) Experimental Procedure for the Synthesis of 1

1.7.6.1	**	**(1*R**,4*S**,7*S**)-3,3-Dimethoxy-5,7-bis(methoxycarbonyl)-**
		7-methylbicyclo[2.2.2]oct-5-en-2-one [8]



182.2 212.2 312.3

A solution of methyl vanillate (1.00 g, 5.49 mmol) in anhydrous MeOH (70 ml) is added over a period of 8 h by means of a syringe pump to a solution of (diacetoxy)iodobenzene (2.12 g, 6.58 mmol) and methyl methacrylate (14.5 ml, 13.7 g, 137 mmol) in anhydrous MeOH (30 ml) at room temperature under nitrogen atmosphere. Stirring is continued for 2 h.

The solvent, excess dienophile, and other volatile products are removed *in vacuo*. Purification by flash chromatography (EtOAc/*n*-hexane, 9 : 1) gives the product as a colorless liquid; 918 mg (54%); R_f = 0.57 (EtOAc/*n*-hexane, 9 : 1).

IR (film): $\tilde{\nu}$ (cm^{-1}) = 2975, 1727.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.09 (dd, *J* = 6.5, 1.7 Hz, 1H, 6-H), 3.65–3.71 (m, 1H, 4-H), 3.74, 3.64 (2 × s, 6H, 2 × CO_2CH_3), 3.48 (d, *J* = 6.5 Hz, 1H, 1-H), 3.34, 3.26 (2 × s, 6H, 2 × OCH_3), 2.19 (dd, *J* = 18.1, 3.1 Hz, 1H, 8-H_A), 1.93 (dd, *J* = 18.1, 2.2 Hz, 1H, 8-H_B), 1.31 (s, 3H, 7-CH_3).

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 201.0 (C-2), 175.7 (C=O), 164.3 (C=O), 137.4 (C-5), 137.4 (C-5), 93.4 (C-3), 57.3 (C-8), 52.4 (C-4), 51.9 (OCH_3), 50.0 (H-1), 49.8 (C3-OCH_3), 46.7 (C3-OCH_3), 38.4 (C-8), 25.4 (C-7).

MS (DCI, NH_3, 200 eV): 643 $[2M+NH_4]^+$, 330 $[2M+NH_4]^+$.

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4. For instructive examples on the synthetic utility of diaryliodonium compounds, see ref. [2] and Tietze, L.F. and Eicher, Th. (1991) *Reaktionen und Synthesen im organisch-chemischen Praktikum und Forschungslaboratorium*, 2nd edn, Georg Thieme Verlag, Stuttgart, p. 315.

5. Phenol oxidation in alkaloid biogenesis: Hesse, M. (2000) *Alkaloide*, Wiley-

VCH Verlag GmbH, Weinheim, p. 265; see also: Fuhrhop, J. and Penzlin, G. (1994**)** *Organic Synthesis*, 2nd edn, Wiley-VCH Verlag GmbH, Weinheim, p. 293.

6. Compound **13** is a central intermediate in a synthesis of the *Amaryllidacea* alkaloid maritidine: (a) Kita, Y., Takada, T., Gyoten, M., Tohma, H., Zenk, M.H., and Eichhorn, J. (1996) *J. Org. Chem.*, **61**, 5857–5864;A spirodienone of type **11** is a key intermediate in a synthesis of the anti-Alzheimer agent galanthamine: (b) Krikorian, D., Tarpanov, V., Parushev, S., and Mechkarova, P. (2000) *Synth. Commun.*, **30**, 2833–2846.

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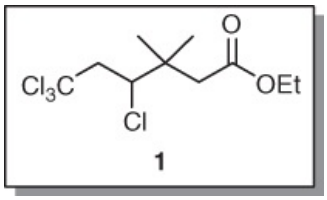
8. Liao, C.-C., Chu, C.-S., Lee, T.-H., Rao, P.D., Ko, S., Song, L.-D., and Shiao, H.-C. (1999) *J. Org. Chem.*, **64**, 4102–4110.

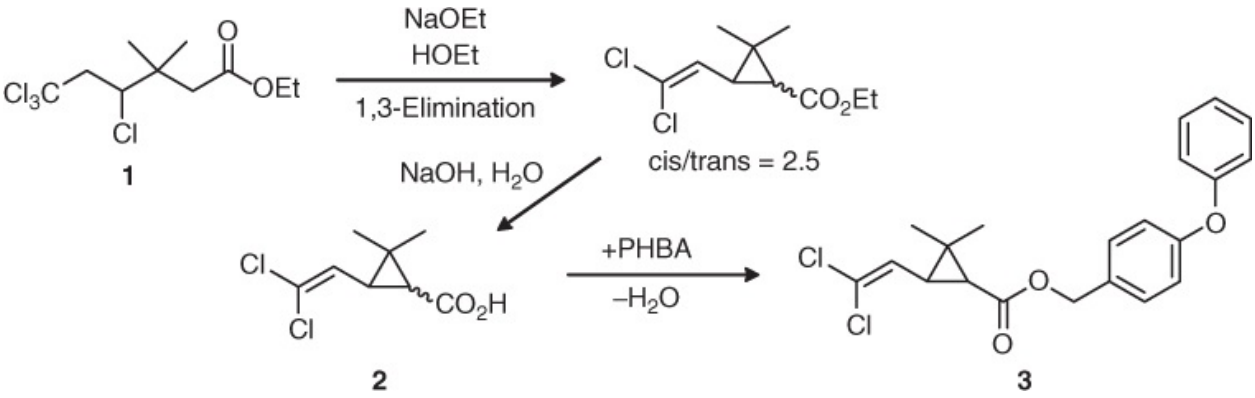
1.8 Radical Reactions

1.8.1 Ethyl 4,6,6,6-tetrachloro-3,3-dimethylhexanoate

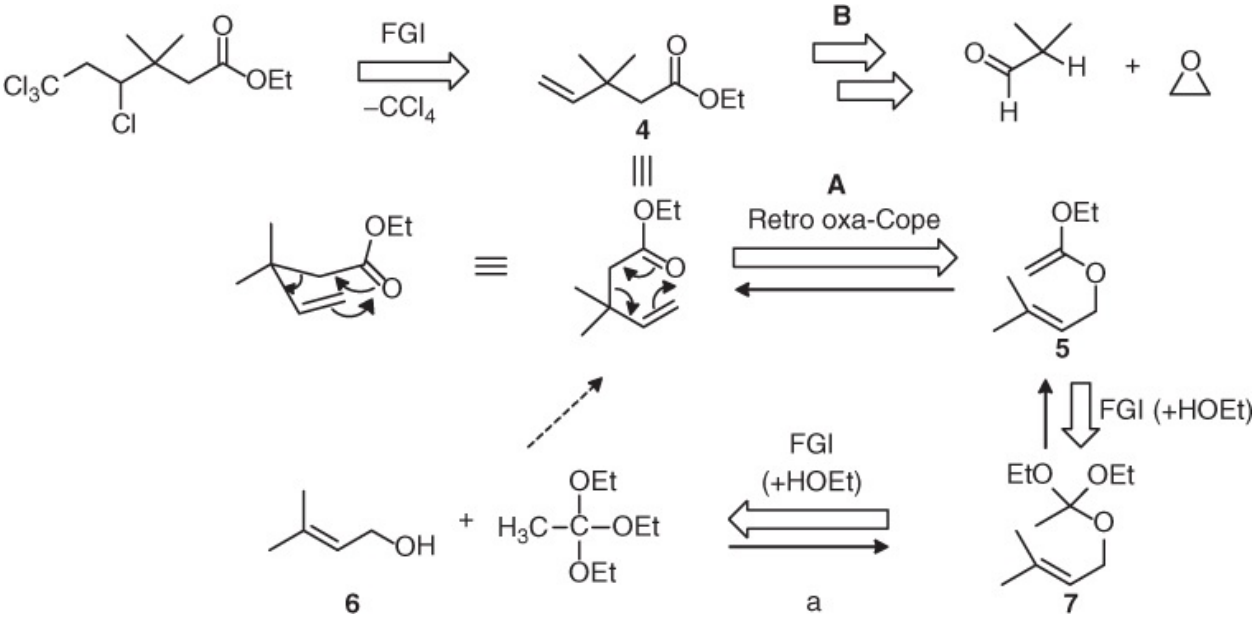
 1	***Topics:***	• Claisen orthoester reaction, [3,3]-sigmatropic rearrangement • Telomerization by radical addition of CCl_4 to an alkene

(a) General

The target molecule **1** is the key intermediate in the synthesis of the (dichlorovinyl)cyclopropane carboxylic acid **2**. Esterification of **2** with (3-phenoxy)benzyl alcohol leads to **3**, which is an important insecticide (Permethrin, cf. Section 4.2.1). Compound **3** was developed as an analog of esters of chrysanthemic acid, a group of natural insecticides mainly isolated from the flowers of an aromatic plant of the genus *Tannacetum* (formerly *Chrysanthemum* or *Pyrethrum*).



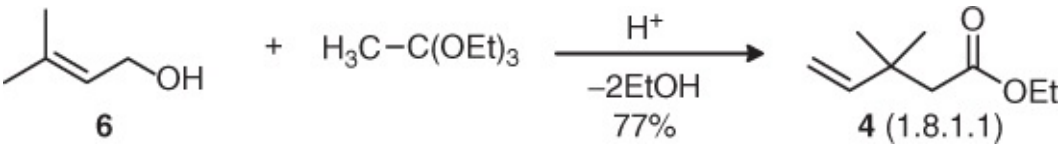
For the retrosynthesis of **1**, two considerations must be taken into account: (i) the left-hand part of **1** may result from addition of CCl_4 to a C=C double bond, and (ii) in the resulting unsaturated ester **4**, the C=C and C=O functionalities are in a 1,5-arrangement and are therefore susceptible to a [3,3]-sigmatropic transformation according to a retro-oxa-Cope rearrangement (A):[9]



Thus, the retrosynthesis of **4** leads to the allylic alcohol **6** and triethyl orthoacetate via **7** and **5** as a simple approach to the γ,δ-unsaturated ester **4** based on a [3,3]-sigmatropic rearrangement. The synthesis of **1** along these lines is described in detail.

(b) Synthesis of 1

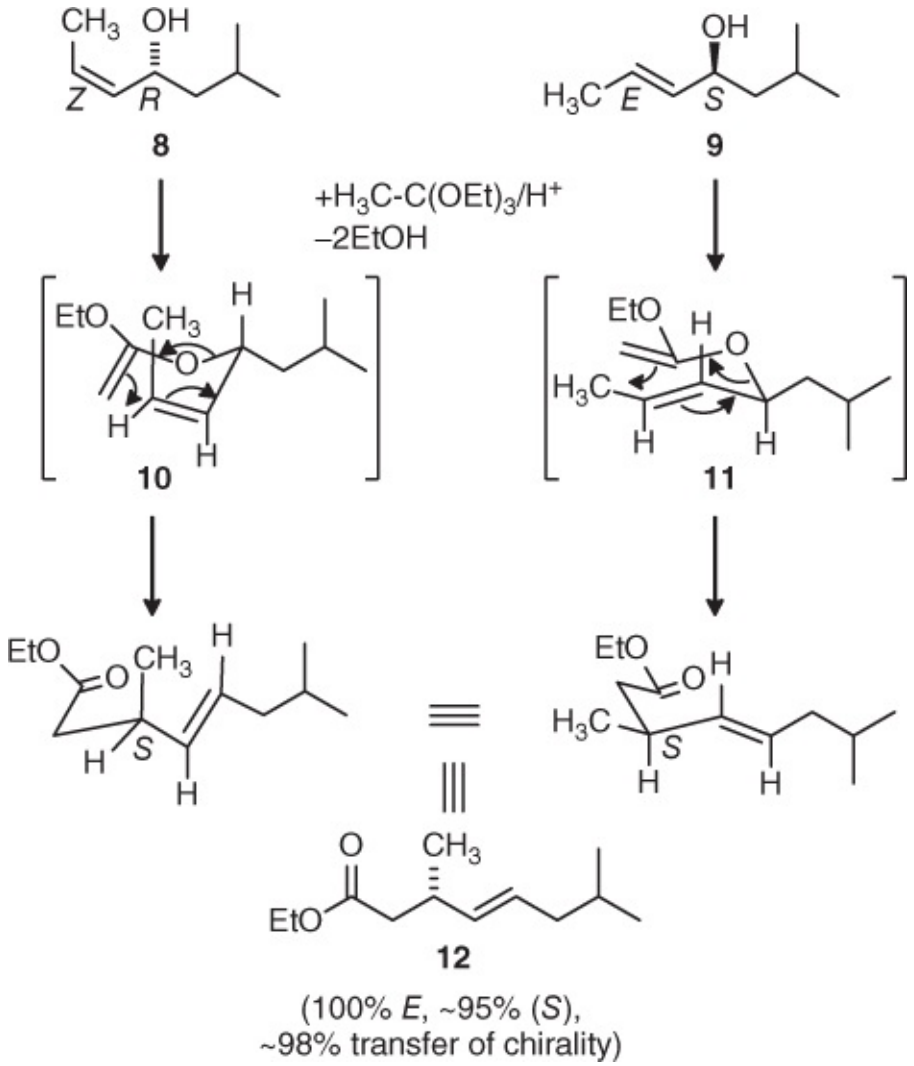
In the first step, the ester **4** is prepared by a Claisen orthoester reaction of 3-methyl-2-buten-1-ol (**6**) with triethyl orthoacetate in the presence of phenol [1]; (G. Künast, Bayer AG, private communication, 1981):



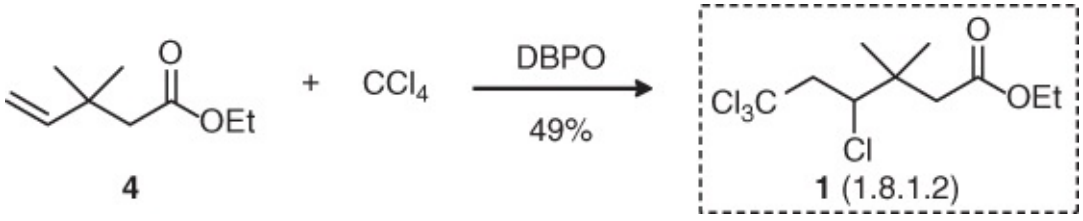
6 4 (1.8.1.1)

First, one molecule of EtOH in the orthoacetate is exchanged by the allylic alcohol **6** (→**7**), and then elimination of a second EtOH transforms the orthoester **7** to the ketene acetal **5** [2]; both reactions require H^+-catalysis. The allyl vinyl ether functionality in **5** is capable of a [3,3]-sigmatropic rearrangement (oxa-Cope reaction; a related rearrangement is the Carroll reaction in Section 1.5.3), leading directly to the γ,δ-unsaturated ester **4**.

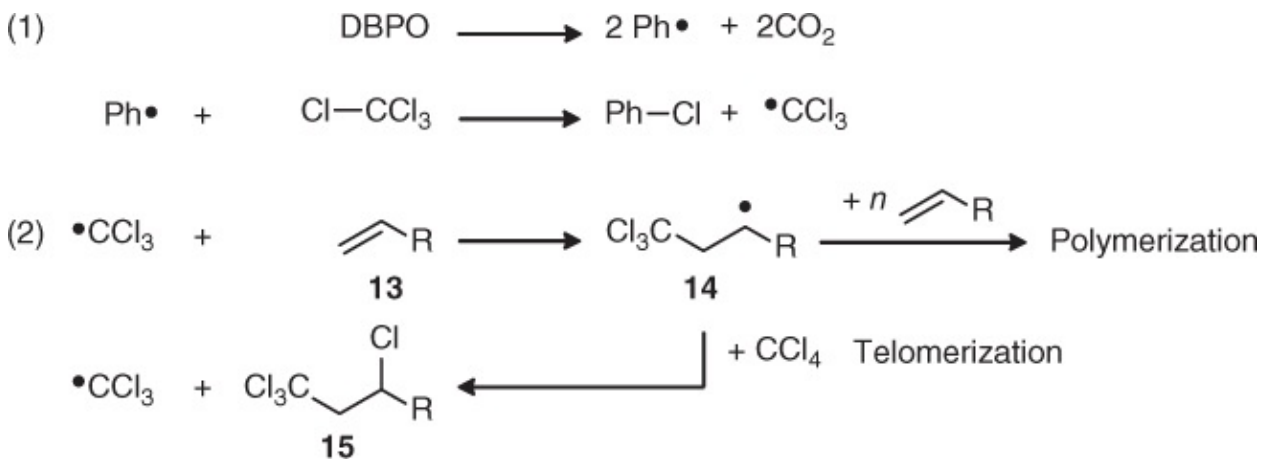
It should be noted that, as a consequence of a highly ordered chair-like transition state, the oxa-Cope process (e.g., **5** → **4**) can be conducted with high stereoselectivity and transfer of stereogenic information from the substrates to the product. This is exemplified by an instructive example [3] describing the formation of the unsaturated ester **12** with (*S*)-*E*-stereochemistry from stereodifferent precursors, namely the (*R*)-*Z*-alcohol **8** and the (*S*)-*E*-alcohol **9**, by reaction with orthoacetate/propionic acid via the intermediates **10**/**11**.[10]



In the second step, CCl_4 is added to the unsaturated ester **4** in the presence of dibenzoyl peroxide (DBPO) to yield **1**:



The reaction proceeds by a radical chain process initiated by DBPO:

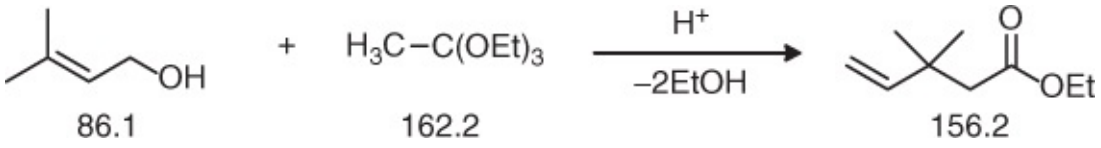


First, DBPO is cleaved thermally to give a phenyl radical, which generates a $\bullet CCl_3$ radical from CCl_4. In the chain propagation reaction (2), the $\bullet CCl_3$ radical adds to the terminal carbon atom of the olefinic substrate (**13**) to generate the secondary radical **14**. This radical may either lead to a polymerization of the olefinic substrate or abstract a chlorine atom from CCl_4, thus perpetuating chain propagation with formation of the addition product **15** (telomerization [4]). The competition between telomerization and polymerization is controlled by steric factors in the radical intermediate and the olefinic substrate. Increased steric hindrance favors telomerization.

Thus, the target molecule **1** is obtained in a two-step sequence with an overall yield of 38%.

(c) Experimental Procedures for the Synthesis of 1

1.8.1.1	**	**Ethyl 3,3-dimethyl-4-pentenoate** [1]



A mixture of 3-methyl-2-buten-1-ol (bp 140 °C; 43.1 g, 0.50 mol), ethyl orthoacetate (distilled, bp 144–146 °C; 97.3 g, 0.60 mol), and phenol (Caution: Irritant! 7.00 g, 74.4 mmol) is heated to 135–140 °C for 10 h with continuous removal of the EtOH formed.

The mixture is then cooled, diluted with Et_2O (200 ml), washed sequentially with aqueous HCl (1 N, 2 × 100 ml, to hydrolyze the excess of orthoacetate), saturated aqueous $NaHCO_3$ solution, and brine, dried over $MgSO_4$, and filtered,

and the solvent is removed *in vacuo*. The residue is distilled over a short column. The yield is 60.4 g (77%), bp_{11} 57–60 °C.

IR (film): $\tilde{\nu}$ (cm^{-1}) = 3090, 1740, 1640, 1370, 1240.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 5.90 (dd, *J* = 18.5, 10.0 Hz, 1H, 4-H), 5.15–4.7 (m, 2H, 5-H_2), 4.07 (q, *J* = 7.0 Hz, 2H, OCH_2), 2.25 (s, 2H, 2-H_2), 1.20 (t, *J* = 7.0 Hz, 3H, CH_3), 1.13 (s, 6H, 2 × 3-CH_3).

1.8.1.2	**	**Ethyl 4,6,6,6-tetrachloro-3,3-dimethylhexanoate** [1]

Ethyl 3,3-dimethyl-4-pentenoate **1.8.1.1** (23.4 g, 150 mmol) and DBPO (Caution: Explosive! 25% H_2O, 2.40 g) in tetrachloromethane (200 ml; Caution: resorption through the skin!) are heated under reflux for 8 h using a Dean–Stark trap. An additional 2.40 g of moist DBPO is added, and refluxing with removal of H_2O is continued for 8 h.

The solution is then cooled and washed twice with ice-cold aqueous NaOH (1 N, to remove benzoic acid) and thrice with brine. The organic phase is dried over Na_2SO_4 and filtered, and the solvent is removed *in vacuo*. The residue is distilled *in vacuo* over a short column. The yield is 22.8 g (49%), $bp_{0.2}$ 132–138 °C.

IR (film): $\tilde{\nu}$ (cm^{-1}) = 2980, 1730, 1465, 1370, 720, 690.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 4.43 (dd, *J* = 8.0, 3.3 Hz, 1H, 4-H), 4.12 (q, *J* = 7.0 Hz, 2H, O–CH_2), 3.19 (d, *J* = 3.3 Hz, 1H, 5-H_A), 3.13 (d, *J* = 8.0 Hz, 1H, 5-H_B), 2.66 (d, *J* = 15.0 Hz, 1H, 2-H_A), 2.26 (d, *J* = 15.0 Hz, 1H, 2-H_B), 1.24 (t, *J* = 7.0 Hz, 3H, CH_3), 1.20 (s, 3H, 3-CH_3), 1.13 (s, 3H, 3-CH_3).

References

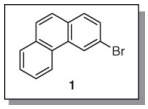
1. (a) Kondo, K., Matsui, K., and Negishi, A. (1976) DOS 2 539 895 (1976), Sagami Chem. Res.;(b) Kondo, K., Matsui, K. and Negishi, A. (1977) *ACS Symp. Ser.*, **42**, 128.

2. (a) Smith, M.B. (2013) *March's Advanced Organic Chemistry*, 7th edn, John Wiley & Sons, Inc., New York, p. 1408;for a review on Claisen rearrangement, see: (b) Martin Castro, A.M. (2004) *Chem. Rev.*, **104**, 3037–3058.

3. Chan, K.-K., Cohen, N., DeNoble, J.P., Specian, A.C. Jr., and Saucy, G. (1976) *J. Org. Chem.*, **41**, 3497–3515.

4. See ref. [2a], p. 977.

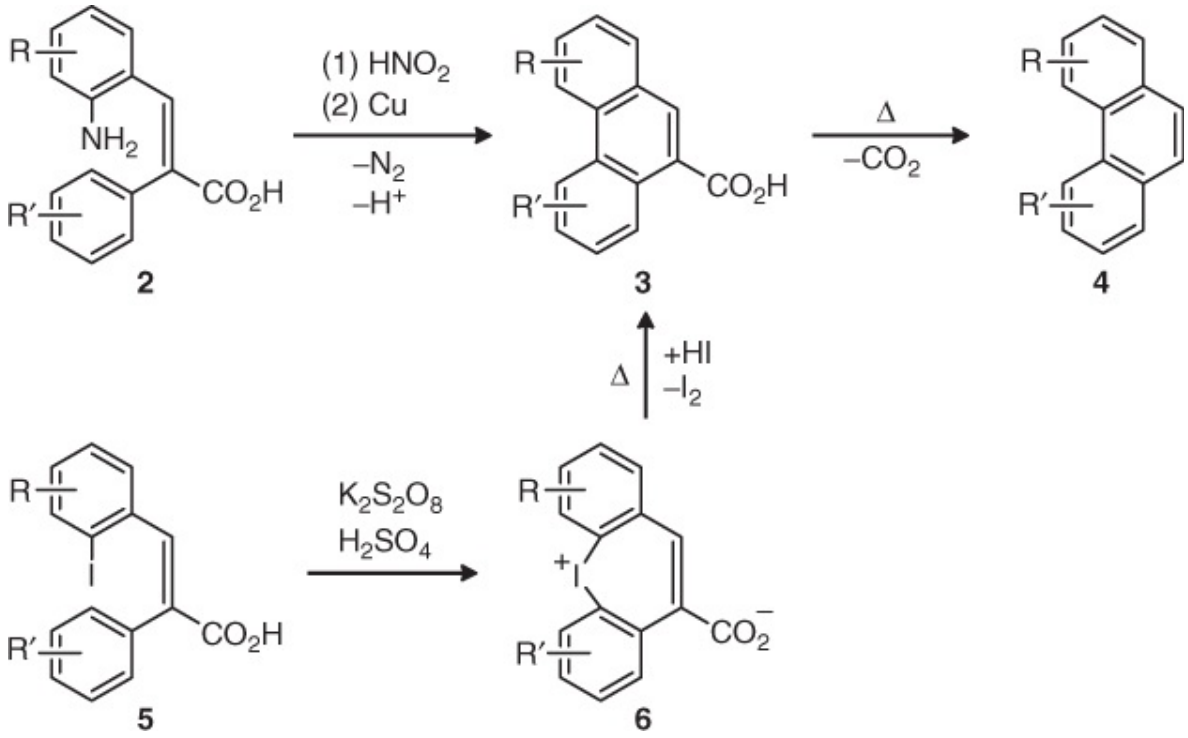
1.8.2 3-Bromophenanthrene

	***Topics:***	• Meerwein arylation (radical addition of arenes to activated alkenes) • 1,2-Elimination • Photoisomerization of *trans*-stilbenes to *cis*-stilbenes, electrocyclization of *cis*-stilbenes to dihydrophenanthrenes, and their dehydrogenation to phenanthrenes

(a) General

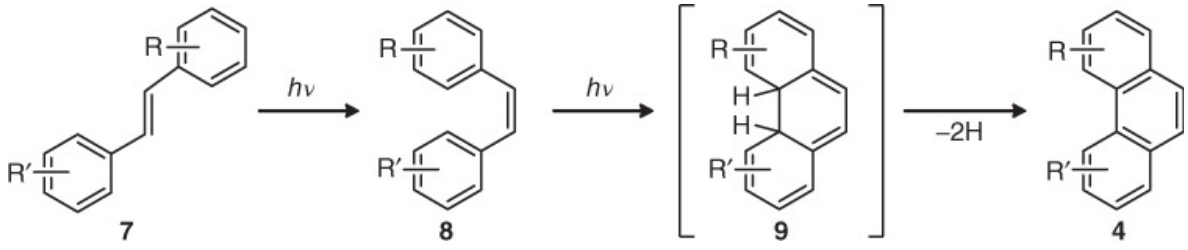
For the synthesis of phenanthrenes, three methods are of preparative importance [1].

1. In the Pschorr phenanthrene synthesis [2], an *o*-amino-*cis*-stilbene carboxylic acid **2** is diazotized, and the resulting diazonium salt is reductively dediazoniated with Cu and cyclized to give a phenanthrene-9-carboxylic acid **3**, which is thermally decarboxylated to a phenanthrene **4**. For the cyclization step, a radical mechanism is likely, in analogy to the Gomberg–Bachmann arylation [2]. The Pschorr method cannot be used for the synthesis of **1** [3].



2. In an oxidative cyclization [4], α-aryl-*o*-iodocinnamic acids **5** are converted to phenanthrenes by reaction with $K_2S_2O_8$. First, cyclic iodonium salts (iodepinium salts) **6** are formed, which on thermolysis lead to phenanthrene carboxylic acids **3**. These compounds can be decarboxylated to give phenanthrenes **4** as described above. The intermediacy of an iodoso arene species as the initial oxidation product of **5** and its S_EAr_i cyclization to **6** have been established, but the mechanism of the cyclization of **6** is not known.

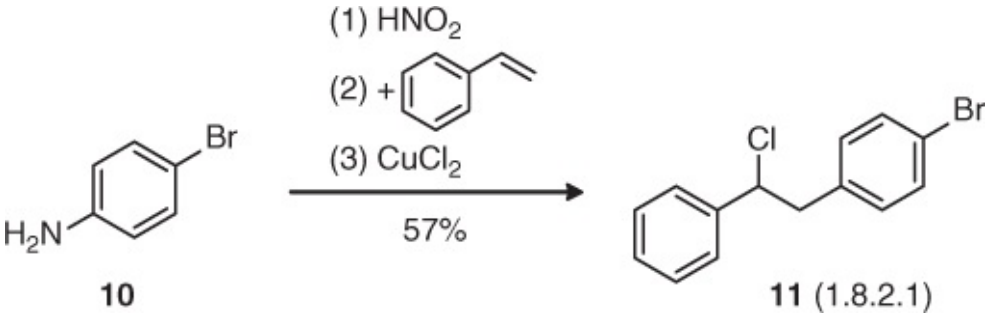
3. In a photochemical domino process [5], *trans*-stilbenes **7** are photoisomerized to give the corresponding *cis*-stilbenes **8**, which undergo 6π-electrocyclization to dihydrophenanthrenes **9** followed by *in situ* dehydrogenation to phenanthrenes **4**:



The target molecule **1** has been synthesized by application of methods (2) and (3). In Section (b), a synthesis based on the photochemical cyclization route [6] is described.

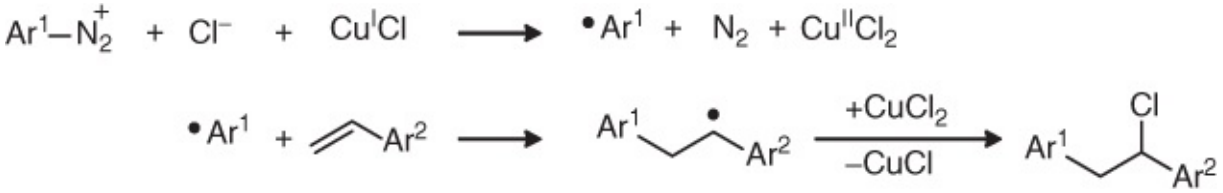
(b) Synthesis of 1

trans-4-Bromostilbene (**12**), the required starting material, is prepared in a two-step sequence from 4-bromoaniline (**10**) by diazotization with HNO_2 and reaction of the diazonium salt with styrene in the presence of Cu(II) chloride in aqueous acetone to afford the bibenzyl derivative **11**:

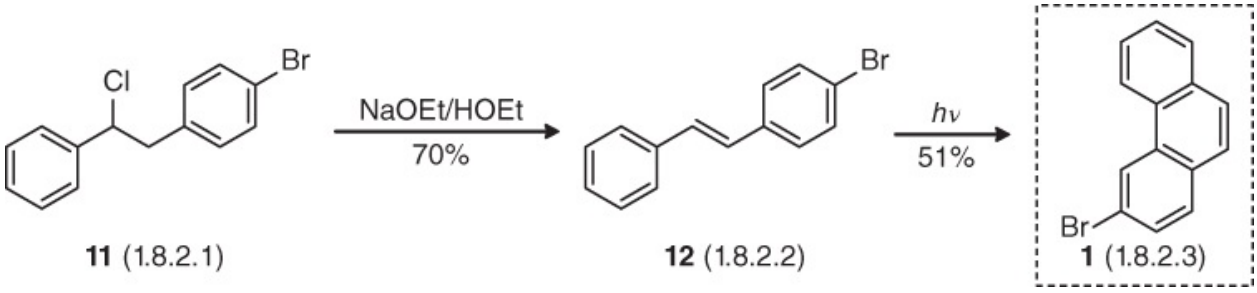


10 **11** (1.8.2.1)

The addition of aryl diazonium salts to activated alkenes (besides styrene, acrylonitrile and acrylates are often used) proceeds with loss of N_2 and is catalyzed by Cu(I) (Meerwein arylation [7]). The Meerwein arylation follows a radical chain mechanism related to the Cu(I)-induced Sandmeyer reaction:



Dehydrochlorination of the bibenzyl **11** with NaOEt/HOEt leads to *trans*-4-bromostilbene (**12**). This is subjected to photolysis in cyclohexane solution in the presence of iodine, resulting in isomerization to the corresponding *cis*-stilbene, electrocyclic ring closure to a dihydrophenanthrene, and subsequent dehydrogenation to give the desired 3-bromophenanthrene (**1**).

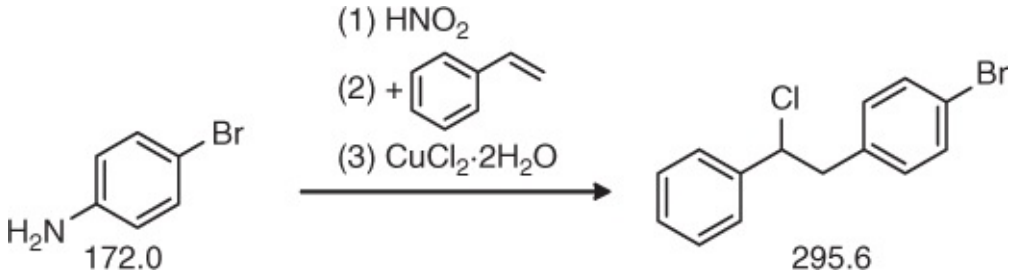


11 (1.8.2.1) **12** (1.8.2.2) **1** (1.8.2.3)

Using this procedure, the target molecule **1** is obtained in a three-step sequence in an overall yield of 20% (based on 4-bromoaniline).

(c) Experimental Procedure for the Synthesis of 1

1.8.2.1	*	**2-(4-Bromophenyl)-1-chloro-1-phenylethane** [8]



Sodium nitrite (7.00 g, 0.10 mol) in water (35 ml) is added dropwise to a stirred solution of *p*-bromoaniline (17.2 g, 0.10 mol) in aqueous hydrochloric acid (5 M, 60 ml) with cooling in an ice–salt bath so as to maintain the reaction temperature below 5 °C (note 1). The solution is brought to pH 4–5 by the addition of solid $NaHCO_3$ (14.3 g) in portions. The solution is then added dropwise over 10 min to a solution of styrene (10.4 g, 0.10 mol; note 2) and $CuCl_2 \cdot 2H_2O$ (4.00 g, 25.0 mmol) in acetone (100 ml). Nitrogen evolution starts slowly, becomes vigorous after approximately 1 h, and ends after 15 h.

Et_2O (100 ml) is added, the dark organic phase is separated, and the aqueous phase is extracted with Et_2O (2 × 50 ml). The combined ethereal phases are dried over $MgSO_4$ and filtered, and the solvent is removed *in vacuo*. The residual brown oil is crystallized by the addition of the minimum volume of petroleum ether (50–70 °C): 16.9 g (57%), mp 81–82 °C. Recrystallization from EtOH gives light-brown needles, mp 87–88 °C.

UV (CH_2Cl_2): λ_{max} (log ϵ) = 316 (3.57), 330 nm (sh).

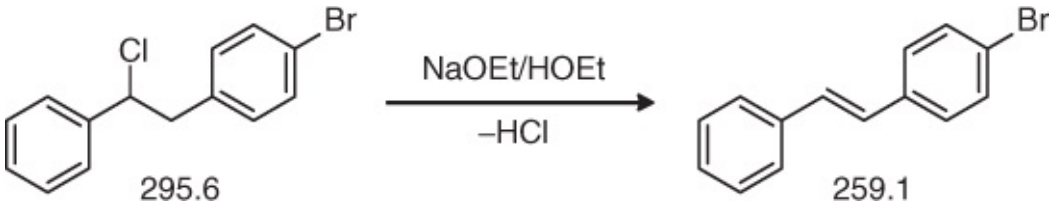
IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 1585, 800, 765, 690.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.30, 6.88 (2 × d, *J* = 8.0 Hz, 4H, 4-bromophenyl-H), 7.25 (s, 5H, Ar–H), 4.88 (t, *J* = 6.0 Hz, 1H, 1-H), 3.24 (d, *J* = 6.0 Hz, 2H, 2-H_2).

Notes:

1. Completeness of the reaction is tested with starch-iodide paper; the presence of HNO_2 results in a blue color.
2. Styrene is distilled from hydroquinone, bp_{12} 33–34 °C, and is stored with hydroquinone.

1.8.2.2 * *trans*-4-Bromostilbene [8]



A sodium ethoxide solution is prepared by dissolving sodium (1.15 g, 0.05 mol) in anhydrous EtOH (50 ml), and then compound **1.8.2.1** (5.90 g, 20.0 mmol) is added with stirring. The suspension is warmed on a steam bath until dissolution is complete. After approximately 2 min, a fine precipitate of sodium chloride begins to form. After approximately 6 min, a voluminous precipitate of the product forms. The mixture is heated under reflux with vigorous stirring for 1 h.

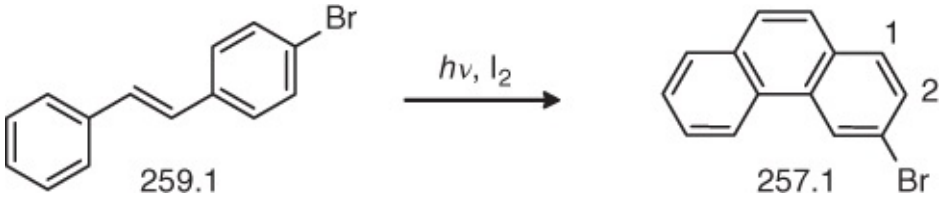
H_2O (5 ml) is added to the hot solution, the mixture is cooled with stirring in an ice bath, and the precipitate is collected by filtration and washed with EtOH (10 ml). The crude product (approximately 5.5 g) is recrystallized from isopropanol (decolorizing with activated charcoal) to give colorless needles; 3.60 g (70%), mp 137–138 °C, TLC: single spot (silica gel; CH_2Cl_2).

UV (CH_2Cl_2): λ_{max} (log ϵ) = 314 (4.52), 427 nm (sh).

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 1580, 820, 750, 700, 690.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.50–7.26 (m, 9H, Ar–H), 7.14–7.00 (m, 2H, 1-H, 2-H).

1.8.2.3 ** 3-Bromophenanthrene [6]



Apparatus: Photolysis apparatus with quartz filter and high-pressure mercury vapor lamp (Philips HPK-125 W or Hanau TQ-150 W).

A solution of *trans*-4-bromostilbene **1.8.2.2** (2.60 g, 10.0 mmol) and iodine (0.13 g, 1.00 mmol) in anhydrous cyclohexane (1000 ml) is irradiated for 16 h while air is passed through it (note).

The solvent is evaporated *in vacuo*, the red residue is dissolved in cyclohexane (50 ml), and the solution is filtered through neutral Al_2O_3 (25 g, activity grade I). The colorless filtrate is concentrated, and the residue (1.35 g, mp 76–78 °C) is recrystallized from EtOH to give colorless needles; 1.30 g (51%), mp 83–84 °C, TLC: single spot (silica gel; CH_2Cl_2).

UV (CH_2Cl_2): λ_{max} (log ϵ) = 298 (4.17), 286 (4.05), 277 (4.18), 268 (sh), 254 nm (4.95).

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 1580, 840, 820, 730.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.80–8.20 (m, 2H, Ar–H), 7.90–7.20 (m, 7H, Ar–H).

Note: Passing oxygen instead of air through the reaction mixture and prolongation of the irradiation time do not improve the yield.

References

1. Another method often mentioned in textbooks, the Haworth synthesis, seems to be of limited scope and is only applicable to phenanthrene itself and some alkyl-substituted derivatives: Beyer, H. and Walter, W. (1998) *Lehrbuch der Organischen Chemie*, 23rd edn, S. Hirzel Verlag, Stuttgart, p. 686.

2. (a) Abramovitch, R.A. (1966) *Adv. Free-Radical Chem.*, **2**, 87;(b) Duclos, R.I. Jr., Tung, J.S., and Rappoport, H. (1984) *J. Org. Chem.*, **49**, 5243–5246.

3. Bachmann, W.E. and Boatner, C.H. (1936) *J. Am. Chem. Soc.*, **58**, 2194–2195.

4. Nesmeyanov, A.N., Tolstaya, T.P., Vanchicova, L.N., and Petrakov, A.V. (1980) *Izv. Akad. Nauk SSSR, Ser. Kim.*, 2530.

5. (a) Mallory, F.B. and Mallory, C.W. (1984) *Org. React.*, **30**, 1–456;(b) Laerhoven, W.H. (1989) *Org. Photochem.*, **10**, 163–195.

6. Wood, C.S. and Mallory, F.B. (1964) *J. Org. Chem.*, **29**, 3373–3377.

7. Rondestved, C.S. Jr. (1976) *Org. React.*, **24**, 225–259.

8. Tashchuk, K.G. and Dombrovski, A.V. (1965) *Zh. Org. Khim.*, **1**, 1995;

Chem. Abstr., (1966), **64**, 9617.

[1] Although the ring opening of *meso* cyclic anhydrides by enantiomerically pure alcohols, amines, and other chiral nucleophiles is highly diastereoselective, the preparative value is limited by the amounts of chiral nucleophile required and by the necessity of further reactions for removal of the chiral auxiliary (see Ref. [2]).

[2] To date, a conventional synthesis of the target molecule **1** has not been reported in the literature.

[3] for a review on asymmetric synthesis with the RAMP/SAMP auxiliaries, see Ref. [3b].

[4] A comparable organocatalyzed three-component cyclization of aldehydes, α,β-unsaturated aldehydes, and nitroalkenes gives rise to highly functionalized cyclohexene derivatives, establishing four stereocenters in a one-pot reaction; see Ref. [9a].

[5] Other retroanalytical approaches may lead to C_5- and C_6-carbohydrates as chiral starting materials for the synthesis of ethyl esters **1**. However, although readily available, carbohydrates are not considered as substrates for the synthesis of **1**, since transformations sacrificing several stereogenic centers in favor of one are regarded as ineffective with respect to atomic and stereochemical economy.

[6] With regard to maximizing the overall yield, it has been considered that the cyclic acetal **8** may be hydrolyzed ($CH_3OH/H_2O/HCl$) to give the diol **6** in practically quantitative yield.

[7] It should be noted that with aryl iodides the rate-determining step is presumably the insertion process ((3) in (a)) leaving most of the Pd sources in the form of (relatively) stable Pd(II) complexes.

[8] In addition, syn-and anti-bridging and oligomethylene-bridging in [14]annulene has been achieved, as well as the synthesis of a “10π pyridine”; see Ref. [1].

[9] Other retrosynthetic pathways, for example, B leading to isobutanal and oxirane as educts of a possible synthesis of **1**, are less favorable (criterion of

simplicity!).

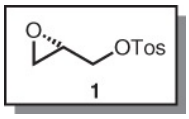
[10] The chair-like transition states of the pericyclic transformations [(*R*)-*Z*-**10** → (*S*)-*E*-**12** ← (*S*)-*E*-**11**] should be favored by virtue of having the smallest number of nonbonding interactions, *i.e.* pseudoaxial substituents [3].

Chapter 2
Oxidation and Reduction

2.1 Epoxidation of C=C Bonds

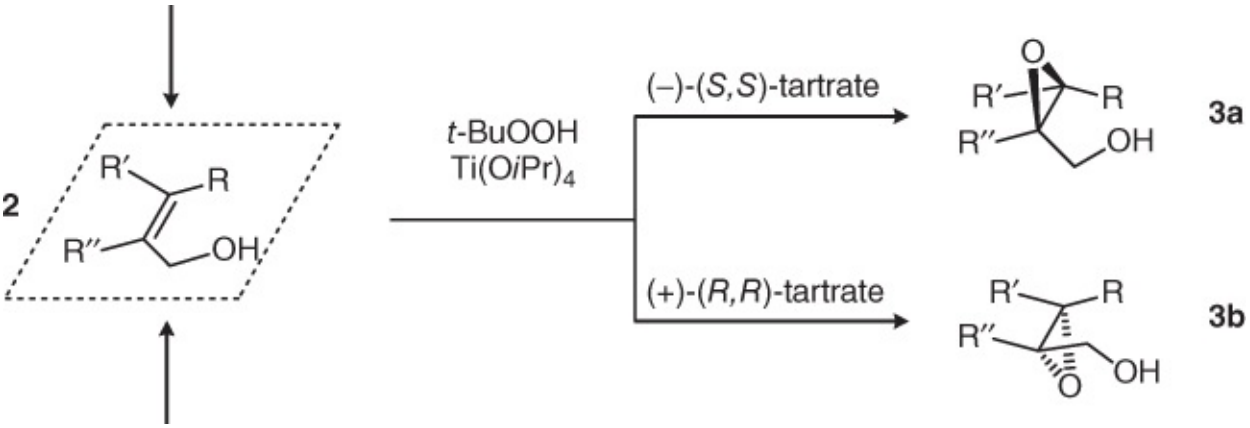
Epoxides (oxiranes) can be used as substrates for a broad spectrum of ring-opening transformations leading to 1,2-disubstituted functionalized alkanes. Therefore, the enantioselective epoxidation of alkenes is of considerable interest in organic synthesis because it allows the generation of stereodefined sp^3-carbon centers [1]. Two methods are of general applicability, namely the Sharpless–Katsuki epoxidation [2] (Section 2.1.1) and the Jacobsen epoxidation [3a] (Section 2.1.2).

2.1.1 Sharpless–Katsuki Epoxidation

	***Topics:***	• Asymmetric epoxidation of an allylic alcohol according to the Sharpless–Katsuki scheme • Tosylation of an alcoholic OH group

(a) General

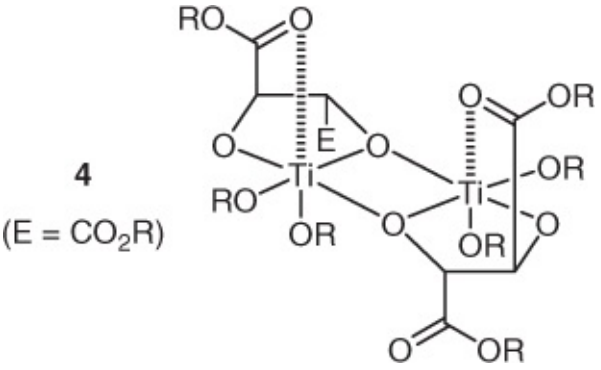
In the Sharpless–Katsuki epoxidation, allyl alcohols **2** are stereoselectively transformed to oxiranes **3** by reaction with a stoichiometric amount of a hydroperoxide (commonly *tert*-butyl or cumene hydroperoxide) as oxidant, in the presence of catalytic amounts of $Ti(OiPr)_4$ and a dialkyl tartrate, usually diethyl tartrate (DET) or diisopropyl tartrate (DIPT), as a chiral ligand:



In general, both enantiomers (**a** and **b**) of the oxiranes **3** can be obtained with >90% ee by using either (+)-(*R*,*R*)- or (−)-(*S*,*S*)-dialkyl tartrates. It should be pointed out that

- allylic alcohol moieties can be epoxidized chemoselectively in the presence of other olefinic double bonds;
- the Sharpless–Katsuki protocol can also be employed to homoallylic alcohols, albeit with lower selectivity;
- racemic mixtures of chiral allylic alcohols may undergo kinetic resolution when subjected to Sharpless–Katsuki epoxidation.

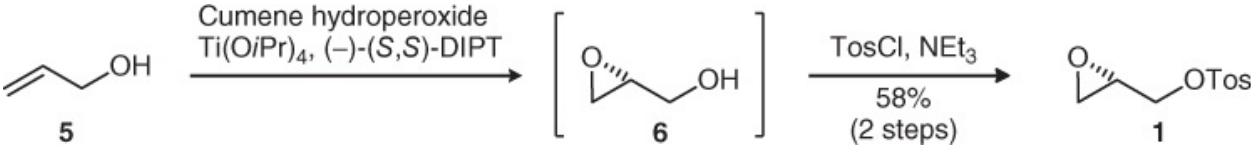
As a mechanism of the Sharpless–Katsuki epoxidation, the intermediate formation of a chiral titanium tartrate complex **4** is proposed [4], which can undergo a substrate–catalyst interaction through coordinative binding to the allylic hydroxyl group, thus allowing a transfer of chiral information to the substrate.



In Section (b), the Sharpless–Katsuki epoxidation of allyl alcohol is described [5], which is the key step in the synthesis of (*S*)-propranolol (cf. Section 3.2.1).

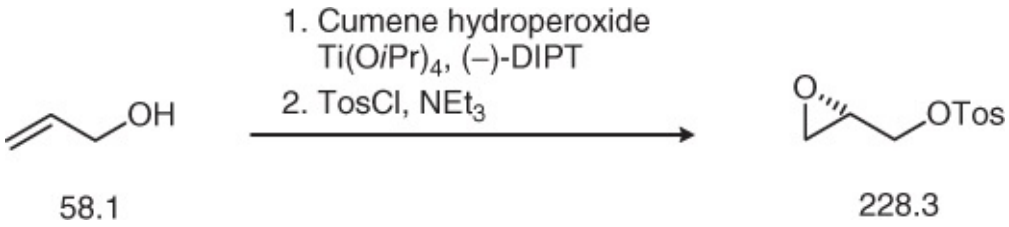
(b) Synthesis of 1

Allyl alcohol (**5**) is reacted with cumene hydroperoxide in the presence of catalytic amounts of Ti(O*i*Pr)$_4$ and (−)-(*S*,*S*)-DIPT at a temperature below 0 °C in dichloromethane as solvent. The excess hydroperoxide is reduced with trimethyl phosphite. The formed (*S*)-glycidol (**6**) is tosylated *in situ* at the OH function in the presence of triethylamine. Thus, the epoxytosylate **1** is obtained in a one-pot procedure from allyl alcohol.



(c) Experimental Procedure for the Synthesis of 1

2.1.1.1	**	**(*S*)-(*O*-Toluenesulfonyl)glycidol** [5]



(−)-(*S*,*S*)-DIPT (1.21 g, 5.17 mmol) in CH_2Cl_2 (1.3 ml) is added under nitrogen to activated 3 Å molecular sieves (3 g) in CH_2Cl_2 (164 ml). Allyl alcohol (5.86 ml, 5.01 g, 86.2 mmol) is then added, and the mixture is cooled to −5 °C. Ti(O*i*Pr)$_4$ (1.29 ml, 1.23 g, 4.30 mmol) is then given to the mixture, which is stirred for 30 min. Precooled (ice bath) cumene hydroperoxide (80%, 30.2 ml, 172 mmol) is added over a period of 45 min, maintaining the internal temperature below −2 °C. Finally, the reaction mixture is stirred vigorously at −5 to 0 °C for 6 h.

After cooling to −20 °C, the excess hydroperoxide is reduced by slow addition of P(OMe)$_3$ (12.7 g, 86.4 mmol) while maintaining the temperature below −10 °C (monitoring by TLC (thin layer chromatography), EtOAc/*n*-hexane, 2 : 3). After 1 h, triethylamine (15.1 ml, 11.0 g, 109 mmol) and thereafter a solution of *p*-toluenesulfonyl chloride (17.3 g, 90.4 mol) in CH_2Cl_2 (80 ml) are added. The flask is kept overnight at −20 °C.

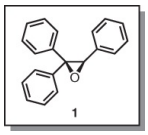
The reaction mixture is gradually warmed to room temperature and then filtered through a pad of Celite®, which is washed with CH_2Cl_2. The yellow filtrate is washed sequentially with 10% aqueous tartaric acid (2 × 250 ml) and brine (2 ×

250 ml), dried over $MgSO_4$, and filtered, and the solvent is removed under high vacuum to remove cumene, 2-phenyl-2-propanol, $P(OMe)_3$, and $PO(OMe)_3$. The residue is filtered through a short pad of silica gel (25 g) with CH_2Cl_2 as eluent under nitrogen pressure. Concentration of the filtrate and purification of the residue by flash chromatography gives the product as a light-yellow oil; 11.2 g (58%), R_f = 0.56 (*n*-pentane/EtOAc); $[\alpha]^{20}_D$ = +17.9 (*c* = 1.5, $CHCl_3$); ee = 98% (optical purity).

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.77 (d, *J* = 8.4 Hz, 2H, 3′-H), 7.32 (d, *J* = 7.8 Hz, 2H, 2′-H), 4.23 (dd, *J* = 11.3, 3.6 Hz, 1H, 3-H), 3.90 (dd, *J* = 11.4, 6.3 Hz, 1H, 3-H), 3.12–3.18 (m, 1H, 2-H), 2.78 (t, *J* = 4.8 Hz, 1H, 1-H), 2.56 (dd, *J* = 4.4, 2.4 Hz, 1H, 1-H), 2.42 (s, 3H, CH_3).

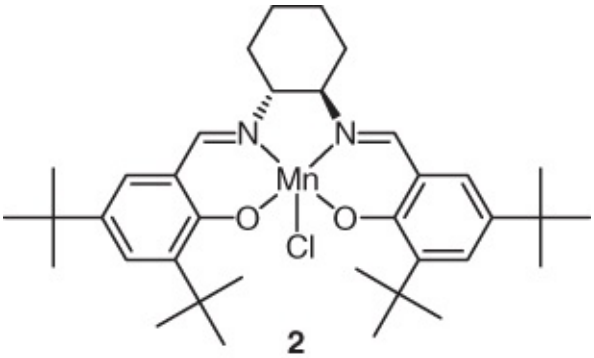
^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 145.1 (C-1′), 132.6 (C-4′), 129.9 (C-2′), 127.9 (C-3′), 70.4 (C-3), 48.8 (C-2), 44.5 (C-1), 21.6 (CH_3).

2.1.2 Jacobsen Epoxidation

	***Topics:***	• Enantioselective epoxidation of a trisubstituted alkene using the Jacobsen catalyst and sodium hypochlorite as oxidizing agent • Synthesis of the Jacobsen Mn-salen catalyst (Duff formylation, resolution of 1,2-diaminocyclohexane, Schiff-base formation, and complexation with Mn(III))

(a) General

The Jacobsen epoxidation allows the transformation of a wide range of unfunctionalized prochiral alkenes into chiral epoxides by reaction with an oxidizing agent, preferentially NaOCl, in the presence of catalytic amounts of the chiral Mn(III)-salen complex **2** (Jacobsen catalyst) [3b]:



2

Jacobsen Mn-salen complex

Most suitable substrates are disubstituted (*Z*)-alkenes (giving up to 99% ee) and trisubstituted alkenes, whereas monosubstituted alkenes are poor substrates for the Jacobsen epoxidation.

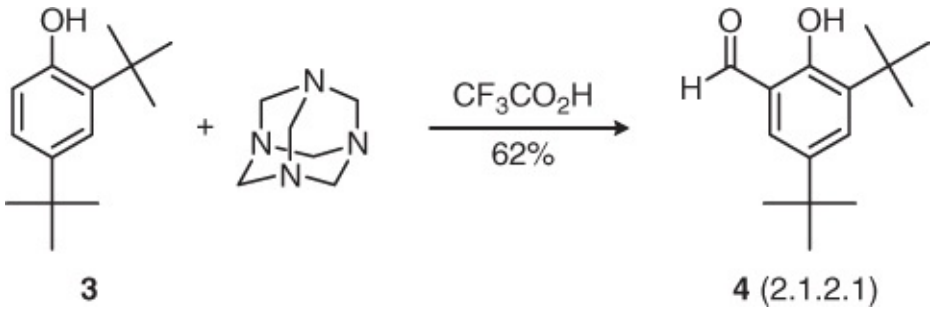
Interestingly, the Sharpless dihydroxylation (cf. Section 2.2) shows a complementary substrate spectrum, since (*E*)-disubstituted alkenes give the best enantiomeric excess values (up to 99% ee) in product formation, whereas monosubstituted alkenes still give 70–80% ee.

The Jacobsen catalyst consists of an Mn(III) complex with the chiral salen ligand (salen = bis-salicylaldimine of (*R*,*R*)-diaminocyclohexane) and was introduced in the early 1990s. The manganese core is coordinated by the ligand in a square-planar geometry and is stabilized by a chlorine atom in the axial position [6]. This geometry is most probably responsible for the stereochemical outcome of the asymmetric alkene epoxidation [7]. The oxidant, normally bleach (aqueous NaOCl), is used in stoichiometric amounts [8]. The Jacobsen epoxidation is applied industrially on a large scale [9].

New developments include the use of ionic liquids and functionalized solid phases such as zeolites or organo-modified silicates, which allow the chiral catalyst to be immobilized, recovered, and recycled [10].

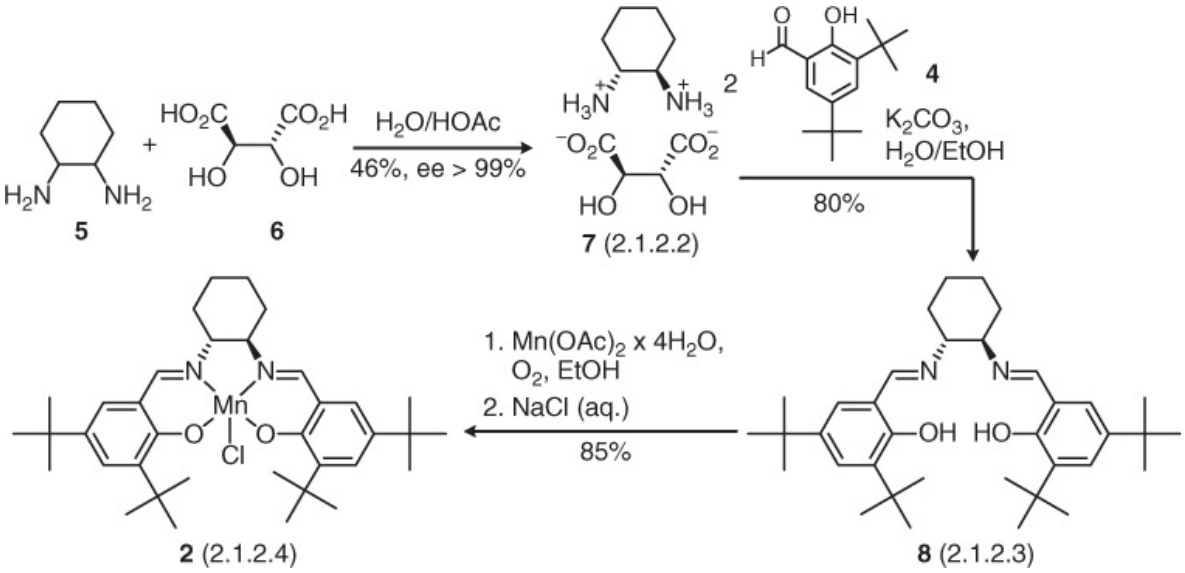
(b) Synthesis of 1

1. The Jacobsen Mn(III)-salen complex (**2**) is prepared in a four-step sequence starting from 2,4-di-*tert*-butylphenol (**3**) [9]. 3,5-Di-*tert*-butylsalicylaldehyde (**4**) is obtained by Duff formylation [11] of the phenol **3** by reaction with hexamethylenetetramine in trifluoroacetic acid:



3 **4** (2.1.2.1)

Resolution of racemic 1,2-diaminocyclohexane (**5**) is carried out by crystallization of its monoammonium salt **7** with (+)-(*R*,*R*)-tartaric acid (**6**), which is thus obtained in high diastereomeric purity.

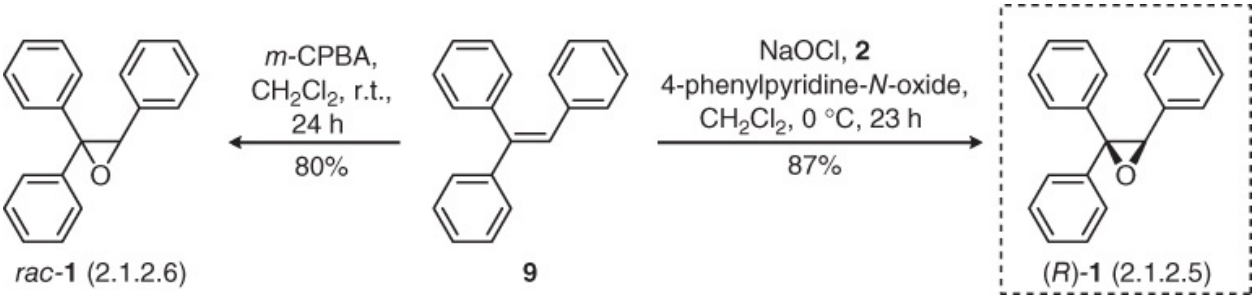


5 **6** **7** (2.1.2.2) **2** (2.1.2.4) **8** (2.1.2.3)

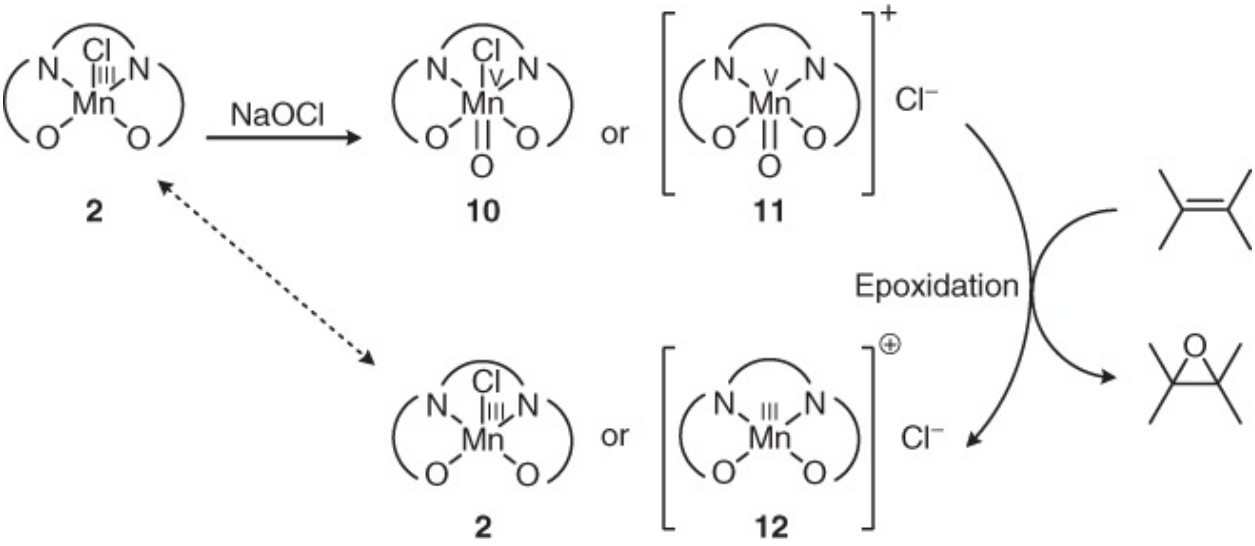
To simplify the procedure, the monotartrate salt **7** is used directly for condensation with the salicylaldehyde **4**, thus avoiding an isolation of the water-soluble and air-sensitive free amine. Finally, the Schiff base **8** is transformed to the Mn(III)-salen complex **2** using Mn(II)acetate and oxidation with air; **2** is obtained as a brown air-and water-stable powder.

2. Triphenylethylene (**9**) is subjected to enantioselective epoxidation by reaction with aqueous NaOCl solution as oxidant in the presence of catalytic amounts of the Jacobsen Mn(III)-salen complex (**2**) and 4-phenylpyridine *N*-oxide as co-oxidant in a two-phase system of CH_2Cl_2/H_2O at 0 °C to afford (*R*)-2,2,3-triphenyloxirane (**1**) in 87% chemical yield with a stereoselectivity of 88% ee.

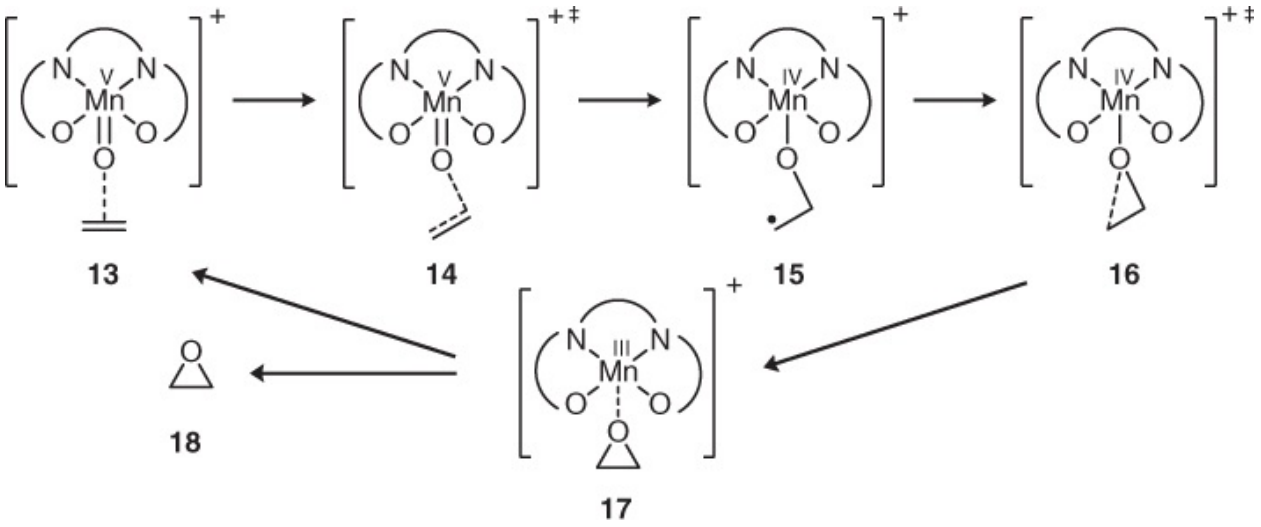
For comparison, a racemic mixture of **1** may be prepared in 80% yield by epoxidation of **9** with *m*-CPBA in CH_2Cl_2.



As the mechanism of the Jacobsen epoxidation, a two-step catalytic cycle is proposed [12]. Oxygen is transferred from the stoichiometric oxidant (NaOCl) to the Mn(III)-salen complex (**2**), generating an intermediate Mn(V)-oxo species (**10** or **11**) [6c]. Whether a neutral (**10**) or a cationic (**11**) Mn(V)-oxo species is formed depends on the oxidant and the solvent. In the second step, the oxygen is transferred to the olefinic double bond to give the epoxide, and the remaining Mn(III) species **2** or **12** can be reoxidized.

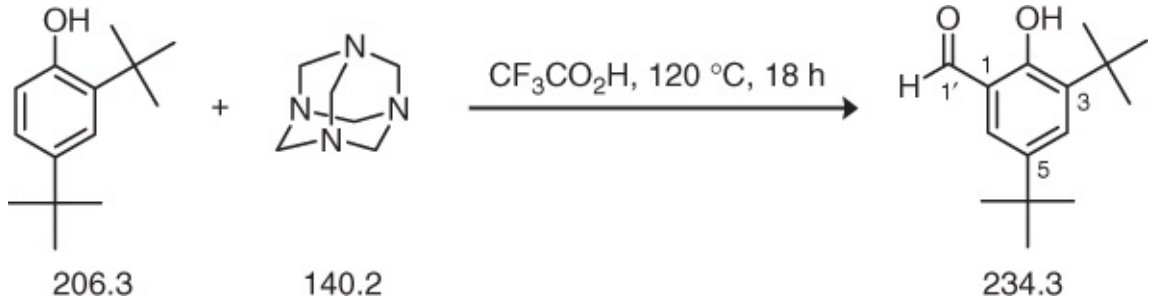


Theoretical studies have shown that the reaction probably proceeds along a radical pathway [13]. In the first step, the alkene approaches the manganese catalyst from the side of the oxo ligand and forms a weakly bonded catalyst–substrate adduct **13**, which reacts via the transition state **14** to give the radical intermediate **15**. The second oxygen–carbon bond is formed via transition state **16** to give a weakly bonded conjugate of the catalyst **17**, which can easily liberate the desired epoxide **18**.



(c) Experimental Procedures for the Synthesis of 1 and 2

2.1.2.1	**	**3,5-Di-*tert*-butyl-2-hydroxybenzaldehyde** [9]



A dry, three-neck, round-bottomed flask equipped with a reflux condenser is charged with trifluoroacetic acid (200 ml), hexamethylenetetramine (25.1 g, 179 mmol), and 2,4-di-*tert*-butylphenol (28.7 g, 139 mmol) at 0 °C under an argon atmosphere. The mixture is heated to reflux at 120 °C over a period of 45 min and maintained at this temperature for 18 h.

After cooling to 0 °C, H_2O (1200 ml), Na_2CO_3 (140 g, 1.32 mol), and, subsequently, aqueous HCl (6 M, 200 ml) are added. The product is extracted with EtOAc (3 × 500 ml), the combined organic fractions are dried over $MgSO_4$, and filtered, and the solvent is removed *in vacuo*. The yellow residue is heated with MeOH (30 ml), and the suspension obtained is subjected to vacuum filtration. The filter cake is washed with MeOH (3 × 50 ml), and the combined filtrates are concentrated under reduced pressure. The oil obtained (20.1 g, 62%) can be used for the next step without further purification. However, purification can be performed by flash chromatography on silica gel (EtOAc/*n*-hexane = 3 : 7).

UV (CH_3CN): λ_{max} (nm) (log ϵ) = 343.5 (3.469), 263.5 (3.998), 219.5 (4.180).

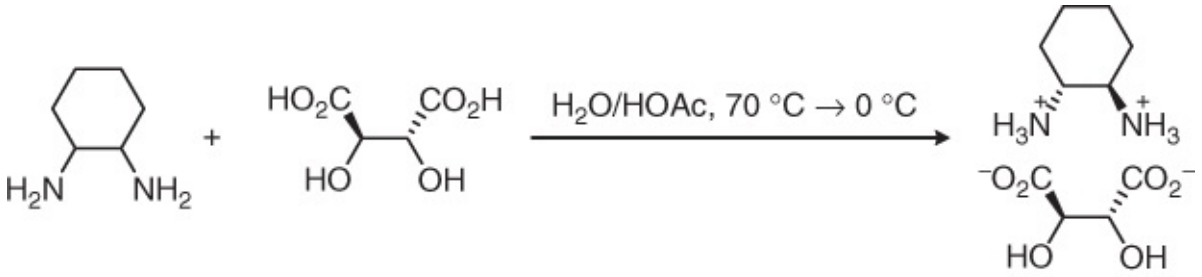
IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 2959, 1650, 1439, 1322, 1206, 894, 829, 737, 534.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 11.65 (s, 1H, OH), 9.87 (s, 1H, 1′-H), 7.60 (d, 1H, *J* = 2.6 Hz, 6-H), 7.35 (d, 1H, *J* = 2.6 Hz, 4-H), 1.43 (s, 9H, 3-*t*Bu), 1.33 (s, 9H, 5-*t*Bu).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 197.4 (C-1′), 159.1 (C-2), 141.6 (C-5), 137.6 (C-3), 131.9 (C-4), 127.0 (C-6), 119.9 (C-1), 34.99 (3-*C*$(CH_3)_3$), 34.22 (5-*C*$(CH_3)_3$), 31.29 (3-C(*C*$H_3)_3$), 29.23 (5-C(*C*$H_3)_3$).

MS (EI, 70 eV): *m*/*z* (%) = 234.1 (13) $[M]^+$, 219.1 (100) $[M-CH_3]^+$, 57 (62) $[C(CH_3)_3]^+$.

2.1.2.2	**	**Resolution of *rac*-*trans*-1,2-diaminocyclohexane**
		(*R*,*R*)-diaminocyclohexane mono-(+)-tartrate salt [9]



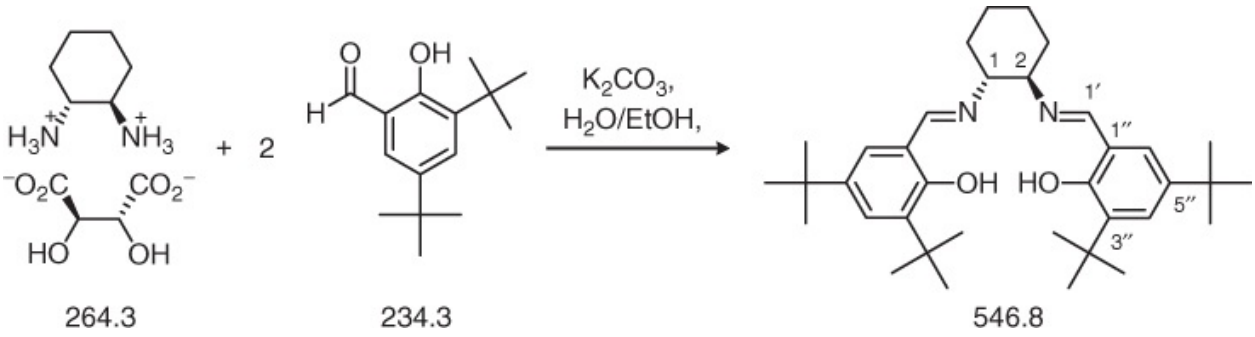
114.2 150.1 264.3

A three-neck, round-bottomed flask equipped with a reflux condenser, an internal thermometer, and an addition funnel is charged with (+)-(*R*,*R*)-tartaric acid (75.0 g, 500 mmol) and H_2O (200 ml). The mixture is stirred until the acid has completely dissolved. Then, *rac*-*cis*/*trans*-1,2-diaminocyclohexane (120 ml, 970 mmol) is added at such a rate that the reaction temperature reaches 60–65 °C. Glacial acetic acid (50 ml, 875 mmol) is then slowly added to the resulting solution at such a rate that the temperature reaches 65–70 °C. The mixture is cooled to room temperature over a period of 2 h, and then cooled to 0 °C for a further 2 h.

The colorless precipitate formed is collected by vacuum filtration, and the filter

cake is washed with ice-cold H_2O (50 ml) and ice-cold MeOH (6 × 50 ml). After drying in high vacuum, the tartrate salt is obtained as a white crystalline solid; 60.8 g (46%), ee > 99%; $[\alpha]^{20}_D$ = +12.7 (*c* = 4.0, H_2O).

2.1.2.3	**	**(*R*,*R*)-*N*,*N*′-Bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediimine** [9]



264.3 234.3 546.8

A three-neck, round-bottomed flask equipped with a reflux condenser and an addition funnel is charged with the tartrate salt **2.1.2.2** (8.33 g, 31.5 mmol), K_2CO_3 (8.72 g, 63.1 mmol), and H_2O (40 ml). The mixture is stirred until complete dissolution is achieved. EtOH (168 ml) is then added, the solution is heated to reflux, and a solution of the aldehyde **2.1.2.1** (15.0 g, 64.0 mmol) in EtOH (70 ml) is steadily added dropwise over 30 min. After heating to reflux for 2 h, H_2O (42 ml) is added. The mixture is cooled to room temperature over a period of 30 min, and then kept at 0–5 °C overnight.

The precipitate is collected by vacuum filtration, and the filter cake is washed with EtOH (40 ml). The solid is redissolved in CH_2Cl_2 (140 ml), and the solution is washed with H_2O (3 × 80 ml) and brine (40 ml). The organic layer is dried over $MgSO_4$ and filtered, and the solvent is removed *in vacuo* to yield the diimine as a yellow powder; 13.8 g (80%); mp 200–203 °C; $[\alpha]^{20}_D$ = −283.0 (*c* = 1.0, CH_2Cl_2).

UV (CH_3CN): λ_{max} (nm) (log ϵ) = 328.5 (3.864), 259.5 (4.296), 218.5 (4.663), 194.0 (4.654).

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 2961, 2864, 1630, 1439, 1361, 1271, 1203, 1174, 1085, 1038, 879, 773.

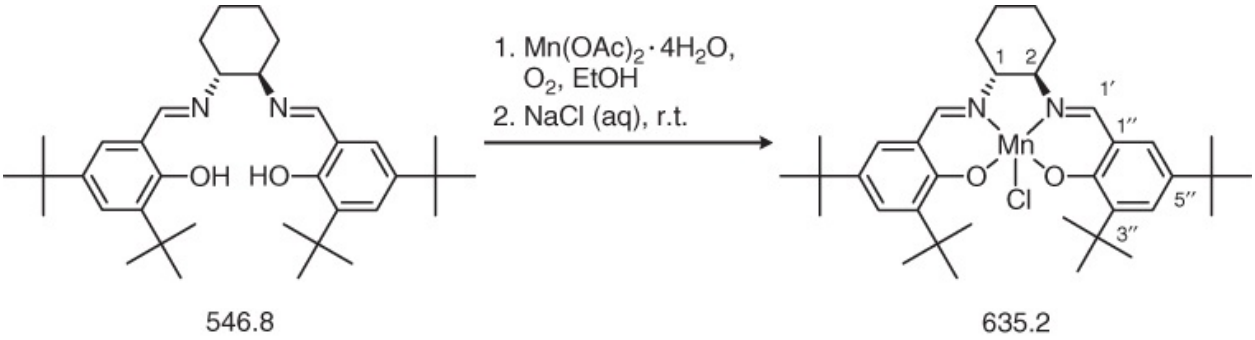
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 13.74 (s, 2H, OH), 8.32 (s, 2H, 2 × 1′-H), 7.32 (d, *J* = 2.4 Hz, 2H, 2 × 6″-H), 7.00 (d, *J* = 2.4 Hz, 2H, 2 × 4″-H),

3.38 to 3.28 (m, 2H, 1-H, 2-H), 2.00 to 1.60 (m, 8H, 3-H_2, 4-H_2, 5-H_2, 6-H_2), 1.43 (s, 18H, 2 × 3″-*t*Bu), 1.25 (s, 18H, 2 × 5″-*t*Bu).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 165.8 (C-1′), 158.0 (C-2″), 139.8 (C-5″), 136.3 (C-3″), 126.7 (C-4″), 126.0 (C-6″), 117.8 (C-1″), 72.40 (C-1, C-2), 34.93 (2 × 5″-*C*$(CH_3)_3$), 34.01 (2 × 3″-*C*$(CH_3)_3$), 33.26 (C-3, C-6), 31.39 (2 × 5″-C(*C*$H_3)_3$), 29.40 (2 × 3″-C(*C*$H_3)_3$), 24.34 (C-4, C-5).

MS (EI, 70.0 eV): *m/z* (%) = 546.3 (63) $[M]^+$, 313.2 (100) $[M-N-CH-C_{14}H_{20}O]^+$.

2.1.2.4	**	**[(*R*,*R*)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediimine]**
		manganese(III) chloride [9]



546.8 635.2

A three-neck round-bottom flask equipped with a reflux condenser and an addition funnel is charged with a solution of manganese(II) acetate tetrahydrate (3.53 g, 14.4 mmol) in EtOH (36 ml). After heating to reflux, a solution of the Schiff base from **2.1.2.3** (3.00 g, 5.46 mmol) in toluene (20 ml) is slowly but steadily added over 35 min. The mixture is heated to reflux for 2 h; then heating is discontinued and air is bubbled through the solution for 3 h. Brine (6 ml) is then added, and the resulting mixture is stirred at room temperature overnight.

Toluene (20 ml) is added and the solution is washed with H_2O (3 × 50 ml) and brine (50 ml). The organic phase is dried over $MgSO_4$ and filtered, and the solvent is removed *in vacuo*. The solid is redissolved in CH_2Cl_2 (18 ml) and *n*-heptane (18 ml), and the solution is concentrated to half of its original volume and left at room temperature overnight. The precipitate formed is collected by vacuum filtration and washed with *n*-heptane (50 ml) to yield the manganese(III) complex as a brown solid; 2.95 g (85%), mp 324–326 °C; $[\alpha]^{20}_D$ = −608.3 (*c* =

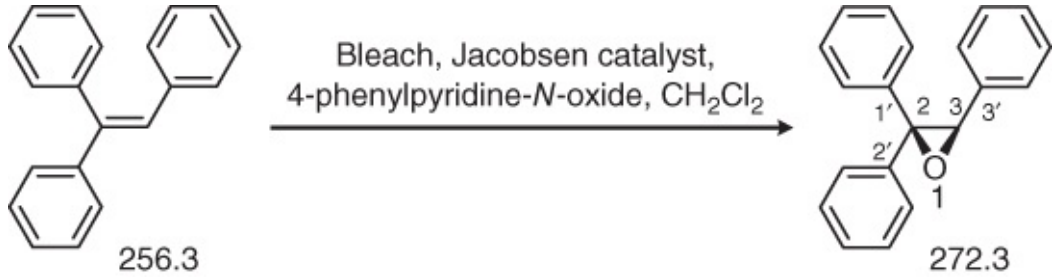
0.012, EtOH).

UV (CH_3CN): λ_{max} (nm) (log ϵ) = 421.0 (3.636), 316.5 (4.105), 239.5 (4.578), 197.0 (4.656).

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 2952, 2866, 1613, 1535, 1433, 1311, 1252, 1175, 1030, 929, 917, 837, 748, 569, 543.

MS (ESI): *m*/*z* (%) = 679.0 (100) $[M+HCO_2]^+$, 633.3 (17) $[M-H]^+$, 599.5 (100) $[M-Cl]^+$.

2.1.2.5	***	**(*R*)-2,2,3-Triphenyloxirane** [14]



Preparation of the Bleach Solution

Aqueous sodium hypochlorite solution (10%, 32.8 ml, 55.0 mmol) and aqueous disodium hydrogen phosphate (Na_2HPO_4) solution (bleach, 10%, 0.05 M, 67.2 ml) are mixed and brought to pH 11.3 under pH control by adding aqueous 1 M NaOH solution.

A single-necked, round-bottomed flask is charged with triphenylethylene (500 mg, 1.95 mmol) and CH_2Cl_2 (2.5 ml) under an argon atmosphere. 4-Phenylpyridine *N*-oxide (66.8 mg, 0.39 mmol) and the Jacobsen catalyst **2.1.2.4** (61.9 mg, 97.5 µmol) are added and the mixture is cooled to 0 °C, whereupon precooled bleach solution (0.55 M, 5.32 ml, 2.93 mmol) is added with stirring and stirring is continued at 0 °C for 23 h. CH_2Cl_2 (10 ml) and H_2O (10 ml) are then added, the organic layer is washed with H_2O (10 ml), and the aqueous layer is extracted with CH_2Cl_2 (3 × 10 ml). The combined organic layers are dried over Na_2SO_4 and filtered, and the solvent is removed *in vacuo*. The crude product is purified by column chromatography on silica gel (*n*-pentane/EtOAc, 100 : 2) to afford the oxirane as a white solid; 464 mg (87%), ee = 88%, $[\alpha]^{20}_D$ =

+61.2 (*c* = 1.0, $CHCl_3$).

UV (CH_3CN): λ_{max} (nm) (log ϵ) = 225.5 (4.273).

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3026, 2972, 1887, 1601, 1491, 1447, 1336, 1074, 1029, 903, 865, 822.

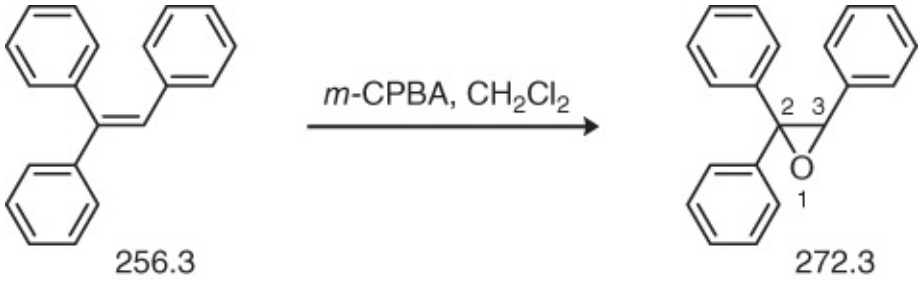
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.40 to 7.00 (m, 15H, 2 × 2-Ph, 3-Ph), 4.34 (s, 1H, 3-H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 140.9 (C-3′), 135.7, 135.4 (C-1′, C-2′), 129.2, 128.3, 127.8, 127.7, 127.6, 127.5, 126.7, 126.3 (15 × Ph–CH), 68.6 (C-2), 68.1 (C-3).

MS (EI, 70.0 eV): *m*/*z* (%) = 272.2 (39) $[M]^+$, 165.1 (100) $[M-PhCH_2O]^+$, 105.1 (62) $[C_8H_9]^+$, 77.0 (31) $[Ph]^+$.

HPLC: Chiralpak IA® (Chiral Technologies Europe); 250 × 4.6 mm; eluent: *n*-hexane/*i*-propanol, 98 : 2; gradient: isocratic; retention time: t_{R1} = 7.21 min; t_{R2} = 8.06 min.

2.1.2.6 * (*rac*)-2,2,3-Triphenyloxirane [15]



A single-neck, round-bottomed flask is charged with triphenylethylene (500 mg, 1.95 mmol) and CH_2Cl_2 (5 ml) under argon atmosphere at 0 °C. *meta*-Chloroperoxybenzoic acid (70%, 722 mg, 2.93 mmol) is added, and the resulting solution is stirred for 24 h at room temperature.

Saturated aqueous $NaHCO_3$ solution (10 ml) is then added, and the mixture is stirred for 30 min, whereupon CH_2Cl_2 (20 ml) is added. The organic layer is washed with saturated aqueous $NaHCO_3$ solution (2 × 10 ml), dried over Na_2SO_4, and filtered. The solvent is removed *in vacuo*, and the residue is

purified by column chromatography on silica gel (*n*-pentane/Et_2O, 100 : 1) to afford the oxirane as a white solid; 425 mg (80%).

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.40 to 7.00 (m, 15H, Ar–H), 4.34 (s, 1H, 3-H).

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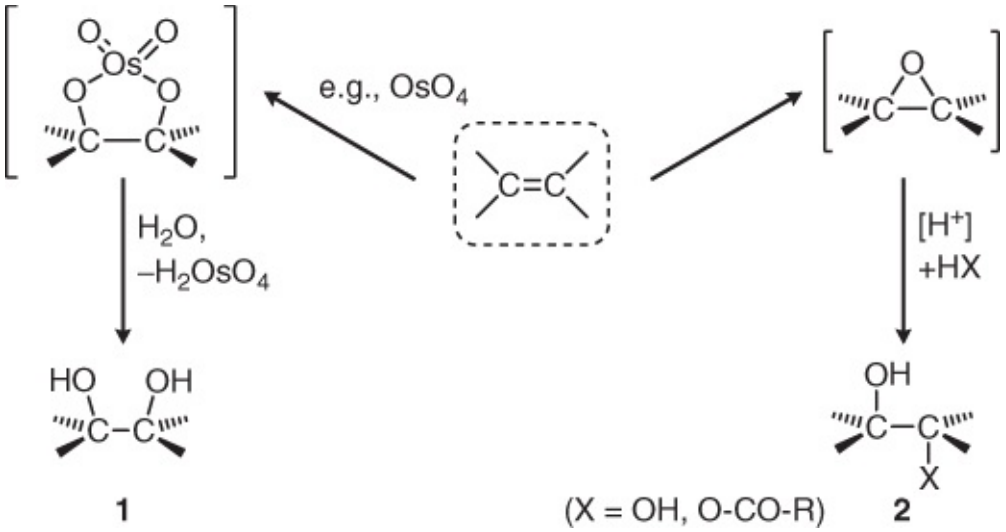
2.2 Dihydroxylation of C=C Bonds

The dihydroxylation of olefinic C=C bonds to give *cis*-1,2-diols **1** is a fundamental oxidative process in alkene chemistry [1]. 1,2-Diols can also be prepared using oxiranes as precursors (cf. Section 2.1) by acid-catalyzed nucleophilic ring opening with water. In this case, the *trans*-1,2-diols **2** (X=OH) are formed [2]. Formation of the oxirane and ring opening can be combined in one process.

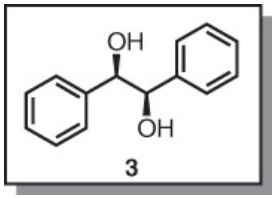


The *cis*-dihydroxylation can be performed with permanganate or osmium tetroxide as oxidants, with cyclic manganate or osmate esters as intermediates. While permanganate shows a tendency for further oxidative transformations [1], the reaction with OsO_4 is a reliable method for the synthesis of *cis*-1,2-diols **1** and is widely used in preparative chemistry [3].

Other methods of dihydroxylation, such as the Prevost method (I_2, silver benzoate; overall anti-addition) and the Woodward method (I_2, silver acetate, presence of H_2O; overall syn-addition) [4], although they proceed stereoselectively, are only of limited preparative importance.

For the enantioselective *cis*-dihydroxylation of alkenes, Sharpless and coworkers [5, 6] have developed an efficient method based on the use of OsO_4, which is presented in Section 2.2.1.

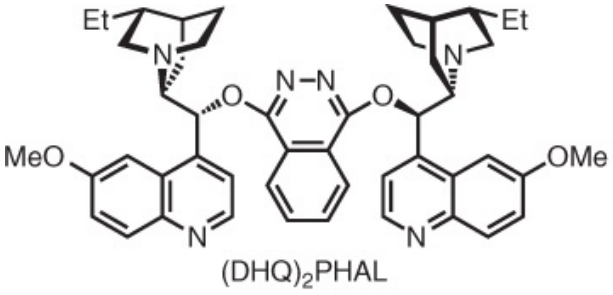
2.2.1 Sharpless Dihydroxylation

 3	***Topic:***	• Asymmetric *cis*-dihydroxylation of an alkene according to Sharpless

(a) General

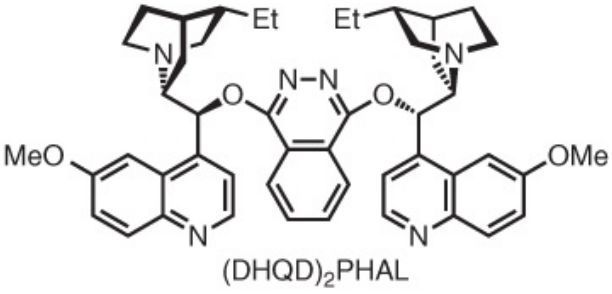
The Sharpless dihydroxylation gives excellent selectivities of up to 99.8% ee for

almost all types of alkenes other than those with (*Z*)-1,2-disubstituted double bonds. In the Sharpless procedure, the so-called AD mixes (AD = asymmetric dihydroxylation) are used as reagents; they contain $OsO_2(OH)_4$ as a catalytic nonvolatile Os(VIII) source, which is coordinated either by dihydroquinine 1,4-phthalazinediyl diether ($(DHQ)_2PHAL$) (**4**)) to give AD-mix-α or by dihydroquinidine 1,4-phthalazinediyl diether ($(DHQD)_2PHAL$) (**5**)) to give AD-mix-β, K_2CO_3, and a stoichiometric amount of $K_3[Fe(CN)_6]$ as a reoxidant. The ligand/osmium molar ratio is 2.5 : 1, and generally only 0.4 mol% of osmium is needed for the catalysis. Ligands based on PHAL [5] show broad applicability toward mono-, 1,1-di-, (*E*)-1,2-di-, tri-, and tetrasubstituted [7] alkenes. For enantioselective Sharpless *cis*-dihydroxylations of (*Z*)-1,2-disubstituted alkenes, special indole ligands belonging to the so-called IND class are used [8]. Furthermore, different ligands [9] have been developed to meet substrate-specific requirements.



$(DHQ)_2PHAL$

4

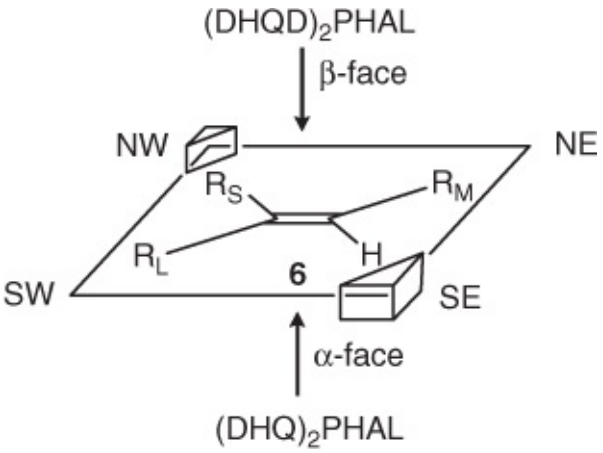


$(DHQD)_2PHAL$

5

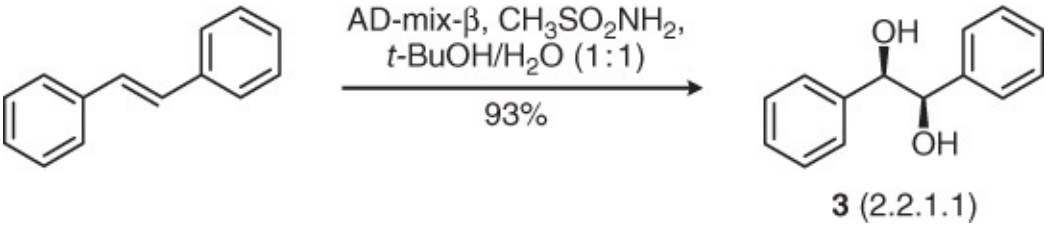
In the PHAL reagents, the osmium atom is coordinated by the ligands **4** or **5**, and the resulting complex provides efficient specific recognition of the prochiral alkene faces because of its steric demand.

An empirical rule helps to understand and predict the stereochemical outcome of the Sharpless dihydroxylation. As shown in the model situation **6**, the southeastern and northwestern quadrants are blocked by the ligand, so the smallest and second smallest substituents ought to be in these positions in order to give a favorable transition state for the dihydroxylation. The $(DHQD)_2PHAL$ system (AD-mix-β) induces attack from the upper β-face, whereas the $(DHQ)_2PHAL$ system (AD-mix-α) induces attack from the lower α-face.



(b) Synthesis of 3

Asymmetric *cis*-dihydroxylation is carried out with (*E*)-stilbene as olefinic substrate using AD-mix-β as oxidation reagent in the presence of methanesulfonamide and *t*BuOH/H_2O as solvent [10]. (+)-1,2-(*R*,*R*)-Diphenyl-1,2-ethanediol (**3**) is obtained in almost quantitative chemical yield and in practically enantiopure form (ee > 99%).



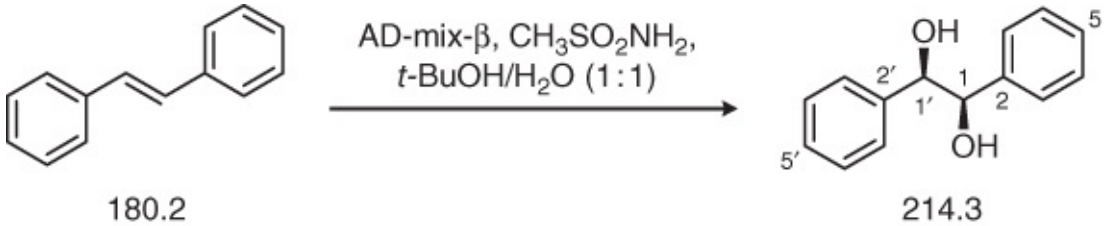
3 (2.2.1.1)

To account for the observed stereoselectivity, the reagent AD-mix-β apparently induces exclusive attack from the β-face of the alkene (cf. Section (a)).

For the dihydroxylation of a non-terminal alkene such as (*E*)-stilbene, the addition of methane sulfonamide effects an acceleration of the osmate(VI) ester hydrolysis and thus shortens the reaction time.

(c) Experimental Procedure for the Synthesis of 3

2.2.1.1	**	**(+)-(*R*,*R*)-1,2-Diphenyl-1,2-ethanediol** [7]



180.2 214.3

A 25-ml round-bottomed flask equipped with a magnetic stirrer is charged with *t*-BuOH (5 ml), H_2O (5 ml), and AD-mix-β (2.00 g), and the mixture is stirred for 15 min. Methanesulfonamide (158 mg, 1.66 mmol) is then added, stirring is continued for a further 15 min, and then (*E*)-stilbene (250 mg, 1.38 mmol) is given to the mixture. After vigorous stirring of the slurry at 20 °C for 24 h, sodium sulfite (2.00 g) is added, and stirring is continued for a further 60 min.

Thereafter, the mixture is treated with H_2O (30 ml) and extracted with CH_2Cl_2 (3 × 50 ml). The combined organic layers are washed with H_2O (30 ml) and brine (30 ml), dried over $MgSO_4$, and filtered, and the solvent is removed *in vacuo*. The crude product is purified by column chromatography on silica gel (petroleum ether/EtOAc, 3 : 1) to afford the diol as white crystalline needles. The enantiomeric excess is determined by HPLC on a chiral stationary phase; 279 mg (93%), ee > 99%, mp 124–125 °C, $[\alpha]^{20}_D$ = +93 (*c* = 0.87, EtOH), R_f = 0.5 (petroleum ether/EtOAc, 2 : 1).

UV (CH_3CN): λ_{max} (nm) (log ϵ) = 263.5 (6.651), 252.0 (6.631), 257.5 (6.641), 194.5 (5.519), 192.5 (6.514).

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3499, 3395, 3063, 2895, 1493, 1452, 1385, 1335, 1252, 1198, 1044, 1012.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.28–7.20 (m, 6H, 2 × 4-H, 2 × 4′-H, 5-H, 5′-H), 7.18–7.09 (m, 4H, 2 × 3-H, 2 × 3′-H), 4.70 (s, 2H, 1-H, 1′-H), 2.85 (s_{br}, 2H, 2 × OH).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 139.8 (C-2, C-2′), 128.1 (C-4, C-4′), 127.9 (C-5, C-5′), 126.9 (C-3, C-3′), 97.1 (C-1, C-1′).

MS (DCI): *m*/*z* (%) = 446.3 $[2\ M + NH_4]^+$, 249.2 $[M+NH_3+NH_4]^+$, 232.1 $[M+NH_4]^+$, 214.1 $[M-H_2O+NH_4]^+$.

HPLC: Chiralpak IA® (Chiral Technologies Europe); 250 × 4.6 mm i.d.

eluent: *n*-hexane/*i*-propanol, 90 : 10

gradient: 0.8 ml min^{-1}.

retention time: t_R = 15.32 min.

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2. When epoxidation is carried out with H_2O_2 in formic acid or acetic acid, monoesters of *trans*-1,2-diols (**2**, X = OCOR) result, which can be saponified to 1,2-diols (**2**, X = OH); compare: Tietze, L.F. and Eicher, Th. (1991) *Reaktionen und Synthesen im organisch-chemischen Praktikum und Forschungslaboratorium*, 2nd edn, Georg Thieme Verlag, Stuttgart, p. 62.

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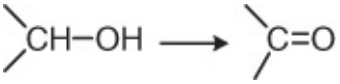
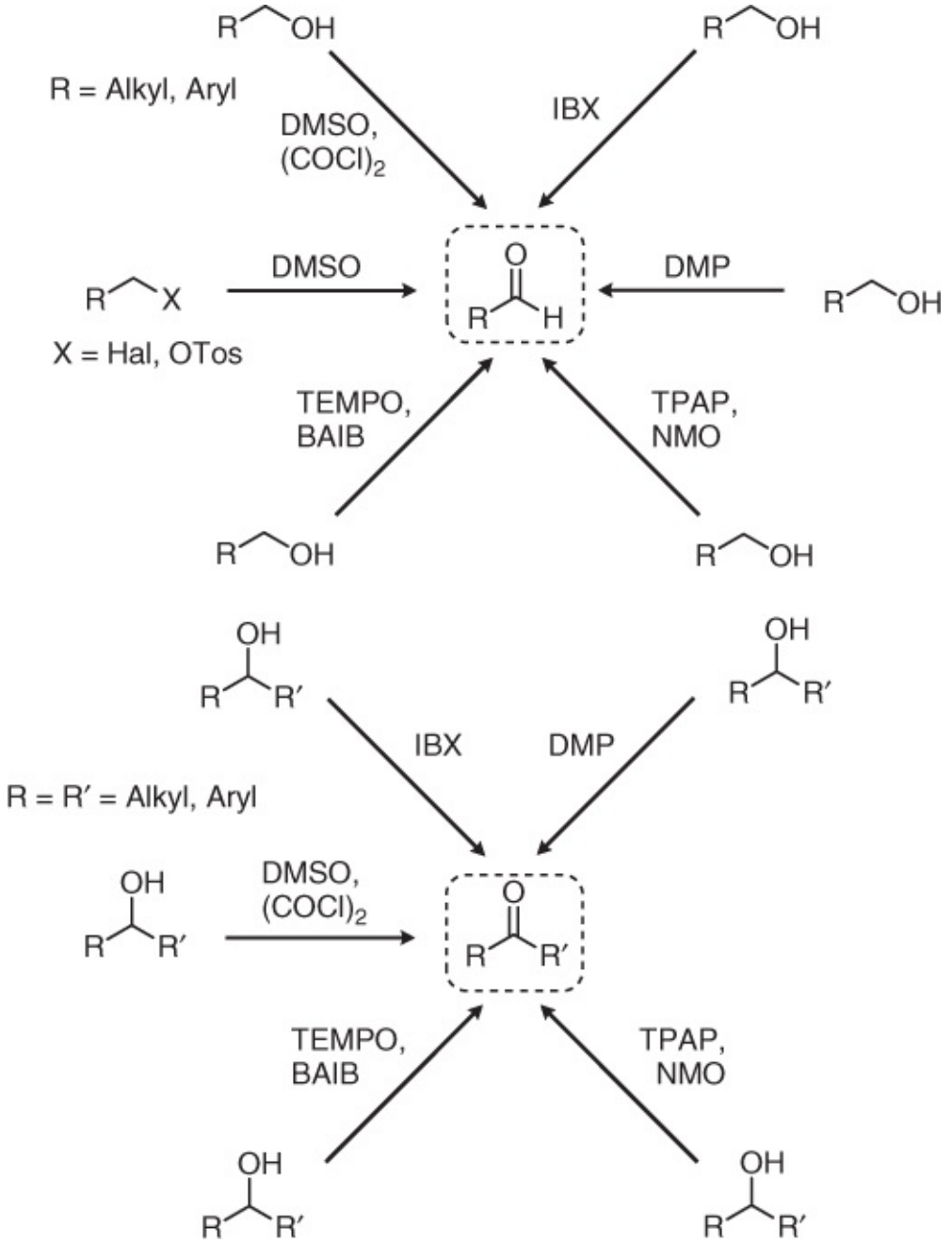
2.3 Oxidation of Alcohols to Carbonyl Compounds



Numerous methods are available for the conversion of primary alcohols to

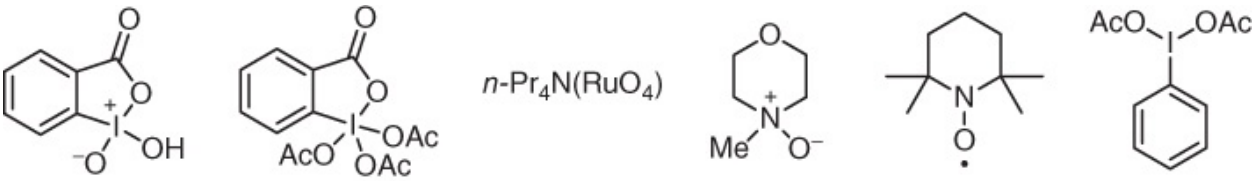
aldehydes and of secondary alcohols to ketones [1]. The chromium(VI) reagents (e.g., chromic acid, dichromate, pyridinium chlorochromate), preferentially used in earlier times, are now set to be replaced almost entirely by less toxic reagents, selected examples of which are indicated in the following scheme:



A very common and reliable procedure for the oxidation of primary and secondary alcohols is the Swern oxidation using oxalyl chloride and dimethyl sulfoxide (DMSO) [2]. A disadvantage of this method is that it should not be employed for the transformation of large quantities. DMSO can also be used for

the conversion of alkyl halides and tosylates to carbonyl compounds. This procedure is known as ***Kornblum oxidation*** ([3], cf. Section 1.2.1); it is, however, of limited importance.

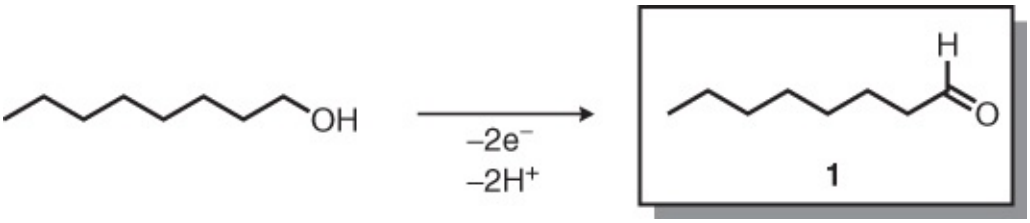
Environmental demands concerning chemical processes have encouraged chemists to search for new clean, high-yielding, and selective oxidation methods. Of particular interest are methods using hypervalent iodine compounds (cf. Section 1.8.6) as mild and selective oxidizing agents of low toxicity [4]. The Dess–Martin periodinane (DMP) and its direct precursor 1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide (IBX) fall into this category, which are employed in organic solvents such as DMSO, CH_2Cl_2, or acetone [5]. However, in spite of their utility, iodine(V) reagents are potentially explosive. Therefore, the use of readily available and relatively stable iodine(III) reagents such as (bisacetoxyiodo)benzene (BAIB) has attracted increased attention [6]. This reagent is used in combination with catalytic amounts of 2,2,6,6-tetramethyl-1-piperdinyloxyl (TEMPO) for regeneration [7]. Sodium hypochlorite can also be used as oxidant instead of BAIB which is relatively expensive.



IBX DMP TPAP NMO TEMPO BAIB

One of the most versatile oxidants is tetrapropylammonium perruthenate (TPAP), which allows a metal-mediated oxidation of alcohols under very mild conditions without any obnoxious or explosive reagents [8]. TPAP is used in catalytic amounts with *N*-methyl-morpholine *N*-oxide (NMO) as a co-oxidant to regenerate the active ruthenium species.

The aforementioned oxidation methods and the preparation of the required reagents are the subjects of the following sections. As a standard reference process, the conversion of the primary alcohol *n*-octanol to the aldehyde *n*-octanal (**1**) is used [9].

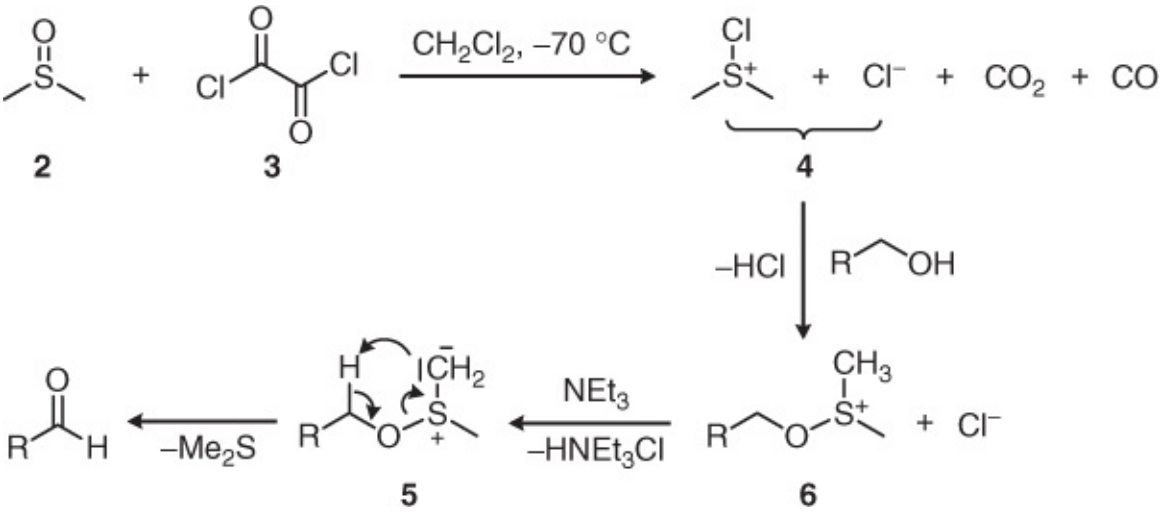


2.3.1 Swern Oxidation

(a) General

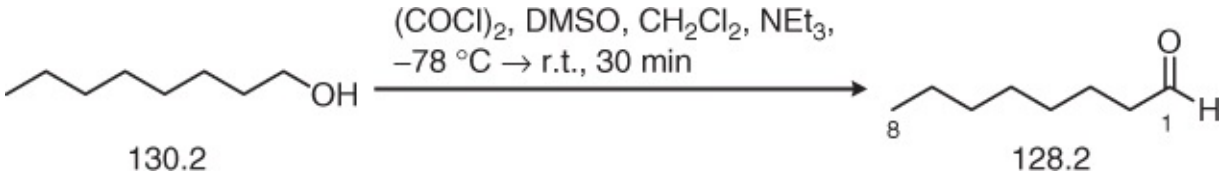
For the Swern oxidation process, the following mechanism is established:

DMSO (**2**) is activated by S-acylation with oxalyl chloride (**3**) followed by loss of CO and CO_2 to give chlorodimethylsulfonium chloride (**4**) as intermediate, which reacts with the alcohol (here: RCH_2OH) to give an alkoxysulfonium ion **6**. Deprotonation of **6** by base (here: triethylamine) generates the ylide **5**, which undergoes proton transfer to the ylide carbon and cleavage at the O–S bond to form the products, the carbonyl compound (here: R–CH=O) and dimethyl sulfide:



(b) Swern Oxidation of *n*-Octanol (experimental procedure)

2.3.1.1	**	***n*-Octanal I** [2]



A solution of oxalyl chloride (15.2 g, 10.3 ml, 120 mmol) in CH_2Cl_2 (150 ml) is prepared under an argon atmosphere in a dry, 500-ml, three-necked, round-bottomed flask, fitted with a mechanical stirrer, a dropping funnel, and an internal thermometer. The solution is cooled to −70 °C, a solution of DMSO (20.3 g, 18.5 ml, 260 mmol) in CH_2Cl_2 (30 ml) is added dropwise, and the reaction mixture is stirred for 30 min at −70 °C. A solution of *n*-octanol (13.0 g,

15.8 ml, 100 mmol) in CH_2Cl_2 (40 ml) is then added dropwise, and the resulting mixture is stirred for a further 30 min at −70 °C before NEt_3 (50.6 g, 69.5 ml, 500 mmol) is cautiously added.

The solution is allowed to warm to room temperature, whereupon H_2O (100 ml) is added and stirring is continued for 10 min. The layers are separated, and the aqueous layer is extracted with CH_2Cl_2 (2 × 100 ml). The combined organic layers are dried over Na_2SO_4 and filtered. The solvent is removed over a Vigreux column (20 cm) under reduced pressure (∼500 mbar, water bath <40 °C (!)) and the residue is fractionated *in vacuo* to afford the aldehyde as a colorless volatile liquid; 12.5 g (98%), bp_{12} 62–63 °C.

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 2928, 2858, 1712, 1465, 1414, 1285, 1232, 1109, 938, 725.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 9.75 (t, *J* = 1.8 Hz, 1H, 1-H), 2.41 (td, *J* = 7.4, 1.8 Hz, 2H, 2-H_2), 1.61 (m_c, 2H, 3-H_2), 1.29 (m_c, 8H, H_{alkyl}), 0.87 (t, *J* = 6.9 Hz, 3H, 8-H_3).

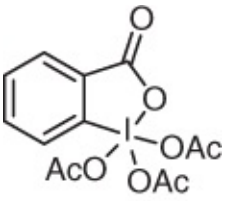
^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 202.9 (C-1), 43.9 (C-2), 31.6 (C-3), 29.1 (C-4), 29.0 (C-5), 22.6 (C-6), 22.1 (C-7), 14.0 (C-8).

Note: n-Octanal should, if possible, be purified by distillation and not by chromatography.

2.3.2 Dess–Martin Oxidation

(a) General

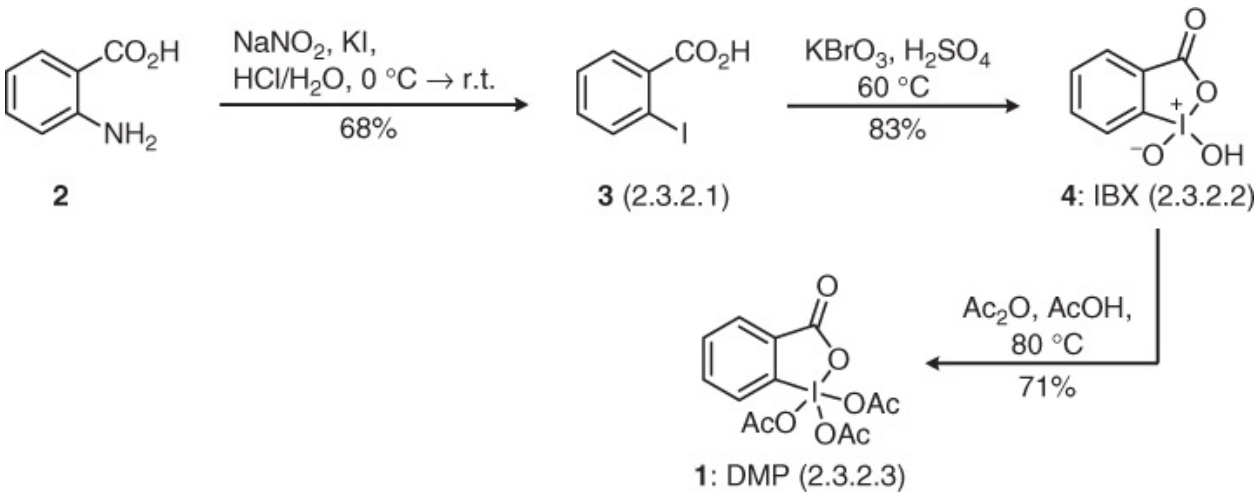
In this method, the oxidizing agent is the DMP (**1**), a hypervalent organo-iodine(V) compound, which is prepared in a three-step sequence from anthranilic acid (**2**).



1

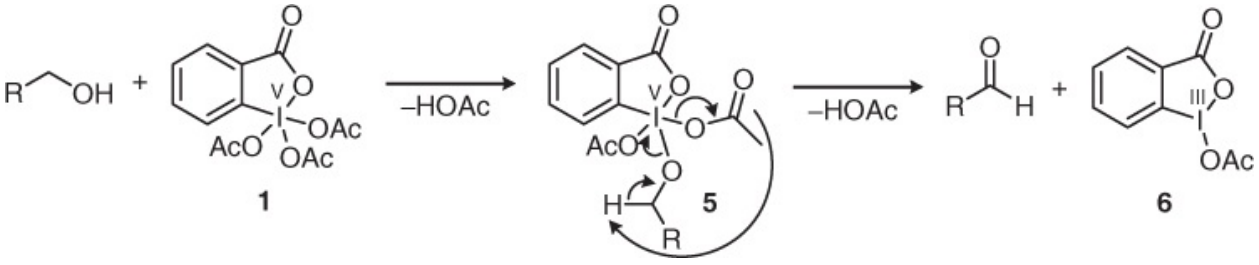
(b) Synthesis of Dess–Martin Periodinane (1)

Anthranilic acid (**2**) is transformed into *o*-iodobenzoic acid (**3**) by diazotization and subsequent displacement of the diazonium group by iodide (S_NAr process). Reaction of **3** with potassium bromate in H_2SO_4 leads to oxidation at the iodine atom followed by cyclization involving the CO_2H group to give 1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide (IBX) (**4**). Peracetylation of **4** with acetic anhydride in acetic acid then affords the desired oxidizing agent 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one (DMP) (**1**):



2 **3** (2.3.2.1) **4**: IBX (2.3.2.2) **1**: DMP (2.3.2.3)

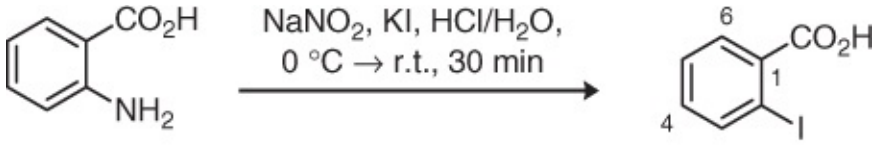
The Dess–Martin oxidation proceeds according to the following mechanistic pathway: Initially, the alcohol (here: RCH_2OH) replaces one of the acetate residues at the iodine atom in the DMP reagent (**1**). Subsequently, the intermediate **5** (still containing iodine(V)) undergoes a disproportionation process, in which HOAc is lost and the carbonyl compound (here: R–CH=O) and the (less reactive) iodine(III) species **6** are formed.



1 **5** **6**

(c) Experimental Procedures for the Synthesis of 1

2.3.2.1	**	***o*-Iodobenzoic acid** [1]



137.1 248.0

Under an argon atmosphere, anthranilic acid (34.2 g, 249 mmol) is dissolved in a mixture of H_2O (250 ml) and concentrated HCl (62.5 ml). The solution is cooled to 0–5 °C, and a solution of sodium nitrite (17.7 g, 257 mmol) in H_2O (50 ml) is added dropwise, the temperature not exceeding 5 °C. The resulting mixture is stirred for 5 min, and then a solution of potassium iodide (42.7 g, 257 mmol) in H_2O (65 ml) is added. Stirring is continued for 5 min without cooling, and the solution is warmed to 40–50 °C, causing rapid gas evolution and the formation of a brown precipitate.

After 15 min at 40–50 °C, the temperature is increased to 70–80 °C for 10 min, and then the solution is cooled with an ice bath. Sodium thiosulfate is added to destroy excess iodine, and the precipitate is collected by filtration and washed with iced water (3 × 200 ml). The solid is dissolved in hot EtOH (175 ml) and treated three times with charcoal. The charcoal is filtered off, and the final filtrate is diluted with hot water (80 ml) and heated to reflux. Cold water (100 ml) is added, and the solution is left in a refrigerator to give the iodobenzoic acid as yellow-orange needles; 41.2 g (68%), mp 159–160 °C, R_f = 0.39 (*n*-pentane/EtOAc, 4 : 1, +1% acetic acid).

UV (CH_3CN): λ_{max} (nm) (log ϵ) = 285.0 (3.130), 205.0 (4.341).

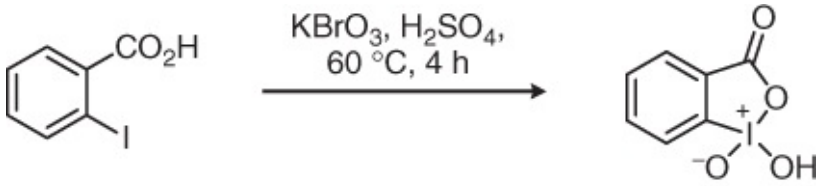
IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 2875, 1681, 1581, 1466, 1402, 1295, 1266, 1109, 1014, 896, 739, 678.

^{1}H NMR (300 MHz, CD_3OD): δ (ppm) = 8.00 (dd, *J* = 8.0, 1.0 Hz, 1H, 3-H), 7.79 (dd, *J* = 7.8, 1.7 Hz, 1H, 6-H), 7.45 (dt, *J* = 7.7, 1.0 Hz, 1H, 5-H), 7.19 (dt, *J* = 7.8, 1.7 Hz, 1H, 4-H).

^{13}C NMR (75 MHz, CD_3OD): δ (ppm) = 170.1 (CO_2H), 142.3 (C-3), 137.8 (C-1), 133.5 (C-4), 131.6 (C-6), 129.1 (C-5), 94.14 (C-2).

MS (EI, 70 eV): *m*/*z* (%) = 248 (100) $[M]^+$, 231 (47) $[M-OH]^+$, 203 (10) $[M-CO_2H]^+$, 121 (2) $[M-I]^+$, 76 (10) $[C_6H_4]^+$.

2.3.2.2	**	**1-Hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide (IBX)** [5f]



248.0 280.0

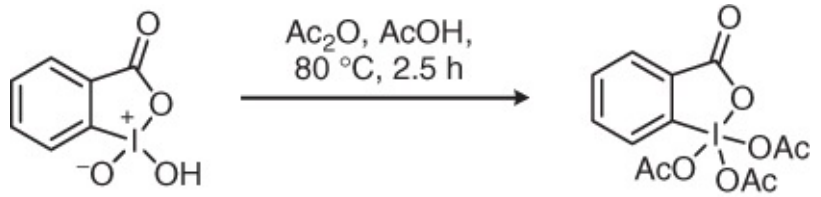
Potassium bromate (30.0 g, 180 mmol) is added in small portions to a mechanically stirred solution of **2.3.2.1** (35.0 g, 141 mmol) in H_2SO_4 (300 ml, 0.73 M) (Caution: the temperature of the solution should not exceed 50 °C during the addition!). The resulting mixture is stirred for an additional 20 min at room temperature, then cautiously heated to 60 °C over a period of 1 h, and stirred for 3 h at this temperature.

The reaction mixture is then cooled to 0 °C, and the solid compounds are filtered off (Caution: explosive!), washed with cold water (350 ml), EtOH (25 ml), and Et_2O (25 ml), and dried under reduced pressure to afford the oxide as a light-yellow powder (*note*); 33.0 g (84%).

^{1}H NMR (300 MHz, [D_6]DMSO): δ (ppm) = 8.00 (m, 4H, ArH), 4.40 (s_{br}, 1H, OH).

Note: Because of its sensitivity (explosive), this compound should be immediately subjected to the next step of the reaction sequence.

2.3.2.3	***	**1,1,1-Triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one (DMP)** [5f]



280.0 424.1

Compound **2.3.2.2** (13.0 g, 46.4 mmol) (Caution: explosive!) is added to a mixture of acetic anhydride (16.6 g, 162 mmol) and acetic acid (13.8 g, 230 mmol) at room temperature. The resulting mixture is heated to 80 °C over 1 h, and then stirred at this temperature for a further 1.5 h before being slowly cooled

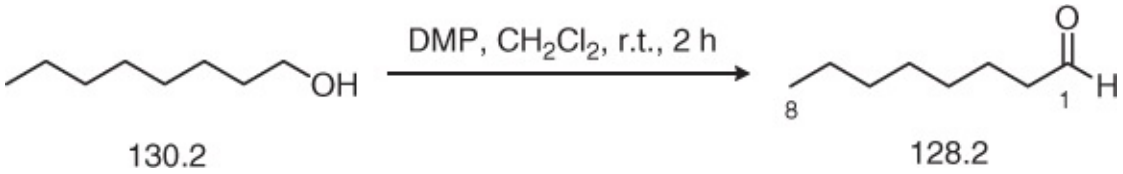
to 0 °C. The resulting colorless crystals are washed with Et_2O (6 × 10 ml). The residual solvent is completely removed under reduced pressure to provide the DMP as a white crystalline solid; 14.0 g (71%), mp 133–134 °C.

^{1}H NMR (300 MHz, [D_6]DMSO): δ (ppm) = 8.31, 8.29 (2 × d, *J* = 8.5 Hz, 2H, 3-H, 6-H), 8.07, 7.80 (2 × dd, *J* = 8.5, 7.3 Hz, 2H, 4-H, 5-H), 2.33 (s, 3H, CH_3), 2.01 (s, 6H, 2 × CH_3).

^{13}C NMR (75 MHz, [D_6]DMSO): δ (ppm) = 175.7, 174.0 (3 × *C*OCH_3), 166.1 (C-3), 142.4 (Ar–C), 135.8, 133.8, 131.8, 126.5, 126.0, 20.4 (CO*C*H_3), 20.3 (2 × CO*C*H_3).

(d) Dess–Martin Periodinane Oxidation of *n*-Octanol (experimental procedure)

2.3.2.4 * ***n*-Octanal II** [5]



Under an argon atmosphere, DMP **2.3.2.3** (489 mg, 1.15 mmol) is added to a solution of *n*-octanol (100 mg, 770 µmol) in CH_2Cl_2 (6.0 ml). The mixture is stirred for 2 h at room temperature, then silica gel is added, and the solvent is removed under reduced pressure (max. 40 °C at 700 mbar; fast!). Flash chromatography on silica gel (*n*-pentane/Et_2O, 10 : 1) provides the aldehyde as a colorless volatile liquid; 89.2 mg (90%), R_f = 0.54 (*n*-pentane/Et_2O, 10 : 1).

For the purification and characterization of the product and further notes, see **2.3.1.1.**

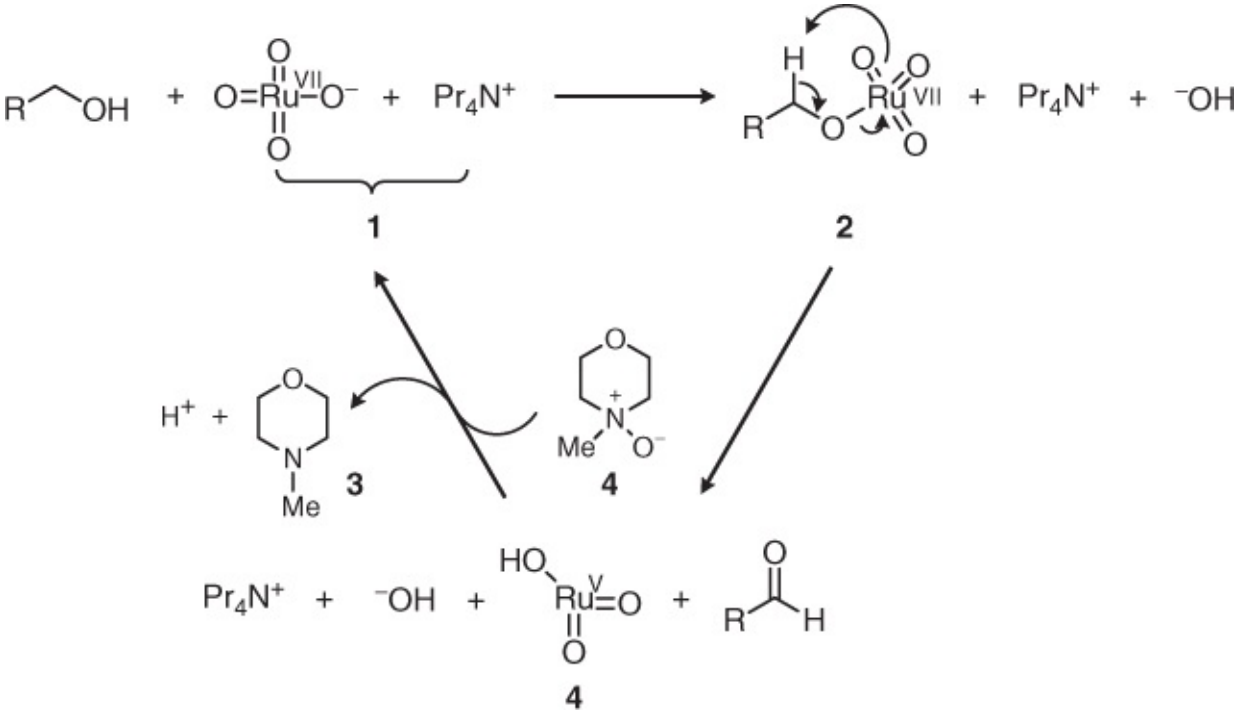
2.3.3 Perruthenate Oxidation

(a) General

The catalytic oxidation of primary and secondary alcohols with TPAP (**1**) requires the use of a stoichiometric amount of NMO (**4**) as a co-oxidant. In the oxidation process, the perruthenate anion reacts with the alcohol (here:

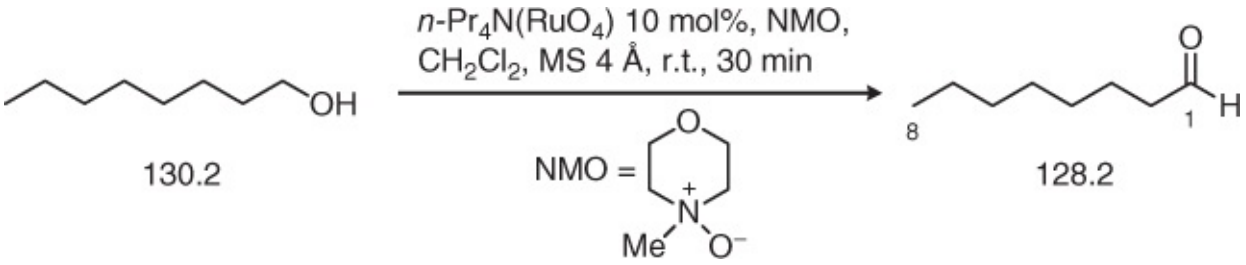
RCH_2OH) to give the Ru(VII) intermediate **2**, which undergoes disproportionation to an Ru(V) species **5** and the expected aldehyde. Finally, the Ru(V) species is reoxidized by NMO (which is concomitantly reduced to the tertiary amine **3**, thus regenerating the Ru(VII) anion in **1**.

The reaction is autocatalytic, which means that the rate is initially slow but accelerates strongly as the concentration of the carbonyl product increases and then slows down once more at the end of the reaction. It is suggested that colloidal RuO_2 is responsible for the autocatalysis, which coordinates to $[RuO_4]^-$ to generate an activated $[RuO_4 \cdot n\ RuO_2]^-$ complex. Perruthenate oxidation is very sensitive to water, which must be coercively removed using molecular sieves. The reason for this effect is the binding of water to the RuO_2 particles, which reduces the number of available coordination sites at $[RuO_4]^-$ and thus inhibits the autocatalytic process. Water can also promote the formation of aldehyde hydrates, which could cause an undesired overoxidation to give carboxylic acids.



(b) Perruthenate Oxidation of *n*-octanol (experimental procedure)

2.3.3.1	*	***n*-Octanal III** [8]



TPAP (28.1 mg, 0.08 mmol, 10 mol%) and NMO (271 mg, 2.31 mmol) are added to a mixture of *n*-octanol (100 mg, 0.77 mmol) and 4 Å molecular sieves (100 mg) in CH_2Cl_2 (4.0 ml). The mixture is shaken for 30 min at room temperature.

It is then concentrated under reduced pressure (max. 40 °C at 500 mbar; fast!), and flash chromatography on silica gel (*n*-pentane/Et_2O, 10 : 1) provides the aldehyde as a colorless volatile liquid; 98 mg (99%), R_f = 0.54 (*n*-pentane/Et_2O, 10 : 1).

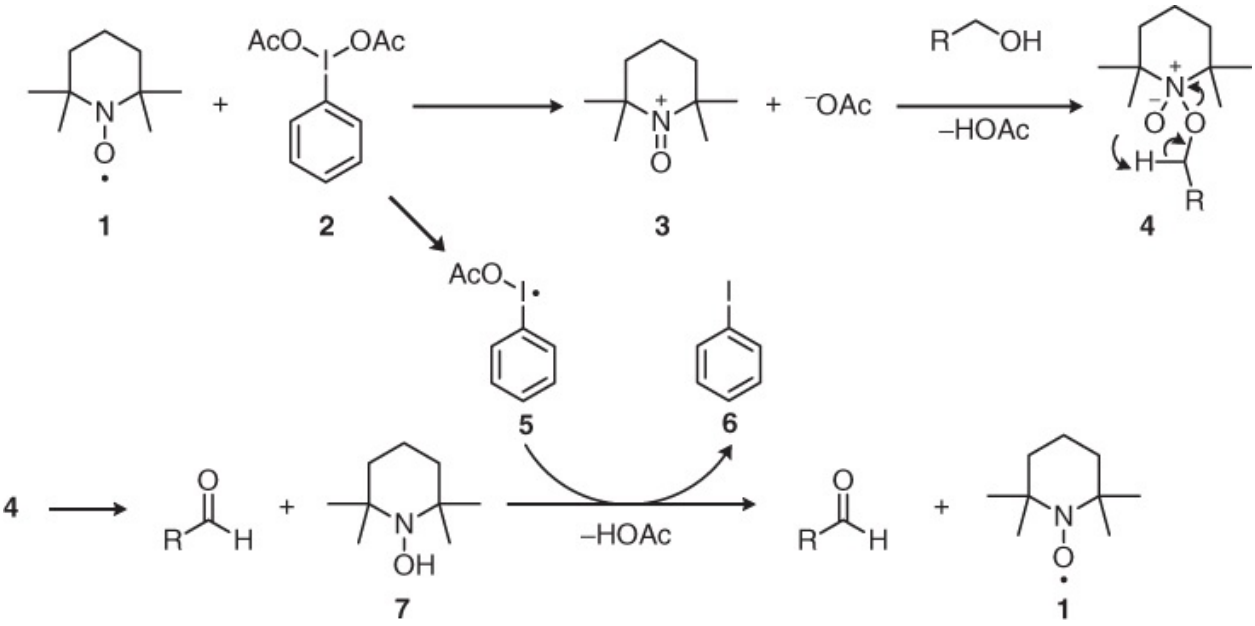
For the purification and characterization of the product and further notes, see **2.3.1.1.**

2.3.4 TEMPO Oxidation

(a) General

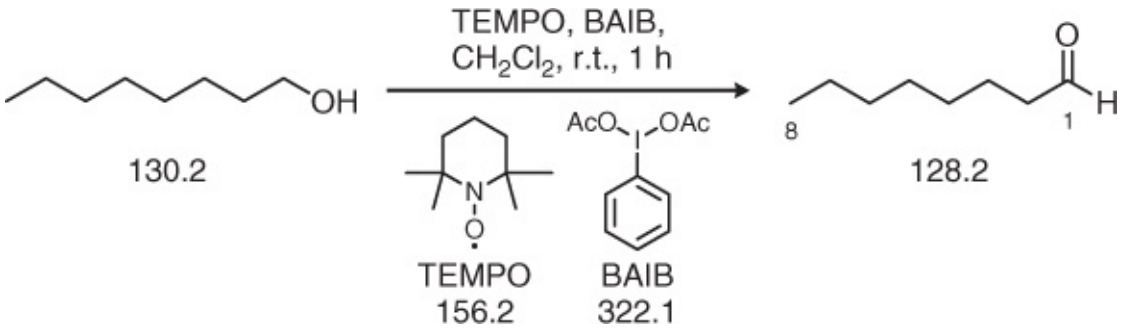
TEMPO oxidation is a highly chemoselective oxidation protocol, which makes use of (bisacetoxyiodo)benzene (BAIB, **2**) as a stoichiometric oxidant in combination with tetramethyl-piperidine-nitroxyl (TEMPO, **1**), which is applied in catalytic amounts.

In the reaction, the TEMPO nitroxyl radical **1** is first oxidized by BAIB (**2**) to the *N*-oxoammonium ion **3**, addition of the alcohol (here: RCH_2OH) to which with loss of HOAc leads to the intermediate **4**. The betaine **4** undergoes disproportionation to the carbonyl compound (here: R–CH=O) and a hydroxylamine derivative **7**, which is reoxidized to the TEMPO radical **1** by the acetoxyiodo radical **5** formed in the primary reaction step (**1** + **2**). Iodobenzene (**6**) and HOAc are also obtained in this step. Overall, in the oxidation process $RCH_2OH \rightarrow$ R–CH=O, the catalyst TEMPO is regenerated and BAIB is consumed, with the formation of iodobenzene (**6**) and acetic acid.



(b) TEMPO Oxidation of *n*-Octanol (experimental procedure)

2.3.4.1	*	***n*-Octanal IV** [7]



BAIB (272.1 mg, 0.85 mmol) is added to a stirred solution of *n*-octanol (121.4 µl, 100 mg, 0.77 mmol) and TEMPO (12.0 mg, 0.07 mmol) in CH_2Cl_2 (0.75 ml) at 20 °C, and stirring is continued for 1 h.

The mixture is then diluted with CH_2Cl_2 (0.75 ml) and washed with saturated sodium thiosulfate solution (1 ml), which is re-extracted with CH_2Cl_2 (4 × 1 ml). The combined organic layers are washed with saturated aqueous $NaHCO_3$ solution (1 ml) and brine (1 ml), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Flash column chromatography of the residue on silica gel with *n*-pentane/Et_2O (10 : 1) as eluent yields the aldehyde as a colorless liquid; 88 mg (89%), R_f = 0.54 (*n*-pentane/Et_2O, 10 : 1).

For the purification and characterization of the product and further notes, see

2.3.1.1.

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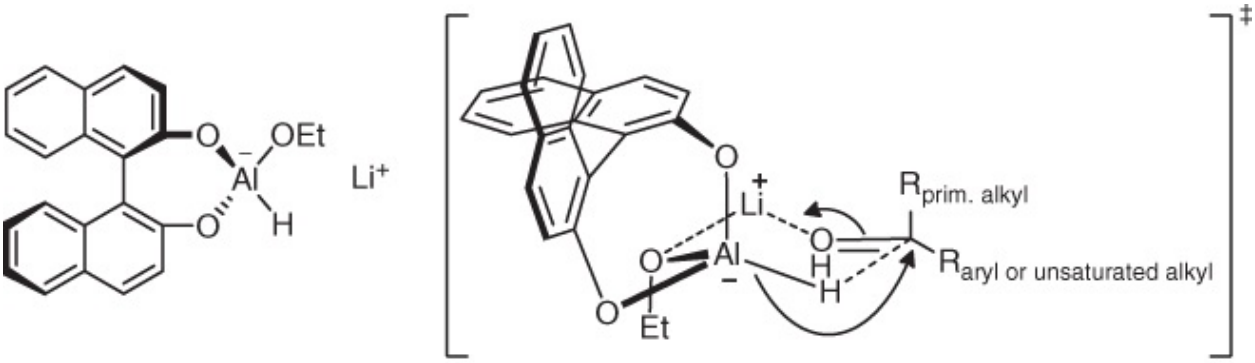
9. For comparison, see the earlier oxidation methods for *n*-octanol → *n*-octanal

in: Tietze, L.F. and Eicher, Th. (1991) *Reaktionen und Synthesen im organisch-chemischen Praktikum und Forschungslaboratorium*, 2nd edn, Georg Thieme Verlag, Stuttgart, p. 96. It should be noted that in application of the oxidation methods **2.3.1**−**2.3.4** to the above reference process, further oxidation aldehyde → carboxylic acid is suppressed.

2.4 Enantioselective Reduction of Ketones

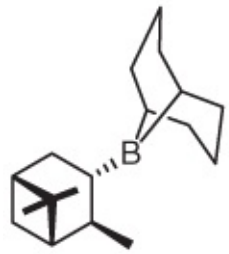
The reduction of aldehydes and ketones with aluminum and boron hydrides to give primary and secondary alcohols, respectively, is a general procedure and has found wide application in organic synthesis. For the enantioselective reduction of prochiral ketones, modified aluminum and boron hydrides associated with a chiral ligand can be employed. In addition, enzymes [1] and hydrogenations in the presence of chiral catalysts [2] have been used.

The most widely applied chiral aluminum and boron compounds are (*R*)-2,2′-dihydroxy-1,1′-binaphthyl-lithium aluminum hydride (BINAL-H) (**1**), (+)-alpine borane (**2**), diisopinocampheyl chloroborane (**3**), and the so-called Corey–Bakshi–Shibata (CBS) reagent (*R*)-**4** and their enantiomers. The reagent **1**, which was developed by Noyori and coworkers [3], has special advantages for the reduction of aryl and unsaturated ketones. It is formed *in situ* by adding an equimolar amount of (*R*)-BINOL to $LiAlH_4$, followed by 1 equiv of an alcohol, usually EtOH, although MeOH may also be used. One can assume that the reaction proceeds via the transition state TS-**1**.

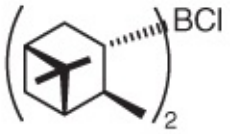


(*R*)-BINAL–H (**1**) TS-**1**

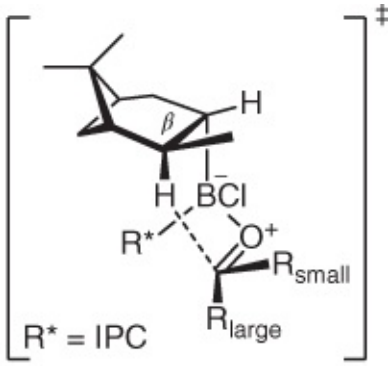
The terpene-modified boron compounds **2** and **3** developed by Midland, Brown, and coworkers [4] are very useful for the reduction of alkynyl ketones. Reagent **3** usually gives better enantiomeric cxcess values, since it is the stronger Lewis acid and therefore the proposed transition structure TS-**3** is tighter.



(+)-Alpine Borane (**2**)



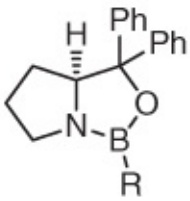
(+)-$(IPC)_2BCl$ (**3**)



TS-**3**

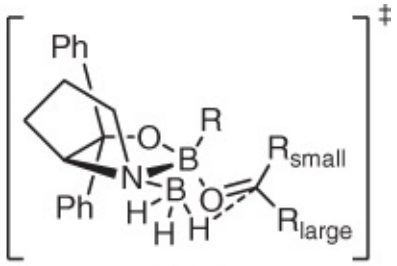
All three reagents have to be applied in equimolar amounts, which is clearly a disadvantage compared to the use of oxazaborolidine **4**, which is employed in catalytic amounts with a BH_3 derivative as the stoichiometric reducing agent. The latter reaction is based on the work of Itsuno and coworkers [5], who succeeded in reducing various ketones by employing mixtures of chiral amino alcohols and BH_3·THF.

Corey, Bakshi, and Shibata then developed the structurally defined chiral oxazaborolidines (*R*)-**4** starting from L-proline, and used them for the enantioselective reduction of prochiral ketones via the transition state TS-**4** [6].



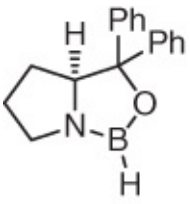
R = H, Me, *n*Bu

CBS reagent (*R*)-**4**

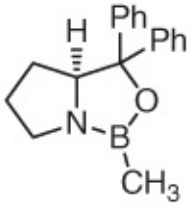


TS-**4**

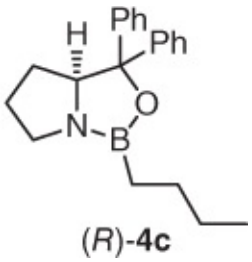
Because of its high sensitivity to air and moisture, the initially employed catalyst (*R*)-**4a** was replaced by the more stable (and therefore nowadays commonly applied) methyl and butyl derivatives (*R*)-**4b** and (*R*)-**4c**, respectively:



(*R*)-**4a**



(*R*)-**4b**



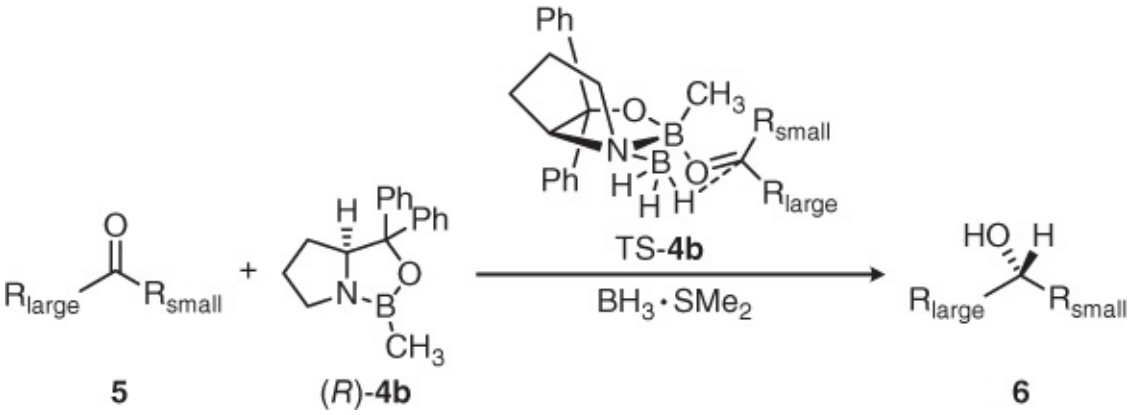
(*R*)-**4c**

As stoichiometric reducing agents, one uses borane complexes such as BH_3·THF

or $BH_3{\cdot}SMe_2$ as well as catecholborane [7]. The latter is usually applied in combination with (*R*)-**4c** at low temperatures and shows a very low "background reduction rate." In a systematic temperature assay by Stone, the best selectivities were obtained between 30 and 50 °C using catalysts (*R*)-**4b** and (*R*)-**4c** and the 1,4-thioxane-BH_3 complex [8].

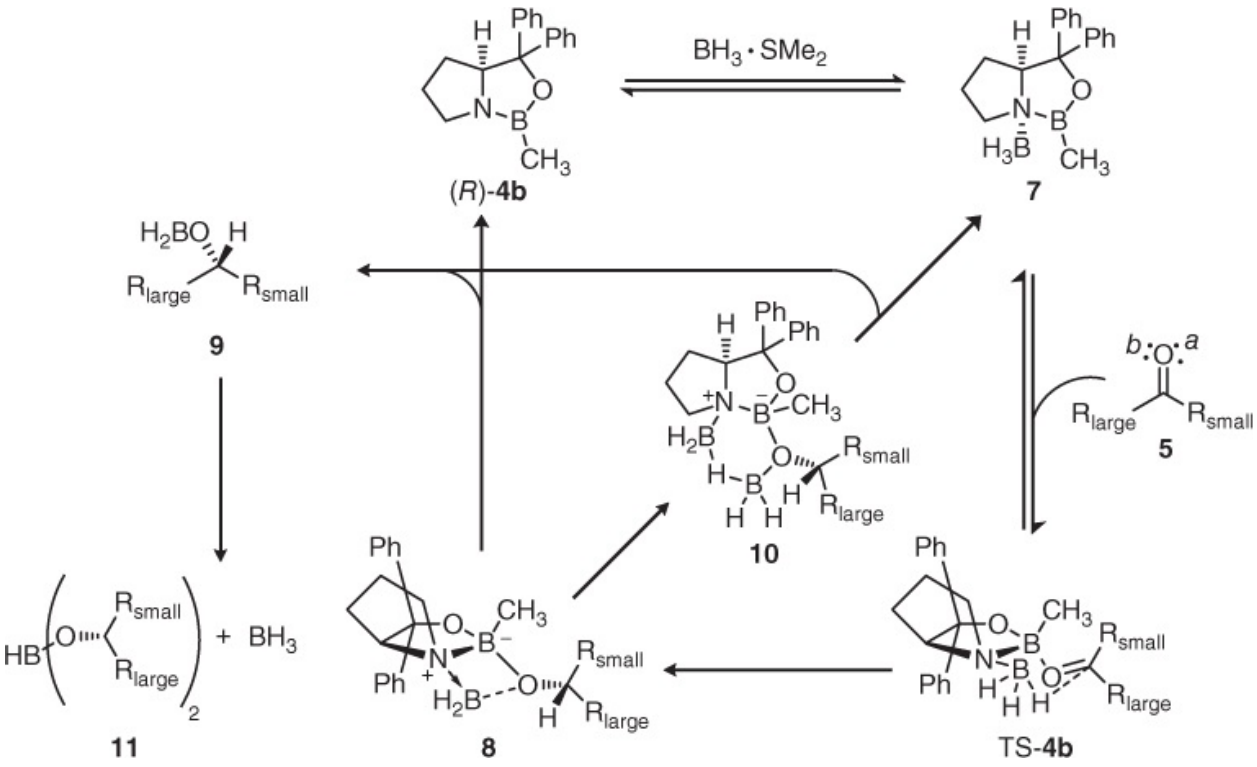
The CBS methodology has been successfully employed for a broad variety of unsymmetrically substituted carbonyl compounds, including alkyl, alkenyl, alkynyl, and aryl ketones. The observed enantioselectivities are generally high if the steric and/or electronic features of the carbonyl substituents are sufficiently different; thus, a large (R_{large}) and a small (R_{small}) substituent in substrate **5** are required [9]. In the important case of the reduction of diaryl ketones with sterically comparable substituents, high enantiomeric excess is obtained for aryl substituents with different electronic properties [9c, 10]. The stereochemical outcome of the CBS reduction can be predicted according to the reaction of **5** with (*R*)-**4b** to give **6** via TS-**4b**.

The proposed intermediates are shown in the following general mechanistic scheme [6]:

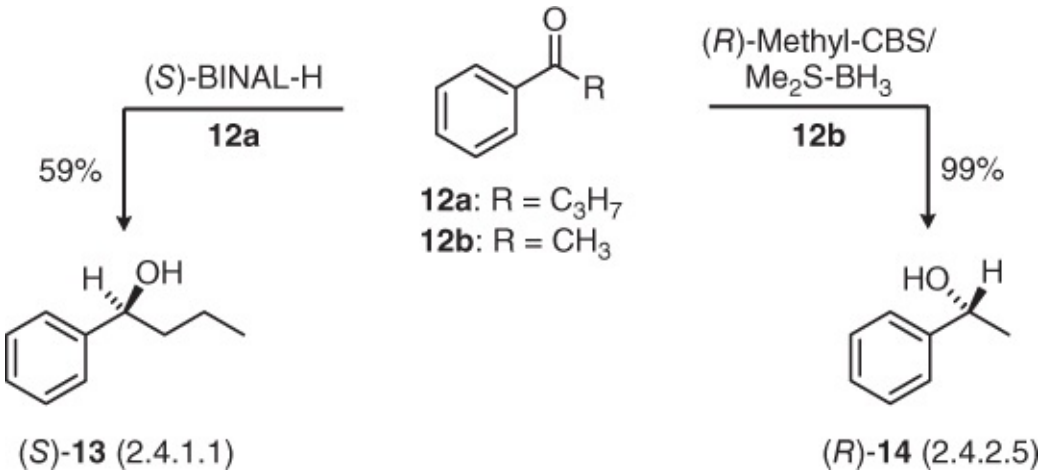


The initial step is the coordination of BH_3 to the nitrogen atom at the α face of the oxazaborolidine **4b** to form the *cis*-fused complex **7**, in which the Lewis basic nitrogen activates BH_3 as a hydride donor while the Lewis acidity of the endocyclic boron atom is strongly increased. The prochiral ketone **5** binds to the endocyclic boron atom through the sterically more accessible nonbonding electron pair *a* at the oxygen and cis to the vicinal BH_3 group to align the carbonyl group and the coordinated BH_3 in a favorable six-membered chair-like transition state TS-**4b**. The hydride transfer then takes place from above to give the complex **8**. Regeneration of the catalyst may occur by two different pathways: (i) dissociation of **8** into the catalyst **4b** and the borinate **9,** or (ii)

addition of BH_3 to **8** to form a six-membered BH_3-bridged species **10**, which decomposes to give the catalyst–BH_3 complex **7** and the borinate **9**. Facile disproportionation of **9** to afford the corresponding dialkoxyborane **11** and BH_3 permits the efficient use of the hydrogen atoms of the stoichiometric reductant. Finally, the desired chiral alcohol **6** is obtained from the dialkoxyborane **11** upon work-up with aqueous MeOH.



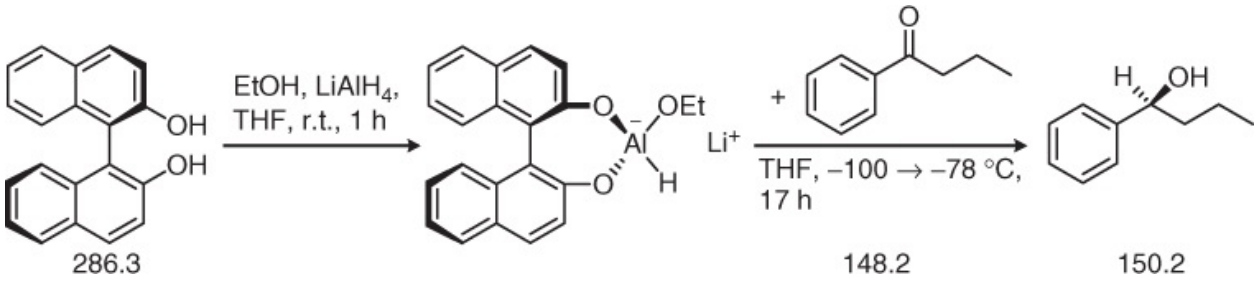
In Sections 2.4.1 and 2.4.2, details are given of the enantioselective reduction of alkyl phenyl ketones **12a**/**12b** as prochiral substrates to the corresponding benzyl alcohols **13**/**14** using the chiral complex aluminum hydride/BINAL-H **1** (prepared *in situ*) and the hydride donor combination Me_2S-BH_3/(*R*)-methyl-CBS **4b**. These two reagents give complementary results with respect to the stereochemistry of product formation: butyrophenone (**12a**) is reduced by **1** to give (*S*)-1-phenylbutanol ((*S*)-**13**), whereas acetophenone (**12b**) is reduced utilizing the CBS reagent **4b** as catalyst to give exclusively (*R*)-1-phenylethanol ((*R*)-**14**):



2.4.1 BINAL-H Reduction of Butyrophenone

The following experimental procedure describes the enantioselective reduction of butyrophenone using a stoichiometric amount of the aluminum hydrido complex obtained by reaction of (+)-(*S*)-BINOL and ethanol with $LiAlH_4$ to give almost enantiopure (−)-(*S*)-1-phenylbutanol.

2.4.1.1	***	**(−)-(*S*)-1-Phenylbutanol** [3]



A solution of EtOH (483 mg, 9.50 mmol, 0.56 ml) in THF (5 ml) is added dropwise to a stirred suspension of $LiAlH_4$ (361 mg, 9.50 mmol) in anhydrous THF (20 ml) at 0 °C under nitrogen. (−)-(*S*)-binaphthol (2.72 g, 9.50 mmol) in THF (30 ml) is then given to the mixture, which is stirred for 1 h at room temperature. After cooling to −100 °C, butyrophenone (415 mg, 2.80 mmol, 0.42 ml) in THF (5 ml) is added with stirring, and stirring is continued for 3 h at −100 °C and for 14 h at −78 °C.

At −78 °C, aqueous HCl (2 M, 32 ml) and Et_2O (100 ml) are added and the phases are separated. The aqueous phase is extracted with Et_2O (3 × 30 ml) and the combined organic phases are washed with brine, dried over Na_2SO_4, and filtered, and the solvent is removed *in vacuo*. The residue is distilled in a

Kugelrohr to give the alcohol as a colorless liquid; 250 mg (59%), bp_{14} 112 °C (oven temperature 120 °C), n^{20}_D = 1.5138, $[\alpha]^{20}_D$ = −43 (*c* = 1, benzene). The optical rotation of the pure enantiomer is $[\alpha]^{20}_D$ = −45.

Recrystallization of the residue of the distillation from benzene (Caution: carcinogenic!) allows recovery of ~80% of the (−)-(*S*)-binaphthol used.

IR (NaCl): $\tilde{\nu}$ (cm^{-1}) = 3400, 1030.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.40 –7.20 (m, 5H, Ar–H), 4.50 (t, *J* = 6.0 Hz, 1H, *C*H–OH), 3.15 (s, 1H, OH), 1.09 to 0.70 (m, 5H, CH_2, CH_3).

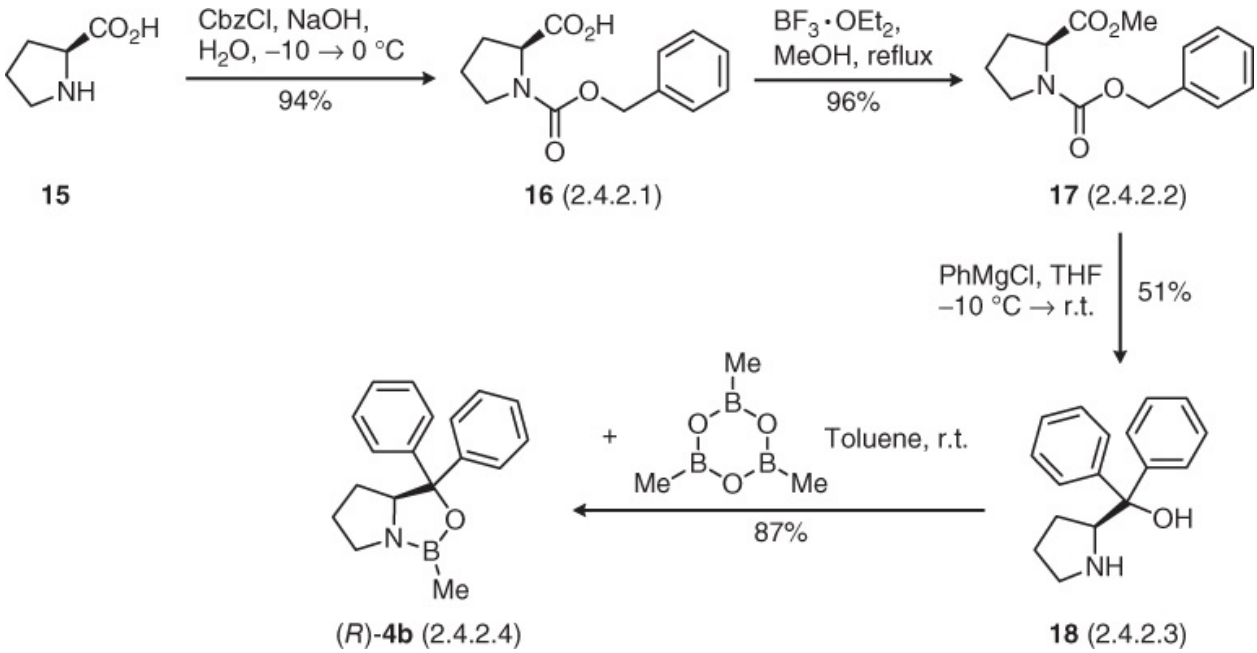
Note: It is important that the reaction is performed with strict exclusion of moisture. The flask and other apparatus must be dried at approximately 130 °C before use. Solutions are best added by means of a syringe (cannula). In several attempts to carry out this reaction, the product was found to be contaminated with butyrophenone.

2.4.2 CBS Reduction of Acetophenone

(a) Synthesis of the Methyl-CBS Catalyst (*R*)-4b

As catalyst for enantioselective reductions, methyl-CBS (*R*)-**4b** is prepared from (*S*)-proline in a linear four-step sequence [11].

In the first step, the NH function of (*S*)-proline (**15**) is protected as carbamate **16** using benzyl chloroformate (CbzCl) in alkaline aqueous solution. Formation of the methyl ester **17** is carried out using methanol in the presence of boron trifluoride etherate ($BF_3{\cdot}OEt_2$) as an activator of the carbonyl group. Grignard reaction of the *N*-Cbz-protected proline methyl ester **17** with phenylmagnesium chloride in THF directly provides the tertiary amino alcohol **18** under cleavage of the carbonyl benzyloxy protecting group. For purification, the crude product is converted into its hydrochloride salt employing HCl gas, and this is recrystallized from $MeOH/Et_2O$. Finally, the pure free amino alcohol is obtained by deprotonation of the amine hydrochloride with NaOH and recrystallization.

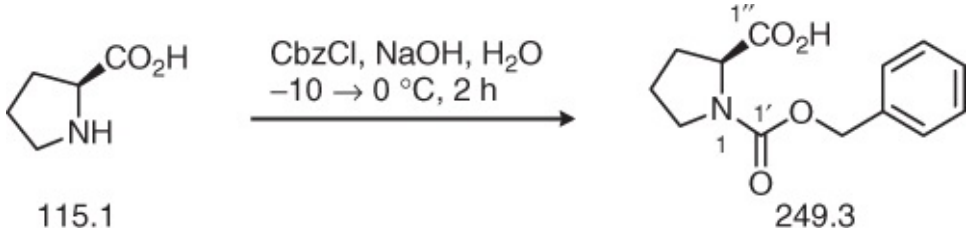


15 16 (2.4.2.1) 17 (2.4.2.2) (*R*)-**4b** (2.4.2.4) **18** (2.4.2.3)

The final step of the oxazaborolidine synthesis is the reaction of the chiral (*S*)-proline-derived amino alcohol **18** with trimethylboroxine in toluene. The desired methyl-CBS catalyst (*R*)-**4b** is obtained after high-vacuum distillation as a white solid which can be stored in closed containers at room temperature and weighed or transferred in air. In some cases, it is possible to prepare the oxaborolidine *in situ* by using a mixture of the alcohol and $BH_3{\cdot}SMe_2$ (cf. **5.2.1.1**). It should also be mentioned that the transformation of **18** to give the oxazaborolidine (*R*)-**4b** is not always easy.

(b) Experimental Procedures for the Synthesis of (*R*)-4b

2.4.2.1	**	***N*-(Benzyloxycarbonyl)-(*S*)-proline** [11]



115.1 249.3

(*S*)-Proline (23.0 g, 0.20 mol) is added to aqueous 2 M NaOH (100 ml, 0.20 mol) at −10 °C, and then benzyl chloroformate (40.9 g, 0.24 mol, 36.4 ml) is added dropwise over 1 h at −5 to 0 °C (internal thermometer). Aqueous NaOH solution (4 M, 0.28 mol, 70 ml) is then added, and stirring is continued for a further 1 h at −5 to 0 °C.

The mixture is then washed with Et_2O (2 × 50 ml). The aqueous solution is acidified to pH 2 with ice-cold aqueous 6 M HCl, then saturated with Na_2SO_4, and extracted with EtOAc (3 × 100 ml). The combined extracts are dried twice over Na_2SO_4 and filtered, and the solvent is removed *in vacuo* to give the protected proline carbamate as a colorless oil; 46.9 g (94%), $[\alpha]^{20}_D$ = −37.0 (*c* = 2.0, EtOH), R_f = 0.17 (CH_2Cl_2).

UV (CH_3CN): λ_{max} (nm) (log ϵ) = 263 (2.136), 257 (2.241), 252 (2.124), 204 (3.980).

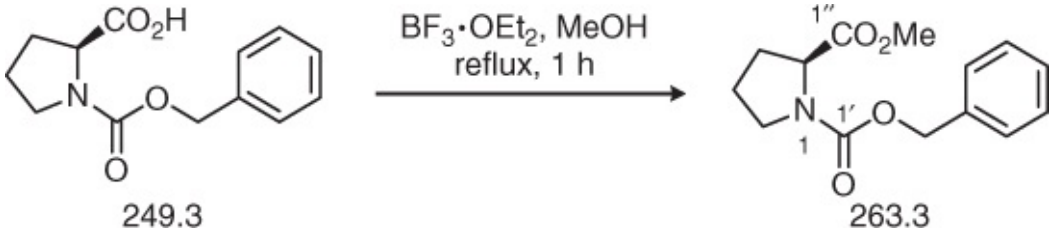
IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 2958, 1707, 1499, 1428, 1359, 1179.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 10.52 (s_{br}, 1H, CO_2H), 7.47–7.20 (m, 5H, Ph–H), 5.24–5.02 (m, 2H, Bn–H_2), 4.47–4.31 (m, 1H, 2-H), 3.70–3.37 (m, 2H, 5-H_2), 2.37–1.78 (m, 4H, 3-H_2, 4-H_2).

^{13}C NMR (76 MHz, $CDCl_3$) (ratio of rotamers: 1 : 1.5): δ (ppm) = 178.1, 176.7 (2 × C-1″), 155.6, 154.4 (2 × C-1′), 136.4, 136.3 (2 × Ph–C), 128.4, 128.3 (2 × Ph–C), 128.0, 127.9 (2 × Ph–C), 127.8, 127.6 (2 × Ph–C), 127.5, 127.0 (2 × Ph–C), 67.4, 67.1 (2 × Bn–C), 59.2, 58.6 (2 × C-2), 46.9, 46.5 (2 × C-5), 30.8, 29.4 (2 × C-3), 24.2, 23.4 (2 × C-4).

MS (EI, 70 eV): *m*/*z* (%) = 249 (12) $[M]^+$, 204 (22) $[M-CO_2H]^+$, 160 (28) $[M-C_7H_6]^+$, 114 (36) $[M-Cbz]^+$, 91 (100) $[C_7H_7]^+$.

2.4.2.2	**	***N*-(Benzyloxycarbonyl)-(*S*)-proline methyl ester** [11]



Under an argon atmosphere, $BF_3{\cdot}OEt_2$ (28.4 g, 0.203 mol, 24.6 ml) is added to a stirred solution of the proline carbamate **2.4.2.1** (33.7 g, 135 mmol) in anhydrous MeOH (400 ml). The resulting solution is heated to reflux for 1 h.

The solvent is removed *in vacuo*, and the residue is stirred with iced water (200 ml) and extracted with EtOAc (3 × 100 ml). The combined extracts are

successively washed with brine (100 ml), aqueous $NaHCO_3$ (1 M, 100 ml), and brine (100 ml), dried over Na_2SO_4, and filtered. The solvent is removed *in vacuo* to yield the Cbz-protected proline methyl ester as a colorless oil; 34.2 g (96%), $[\alpha]^{20}_D$ = −55.7 (*c* = 1.0, MeOH), R_f = 0.32 (CH_2Cl_2).

UV (CH_3CN): λ_{max} (nm) (log ϵ) = 267 (2.177), 263 (2.335), 257 (2.442), 252 (2.368), 204 (3.994).

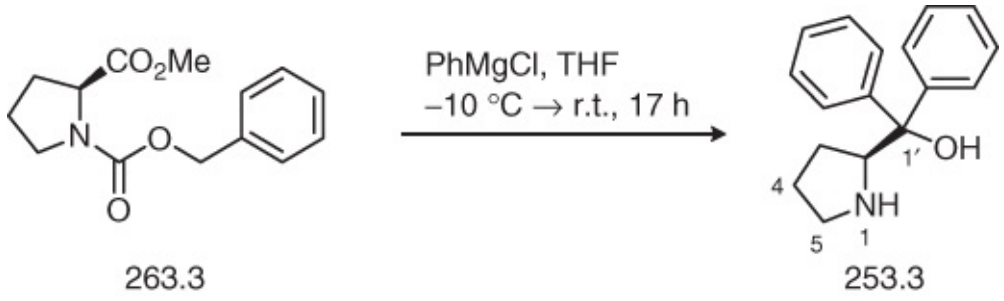
IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3479, 3033, 2954, 2882, 1748, 1707, 1416.

^{1}H NMR (300 MHz, $CDCl_3$) (ratio of rotamers: 1 : 1): δ (ppm) = 7.43–7.23 (m, 5H, Ph–H), 5.25–5.00 (m, 2H, Bn–H), 4.45–4.30 (2 dd, not resolved, 1H, 2-H), 3.74, 3.58 (2 × s, 2 × 3H, OCH_3), 3.65–3.37 (m, 2H, 5-H_2), 2.33–2.11 (m, 1H, 3-H_A), 2.09–1.81 (m, 3H, 3-H_B, 4-H_2).

^{13}C NMR (76 MHz, $CDCl_3$) (ratio of rotamers: 1 : 1): δ (ppm) = 173.2, 173.1 (2 × C-1″), 154.8, 154.2 (2 × C-1′), 136.6, 136.5 (2 × Ph–C), 128.4, 128.3 (2 × Ph–C), 128.3, 128.1 (2 × Ph–C), 127.9, 127.8 (2 × Ph–C), 127.8, 127.7 (2 × Ph–C), 127.4, 126.9 (2 × Ph–C), 66.9, 66.9 (2 × Bn–C), 52.2, 52.0 (2 × C-2), 46.8, 46.3 (2 × C-5), 30.8, 29.8 (2 × C-3), 24.2, 23.5 (2 × C-4).

MS (EI, 70 eV): *m*/*z* (%) = 263 (4) $[M]^+$, 204 (10) $[M-CO_2CH_3]^+$, 160 (12) $[M-CH_3-C_7H_6]^+$, 108 (100) $[M-C_7H_8O]^+$, 91 (46) $[C_7H_7]^+$, 77 (30) $[C_6H_5]^+$.

2.4.2.3	***	**(*S*)-2-(Diphenylhydroxymethyl)pyrrolidine** [11]



263.3 253.3

Under an argon atmosphere, a solution of the Cbz-protected proline methyl ester **2.4.2.2** (26.3 g, 100 mmol) in anhydrous THF (100 ml) is added to a stirred 2 M solution of phenylmagnesium chloride in THF (400 ml, 800 mmol) over 1 h at

−10 to 0 °C. The cooling bath is then removed, and stirring is continued for 16 h. The reaction mixture is then poured onto a mixture of ice (300 g), NH_4Cl (60 g), and H_2O (100 ml), and the resulting mixture is concentrated *in vacuo* to a volume of about 500 ml. After extraction with Et_2O (4 × 300 ml), the combined extracts are washed with brine (400 ml), dried over anhydrous K_2CO_3, and concentrated under reduced pressure to a volume of about 500 ml. Anhydrous HCl gas is then bubbled into the solution until the mixture is acidic. The precipitated amine hydrochloride is collected by filtration, washed with Et_2O, and recrystallized from MeOH/Et_2O (1 : 4). The hydrochloride is then suspended in Et_2O (300 ml) and treated with aqueous NaOH (2 M, 60 ml) for 45 min. The resulting solution is extracted with Et_2O (3 × 200 ml). The combined extracts are washed with brine (400 ml), dried over anhydrous K_2CO_3, and concentrated under reduced pressure to give a yellow solid, which is recrystallized from MeOH/H_2O to afford the pyrrolidine as colorless crystals; 12.7 g (51%), $[\alpha]^{20}_D$ = −56.0 (*c* = 3.0, MeOH), R_f = 0.34 (EtOAc).

UV (CH_3CN): λ_{max} (nm) (log ϵ) = 258 (2.678), 252.5 (2.619), 201.5 (4.365).

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3406, 3329, 2972, 1493, 1446, 1403.

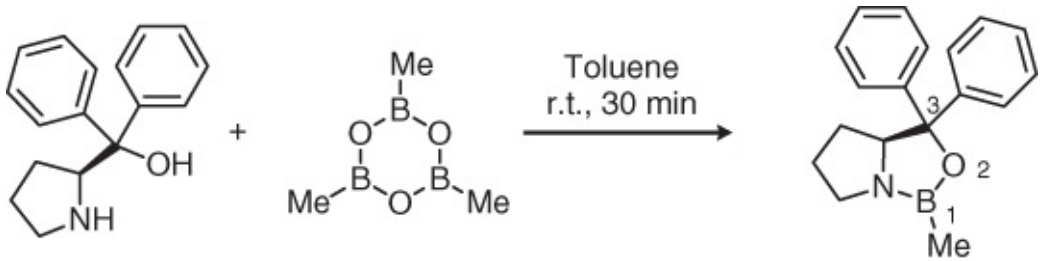
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.65–7.42 (m, 4H, Ph–H), 7.37–7.05 (m, 6H, Ph–H), 4.31–4.17 (m, 1H, 2-H), 3.09–2.84 (m, 2H, 5-H_2), 1.83–1.45 (m, 4H, 4-H_2, 3-H_2).

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 148.2, 145.4, 128.2, 127.9, 126.4, 126.3, 125.8, 125.5 (12 × Ph–C), 77.1 (C-1′), 64.5 (C-2), 46.7 (C-5), 26.3 (C-3), 25.5 (C-4).

MS (DCI): *m*/*z* (%) = 254 (100) $[M+H]^+$.

Note: **2.4.2.3** is also used in **5.2.1.1**.

2.4.2.4	***	**(*S*)-2-Tetrahydro-1-methyl-3,3-diphenyl-1*H*,3*H*-pyrrolo[1,2-*c*][1,3,2]**
		oxazaborolidine [11]



253.3 125.5 277.2

Under an argon atmosphere, trimethylboroxine (0.33 g, 2.64 mmol) is added to a solution of the pyrrolidine **2.4.2.3** (1.00 g, 3.95 mmol) in anhydrous toluene (10 ml). After 2 min, a white precipitate is formed.

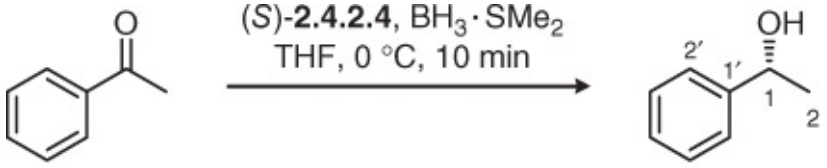
After 30 min, further toluene (10 ml) is added, and a portion of toluene (13 ml) is distilled off for azeotropic removal of trimethylboroxine (with air cooling to avoid crystallization of the trimethylboroxine). Fresh toluene (10 ml) is added, and the mixture is distilled to dryness; the process is repeated once more. The obtained yellow oil is distilled (150 °C, 0.05 mbar, sublimation apparatus) to give the oxazaborolidine as a white solid; 0.95 g (87%).

MS (EI, 70 eV): *m*/*z* (%) = 277 (72) $[M]^+$, 165 (60) $[C_8H_{12}BNO_2]^+$, 70 (100) $[C_4H_8N]^+$.

(c) CBS Reduction of Acetophenone

As a standard procedure, the enantioselective reduction of acetophenone to give almost enantiopure (*R*)-(+)-1-phenylethanol is described, which involves the use of a catalytic amount of methyl-CBS and a stoichiometric amount of borane dimethyl sulfide complex.

2.4.2.5	**	**(+)-(*R*)-1-Phenylethanol** [9a]



120.1 122.2

A solution of acetophenone (240.3 mg, 2.00 mmol) in THF (20 ml) is added to a stirred ice-cold solution of the oxazaborolidine **2.4.2.4** (55.4 mg, 200 µmol) and borane dimethyl sulfide complex (2 M in THF, 600 µl, 1.20 mmol) in THF (20

ml). Stirring is continued at 0 °C for 10 min.

MeOH (2 ml) is then added, the solvent is removed *in vacuo*, and the residue is adsorbed on silica (0.5 g). After column chromatography eluting with CH_2Cl_2, the phenylethanol is obtained as a colorless liquid; 241.8 mg (99%), ee = 97.3%, $[\alpha]^{20}_D$ = +41.0 (*c* = 5.0, MeOH), R_f = 0.37 (CH_2Cl_2).

UV (CH_3OH): λ_{max} (nm) (log ϵ) = 263 (2.339), 257 (2.441), 252 (2.381), 247 (2.299), 207 (3.970).

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3354, 2973, 2927, 1603, 1493, 1452, 1302, 1204, 1078.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.39–7.22 (m, 5H, Ph–H), 4.86 (q, 1H, *J* = 6.3 Hz, 1H, 1-H), 2.09 (1H, OH), 1.48 (d, *J* = 6.3 Hz, 3H, 2-H).

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 145.8 (C-1′), 128.4 (C-3′, C-5′), 127.4 (C-4′), 125.3 (C-2′, C-6′), 70.3 (C-1), 25.1 (C-2).

MS (EI, 70 eV): *m*/*z* (%) = 122 (44) $[M]^+$, 107 (100) $[C_7H_7]^+$, 79 (87) $[C_6H_7]^+$.

GC: column: wall-coated open tubular (WCOT) fused silica CP-Chiralsil-DEX CB (25 m × 0.25 mm)

carrier: H_2

temperature: 135 °C

retention time: t_{R1} = 1.04 min (major enantiomer)

t_{R2} = 1.11 min (minor enantiomer).

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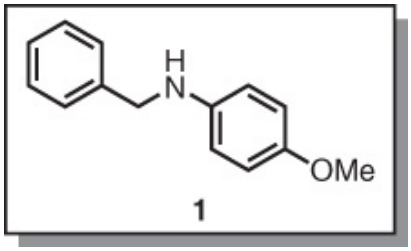
2.5 Biomimetic Reductive Amination

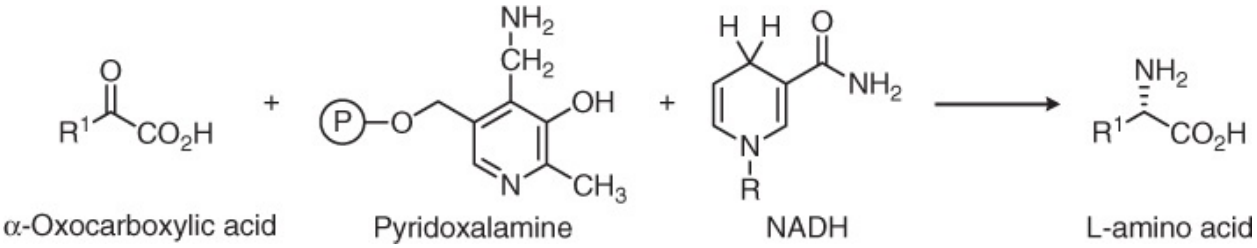
2.5.1 Synthesis of Benzyl-4-methoxyphenylamine

 1	***Topics:***	• Reductive amination • Synthesis of Hantzsch 1,4-

		dihydropyridines

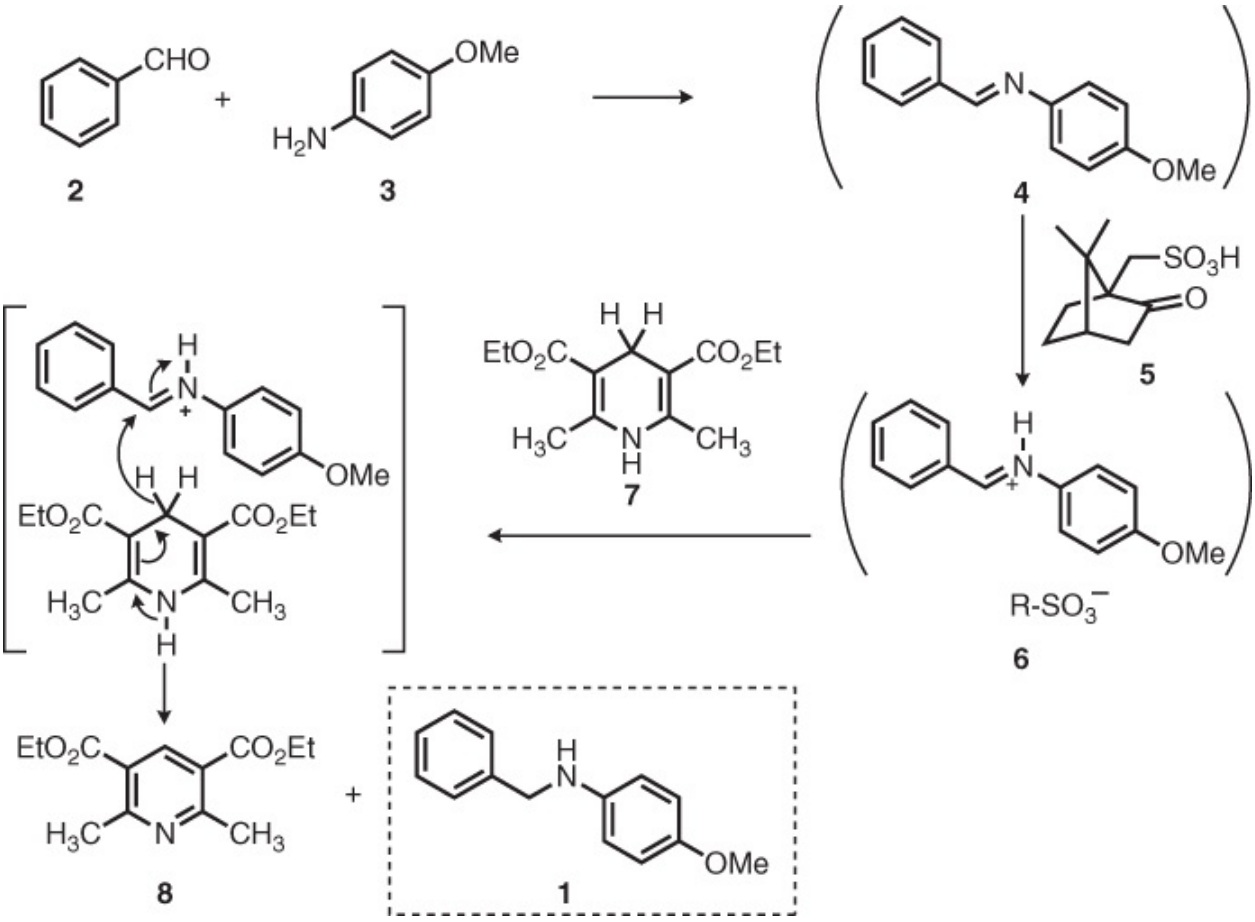
(a) General

The reductive amination of α-oxocarboxylic acid to give α-amino acids is a very important process in Nature. In this reaction, an imine is intermediately formed by reaction of the α-oxocarboxylic acid with pyridoxalamine, which is then reduced using a dihydropyridine cosubstrate such as nicotinamide adenine dinucleotide (NADH) [1].



Nowadays, the reductive amination of any type of aldehyde and ketone is a general procedure for the synthesis of preferentially secondary and tertiary amines. In most cases, sodium cyanoborohydride [2] at pH 3–4 or sodium triacetoxyborohydride [3] are employed. But many other procedures are also known as the use of Pd/C and other transition-metal catalysts in the presence of hydrogen, $B_{10}H_{14}$, HCO_2NH_4, and isopropanol [4]. In some cases, also $NaBH_4$ and $Et_3SiH/InCl_3$ [5] are useful reagents. A very mild procedure is the biomimetic reductive amination using thiourea and a Hantzsch ester [6]. Herein, we describe a reductive amination of benzaldehyde and 4-methoxyaniline in the presence of a 1,4-dihydropyridine and a Brønsted acid (M. Rueping, M. Leiendecker, and A. Teppler, personal communication, **2013)**. The process is also very suitable for an enantioselective transformation using a chiral Brønsted acid [7].

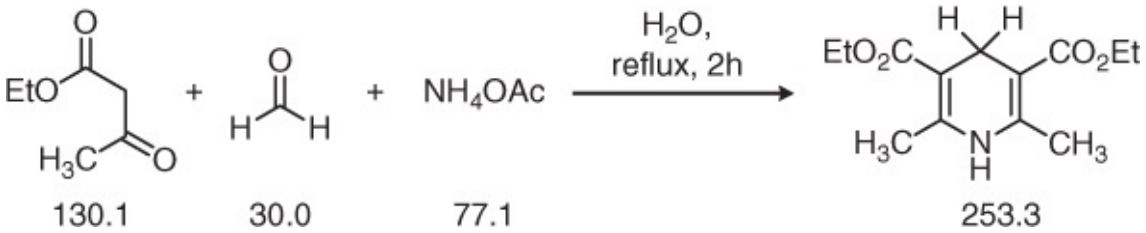
In the one-pot reaction of benzaldehyde (**2**) with 4-methoxyaniline (**3**), the imine (**4**) is formed which gives the more reactive iminium salt **6** by protonation with camphorsulfonic acid (**5**). The iminium salt (**6**) then reacts with the 1,4-dihydropyridine **7** in a hydrogen transfer reaction whereby **7** takes over the role of the nicotinamide adenine dinucleotide phosphate (NADPH) in the biological process with the formation of the corresponding pyridine **8**, which must be removed after the completion of the process by chromatography. As the desired product, the secondary amine **1** is formed.



The 1,4-dihydropyridine can easily be obtained by a four-component domino process using ethyl acetoacetate, formaldehyde, and an ammonium salt according to the method developed by Hantzsch [8] (see also **3.4.1.1**).

(b) Experimental Procedures for the Synthesis of 1[1]

2.5.1.1	**	**Diethyl 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate**

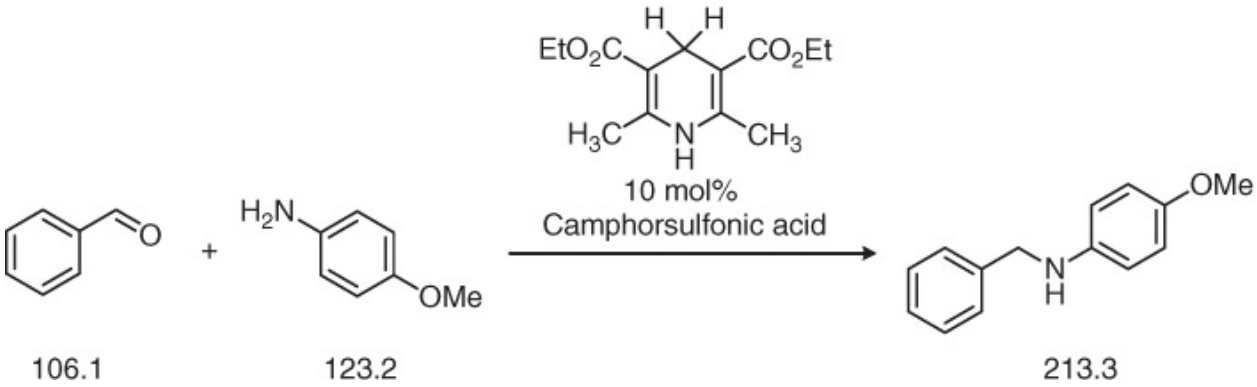


A stirred mixture of ethyl acetoacetate (3.81 ml, 3.89 g, 29.9 mmol), aqueous formaldehyde (37%) (0.56 ml, 0.60 g, 7.46 mmol), and ammonium acetate (1.16 g, 15.0 mmol) in water (15 ml) is heated to reflux for 2 h. After cooling to room temperature, the solid is collected by filtration and washed with cold water (3 ×

10 ml). Drying *in vacuo* gives the pure product as pale-yellow solid; 1.71 g, 90%, mp 166–168 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 5.07 (s_{br}, 1H, NH), 4.15 (q, *J* = 7.2 Hz, 4H, 2 × $CO_2CH_2CH_3$), 3.25 (s, 2H, 4-H_2), 2.18 (s, 6H, 2 × CH_3), 1.27 (t, *J* = 7.2 Hz, 6H, 2 × $CO_2CH_2CH_3$).

2.5.1.2	**	**Benzyl-(4-methoxyphenyl)amine**



A solution of benzaldehyde (0.30 ml, 320 mg, 3.02 mmol), *p*-anisidine (372 mg, 3.02 mmol), camphorsulfonic acid (69.7 mg, 0.30 mmol), and 1,4-dihydropyridine **2.5.2.1** (1.01 g, 3.99 mmol) in THF (40 ml) is stirred for 16 h at room temperature.

After addition of dichloromethane (30 ml) and saturated aqueous $NaHCO_3$ (20 ml), the organic phase is separated and the aqueous phase extracted with dichloromethane (4 × 30 ml). The combined organic phases are washed with brine, dried over Na_2SO_4, and filtered. After removal of the solvent *in vacuo*, the residue is purified by chromatography on silica gel (toluene/ethyl acetate) = 10 : 1; R_f (product) = 0.52; R_f (Hantzsch pyridine) = 0.19. The product is obtained as yellow oil (505 mg, 79%).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.37–7.22 (m, 5H, Ar), 6.77 (d, *J* = 12 Hz, 2H, Ar), 6.60 (d, *J* = 8 Hz, 2H, Ar), 4.30 (s, 2H, $NHCH_2$), 3.83 (s, 1H, NH), 3.75 (s, 3H, OCH_3).

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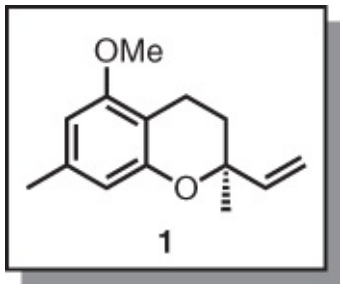
2.6 Enantioselective Wacker Oxidation

2.6.1 (*S*)-5-Methoxy-2,7-dimethyl-2-vinylchroman



1

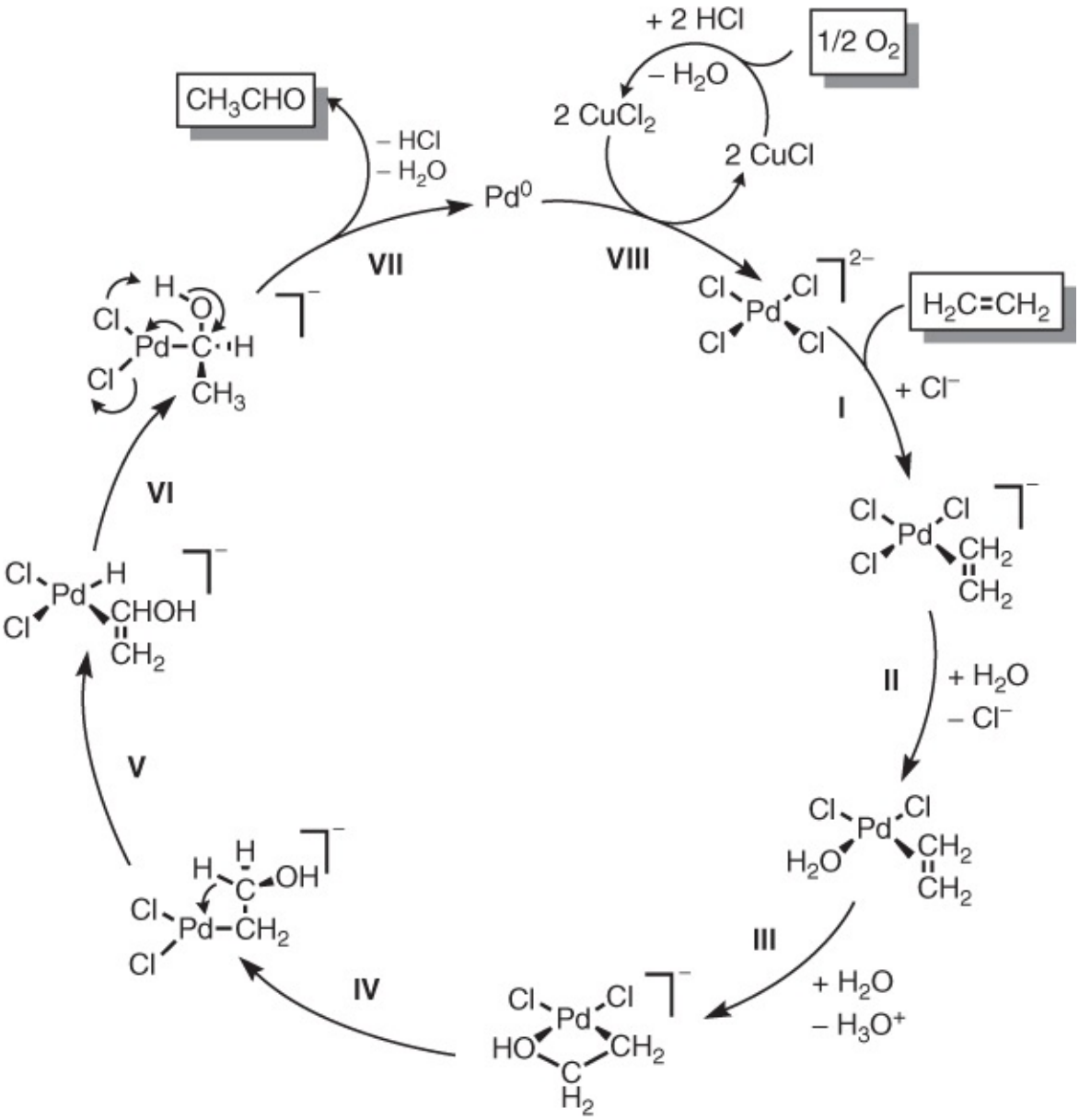
Topics:

- O-Alkylation of a phenol
- Formylation
- Aldol reaction

		• Wittig reaction • Radical bromination • Pinnick oxidation • Glaser coupling • Enantioselective Wacker oxidation

(a) General

The Wacker oxidation [1] is an industrial Pd(II)-catalyzed process, in which ethylene is transformed into acetaldehyde in the presence of CuCl and oxygen according to the following catalytic cycle in the case of a low concentration of Cl^-:



The mechanism is still under discussion and may be different for different concentrations of the reaction partners. The general equation is given below:

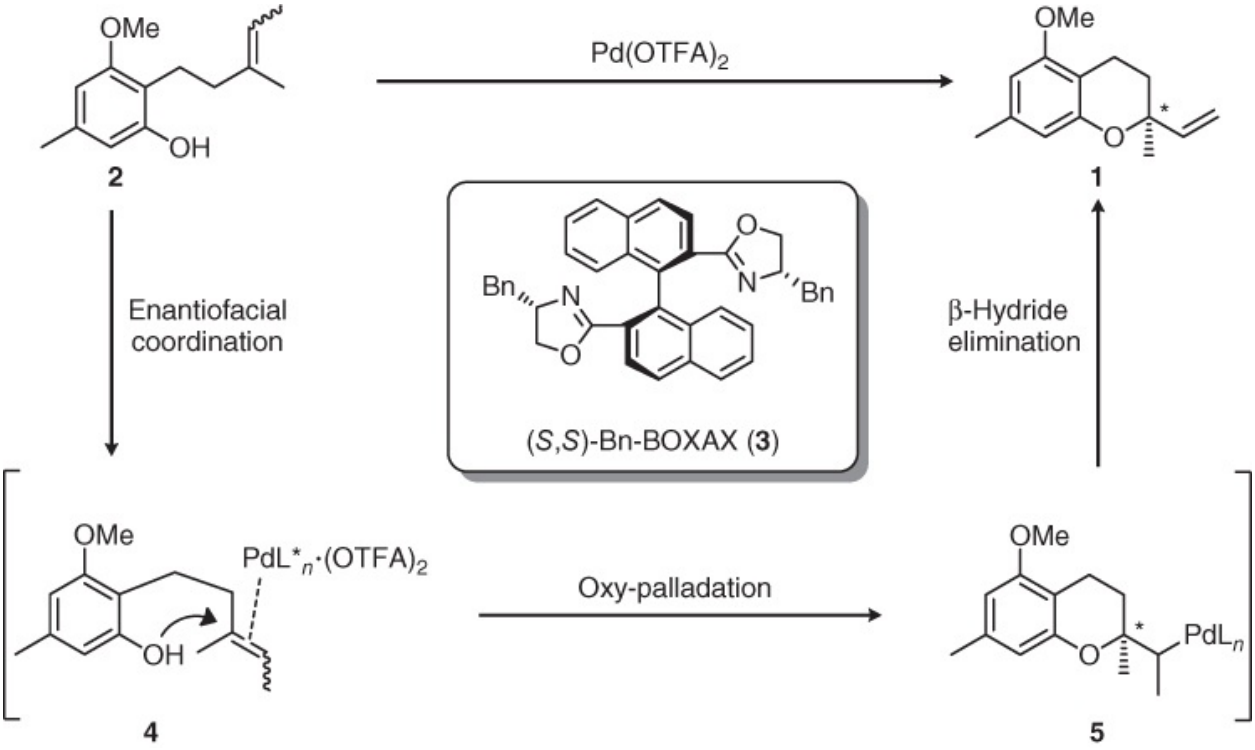
$$[PdCl_4]^{2-} + C_2H_4 + H_2O \rightarrow CH_3CHO + Pd + 2\,HCl + 2\,Cl^-$$

$$Pd + 2\,CuCl_2 + 2\,Cl^- \rightarrow [PdCl_4]^{2-} + 2\,CuCl$$

$$2\,CuCl + \frac{1}{2}\,O_2 + 2\,HCl \rightarrow 2\,CuCl_2 + H_2O$$

The Wacker oxidation is also usable for the synthesis of heterocycles such as the chroman **1** using the alkenyl phenol **2** as starting material [2]. To perform an enantioselective reaction, the 2,2'- bis(oxazolin-2-yl)-1,1'-binaphthyl (BOXAX) ligand **3** can be employed [3], which allows a facial selective nucleophilic

addition of the phenolic hydroxyl group to the C=C bond after an enantiofacial coordination with the *in situ* formed Pd(II)L* complex with 87% ee via **4** and **5**. The enantioselectivity of the Wacker oxidation could be improved to 93% ee by employing the pure (*E*)-compound, whereas the (*Z*)-compound gave 83% ee. However, the separation of the (*E*/*Z*)-mixture of **2** by chromatography is rather tedious and not practicable for larger amounts. On the other hand, using the corresponding *iso*-propyl-BOXAX ligand (**3**, *iso*-propyl instead of Bn), 96% ee can be obtained even using a (*E*/*Z*)-mixture [4].

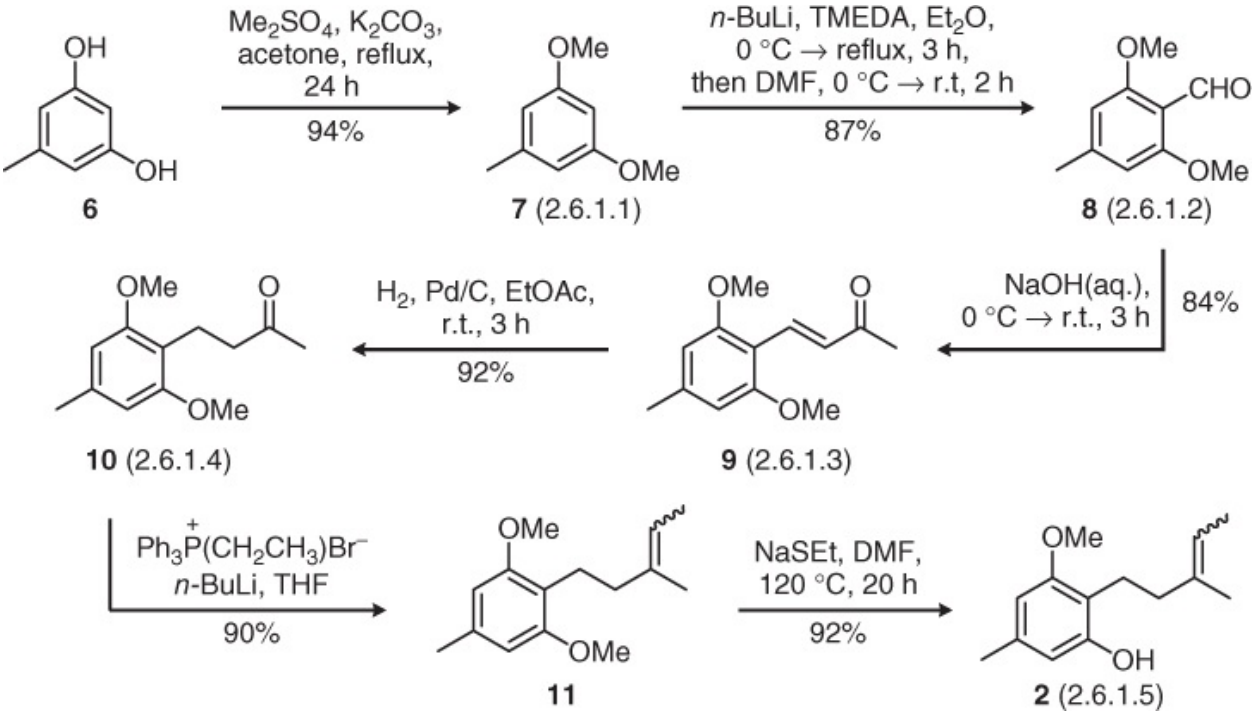


(b) Synthesis of 1

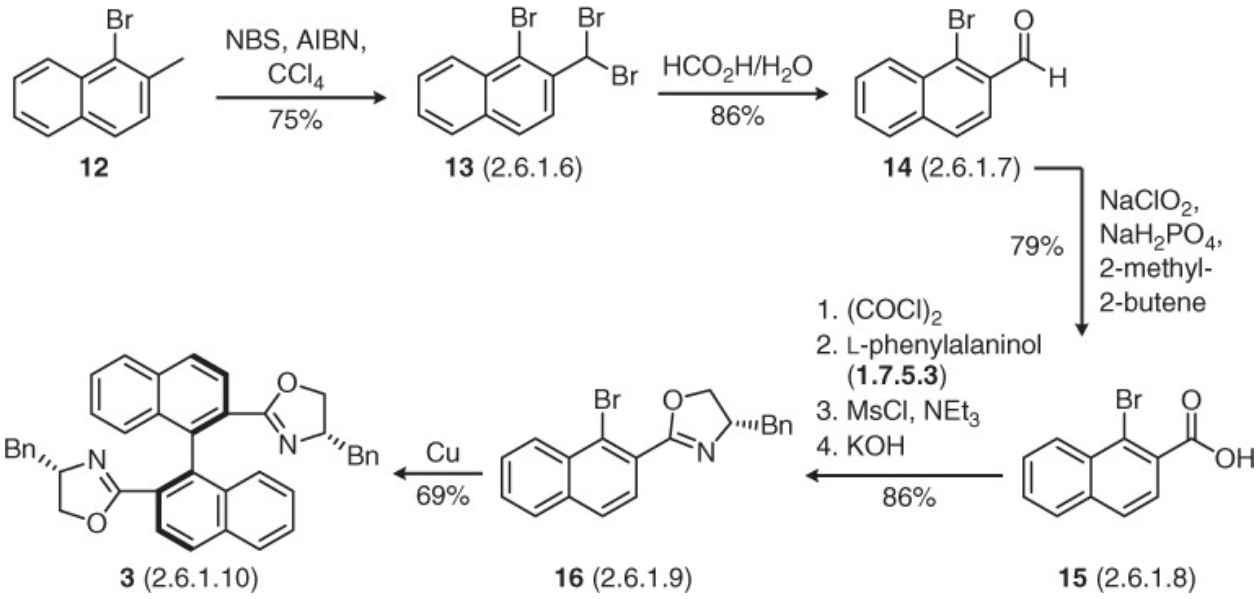
For the synthesis of **1**, the precursor **2** for the Wacker oxidation is prepared starting from commercially available orcinol (**6**), which is transformed into the dimethyl ether **7 (2.6.1.1)** by treatment with dimethylsulfate and potassium carbonate via the corresponding phenolate anions [5]. Treatment with *n*-BuLi and TMEDA (tetramethylethylendiamine) followed by addition of dimethylformamide (DMF) leads to the benzaldehyde **8** (**2.6.1.2**) [6]. As intermediate in this transformation, the corresponding aryl lithium compound is formed *in situ* which is stabilized by chelation with the two methoxy groups. The following nucleophilic addition to formamide leads to a formyl group after aqueous work-up. It follows an aldol condensation with acetone to give the α,β-unsaturated ketone **9** (**2.6.1.3**). After hydrogenation of the double bond using

palladium on charcoal to afford **10** (**2.6.1.4),** a Wittig reaction is performed to give the alkene **11** (**2.6.1.5**) as an (*E/Z*)-mixture.

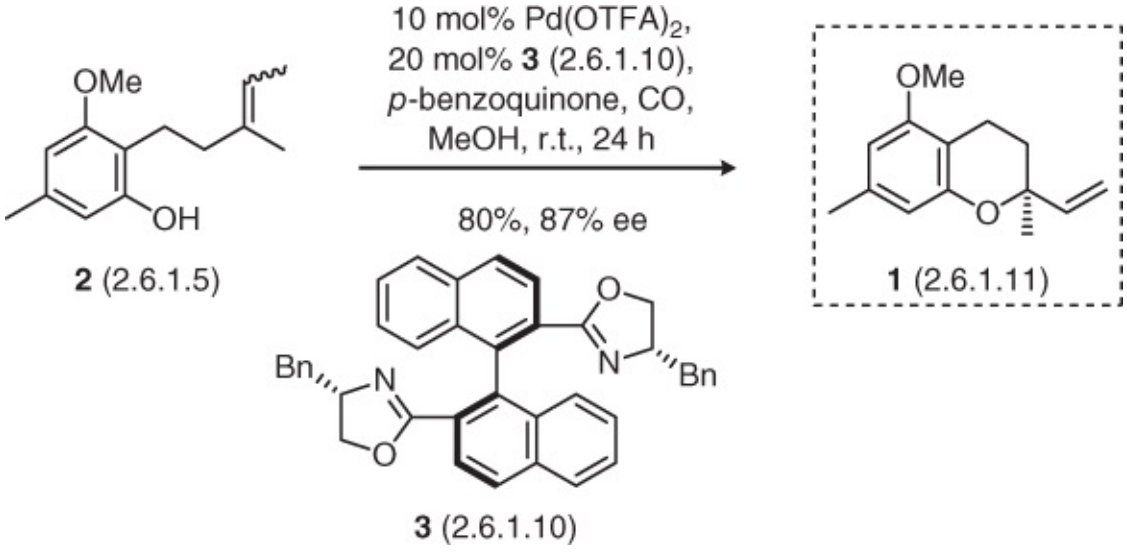
The final step in the preparation of substrate **2** (**2.6.1.5)** for the enantioselective Wacker oxidation is the selective cleavage of one of the methyl ether moieties in **11** using sodium ethylthiolate. The selectivity in this nucleophilic substitution is caused by the intermediate formation of a phenolate anion, which prohibits a second attack of the thiolate because of electrostatic repulsion.



The BOXAX ligand **3** (**2.6.1.10**) [3] for the enantioselective Wacker oxidation is synthesized in five steps starting from commercially available 1-bromo-2-methylnaphthalene (**12**), which is transformed via radical bromination into **13** (**2.6.1.6**). Subsequent formation of the aldehyde **14** (**2.6.1.7**) using aqueous formic acid followed by Pinnick oxidation [6] yields acid **15** (**2.6.1.8**). Cyclocondensation of **15** and L-phenylalaninol (**1.8.5.3**) gives the oxazoline **16** (**2.6.1.9**), which is dimerized in a Glaser coupling to afford Bn-BOXAX **3** (**2.6.1.10**).

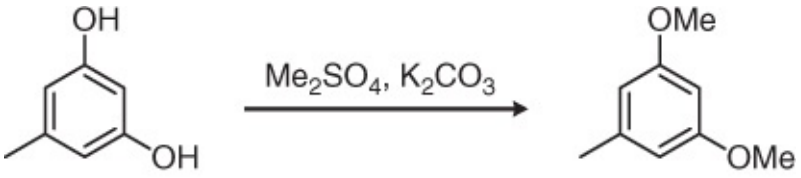


For the enantioselective Wacker oxidation of **2** (**2.6.1.5**) in the presence of the Bn-BOXAX ligand **3** (**2.6.1.10**), catalytic amounts of palladium(II)trifluoroacetate [$Pd(OTFA)_2$] in methanol as solvent are used to give **1** (**2.6.1.11**) in 80% yield and 87% ee. In this process, *p*-benzoquinone is employed to oxidize the formed Pd^0 into Pd^{II} needed for the Wacker oxidation.



(c) Experimental Procedures for the Synthesis of 1

2.6.1.1	**	**1,3-Dimethoxy-5-methylbenzene** [5]



124.1 152.2

Dimethyl sulfate (54.0 ml, 72.4 g, 575 mmol; Caution: carcinogenic!) is added dropwise to a stirred mixture of orcinol monohydrate (**6**) (35.5 g, 250 mmol) and anhydrous K_2CO_3 (70.0 g, 507 mmol) in acetone (500 ml) at room temperature. The resulting mixture is heated at reflux for 24 h before being treated with concentrated aqueous NH_3 solution (25 ml) and heated for further 15 min.

After cooling to room temperature, the mixture is filtered and the filtrate is concentrated *in vacuo*. The residue is dissolved in water (400 ml) and Et_2O (100 ml), the layers are separated, and the aqueous layer is extracted with Et_2O (2 × 100 ml). The combined organic layers are washed with water (100 ml), 3 M aqueous NaOH solution (2 × 100 ml), and brine (100 ml). The organic layer is dried over $MgSO_4$, filtered, and the solvent is removed *in vacuo*. Distillation *in vacuo* yields orcinol dimethyl ether (**2.6.1.1**) as a colorless liquid; 35.8 g (94%). R_f = 0.56 (*n*-pentane/EtOAc 9 : 1); bp 110–112 °C (20 mbar).

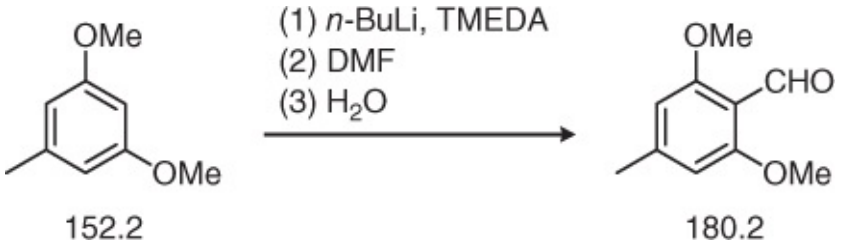
IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3059, 2955, 2838, 1597, 1461, 1321, 1295, 1205, 1151, 1070, 921, 828, 686.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 6.35 (m_c, 2H, 4-H, 6-H), 6.30 (m_c, 1H, 2-H), 3.78 (s, 6H, 2 × OCH_3), 2.32 (s, 3H, Ar–CH_3).

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 160.7 (C-1, C-3), 140.2 (C-5), 107.1 (C-4, C-6), 97.5 (C-2), 55.2 (OCH_3), 21.8 (Ar–CH_3).

MS (70 eV, EI): *m*/*z* (%): 152.2 (100) $[M]^+$, 123.1 (37) $[M-2CH_3+H]^+$.

2.6.1.2	***	**2,6-Dimethoxy-4-methylbenzaldehyde** [7]



152.2 180.2

n-Butyllithium (32.4 ml of a 2.5 M solution in *n*-hexane, 81.0 mmol) is added dropwise to a solution of orcinol dimethyl ether (**2.6.1.1**) (10.3 g, 67.4 mmol) and TMEDA (20.4 ml, 15.7 g, 135 mmol) in Et_2O (100 ml) at 0 °C. The resulting mixture is heated at reflux for 3 h before being cooled to 0 °C and treated dropwise with DMF (19.0 ml, 203 mmol). Stirring is continued at room temperature for further 2 h.

The reaction is quenched with water (300 ml). After separation of the organic layer, the aqueous layer is extracted with EtOAc (2 × 100 ml). The combined organic layers are dried over Na_2SO_4 and filtered, and the solvent is removed *in vacuo*. Column chromatography on silica gel (*n*-pentane/EtOAc 7 : 3) provides the aldehyde **2.6.1.2** as a pale yellow solid; 10.6 g (87%). R_f = 0.28 (*n*-pentane/EtOAc 7 : 3). (Caution: Sensitive to oxygen; should not be stored for a long period).

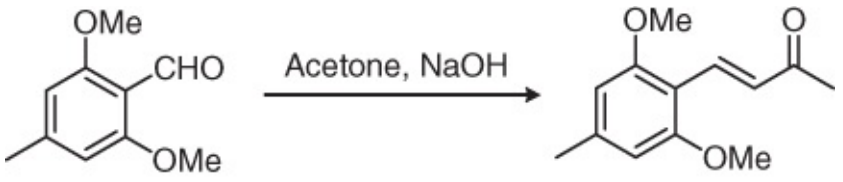
IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3026, 2974, 2787, 1668, 1611, 1241, 1124, 814, 575.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 10.39 (s, 1H, CHO), 6.34 (s, 2H, 2 × Ar–H), 3.82 (s, 6H, 2 × OCH_3), 2.32 (s, 3H, Ar–CH_3).

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 189.0 (CHO), 162.2 (C-2, C-6), 147.7 (C-4), 111.9 (C-3, C-5), 104.6 (C-1), 55.7 (OCH_3), 22.6 (Ar–CH_3).

MS (70 eV, EI): *m*/*z* (%): 180.2 (100) $[M]^+$, 165.2 (11) $[M-CH_3]^+$.

2.6.1.3	*	**4-(2,6-Dimethoxy-4-methylphenyl)but-3-en-2-one** [2]



180.2 220.3

A solution of the aldehyde **2.6.1.2** (10.0 g, 55.5 mmol) in acetone (80 ml) is treated dropwise with 1 M aqueous NaOH solution (35 ml) at 0 °C. The resulting mixture is stirred at room temperature for 3 h before being cooled to 0 °C and treated dropwise with 1 M aqueous HCl solution (40 ml).

Water (300 ml) is added, and the mixture is extracted with EtOAc (3 × 100 ml). The combined extracts are dried over Na_2SO_4, filtered, and the solvent is removed *in vacuo*. After column chromatography on silica gel (*n*-pentane/EtOAc 7 : 3), the unsaturated ketone **2.6.1.3** is obtained as a colorless solid; 10.3 g (84%). R_f = 0.34 (*n*-pentane/EtOAc 7 : 3).

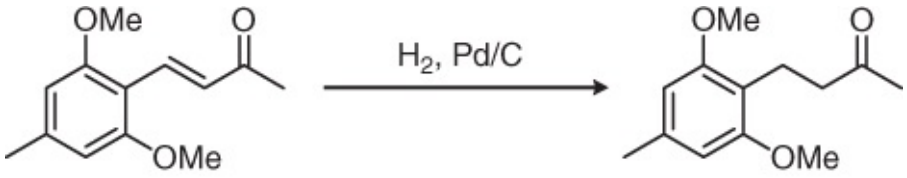
IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3052, 3006, 2975, 2945, 2845, 1677, 1567, 1250, 1116, 994, 823, 549.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.96 (d, *J* = 16.7 Hz, 1H, 4′-H), 7.12 (d, *J* = 16.7 Hz, 1H, 3′-H), 6.38 (s, 2H, 2 × Ar–H), 3.86 (s, 6H, 2 × OCH_3), 2.36 (s, 6H, 1′-H_3, Ar–CH_3).

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 200.6 (C-2′), 159.9 (C-2, C-6), 143.6 (C-4), 135.0 (C-4′), 129.2 (C-3′), 109.4 (C-3, C-5), 104.6 (C-1), 55.7 (OCH_3), 26.9 (C-1′), 22.5 (Ar–CH_3).

MS (70 eV, EI): *m*/*z* (%): 220.1 (15) $[M]^+$, 205.1 (21) $[M-CH_3]^+$, 189.1 (100) $[M-2CH_3-H]^+$.

2.6.1.4	*	**4-(2,6-Dimethoxy-4-methylphenyl)-butan-2-one** [2]



220.3 222.3

To a solution of the unsaturated ketone **2.6.1.3** (9.75 g, 44.5 mmol) in EtOAc (250 ml) is added Pd/C (1.45 g, 10% Pd, 1.34 mmol) at room temperature under a nitrogen atmosphere. Hydrogen is passed through the resulting mixture for 30 min before being stirred under a hydrogen atmosphere for further 2.5 h (TLC monitoring).

The catalyst is removed by filtration over Celite® (washing with CH_2Cl_2) and the solvent removed *in vacuo*. Column chromatography on silica gel (*n*-pentane/EtOAc 3 : 1) yields saturated ketone **2.6.1.4** as a colorless solid; 9.10 g (92%), R_f = 0.35 (*n*-pentane/EtOAc 3 : 1).

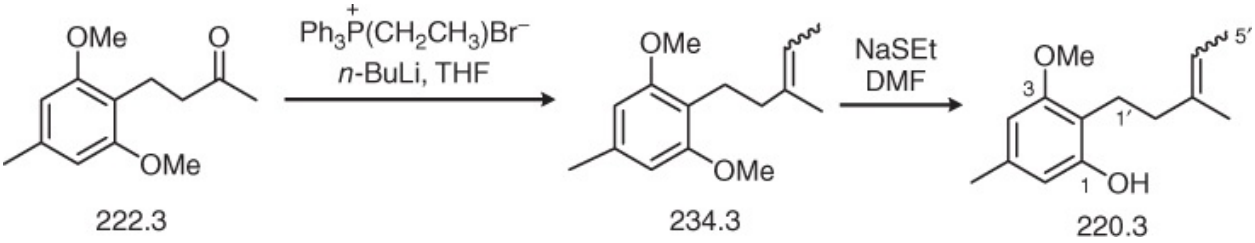
IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3064, 2994, 2938, 2838, 1704, 1589, 1466, 1246, 1127, 968, 814, 579.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 6.36 (s, 2H, 2 × Ar–H), 3.78 (s, 6H, 2 × OCH_3), 2.83–2.93 (m, 2H, 4′-H_2), 2.57–2.63 (m, 2H, 3′-H_2), 2.34 (s, 3H, Ar–CH_3), 2.15 (s, 3H, 1′-H_3).

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 209.6 (C-2′), 157.8 (C-2, C-6), 137.1 (C-4), 113.9 (C-1), 104.4 (C-3, C-5), 55.4 (OCH_3), 43.3 (C-3′), 29.5 (C-1′), 21.9 (Ar–CH_3), 17.5 (C-4′).

MS (70 eV, EI): *m*/*z* (%): 245.1 (100) $[M+Na]^+$, 223.1 (27) $[M+H]^+$.

2.6.1.5	**	**(*E*)-3-Methoxy-5-methyl-2-(3-methylpent-3-en-1-yl)phenol and**
		(*Z*)-3-Methoxy-5-methyl-2-(3-methylpent-3-en-1-yl)phenol [2]



A suspension of ethyl triphenylphosphonium bromide (30.0 g, 80.8 mmol) in THF (260 ml) is treated with *n*-BuLi (30.2 ml of a 2.5 M solution in *n*-hexane, 75.6 mmol) at 0 °C, and the reaction mixture is stirred for 30 min at 0 °C and for further 30 min at room temperature. A solution of the ketone **2.6.1.4** (6.00 g, 27.2 mmol) in THF (160 ml) is added at 0 °C, and the reaction mixture stirred at room temperature for 2.5 h.

The reaction is quenched by addition of saturated aqueous NH_4Cl solution (100 ml) and water (10 ml) at 0 °C. The aqueous layer is extracted with methyl *t*-butyl ether (MTBE) (3 × 100 ml), the combined organic layers are dried over Na_2SO_4 and filtered, and the solvent is removed *in vacuo*. Column chromatography on

silica gel (petroleum ether/MTBE = 50 : 1) furnishes the alkene **11** as a colorless oil (5.67 g, 24.2 mmol, 90%) with an (*E/Z*)-ratio of 1 : 2.4, which is used for the next step.

A solution of alkene **11** (5.67 g, 24.2 mmol) in DMF (40 ml) is treated with NaSEt (90%, 4.27 g, 50.8 mmol) and the resulting mixture heated at 120 °C for 20 h. The reaction mixture is cooled to room temperature and quenched by addition of water (200 ml). The aqueous layer is extracted with MTBE (3 × 100 ml), the combined organic layers are washed with water (2 × 100 ml) and brine (1 × 100 ml), dried over Na_2SO_4, and filtered, and the solvent is removed *in vacuo*. Column chromatography on silica gel (petroleum ether/EtOAc = 30 : 1) furnishes the mono-phenol **2.6.1.5** as a pale-yellow oil, which solidifies upon storage at −30 °C (*E*/*Z* = 1 : 2.4). The two stereoisomers can be separated by HPLC (column: Daicel Chiralcel IA: 250 × 20 mm, 5 µm, λ = 210 nm, flow: 18 ml min^{-1}, eluent: *n*-hexane/isopropanol 99 : 1, t_R = 39.6 min (*Z*-isomer), 51.1 min (*E*-isomer).

Analytical data for the *Z*-Isomer:

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3435, 2959, 2923, 2857, 1617, 1591, 1454, 1416, 1219, 1154, 1099, 1070, 995, 973, 812, 584.

^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 6.29 (s, 1H, Ar–H), 6.26 (s, 1H, Ar–H), 5.22 (q, *J* = 6.8 Hz, 1H, 4′-H), 4.79 (s_{br}, 1H, OH), 3.78 (s, 3H, 3-OCH_3), 2.66 (dd, *J* = 8.6, 7.0 Hz, 2H, 1′-H_2), 2.26 (s, 3H, 5-CH_3), 2.21 (dd, *J* = 8.8, 6.3 Hz, 2H, 2′-H_2), 1.74 (t, *J* = 1.4 Hz, 3H, 3′-CH_3), 1.51 (dd, *J* = 6.6, 1.5 Hz, 3H, 4′-CH_3).

^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) = 158.5, 154.2 (C-1, C-3), 136.9, 136.8 (C-3′, C-5), 119.5 (C-4′), 113.9 (C-2), 109.0, 104.3 (C-4, C-6), 55.6 (3-OCH_3), 31.1 (C-2′), 23.7 (3′-CH_3), 21.6, 21.5 (C-1′, 5-CH_3), 13.0 (4′-CH_3).

MS (ESI): *m*/*z* (%) = 243.1 (100) $[M+Na]^+$, 221.2 (66) $[M+H]^+$.

Analytical data for the *E*-Isomer:

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3432, 2921, 2855, 1617, 1591, 1510, 1462, 1416,

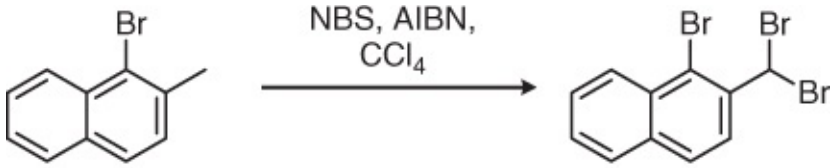
1313, 1165, 1100, 1082, 973, 921, 812, 571.

^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 6.28 (s, 1H, Ar–H), 6.26 (s, 1H, Ar–H), 5.25 (q, *J* = 6.6 Hz, 1H, 4′-H), 4.71 (s_{br}, 1H, OH), 3.77 (s, 3H, 3-OCH_3), 2.66 (t, *J* = 8.0 Hz, 2H, 1′-H_2), 2.25 (s, 3H, 5-CH_3), 2.12 (t, *J* = 8.3 Hz, 2H, 2′-H_2), 1.66 (s, 3H, 3′-CH_3), 1.56 (dd, *J* = 6.7, 1.0 Hz, 3H, 4′-CH_3).

^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) = 158.3, 154.1 (C-1, C-3), 136.8, 136.6 (C-3′, C-5), 118.5 (C-4′), 113.8 (C-2), 109.0, 104.3 (C-4, C-6), 55.6 (3-OCH_3), 38.9 (C-2′), 22.2 (C-1′), 21.5 (5-CH_3), 15.9 (3′-CH_3), 13.4 (4′-CH_3).

MS (ESI): *m*/*z* (%) = 243.1 (100) $[M+Na]^+$, 221.2 (59) $[M+H]^+$.

2.6.1.6 * 1-Bromo-2-(dibromomethyl)naphthalene [2, 3]



221.1 378.9

To a stirred solution of 1-bromo-2-methylnaphthalene (**12**) (15.0 g, 67.8 mmol) in CCl_4 (300 ml) (Caution: resorption through the skin!) are added *N*-bromosuccinimide (36.3 g, 204 mmol) and azobis(isobutyro)nitrile (AIBN) (2.23 g, 13.6 mmol), and stirring is continued for 26 h at 85 °C.

The reaction mixture is cooled to room temperature and filtered, and the filter cake is washed with CCl_4 (150 ml). The organic phase is concentrated *in vacuo* to about 150 ml, washed with saturated aqueous $NaHSO_3$ (150 ml), dried over Na_2SO_4, and filtered. The solvent is removed *in vacuo*, and the residue is recrystallized from ethanol to give **2.6.1.6** as colorless crystals; 19.3 g, 50.9 mmol, (75%). R_f = 0.48 (petroleum ether).

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3033, 1908, 1619, 1595, 1556, 1501, 1459, 1382, 1348, 1323, 1301, 1258, 1218, 1206, 1141, 1033, 973, 958, 906, 863, 804, 770, 747, 734, 677, 665, 646, 596, 528, 515.

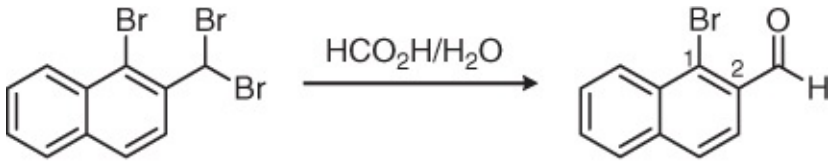
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.30 (d, *J* = 8.5 Hz, 1H, 8-H), 8.07

(d, J = 8.7 Hz, 1H, 3-H), 7.89 (d, J = 8.7 Hz, 1H, 4-H), 7.83 (d, J = 8.1 Hz, 1H, 5-H), 7.60–7.68 (m, 1H, 7-H), 7.53–7.60 (m, 1H, 6-H), 7.50 (d, J = 0.4 Hz 1H, $CHBr_2$).

^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) = 138.0 (C-2), 134.7 (C-4a), 131.2 (C-8a), 129.1 (C-4), 128.4, (C-7, C-8), 128.3 (C-5), 128.0 (C-6), 126.8 (C-3), 119.6 (C-1), 41.4 ($CHBr_2$).

MS: (EI, 70 eV): m/z (%) = 379.8 (5) $[M]^+$, 298.9 (100) $[M-Br]^+$, 219.0 (5) $[M-2Br]^+$, 139.1 (71) $[M-3Br]^+$.

2.6.1.7	*	**1-Bromo-2-naphthalenecarbaldehyde** [2, 3]



378.9 235.1

A mixture of 1-bromo-2-(dibromomethyl)naphthalene (**2.6.1.6**) (18.0 g, 47.5 mmol) and formic acid (88%, 225 ml) is stirred for 20 h at 120 °C. After evaporation of the solvent *in vacuo*, the residue is dissolved in H_2O (225 ml) and extracted with CH_2Cl_2 (3 × 150 ml). The organic phases are dried over Na_2SO_4, filtered, and concentrated. The residue is purified by flash chromatography on silica gel (petroleum ether/EtOAc = 30 : 1). The aldehyde **2.6.1.7** is obtained as a white solid; 9.59 g, 40.8 mmol, (86%). R_f = 0.25 (petroleum ether/EtOAc = 30 : 1).

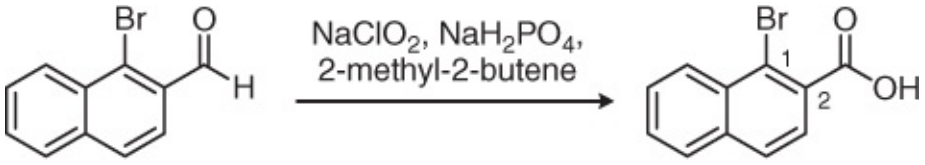
IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 1684, 1323, 1215, 888, 810, 752.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 10.65 (s, 1H, CHO), 8.43–8.51 (m, 1H, 8-H), 7.91 (d, J = 8.5 Hz, 1H, 3-H), 7.88 to 7.79 (m, 2H, 4-H, 5-H), 7.70 to 7.63 (m, 2H, 6-H, 7-H).

^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) = 192.7 (CHO), 137.2, 132.1, 131.3, 131.2 (C-1, C-2, C-4a, C-8a), (C-1), 129.7 (C-6), 128.5, 128.3, 128.2, 128.1 (C-4, C-5, C-7, C-8), 124.1 (C-3).

MS: (EI, 70 eV): m/z (%) = 235.0 (9) $[M]^+$, 126.0 (14) $[M-Br-CHO]^+$.

2.6.1.8	*	**1-Bromo-2-naphthalenecarboxylic acid** [2, 3]



235.1 251.1

To a stirred solution of 1-bromo-2-naphthalenecarbaldehyde (**2.6.1.7**) (8.50 g, 36.2 mmol) and 2-methyl-2-butene (27 ml) in acetone (460 ml) at 0 °C is added dropwise a solution of $NaClO_2$ (19.6 g, 217 mmol) and $NaH_2PO_4 \cdot H_2O$ (34.9 g, 253 mmol) in H_2O (230 ml), and stirring is continued for 20 h at room temperature.

After evaporation of the solvent *in vacuo*, the residue is dissolved in 2 N aqueous HCl (280 ml) and extracted with Et_2O (3 × 180 ml). The organic phases are concentrated, dried over Na_2SO_4, and filtered, and the residue is recrystallized from EtOAc to afford **2.6.1.8** as colorless solid; 7.19 g, 28.6 mmol (79%).

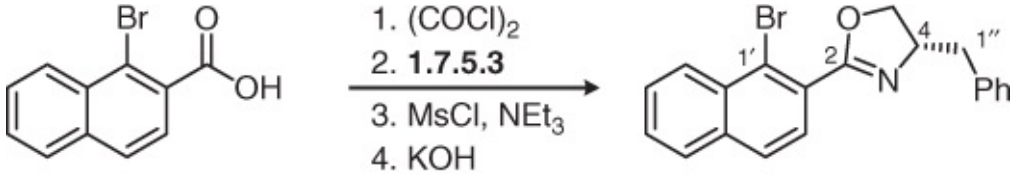
IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 1684, 1323, 1215, 888, 810, 752.

^{1}H NMR (300 MHz, acetone-d_6): δ (ppm) = 8.41 (d, J = 8.5 Hz, 1H, 8-H), 8.04–7.92 (m, 2H, 4-H, 5-H), 7.79–7.60 (m, 3H, 3-H, 6-H, 7-H).

^{13}C NMR (126 MHz, acetone-d_6): δ (ppm) = 168.3 (CO_2H), 135.8, 133.4, 132.7 (C-2, C-4a, C-8a), 129.2, 129.1, 128.8, 128.8, 128.6 (C-4, C-5, C-6, C-7, C-8), 126.4 (C-3), 121.6 (C-1).

MS: (EI, 70 eV): m/z (%) = 235.0 (9) $[M]^+$, 126.0 (14) $[M-Br-CHO]^+$.

2.6.1.9	**	(*S*)-2-(4-Benzyl-4,5-dihydrooxazol-2-yl)-1-bromonaphthalene [2, 3]



251.1 366.3

To a solution of 1-bromo-2-naphthalenecarboxylic acid (**2.6.1.8**) (7.00 g, 27.9 mmol) and a catalytic amount of DMF (0.2 ml) in toluene (60 ml) is added dropwise oxalylchloride (4.89 ml, 7.22 g, 55.8 mmol) at 0 °C. The resulting clear solution is stirred for 3 h at room temperature, the solvent is removed *in vacuo*, and the residue is dried in high vacuum. The acid chloride is dissolved in CH_2Cl_2 (280 ml), and a solution of L-phenylalaninol **1.8.5.3** (4.64 g, 30.7 mmol) and NEt_3 (8.00 ml, 5.84 g, 57.7 mmol) in CH_2Cl_2 (55 ml) is added dropwise at 0 °C. The reaction mixture is stirred for 19 h at room temperature.

The reaction is quenched by the addition of 1 M aqueous HCl solution (180 ml), the phases are separated, the organic phase is washed with saturated aqueous NaCl solution (180 ml), and the combined aqueous phases are extracted with EtOAc (5 × 200 ml). The combined organic phases are dried over Na_2SO_4 and filtered, and the solvent is removed *in vacuo*.

The carboxamide is suspended in CH_2Cl_2 (440 ml), NEt_3 (11.6 ml, 8.46 g, 83.6 mmol) and mesyl chloride (3.24 ml, 4.79 g, 41.8 mmol) are added at 0 °C, and then the reaction mixture is stirred for 2 h at room temperature. The solvent is removed *in vacuo*, and the mesylate is afterwards suspended in MeOH (350 ml), treated with KOH (7.82 g, 139 mmol), and stirred for 2.5 h at room temperature.

The solvent is removed *in vacuo*, and the residue is dissolved in H_2O (440 ml) and extracted with EtOAc (3 × 220 ml). The combined organic phases are dried over Na_2SO_4 and filtered, and the solvent is removed *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether/EtOAc = 5 : 1) yields the product **2.6.1.9** as colorless oil; 9.12 g, 24.9 mmol, (86%); R_f = 0.30; $[\alpha]^{20}_D$ = +4.1 (*c* = 1.0, $CHCl_3$).

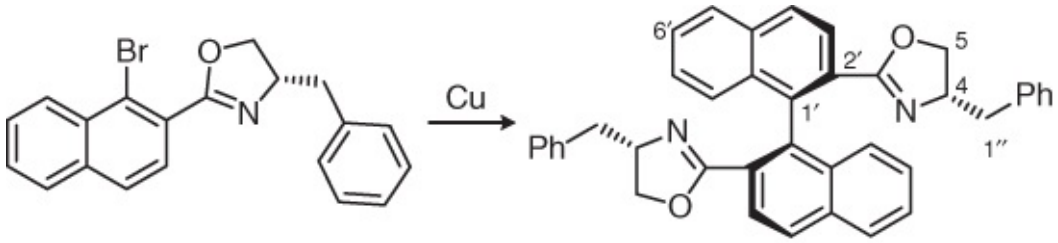
IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3060, 2892, 1642, 1495, 1454, 1362, 1239, 1098, 1057, 973, 866, 824, 753, 701, 563, 505.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.05 (d, *J* = 8.8 Hz, 2H, 2 × 8-H), 7.95 (d, *J* = 8.6 Hz, 4H, 2 × 3-H, 2 × 4-H), 7.47 (m_c, 2H, 2 × 6-H), 7.35–7.23 (m, 4H, 2 × 5-H, 2 × 7-H), 7.22–7.08 (m, 6H, 4 × Ph-H_m, 2 × Ph-H_p), 6.98–6.89 (m, 4H, 4 × Ph-H_o), 4.12 (m_c, 2H, 2 × 4′-H), 3.62 (d, *J* = 7.9 Hz, 4H, 2 × 5′-H_2), 2.57 (dd, *J* = 13.7, 5.0 Hz, 2H, 2 × 1″-H_a), 1.86 (dd, *J* = 13.7, 9.4 Hz, 2H, 2 × 1″-H_b).

^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) = 164.3 (2 × C-2′), 138.2, 137.8, (2 × C-1, 2 × Ph–C_i), 134.3, 132.7 (2 × C-2, 2 × C-4a), 128.9, 128.3, 127.8, 127.6, 126.9, 126.8, 126.4, 126.1, 125.9, (2 × C-3, 2 × C-4, 2 × C-5, 2 × C-6, 2 × C-7, 2 × C-8, 4 × Ph–C_o, 4 × Ph–C_m, 2 × Ph–C_p), 125.9 (2 × C-8a), 71.6 (2 × C-5′), 67.8 (2 × C-4′), 41.1 (2 × C-1″).

MS: (EI, 70 eV): *m*/*z* (%) = 573.3 (100) $[M+H]^+$.

2.6.1.10	**	**(*S*)-2,2′-Bis-[(*S*)-4-benzyl-4,5-dihydrooxazol-2-yl]-**
		1,1′-binaphthalene [2, 3]



366.3 572.7

A mixture of **2.6.1.9** (8.09 g, 22.1 mmol) and freshly activated copper powder (35.1 g, 553 mmol; *note*) in pyridine (200 ml) is stirred for 46.5 h at 130 °C.

The solvent is removed *in vacuo*, and the residue dissolved in CH_2Cl_2 (400 ml) and filtered over silica gel/Celite®, which is washed with CH_2Cl_2 (2 × 400 ml). The combined organic phases are washed with concentrated aqueous NH_3 solution (3 × 400 ml) until the aqueous phase remains colorless and dried over Na_2SO_4, and the solvent is removed *in vacuo*. The crude product is purified by flash column chromatography on silica gel (petroleum ether/EtOAc = 100 : 1→9 : 1) to give enantio and diastereopure **2.6.1.10** as a colorless foam; 4.38 g, 7.65 mmol, (69%), R_f = 0.14 (petroleum ether/EtOAc = 4 : 1), $[\alpha]^{20}_D$ = −98.3 (*c* = 0.7, $CHCl_3$).

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3061, 2923, 1661, 1599, 1556, 1497, 1454, 1376, 1347, 1241, 1106, 976, 958, 865, 817, 750, 702, 663.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.41 (d, *J* = 8.4 Hz, 8′-H), 7.85–7.78 (m, 2H, 3′-H, 4′-H), 7.66–7.53 (m, 3H, 5′-H, 6′-H, 7′-H), 7.37–7.20 (m, 5H, 5 × Ph–H), 4.69 (m_c, 1H, 4-H), 4.44 (dd, *J* = 8.6, 8.6 Hz, 1H, 5-H_a),

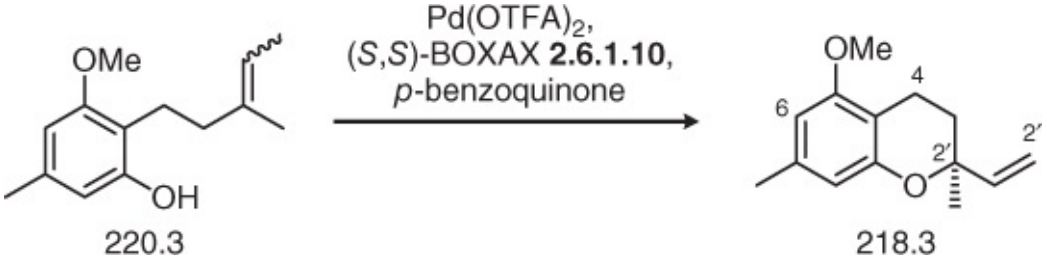
4.24 (dd, J = 8.6, 7.2 Hz, 1H, 5-H_b), 3.28 (dd, J = 13.9, 5.2 Hz, 1H, 1″-H_a), 2.86 (dd, J = 13.9, 8.4 Hz, 1H, 1″-H_b).

^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) = 164.2 (C-2), 137.7, 134.8, (C-2′, Ph–C_i), 132.2 (C-4a′), 128.3 (C-8a′), 129.3, 128.5, 128.2, 128.1, 127.8, 127.7, 127.6, 126.7, 126.5, (C-3′, C-4′, C-5′, C-6′, C-7′, C-8′, 2 × Ph–C_o, 2 × Ph–C_m, Ph–C_p), 123.2 (C-1′), 72.1 (C-5), 68.3 (C-4), 41.7 (C-1″).

MS: (EI, 70 eV): m/z (%) = 365.3 (4) $[M]^+$, 274.2 (100) $[M-C_7H_7]^+$

Note: Activation of the copper: Copper powder is washed with acetic acid (3×), MeOH (3×), and Et_2O (3×), and dried under high vacuum overnight.

2.6.1.11	**	**(*S*)-5-Methoxy-2,7-dimethyl-2-vinylchroman** [2]



A solution of $Pd(OTFA)_2$ (7.8 mg, 23.6 µmol, 10 mol%) and (*S*,*S*)-Bn-BOXAX **2.6.1.10** (27.0 mg, 47.2 µmol, 20 mol%) in MeOH (0.5 ml) is stirred at room temperature for 15 min and, after addition of a solution of phenol **2.6.1.5** (52.0 mg, 236 µmol) (*E*/*Z* = 1 : 2.4) (note) in MeOH (1.0 ml) and *p*-benzoquinone (102 mg, 944 µmol), stirring is continued for 22 h. The mixture is poured into 1 N aqueous HCl (20 ml) and extracted with MTBE (4 × 10 ml). The combined extracts are washed with 1 N aqueous NaOH (3 × 10 ml), dried over Na_2SO_4, and filtered, and the solvent is removed *in vacuo*. Column chromatography on silica gel (petroleum ether/EtOAc = 100 : 1 → 70 : 1) gives the vinylchroman **2.6.1.11** as yellowish oil (38.4 mg, 176 µmol, yield 75%, 87% ee); $[\alpha]^{20}_D$ = −55.7 (c = 0.5, $CHCl_3$); analytical HPLC (column: Daicel Chiralcel OD): 250 × 4.6 mm, 5 µm, λ = 275 nm, flow: 0.8 ml min^{-1}, eluent: *n*-hexane/isopropanol 99.5 : 0.5, t_R = 10.1 min ((−)-**2.6.1.11**), 11.9 min ((+)-**2.6.1.11**).

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3082, 2952, 2927, 1615, 1583, 1459, 1409, 1350, 1261, 1229, 1209, 1126, 1091, 1023, 1013, 923, 814, 583.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 6.36 (s, 1H, 8′-H), 6.22 (s, 1H, 6′-H), 5.85 (dd, *J* = 17.3, 10.8 Hz, 1H, 1-H), 5.17 (dd, *J* = 17.3, 1.3 Hz, 1H, 2-H_{trans}), 5.05 (dd, *J* = 10.8, 1.3 Hz, 1H, 2-H_{cis}), 3.78 (s, 3H, 5′-OCH_3), 2.65 (dt, *J* = 17.0, 5.4 Hz, 1H, 4′-H_b), 2.44 (ddd, *J* = 16.7, 9.8, 6.0 Hz, 1H, 4′-H_a), 2.28 (s, 3H, 7′-CH_3), 1.90 (ddd, *J* = 13.5, 6.1, 5.0 Hz, 1H, 3′-H_b), 1.76 (ddd, *J* = 13.5, 9.8, 5.9 Hz, 1H, 3′-H_a), 1.40 (s, 3H, 2′-CH_3).

^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) = 157.5, 154.4 (C-5′, C-8a′), 141.4 (C-1), 136.9 (C-7′), 113.6 (C-2), 110.1 (C-6′), 107.3 (C-4a′), 102.7 (C-8′), 76.2 (C-2′), 55.3 (5′-OCH_3), 31.3 (C-3′), 26.8 (2′-CH_3), 21.6 (7′-CH_3), 16.7 (C-4′).

MS (ESI): *m*/*z* (%) = 241.1 (33) $[M+Na]^+$, 219.1 (100) $[M+H]^+$.

Note: The enantioselectivity of the Wacker oxidation could be improved to 93% by employing the pure (*E*)-compound, whereas the (*Z*)-compound gave 83% ee. However, the separation of the (*E*/*Z*)-mixture of **2.6.1.5** by chromatography is rather tedious and not practicable for larger amounts.

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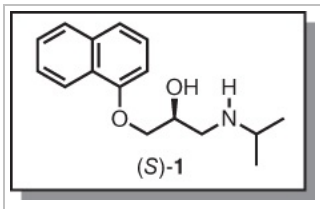
Chapter 3
Heterocyclic Compounds

Heterocycles constitute the largest group of organic compounds and are found in a vast number of natural products (e.g., vitamins, alkaloids, antibiotics) as well as in products with biological, medicinal, and technical relevance (e.g., pharmaceuticals, biocides, dyes). In the following sections, (3.1–3.5), selected syntheses and reactions of a series of aromatic and non-aromatic heterocycles are presented, which are organized according to ring size and structural complexity.

Section 3.1 deals with three-and four-membered heterocycles such as oxiranes, oxetanes, and β-lactams and Section 3.2 with five-membered heterocycles such as furans, pyrroles, imidazoles as well as their benzo derivatives such as benzothiophenes, indoles, and indazolones. In Section 3.3, six-membered heterocycles and their benzo derivatives such as azines, diazines, dihydropyridines, pyrimidines, isoquinolines, 2-pyrimidinyl-substituted pyrazolone, and benzophenanthridine derivatives including a multistep synthesis of a Ras farnesyltransferase (FT) inhibitor are discussed. Finally, Section 3.4 deals with condensed heterocycles in which different heterocycles are combined by annulation, such as naphthoindolizinequinone, pyrrolo[2,3-*d*]pyrimidine, naphthyridine, caffeine, a nedocromil analogon, and a polyheterocycle, which is formed under a high-pressure cyclization of a Knoevenagel product. In Section 3.5, heterocyclic systems are treated which constitute crown ethers and rotaxanes as well as heterocyclic dyes such as porphyrines, indigo, and cyanines.

3.1 Three-and Four-Membered Heterocycles

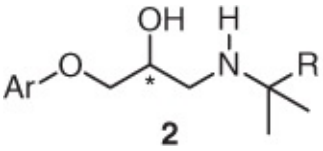
3.1.1 (*S*)-Propranolol

 (*S*)-**1**	***Topics:***	• Synthesis of propranolol (i) as the racemate and (ii) as the (*S*)-enantiomer • O-Alkylation of 1-naphthol

		• Stereo and regioselective oxirane opening by an amine

(a) General

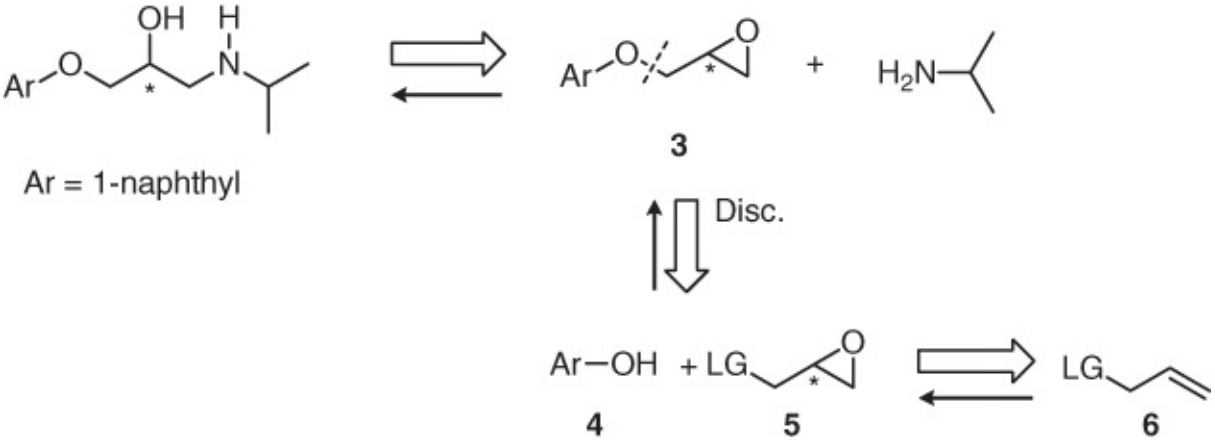
Propranolol (**1**) belongs to the class of aroyloxy-or hetaroyloxy-propanolamines **2**, which are medicinally applied as β-adrenolytics (β-blocker) and which in their activity profile show cardioselectivity, intrinsic sympathomimetic activity, and membrane effects. Propranolol is manufactured as the racemate, although it is known that the (*S*)-enantiomer is far more effective than the (*R*)-enantiomer [1–3].



2

Ar = aryl, hetaryl
R = H, CH_3
* = Stereogenic center

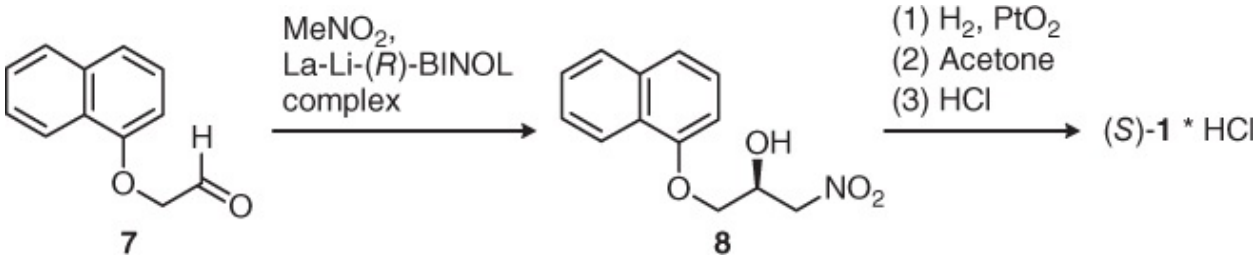
Retrosynthesis of propranolol (**2**, Ar = 1-naphthyl, R = H) follows the conventional disconnection pattern for 1,2-diol derivatives. Thus, the synthesis could start with O-alkylation of α-naphthol (**4**) by using glycidol **5** containing a leaving group and may proceed via an oxirane ring-opening of the formed glycidol ether **3** by isopropylamine. Glycidol **5** can be obtained by epoxidation of an allylic compound **6** (**6**→**5**), which can be performed in an enantioselective way, thus allowing the stereocontrolled formation (cf. **2.1.1.1**) of the stereogenic center in **1**.



The described concept is used for the preparation of *rac*-propranolol as well as of its (*S*)-enantiomer.

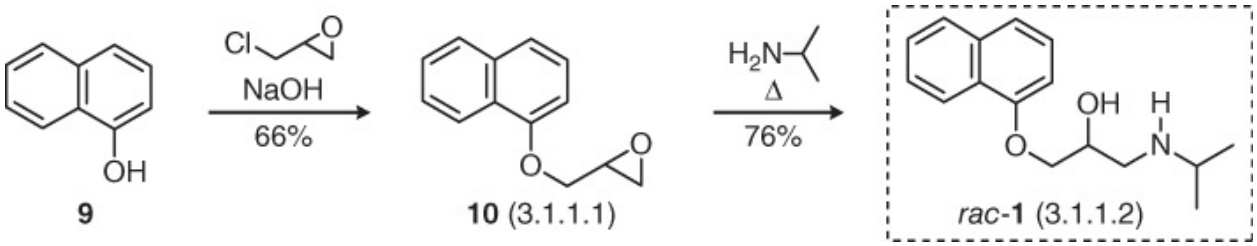
A different enantioselective synthesis of **1** was developed using an asymmetric nitroaldol reaction of aldehyde **7** with nitromethane catalyzed by a chiral La(III)-Li-(*R*)-BINOL (1,1′-bi-2-naphthol) complex [4]. The nitroaldol **8** possessing (*S*)-

configuration at the stereogenic center was transformed into (*S*)-propranolol by catalytic reduction $NO_2 \rightarrow NH_2$ with H_2/PtO_2 and subsequent introduction of the isopropyl moiety by reductive amination with acetone:



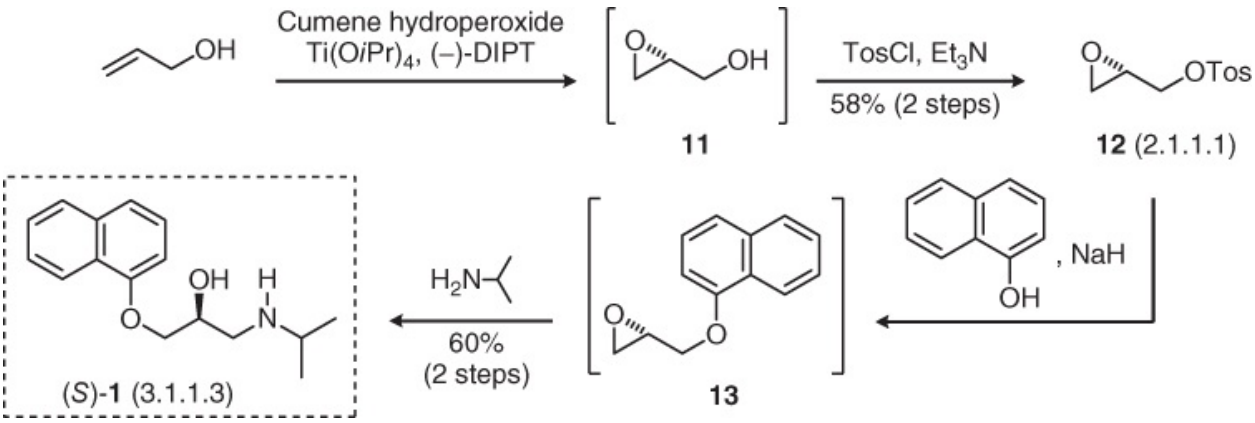
(b) Synthesis of 1

The synthesis of racemic propranolol (*rac*-**1**) [5, 6] starts with O-alkylation of 1-naphthol (**9**) with epichlorohydrin, which proceeds via an S_N reaction of the 1-naphtholate anion to give the glycidol ether **10**:

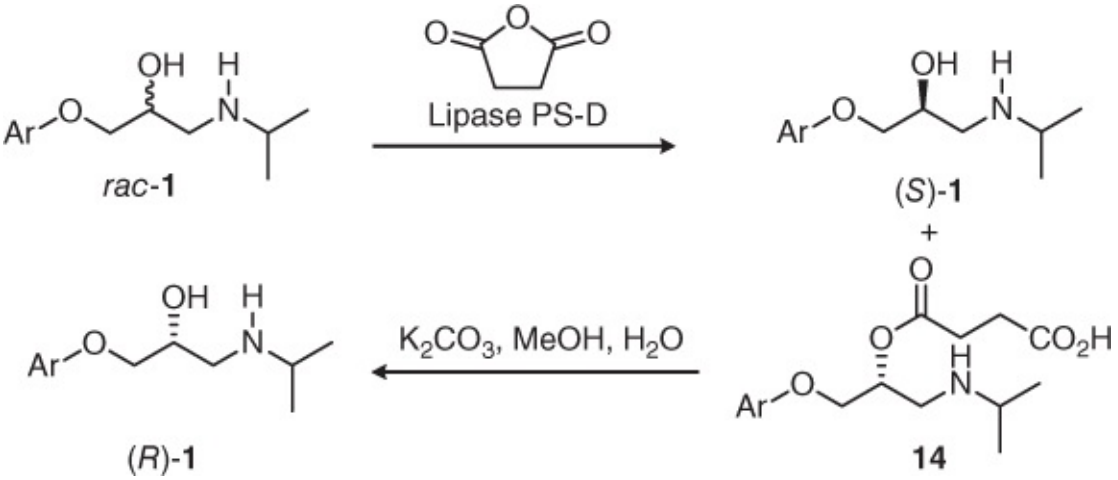


Subsequent reaction of **10** with isopropylamine leads to *rac*-propranolol (*rac*-**1**). As expected, opening of the oxirane ring in **10** occurs regioselectively by attack of the N-nucleophile at the sterically less hindered CH_2 site.

The asymmetric synthesis of (*S*)-**1** [7] starts with the enantioselective epoxidation of allyl alcohol using cumene hydroperoxide in the presence of catalytic amounts of $Ti(O\textit{i}Pr)_4$ and (−)-diisopropyl tartrate according to the Sharpless–Katsuki protocol (for details, see **2.1.1.1** and Refs. [7, 8]). The initially formed (*S*)-glycidol (**11**) is sulfonylated *in situ* with $TosCl/NEt_3$ to give the (2*S*)-glycidyl tosylate (**12**). Treatment of the tosylate **12** with sodium 1-naphthoxide in DMF (dimethylformamide) affords the chiral 1-naphthyl epoxy ether **13**, which is subjected *in situ* to regioselective oxirane ring-opening by reaction with isopropylamine to give (*S*)-propranolol ((*S*)-**1**):



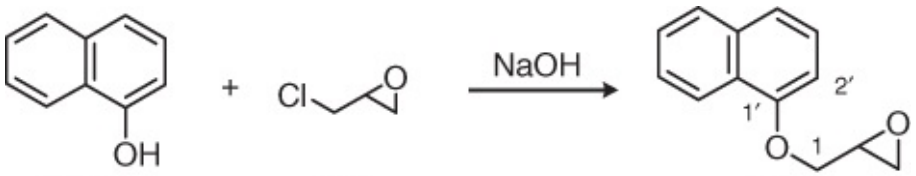
It should be noted that (*S*)-propranolol **1** can also be obtained from *rac*-**1** by chemoenzymatic resolution [9]. Enantioselective esterification of *rac*-**1** with succinic anhydride mediated by lipase (PS-D) leads directly to (*S*)-**1** and the hemisuccinate **14** of (*R*)-**1**. In this way, (*R*)-propranolol may also be prepared, namely by hydrolysis of **14** in MeOH/H_2O in the presence of K_2CO_3:



The procedure described below allows the synthesis of *rac*-**1** in a two-step sequence with an overall yield of 50% (based on 1-naphthol), and of the (*S*)-enantiomer in a three-step sequence (two separate operations) with an overall yield of 32% (based on allylic alcohol).

(c) Experimental Procedures for the Synthesis of 1

3.1.1.1	*	**2,3-Epoxypropyl-1-(1-naphthyl) ether** [5]



1-Naphthol (7.21 g, 50.0 mmol) is dissolved in a solution of NaOH (2.00 g, 50.0 mmol) in H_2O (10 ml). With vigorous stirring, epichlorohydrin (4.67 g, 50.0 mmol) (note) is added dropwise at such a rate that the internal temperature does not exceed 35 °C. When the addition is complete, stirring is continued for 12 h at room temperature.

The reaction product (which separates as an oil) is extracted with Et_2O (2 × 20 ml). The combined organic layers are washed with 1 N aqueous NaOH (2 × 20 ml), dried over Na_2SO_4, filtered, and the solvent is removed *in vacuo*. The residue is fractionated *in vacuo* to yield the product as a colorless oil; 6.63 g (66%), $bp_{0.5}$ 124–125 °C, TLC (thin-layer chromatography) ($CHCl_3$): R_f = 0.75.

IR (film): $\tilde{\nu}$ (cm^{-1}) = 3070, 2930 (CH), 1600, 1590, 1520 (C = C), 1410, 1280, 1110, 800, 780.

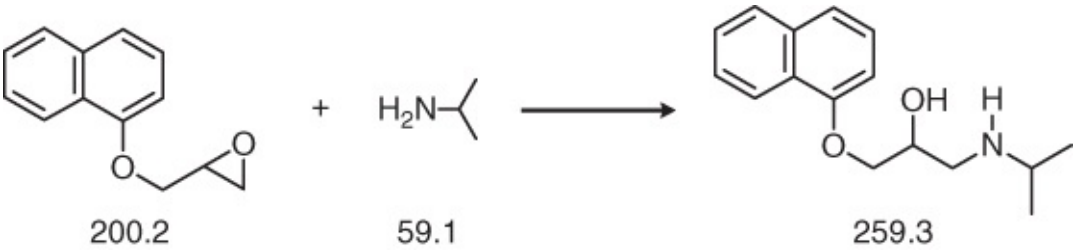
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.37–8.26 (m, 1H, 8′-H), 7.83–7.78 (m, 1H, 2′-H), 7.54–7.33 (m, 4H, 4′-H, 5′-H, 6′-H, 7′-H), 6.80 (dd, *J* = 9.0, 1.0 Hz, 1H, 3′-H), 4.39 (dd, *J* = 11.0, 3.0 Hz, 1H, 1-H_A), 4.13 (dd, *J* = 11.5, 6.0 Hz, 1H, 1-H_B), 3.53–3.43 (m, 1H, 2-H), 2.96 (dd, *J* = 5.0, 4.0 Hz, 1H, 3-H_A), 2.84 (dd, *J* = 5.0, 1.0 Hz, 1H, 3-H_B).

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 154.2 (C-1′), 134.5 (C-5′), 127.4 (C-6′), 126.5 (C-7′), 125.7 (C-3′), 125.5 (C-8′), 125.2 (C-10′), 122.0 (C-9′), 120.8 (C-4′), 104.9 (C-2′), 68.9 (C-1), 50.2 (C-2), 44.7 (C-3).

MS (EI, 70 eV): *m*/*z* (%) = 200.2 (76) $[M]^+$, 144.1 (68) $[M-C_3H_4O]^+$, 115.1 (100) $[M-C_4H_5O_2]^+$.

Note: Epichlorohydrin has to be distilled before use, bp_{760} 116–117 °C, n^{20}_D = 1.4380.

3.1.1.2	*	**1-Isopropylamino-3-(1-naphthyloxy)-2-propanol (*rac*-propranolol)** [6]



200.2 59.1 259.3

A mixture of epoxy ether **3.1.1.1** (5.52 g, 28.0 mmol) and isopropylamine (5.10 g, 86.0 mmol) (note 1) is heated under reflux for 16 h.

The excess amine is then removed *in vacuo*, the residue is poured into aqueous HCl (2 N, 75 ml), and the acidic phase is extracted with Et_2O (2 × 30 ml) (note 2). The acidic phase is added dropwise with stirring to ice-cold aqueous NaOH (2 N, 150 ml). The product precipitates as colorless crystals, which are collected by suction filtration, dried *in vacuo* over P_4O_{10}, and recrystallized from cyclohexane. *rac*-Propranolol is obtained as colorless needles; 5.45 g (76%), mp 94–96 °C, TLC (MeOH): R_f = 0.20

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3280 (NH), 1600, 1590, 1410, 1280, 1110.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.23–8.20 (m, 1H, 8′-H), 7.80–7.76 (m, 1H, 2′-H), 7.51–7.31 (m, 4H, 4′-H, 5′-H, 6′-H, 7′-H), 6.80 (dd, *J* = 7.5, 1.0 Hz, 1H, 3′-H), 4.20–4.10 (m, 3H, 1-H_2, 2-H), 3.02–2.80 (m, 3H, 3-H_2, 5-H), 2.56 (s_{br}, 2H, OH, NH), 1.10 (d, *J* = 6.0 Hz, 6H, 2 × 6-H_3).

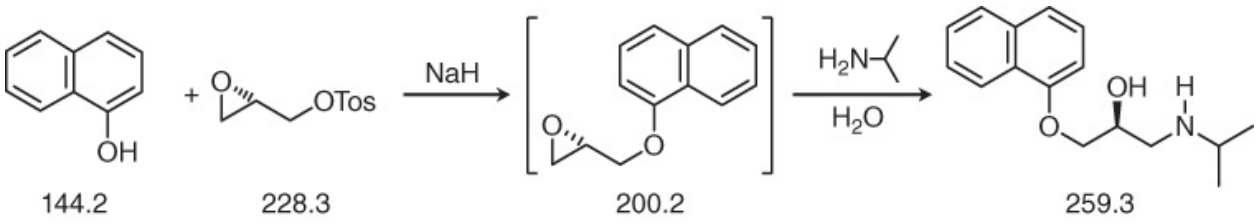
^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 154.3 (C-1′), 134.4 (C-5′), 127.5 (C-6′), 126.4 (C-7′), 125.8 (C-3′), 125.5 (C-8′), 125.2 (C-10′), 121.8 (C-9′), 120.5 (C-4′), 104.8 (C-2′), 70.7 (C-1), 68.5 (C-2), 49.5 (C-3), 48.9 (C-2″), 23.1, 23.0 (2 × CH_3).

MS (EI, 70 eV): *m*/*z* (%) = 259.3 (9) $[M]^+$, 72.1 (100) $[M-C_{12}H_{11}O_2]^+$.

Notes:

1. Isopropylamine is dried over solid KOH and distilled before use, bp_{760} 33–34 °C.
2. This extraction removes neutral impurities.

3.1.1.3	**	**(*S*)-Propranolol** [7]



1-Naphthol (1.35 g, 9.4 mmol) in anhydrous DMF (5 ml) is added to a stirred suspension of NaH (60%, 428 mg, 10.7 mmol) in anhydrous DMF (9 ml) under an argon atmosphere at room temperature to produce a foamy green sludge. After 30 min, (2*S*)-glycidyl tosylate (cf. **2.1.1.1**) (2.0 g, 8.9 mmol) is added and stirring is continued for 3.5 h (the reaction is monitored by TLC, EtOAc/*n*-hexane, 2 : 3). Isopropylamine (7.58 ml, 89.2 mmol) and H_2O (0.76 ml, 42.4 mmol) are added and the mixture is heated to reflux for 3.5 h (the reaction is monitored by TLC, CH_2Cl_2/*n*-hexane, 1 : 1).

After cooling to room temperature, the reaction mixture is diluted with H_2O (25 ml) and extracted with Et_2O (3 × 25 ml). The combined organic extracts are washed with aqueous NaOH (1 N, 50 ml) and brine (50 ml). After extraction with aqueous HCl (2 N, 40 ml), aqueous NaOH (2 N, 50 ml) is added. The residue is collected by suction filtration and recrystallized from *n*-hexane/Et_2O to give (2*S*)-propranolol as colorless needles; 1.29 g (56%), mp 72–73 °C, $[\alpha]^{20}_D$ = −8.5 (*c* = 1.0, EtOH), ee = 85%, R_f = 0.22 (MeOH/EtOAc, 1 : 1). The enantiomeric excess is determined by HPLC (high-performance liquid chromatography) on a chiral stationary phase.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.27–8.21 (m, 1H, 9′-H), 7.82–7.75 (m, 1H, 6′-H), 7.40–7.20 (m, 3H, 4′-H, 7′-H, 8′-H), 7.37 (t, *J* = 12.0 Hz, 1H, 3′-H), 6.80 (dd, *J* = 1.2, 6.8 Hz, 1H, 2′-H), 4.20–4.08 (m, 3H, 2-H, 1-H), 2.98 (dd, *J* = 3.6, 12.0 Hz, 1H, 3-H), 2.89–2.77 (m, 2H, 3-H, 2″-H), 1.10 (d, *J* = 6.3 Hz, 6H, 2 × CH_3).

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 154.3 (C-1′), 134.4 (C-2′), 127.5 (C-6′), 126.4 (C-7′), 125.8 (C-3′), 125.5 (C-8′), 125.2 (C-10′), 121.8 (C-9′), 120.5 (C-4′), 104.8 (C-2′), 70.7 (C-1), 68.5 (C-2), 49.6 (C-3), 48.9 (C-2″), 23.1, 23.0 (2 × CH_3).

HPLC: Chiralpak IB (Daicel); 250 × 4.6 mm; eluent: *n*-hexane/EtOAc, 1 : 1, isocratic; flow: 1.0 ml min^{-1}; detection: UV 270 nm; retention time: t_R =

3.54 min (minor enantiomer), 3.98 min (major enantiomer).

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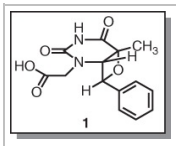
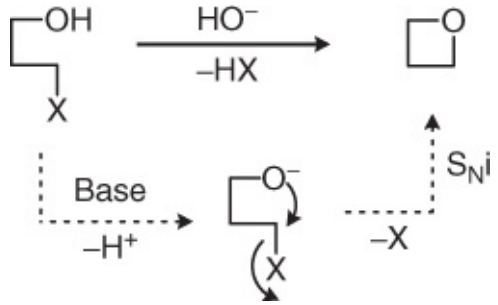
3.1.2 Oxetane Derivative

	***Topic:***	• Formation of an oxetane derivative by photochemical [2+2]-cycloaddition of a C=O group and a C=C double bond (Paterno–Büchi reaction)

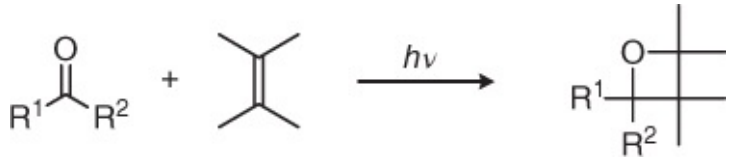
(a) General

Oxetanes are the higher homologs of oxiranes and possess a slightly distorted, nonplanar square structure [1]. For the synthesis of oxetanes [2], two methods (1 and 2) are useful.

1. Alcohols with a leaving group in the γ-position can be cyclized to oxetanes by S_Ni processes upon interaction with bases, viz.:

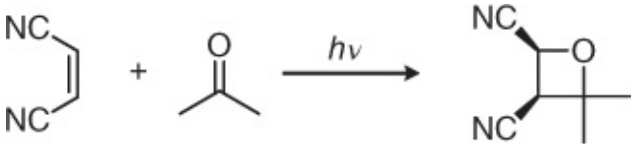


2. The photochemical [2+2]-cycloaddition of carbonyl compounds (aldehydes/ketones) and alkenes, known as the ***Paterno–Büchi reaction*** [3], likewise leads to oxetanes:



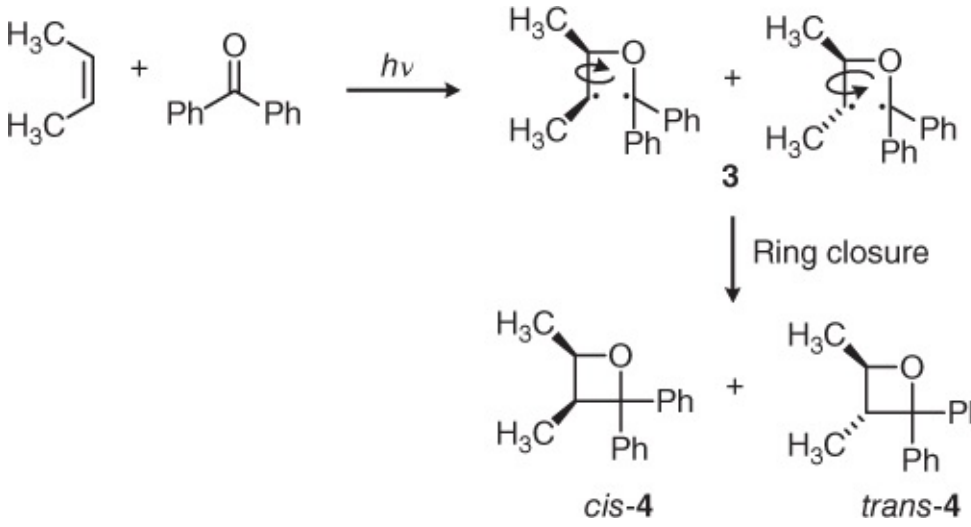
The carbonyl group is first excited to the singlet state by an n → π* transition, which is followed by intersystem crossing to the lower-energy triplet state; if the addition to the C=C bond takes place from the singlet state, according to the Woodward–Hoffman rules, the cycloaddition should be a concerted, stereospecific process.

In fact, stereospecificity in oxetane formation (e.g., →**2**) is observed with alkenes bearing electron-withdrawing substituents:



cis-**2**

In contrast, alkenes with donor substituents react in a nonstereoselective manner, as shown for the formation of the cis/trans isomeric oxetanes **4**.

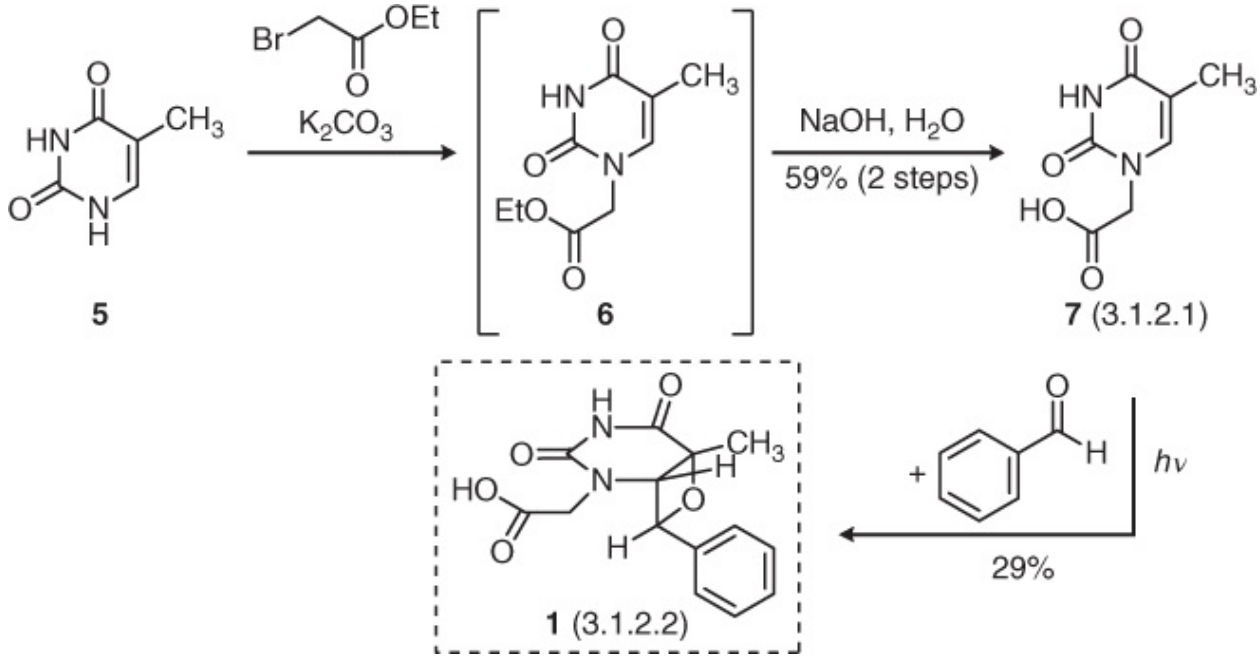


This is interpreted in terms of the intermediacy of diradical species **3** and their capacity to undergo rotation about the C-2/C-3 bond before ring closure.

Oxetane formation by [2+2]-photocycloaddition is generally possible with acceptor-substituted alkenes, quinones, and electron-deficient heterocycles. A typical example of a Paterno–Büchi reaction of such heterocyclic systems is presented in Section (b).

(b) Synthesis of 1

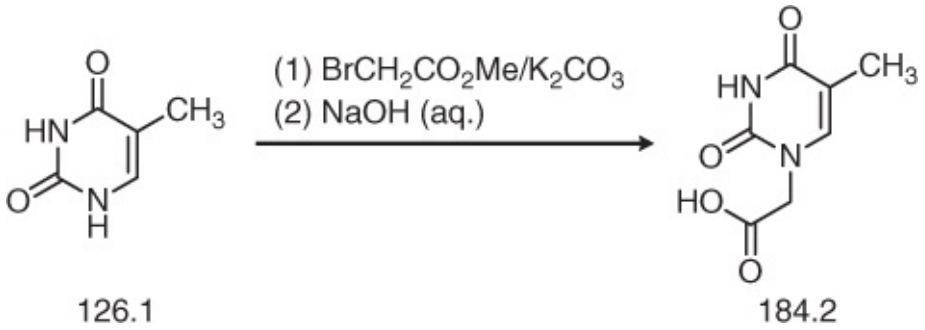
The substrate for the Paterno–Büchi reaction is thymine-1-acetic acid (**7**), which is easily accessible from thymine (**5**) by N-alkylation with ethyl bromoacetate to give **6** and subsequent saponification of the ester group:



When thymine-1-acetic acid (**7**) is irradiated together with benzaldehyde in H_2O/acetonitrile solution, the bicyclic oxetane derivative **1** is formed as a cycloadduct, in which the phenyl residue at the four-membered ring is oriented exclusively in an exo-configuration according to its spectroscopic data [4]. Since the photochemically induced [2+2]-cycloaddition of the aldehyde C=O group to the thymine 5,6-C=C double bond apparently occurs with complete regio-and stereospecificity, it is likely that oxetane formation proceeds in a concerted manner.

(c) Experimental Procedures for the Synthesis of 1

3.1.2.1	**	**Thymine-1-acetic acid** [5, 6]



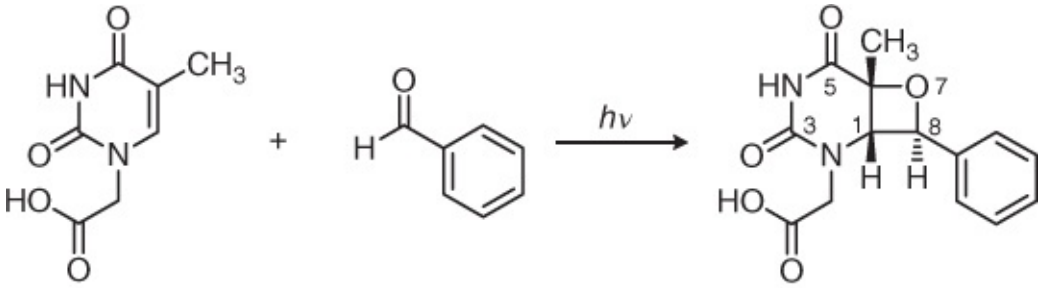
Methyl bromoacetate (11 ml, 119 mmol) is added to a suspension of thymine (15.0 g, 119 mmol) and K_2CO_3 (16.5 g, 119 mmol) in anhydrous DMF (300 ml), and the mixture is vigorously stirred overnight under an N_2 atmosphere.

The mixture is then filtered and concentrated to dryness *in vacuo*. The solid residue is treated with ice-cold H_2O (250 ml) and aqueous HCl (2 N, 10 ml) and the resulting mixture is stirred for 30 min at 0 °C. The precipitate is collected by filtration and washed with ice-cold H_2O (3 × 100 ml). It is then suspended in H_2O (120 ml) and NaOH (7.20 g) is added. The reaction mixture is heated to 100 °C for 10 min, cooled to 0 °C, treated with concentrated HCl (36%, 12 ml), and stirred for 30 min at 0 °C. The precipitate formed is collected by filtration, washed with ice-cold H_2O (3 × 100 ml), and dried over P_2O_5; 19.9 g (59%), mp 260–261 °C.

^{1}H NMR (300 MHz, [D_6]DMSO): δ (ppm) = 11.3 (s, 1H, CO_2H), 7.47 (s, 1H, 6-H), 4.36 (s, 2H, N-CH_2), 1.75 (s, 3H, 5-CH_3).

^{13}C NMR (50 MHz, [D_6]DMSO): δ (ppm) = 169.6 (CO_2H), 164.3 (C-4), 150.9 (C-2), 141.7 (C-6), 108.3 (C-5), 48.4 (N-CH_2), 11.8 (C-5-*C*H_3).

3.1.2.2	***	**(6-Methyl-3,5-dioxo-8-phenyl-7-oxa-2,4-diazabicyclo[4.2.0]oct-2-yl)-acetic acid** [4]



184.2 106.1 290.3

Thymine-1-acetic acid (cf. **3.1.2.1)** (4.00 g, 21.7 mmol) and benzaldehyde (10 ml, 95 mmol) are suspended in CH_3CN (240 ml). H_2O (40 ml) is added under vigorous stirring at 45 °C until a clear solution is obtained. The solution is degassed under argon and irradiated for 50 h with a water-cooled 300-W high-pressure Hg lamp without the use of filters (Caution: Do not look into the lamp!).

The solvent is then removed *in vacuo* and the residue is dissolved in EtOAc (500 ml). The organic phase is extracted with aqueous $KHCO_3$ solution (0.5 M, 5 × 100 ml), and the combined aqueous phases are extracted with EtOAc (3 × 150 ml). The aqueous phase is cooled and treated with ice-cold concentrated HCl (12 N) until pH 2 is reached. The precipitate formed is collected by filtration, washed with aqueous HCl (0.1 N, 100 ml, 0 °C), and dried *in vacuo*. The desired oxetane derivative is obtained as the pure exo product; 1.81 g (28%); mp 240–241 °C.

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3430, 1717, 1671, 1489, 1406, 1282, 1237, 886, 774.

^{1}H NMR (300 MHz, [D_6]DMSO): δ (ppm) = 12.81 (s, 1H, OH), 10.84 (s, 1H, NH), 7.46–7.31 (m, 5H, Ph), 5.64 (d, *J* = 6.6 Hz, 1H, 8-H), 4.35 (d, *J* = 6.6 Hz, 1H, 1-H), 4.09 (d, *J* = 17.6 Hz, 1H, N-CH_A), 3.80 (d, *J* = 17.6 Hz, 1H, N-CH_B), 1.66 (s, 3H, 6-CH_3).

^{13}C NMR (76 MHz, [D_6]DMSO): δ (ppm) = 170.3, 170.2 (CO_2H, C-5),

151.3 (C-3), 139.2, 128.5, 128.3, 126.4 (4 × Ph), 85.5 (C-6), 77.1 (C-8), 64.3 (C-1), 48.2 (N–CH_2), 22.3 (6-CH_3).

ESI-HRMS: *m*/*z* = 291.09774 $[M+H]^+$.

References

1. Eicher, Th., Hauptmann, S., and Speicher, A. (2012) *The Chemistry of Heterocycles*, 3rd edn, Wiley-VCH Verlag GmbH, Weinheim, p. 45.

2. Eicher, Th., Hauptmann, S., and Speicher, A. (2012) *The Chemistry of Heterocycles*, 3rd edn, Wiley-VCH Verlag GmbH, Weinheim, p. 46.

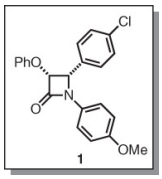
3. Smith, M.B. (2013) *March's Advanced Organic Chemistry*, 7th edn, John Wiley & Sons, Inc., New York, p. 1243.

4. (a) Stafforst, T. and Diederichsen, U. (2005) *Chem. Commun.*, **27**, 3430–3432; (b) Stafforst, T. and Diederichsen, U. (2007) *Eur. J. Org. Chem.*, 681–688.

5. Dueholm, K.L., Egholm, M., Behrens, C., Christensen, L., Hansen, H.F., Vulpius, T., Petersen, K.H., Berg, R.H., Nielsen, P.E., and Buchardt, O. (1994) *J. Org. Chem.*, **59**, 5767–5773.

6. Rabinowitz, J.L. and Gurin, S. (1953) *J. Am. Chem. Soc.*, **75**, 5758–5759.

3.1.3 Azetidin-2-one Derivative

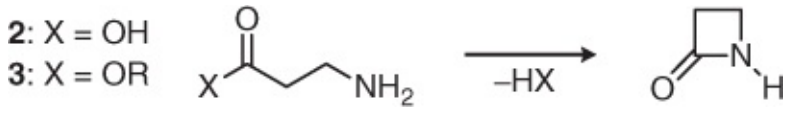
	***Topics:***	• Imine formation from Ar–NH_2 and Ar–CH=O • Dehydration of a carboxylic acid R–CH_2–CO_2H to a ketene R–CH=C=O using the Mukaiyama reagent; preparation of the Mukaiyama reagent • [2+2]-Cycloaddition of a ketene to an imine, cis-stereoselective β-lactam formation (Staudinger reaction)

(a) General

The ß-lactam moiety (azetidin-2-one) represents the pharmacophoric structural

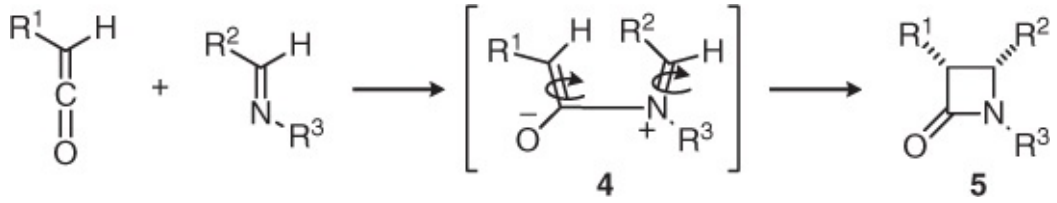
The β-lactam moiety (azetidin-2-one) represents the pharmacophore structural subunit in penicillins, cephalosporins, and related antibiotics [1]. For the synthesis of azetidin-2-ones, the following methods are representative [2]:

1. Cyclization of β-amino carboxylic acids (**2**) or the corresponding esters (**3**):



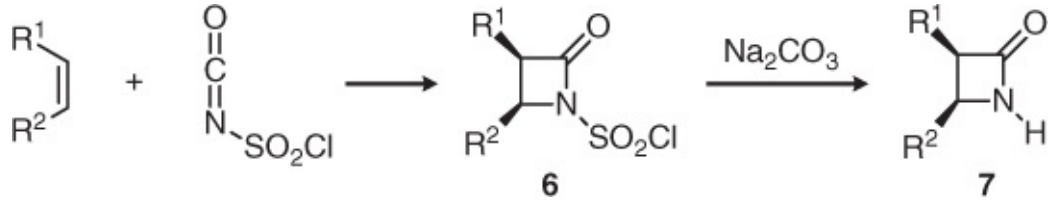
2. Cyclodehydration of **2** can be performed with, for example, $CH_3SO_2Cl/NaHCO_3$, while cyclization of **3** may be accomplished by treatment with a strong base, for example, a Grignard reagent or an amide (e.g., LDA (lithium diisopropylamide)). If the β-amino ester carries defined stereochemical information, stereodefined β-lactams are obtained [3].

3. [2+2]-Cycloaddition of ketenes to imines (Staudinger reaction):



As in similar cycloadditions of ketenes and alkenes, the Staudinger reaction is likely to occur via dipolar intermediates **4** in a thermally allowed two-step [2+2] process [4] to give *cis*-3,4-disubstituted azetidin-2-ones **5** stereoselectively.

4. [2+2]-Cycloaddition of alkenes to isocyanates, preferentially $ClSO_2–N=C=O$:



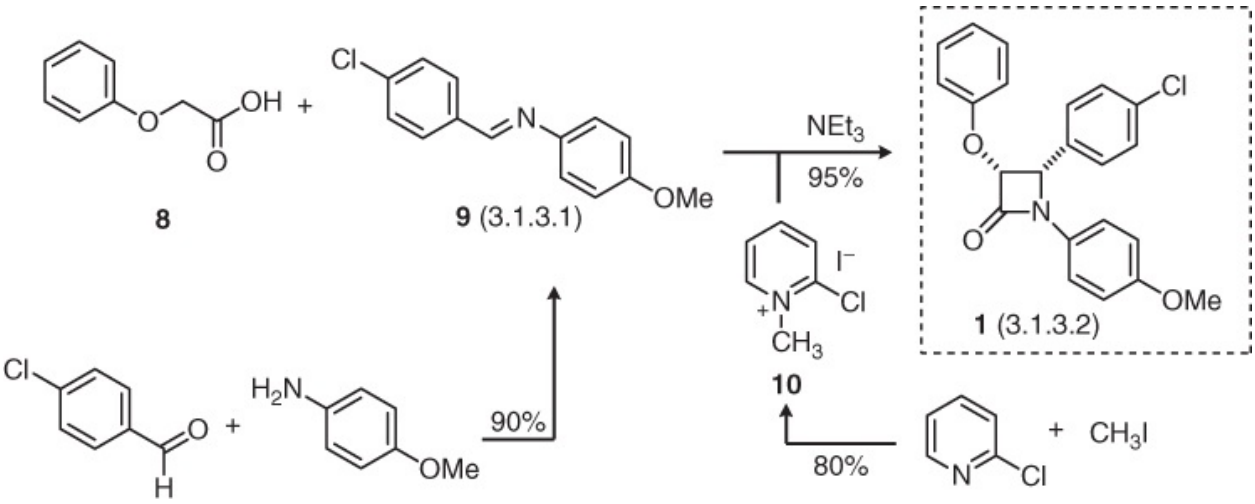
As in (2), this cycloaddition also occurs stereoselectively; thus, the stereochemistry of the alkene is transferred to the NH-azetidin-2-one **7**, which is obtained from the cycloadduct **6** by removal of the chlorosulfonyl group with base.

In Section (b), an example of the Staudinger method (2) of β-lactam formation is presented, which can also be performed in an asymmetric way [5].

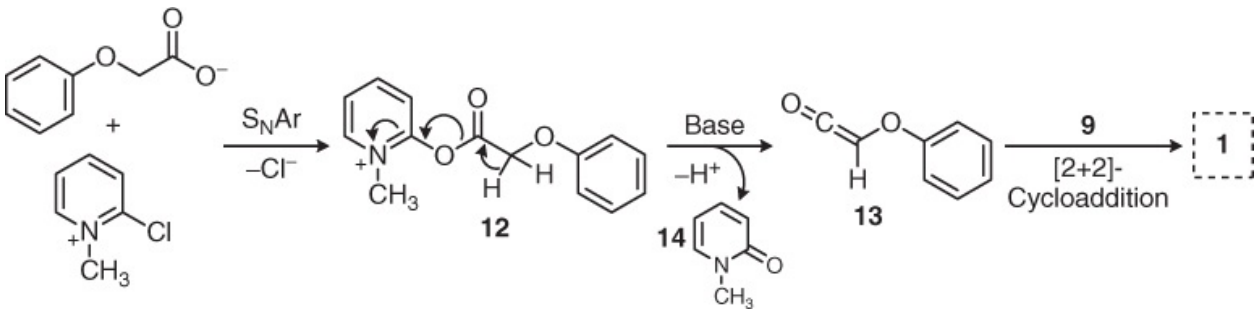
(b) Synthesis of 1

As precursors of the ketenes required in the Staudinger reaction, either acid chlorides in the presence of a base or carboxylic acids R–CH_2–CO_2H in the presence of a dehydrating agent are used. Thus, 2-chloro-1-methylpyridinium salts (e.g., **10**) – known as ***Mukaiyama reagents*** [6] – have been shown to allow dehydration of carboxylic acids to ketenes under mild conditions in an efficient one-pot procedure [5]. Compound **10**, originally developed for the synthesis of esters and amides from carboxylic acids, can be obtained from 2-chloropyridine by N-alkylation with methyl iodide.

Thus, the reaction of phenoxyacetic acid (**8**) with the imine **9** in the presence of triethylamine and 2-chloro-1-methylpyridinium iodide (**10**) proceeds smoothly at room temperature in CH_2Cl_2 and affords the azetidin-2-one **1** in almost quantitative yield with complete cis-stereoselectivity (ratio of *cis/trans* diastereomers of 99 : 1):

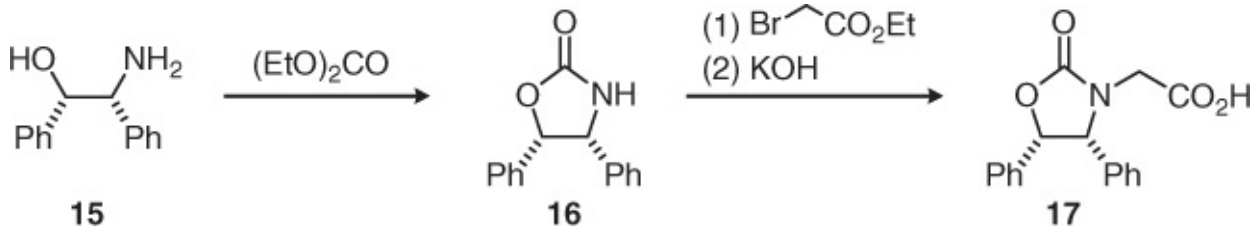


Initially, the pyridinium ion **10** undergoes a nucleophilic displacement (addition/elimination) of the 2-chloro substituent by the carboxylate (formed from **8** with NEt_3) to give the 2-acyloxypyridinium ion **12**; subsequently, **12** is deprotonated and cleaved to give 1-methyl-2-pyridone (**14**) and phenoxyketene (**13**). Compound **13** then undergoes the cis-selective [2+2]-cycloaddition with the imine **9** to give **1**.

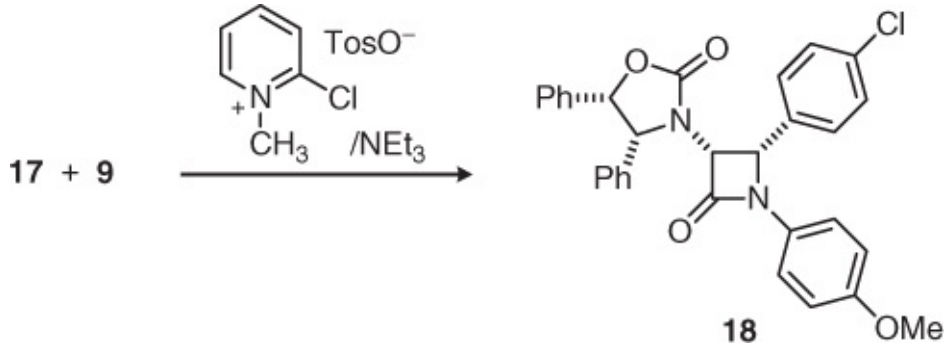


The imine **9** is prepared by condensation of 4-chlorobenzaldehyde with *p*-anisidine in the presence of $MgSO_4$.

It should be noted that an asymmetric version of the Staudinger reaction with **10** has been developed [5] by utilizing (+)-*erythro*-2-amino-1,2-diphenylethanol (**15**) as an auxiliary. Thus, a chiral glycine derivative **17** is prepared from oxazolidinone **16** (obtained from **15** by cyclization with diethyl carbonate) by N-alkylation with ethyl bromoacetate and saponification of the ester group:

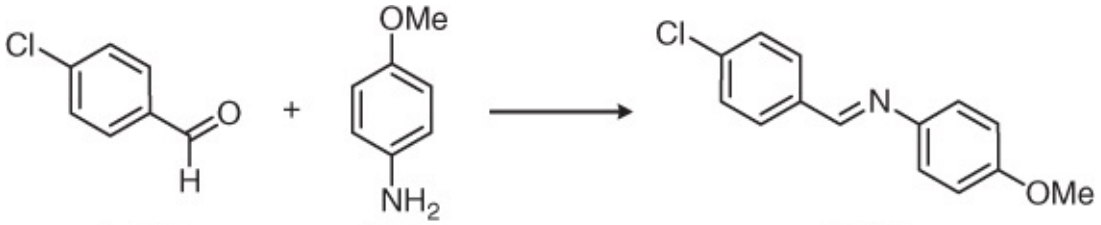


When the chiral carboxylic acid **17** is reacted with the imine **9** in the presence of 2-chloro-1-methylpyridinium *p*-toluenesulfonate **10** ($TosO^-$ instead of I^- and NEt_3 under the same conditions as described above), the *cis*-β-lactam **18** is obtained in diastereomerically pure form [6, 7].



(c) Experimental Procedures for the Synthesis of 1

3.1.3.1	**	**(*p*-Chlorobenzylidene)-(*p*-methoxyphenyl)-imine** [5]



A solution of *p*-anisidine (2.46 g, 20.0 mmol) in anhydrous CH_2Cl_2 (10 ml) is added over a period of 5 min to a stirred solution of *p*-chlorobenzaldehyde (2.81 g, 20.0 mmol) in anhydrous CH_2Cl_2 (20 ml) under argon atmosphere. A large excess of magnesium sulfate (3.00 g) is added, and the resulting mixture is stirred for 17 h at room temperature.

The solution is then filtered and the solvent removed *in vacuo* to afford the crude imine. Recrystallization from *n*-hexane/CH_2Cl_2 (1 : 1) gives the product as a colorless solid; 3.98 g (81%), mp 113–115 °C; TLC ($CHCl_3$/MeOH, 19 : 1): R_f =0.76.

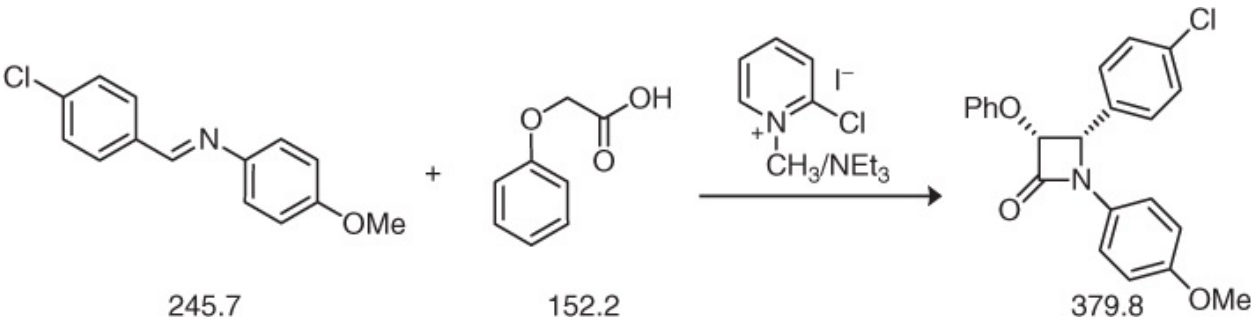
IR (KBr) $\tilde{\nu}$ (cm^{-1}) = 1620, 1506, 1255, 839.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.42 (s, 1H, N = CH), 7.85–7.75 (m, 2H, Ar), 7.47 to 7.35 (m, 2H, Ar), 7.25–7.17 (m, 2H, Ar), 6.94–6.86 (m, 2H, Ar), 3.82 (s, 3H, OCH_3).

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 158.4 (C_qCH=N), 156.6 (N=CH), 144.3, 136.8, 134.8 (3 × Ar–C_q), 129.6, 128.9, 122.2, 114.3 (4 × Ar–C), 55.43 (OCH_3).

MS (EI, 70 eV): *m*/*z* = 245 [M+H$^+$].

3.1.3.2	**	***cis*-4-(*p*-Chlorophenyl)-1-(*p*-methoxyphenyl)-3-phenoxy-azetidin-2-one** [5]



Under an argon atmosphere, triethylamine (0.64 ml, 4.59 mmol) is added to a stirred solution of phenoxyacetic acid (298.8 mg, 1.96 mmol) and 2-chloro-1-methylpyridinium iodide (515.2 mg, 2.02 mmol) in anhydrous CH_2Cl_2 (5.0 ml) at room temperature. The imine **3.1.3.1** (562.8 mg, 2.29 mmol) in CH_2Cl_2 (2.0 ml) is then added, and stirring is continued for 17 h (after a few minutes, a suspension is formed).

Afterwards, H_2O (5.0 ml) is added and the mixture is extracted with CH_2Cl_2 (3 × 30 ml). The combined organic layers are washed with brine (30 ml), dried over $MgSO_4$, filtered, and the solvent is removed *in vacuo*. Recrystallization ($CHCl_3$) yields the product as colorless crystals; 702.5 mg (94%), mp 168–170 °C; TLC (CH_2Cl_2): R_f = 0.37; $[\alpha]^{20}_D$ = 0.0 (*c* = 0.5, DMSO (dimethyl sulfoxide)).

IR (KBr) $\tilde{\nu}$ (cm^{-1}) = 1745, 1598, 1514, 1394, 1240, 1113, 839, 751.

^{1}H NMR (300 MHz, $CDCl_3$, 50 °C): δ (ppm) = 7.36–7.11 (m, 8H, Ar), 6.97–6.75 (m, 5H, Ar), 5.53 (d, *J* = 4.6 Hz, 1H, PhOC*H*), 5.31 (d, *J* = 4.6 Hz, 1H, *p*-ClC_6H_4CH), 3.74 (s, 3H, OCH_3).

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 162.3 (NC = O), 157.0 (Ar–C_q), 156.8 (Ar–C_q), 134.7 (Ar–C_q), 131.6 (Ar–C_q), 130.4 (Ar), 129.5 (2 × Ar), 129.4 (2 × Ar), 128.7 (2 × Ar), 122.4 (Ar), 118.9 (2 × Ar), 115.8 (2 × Ar), 114.6 (2 × Ar), 81.4 (PhOCH), 61.5 (*p*-ClC_6H_4CH), 55.5 (OCH_3).

MS (ESI): *m*/*z* (%) = 783 (100) $[2M+Na]^+$, 402 (88) $[M+Na]^+$.

References

1. (a) Eicher, Th., Hauptmann, S., and Speicher, A. (2012) *The Chemistry of Heterocycles*, 3rd edn, Wiley-VCH Verlag GmbH, Weinheim, p. 52/212/455;(b)

Coates, C., Kabir, J., and Turos, E. (2005) *Sci. Synth.*, **21**, 609–646.

2. Miller, M.J. (2000) *Tetrahedron*, **56**, 5553–5742.

3. For instructive examples, see: (a) Bull, S.D., Davies, S.G., Kelly, P.M., Gianotti, M., and Smith, A.D. (2001) *J. Chem. Soc., Perkin Trans. 1*, 3106–3111;(b) Córdova, A., Watanabe, S., Tanaka, F., Notz, W., and Barbas, C.F. III (2002) *J. Am. Chem. Soc.*, **124**, 1866–1867.

4. Smith, M.B. (2013) *March's Advanced Organic Chemistry*, 7th edn, John Wiley & Sons, Inc., New York, p. 1529.

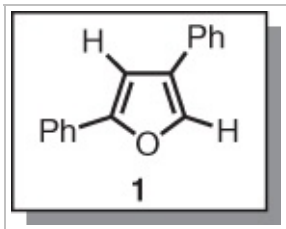
5. Matsui, S., Hashimoto, Y., and Saigo, K. (1998) *Synthesis*, 1161–1166.

6. Alternative methods for the stereoselective formation of *cis*-3,4-disubstituted β-lactams by the Staudinger reaction have been reported: (a) France, S., Wack, H., Hafez, A.M., Taggi, A.E., Witsil, D.R., and Lectka, T. (2002) *Org. Lett.*, **4**, 1603–1605;(b) Shah, M.H., France, S., and Lectka, T. (2003) *Synlett*, 1937–1939.

7. For the formation of *trans*-3,4-disubstituted β-lactams by the Staudinger reaction, see: (a) Nahmany, M. and Melman, A. (2006) *J. Org. Chem.*, **71**, 5804–5806;(b) Yuan, Q., Jiang, S.-Z., and Wang, Y.-G. (2006) *Synlett*, 1113–115 (auxiliary-assisted enantioselective synthesis).

3.2 Five-Membered Heterocycles

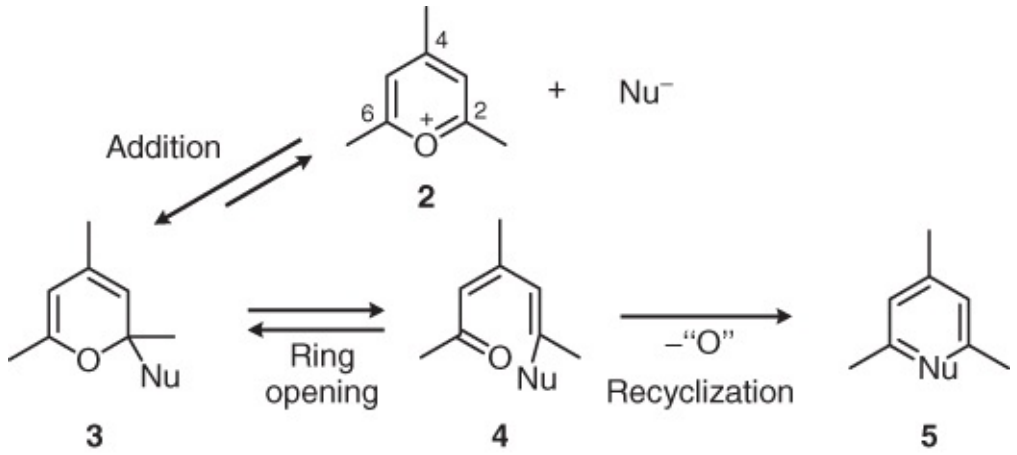
3.2.1 2,4-Diphenylfuran

 1	***Topics:***	• Transformation of pyrylium salts to furans • Ring opening of pyrylium ions and recyclization • Haller–Bauer cleavage of non-enolizable ketones

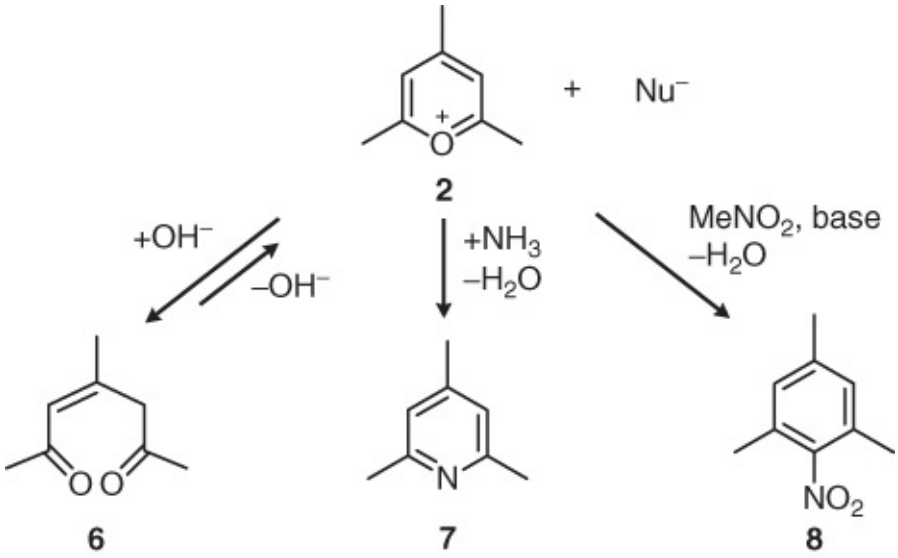
(a) General

Pyrylium ions such as **2** are positively charged aromatic heterocycles with one

oxygen in a six-membered ring system. They can easily add a nucleophile at the positions 2, 4, and 6.



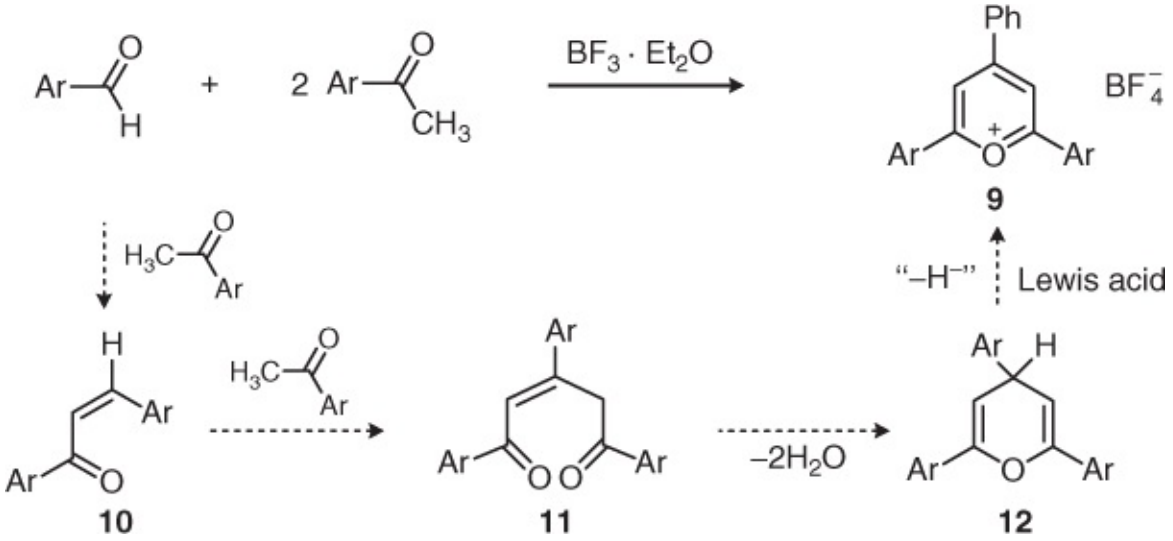
Attack of the nucleophile at the 2-position leads to 2*H*-pyrans **3**, which by electrocyclic ring opening gives products of type **4**. If the reacting nucleophile is OH^-, the pyrylium system is reconstituted in acid media; however, if N-, S-, P-, or C-containing nucleophiles are used, new heterocyclic or carbocyclic systems **5** are formed with the incorporation of the attacking atom. As illustrated by the examples **6–8**, the transformation of pyrylium ions is of considerable preparative value [1]:



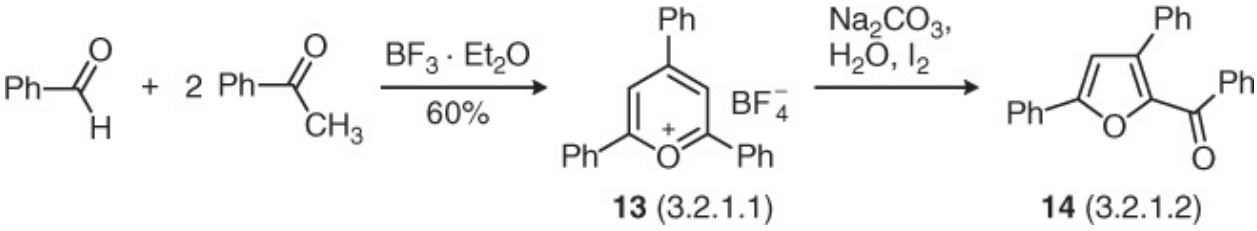
In this way, reaction of the pyrylium ion **9** with iodine in the presence of sodium carbonate in aqueous medium allows a convenient and regioselective synthesis of 2,4-disubstituted furans [2], which are otherwise difficult to obtain [3].

(b) Synthesis of 1

2,4,6-Triphenylpyrylium tetrafluoroborate (**13**) is prepared by means of a modified Dilthey synthesis [2, 4]. In this method of pyrylium ion formation, an aryl aldehyde is cyclocondensed with two molecules of an acetophenone in the presence of BF_3-etherate; intermediates are the chalcones **10** (resulting from aldol condensation of the first acetophenone with the aryl aldehyde), the pentane-1,5-diones **11** (resulting from Michael addition of the second acetophenone to **10**), and the 4*H*-pyrans **12** (resulting from cyclodehydration of **11**); the final step is a (formal) hydride abstraction from **12** by the Lewis acid, providing the 2,4,6-triarylpyrylium salt **9**:

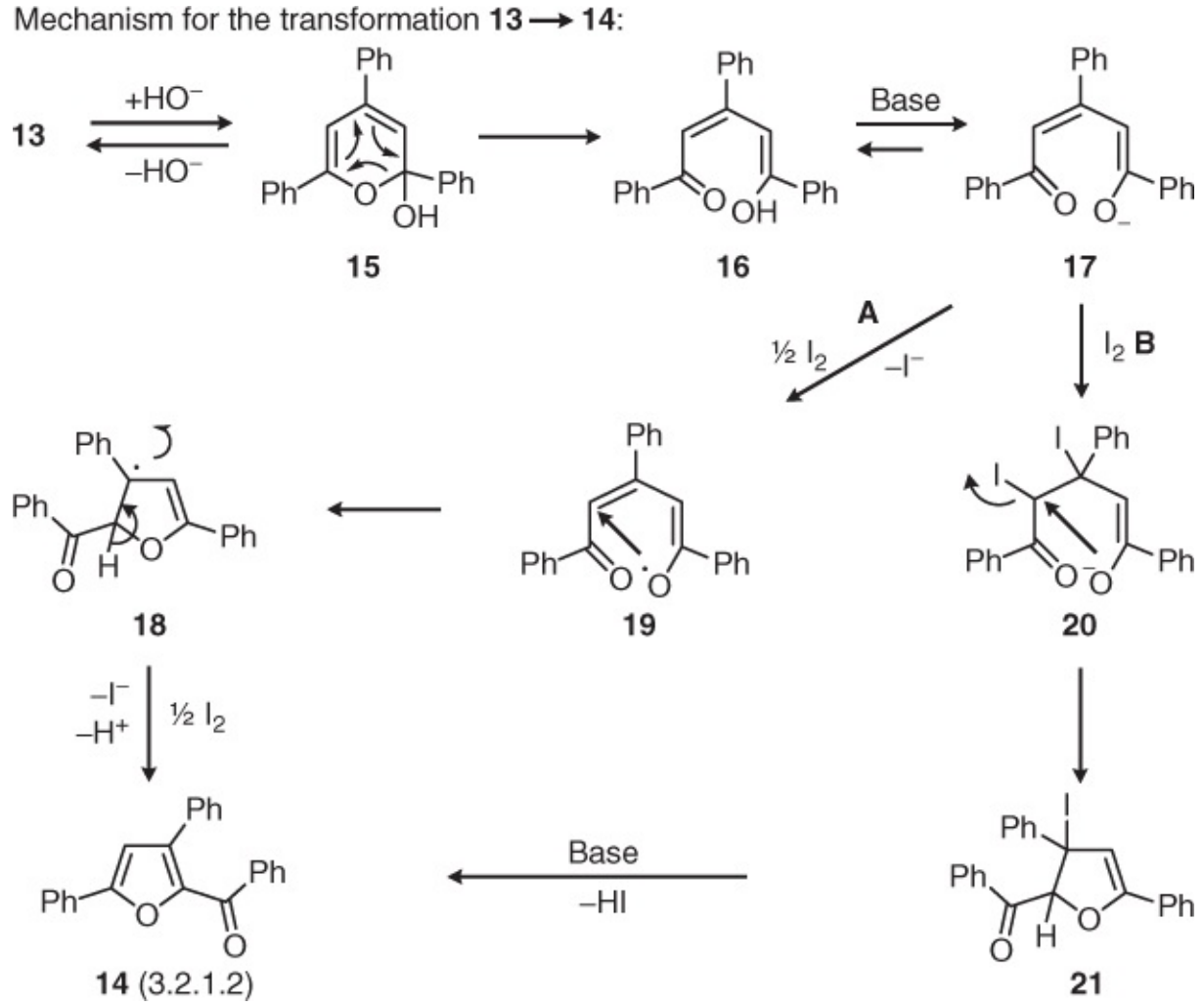


Accordingly, the 2,4,6-triphenylpyrylium salt **13** is obtained from cyclocondensation of benzaldehyde and 2 equiv of acetophenone mediated by BF_3-etherate in benzene solution. Without further purification, **13** is treated first with Na_2CO_3 in H_2O/acetone and then with iodine to afford 2-benzoyl-3,5-diphenylfuran (**14**):

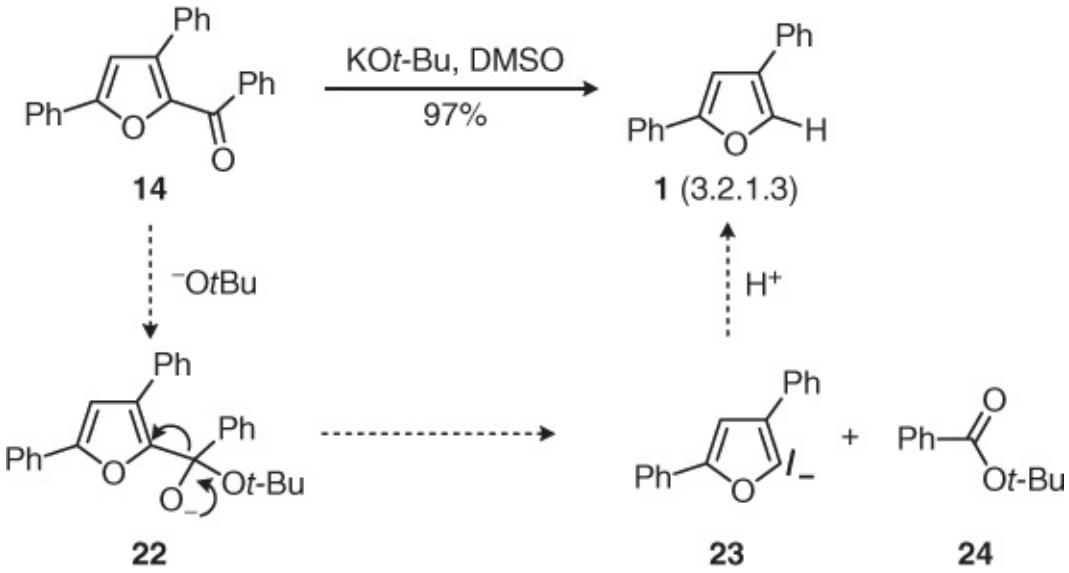


The ring contraction of **13** to give **14** can be interpreted in terms of initial addition of OH^- to C-2 of the pyrylium ion **13** (→**15**) followed by electrocyclic ring opening to yield the pentene-1,5-dione (formulated as enol **16**). Since the transformation of **13** to **14** requires a basic medium, it is likely that the anion **17** plays a central role in the furan formation upon reaction with iodine.

For the conversion of the anion **17** to **14**, two mechanistic alternatives (A/B) can be considered. In A, single-electron transfer (SET) leads to a radical **19** and its cyclization product **18** (both highly delocalized); a second SET step then yields the 2-benzoylfuran **14**. In B, iodine is added to the α,β-double bond of **17** to give an iodoenolate **20**, which may cyclize to the dihydrofuran **21** by S_Ni displacement of iodide and aromatize to **14** by base-induced elimination of HI. For both pathways A/B, the overall stoichiometry is that one molecule of I_2 is consumed and two I^- and two H^+ ions are formed [5].

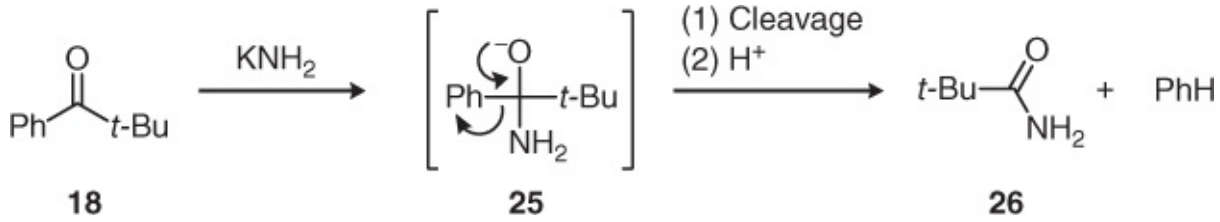


Finally, the 2-benzoyl group in the furan **14** has to be replaced by hydrogen. This transformation is accomplished by application of a Haller–Bauer-type reaction of **14** with KO*t*Bu in DMSO, leading to 2,4-diphenylfuran (**1**) upon hydrolysis:



In the transformation of **14** with KO*t*-Bu, an α-furyl carbanion **23** or a phenyl anion might result by cleavage of the primary adduct **22**. Since **23** is more stable than the phenyl anion, furan **1** and *tert*-butyl benzoate (**24**) are formed as the only products.

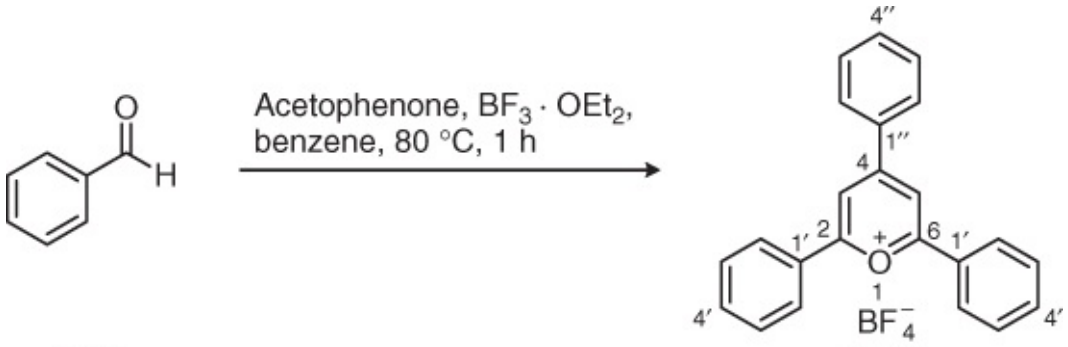
The Haller–Bauer reaction [6] involves a base-promoted acyl cleavage of a non-enolizable ketone; traditionally, the reaction is carried out with sodium amide as the base, thus representing a synthesis of amides from ketones. Cleavage of unsymmetrical ketones such as **18** is directed by the stability of the anion formed:



Because of the better stabilization of a phenyl anion compared to a *tert*-butyl anion, the intermediate **25**, which is formed by addition of the amide to ketone **18**, delivers benzene and the amide **26**.

(c) Experimental Procedures for the Synthesis of 1

3.2.1.1	*	**2,4,6-Triphenylpyrylium tetrafluoroborate** [3, 4]



106.1 396.2

Freshly distilled benzaldehyde (1.00 ml, 9.42 mmol) and acetophenone (2.50 ml, 20.7 mmol) in anhydrous benzene (10 ml; Caution: carcinogenic!) are added to a stirred solution of boron trifluoride etherate (6.00 ml, 22.6 mmol) under N_2 atmosphere. The mixture is heated to reflux for 2 h.

After cooling to room temperature, acetone (10 ml) is added and the dark red solution is poured into Et_2O (100 ml). The yellow precipitate of the pyrylium salt is collected by filtration, washed with Et_2O, and dried *in vacuo* for 12 h; 972 mg (26%), mp 247–248 °C.

UV (CH_3CN): λ_{max} (nm) (log ε) = 406.0 (7.219), 353.5 (7.159), 275.5 (7.051).

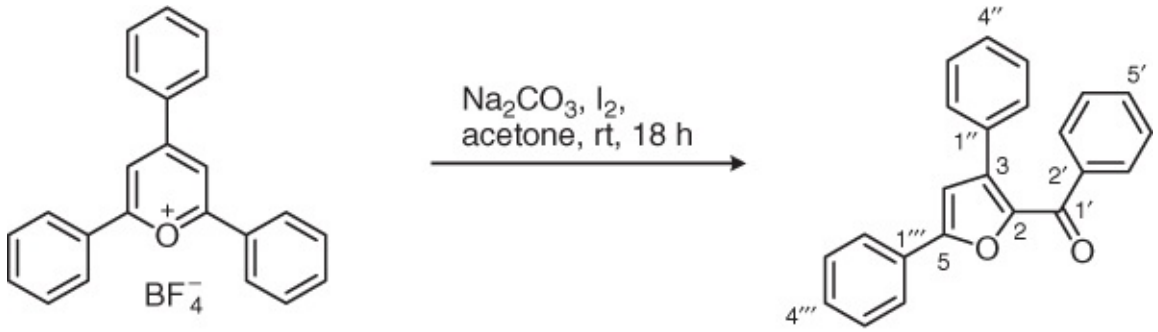
IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3070, 1745, 1624, 1593, 1579, 1527, 1497, 1470, 1273, 1248, 1194, 1167, 1057.

^{1}H NMR (300 MHz, [D_6]DMSO): δ (ppm) = 9.18 (s, 2H, 5-H, 3-H), 8.60 (d, *J* = 7.2 Hz, 4H, 2 × 2′-H, 2 × 6′-H), 7.95–7.78 (m, 11H, 11 × Ph–H).

^{13}C NMR (76 MHz, [D_6]DMSO): δ (ppm) = 172.1 (C-2, C-6), 167.4 (2 × C-1′), 136.1*, 133.9 (C-4), 130.9*, 130.7* (* = 15 × Ph–C), 130.2 (C-1″), 129.7, 116.4 (C-3, C-5).

MS (EI, 70 eV): *m*/*z* (%) = 396 (10) $[M]^+$, 309 (100) $[M-BF_4]^+$, 202 (46) $[M-C_7H_7BF_4O]^+$, 105 (69) $[M-C_{16}H_{12}BF_4]^+$, 77 (100) $[M-C_{17}H_{12}BF_4O]^+$, 49 (41) $[M-C_{19}H_{16}BF_4O]^+$.

3.2.1.2	*	**2-Benzoyl-3,5-diphenylfuran** [3]



396.2 324.4

A solution of Na_2CO_3 (500 mg, 4.71 mmol) in H_2O (1.6 ml) is added to a stirred suspension of the pyrylium salt **3.2.1.1** (972 mg, 2.46 mmol) in acetone (15 ml) and the mixture is stirred for 2 h at room temperature. Iodine (1.00 g, 3.93 mmol) is added, and stirring is continued for 16 h.

The dark mixture is then poured into a solution of $Na_2S_2O_3$ (6.21 g) in H_2O (75 ml), and the aqueous layer is extracted with CH_2Cl_2 (3 × 50 ml). The combined organic layers are washed with H_2O (50 ml) and brine (50 ml), dried over $MgSO_4$, and filtered, and the solvent is removed *in vacuo*. The residue is purified by column chromatography on silica gel (petroleum ether/EtOAc, 10 : 1) to afford the product as a yellow solid; 542 mg (68%), mp 119–120 °C, R_f = 0.43 (petroleum ether/EtOAc, 10 : 1).

UV (CH_3CN): λ_{max} (nm) (log ε) = 341.5 (6.954), 265 (6.844).

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3051, 2924, 2854, 1965, 1641, 1599, 1576, 1570, 1523, 1472.

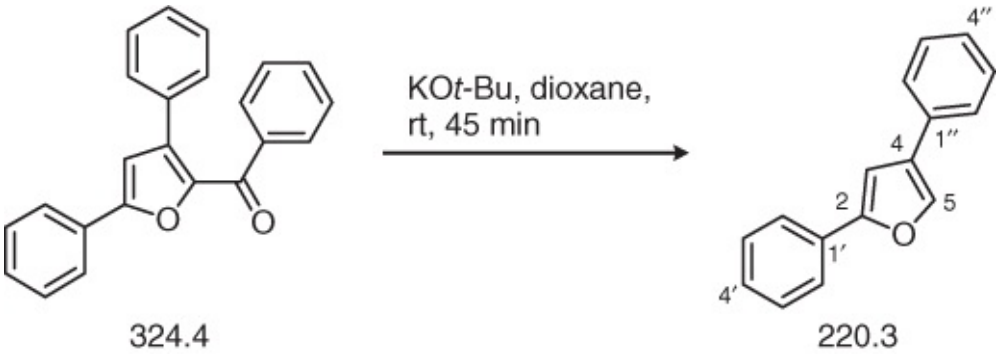
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.32–8.11 (m, 2H, 3′-H, 7′-H), 7.80 to 7.70 (m, 2H, 2‴-H, 6‴-H), 7.61–7.58 (m, 2H, 2″-H, 6″-H), 7.57–7.17 (m, 9H, 9 × Ar–H), 6.98 (s, 1H, 4-H).

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 183.5 (C-1′), 156.0 (C-2), 146.0 (C-5), 138.0 (C-1‴), 137.7 (C-3), 132.2 (C-1″), 132.2 (C-5′), 129.7, 129.3, 129.2 (6 × Ph–C), 129.0 (C-4‴), 128.4 (C-4″), 128.2, 128.1, 125.0 (6 × Ph–C), 109.8 (C-4).

MS (EI, 70 eV): *m*/*z* (%) = 324 (100) $[M]^+$, 247 (6) $[M-C_6H_5]^+$, 191 (10) $[M-C_8H_5O_2]^+$, 105 (8.5) $[M-C_{16}H_{11}O]^+$, 77 (17) $[M-C_{17}H_{11}O_2]^+$, 51 (10)

$[M-C_{21}H_{14}O_2]^+$.

3.2.1.3 * 2,4-Diphenylfuran [3]



H_2O (34.0 µl (!)) and the benzoyldiphenylfuran **3.2.1.2** (200 mg, 0.62 mmol) are added to a stirred suspension of potassium *tert*-butoxide (800 mg, 7.08 mmol, *note*) in 1,4-dioxane (5.00 ml), and stirring is continued for 30 min.

The mixture is then slowly poured into iced water (30 ml) and stirred for 15 min. The product is extracted with CH_2Cl_2 (3 × 10 ml), and the combined organic layers are washed with H_2O (10 ml) and brine (10 ml). The organic layer is dried over $MgSO_4$ and filtered, and the solvent is removed *in vacuo.* The residue is purified by column chromatography on silica gel (petroleum ether/EtOAc, 10 : 1) to afford 225 mg (97%) of 2,4-diphenylfuran as colorless needles; mp 109–110 °C, R_f = 0.60 (SiO_2, petroleum ether/EtOAc, 10 : 1).

UV (CH_3CN): λ_{max} (nm) (log ε) = 275.5 (6.696), 242.0 (6.64), 226.5 (6.611), 199.5 (6.556), 197.5 (6.551).

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3441, 3135, 3106, 3036, 1609, 1538, 1490, 1453, 1199.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.95–7.91 (m, 2H, 2′-H, 6′-H), 7.77–7.74 (m, 2H, 2″-H, 6″-H), 7.62–7.56 (m, 4H, 3′-H, 5′-H, 3″-H, 5″-H), 7.44–7.30 (m, 2H, 4′-H, 4″-H), 7.24 (s, 1H, 2-H), 6.97 (s, 1H, 5-H).

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 154.8 (C-2), 137.9 (C-5), 132.3 (C-1′), 130.6 (C-4), 128.8, 128.7 (2 × Ph–C), 128.3 (C-1″), 127.6, 127.1, 123.8, 123.9 (8 × Ph–C), 103.9 (C-3).

MS (EI, 70 eV): *m*/*z* (%) = 220 (100) $[M]^+$, 192 (15) $[M-CO]^+$, 191 (53) $[M-CHO]^+$, 189 (16) $[M-CH_3O]^+$; 165 (7) $[M-C_{13}H_9]^+$.

Note: KO*t*Bu is a highly hygroscopic reagent and loses quality after short time of exposure to air.

References

1. (a) Eicher, Th., Hauptmann, S., and Speicher, A. (2012) *The Chemistry of Heterocycles*, 3rd edn, Wiley-VCH Verlag GmbH, Weinheim, p. 299ff;(b) Balaban, T.S. and Balaban, A.T. (2003) *Sci. Synth.*, **14**, 11–200;(c) Kreher, R.P. (Ed.) (1992) *Methoden der organischen Chemie (Houben-Weyl)*, 4th edn, vol. E 7b, Georg Thieme Verlag, Stuttgart, p. 755.

2. For the chemistry and synthesis of furans, see: (a) Koenig, B. (2002) *Sci. Synth.*, **9**, 183–285;(b) Eberbach, W. in Müller, E. (Ed) (1992) *Methoden der Organischen Chemie (Houben-Weyl)*, 4th edn, vol. E 6a, Georg Thieme Verlag, Stuttgart, p. 16.

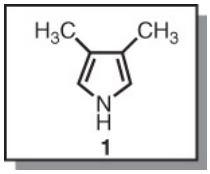
3. Francesconi, I., Patel, A., and Boykin, D.W. (1999) *Synthesis*, 61–67.

4. Lombard, R. and Stephan, J.-P. (1958) *Bull. Soc. Chim. Fr.*, **1**, 1458–1462.

5. When the pyrylium ion **13** is reacted with Na_2S and the product is oxidized with I_2 or air, the thiophene compound analogous to **14** is obtained: Pedersen, C.L. (1975) *Acta Chem. Scand. Ser. B*, **29**, 791–796.

6. For a review, see: Gilday, J.P. and Paquette, L.A. (1990) *Org. Prep. Proced. Int.*, **22**, 167–201.

3.2.2 3,4-Dimethylpyrrole

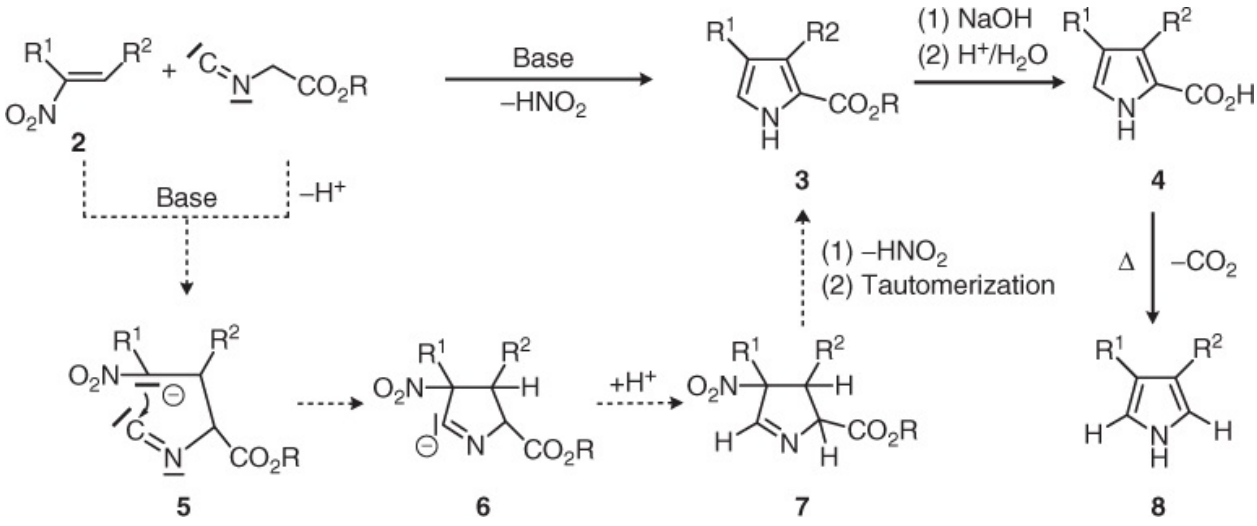
 1	***Topics:***	• Barton–Zard synthesis of pyrroles • Nitroaldol addition • Acetylation of a nitroaldol • Saponification of a carboxylic ester, decarboxylation

		of a pyrrole carboxylic acid • Formation of an isocyanoacetate by dehydration of a *N*-formyl-α-amino ester

(a) General

Numerous methods are available for the synthesis of pyrroles [1]. While the classical Paal–Knorr synthesis (cf. Section 3.5.3) is still the method of choice for the preparation of 2,5-disubstituted pyrroles, 3,4-disubstituted pyrroles such as **1** are conveniently obtained by isocyanide-based methods, among them the Barton–Zard synthesis and the van Leusen synthesis.

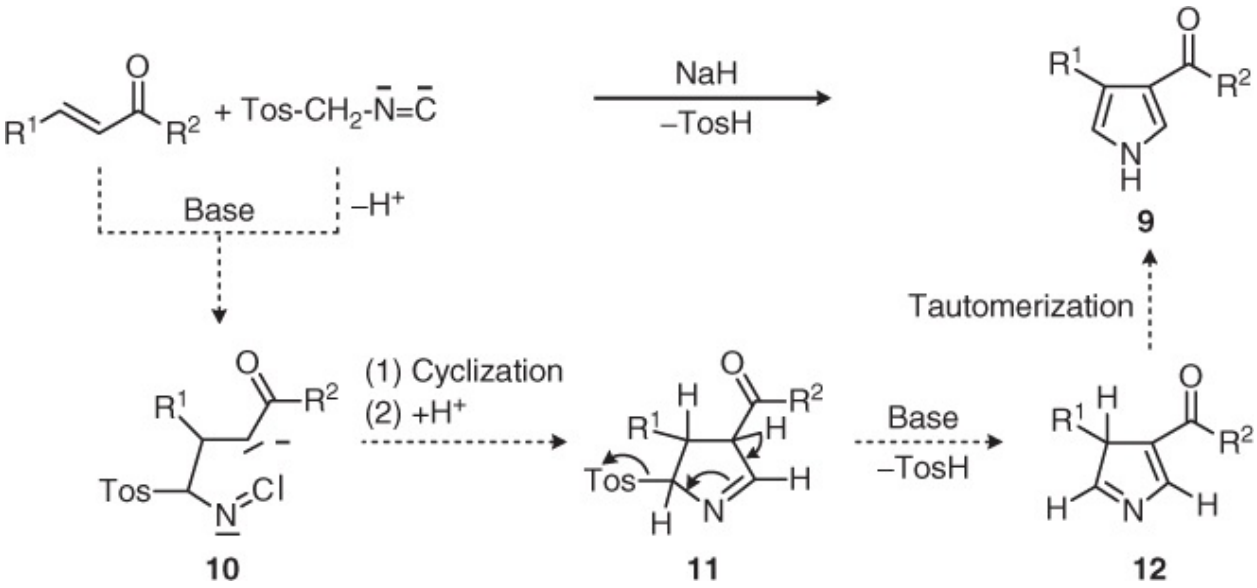
In the Barton–Zard synthesis [2], 5-unsubstituted 3,4-disubstituted pyrrole-2-carboxylates **3** are formed from isocyanoacetates and nitroalkenes **2** in the presence of a base (e.g., DBU (1,8-diazabicyclo[5.4.0]undec-7-ene), tetramethylguanidine (TMG), K_2CO_3 [3]):



This cyclocondensation is thought to proceed via Michael addition of deprotonated isocyanoacetate to the nitroalkene, intramolecular trapping of the resulting nitronate anion **5** by the isocyanide functionality (→**6**), reprotonation (**6**→**7**), and base-induced elimination of HNO_2, followed by tautomerization of the resulting 2*H*-pyrroles to 1*H*-pyrroles **3**. The pyrrole-2-carboxylates **3** can be saponified to give the pyrrole-2-carboxylic acids **4**, which undergo thermal decarboxylation to the 3,4-disubstituted pyrroles **8**.

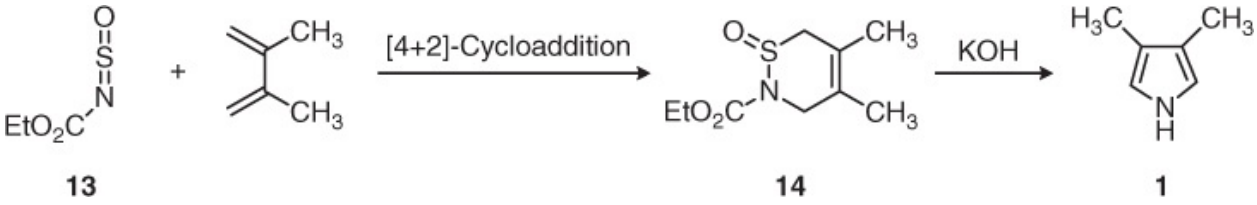
Closely related to the Barton–Zard method is the van Leusen pyrrole synthesis [4], in which (tosylmethyl)isocyanide is cyclocondensed with α,β-unsaturated

ketones in the presence of a base (e.g., NaH) to give 3-acyl-4-substituted pyrroles **9**:



In van Leusen synthesis, conjugate addition of deprotonated (tosylmethyl) isocyanide to the enone produces an enolate **10**, which is intramolecularly trapped by the isocyanide function with ring closure and reprotonation (**10** → **11**); deprotonation of **11** at 3-CH gives an enolate, which undergoes 1,4-elimination of sulfinate and formation of a 3*H*-pyrrole **12**, which finally tautomerizes to the 2,5-unsubstituted 1*H*-pyrrole **9**.

3,4-Dimethylpyrrole has been synthesized via several routes [5]. One of them utilizes a Diels–Alder reaction of the sulfoximine **13** with 2,3-dimethylbuta-1,3-diene followed by base-induced ring contraction of the cycloadduct **14** [6]:



However, owing to the preparative disadvantages of this conceptually elegant approach, the Barton–Zard protocol [5] is preferred for the synthesis of **1** and is thus presented in Section (b).

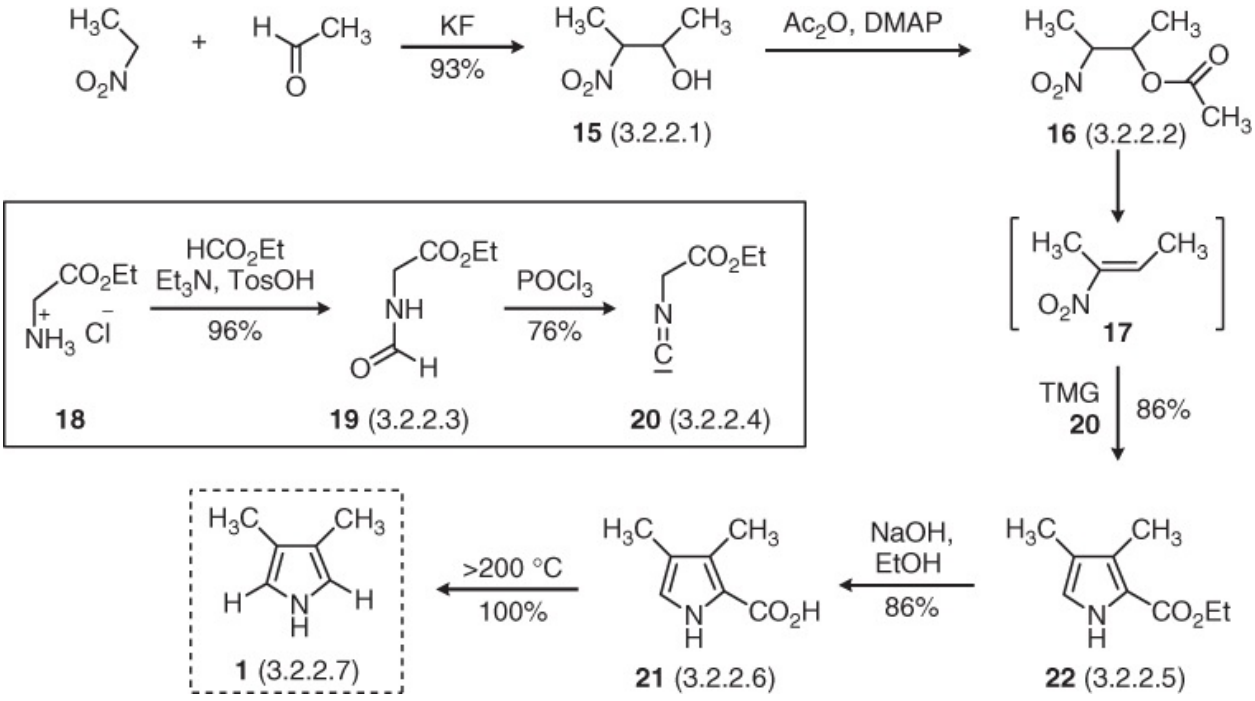
(b) Synthesis of 1

First, 2-acetoxy-3-nitrobutane (**16**) is prepared by fluoride-mediated nitroaldol addition (Henry reaction) of nitroethane to acetaldehyde (→ **15**) and subsequent

dimethylaminopyridine (DMAP)-catalyzed acetylation of the nitroaldol **15** with acetic anhydride.

Second, ethyl isocyanoacetate (**20**) is prepared by N-formylation of ethyl glycinate hydrochloride (**18**) by aminolysis of ethyl formate (→**19**) followed by dehydration of *N*-formyl glycine **19** with $POCl_3$. The dehydration of primary *N*-formyl amines, preferentially with $POCl_3$, is a widely used method for isonitrile formation [7].

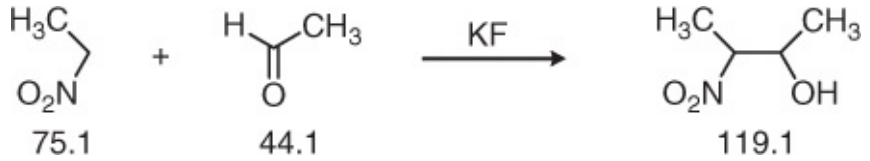
Then, 2-acetoxy-3-nitrobutane (**16**) and ethyl isocyanoacetate (**20**) are subjected to the Barton–Zard cyclocondensation in the presence of TMG as a base to give the pyrrole-2-carboxylate **22**. 2-Nitro-2-butene (**17**) required for the Barton–Zard process is initially produced *in situ* by base-induced elimination of acetic acid from the acetoxybutane **16**:



The synthesis of **1** is completed by saponification of the ester **22** using NaOH in ethanol followed by thermal decarboxylation of the thus formed pyrrole-2-carboxylic acid **21** to yield the 3,4-dimethyl-pyrrole (**1**) [8].

(c) Experimental Procedures for the Synthesis of 1

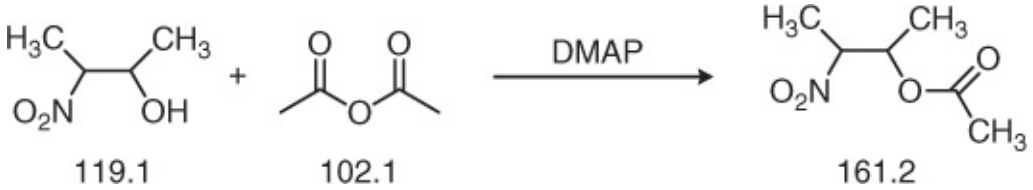
3.2.2.1	*	**2-Nitrobutan-3-ol** [5]



Nitroethane (75.1 g, 1.00 mol) is added dropwise over 30 min to a stirred mixture of acetaldehyde (44.1 g, 56.5 ml, 1.00 mol), potassium fluoride (2.95 g, 50.0 mmol), and isopropanol (40 ml) at 0 °C. The temperature is raised to ambient to start the weakly exothermic aldol addition reaction, and then the mixture is maintained at 35–40 °C by cooling with an ice/water mixture. After 30 min, stirring is continued for 12 h at room temperature.

The solvent is removed *in vacuo*, and the residue is dissolved in CH_2Cl_2 (100 ml). The solution is filtered through a G-4 fritted disc, and the solvent is removed *in vacuo*. The oily residue (110.6 g, 93%) consists of the almost pure product, which is used in the next step without further purification; TLC (CH_2Cl_2): R_f = 0.25; for NMR data, see Ref. [7].

3.2.2.2 ** 3-Acetoxy-2-nitrobutane [5]



Acetic anhydride (77.2 g, 0.75 mol) is added dropwise to a stirred solution of the nitro alcohol **3.2.2.1** (59.5 g, 0.50 mol) and DMAP (2.00 g, 244 mmol) in anhydrous CH_2Cl_2 (100 ml). An exothermic reaction occurs, and the temperature should be kept below 40 °C (occasional cooling with an ice bath). When the addition is complete, stirring is continued at 35–40 °C (inner temperature) for 2 h; the solution develops a green color.

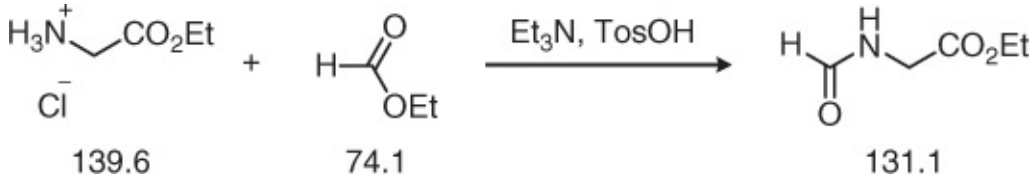
The reaction mixture is brought to 30 °C, whereupon methanol (32.0 g, 1.00 mol) is added dropwise and stirring is continued for 2 h at room temperature. The solvent is evaporated *in vacuo*, the residue is dissolved in CH_2Cl_2 (20 ml), and DMAP is removed by rapid filtration through SiO_2 (eluent: CH_2Cl_2). After evaporation of the solvent, the residue is distilled *in vacuo*, wherein the bath temperature should not exceed 60 °C (shield) to afford the product as blue oil; 58.0 g (72%), $bp_{0.01}$ 50–53 °C; R_f = 0.75 (CH_2Cl_2) (note).

IR (film): $\tilde{\nu}$ (cm^{-1}) = 3471, 2954, 2860, 1743, 1555, 1455 [7].

^{1}H NMR (400 MHz, $CDCl_3$, diastereomeric mixture): δ (ppm) = 5.25–4.60 (m, 2H, 2 × CH), 2.01, 1.97 (2 × s, 3H, $OC(O)CH_3$), 1.50–1.25 (m, 6H, 2 × CH_3).

Note: In Ref. [7], it is reported that an explosion occurred upon attempted vacuum distillation on a small scale. Therefore, in Ref. [7], the crude product was used for pyrrole synthesis (→**3.2.2.5**). In our experience, the nitroacetate can be safely handled under the above-described conditions for distillative purification. The origin of the blue color is unknown.

3.2.2.3	*	***N*-Formylglycine ethyl ester**[1]



139.6 74.1 131.1

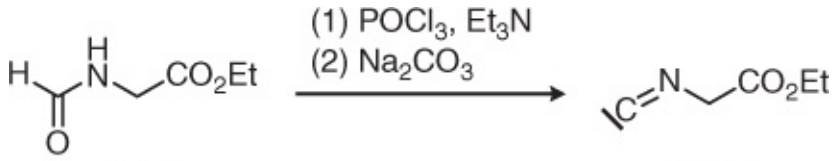
Triethylamine (111 g, 1.10 mol) is added dropwise to a refluxing solution of glycine ethyl ester hydrochloride (140 g, 1.00 mol) and *p*-toluenesulfonic acid monohydrate (100 mg) in ethyl formate (500 ml). Heating under reflux is continued for 20 h.

The solution is then cooled to 20 °C, the precipitated triethylamine hydrochloride is removed by filtration, and the solution is concentrated *in vacuo* to a volume of approximately 150 ml. On cooling to −5 °C, more hydrochloride precipitates, which is removed by filtration. The filtrate is distilled *in vacuo* to give a colorless oil; 126 g (96%), $bp_{0.1}$ 110–111 °C.

IR (film): $\tilde{\nu}$ (cm^{-1}) = 3300, 1740, 1655.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.24 (s, 1H, CHO), 6.28 (s_{br}, 1H, NH), 4.22 (q, *J* = 7.1 Hz, 2H, OCH_2), 4.08/4.07 (2s, 2H, NCH_2), 1.29 (t, *J* = 7.1 Hz, 3H, CH_3).

3.2.2.4	**	**Ethyl Isocyanoacetate** [9]



Phosphorus oxychloride (76.5 g, 0.50 mol) is added dropwise to a stirred solution of the *N*-formyl ester **3.2.2.3** (65.5 g, 0.50 mol) and NEt_3 (125 g, 1.24 mol) in CH_2Cl_2 (500 ml) at 0 °C. Stirring is continued for 1 h.

Sodium carbonate (100 g) in water (400 ml) is then added, keeping the temperature at 20–25 °C with rapid stirring (Caution: foaming!). Stirring is continued at room temperature for 30 min.

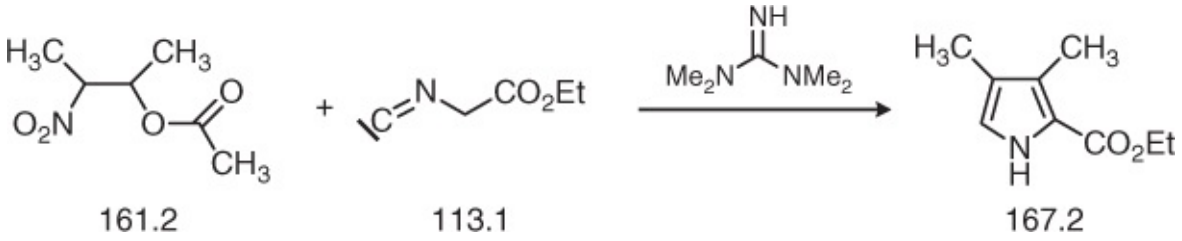
The aqueous phase is diluted with water (600 ml) and extracted with CH_2Cl_2 (2 × 250 ml). The organic phase is washed with brine (250 ml), dried over Na_2SO_4, and filtered, and the solvent is removed *in vacuo*. The residue is distilled *in vacuo* to give the product as a colorless oil; 43.1 g (76%), bp_{12} 80–82 °C (note).

IR (film): $\tilde{\nu}$ (cm^{-1}) = 2150, 1750.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 4.28 (q, *J* = 7.1 Hz, 2H, OCH_2), 4.22 (s, 2H, NCH_2), 1.31 (t, *J* = 7.1 Hz, 3H, CH_3).

Note: Caution: All reactions must be conducted in a hood, and rubber gloves must be worn!

3.2.2.5	**	**3,4-Dimethylpyrrole-2-carboxylic acid ethyl ester** [5]



The acetoxynitrobutane **3.2.2.2** (40.0 g, 248 mmol) is added dropwise to a stirred solution of the isocyano ester **3.2.2.4** (22.6 g, 200 mmol) and TMG (60.0 g, 508 mmol) in anhydrous THF (tetrahydrofuran) (200 ml) and isopropanol (200 ml) at 0 °C. An exothermic reaction occurs, and the inner temperature is kept at 0 °C by cooling (solid CO_2/methanol bath). When the addition is complete, stirring is

continued for 12 h at room temperature.

Water (1000 ml) is then added to the reaction mixture, and the product is extracted with CH_2Cl_2 (2 × 200 ml). The organic phase is dried over Na_2SO_4 and filtered, and the solvent is removed *in vacuo.* The residue is dissolved in Et_2O (20 ml), and the solution obtained is rapidly filtered through silica gel (eluent: Et_2O). After removal of the solvent, the solid residue is washed with cold *n*-hexane; 28.7 g (86%), colorless crystals, mp 82–83 °C; R_f = 0.30 (CH_2Cl_2) (note).

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 1743 [7].

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 6.63 (s, 1H, pyrrole-5-H), 4.29 (q, *J* = 14 Hz, 2H, OCH_2), 2.25, 1.99 (s, 3H, CH_3), 1.33 (t, *J* = 14 Hz, 3H, CH_3).

^{13}C NMR (400 MHz, $CDCl_3$): δ (ppm) = 161.7 (C = O), 126.5, 120.5, 120.0, 119.2 (pyrrole-C), 59.7 (OCH_2), 14.5, 10.2, 9.85 (CH_3).

When crude **3.2.2.2** was used for the above pyrrole synthesis (see note under **3.2.2.2**), the yield of **3.2.2.5** dropped to 58%.

Note: The ester **3.2.2.5** can be recrystallized from CH_2Cl_2/*n*-hexane, mp 92–94 °C [7]. However, the above product does not show any impurities (^{1}H NMR and TLC).

3.2.2.6 * 3,4-Dimethylpyrrole-2-carboxylic acid [5]

167.2 139.2

The pyrrole ester **3.2.2.5** (25.0 g, 150 mmol) is suspended in EtOH (100 ml), and 30% aqueous potassium hydroxide solution (140 ml) is added with stirring. The mixture is heated to reflux for 2 h to give a yellowish solution.

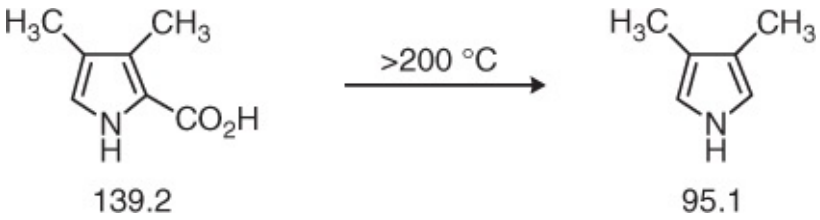
After cooling to 0 °C, the solution is brought to pH = 1 by the addition of ice-cold concentrated hydrochloric acid with stirring. A microcrystalline precipitate of the pyrrole carboxylic acid is formed, which cannot be conveniently filtered

off by suction; it is therefore taken up in Et_2O (4 × 1.0 l). The combined extracts are dried over Na_2SO_4 and filtered, and the solvent is removed *in vacuo*. The crystalline residue is triturated with Et_2O (50 ml) at −30 °C, collected by suction filtration, and washed with a small amount of cold Et_2O; 18.0 g (86%), colorless crystals, mp >200 °C (dec.); TLC (Et_2O): R_f = 0.30.

^{1}H NMR (400 MHz, [D_6]DMSO): δ (ppm) = 10.97 (s_{br}, 1H, CO_2H), 6.64 (s, 1H, pyrrole-5-H), 2.14, 1.90 (s, 3H, CH_3).

^{13}C NMR (400 MHz, [D_6]DMSO): δ (ppm) = 162.8 (*C*O_2H), 125.2, 125.9, 119.1, 118.9 (4 × pyrrole-C), 10.37, 10.02 (2 × CH_3).

3.2.2.7 ** 3,4-Dimethylpyrrole [5]



The pyrrole carboxylic acid **3.2.2.6** (15.9 g, 100 mmol) is placed in a 50-ml round-bottomed flask connected to a short-path distillation apparatus and heated to approximately 300 °C *in vacuo* (approximately 20 mbar). Gas evolution (decarboxylation) occurs and the product distils at approximately 160 °C as a colorless oil, which solidifies on standing in a refrigerator to give long needles; 9.50 g (100%); TLC: R_f = 0.65 (CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.76 (s_{br}, 1H, NH), 6.55 (s, 2H, 2-H, 5-H), 2.10 (s, 6H, 2 × CH_3).

^{13}C NMR (400 MHz, $CDCl_3$): δ (ppm) = 118.1, 115.5 (4 × pyrrole-C), 9.91 (2 × CH_3).

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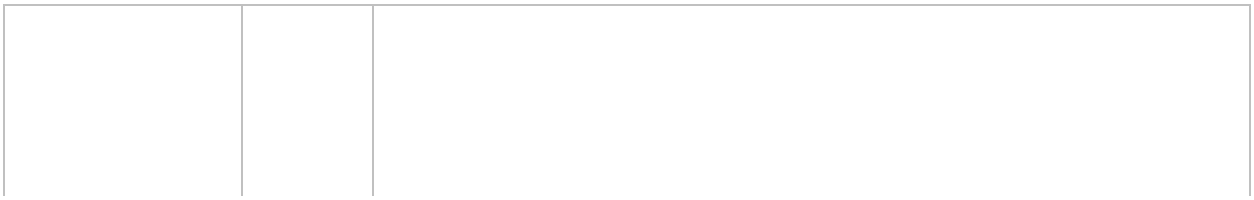
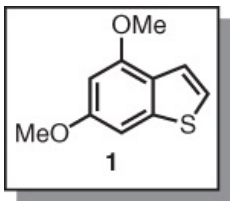
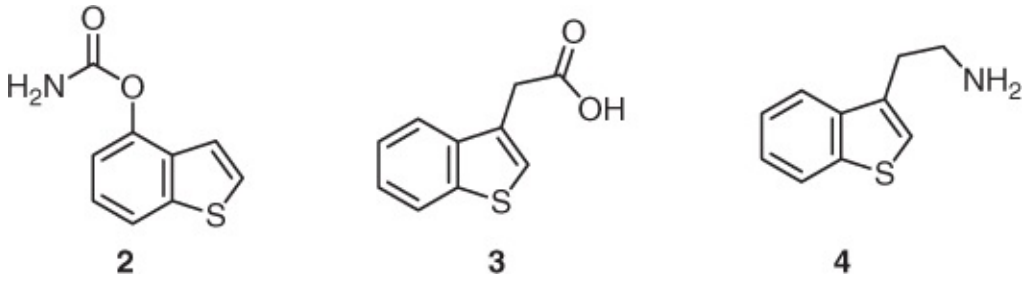
3.2.3 4,6-Dimethoxybenzo[*b*]thiophene



 1	***Topics:***	• Synthesis of a benzothiophene derivative • Transformation of a carboxylic acid to an amide • Directed metalation of an arene • α-Metalation of an alkyl aryl thioether • Intramolecular acylation of an organolithium compound by an amide • Reduction C=O → CH–OH, dehydration of a carbinol

(a) General

Benzo[*b*]thiophene derivatives exhibit various biological activities. The system shows bioisosterism with naphthalene and indole. Thus, compound **2** is an insecticide, like the corresponding naphthalene compound; **3** acts as a plant growth inhibitor like indolyl-3-acetic acid, and **4** has an even stronger effect on the central nervous system than the indole analog tryptamine [1]:

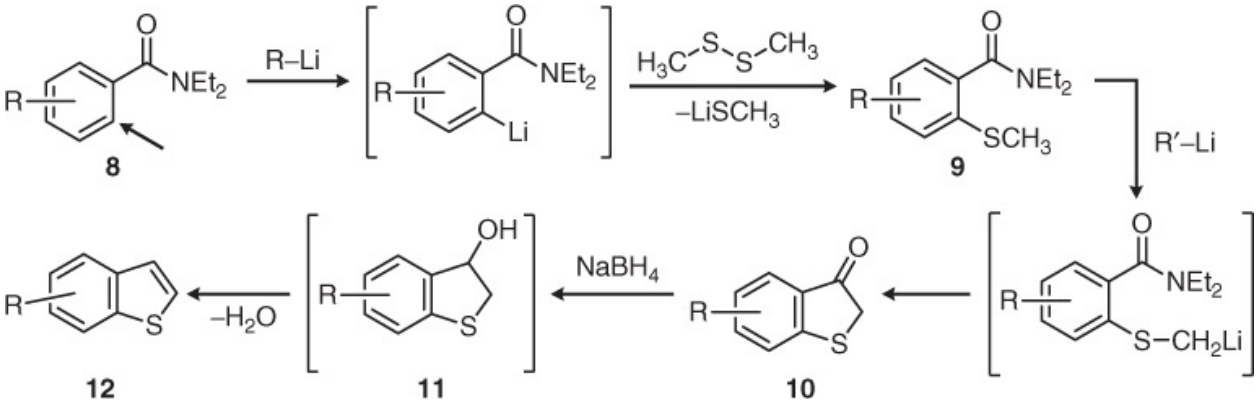


2 **3** **4**

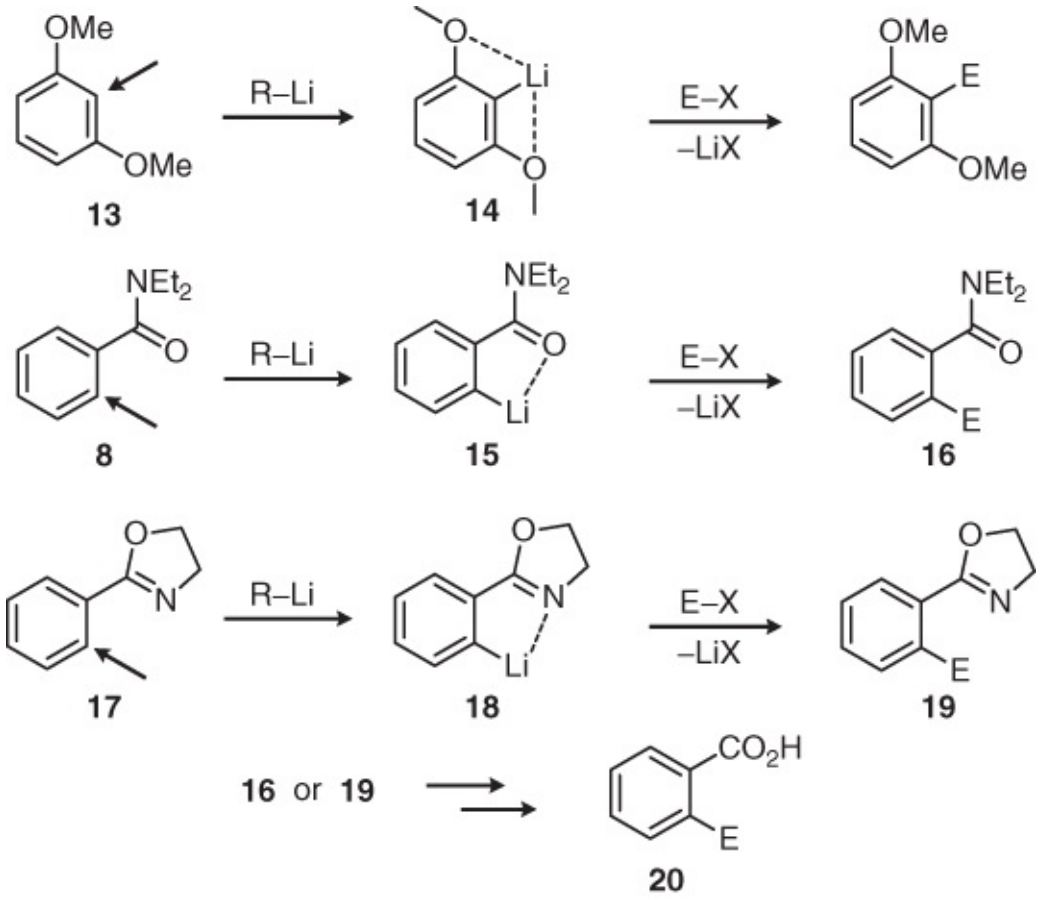
There are numerous methods for the synthesis of benzo[*b*]thiophenes, utilizing aryl thiols as starting materials [2], but their general scope and applicability are limited. One of these methods [1, 2] starts with S-alkylation of thiophenolate **5** with α-halogeno carbonyl compounds to give the (α-phenylthio) carbonyl compounds **6**, which undergo an intramolecular hydroxyalkylation (S_EAr) and subsequent dehydration in the presence of $ZnCl_2$ to afford benzo[*b*]thiophenes **7**:

Needless to say, this method is restricted to derivatives of type **7** substituted at the hetero ring, since the presence of substituents at the benzo ring can cause regioselectivity problems in the S_EAr ring closure.

In a recent method [3], the use of the expensive and environmentally offensive thiophenol is avoided; instead, the readily available *N*,*N*-dialkylbenzamides **8** are used as substrates. A methylsulfanyl group is introduced at a position ortho to the amide function by directed metalation [4] and electrophilic reaction of the Ar-*ortho*-Li intermediate with $CH_3–S–S–CH_3$ (→**9**). The SCH_3 group in **9** is then subjected to another metalation, which is followed by cyclization through intramolecular acylation of the formed thiomethyl carbanion by the adjacent amide function. The thioindoxyls **10**[2] thus obtained are reduced with $NaBH_4$ to the carbinols **11**, which spontaneously eliminate H_2O to provide benzo[*b*]thiophenes **12**:

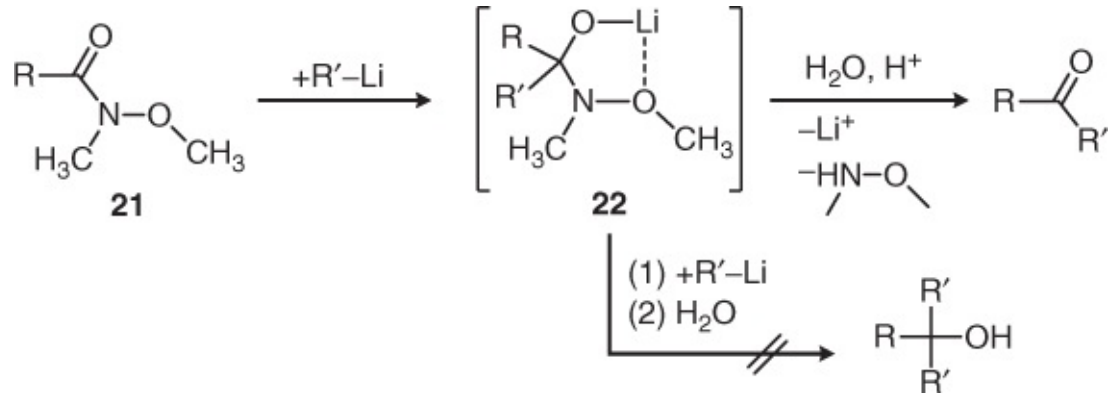


Directed metalation of arenes and hetarenes generally occurs regioselectively at positions ortho to functional groups capable of stabilizing the lithio arenes that result from hydrogen–metal exchange through intramolecular complexation. Even methoxy groups may serve as complexing donor systems (e.g., **13**→**14**), but of greater directing power are *N*,*N*-dialkylamide and oxazoline functions (e.g., **8**→**15** and **17**→**18**) [5], as demonstrated by the regiochemical outcome of arene metalation in the synthesis of the target molecule **1** outlined in (b).



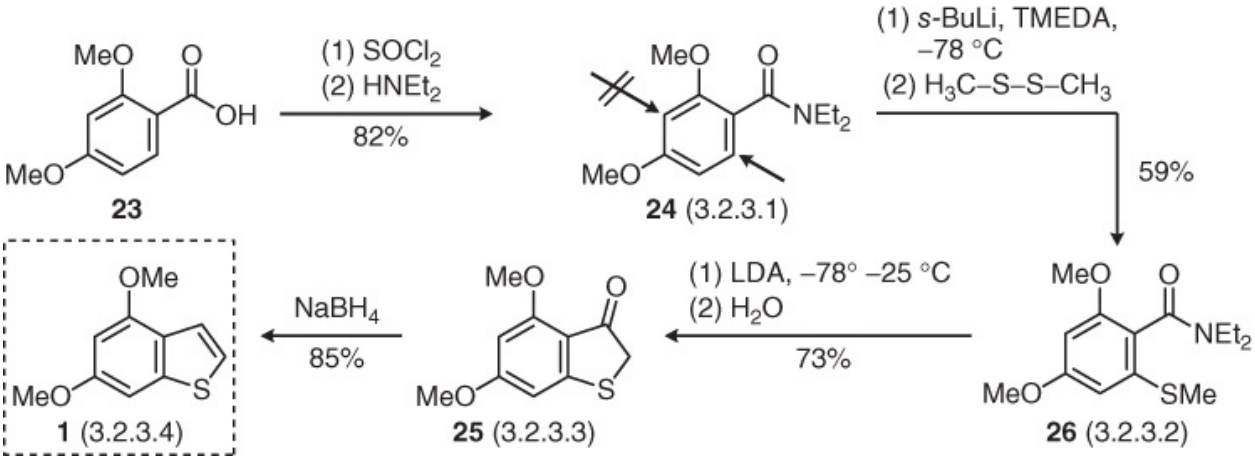
Since substrates **8** and **17** are derived from benzoic acids, their ortho-metalation and concomitant electrophilic transformation (**15**→**16** and **18**→**19**) represents a directed regioselective ortho-functionalization of these acids (**16**/**19**→**20**). Possible functionalizations are alkylation, acylation, carboxylation, alkylsulfamation, and so on.

It should be noted that acylation of organolithium compounds (as in **9**→**10**) is advantageously performed with Weinreb amides (*N*-methyl-*N*-alkoxyamides) **21** [6], which prevent the addition of a second R–Li moiety to the carboxyl function (as observed in the case of esters and acid chlorides) by chelate stabilization of the primary addition product **22** [7]:

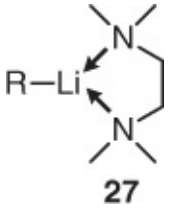


(b) Synthesis of 1

N,*N*-Diethyl-2,4-dimethoxybenzamide (**24**) is conveniently prepared by aminolysis of the acid chloride from 2,4-dimethoxybenzoic acid (**23**) with $HNEt_2$ [8]:



The *N*,*N*-diethylbenzamide **24** is metalated regioselectively using *sec*-BuLi at −78 °C in the presence of TMEDA (*N*,*N*,*N*′,*N*′-tetramethylethylenediamine), and the *ortho*-Li compound intermediately formed is quenched by reaction with dimethyl disulfide to give the *o*-(methylsulfanyl)benzamide **26**. In general, the addition of TMEDA enhances metalation reactions because the oligomeric organolithium compounds are monomerized (and thus activated) by complex formation (**27**) with this reagent [9]:



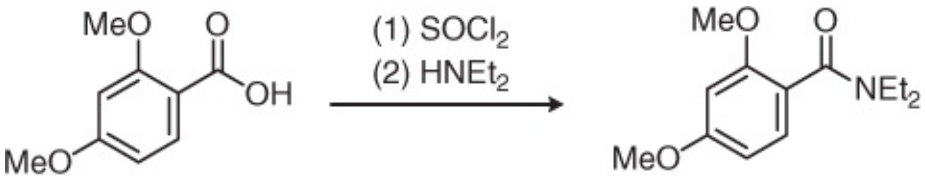
Cyclization of the *o*-(methylsulfanyl)benzamide **26** to the thioindoxyl **25** occurs

readily on metalation with LDA at −78 °C and the subsequent intramolecular acylation of the initially formed carbanion in the side chain. When **25** is reacted with $NaBH_4$, reduction of the carbonyl group and concomitant H_2O elimination takes place to yield the benzo[*b*]thiophene **1**.

Thus, the target molecule **1** is obtained in a four-step sequence with an overall yield of 30% (based on 2,4-dimethoxybenzoic acid (**23**)).

(c) Experimental Procedures for the Synthesis of 1

3.2.3.1	**	***N*,*N*-Diethyl-2,4-dimethoxybenzamide** [8]



2,4-Dimethoxybenzoic acid (3.20 g, 17.6 mmol) and thionyl chloride (12.7 g, 107 mmol) are dissolved in anhydrous benzene (100 ml; Caution: carcinogenic!) and heated to reflux with stirring for 2 h. The solvent and excess thionyl chloride are removed *in vacuo*.

The crude acid chloride (3.60 g, 17.6 mmol) is dissolved in anhydrous benzene (40 ml; Caution: carcinogenic!) and the reaction mixture is cooled to 0 °C. A solution of diethylamine (3.96 g, 54.1 mmol) in anhydrous benzene (15 ml) is slowly added at 0 °C with stirring. The reaction mixture is then stirred for 2 h at 0 °C and thereafter for 15 h at room temperature.

The solvent is removed *in vacuo*, and the residue is dissolved in CH_2Cl_2 (40 ml), washed with 5% aqueous $NaHCO_3$ (100 ml), 5% aqueous HCl (100 ml), and water (100 ml). The organic layer is dried over Na_2SO_4 and filtered, and the solvent is removed *in vacuo* to afford the amide as a yellow liquid; 3.49 g (82%).

IR (film): $\tilde{\nu}$ (cm^{-1}) = 2838, 1606, 1427, 1277, 1207, 1157, 1028.

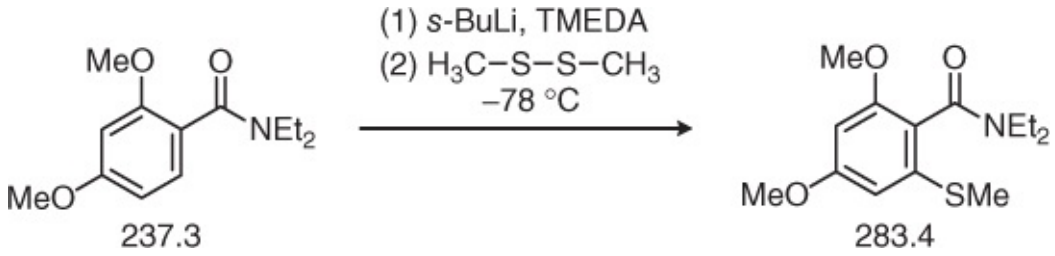
^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.12 (d, *J* = 8.3 Hz, 1H, 6-H), 6.49 (dd, *J* = 8.3, 2.2 Hz, 1H, 5-H), 6.46 (d, *J* = 2.2 Hz, 1H, 3-H), 3.81, 3.79 (2 × s, 2 × 3H, 2 × OCH_3), 3.52, 3.16 (2 × q, *J* = 7.1 Hz, 2 × 2H, 2 × CH_2CH_3), 1.23, 1.03 (2 × t, *J* = 7.1 Hz, 2 × 3H, 2 × CH_2CH_3).

^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) = 168.8 (*C*(O)NEt_2), 161.2 (C-4), 156.6 (C-2), 128.4, 119.9, 104.6, 98.7 (4 × Ar–C), 55.5, 55.4 (2 × OCH_3), 42.9, 38.9 (2 × O*C*H_2CH_3), 14.0, 12.9 (2 × OCH_2CH_3).

MS (EI, 70 eV): *m*/*z* (%) = 236.2 (20) $[M]^+$, 165.1 $[M–N(CH_2CH_3)_2]^+$.

Note: The product can be purified by column chromatography (EtOAc/hexane, 2 : 1; R_f = 0.25).

3.2.3.2	***	***N*,*N*-Diethyl-2-methylsulfanyl-4,6-dimethoxybenzamide** [3]



sec-BuLi (9.08 ml, 1.3 M in cyclohexane) is introduced through a septum by means of a syringe into a stirred solution of TMEDA (1.37 g, 11.8 mmol) in anhydrous THF (30.0 ml) at −78 °C. Stirring is continued for 20 min, and then a solution of the benzamide **3.2.3.1** (1.87 g, 7.88 mmol) in anhydrous THF (15 ml) is added to the reaction mixture at −78 °C (note 1). After stirring for an additional 30 min, dimethyl disulfide (2.08 g, 22.1 mmol) in anhydrous THF (10 ml) is added at −78 °C. Stirring is continued for 15 min, and then the reaction mixture is allowed to warm to room temperature and left under ambient conditions for 15 h.

The solvent is then removed *in vacuo*, saturated aqueous NH_4Cl solution (100 ml) is added, and the product is extracted with Et_2O (3 × 40 ml). The combined organic layers are washed with brine (100 ml), dried over Na_2SO_4, and filtered. Removal of the solvent *in vacuo* affords the thioether as a colorless solid (note 2), mp 83–84 °C; 1.31 g (59%).

IR (solid): $\tilde{\nu}$ (cm^{-1}) = 2932, 1619, 1395, 1277, 1152, 831.

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 6.43 (d, *J* = 2.1 Hz, 1H, Ar), 6.29 (d, *J* = 2.1 Hz, 1H, Ar), 3.82, 3.77 (2 × s, 2 × 3H, 2 × OCH_3), 3.77 (dq, *J* = 15.0, 7.1 Hz, 1H, C$H_A$$H_B$$CH_3$), 3.40 (dq, *J* = 15.0, 7.1 Hz, 1H, $CH_A$$H_B$$CH_3$),

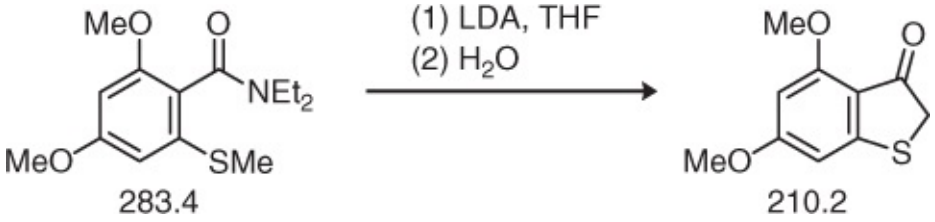
3.13 (q, J = 7.1 Hz, 2H, CH_2CH$_3$), 2.45 (s, 3H, SCH$_3$), 1.25, 1.04 (2 × t, J = 7.1 Hz, 2 × 3H, 2 × CH$_2$CH_3).

^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) = 166.8 (C(O)NEt$_2$), 160.8, 156.8, 137.4, 119.4, 104.0, 95.7 (6 × Ar–C), 55.7, 55.5 (2 × OCH$_3$), 42.6, 38.7 (2 × CH$_2$CH$_3$), 16.4 (SCH$_3$), 13.9, 12.6 (2 × CH$_2$$CH_3$).

Notes:

1. The use of 1.5 equiv of *sec*-BuLi proved to be essential for this reaction step.
2. The product can be purified by column chromatography (EtOAc/*n*-hexane, 2 : 1, R_f = 0.21).

3.2.3.3	***	**2,3-Dihydro-4,6-dimethoxybenzo[*b*]thiophen-3-one** [3]



n-BuLi (1.38 ml, 2.5 M in *n*-hexane, 1.5 equiv) is added through a septum by means of a syringe to a stirred solution of diisopropylamine (580 mg, 5.73 mmol) in anhydrous THF (20 ml) at 0 °C. Stirring is continued for 20 min at 0 °C and then the reaction mixture is cooled to −78 °C. A solution of 2-methylsulfanyl benzamide (cf. **3.2.3.2**) (0.65 g, 2.29 mmol) in anhydrous THF (5 ml) is added dropwise and stirring is continued for 30 min at −78 °C. The reaction mixture is then allowed to warm to room temperature and is stirred under ambient conditions for 15 h.

Saturated aqueous NH_4Cl solution (100 ml) is then added and the mixture is extracted with Et_2O (3 × 40 ml). The combined organic layers are dried over Na_2SO_4 and filtered, and the solvent is removed *in vacuo*. The crude thioindoxyl is crystallized from EtOH to yield colorless needles (notes 1 and 2), mp 110–112 °C; 350 mg (73%).

IR (solid): $\tilde{\nu}$ (cm^{-1}) = 2933, 1568, 1277, 1209, 1152, 831.

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 6.45 (d, J = 1.9 Hz, 1H, Ar), 6.15

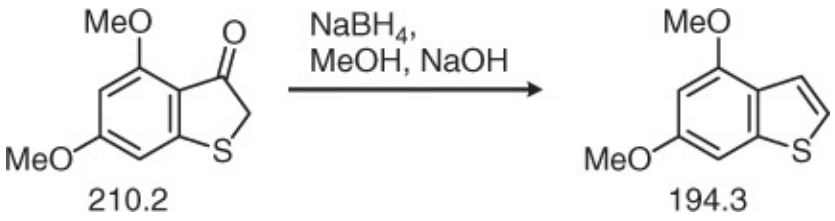
(d, J = 1.9 Hz, 1H, Ar), 3.91, 3.87 (2 × s, 2 × 3H, 2 × OCH_3), 3.76 (s, 2H, SCH_2).

^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) = 196.0 (C=O), 167.4, 161.5, 159.7, 113.6, 99.8, 95.7 (6 × Ar–C), 55.9 (2 × OCH_3), 39.7 (SCH_2).

Notes:

1. The product can be purified by column chromatography (EtOAc/*n*-hexane, 2 : 1; R_f = 0.53).
2. The thioindoxyl is air-sensitive and should be kept under argon in a refrigerator.

3.2.3.4 * 4,6-Dimethoxybenzo[*b*]thiophene [3]



210.2 194.3

A solution of $NaBH_4$ (70 mg, 1.90 mmol) in MeOH/10% aqueous NaOH (10 : 3) (15 ml) is added dropwise to a stirred solution of the thioindoxyl **3.2.3.3** (200 mg, 0.95 mmol) in MeOH/10% aqueous NaOH (6 : 1) (20 ml). The reaction mixture is heated to reflux with stirring for 16 h.

The solvent is then removed *in vacuo*, 10% aqueous H_2SO_4 (30 ml) is added to the residue, and the resulting mixture is extracted with Et_2O (3 × 40 ml). The combined organic layers are washed with water (100 ml), dried over Na_2SO_4, and filtered. Removal of the solvent *in vacuo* affords the benzo[*b*]thiophene as yellow crystals (note), mp 77–79 °C; 155 mg (85%).

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.38 (d, J = 5.6 Hz, 1H), 7.15 (d, J = 5.5 Hz, 1H) (2-H, 3-H), 6.93 (d, J = 1.5 Hz, 1H), 6.41 (d, J = 1.9 Hz, 1H) (5-H, 6-H), 3.92, 3.86 (2 × s, 2 × 3H, 2 × OCH_3).

^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) = 158.8, 155.4, 142.1, 125.0, 121.8, 120.2, 96.2, 95.8 (C-2, C-3, C-3a, C-4, C-5, C-6, C-7, C-7a) 55.7, 55.4 (2 × OCH_3).

Note: The product can be purified by column chromatography (EtOAc/hexane, 2 : 1; R_f = 0.53).

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3. Mukherjee, C., Kamila, S., and De, A. (2003) *Tetrahedron*, **59**, 4767–4774.

4. (a) Krause, N. (1996) *Metallorganische Chemie*, Spektrum Akademischer Verlag, Heidelberg, p. 45;(b) Schlosser, M. (2005) *Angew. Chem.*, **117**, 380–398; *Angew. Chem. Int. Ed.*, (2005), **44**, 376–393.

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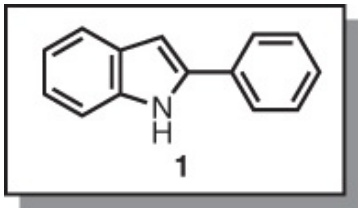
6. Nahm, S. and Weinreb, S.M. (1981) *Tetrahedron Lett.*, **22**, 3815–3818.

7. An instructive example utilizing directed ortho-metalation and acylation of an organolithium compound with a Weinreb amide as key transformations is the synthesis of the natural product mamanutha quinone: Yoon, T., Danishefsky, S.J., and de Gala, S. (1994) *Angew. Chem.*, **106**, 923–925; *Angew. Chem., Int. Ed. Engl.*, (1994), **33**, 853–855.

8. Mukherjee, C., Kamila, S., De, A., and Mondal, S.S. (2003) *Tetrahedron*, **59**, 1339–1348.

9. Krause, N. (1996) *Metallorganische Chemie*, Spektrum Akademischer Verlag, Heidelberg, p. 14.

3.2.4 2-Phenylindole



Topics:

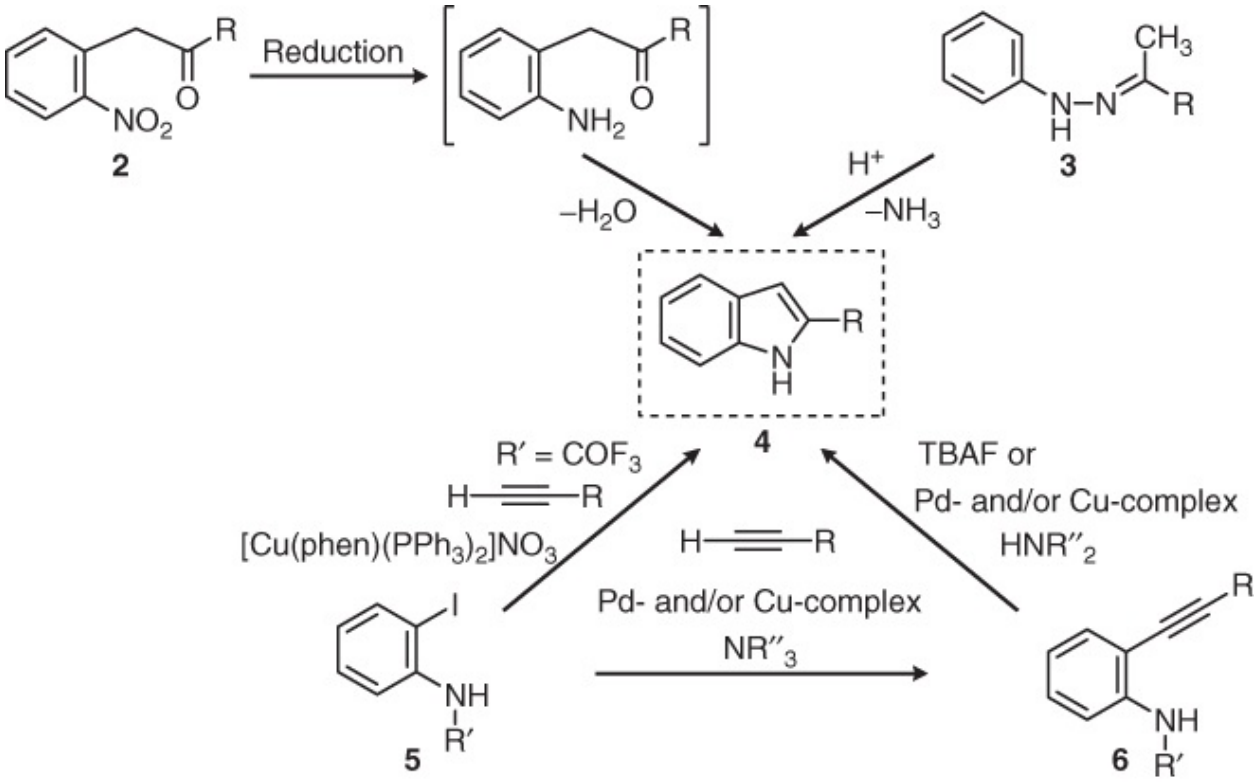
- Transition-metal-mediated indole synthesis
- Sonogashira cross-coupling reaction

		• Acetylation of a primary amine • Formation of indoles from (*o*-ethynyl) anilines

(a) General

Indole is one of the most important heterocycles, since a large number of natural products (e.g., the amino acid tryptophan and many alkaloids) and pharmaceuticals are derived from this ring system. Therefore, numerous synthetic approaches to indoles have been developed [1].

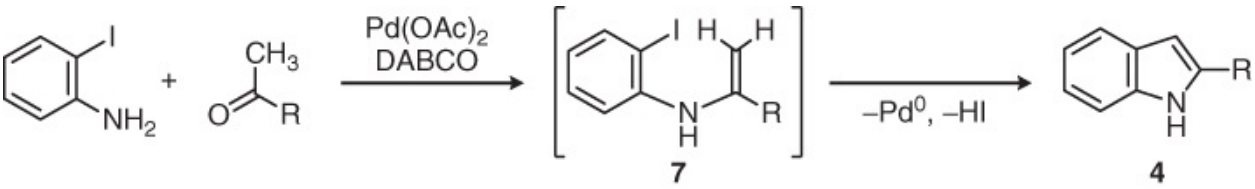
For the synthesis of 2-substituted indoles **4** (as in the case of the target molecule **1**), two of the classical methods are relevant, namely the Reissert synthesis (reductive cyclization of *o*-nitrobenzyl ketones **2**) and the Fischer synthesis (acid-catalyzed eliminative cyclization of *N*-arylhydrazones of methyl ketones **3**):



The repertoire of methods for the synthesis of indoles of type **4** is considerably enlarged by a series of transition-metal-mediated reactions [2]. Thus, the *N*-acyl or *N*-sulfonyl derivatives of (*o*-ethynyl)-arylamines **6** cyclize to the corresponding 2-substituted indoles upon interaction with TBAF (tetra-*n*-

butylammonium fluoride) or Pd and/or Cu complexes. The (*o*-ethynyl)arylamines **6** are conveniently obtained from Pd-mediated Sonogashira cross-coupling reactions (cf. Section 1.6.3) of *o*-iodoanilines **5** with terminal acetylenes [3–5]. The potential of this method is demonstrated by a solid-phase version utilizing polymer-bound (*o*-halogeno)anilines [6]. Recently, a one-step procedure (**5** → **4**) starting from *N*-trifluoroacetates **5** (R′ = $C(O)CF_3$) was introduced utilizing a Cu complex as catalyst [7].

Another transition-metal-assisted formation of 2-substituted indoles is the Pd-catalyzed annulation of iodoanilines and ketones [8]:

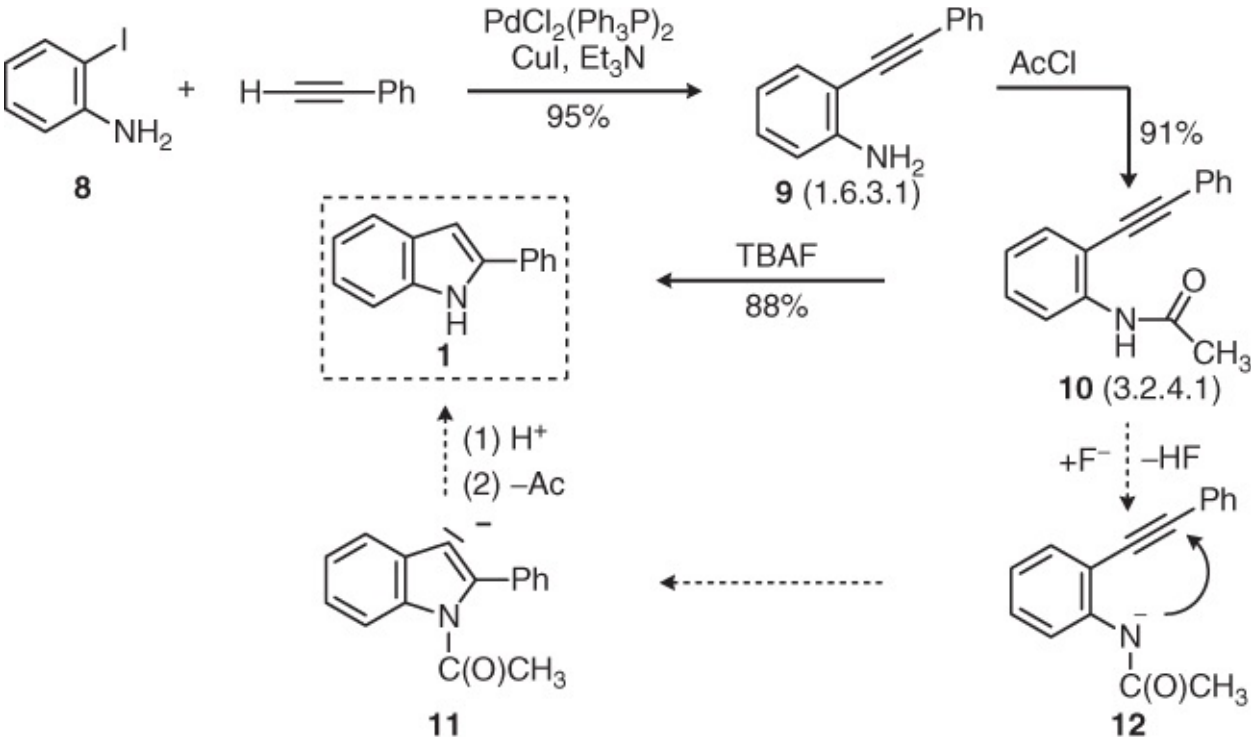


This transformation was shown to proceed via enamine formation (→ **7**) and subsequent intramolecular Heck reaction (cf. Section 1.6.1) (**7** → **4**).

The target molecule **1** has been prepared from the phenylhydrazone of acetophenone (**3**, R = Ph) by application of the Fischer indole synthesis [9]. Here, as a modern alternative, a Pd-mediated approach [3] is presented (Section (b)).

(b) Synthesis of 1

The starting material for the synthesis of **1** is the commercially available *o*-iodoaniline (**8**), which is subjected to a Sonogashira cross-coupling reaction with phenylacetylene in the presence of $(Ph_3P)_2PdCl_2$, CuI, and triethylamine, providing an almost quantitative yield of (*o*-phenylethynyl)aniline (**9**, cf. **1.6.3.1**):



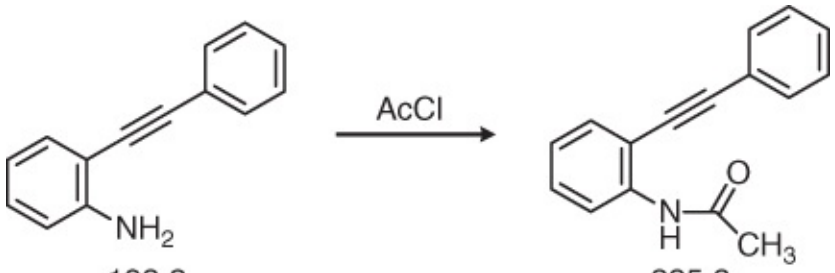
The aniline derivative **9** is acylated using acetyl chloride to give the *N*-acetyl compound **10**, which readily cyclizes to 2-phenylindole (**1**) on treatment with TBAF in refluxing THF.

In contrast to that of Pd-assisted cyclization [1, 7], the mechanism of the TBAF-promoted process (**10** → **1**) remains speculative. It was found that anilines **6** (R′ = H) do not cyclize under these conditions. Moreover, for the reaction of **10** to give **1**, 3 equiv of TBAF have to be used. It can therefore be assumed that deprotonation of **10** to afford the anion **12** initiates the cyclization (**12** → **11**), which is completed by reprotonation and fluoride-induced N-deacylation of the indole (**11** → **1**). Alternatively, (2-phenylethynyl)aniline (**9**) can be directly cyclized to 2-phenylindole (**1**) upon treatment with the stronger base KO*t*-Bu in NMP (*N*-methyl-2-pyrrolidinone) (79% yield) [10].

Using the first approach, the target molecule **1** is prepared in a three-step sequence with an overall yield of 73% (based on *o*-iodoaniline (**8**)).

(c) Experimental Procedures for the Synthesis of 1

3.2.4.1	*	***N*-Acetyl-2-(phenylethynyl)aniline** [3]



193.2 235.3

Acetyl chloride (785 mg, 10.0 mmol) is added dropwise to a stirred solution of the aniline **1.6.3.1** (1.75 g, 9.05 mmol) in a pyridine/THF mixture (1 : 2, 15 ml), and stirring is continued for 24 h at room temperature.

The reaction mixture is then diluted with H_2O (20 ml) and extracted with $CHCl_3$ (3 × 20 ml), and the combined extracts are dried over $MgSO_4$ and filtered. The solvent is removed *in vacuo* and the residue is purified by recrystallization from *n*-hexane/acetone (5 : 1) to give colorless needles; yield 1.83 g (86%); mp 119–121 °C.

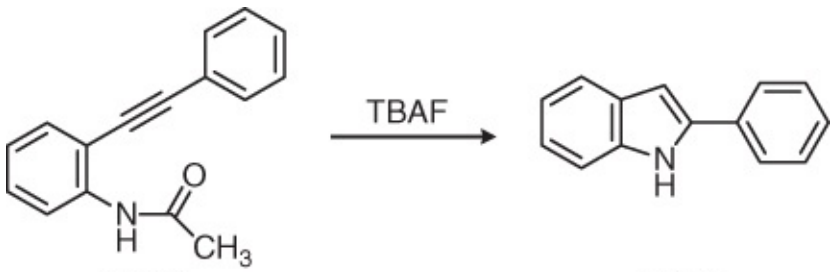
IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3300, 1660.

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 8.41 (d, *J* = 8.2 Hz, 1H, Ar), 7.98 (s_{br}, 1H, NH), 7.56–7.26 (m, 7H, Ar), 7.07 (t, *J* = 7.7 Hz, 1H, Ar), 2.24 (s, 3H, CH_3).

^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) = 168.1 (C(O)*C*H_3), 138.9, 131.7, 131.5, 129.8, 129.0, 128.6, 123.4, 122.4, 119.3, 111.8 (10 × Ar–C), 96.4, 84.3 (2 × alkin-C), 25.0 (C(O)*C*H_3).

MS (EI, 70 eV): *m*/*z* (%) = 235 (31) $[M]^+$, 193 (100) $[M-C_2H_3O]$.

3.2.4.2	*	**2-Phenylindole** [3]



235.3 193.2

A mixture of the acetamide **3.2.4.1** (1.65 g, 7.00 mmol) and TBAF (1 M soln. in THF, 14.0 mmol) in THF (35 ml) is heated to reflux for 12 h.

After removal of the THF *in vacuo*, H_2O (50 ml) is added to the residue and the resulting mixture is extracted with EtOAc (3 × 20 ml). The combined EtOAc extracts are dried over $MgSO_4$ and filtered, and the solvent is removed *in vacuo*. The residue is purified by column chromatography (SiO_2, CH_2Cl_2); colorless crystals; yield 1.19 g (88%); mp 185–187 °C.

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3445, 1655.

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 8.42–8.28 (s_{br}, 1H, NH), 7.68–7.62 (m, 3H, Ar), 7.48–7.22 (m, 4H, Ar), 7.20 (dt, *J* = 8.2, 1.1 Hz, 1H, Ar), 7.12 (dt, *J* = 7.1, 1.1 Hz, 1H, Ar), 6.83 (dd, *J* = 1.9, 1.1 Hz, 1H, Ar).

^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) = 137.9, 136.8, 132.4, 129.3, 129.0, 127.7, 125.2, 122.4, 120.7, 120.3, 110.9 (14 × Ar–C), 100.0 (C-3).

MS (EI, 70 eV): *m*/*z* (%) = 193 (100) $[M]^+$.

References

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2584.

5. 2-Iodoanilines (**5**, R′ = H) are easily prepared by ortho-lithiation of anilines and subsequent iodination: Snieckus, V. (1990) *Chem. Rev.*, **90**, 879–933.

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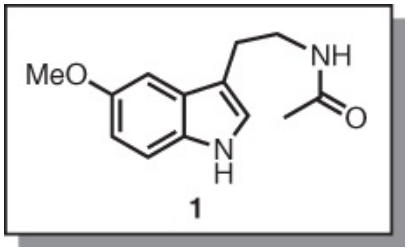
3.2.5 Melatonin



1

Topics:

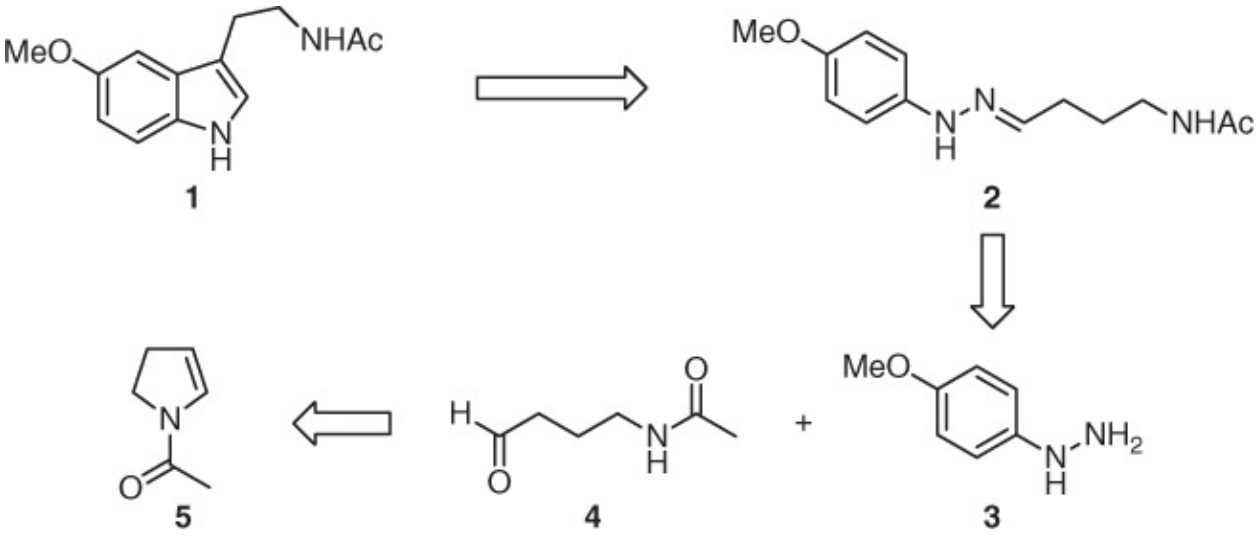
- Synthesis of an indole-derived natural product
- Japp–Klingemann reaction
- Fischer indole synthesis
- Ester and amide hydrolysis
- Thermal decarboxylation, N-acetylation

(a) General

Melatonin (**1**, 5-methoxy-(*N*-acetyl)tryptamine) is a naturally occurring hormone produced by the pineal gland in vertebrates. Its formation and secretion is increased at night, which leads to the onset of sleep. Melatonin has been shown to exhibit medicinally useful activities in treating sleep disorders, in protection against oxidative stress, and as an inhibitor of the onset of Alzheimer's disease

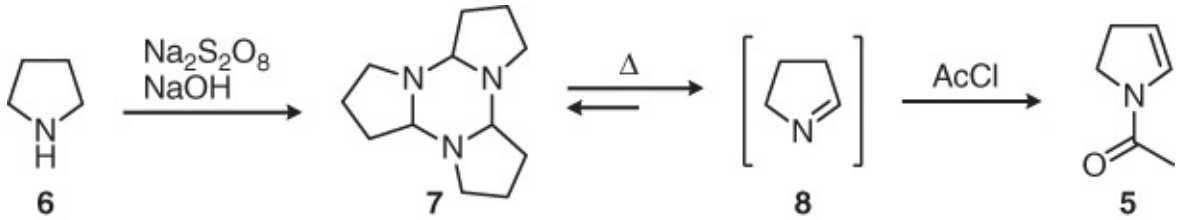
[1].

Retrosynthesis of melatonin (**1**) using a retro-Fischer indole synthesis [2] approach leads to the hydrazine **3** and the aldehyde **4** via the hydrazone **2**; **4** is accessible from the dihydropyrrole **5**.



Numerous syntheses of melatonin (**1**) have been performed according to this retrosynthetic analysis [3].

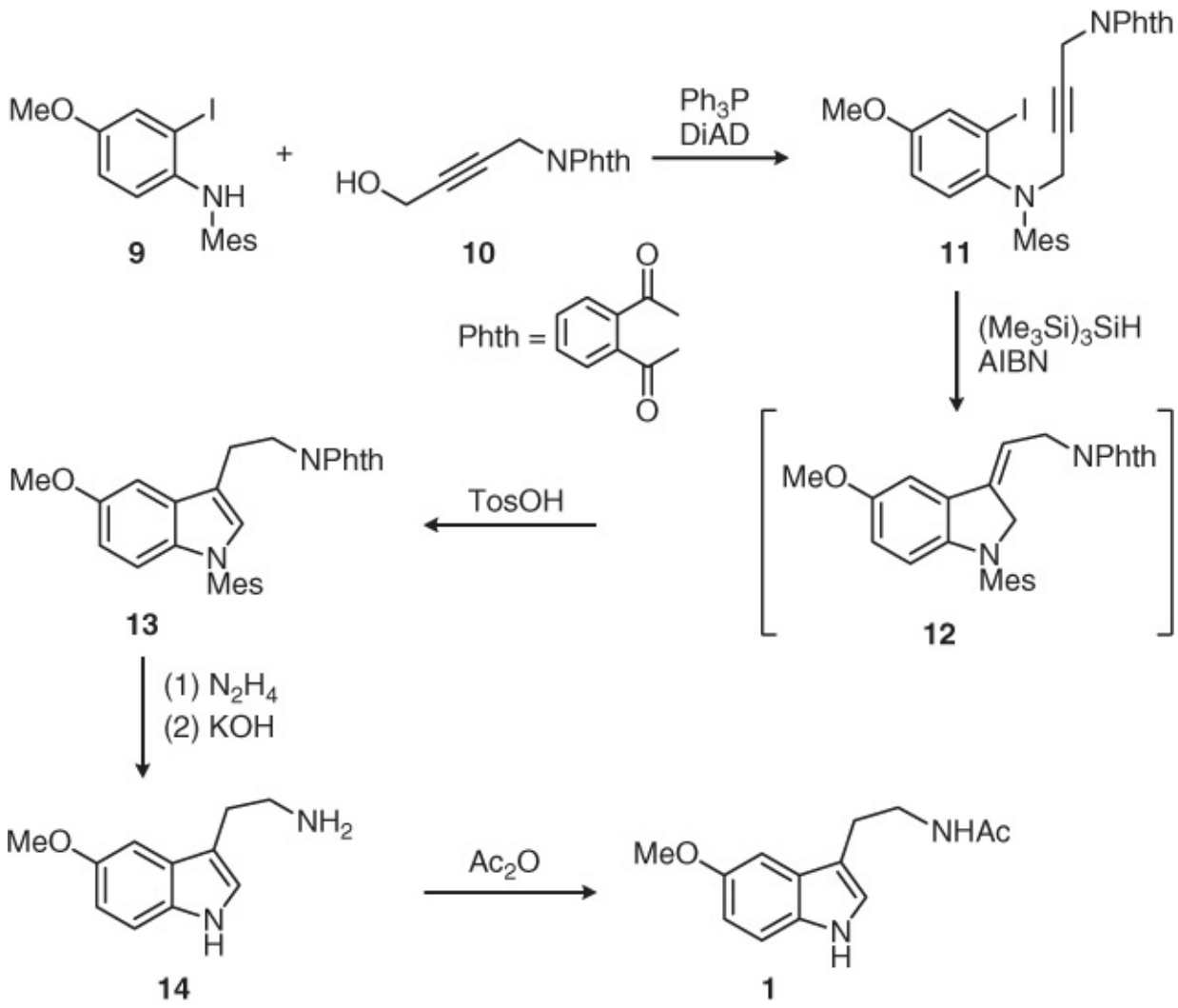
For example, **1** has been formed by reaction of the enamide **5** (as precursor of the aldehyde **4**) with the hydrochloride of **3**. Compound **5** can be prepared by oxidation of pyrrolidine (**6**) with persulfate to give the trimer **7** and subsequent N-acetylation of dihydropyrrole **8** formed by thermal cleavage of **7** [4]:



Another synthesis according to a Fischer strategy is presented in Section (b).

A different approach (not discussed in the retrosynthesis) utilizes radical-based indole formation [1]. The key intermediate is the acetylene **11**, which is obtained by Mitsunobu reaction (cf. Section 3.3.4) of 2-iodo-(*N*-mesyl)-*p*-anisidine (**9**) with the phthalimide **10**. The acetylene **11** undergoes an exo-trig radical cyclization mediated by $(Me_3Si)_3SiH$ and AIBN (2,2′-azobisisobutyronitrile) to give a mixture of the indolenine **12** and the indole **13**. The indolenine is converted *in situ* to the indole by treatment with TosOH. Removal of the phthalyl protecting group by hydrazinolysis and the mesyl group by cleavage

with KOH liberates the NH-indole moiety and the primary amino function of the tryptamine **14**, which is then acetylated to furnish melatonin (**1**).

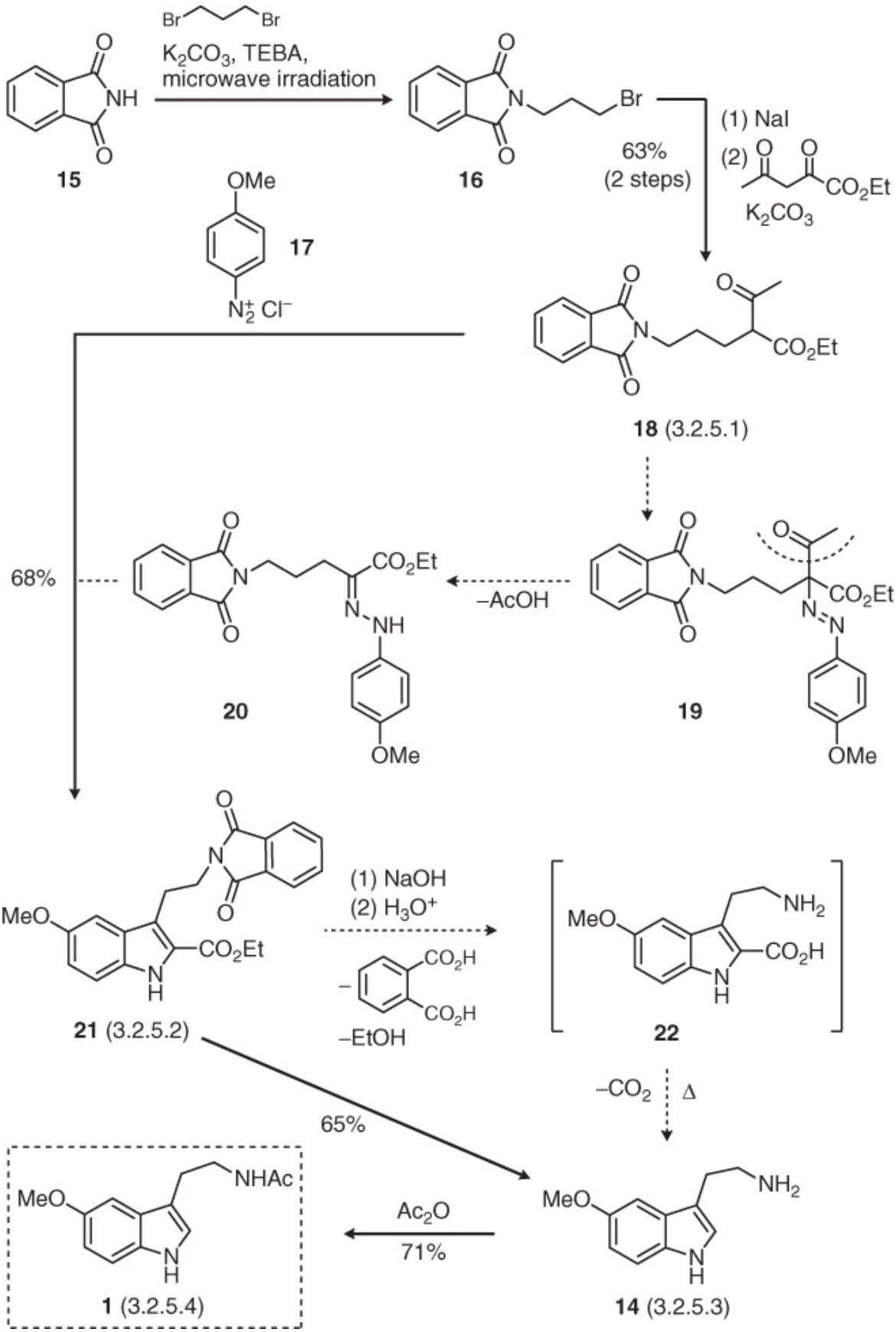


(b) Synthesis of 1

The synthesis of melatonin (**1**) described here is easy to perform, avoids expensive educts, and is scalable to an industrial process [5, 6].

Phthalimide (**15**) is alkylated with 1,3-dibromopropane under microwave irradiation to give the 1-bromopropyl compound **16**, which, after Finkelstein exchange of bromide by iodide, is used for α-alkylation of ethyl acetoacetate to give **18**. Subsequent Japp–Klingemann reaction with the (4-methoxyphenyl) diazonium salt **17** affords the indole-2-carboxylate **21** directly. This domino process [7] includes the formation of the hydrazone **20** via the azo compound **19** followed by a Fischer indole synthesis to give **21**. Subsequent hydrolysis of the phthalimide and the ester moiety (via the unstable carboxylic acid **22**) furnishes

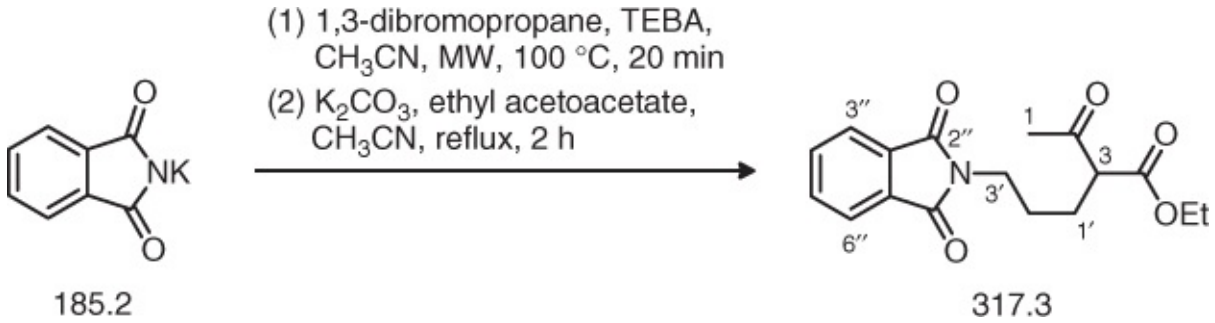
5-methoxytryptamine (**14**), which in the final step is acetylated at the primary amino group to give melatonin (**1**).


Br
Br
K_2CO_3, TEBA,
microwave irradiation
NH
15
16
Br
63%
(2 steps)
(1) NaI
(2)
CO_2Et
K_2CO_3
OMe
17
N_2^+ Cl^-
18 (3.2.5.1)
CO_2Et
68%
–AcOH
20
19
OMe
(1) NaOH
(2) H_3O^+
MeO
CO_2Et
21 (3.2.5.2)
CO_2H
CO_2H
–EtOH
NH_2
CO_2H
22
$-CO_2$
Δ
65%
NHAc
Ac_2O
71%
1 (3.2.5.4)
14 (3.2.5.3)

Thus, for the synthesis of the target molecule, a linear sequence consisting of four individual steps is performed, which leads to **1** in an overall yield of 20% (based on **15**).

(c) Experimental Procedures for the Synthesis of 1

3.2.5.1	***	**Ethyl 2-(3-phthalimidopropyl)acetoacetate** [6]



A suspension of potassium phthalimide (1.27 g, 6.84 mmol), 1,3-dibromopropane (2.77 g, 13.7 mmol), and triethylbenzylamine chloride (TEBA, 154 mg, 0.67 mmol, 10.0 mol%) in CH_3CN (10 ml) and water (3.0 ml) is heated to 100 °C for 20 min under microwave irradiation.

After cooling to room temperature, Et_2O (25 ml) is added and the precipitate (KBr and the side product bisphthalimidopropane) is removed by filtration. The filtrate is concentrated *in vacuo* and the residue (crude *N*-(3-bromopropyl)phthalimide) is dissolved in CH_3CN (2.00 ml). Then K_2CO_3 (4.73 g, 34.2 mmol) and ethyl acetoacetate (980 mg, 7.53 mmol) are added, and the resulting suspension is heated to reflux for 2 h.

After cooling to room temperature, acetone (25 ml) is added and the mixture is filtered. The filtrate is concentrated *in vacuo* and the residue is recrystallized from EtOAc/ligroin to give the product as colorless disks; 1.37 g (63%), mp 65–66 °C, R_f = 0.45 (*n*-pentane/EtOAc, 1 : 1).

UV (CH_3CN): λ_{max} (nm) (log ε) = 292 (3.248), 241 (4.039), 232 (4.163), 219 (4.624).

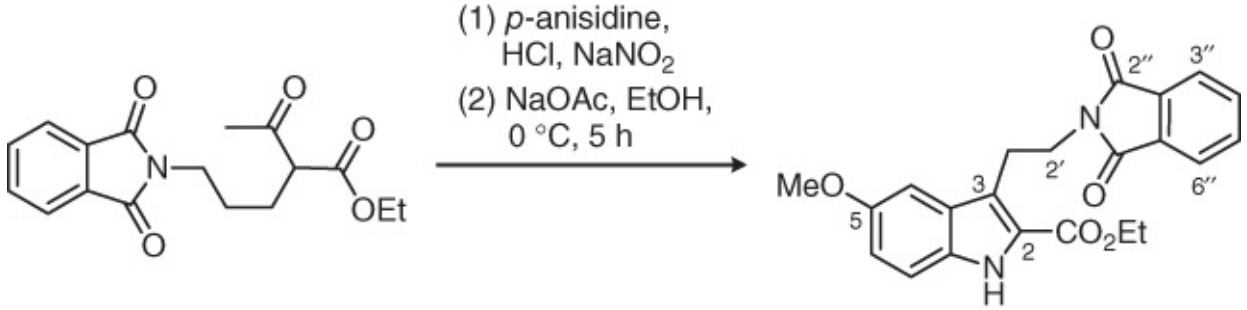
IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3459, 2969, 2934, 1772, 1738, 1713, 1613, 1463, 1438, 1402, 1368, 1368, 1341, 1283, 1243, 1192, 1144, 1124, 1091, 1043, 882, 848, 831, 795, 724, 632, 532.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.83–7.79 (m, 2H, 3″-H, 6″-H), 7.70–7.67 (m, 2H, 4″-H, 5″-H), 4.15 (q, *J* = 7.0 Hz, 2H, OCH_2CH_3), 3.68 (t, *J* = 7.0 Hz, 2H, 3′-H_2), 3.47 (t, *J* = 7.0 Hz, 1H, 3-H), 2.20 (s, 3H, 1-H_3), 1.92 to 1.80 (m, 2H, 2′-H_2), 1.70–1.55 (m, 2H, 1′-H_2), 1.24 (t, *J* = 7.0 Hz, 3H, OCH_2CH_3).

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 202.6 (C-2), 169.4 (C-4), 168.3 (C-2″, C-7″), 133.9 (C-4″, C-5″), 132.0 (C-2″a, C-7″a), 123.2 (C-3″, C-6″), 61.44 (OCH_2CH_3), 58.94 (C-3), 37.24 (C-3′), 28.94 (C-2′), 26.22 (C-1), 25.05 (C-1′), 14.04 (OCH_2CH_3).

MS (EI, 70 eV): *m*/*z* (%) = 317 (3) $[M]^+$, 275 (16) $[M-CH_3CO]^+$, 201 (41) $[M-CH_3CO-CO_2Et]^+$, 160 (100) $[Phth-CH_2]^+$, 77 (16) $[Ph]^+$, 43 (60) $[CH_3CO]^+$.

3.2.5.2	**	**5-Methoxy-3-(2-phthalimidoethyl)-indole-2-carboxylic acid ethyl ester** [6]



317.3 392.4

A solution of sodium nitrite (104 mg, 1.51 mmol) in H_2O (0.4 ml) is added dropwise to a stirred solution of *p*-anisidine (185 mg, 1.50 mmol) in H_2O (3.4 ml) and concentrated HCl (1.1 ml) at 0 °C, and stirring is continued for 30 min at 0 °C (solution A). A solution of the ester **3.2.5.1** (512 mg, 1.62 mmol) in EtOH (2.6 ml) is added dropwise to a stirred suspension of NaOAc (1.38 g, 16.8 mmol) in EtOH (2.6 ml) at 0 °C and stirring is continued for 30 min, whereupon ice (5 g) is added (solution B). Solution A is then added to solution B by transfer cannulation at 0 °C, and the mixture is allowed to warm to room temperature and is stirred for a further 3 h.

The reaction mixture is then basified by slow addition of saturated aqueous

Na_2CO_3 solution at 0 °C and extracted with CH_2Cl_2 (3 × 25 ml). The combined organic layers are washed with H_2O (25 ml), dried over $MgSO_4$, and filtered, and the solvent is removed *in vacuo*. The red residue is dissolved in anhydrous EtOH (20 ml), treated with a saturated solution of HCl in anhydrous EtOH (2 ml; prepared from acetyl chloride (1.18 g, 15.0 mmol) and EtOH (692 mg, 15.0 mmol)), and the mixture is heated to reflux for 1 h. After cooling to room temperature, the solvent is removed under reduced pressure and the residue is partitioned between H_2O (10 ml) and CH_2Cl_2 (25 ml). The aqueous layer is basified by the addition of saturated aqueous Na_2CO_3 solution (25 ml) and extracted with CH_2Cl_2 (3 × 25 ml). The combined organic layers are washed with brine (10 ml), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Crystallization from EtOH provides the indole ester as a yellow solid; 398 mg (68%), mp 238–239 °C, R_f = 0.58 (*n*-pentane/EtOAc, 1 : 1).

UV (CH_3CN): λ_{max} (nm) (log ε) = 326 (3.763), 299 (4.293), 240 (4.271), 218 (4.777).

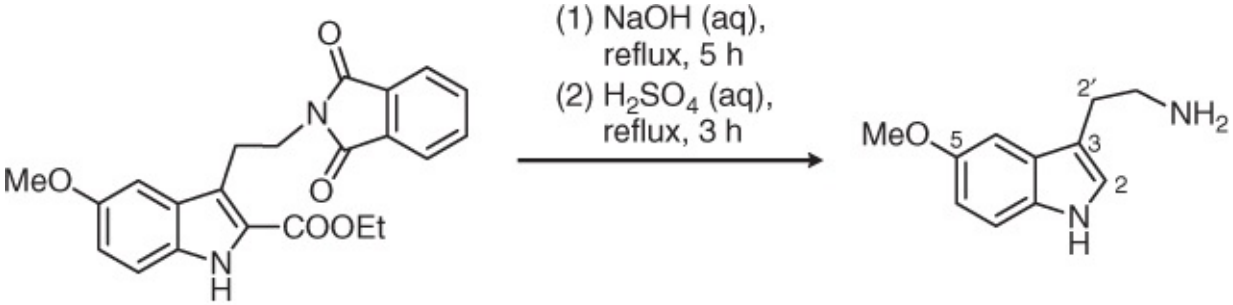
IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3322, 2940, 1771, 1719, 1682, 1545, 1467, 1437, 1394, 1355, 1261, 1220, 1016, 808, 716, 653, 530.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.65 (s_{br}, 1H, 1-H), 7.83–7.79 (m, 2H, 3″-H, 6″-H), 7.67–7.64 (m, 2H, 4″-H, 5″-H), 7.21 (d, *J* = 8.9, 1H, 7-H), 7.06 (d, *J* = 2.3 Hz, 1H, 4-H), 6.90 (dd, *J* = 8.9, 2.3 Hz, 1H, 6-H), 4.40 (q, *J* = 7.2 Hz, 2H, OCH_2CH_3), 3.77 (s, 3H, OCH_3), 3.98 (t, *J* = 7.9 Hz, 2H, 2′-H_2), 3.42 (t, *J* = 7.9 Hz, 2H, 1′-H_2), 1.43 (t, *J* = 7.2 Hz, 3H, OCH_2CH_3).

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 168.3 (C-2″, C-7″), 162.1 (CO_2Et), 154.5 (C-5), 133.8 (C-4″, C-5″), 132.2 (C-2″a, C-7″a), 131.0 (C-3a), 128.4 (C-7a), 124.5 (C-2), 123.0 (C-3″, C-6″), 119.3 (C-3), 117.4 (C-7), 112.8 (C-6), 110.1 (C-4), 60.97 (OCH_2CH_3), 55.56 (OCH_3), 38.13 (C-2′), 24.03 (C-1′), 14.40 (OCH_2CH_3).

MS (EI, 70 eV): *m*/*z* (%) = 392 (32) $[M]^+$, 232 (40) $[M-CH_2Phth]^+$, 186 (100) $[M-OCH_3-(CH_2)_2Phth]^+$, 77 (6) $[Ph]^+$.

3.2.5.3	*	**5-Methoxytryptamine** [6]



392.4 190.2

A mixture of the indole ester **3.2.5.2** (1.00 g, 2.55 mmol) and aqueous NaOH solution (2 M, 25 ml) is heated to reflux for 5 h to provide a homogeneous solution. Aqueous H_2SO_4 (20% (v/v), 50 ml) is then added dropwise over 20 min and the reaction mixture is heated to reflux for a further 3 h.

The solution is cooled for 3 h with an ice bath, and the precipitated phthalic acid is removed by filtration. The solution is made alkaline by the addition of aqueous NaOH (30% (v/v)) and extracted with CH_2Cl_2 (5 × 10 ml). The combined organic layers are washed with H_2O (10 ml) and brine (10 ml), and dried over Na_2SO_4, and filtered, and the solvent is removed *in vacuo* to give the amine as light-yellow crystals; 317 mg (65%), mp 121–122 °C.

UV (CH_3CN): λ_{max} (nm) (log ε) = 296.5 (3.677), 278.0 (3.789), 224.5 (4.369), 202.0 (4.418).

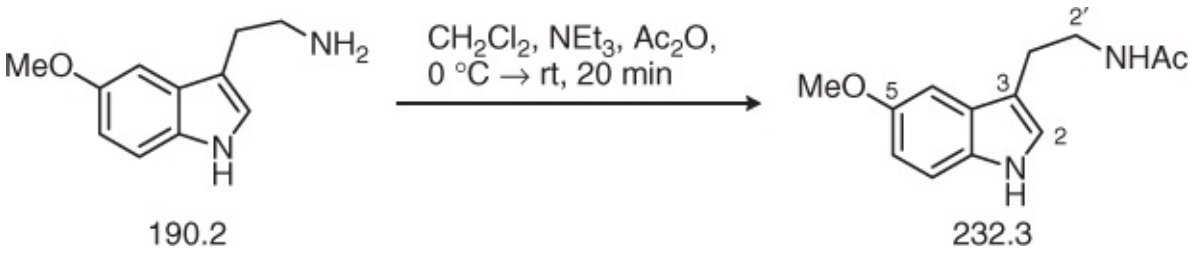
IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3335, 2595, 1586, 1492, 1305, 1218, 1048, 1010, 957, 922, 791, 638.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.27 (s_{br}, 1H, NH), 7.24 (dd, *J* = 8.8, 0.6 Hz, 1H, 7-H), 7.04 (d, *J* = 2.2 Hz, 1H, 4-H), 6.99 (d, *J* = 2.1 Hz, 1H, 2-H), 6.86 (dd, *J* = 8.8, 2.4 Hz, 1H, 6-H), 3.86 (s, 3H, OMe), 3.03 (t, *J* = 6.8 Hz, 2H, 2′-H_2), 2.88 (t, *J* = 6.8 Hz, 2H, 1-H_2), 1.35 (s_{br}, 2H, NH_2).

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 153.8 (C-5), 131.5 (C-7a), 127.8 (C-3a), 122.9 (C-2), 113.3 (C-3), 112.1 (C-7), 111.8 (C-6), 100.6 (C-4), 55.89 (OCH_3), 42.21 (C-2′), 29.42 (C-1′).

MS (EI, 70 eV): *m*/*z* (%) = 190 (36) $[M]^+$, 160 (100) $[M-CH_3NH_2]^+$, 145 (28) $[M-CH_3NH_2-CH_3]^+$.

3.2.5.4 * *N*-[2-(5-Methoxy-1*H*-indol-3-yl)ethyl]acetamide (melatonin) [6]



NEt_3 (33.2 mg, 32.8 µmol) and acetic anhydride (40.7 mg, 39.9 µmol) are added dropwise to a solution of the amine **3.2.5.3** (50.0 mg, 26.3 µmol) in anhydrous CH_2Cl_2 (2 ml) at 0 °C. The ice bath is removed and the solution is stirred at room temperature for 20 min and then poured into iced water (5 ml).

Melatonin precipitates as a colorless solid and is collected by filtration. The compound is then dried *in vacuo*; 43.4 mg (71%), mp 117–118 °C.

UV (CH_3CN): λ_{max} (nm) (log ε) = 297.0 (3.592), 275.5 (3.701), 223.5 (4.272), 200.5 (4.420).

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3294, 2934, 1651, 1486, 1217, 1036.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.44 (s_{br}, 1H, NH), 7.24 (d, *J* = 8.8 Hz, 1H, 7-H), 7.01 (d, *J* = 2.5 Hz, 1H, 4-H), 6.83 (dd, *J* = 8.8, 2.7 Hz, 1H, 6-H), 5.71 (s_{br}, 1H, NHAc), 3.83 (s, 3H, OMe), 3.56 (t, *J* = 6.8 Hz, 1H, 2′-H_b), 3.54 (t, *J* = 6.8 Hz, 1H, 2′-H_a), 2.93 (t, *J* = 6.8 Hz, 2H, 1′-H_2), 1.90 (s, 3H, 1″-H_3).

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 170.2 (C-2″), 154.0 (C-5), 131.6 (C-7a), 127.7 (C-3a), 122.9 (C-2), 112.5 (C-3), 112.3 (C-7), 112.1 (C-6), 100.4 (C-4), 55.9 (OCH_3), 39.8 (C-2′), 25.3 (C-1′), 23.3 (C-1″).

MS (EI, 70 eV): *m*/*z* (%) = 232 (30) $[M]^+$, 173 (100) $[M-Ac-CH_3]^+$, 160 (93) $[M-CH_3NHAc]^+$, 145 (15) $[M-CH_3NHAc-CH_3]^+$.

References

1. Thomson, D.W., Commeureuc, A.G.J., Berlin, S., and Murphy, J.A. (2003) *Synth. Commun.*, **33**, 3631–3641.

2. For discussion of the Fischer indole synthesis and its detailed mechanism, see: (a) Eicher, Th., Hauptmann, S., and Speicher, A. (2012) *The Chemistry of Heterocycles*, 3rd edn, Wiley-VCH Verlag GmbH, Weinheim, p. 142;for further information on indole synthesis, see: (b) Kreher, R. (ed.) (1994) *Methoden der organischen Chemie (Houben-Weyl)*, 4th edn, vol. E 6b1/E 6b2, Georg Thieme Verlag, Stuttgart.

3. Hügel, H.M. and Nurlawis, F. (2003) *Heterocycles*, **60**, 2349–2354.

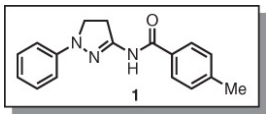
4. Marais, W. and Holzapfel, C.W. (1998) *Synth. Commun.*, **28**, 3681–3691.

5. Prabhakar, C., Kumar, N.V., Reddy, M.R., Sarma, M.R., and Reddy, G.O. (1999) *Org. Process Res. Dev.*, **3**, 155–160.

6. He, L., Li, J.-L., Zhang, J.-J., Su, P., and Zheng, S.-L. (2003) *Synth. Commun.*, **33**, 741–747; the microwave-assisted indole formation described in this paper proved to be irreproducible.

7. (a) Tietze, L.F. (1996) *Chem. Rev.*, **96**, 115–136;(b) Tietze, L.F., Brasche, G., and Gericke, K. (2006) *Domino Reactions in Organic Synthesis*, Wiley-VCH Verlag GmbH, Weinheim;(c) Tietze, L.F. (ed.) (2014) *Domino Reactions - Concepts for Efficient Organic Synthesis*, Wiley-VCH Verlag GmbH, Weinheim.

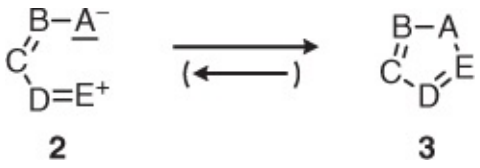
3.2.6 3-(4-Methylbenzoylamino)-1-phenyl-4,5-dihydropyrazole

	***Topics:***	• Cyanoethylation of a primary amine • Formation of an amidoxime • Formation of a 1,2,4-oxadiazole • Thermal heterocycle isomerization: 3-(β-aminoethyl)-1,2,4-oxadiazole → (3-arylamino)-4,5-dihydropyrazole

(a) General

The formation of five-membered heterocycles with two or more heteroatoms (of the general formula **3**) is often accomplished by ring closure of 1,5-dipolar

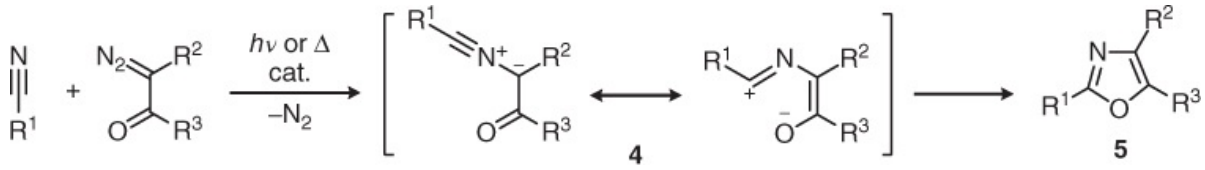
acyclic species of the general formula **2**. This process has been interpreted in terms of an – in principle reversible – 6π-electrocyclization [1–3]:



2 **3**

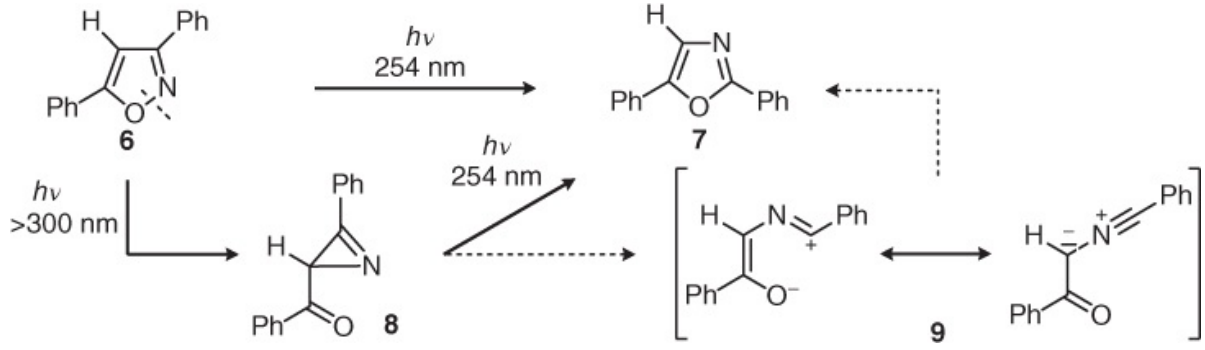
The 1,5-dipolar species can be envisaged as reactive intermediates, which are generated (i) by combination of suitable acyclic precursors or (ii) by ring-opening reactions of heterocycles, as illustrated by the following examples.

1. α-Diazocarbonyl compounds undergo additions to nitriles with elimination of N_2 catalyzed by Lewis acids or transition-metal ions (Cu(II), Pd(II), and especially Rh(II)) to give 1,3-oxazoles **5**. The reaction is likely to proceed via intermediary formation of nitrile ylides **4** and their ring closure to **5** in a 1,5-dipolar manner [3]:



4 **5**

2. 1,2-Oxazoles (e.g., **6**) are isomerized photochemically to give 1,3-oxazoles (e.g., **7**). In this rearrangement, an (isolable) 3-acylazirine (e.g., **8**) is involved as an intermediate, which is transformed to the 1,3-oxazole system by 1,5-electrocyclization of the nitrile ylide **9** [4, 5]:



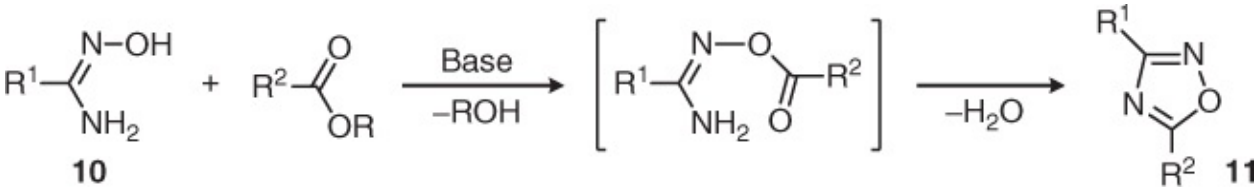
6 **7** **8** **9**

For further examples of 1,5-electrocyclic processes, see Ref. [1].

(b) Synthesis of 1

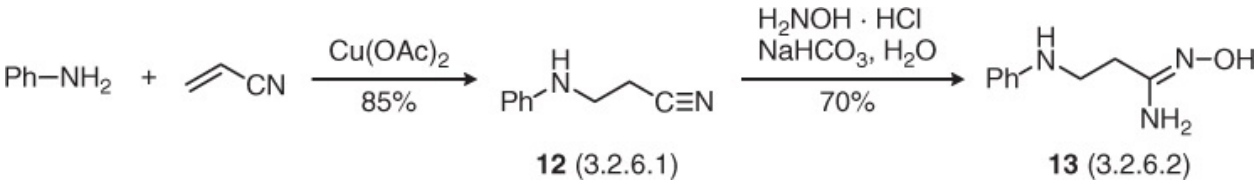
(3-Acylamino)-4,5-dihydropyrazoles, such as **1**, can be prepared by thermal isomerization of 3-(β-aminoethyl)-1,2,4-oxadiazoles [6]. In general, 1,2,4-oxadiazoles **11** are obtained by cyclocondensation of amidoximes **10** with

carboxylic esters in the presence of a base:

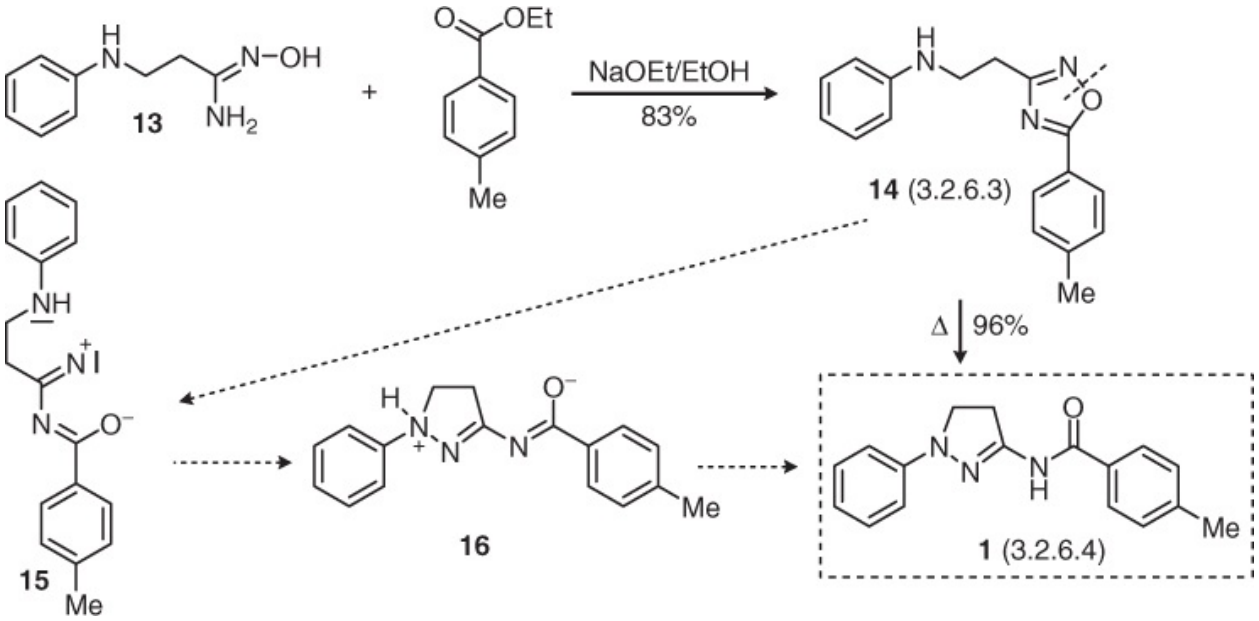


Therefore, in the first part of the synthesis of **1**, the amidoxime **13** is synthesized.

Aniline is mono-alkylated by conjugate addition to acrylonitrile in the presence of $Cu(OAc)_2$ (cyanoethylation [7]) yielding β-anilinopropionitrile (**12**), from which the required amidoxime **13** is obtained by addition of hydroxylamine to the C≡N triple bond:



In the second part of the synthesis, the amidoxime **13** is cyclocondensed with ethyl *p*-toluate, which occurs readily on treatment with sodium ethoxide in refluxing EtOH and provides the 1,2,4-oxadiazole **14** in 83% yield. When the 3-(β-aminoethyl)-1,2,4-oxadiazole **14** is heated in *n*-butanol solution, it readily isomerizes to afford the (3-acylamino)-4,5-dihydropyrazole **1**:



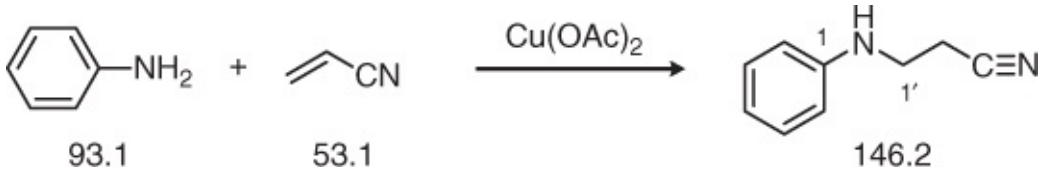
The thermal isomerization **14** → **1** can be rationalized mechanistically in analogy to the examples in Section (a). Opening of the 1,2,4-oxadiazole system in **14** at

the (relatively weak) O–N bond produces a 1,5-dipole **15**, which is intercepted by intramolecular nucleophilic attack of the aniline nitrogen (probably favored by proximity effects) to yield the 4,5-dihydropyrazole **16** and thereafter the product **1** by prototropy.

In this way, the target molecule is obtained by a four-step sequence in an overall yield of 47% (based on aniline).

(c) Experimental Procedures for the Synthesis of 1

3.2.6.1 * β-Anilinopropionitrile [8]



A stirred mixture of aniline (93.1 g, 1.00 mol), acrylonitrile (53.1 g, 1.00 mol) (note), and Cu(II) acetate (1.85 g) is heated to reflux (approximately 95 °C). The bath temperature is raised to 110 °C over a period of 30 min and is held there for 1 h.

The mixture is then cooled to approximately 80 °C, and unreacted aniline and acrylonitrile are distilled off *in vacuo* (20 mbar); approximately 29 g of aniline is recovered. The dark residue is fractionally distilled to give a forerun, followed by a yellowish oil, which crystallizes in the receiver. Recrystallization from EtOH gives colorless needles; 84.5 g (85%, based on reacted aniline), $bp_{0.02}$ 115–120 °C, mp 50–51 °C.

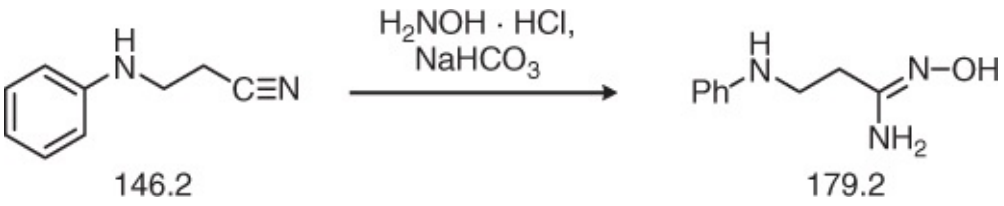
IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3360, 2260.

^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 7.21 (dt, *J* = 7.2, 1.8 Hz, 2H, 3-H, 5-H), 6.77 (tt, *J* = 7.2, 1.7 Hz, 1H, 4-H), 6.61 (m, 2H, 2-H, 6-H), 3.99 (s_{br}, 1H, NH), 3.49 (t, *J* = 5.5 Hz, 2H, 1′-H_2), 2.48 (t, *J* = 5.5 Hz, 2H, 2′-H_2).

^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) = 146.1 (C-1), 129.4 (C-3, C-5), 118.4 (C-4), 118.2 (CN), 112.9 (C-2, C-6), 39.6 (C-1′), 17.9 (C-2′).

Note: Aniline (bp_{20} 84–85 °C) and acrylonitrile (bp_{760} 74–75 °C) are distilled before use.

3.2.6.2 * β-Anilinopropionamide oxime [6]



146.2 179.2

Sodium hydrogencarbonate (16.8 g, 0.20 mol) is added in portions to a solution of hydroxylamine hydrochloride (14.0 g, 0.20 mol) in water (50 ml). A solution of β-anilinopropionitrile (cf. **3.2.6.1**) (14.6 g, 0.10 mol) in EtOH (100 ml) is then added and the mixture is heated under reflux for 6 h.

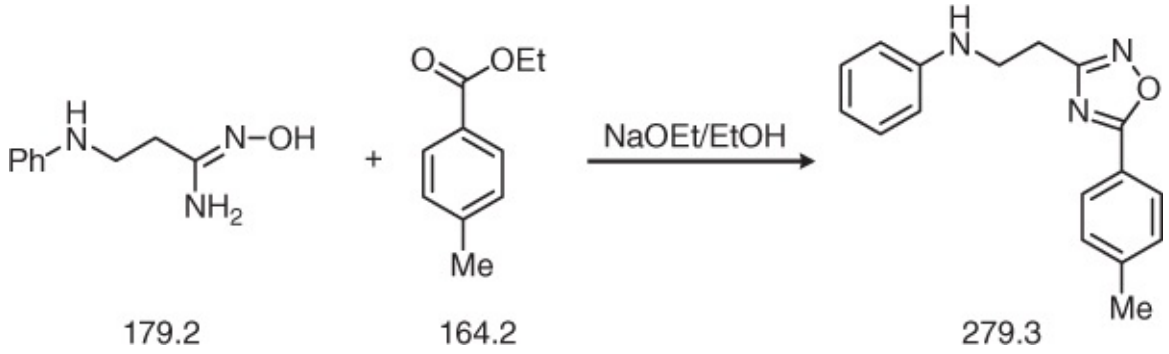
The solution is then concentrated *in vacuo* to one-third of its original volume to give a greenish oil, which is extracted with Et_2O (3 × 100 ml). The combined organic layers are dried over Na_2SO_4 and filtered, and the solvent is removed *in vacuo* to give an oily residue (14.6 g), which is pure by TLC and can be crystallized from *n*-hexane/EtOAc (1 : 1; 80 ml); 12.6 g (70%), mp 84–86 °C. Recrystallization from the same solvent mixture gives pale-reddish needles, mp 90–92 °C (note).

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3500, 3370, 3390, 1660.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.22–7.18 (m, 2H, Ar), 6.80–6.72 (m, 1H, Ar), 6.70–6.62 (m, 2H, Ar), 4.63 (s_{br}, 1H, NH), 3.49, 2.49 (2 × t, *J* = 4.8 Hz, 2 × CH_2).

Note: If the crystallization is unsuccessful, the residue is chromatographed on silica gel (200 g) eluting with Et_2O. One recrystallization of the product gives colorless needles, mp 91–92 °C.

3.2.6.3 * 3-(β-Anilinoethyl)-5-(*p*-tolyl)-1,2,4-oxadiazole [6]



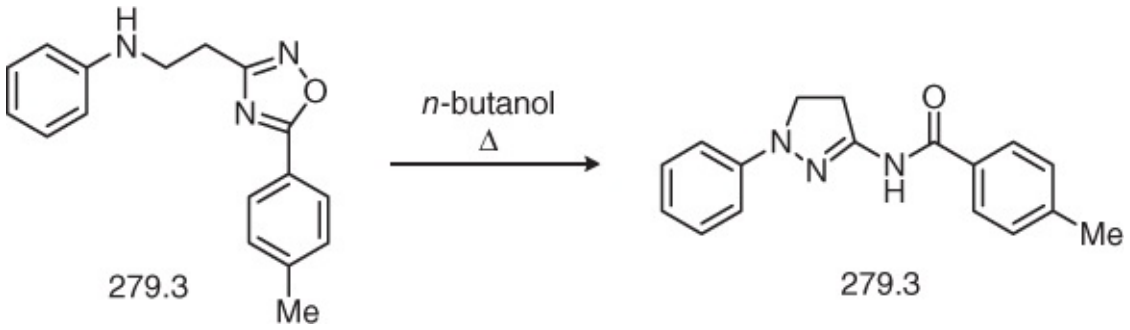
A mixture of amidoxime **3.2.6.2** (8.95 g, 50.0 mmol) and ethyl *p*-toluate (16.4 g, 0.10 mol) in anhydrous EtOH (50 ml) is added over 3 min to a stirred solution of sodium ethoxide 1.20 g, 52.0 mmol, of sodium in anhydrous EtOH (50 ml). The solution becomes yellow and a crystalline precipitate begins to form after approximately 10 min. The mixture is refluxed for 8 h.

It is then cooled and filtered, and the solid is washed with EtOH. The solid is then suspended in H_2O (250 ml), stirred for 10 min, collected by filtration, and dried; 8.42 g, mp 96–99 °C. The EtOH mother liquor is concentrated *in vacuo*, the residue is taken up in H_2O (100 ml), and the resulting solution is extracted with CH_2Cl_2 (3 × 100 ml). The combined extracts are dried over $MgSO_4$ and filtered, and the solvent is removed *in vacuo*. The residue is crystallized from EtOH; 3.20 g, mp 94–98 °C. The total yield is 11.6 g (83%); recrystallization from EtOH gives colorless platelets, mp 101–102 °C.

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3400, 1630.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.05–8.10 (m, 2H, Ar), 7.37–7.31 (m, 2H, Ar), 7.25–7.18 (m, 2H, Ar), 6.78–6.69 (m, 3H, Ar), 4.25 (s_{br}, 1H, NH), 3.74 (t, *J* = 6.7 Hz, 2H, CH_2), 3.05 (t, *J* = 6.7 Hz, 2H, CH_2), 2.42 (s, 3H, CH_3).

3.2.6.4	*	**3-(4-Methylbenzoylamino)-1-phenyl-4,5-dihydropyrazole** [6]



The oxadiazole **3.2.6.3** (5.60 g, 20.0 mmol) is heated under reflux in anhydrous *n*-butanol (30 ml) for 8 h.

The solution is then cooled to room temperature and the acylaminodihydropyrazole crystallizes as yellow needles in pure form (TLC). The yield is 5.41 g (96%), mp 182–183 °C (note).

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3310, 1665, 1620.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.45 (s_{br}, 1H, NH), 7.80–7.75 (m, 2H, Ar), 7.35–7.26 (m, 4H, Ar), 7.02–6.97 (m, 2H, Ar), 6.89–6.82 (m, 1H, Ar), 3.92–3.83 (m, 2H, CH_2), 3.72–3.63 (m, 2H, CH_2), 2.47 (s, 3H, CH_3).

Note: Recrystallization from *n*-butanol does not change the melting point.

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6. Korbonits, D., Bako, E.M., and Horvath, K. (1979) *J. Chem. Res. (S)*, 64.

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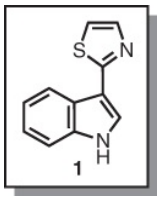
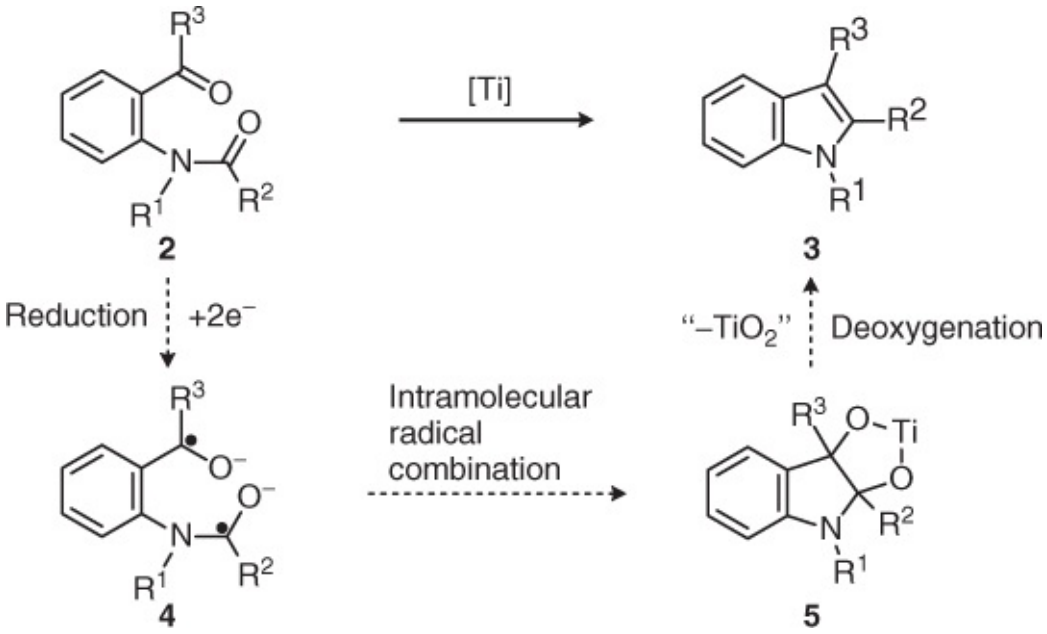
3.2.7 Camalexin

 1	***Topics:***	• Synthesis of a phytoalexin • Halogen–metal exchange • Addition of an organolithium compound to an aryl aldehyde • Oxidation CH–OH → C=O, reduction Ar–NO_2 → Ar–NH_2 • N-Formylation of a primary amine • Fürstner indole synthesis: low-valent titanium-induced reductive cyclization of (2-acyl)anilides

(a) General

Camalexin (**1**, 3-(2-thiazolyl)indole) belongs to the class of phytoalexins that play an important role in the antimicrobial defense mechanism of plants. Camalexin and its 6-methoxy derivative are produced in the leaves of the false flax (*Camelina sativa*) in response to infection by *Alternaria brassicae* and thus display antifungal activity [1].

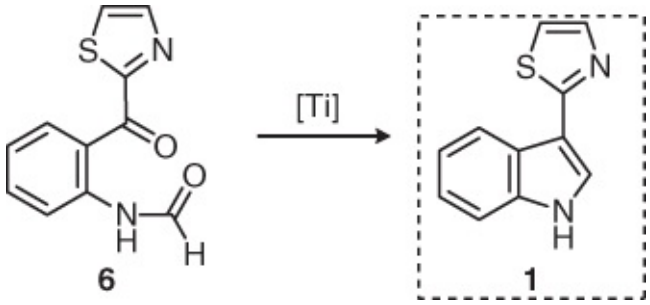
Among the numerous concepts for the construction of indoles [2], the Fürstner indole synthesis has been successfully applied to the synthesis of **1** and other indole-based natural products [1, 3]:



In the Fürstner indole synthesis, (2-acyl)anilides **2** are cyclized by intramolecular reductive coupling of the two carbonyl groups mediated by "low-valent titanium" (abbreviated as [Ti]), thus creating the C-2/C-3 bond of indoles **3**. This process is similar to the classical McMurry reaction [4], that is, the reductive dimerization of aldehydes and ketones forming olefinic C=C double bonds. Its mechanism presumably involves one-electron transfers to the carbonyl groups (**2** → **4**) and intramolecular radical combination of **4** to give a titanium dioxygen species **5**, which finally is deoxygenated to give the indole system **3** [5].

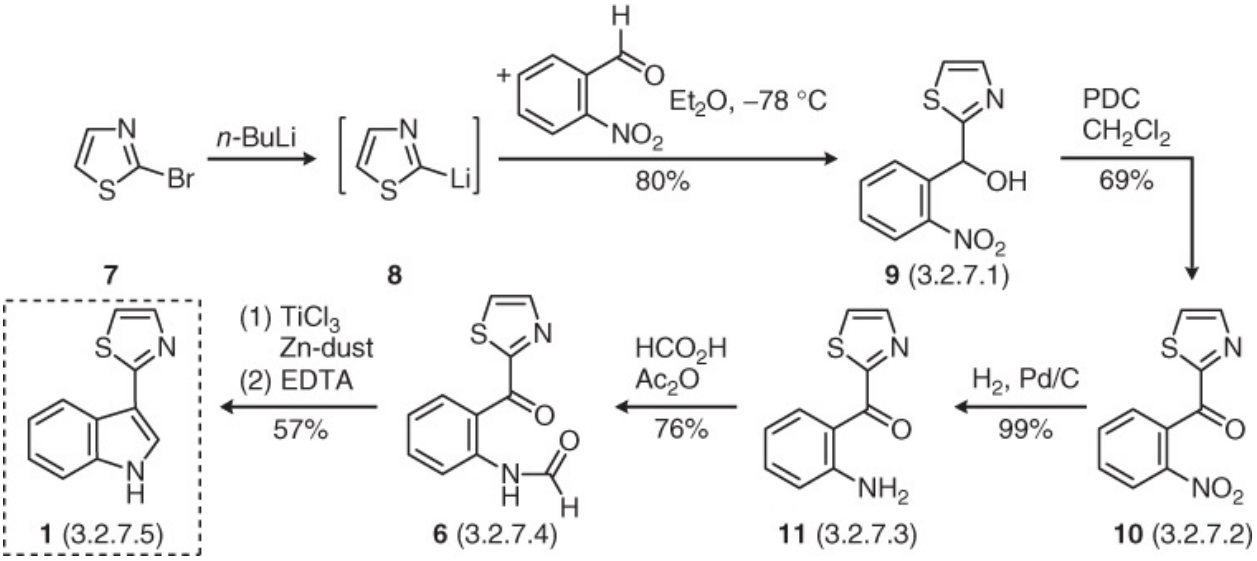
The Fürstner method is highly flexible with respect to the substitution pattern in the heterocyclic indole part and has proved to be compatible with a great number of Lewis acidic and reducible functional groups in the substrate **2**. The low-valent titanium species [Ti] can be generated from $TiCl_3$ and reducing agents such as Zn, Mg, or potassium-graphite laminate C_8K [3].

In the synthesis of **1** presented in Section (b), the titanium reagent is prepared directly ("instant method") in the presence of the substrate **6** required for the reductive cyclization.



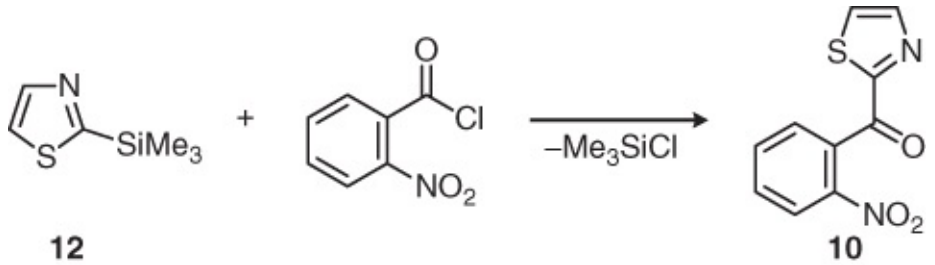
(b) Synthesis of 1

Commercially available 2-bromothiazole (**7**) is subjected to halogen–metal exchange by reaction with *n*-butyllithium. The resulting 2-lithiothiazole (**8**) is subsequently added to the carbonyl group of 2-nitrobenzaldehyde at −78 °C in Et_2O to give (after hydrolytic work-up) the secondary carbinol **9**, which is oxidized to the ketone **10** by pyridinium dichromate:



Chemoselective catalytic reduction of the nitro group in **10** by H_2 over Pd on charcoal followed by formylation of the NH_2 group in the amino ketone **11** yields the (2-acyl)-*N*-formylaniline **6**, which is reductively cyclized by treatment with $TiCl_3$/zinc dust in THF. Work-up with ethylenediaminetetraacetic acid (EDTA) in order to de-complex the Lewis-acidic titanium salts from the basic thiazole nitrogen affords camalexin (**1**).

It should be noted that, alternatively, the (2-nitrophenyl)-(2-thiazolyl)-ketone (**10**) can be obtained from C–Si acylation of (2-trimethylsilyl)thiazole (**12**) by (2-nitro)benzoyl chloride [1]:



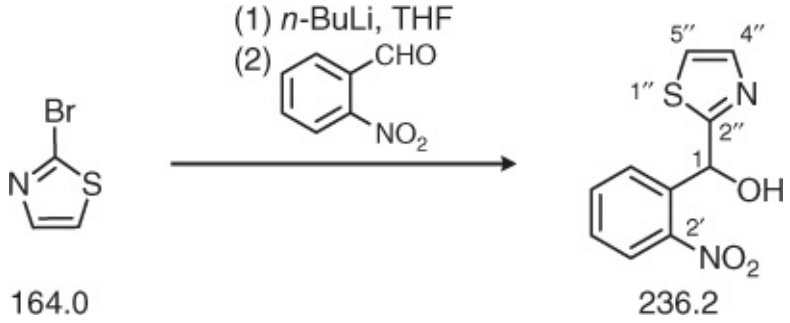
Since **12** (“Dondoni's thiazole”) is a noxious compound and is difficult to separate from the product **10**, the preparation of **10** starting with 2-

nitrobenzaldehyde (as described above) is preferred.

In this way, the target molecule **1** is prepared in a five-step sequence with an overall yield of 24% (based on **7**).

(c) Experimental Procedures for the Synthesis of 1

3.2.7.1	**	**(2-Nitrophenyl)-(2-thiazolyl)methanol** [1]

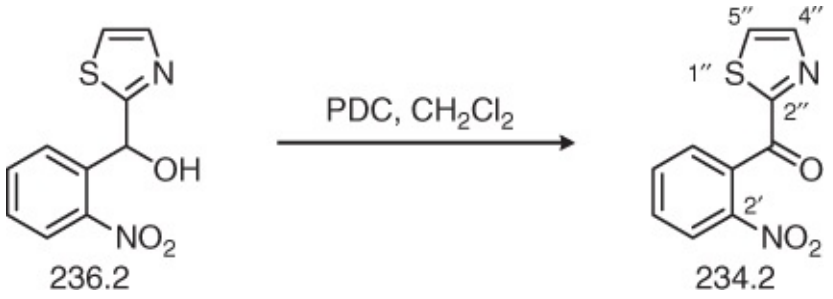


A solution of 2-bromothiazole (5.0 g, 30.5 mmol) in anhydrous Et_2O/THF (2 : 1; 20 ml) is added to a stirred solution of *n*-BuLi (1.6 M in *n*-hexane, 20 ml, 32.0 mmol) in Et_2O (80 ml) at −78 °C under argon over a period of 45 min. After stirring for a further 15 min at −78 °C, a solution of 2-nitrobenzaldehyde (4.50 g, 30.0 mmol) in anhydrous THF (20 ml) is added dropwise to the reaction mixture over a period of 45 min. Stirring is continued for a further 30 min at −78 °C.

The cold mixture is then carefully added to a 10% aqueous NH_4Cl solution (100 ml), the aqueous layer is extracted with EtOAc (3 × 30 ml), the combined organic phases are washed with brine (20 ml), dried over $MgSO_4$, filtered, and the solvent is removed *in vacuo*. The residue is recrystallized from toluene to give the product as pale-yellow crystals; 4.62 g (80%), mp 130–131 °C; R_f = 0.17 (*n*-pentane/EtOAc, 4 : 1).

^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) = 8.03 (m, 1H, 3′-H), 7.58 (m, 3H, 4′-H, 5′-H, 6′-H), 7.48 (m, 1H), 7.32 (d, *J* = 8 Hz 1H) (4″-H, 5″-H), 6.62 (s, 1H, 1-H), 4.50 (s_{br}, 1H, OH).

3.2.7.2	*	**(2-Nitrophenyl)-(2-thiazolyl) ketone** [1]



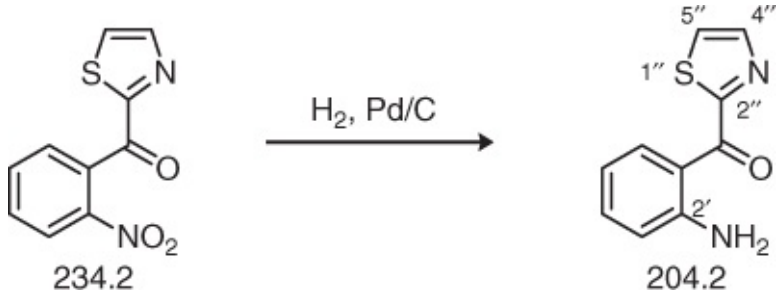
Pyridinium dichromate (PDC) (12.1 g, 32.1 mmol) is added to a solution of the carbinol **3.2.7.1** (3.8 g, 16.1 mmol) in CH_2Cl_2 (150 ml) under an argon atmosphere. The suspension is stirred for 5 h at room temperature.

It is then filtered through a short pad of Celite®, the pad is washed with CH_2Cl_2 (250 ml), and the combined filtrate and washings are dried over $MgSO_4$ and filtered, and the solvent is removed *in vacuo*. The residue is recrystallized from MeOH to give (2-nitrophenyl)-(2-thiazolyl) ketone as pale-yellow crystals; 2.60 g (69%), mp 119–120 °C; R_f = 0.39 (*n*-pentane/EtOAc, 4 : 1).

IR (film): $\tilde{\nu}$ (cm^{-1}) = 3448, 3335, 3155, 3114, 3093, 3059, 3031., 2950, 2919, 2853, 1976, 1951, 1864, 1849, 1821, 1754, 1734, 1718, 1675, 1638, 1611, 1575, 1519, 1480, 1438, 1384, 1371, 1348, 1330, 1309, 1296, 1257, 1174, 1136, 1064, 988, 964, 912, 898, 867, 854, 790, 768, 737, 707.

^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) = 8.24 (d, *J* = 4 Hz, 1H), 8.06 (d, *J* = 4 Hz, 1H) (4″-H, 5″-H), 7.78–7.97 (m, 4H, 3′-H, 4′-H, 5′-H, 6′-H).

3.2.7.3	**	**(2-Aminophenyl) (2-thiazolyl) ketone** [1]



The nitro ketone **3.2.7.2** (1.00 g, 4.27 mmol) is dissolved in EtOAc (25 ml), and 5% palladium on charcoal (112 mg) is added. The reaction mixture is flushed with H_2 for 3 h.

The solution is then filtered through a short pad of Celite® (5 g). The pad is

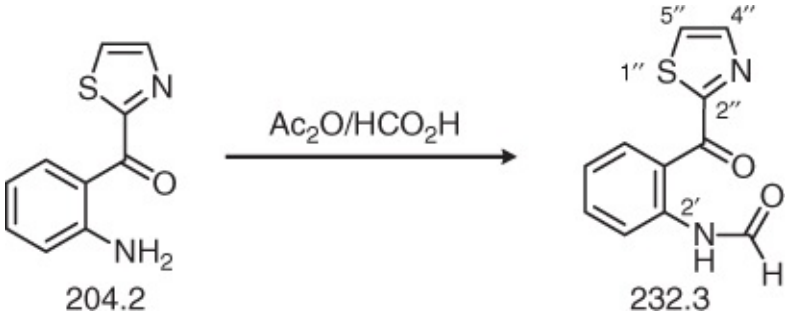
washed with EtOAc, the combined filtrate and washings are dried over $MgSO_4$ and filtered, and the solvent is removed *in vacuo* to give the amino ketone as yellow needles; 860 mg (99%), mp 116–117 °C; R_f = 0.49 (*n*-pentane/EtOAc, 4 : 1).

IR (film): $\tilde{\nu}$ (cm^{-1}) = 3443, 3335, 3156, 3114, 3093, 2949, 2921, 2853, 2618, 1976, 1951, 1849, 1821, 1754, 1734, 1718, 1674, 1638, 1611, 1575, 1519, 1481, 1439, 1384, 1330, 1309, 1296, 1257, 1174, 1135, 1064, 988, 964, 940, 912, 899, 867, 854, 790, 768, 737, 707, 673, 642, 612.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.90 (dd, *J* = 8.2, 1 Hz, 1H), 8.10 (d, *J* = 1 Hz, 1H), 7.58 (d, *J* = 1 Hz, 1H), 7.37 (dt, *J* = 8.2, 1 Hz, 1H), 6.74 (dt, *J* = 8.2, 1 Hz, 2H), 4.80 (s_{br}, 2H, NH_2).

MS (ESI): *m*/*z* = 206 $[M+H]^+$.

3.2.7.4	**	**(2-Formamidophenyl) (2-thiazolyl) ketone** [1]



Formic acid (10.9 ml, 290 mmol) and acetic anhydride (25 ml, 264 mmol) are stirred for 3 h at 60 °C and then added to the amino ketone **3.2.7.3** (572 mg, 28.0 mmol). The mixture is stirred for 30 min at room temperature.

The reaction is then carefully quenched by the addition of saturated aqueous $NaHCO_3$ solution (15 ml). The aqueous layer is extracted with EtOAc (5 × 15 ml), the combined organic layers are dried over $MgSO_4$ and filtered, and the solvent is removed *in vacuo*. The residue is purified by flash chromatography (SiO_2, *n*-pentane/EtOAc, 4 : 1). The product is obtained as pale-yellow needles; 492 mg (76%), mp 110–111 °C; R_f = 0.18 (*n*-pentane/EtOAc, 4 : 1).

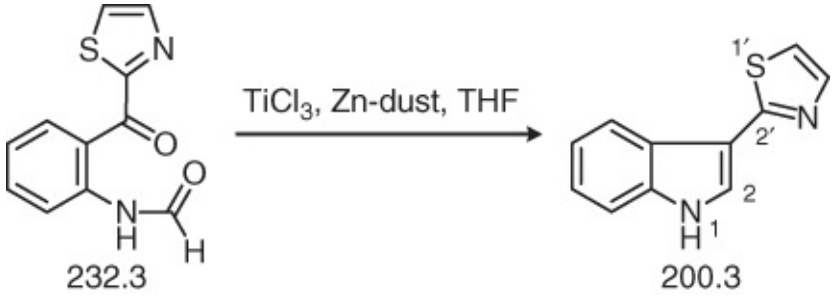
IR (film): $\tilde{\nu}$ (cm^{-1}) = 3407, 2922, 2851, 1657, 1548, 1480, 1381, 1328,

1300, 1276, 1200, 1160, 1096, 1069, 1034, 897, 876, 752.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 10.9 (s_{br}, 1H, NH), 8.88 (d, *J* = 8 Hz, 1H), 8.72 (d, *J* = 8 Hz, 1H), 8.52 (s, 1H), 8.12 (d, *J* = 3.2 Hz, 1H), 7.79 (d, *J* = 3.2 Hz, 1H), 7.67 (t, *J* = 8.1 Hz, 1H, 1H), 7.26 (t, *J* = 8 Hz, 1H).

MS (ESI): *m*/*z* = 255 $[M+Na]^+$, 233 $[M+H]^+$.

3.2.7.5	**	**Camalexin** [1]



Formamide **3.2.7.4** (50 mg, 216 µmol), $TiCl_3$ (166 mg, 1.1 mmol), and Zn dust (70.6 mg, 1.08 mmol) are suspended in anhydrous THF (2.5 ml) and heated under reflux in an argon atmosphere for 3 h.

The mixture is then allowed to cool to room temperature, diluted with EtOAc (5 ml), and washed with a saturated aqueous solution of EDTA (3 × 2 ml). The aqueous layer is extracted with EtOAc (5 × 5 ml), and the combined organic layers are dried over $MgSO_4$ and filtered, and the solvent is removed *in vacuo*. The residue is purified by flash chromatography (SiO_2, *n*-pentane/EtOAc, 4 : 1). Camalexin is obtained as pale-yellow crystals; 24.6 mg (57%), mp 132–133 °C; R_f = 0.58 (*n*-pentane/EtOAc, 4 : 1).

IR (film): $\tilde{\nu}$ (cm^{-1}) = 3386, 2960, 2923, 2852, 2346, 1720, 1654, 1550, 1498, 1460, 1377, 1325, 1260, 1093, 1029, 865, 798, 745.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 9.25 (s_{br}, 1H, NH), 8.25 (m, 1H,), 7.85 (t, *J* = 8 Hz, 2H), 7.43–7.20 (m, 4H).

MS (ESI): *m*/*z* = 200 $[M+H]^+$.

References

1. Fürstner, A. and Ernst, A. (1995) *Tetrahedron*, **51**, 773–786.

2. Kreher, R. (ed.) (1994) *Methoden der Organischen Chemie (Houben-Weyl)*, vol. E 6 b1/E 6 b2 Georg Thieme Verlag Stuttgart.

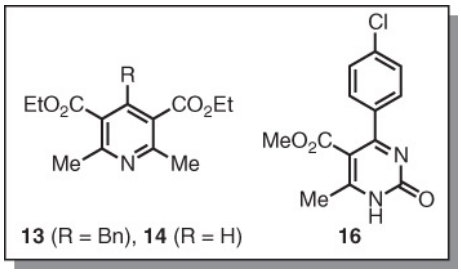
3. Fürstner, A., Ernst, A., Krause, H., and Ptok, A. (1996) *Tetrahedron*, **52**, 7329–7344.

4. McMurry, J.E. (1989) *Chem. Rev.*, **89**, 1513–1524.

5. Smith, M.B. (2013) *March's Advanced Organic Chemistry*, 7th edn, John Wiley & Sons, Inc., New York, p. 1559, and literature cited therein.

3.3 Six-Membered Heterocycles

3.3.1 Azine and Diazine Syntheses with Acetoacetate



13 (R = Bn), **14** (R = H) **16**

Topics:

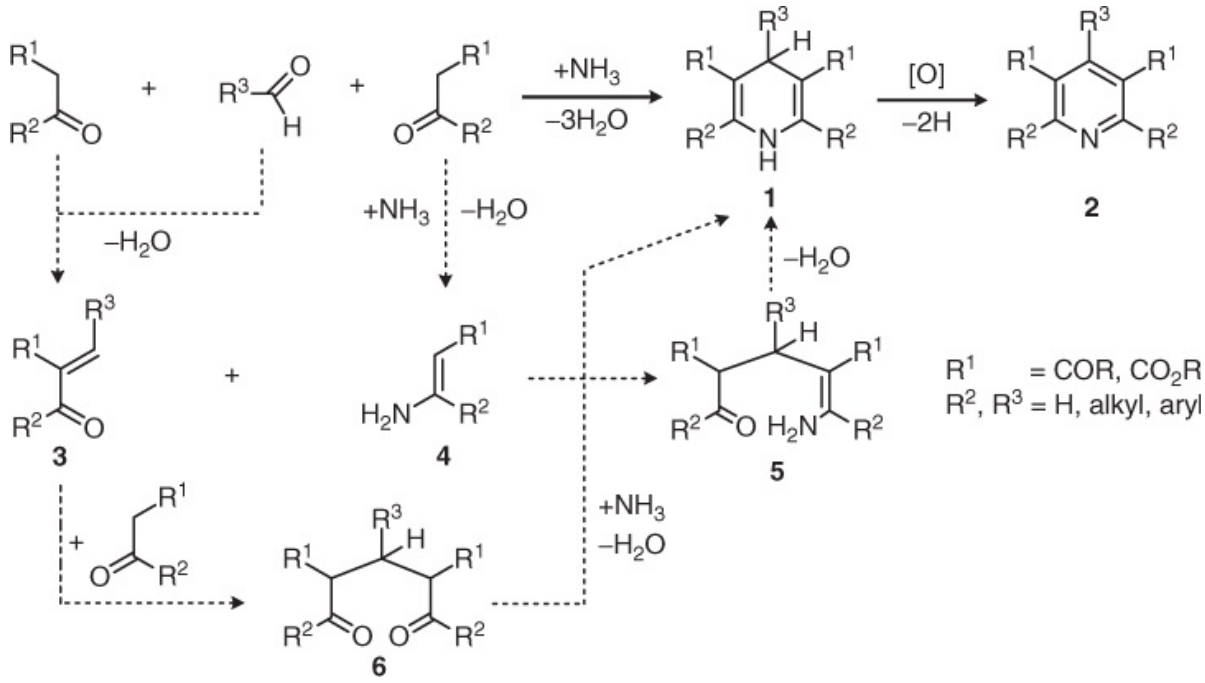
- Hantzsch synthesis of pyridines
- Biginelli synthesis of 3,4-dihydropyrimidin-2-ones
- Dehydrogenation of a dihydropyrimidinone to a pyrimidinone

(a) General

Several highly efficient synthetic methods are known for the construction of six-membered heterocycles, in which β-dicarbonyl compounds, preferentially β-keto esters, are incorporated as C_2-building blocks by, in general, one-pot multicomponent processes. Two of these methods are illustrated in (1) and (2).

1. In the Hantzsch synthesis of pyridines, two molecules of a β-dicarbonyl compound (β-keto-ester or β-diketone), an aldehyde, and ammonia are combined in a four-component cyclocondensation to give 1,4-

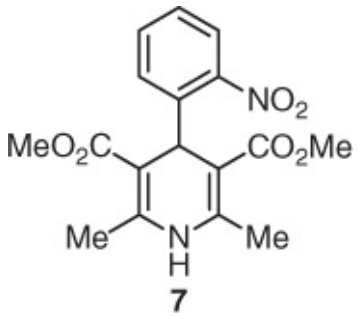
dihydropyridines **1**, which can be oxidized to pyridines **2** [1]:



The process can be performed in two different ways. First, one molecule of the β-dicarbonyl compound combines with the aldehyde to form the corresponding Knoevenagel product **3**, which then reacts with the β-enaminone **4** preformed by addition of NH_3 (or a primary amine) to another molecule of the β-dicarbonyl compound. This Michael addition yields 5-aminopent-4-enone **5**, cyclization of which provides the 1,4-dihydropyridine **1**.

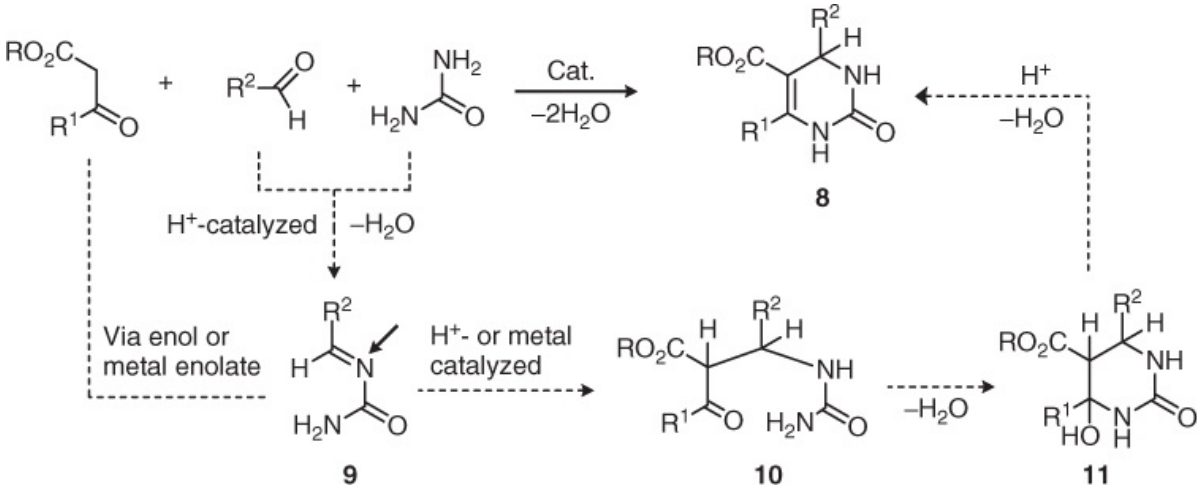
The procedure allows the preparation of unsymmetrical 1,4-dihydropyridines. Thus, in this modification of the Hantzsch synthesis using preformed β-enaminones, different β-dicarbonyl compounds for the formation of the β-enaminones and for the Knoevenagel condensation can be used [2]. In the second approach, the two molecules of the β-dicarbonyl compound react with the aldehyde in a domino Knoevenagel–Michael addition process to yield the 1,5-dicarbonyl system **6**, which undergoes cyclocondensation with NH_3 leading to **1**. Only symmetrical compounds can be prepared by this route.

It should be noted that 1,4-dihydropyridines such as nifedipine **7** and analogs are potent Ca antagonists and coronary dilators and are therefore medicinally important as antihypertensives [3].



7

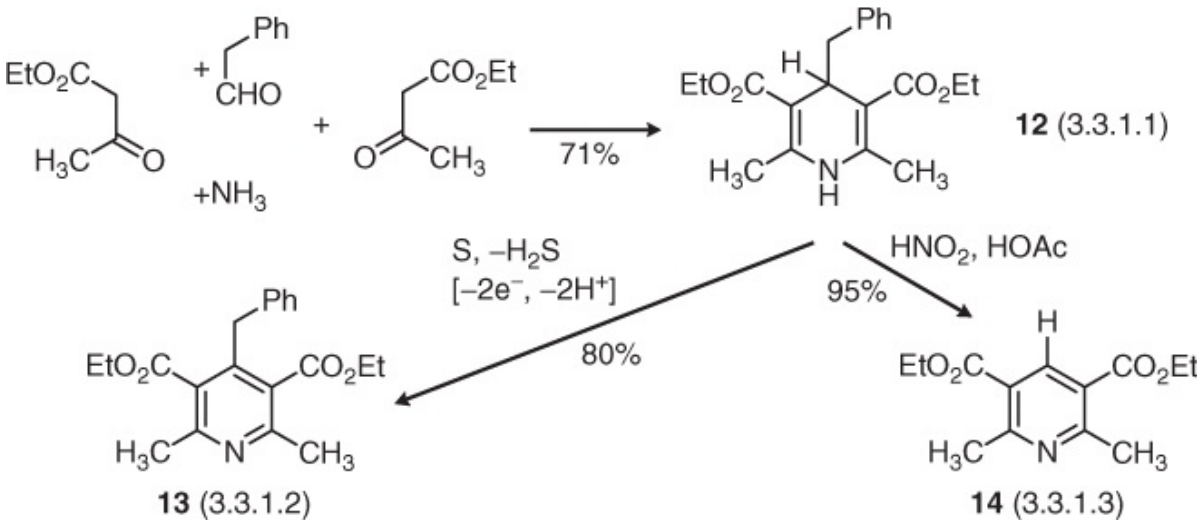
2. In the Biginelli synthesis of 3,4-dihydropyrimidinones such as **8** [4], a β-keto ester, an aldehyde, and urea undergo an acid-or metal ion-catalyzed three-component cyclocondensation:



Despite the formal resemblance to the synthesis of 1,4-dihydropyridines described in (1), the mechanism of the Biginelli reaction is quite different [5]. The rate-determining step is the acid-catalyzed formation of an acylimine intermediate **9** from the aldehyde and urea. By N-protonation or N-coordination with metal ions (Fe(III), Ni(II), etc.), the acylimine **9** can be activated as an iminium ion and intercepted by the β-keto ester (as an enol or metal enolate) to produce an open-chain ureide **10**, which subsequently cyclizes (via the cyclic ureide **11** and its dehydration) to give the 3,4-dihydropyrimidinone **8**.

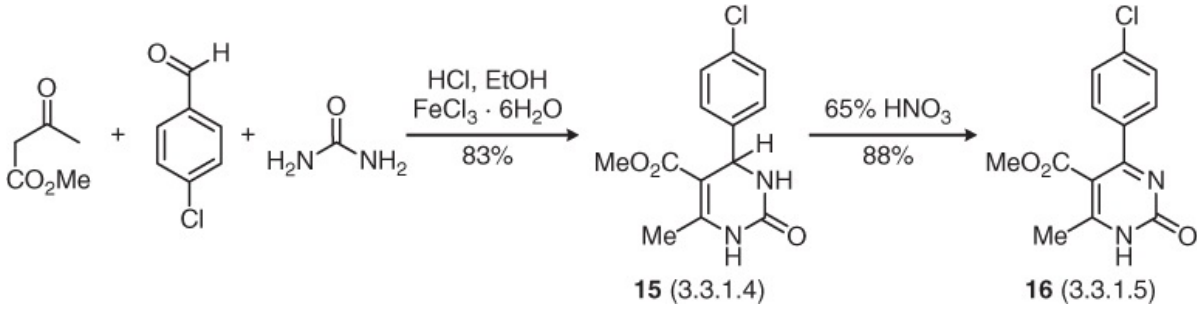
(b) Syntheses of 13, 14, 16

1. For the synthesis of **13** and **14**, the 4-benzyl-1,4-dihydropyridine **12** is prepared by a four-component cyclocondensation according to the Hantzsch method by reacting two molecules of ethyl acetoacetate, one molecule of phenylacetaldehyde, and ammonia [6]:



The obtained 1,4-dihydropyridine **12** can be further transformed in two different ways. On reaction with sulfur, **12** is dehydrogenated with preservation of the 4-benzyl substituent to yield the pyridine dicarboxylate **13** [7]. On reaction with HNO_2 in acetic acid, **12** undergoes an oxidative dealkylation with loss of the 4-substituent (probably via the benzyl cation, as indicated by the concomitant formation of benzyl alcohol, benzyl acetate, and benzaldehyde) to give the pyridine dicarboxylate **14** [6]. An SET mechanism has been suggested [8] to explain the results of "normal" and "anomalous" oxidative aromatization of 1,4-dihydropyridines.

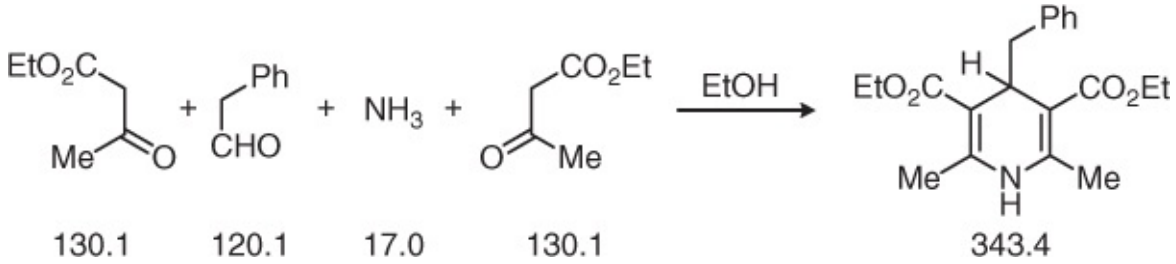
2. For the synthesis of **16**, first the 4-(*p*-chlorophenyl)-3,4-dihydropyrimidin-2(1*H*)-one **15** is prepared in a three-component cyclocondensation of methyl acetoacetate, *p*-chlorobenzaldehyde, and urea in the presence of HCl and $FeCl_3$ in EtOH according to the Biginelli approach [5]. The dihydropyrimidinone thus obtained is then oxidized to the corresponding pyrimidin-2(1*H*)-one **16** with concentrated HNO_3 [9].



(c) Experimental Procedures for the Syntheses of 13, 14, and 16

3.3.1.1	*	**4-Benzyl-3,5-bis(ethoxycarbonyl)-1,4-dihydro-2,6-**

		dimethylpyridine [6]



Ethyl acetoacetate (44.2 g, 0.34 mol), phenylacetaldehyde (20.2 g, 0.17 mol) (note), and concentrated ammonia (20 ml, approximately 0.3 mol) are dissolved in EtOH (40 ml) and heated to reflux for 2 h.

After cooling to room temperature, the reaction mixture is poured into ice water (500 ml), from which a yellow oil separates. The oil solidifies within 1 h, and is collected by filtration, washed with H_2O, and dried *in vacuo*. Recrystallization from cyclohexane gives pale-yellow needles; 41.5 g (71%), mp 115–116 °C. For further purification, it may also crystallized from MeOH.

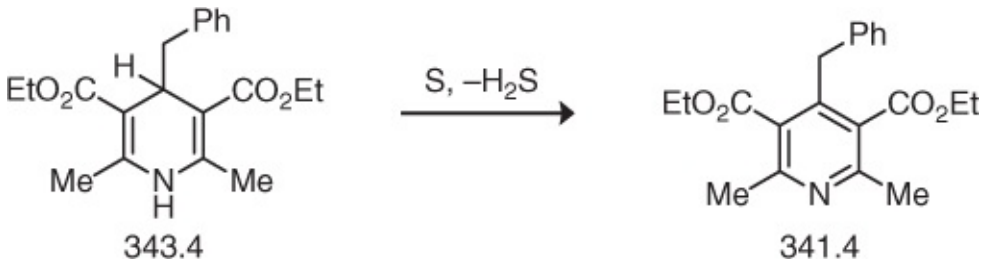
IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3320, 1690, 1650.

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.20–7.10 (m, 3H, Ph–H), 7.02 (m_c, 2H, Ph–H), 5.37 (s_{br}, 1H, NH), 4.20 (t, *J* = 5.6 Hz, 1H, allyl–H), 4.07, 4.03 (2 × q, *J* = 7.2 Hz, 4H, OCH_2), 2.58 (d, *J* = 5.6 Hz, 2H, CH_2Ph), 2.17 (s, 6H, 2 × CH_3), 1.23 (t, *J* = 7.2 Hz, 6H, 2 × CH_2CH_3).

^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) = 167.8 (2 × C=O), 145.4 (C-2, C-6), 139.3, 130.1, 127.3, 125.6 (6 × Ph–C), 101.9 (C-3, C-5), 59.57 (2 × CH_2CH_3), 42.31, 35.51 (C-4, CH_2Ph), 19.21 (2 × CH_3), 14.35 (2 × CH_2CH_3).

Note: Ethyl acetoacetate has to be distilled before use (bp_{18} 75–76 °C); phenylacetaldehyde may be purified as the bisulfite addition product [10].

3.3.1.2	*	**4-Benzyl-3,5-bis(ethoxycarbonyl)-2,6-dimethylpyridine** [7]



The dihydropyridine **3.3.1.1** (4.00 g, 11.6 mmol) and sulfur (0.38 g, 11.8 mmol) are heated to 200 °C for 1 h until the molten mixture becomes clear and free from gas bubbles, with the sulfur being completely consumed.

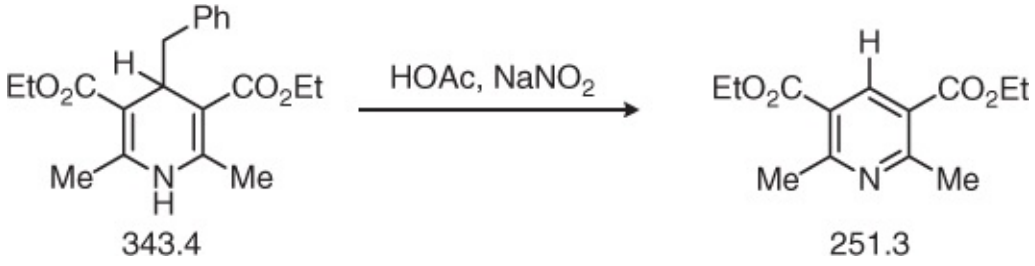
After cooling, the thick mixture is extracted with aqueous HCl (4 N, 30 ml) and the extract is filtered and neutralized with solid Na_2CO_3. The liberated oil is extracted with Et_2O (3 × 50 ml), the combined extracts are dried over $MgSO_4$ and filtered, and the solvent is removed *in vacuo*. The resulting yellowish oil (3.60 g, 91%) is sufficiently pure for the next transformations according to NMR. Distillation yields a colorless oil, bp_1 170 °C, which solidifies on prolonged standing; 3.16 g (80%), mp 45–46 °C.

IR (oil): $\tilde{\nu}$ (cm^{-1}) = 3062, 3029, 2980, 1720, 1570, 1446, 1233, 1194, 1106, 1080.

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.25–7.13 (m, 3H, Ph–H), 7.08 (m_c, 2H, Ph–H), 4.18 (q, *J* = 7.1 Hz, 4H, 2 × C*H*$_2$CH$_3$), 4.05 (s, 2H, CH_2Ph), 2.53 (s, 6H, 2 × CH_3), 1.17 (t, *J* = 7.1 Hz, 6H, 2 × CH_3).

^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) = 168.3 (C=O), 155.3, 144.6, 138.0, 129.1, 128.3, 127.9, 126.5 (12 × Ar–C), 61.52 (2 × *C*H_2CH$_3$), 36.20 (*C*H_2Ph), 23.02 (2 × CH_3), 13.85 (2 × CH_2*C*H_3).

3.3.1.3	*	**3,5-Bis(ethoxycarbonyl)-2,6-dimethylpyridine** [6]



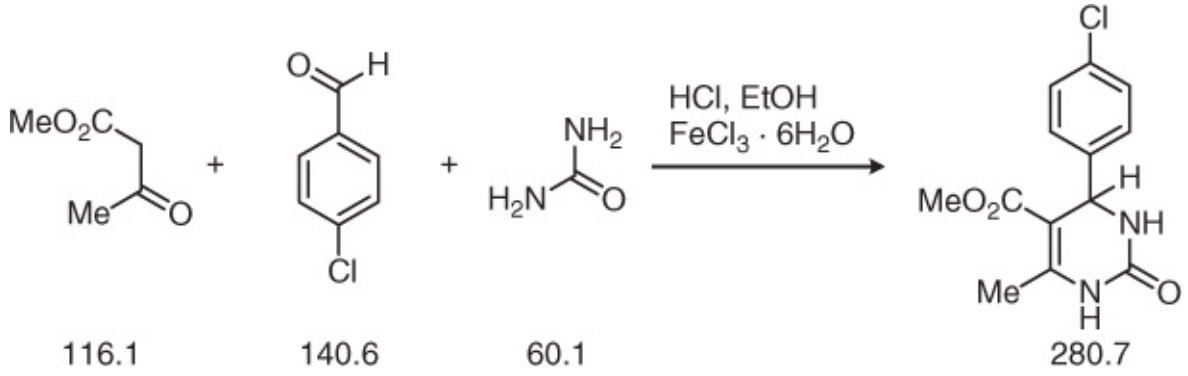
Sodium nitrite (10.0 g, 145 mmol) is added in small portions (hood!) to a well-stirred solution of the pyridine derivative **3.3.1.1** (10.0 g, 29.2 mmol) in glacial acetic acid (10 ml), keeping the temperature below 50 °C. Stirring is continued for approximately 30 min at room temperature until no more nitrous gases evolve.

The solution is poured into iced water (400 ml) and extracted with Et_2O (3 × 300 ml). The combined ethereal phases are extracted with aqueous HCl (2 N, 2 × 200 ml), and the aqueous extracts are separated and neutralized by the addition of solid $NaHCO_3$. The product precipitates and is collected by filtration, dried, and recrystallized from cyclohexane to give pale-yellow leaflets; 7.00 g (95%), mp 69–71 °C.

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 2980, 1725, 1592, 1557, 1445, 1368, 1292, 1255, 1223, 1107, 1044, 771.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.63 (s, 1H, 4-H), 4.38 (q, *J* = 7 Hz, 4H, 2 × C*H*$_2$CH$_3$), 2.82 (s, 6H, 2 × CH_3), 1.40 (t, *J* = 7 Hz, 6H, 2 × CH_3).

3.3.1.4	*	**4-(*p*-Chlorophenyl)-3,4-dihydro-5-methoxycarbonyl-6-methylpyrimidin-2(1*H*)-one** [5]



A solution of methyl acetoacetate (2.32 g, 20.0 mmol), 4-chlorobenzaldehyde (2.81 g, 20.0 mmol), urea (1.80 g, 30.0 mmol), and $FeCl_3 \cdot 6H_2O$ (1.35 g, 5.00 mmol) in EtOH (40 ml) containing four drops of concentrated HCl is heated under reflux for 5 h.

After cooling, the reaction mixture is poured onto crushed ice (200 g) and the resulting mixture is stirred for 15 min. The precipitate formed is collected by filtration and washed first with cold H_2O (2 × 50 ml) and then with a mixture of

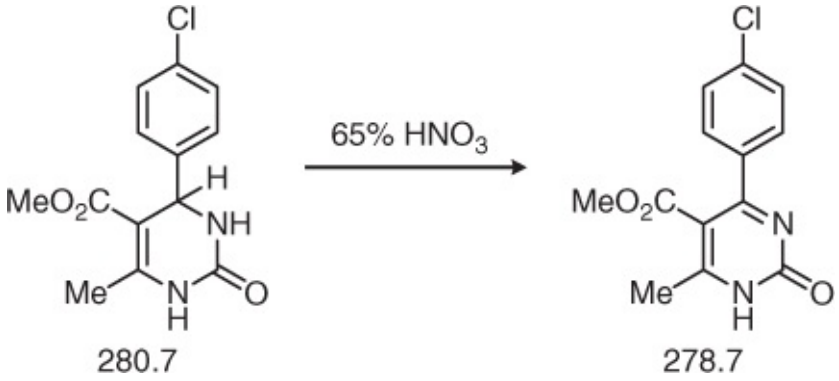
EtOH/H_2O (1 : 1, 3 × 40 ml). The crude product is dried and recrystallized from EtOH; colorless crystals, 4.85 g (83%), mp 200–201 °C.

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3364, 3218, 3093, 2947, 1712, 1687, 1633, 1488.

^{1}H NMR (500 MHz, [D_6]DMSO): δ (ppm) = 9.26 (s, 1H, NH), 7.78 (s, 1H, NH), 7.39 (d, *J* = 8.4 Hz, 2H, Ar), 7.25 (d, *J* = 8.4 Hz, 2H, Ar), 5.14 (d, *J* = 3.5 Hz, 1H, 4-H), 3.53 (s, 3H, OCH_3), 2.25 (s, 3H, CH_3).

^{13}C NMR (126 MHz, [D_6]DMSO): δ (ppm) = 165.7 (*C*O_2Me), 151.9 (N*C*(O)N), 149.0 (C-6), 143.6, 131.8, 128.4, 128.1 (6 × Ar–C), 98.6 (C-5), 53.2, 50.8 (C-4, OCH_3), 17.8 (CH_3).

3.3.1.5	*	**4-(*p*-Chlorophenyl)-5-methoxycarbonyl-6-methylpyrimidin-2(1*H*)-one** [9]



280.7 278.7

Nitric acid (65%, 20 ml) is cooled to 0 °C and the dihydropyrimidinone **3.3.1.4** (2.81 g, 10.0 mmol) is added in portions over 5 min. The mixture is stirred for an additional 2 min at 0 °C resulting in a yellow solution, which is allowed to warm to room temperature over 15 min.

The solution is immediately poured onto crushed ice (50 g) and brought to pH 8 with solid K_2CO_3 (Caution: CO_2 evolution!). The resulting mixture is extracted with $CHCl_3$ (4 × 100 ml) and the combined organic layers are washed with H_2O (100 ml), dried over $MgSO_4$, and filtered, and the solvent is removed *in vacuo*. The crude product is recrystallized from EtOH; 2.45 g (88%), yellow-green solid, mp 173–174 °C.

^{1}H NMR (500 MHz, [D_6]DMSO): δ (ppm) = 8.31 (s, 1H, NH), 7.54 (d, *J* =

8.4 Hz, 2 × Ar), 7.47 (d, *J* = 8.4 Hz, 2H, Ar), 3.52 (s, 3H, OCH_3), 2.40 (s, 3H, CH_3).

^{13}C NMR (126 MHz, [D_6]DMSO): δ (ppm) = 169.4, 166.3, 162.2, 155.6 (*C*O_2Me, C-2, C-4, C-6), 136.7, 135.0, 129.4, 128.4 (6 × Ar–C), 108.5 (C-5), 51.99 (OCH_3), 18.58 (CH_3).

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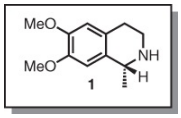
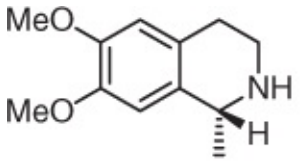
3.3.2 (*R*)-Salsolidine

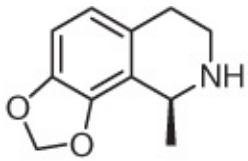
	***Topics:***	• Synthesis of an isoquinoline alkaloid • Bischler–Napieralski synthesis of a 3,4-dihydroisoquinoline • Noyori hydrogenation of an imine (here: 3,4-dihydroisoquinoline → 1,2,3,4-tetrahydroisoquinoline) by use of a chiral Ru catalyst

(a) General

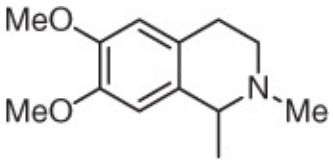
Salsolidine (**1**) belongs to the group of anhalonium alkaloids and is found in *Salsola richteri* (Chenopodiaceae). In general, anhalonium alkaloids are constituents of the Mexican peyotl cactus; further representatives of these highly toxic isoquinoline-based alkaloids are anhalonine (**2**) and carnegine (**3**) [1, 2]:



1: (+)-(*R*)-salsolidine

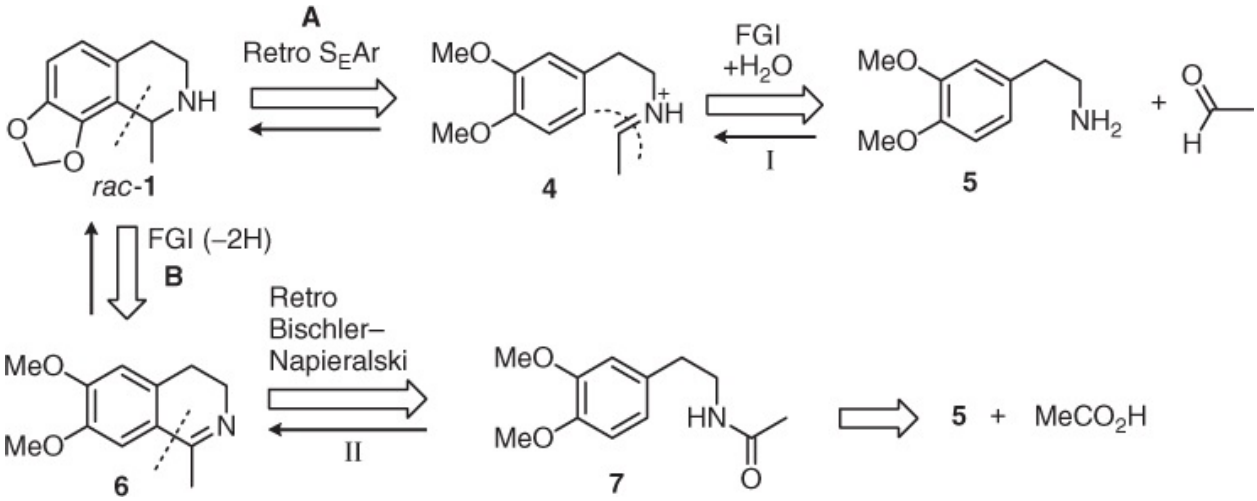


2: (–)-(*S*)-anhalonine

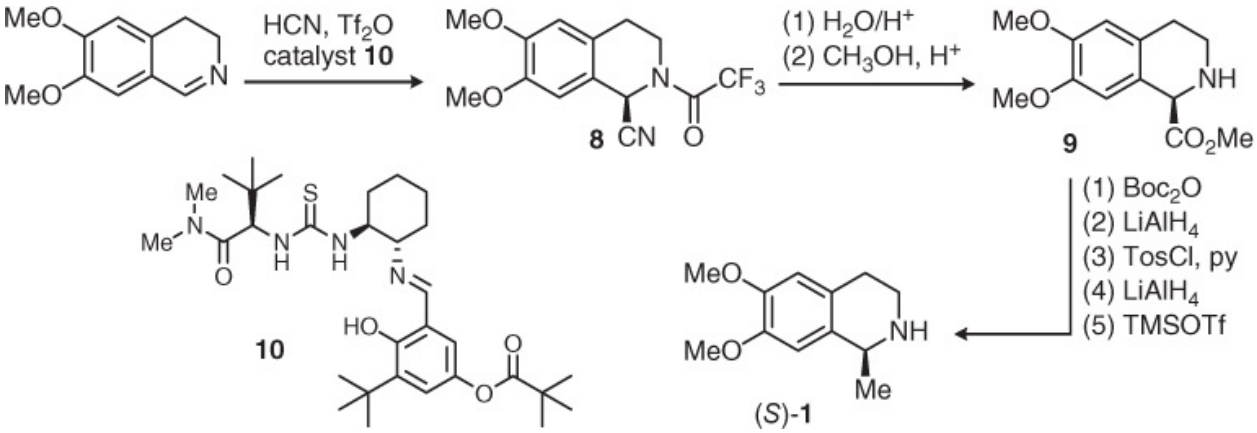


3: (±)-carnegine

Retrosynthesis of *rac*-**1** can be conducted in two directions (A/B). According to A, reversal of a Pictet–Spengler synthesis [3, 4] (the most common method for 1,2,3,4-tetrahydro-β-carboline formation) leads to the iminium ion **4** and thereafter to the β-arylethylamine **5** and acetaldehyde as substrates (I) [5]. According to B, FGI (functional group interconversion) (dehydrogenation at the N–C-1 bond) leads to the 3,4-dihydroisoquinoline **6**, which may be obtained by cyclization of the amide **7**, the *N*-acetyl derivative of **5**, by means of a Bischler–Napieralski reaction (II) [6]. Moreover, approach II offers the possibility of synthesizing (*R*)-**1** by asymmetric catalytic hydrogenation of the imine moiety in **6** using the Noyori method [7]. For the synthesis of isoquinolines, the Bischler–Napiralski reaction is superior to the Pictet–Spengler reaction.



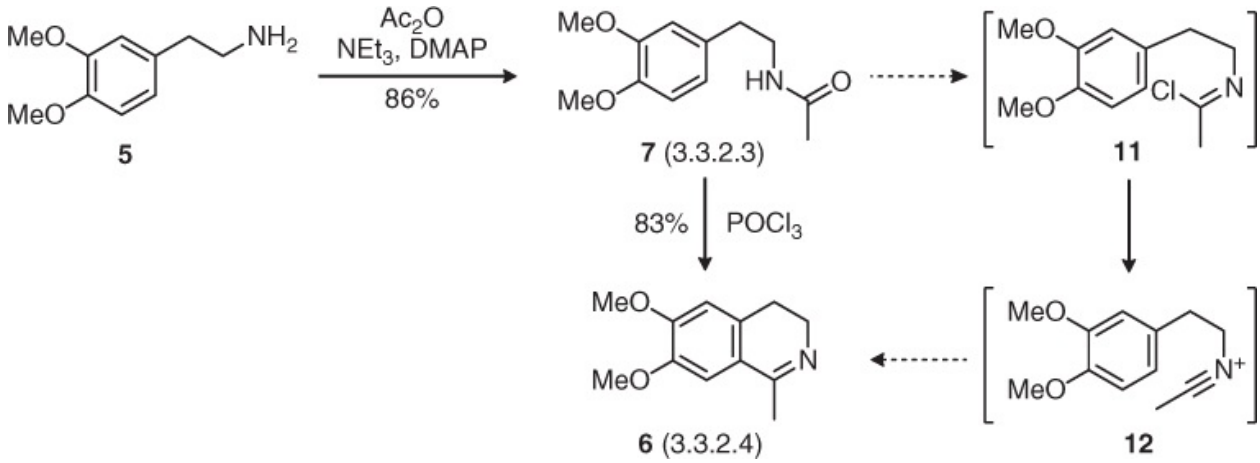
Another enantioselective approach for the synthesis of (*S*)-salsolidine ((*S*)-**1**) has recently been reported [8]. The substrate is 6,7-dimethoxy-3,4-dihydroisoquinoline, which is subjected to an enantioselective Strecker reaction [9] by hydrocyanation in the presence of the Jacobsen catalyst **10** and trifluoroacetic anhydride:



The crucial intermediate **8** is obtained in high chemical yield and enantiomeric excess (86% yield, 95% ee) and can be transformed into (*S*)-**1** via ester **9** and reduction ($CO_2Me \rightarrow CH_3$).

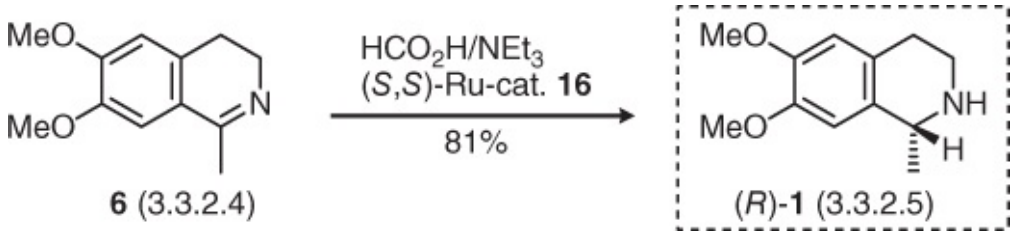
(b) Synthesis of 1

2-(3,4-Dimethoxyphenyl)ethylamine (**5**) is N-acylated with acetic anhydride in the presence of triethylamine and a catalytic amount of DMAP to give the amide **7**, which is transformed to the dihydroisoquinoline **6** by cyclization with $POCl_3$ (Bischler–Napieralski reaction) [10, 11]. Instead of $POCl_3$, polyphosphoric acid, H_2SO_4, CF_3CO_2H, or CF_3SO_3H may also be used.

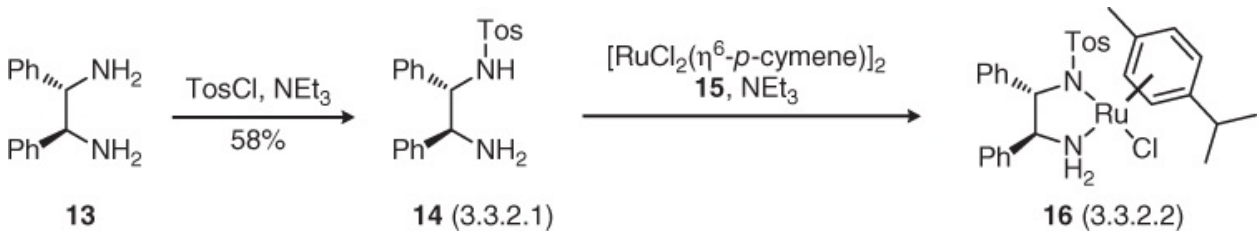


Presumably, in the $POCl_3$-mediated Bischler–Napieralski reaction, chloroimines (such as **11**) and the corresponding nitrilium ions (such as **12**) are intermediates, which cyclize to the 3,4-dihydro-isoquinoline system in an intramolecular S_EAr process. Chloroimine **11** resembles the Vilsmeier reagent [12].

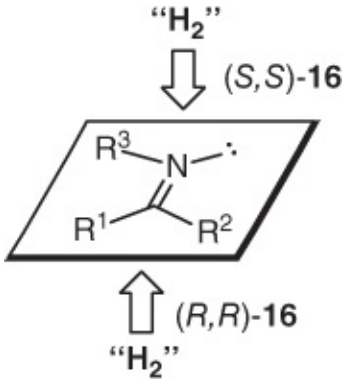
For the synthesis of (*R*)-salsolidine (**1**), the 1-methyl-3,4-dihydroisoquinoline **6** is subjected to transfer hydrogenation with formic acid/NEt_3 in the presence of the chiral Ru catalyst **16** [7], which leads to the chiral 1-methyl-1,2,3,4-tetrahydroisoquinoline **1** possessing (*R*)-configuration at the stereogenic center C-1 with 95% ee and a chemical yield of 81%.



The required chiral ruthenium complex **16** can be obtained in two steps: (1*S*,2*S*)-1,2-diphenylethylenediamine (**13**) is monotosylated with *p*-toluenesulfonyl chloride in the presence of NEt_3 to give the sulfonamide **14**. The chiral Ru complex (**16**) is prepared *in situ* by addition of the chiral sulfonamide **14** to the achiral ruthenium complex $[RuCl_2(\eta^6\text{-}p\text{-cymene})]_2$ (**15**) [7].

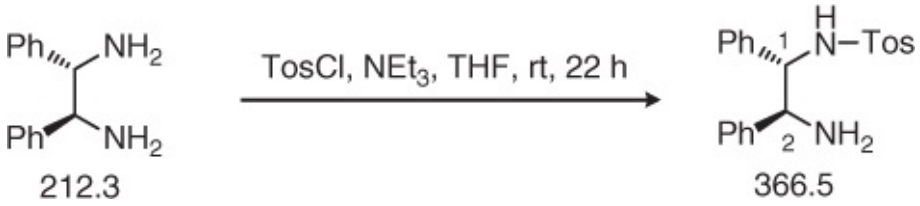


The direction of asymmetric transfer hydrogenation catalyzed by the chiral ruthenium complex is illustrated schematically in the following figure:



(c) Experimental Procedures for the Synthesis of 1

3.3.2.1	*	**(1*S*,2*S*)-*N*-Tosyl-1,2-diphenylethylenediamine** [13]



A solution of *p*-toluenesulfonyl chloride (450 mg, 2.40 mmol) in anhydrous THF (5 ml) is added to a solution of (1*S*,2*S*)-(−)-1,2-diphenylethylenediamine (500 mg, 2.40 mmol) in anhydrous THF (20 ml) and NEt_3 (1 ml) over a period of 0.5 h at 0 °C, and the mixture is stirred for 12 h at room temperature.

The solvent is removed under reduced pressure and the residue is treated with saturated aqueous $NaHCO_3$ solution (40 ml) and CH_2Cl_2 (40 ml). The organic phase is separated, washed with brine (40 ml), dried over Na_2SO_4, and then concentrated under reduced pressure. The crude product is purified by chromatography, eluting with EtOAc/*n*-pentane (1 : 1) to give the monosulfonamide as a white solid; 790 mg (90%), $[\alpha]^{20}_D$ = +25.0 (*c* = 0.2, $CHCl_3$); R_f = 0.40 (EtOAc:*n*-pentane 1 : 1).

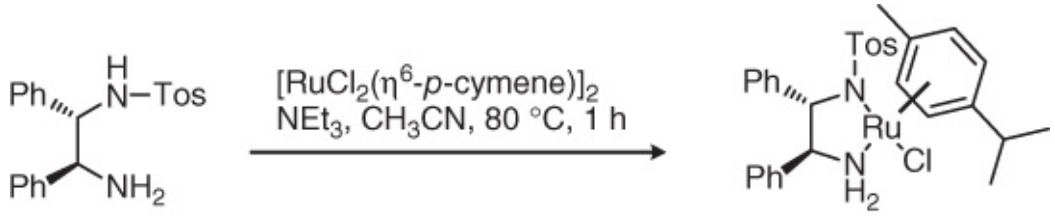
^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 7.55–7.00 (m, 10H, Ph–H), 7.25 (d, *J* = 8.0 Hz, 2H, Ar), 6.88 (d, *J* = 8.0 Hz, 2H, Ar), 4.30 (d, *J* = 5.5 Hz, 1H, C*H*–$NHSO_2$), 4.05 (d, *J* = 5.5 Hz, 1H, C*H*–NH_2), 2.25 (s, 3H, CH_3).

^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) = 142.4, 141.4, 139.3, 137.1, 129.1,

128.3, 128.2, 127.3, 127.2, 126.9, 126.8, 126.5 (18 × Ar–C), 63.3, 60.4 (CH_2), 21.4 (CH_3).

MS (DCI): *m*/*z* (%) = 367 $[M+H]^+$, 384 $[M+NH_4]^+$.

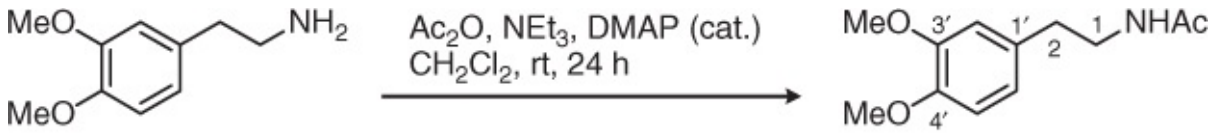
3.3.2.2	***	**(*S*,*S*)-Ruthenium Catalyst** [13]



366.5 636.2

Under an argon atmosphere, a mixture of $[RuCl_2(\eta^6\text{-}p\text{-cymene})]_2$ (202 mg, 330 µmol), the monosulfonamide **3.3.2.1** (290 mg, 792 µmol), and NEt_3 (0.18 ml) in CH_3CN (3.3 ml) is heated at 80 °C for 1 h. The warm orange solution is then used immediately for the transfer hydrogenation of the dihydroisoquinoline **3.3.2.4**.

3.3.2.3	*	***N*-Acetyl-2-(3,4-dimethoxyphenyl)ethylamine** [10]



181.2 223.3

NEt_3 (12.5 ml) is added to a stirred solution of 2-(3,4-dimethoxyphenyl)ethylamine (4.50 g, 24.8 mmol) and 4-DMAP (303 mg, 2.48 mmol) in anhydrous CH_2Cl_2 (25 ml) at 0 °C. Acetic anhydride (2.50 ml, 26.4 mmol) is then added dropwise, and stirring is continued for 24 h at room temperature.

The mixture is then washed with H_2O (200 ml), aqueous HCl (2 M, 100 ml), saturated aqueous $NaHCO_3$ solution (2 × 200 ml), and brine (200 ml), dried over $MgSO_4$ and filtered, and the solvent is removed *in vacuo*. The crude product thus obtained is crystallized from EtOAc/*n*-pentane to give the *N*-acetylamine as colorless needles. A further batch of the product can be obtained by evaporation of the solvent and a second crystallization from EtOAc/*n*-pentane; 4.74 g (86%),

mp 94–95 °C, R_f = 0.71 (CH_2Cl_2/MeOH, 7 : 1).

UV (CH_3CN): λ_{max} (nm) (log ε) = 280.0 (0.164), 230.0 (0.468), 201.5 (2.611).

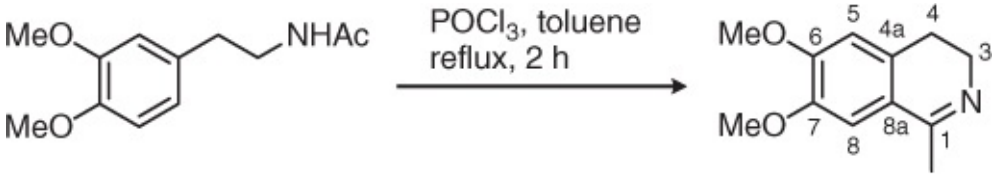
IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3254, 1634, 1518, 1263, 1156, 1139, 1020, 815, 767, 611.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 6.82–6.71 (m, 3H, 3 × Ar–H), 5.93 (s_{br}, 1H, NH), 3.86, 3.85 (2 × s, 2 × 3H, 2 × OCH_3), 3.48 (dt, *J* = 7.0, 6.0 Hz, 2H, 2-H_2), 2.76 (t, *J* = 7.0 Hz, 2H, 1-H_2), 1.90 (s, 3H, CH_3).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ (ppm) = 170.0 (C=O), 148.8 (C-3′), 147.4 (C-4′), 131.2 (C-1′), 120.4, 111.7, 111.2 (C-2′, C-5′, C-6′), 55.71, 55.65 (2 × OCH_3), 40.64 (C-2), 35.01 (C-1), 23.08 (CH_3).

MS (DCI, NH_3, 200 eV): *m*/*z* (%) = 241 (100) $[M+18]^+$, 447 (11) $[2M+1]^+$, 464 (11) $[2M+18]^+$.

3.3.2.4 ** 6,7-Dimethoxy-1-methyl-3,4-dihydroisoquinoline [11]



223.3 205.3

Phosphorus oxychloride (6.0 ml) is added dropwise to a stirred solution of the *N*-acetylamine **3.3.2.3** (6.00 g, 26.9 mmol) in anhydrous toluene (30 ml) over 15 min. The resulting solution is stirred under reflux for 2 h and then stored at 4 °C for 12 h to give a yellow precipitate.

The precipitate is collected by filtration and washed with cold MeOH and EtOAc. Recrystallization from MeOH/EtOAc gives the dihydroxyisoquinoline as a white powder. Another batch of the product can be obtained by evaporation of the solvent and crystallization from EtOAc/*n*-pentane; 4.55 g (83%), mp 202–203 °C, R_f = 0.69 (CH_2Cl_2/MeOH, 7 : 1).

UV (CH_3CN): λ_{max} (nm) (log ε) = 352.0 (0.309), 301.5 (0.398), 243.5

(0.671), 231.0 (0.551).

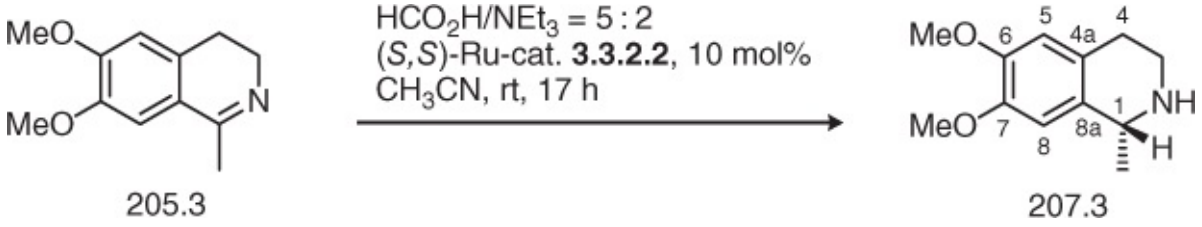
IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 2611, 1656, 1565, 1335, 1278, 1167, 1069.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 6.98 (s, 1H, 8-H), 6.68 (s, 1H, 5-H), 3.92, 3.88 (2 × s, 2 × 3H, 2 × OCH_3), 3.63 (td, *J* = 7.0, 1.5 Hz, 2H, 3-H_2), 2.64 (t, *J* = 7.0 Hz, 2H, 4-H_2), 2.36 (s, 3H, 1-CH_3).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ (ppm) = 173.5 (C-1), 156.1 (C-6), 148.5 (C-7), 132.7 (C-10), 117.7 (C-), 111.0 (C-5), 110.6 (C-8), 56.38, 56.24 (2 × OCH_3), 40.43 (C-3), 24.89 (C-4), 19.38 (CH_3).

MS (EI, 70 eV): *m/z* (%) = 205 (100) $[M]^+$, 190 (48) $[M-CH_3]^+$, 174 (9) $[M-OCH_3]^+$.

3.3.2.5	***	**(*R*)-6,7-Dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline ((*R*)-salsolidine)** [7a]



A mixture of formic acid and NEt_3 (5 : 2, 3.3 ml) is added to a stirred solution of the dihydroisoquinoline **3.3.2.4** (1.35 g, 6.60 mmol) and the preformed (*S*,*S*)-ruthenium catalyst **3.3.2.2** (430 mg, 0.66 mmol, 10.0 mol%) in CH_3CN (13 ml). Stirring is continued for 17 h at room temperature.

The mixture is then basified to pH 8–9 by the addition of saturated aqueous Na_2CO_3 solution and extracted with EtOAc (3 × 20 ml). The combined organic layers are washed with brine (1 × 20 ml), dried over $MgSO_4$, and filtered, and the solvent is removed *in vacuo*. The residue is purified by flash chromatography on silica gel (EtOAc/MeOH/NEt_3, 92 : 5 : 3) to give (*R*)-salsolidine as a brown oil; 1.11 g (81%), $[\alpha]^{20}_D$ = +51.1 (*c* = 2.70, EtOH), R_f = 0.38 (CH_2Cl_2/MeOH, 7 : 1). The measured optical rotation corresponds to 95% ee.

UV (CH_3CN): λ_{max} (nm) (log ε) = 282.5 (0.186), 201.0 (1.759).

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 2932, 1610, 1512, 1464, 1372, 1256, 1126, 1030, 857, 790.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 6.62, 6.57 (2 × s, 2H, 5-H, 8-H), 4.04 (q, *J* = 6.7 Hz, 1H, 1-H), 3.86, 3.85 (2 × s, 2 × 3H, 2 × OCH_3), 3.25 (dt, *J* = 12.0, 4.5 Hz, 1H, 3-H_b), 2.99 (m_c, 1H, 3-H_a), 2.88–2.55 (m, 2H, 4-H_2), 1.66 (s_{br}, 1H, NH), 1.42 (d, *J* = 6.7 Hz, 3H, CH_3).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 147.2 (C-7), 147.1 (C-6), 132.4 (C-8a), 126.7 (C-4a), 111.6 (C-5), 108.9 (C-8), 55.86, 55.73 (2 × OCH_3), 51.13 (C-1), 41.77 (C-3), 29.48 (C-4), 22.78 (CH_3).

MS (EI, 70 eV): *m*/*z* (%) = 192 (100) $[M-CH_3]^+$, 207 (10) $[M]^+$.

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4. The Pictet–Spengler reaction is verified by nature in the biogenesis of 1,2,3,4-tetrahydroisoquinoline alkaloids, cf. Refs. [2, 3], and Gremmen, C., Wanner, M.J., and Koomen, G.-J. (2001), *Tetrahedron Lett.*, **42**, 8885–8888.

5. In fact, *rac*-salsolidine has been obtained by Pictet–Spengler cyclization of the β-arylethylamine **5** with acetaldehyde or acetaldehyde equivalents: Singh, H. and Singh, K. (1989) *Indian J. Chem., Sect. B*, **28**, 802–805, and literature cited therein.

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Tomioka, K. (2000) *Tetrahedron Lett.*, **41**, 5533–5536;for an alternative asymmetric synthesis of (*S*)-salsolidine, see (d) Wu, J., Wang, F., Ma, Y., Cui, X., Cun, L., Zhu, J., Deng, J., and Yu, B. (2006) *Chem. Commun.*, 1766–1768.

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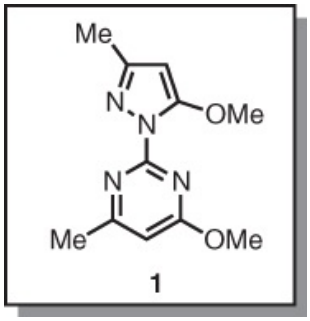
3.3.3 Epirizole



1

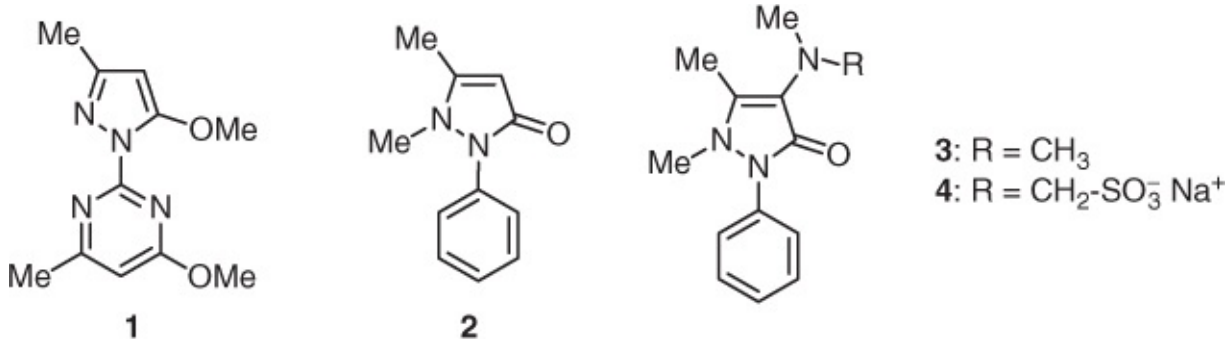
Topics:

- Synthesis of a drug
- Pinner synthesis of pyrimidines
- Knorr synthesis of pyrazolones
- OMethylation at the pyrimidinone and pyrazolone system

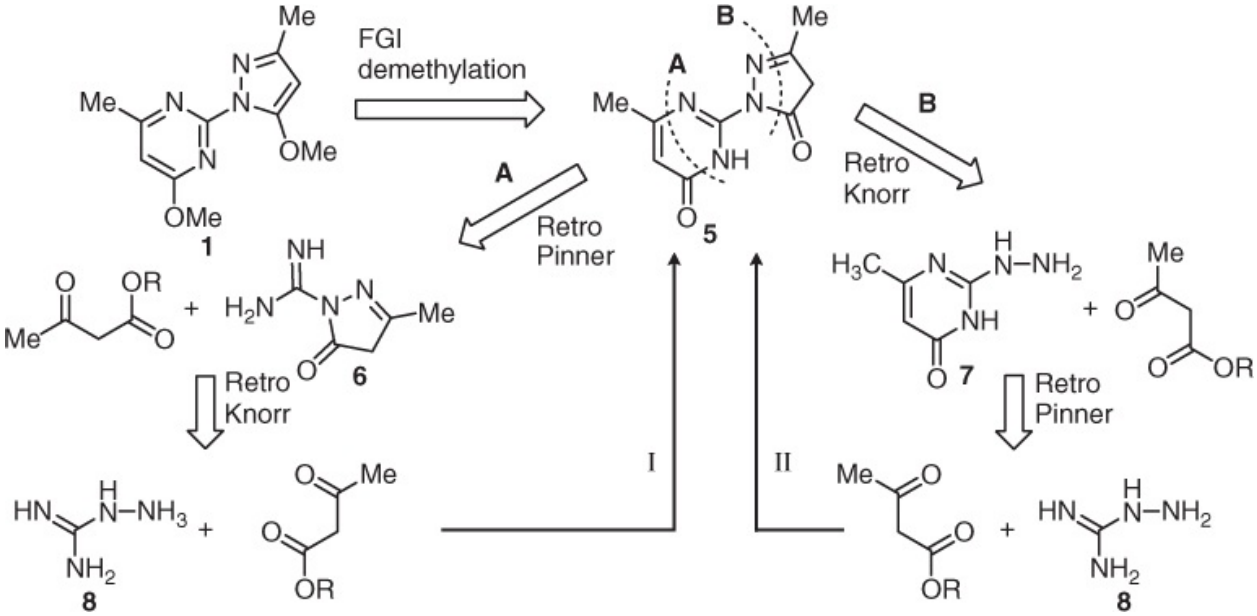
(a) General

Epirizole (**1**), a (2-pyrimidinyl)-substituted methoxypyrazole, belongs to the large family of pyrazolone derivatives, which are medicinally applied as

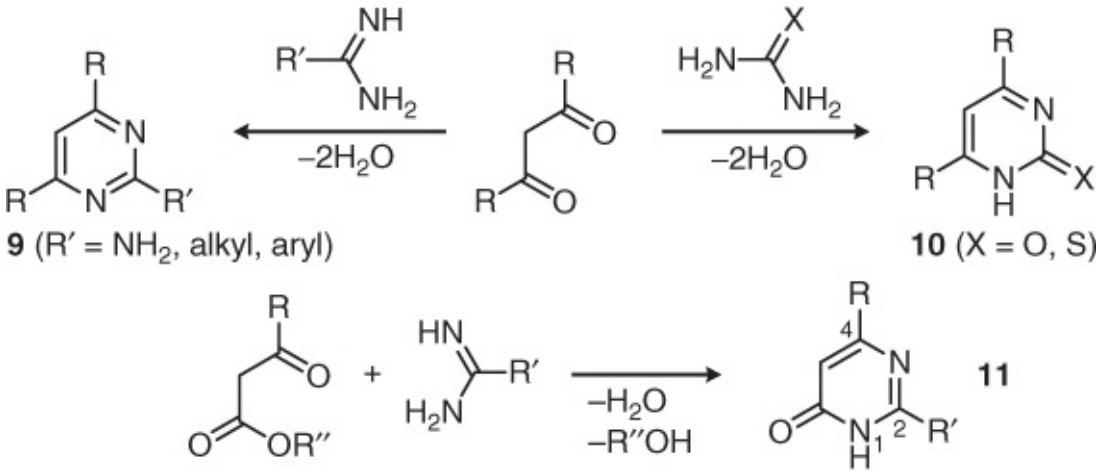
antipyretics and antirheumatics and were widely used in the last century. Epirizole exhibits analgesic and anti-inflammatory properties [1]. Other examples of this family are antipyrine (**2**), pyramidone (**3**), and metamizole (**4**):



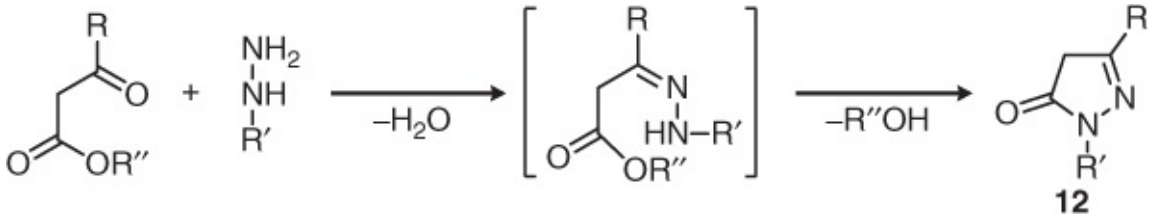
Retrosynthesis of **1** starts with O-demethylation (FGI), transforming **1** to the pyrimidinone-pyrazolone **5**. Further disconnections can be performed (A) at the pyrimidine and (B) at the pyrazolone part of **5**, making use of a retro-Pinner and a retro-Knorr approach. The Pinner and the Knorr methods are valuable and widely used procedures for the synthesis of pyrimidines and pyrazolones, respectively.



In the Pinner synthesis [2], 1,3-diketones are cyclocondensed with N–C–N building blocks such as ureas, thioureas, amidines, and guanidines to give pyrimidine derivatives of types **9** or **10**. β-Keto esters react analogously; thus, with amidines, pyrimidin-4(3*H*)-ones **11** are formed, which display the 2,4,6-substitution pattern at the pyrimidine part of the key intermediate **5** in the epirizole synthesis.

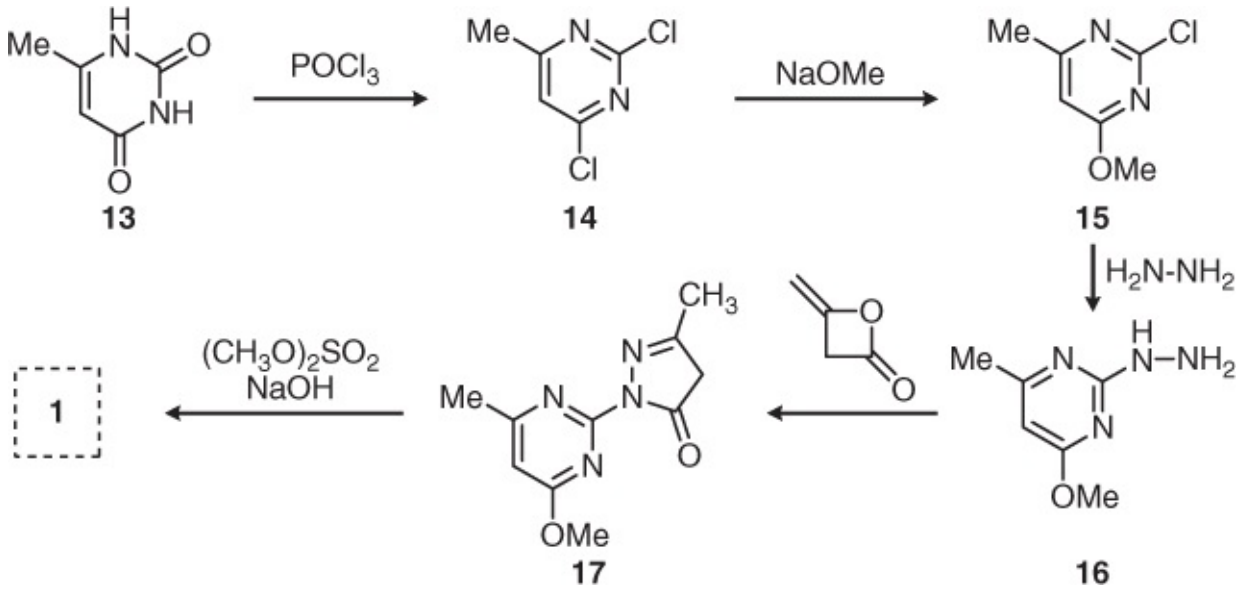


In the Knorr synthesis [3], β-keto esters undergo cyclocondensation with hydrazine or monosubstituted hydrazines to give 2,4-dihydro-3*H*-pyrazol-3-ones **12** (via hydrazones or their enehydrazine tautomers as intermediates). Notably, **12** corresponds structurally to the pyrazolone part of the key compound **5**.



As a consequence, for the synthesis of epirizole, two approaches (I/II) using Pinner and Knorr cyclizations must be considered. In approach I, the pyrazolone part of **1** is constructed first, and the pyrimidine part follows; in approach II, the pyrimidine part is constructed first, followed by the pyrazolone part; in both approaches, Omethylation concludes the synthesis. However, only approach I can be realized because aminoguanidine (**8**) and acetoacetate – identified as starting materials for both approaches I and II according to the retrosynthesis – lead exclusively to pyrazolone formation (**6**) via participation of the hydrazine functionality of **8** and *not* to pyrimidinone formation (**7**) via the amidine function [4].

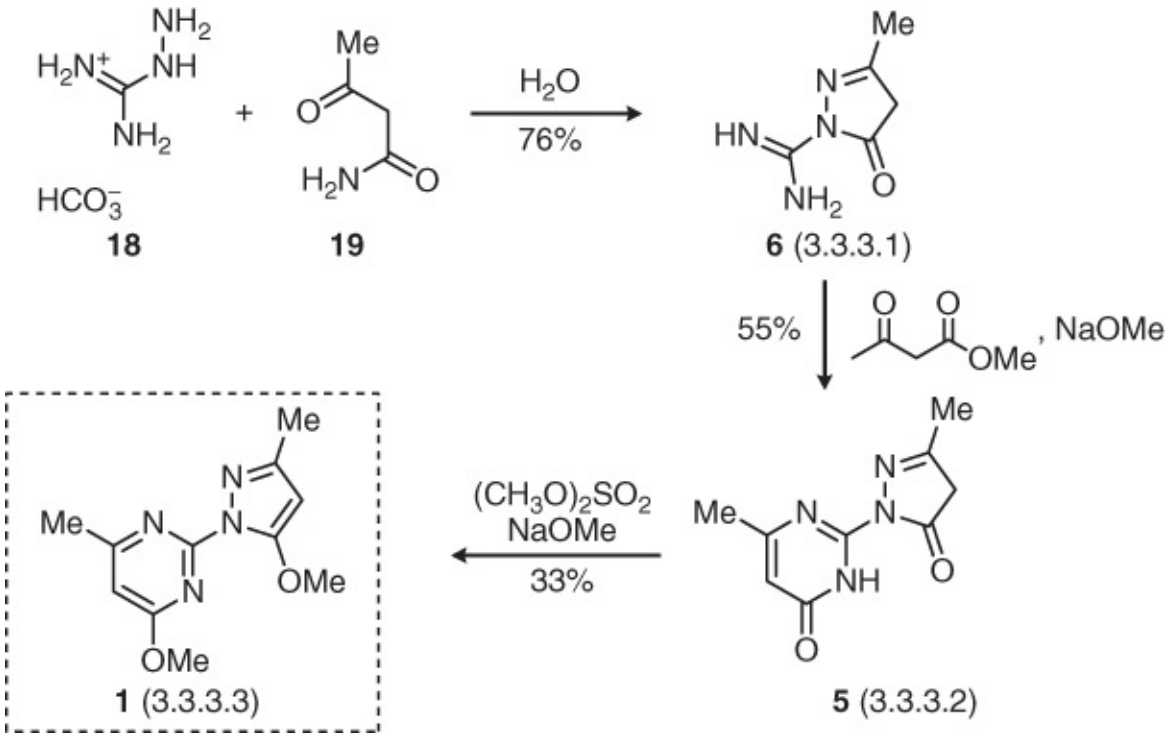
Alternatively, epirizole has been synthesized by a strategy different from I/II [1, 4], starting from a suitable pyrimidine building block:



Thus, 6-methyluracil (**13**), easily accessible by Pinner condensation of acetoacetate with urea, is transformed into the 2,4-dichloropyrimidine **14** by treatment with $POCl_3$. In an S_NAr reaction with methoxide, the 4-Cl substituent of **14**, being more reactive than 2-Cl, is displaced chemoselectively to give **15** [5]. Subsequently, the 2-Cl is substituted by hydrazine to afford **16**, which undergoes a Knorr cyclocondensation with diketene (as an acetoacetate equivalent) providing the pyrazolone part of intermediate **17**. Finally, Omethylation of **17** with dimethyl sulfate yields epirizole (**1**).

(b) Synthesis of 1

The presented laboratory synthesis of epirizole (**1**) [4] is based on the retrosynthesis (A) realizing approach I. In the first step, Knorr cyclocondensation is performed with acetoacetamide (**19**) and aminoguanidine (as hydrogencarbonate **18**) to give the 1-guanidino-substituted pyrazolone **6**:

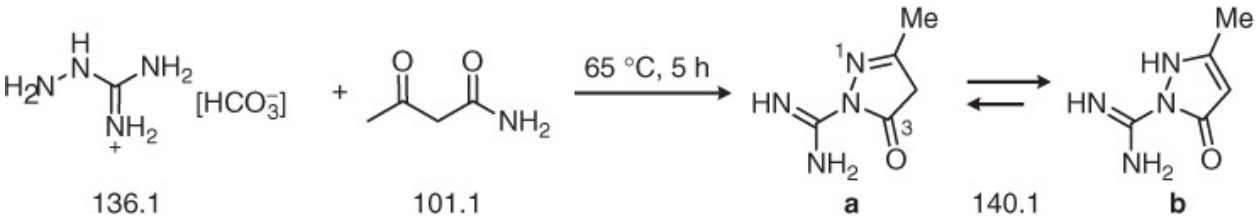


In the second step, methyl acetoacetate is cyclocondensed with the guanidinopyrazolone **6** in the presence of NaOMe, which, by way of a Pinner synthesis, leads to the formation of the pyrimidine part of the key intermediate **5**. In the last step, Omethylation of both the pyrazolone and pyrimidinone subunits of **5** is accomplished by reaction with dimethyl sulfate in alkaline medium, furnishing epirizole (**1**).

Thus, the target molecule **1** is obtained in a three-step sequence from low-cost substrates in an overall yield of 52% based on **19**.

(c) Experimental Procedures for the Synthesis of 1

3.3.3.1	**	**2-Formamidino-5-methyl-2,4-dihydro-3*H*-pyrazol-3-one** [4]



Aminoguanidine bicarbonate (5.00 g, 36.8 mmol) is added to a solution of acetoacetamide (3.08 g, 30.6 mmol) in water (70 ml), and the reaction mixture is heated to 60–70 °C for 5 h.

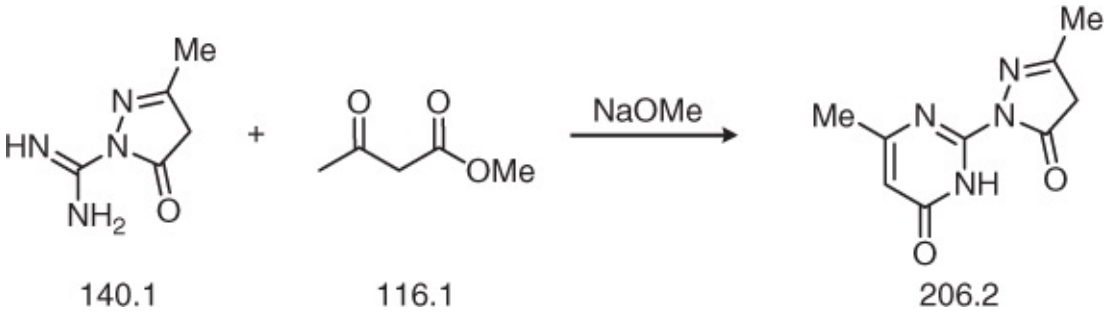
After cooling to room temperature, the precipitate is filtered off, washed with H_2O, and dried. The product is obtained as a colorless solid; 3.26 g (76%), mp 180–181 °C.

^{1}H NMR (300 MHz, [D_6]DMSO): δ (ppm) = 8.31 (s_{br}, 3H, NH, NH_2), 4.41 (s, 1H, 4-H), 1.96 (s, 3H, CH_3) [6].

^{13}C NMR (76 MHz, [D_6]DMSO): δ (ppm) = 167.5 (C-3), 155.9 ($NH_2C(NH)N$), 153.0 (C-5), 82.1 (C-4), 14.9 (CH_3).

MS (EI, 70 eV): *m*/*z* = 140 $[M]^+$.

3.3.3.2	**	**2-(5-Methyl-2,4-dihydro-3*H*-pyrazol-3-on-2-yl)-6-methylpyrimidin-4(3*H*)-one** [4]



A solution of sodium methoxide is prepared from anhydrous methanol (12.5 ml) and sodium (0.44 g, 19.0 mmol). Pyrazolone **3.3.3.1** (2.61 g, 19.2 mmol) and methyl acetoacetate (2.17 g, 18.7 mmol) are then added and the solution is heated under reflux for 4 h.

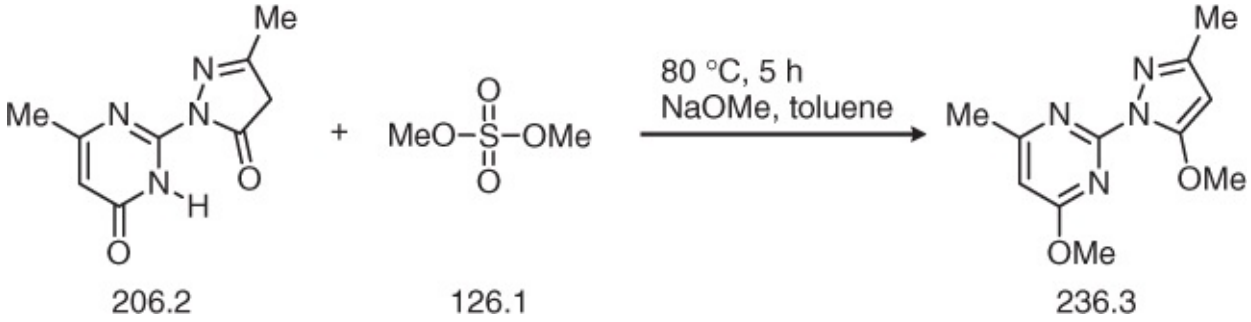
The solvent is then evaporated, the residue is dissolved in H_2O (40 ml), and the pH is adjusted to 3 by adding 10% aqueous HCl. The precipitate formed is filtered off, washed with H_2O, and dried. The product is obtained as a colorless solid; 2.16 g (55%), mp 165–166 °C.

^{1}H NMR (300 MHz, [D_6]DMSO): δ (ppm) = 6.09 (s, 1H, 3′-H), 5.25 (s, 1H, 3-H), 2.22 (s, 3H, CH_3), 2.19 (s, 3H, CH_3) [6].

^{13}C NMR (76 MHz, [D_6]DMSO): δ (ppm) = 107.4 (C-3′), 90.9 (C-3), 12.3 (CH_3), 3.0 (CH_3).

MS (ESI): *m*/*z* = 435 $[2M+Na]^+$, 229 $[M+Na]^+$, 207 $[M+H]^+$, 205 $[M-H]^+$.

3.3.3.3	****	**4-Methoxy-2-(5-methoxy-3-methyl-1*H*-pyrazol-1-yl)-6-methylpyrimidine (epirizole)** [4]



The pyrimidinone **3.3.3.2** (500 mg, 2.43 mmol) is dissolved in anhydrous toluene (25 ml), NaOMe (9.72 mmol, preparation see **3.3.3.2**) is added, and the mixture is heated to 80 °C. Then dimethyl sulfate (1.82 g, 14.4 mmol; Caution: carcinogenic!) is added dropwise over 10 min. The reaction mixture is heated under reflux for 5 h.

The solvent is then evaporated *in vacuo* and the residue is purified by flash chromatography (EtOAc/MeOH, 4 : 1). Epirizole is obtained as a yellowish solid; 192 mg (33%), mp 217–218 °C.

^{1}H NMR (300 MHz, $[D_6]$DMSO): δ (ppm) = 6.85 (1H, 3′-H), 5.41 (1H, 3-H), 3.98 (3H, OCH_3), 3.30 (3H, OCH_3), 2.45 (3H, CH_3), 2.28 (3H, CH_3).

^{13}C NMR (76 MHz, $[D_6]$DMSO): δ (ppm) = 104.1 (C-3′), 94.1 (C-3), 54.5 (OCH_3), 52.7 (OCH_3), 22.4 (CH_3), 12.4 (CH_3).

MS (ESI): *m*/*z* = 491 $[2M+Na^+]$, 235 $[M+H^+]$.

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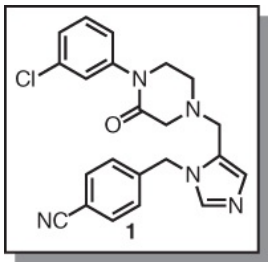
4. Daiichi Seiyaku Co., Ltd., Tokio (1973) German Patent DE2237632.

5. For selectivities in S_NAr displacement reactions of halogenopyrimidines, see Eicher, Th., Hauptmann, S., and Speicher, A. (2012) *The Chemistry of Heterocycles*, 3rd edn, Wiley-VCH Verlag GmbH, Weinheim, p. 464.

6. According to NMR, pyrazolones **3.3.3.1** and **3.3.3.2** predominantly exist in the tautomeric form **b** in DMSO solution. For the issue of pyrazolone tautomerism and the systematic nomenclature of pyrazolones, see Eicher, Th., Hauptmann, S., and Speicher, A. (2012) *The Chemistry of Heterocycles*, 3rd edn, Wiley-VCH Verlag GmbH, Weinheim, p. 247.

3.3.4 Ras Farnesyltransferase Inhibitor



1

Topics:

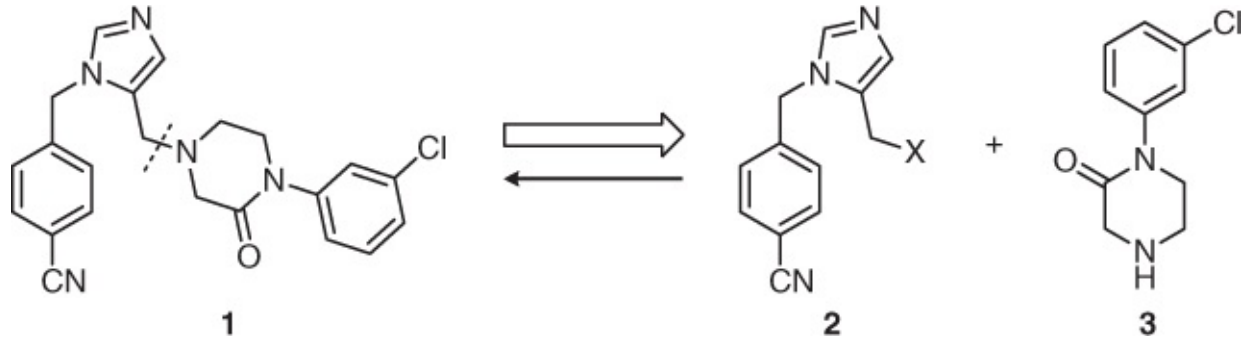
- Synthesis of a clinically investigated drug of the imidazole-piperazinone type
- Marckwald imidazole synthesis
- Formation of a piperazinone
- Delepine reaction
- Oxidative dethionation of a mercapto heterocycle
- Mitsunobu reaction

(a) General

Mutant ras proteins, the products of ras oncogenes, are involved in a significant proportion of human cancers. The enzyme farnesyl-protein transferase (FPTase) catalyzes farnesylation of the ras protein, thereby activating it. Thus, FPTase inhibitors are currently the subject of intense interest as novel and improved anticancer agents [1]. The imidazole/piperazinone-based compound **1** (as its hydrochloride) has been identified as an FPTase inhibitor showing efficacy in

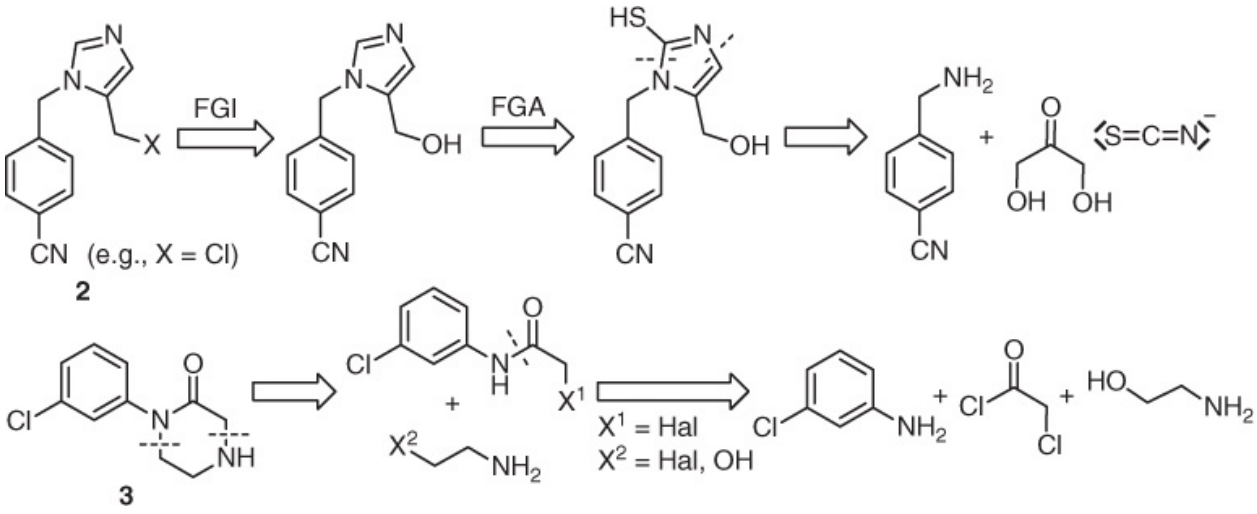
animal models with a high therapeutic index and has been tested in phase I and phase II clinical studies.

A possible retrosynthesis of **1** leads to a disconnection at the non-amide piperazinone nitrogen to give two heterocyclic building blocks, namely the 1-benzyl-5-halogenomethylimidazole **2** and the *N*-arylpiperazinone **3**. The synthetic step would be a simple N-alkylation.



The retrosynthesis of the building block **2** affords *p*-cyanobenzylamine, dihydroxyacetone, and thiocyanate. Thus, for the synthesis of the 1,5-disubstituted imidazole, a modified Marckwald approach [2] would be most suitable.

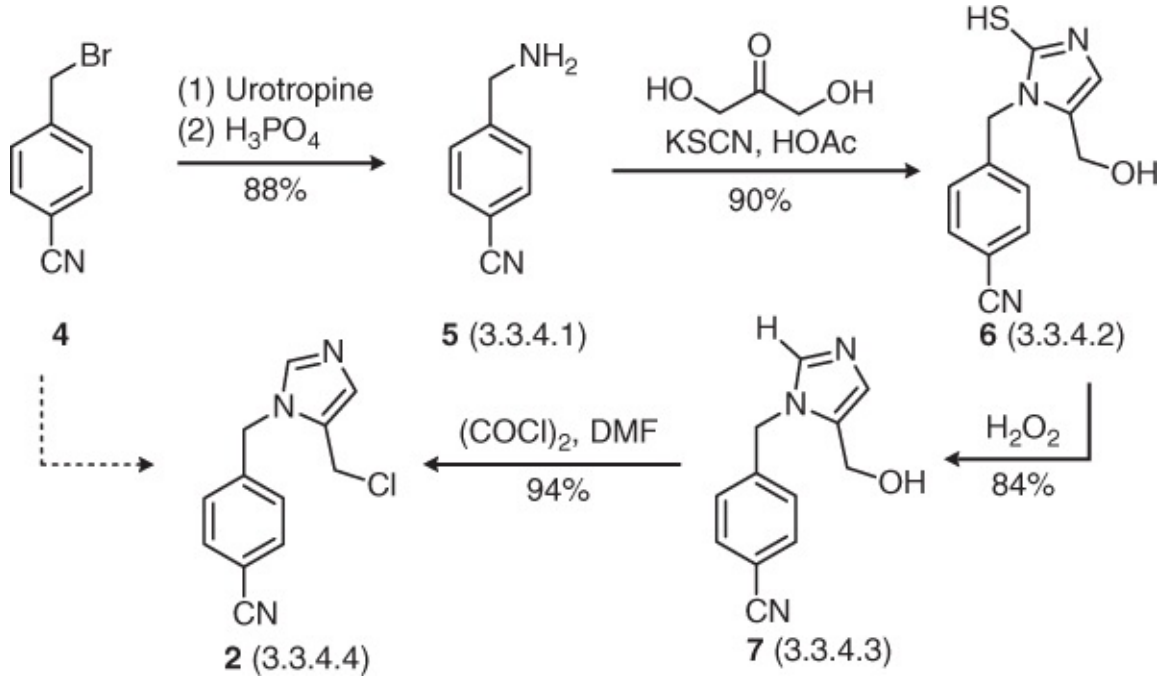
For building block **3**, a series of FGI and disconnections leads to *m*-chloroaniline, chloroacetyl chloride, and ethanolamine as suitable substrates for *N*-aryl piperazinone formation.



As shown in Section (b), the synthesis of **1–3** [1] is accomplished on the basis of these retro-analytical considerations.

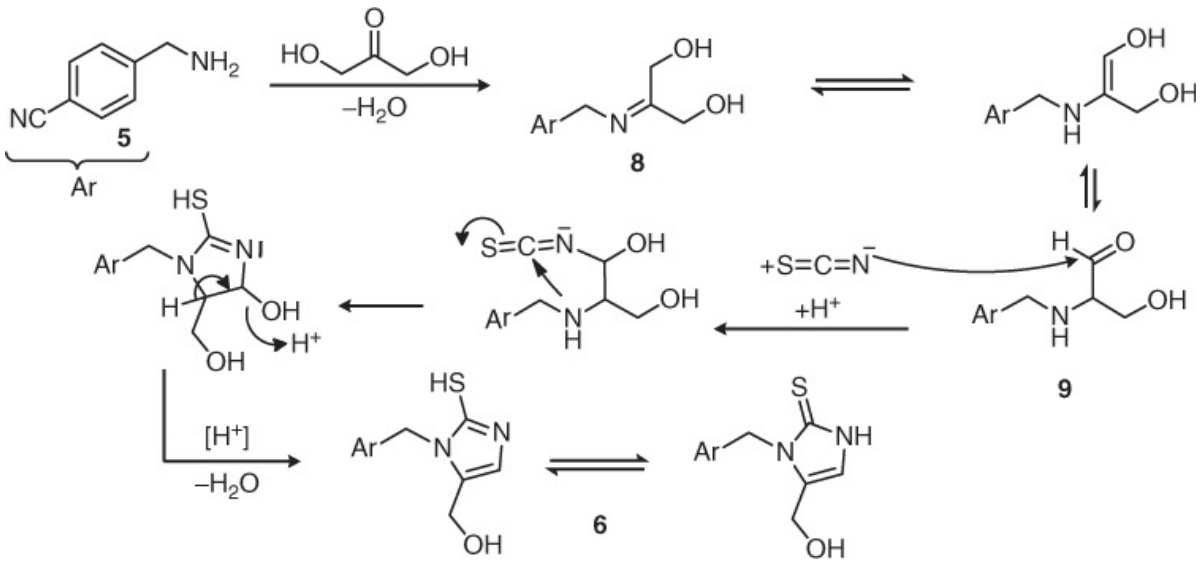
(b) Synthesis of 1

1. Building block **2** is synthesized via the preparation of 4-cyanobenzylamine (**5**) by Delepine reaction [3] of 4-cyanobenzyl bromide (**4**) [4] with hexamethylenetetramine (HMTA) followed by treatment with H_3PO_4:

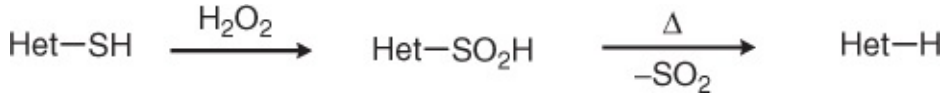


Then, a Marckwald synthesis of the 5-hydroxymethyl-2-mercaptoimidazole **6** is performed by cyclocondensation of the benzylamine **5** (as its H_3PO_4 salt) with 1,3-dihydroxyacetone and potassium thiocyanate in the presence of acetic acid.

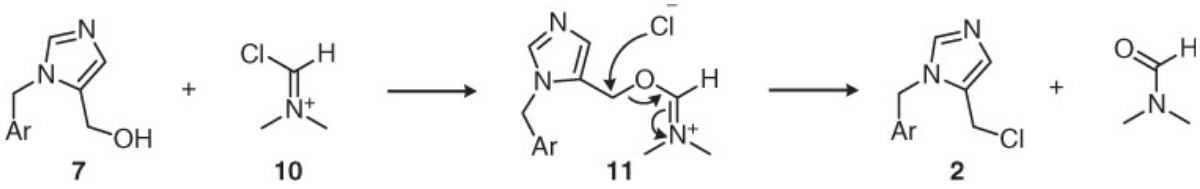
A reasonable mechanistic interpretation of the reaction **5** → **6** (as given in Ref. [1]) starts with the formation of an imine **8** from **5** and 1,3-dihydroxyacetone, which is in tautomeric equilibrium with an α-amino carbonyl compound **9** as the key intermediate of the Marckwald process. This is followed by addition of thiocyanate with concomitant ring closure to give the imidazole **6**. It can be assumed that a heterocumulene acts as an intermediate.



To obtain the desired **2** from **6**, the thiol group in **6** has to be replaced by hydrogen. This is accomplished by oxidation of the thiol to a sulfinic acid moiety, which thermally eliminates SO_2; for this oxidative dethionation (**6**→**7**), hydrogen peroxide in aqueous acetic acid is the reagent of choice:

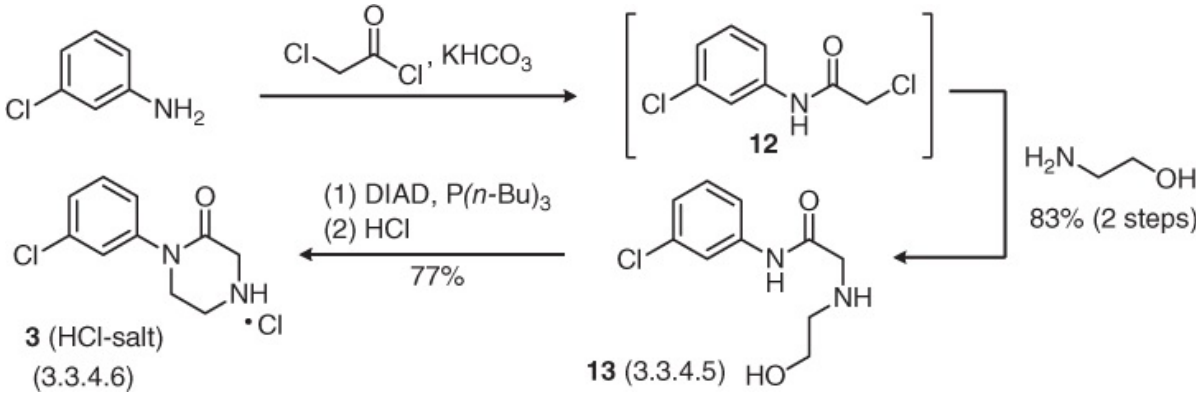


Finally, the hydroxy group in the side chain in **7** is substituted by a chlorine atom using oxalyl chloride in DMF. It has been shown [1] that the chlorinating agent is the Vilsmeier reagent **10** derived from $(COCl)_2$ and DMF, which converts **7** into an iminium ion **11** as intermediate. This is subsequently dealkylated by the attack of chloride at the heterobenzylic position to give **2**:

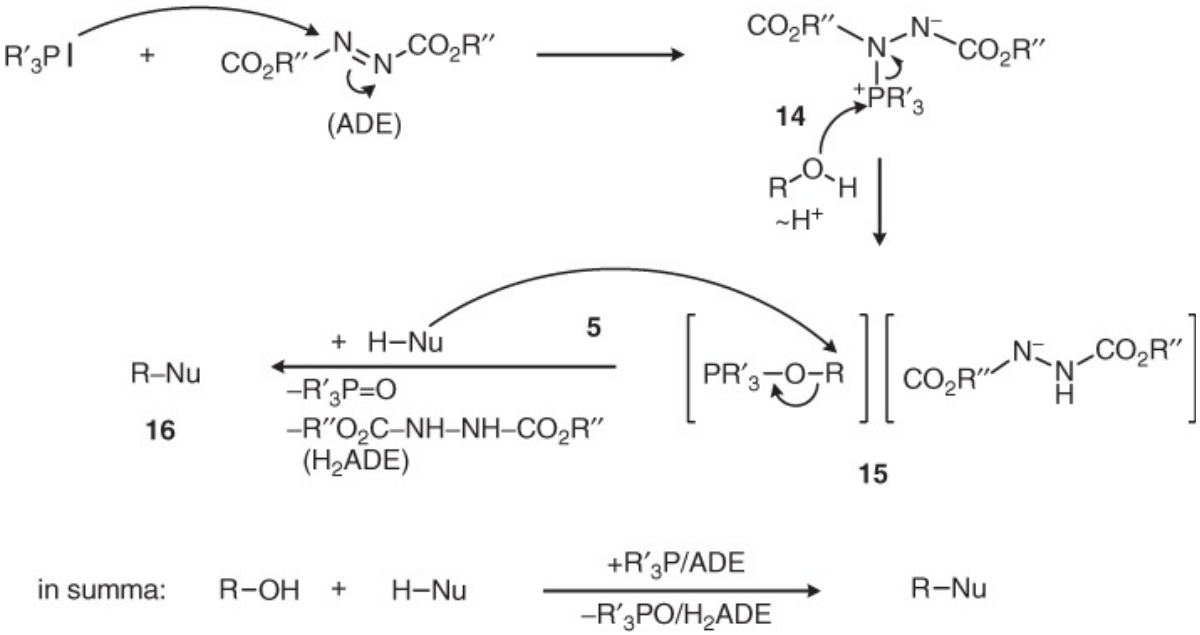


2. Building block **3** is synthesized in a two-step procedure. First, *m*-chloroaniline is acylated under Schotten–Baumann conditions with chloroacetyl chloride in the two-phase system isopropyl acetate/aqueous $KHCO_3$ solution to give a quantitative yield of the chloroacetamide **12**. Without isolation, this is treated with ethanolamine to give the hydroxy amide **13** in an S_N process. Second, **13** is cyclodehydrated under Mitsunobu conditions [5, 6] with diisopropylazodicarboxylate (DIAD) and tri-*n*-

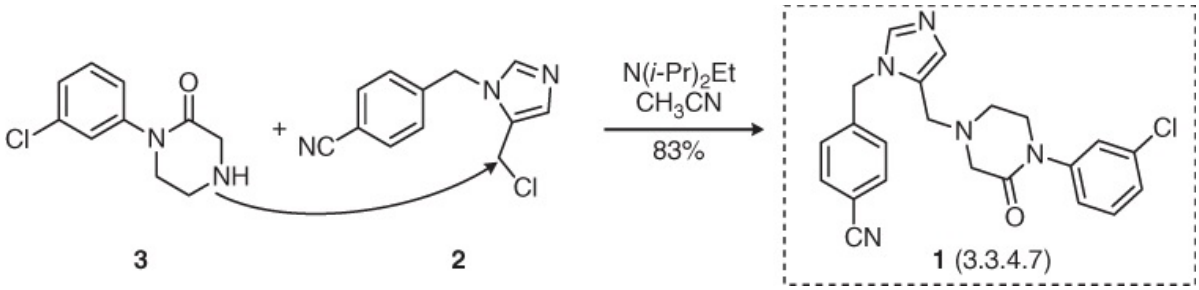
butylphosphine to yield the piperazinone **3** (isolated as its HCl salt):



The generally accepted mechanism of the Mitsunobu reaction is as follows: The tertiary phosphine and azodicarboxylate (ADE) initially form a betaine **14**, which is transformed to an alkoxyphosphonium salt **15** by reaction with an alcohol R–OH. This then reacts with a nucleophile H–Nu in a disproportionation process, in which the substitution product R–Nu (**16**), a phosphine oxide, and hydrazinodicarboxylate are formed. Overall, a nucleophilic substitution at the OH-bearing C atom of the alcohol takes place; if this C atom is a stereogenic center of defined stereochemistry, the Mitsunobu reaction leads to inversion of configuration.



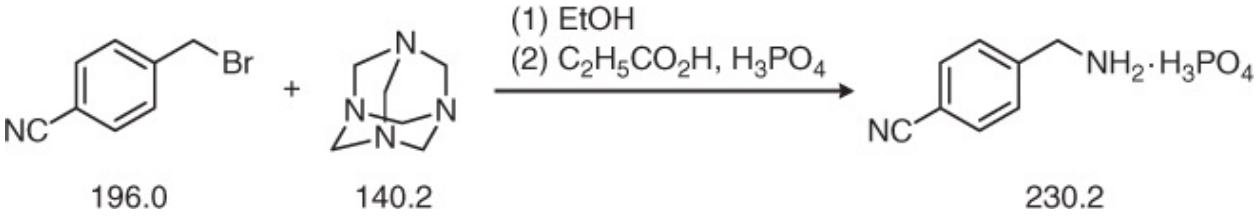
3. Finally, the piperazinone **3** is combined with the chloromethylimidazole **2** by alkylation at the secondary NH group in acetonitrile in the presence of diisopropylethylamine (Hünig base) to give **1** in 83% yield:



Following this route for the synthesis of the target molecule **1**, six reaction steps have to be performed. Building block **2** is obtained in four steps in an overall yield of 63% (based on **4**), and building block **3** is obtained in two steps in an overall yield of 77% (based on *m*-chloroaniline).

(c) Experimental Procedures for the Synthesis of 1

3.3.4.1	**	**4-Cyanobenzylamine** [1]

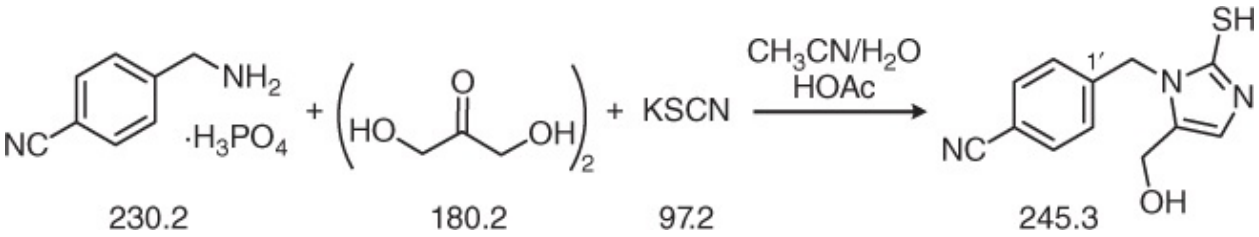


A slurry of urotropine (HMTA) (3.65 g, 26.0 mmol) in EtOH (25 ml) is added to a stirred slurry of 4-cyanobenzyl bromide (5.00 g, 25.5 mmol) in EtOH (25 ml) maintained at 50 °C over 10 min. EtOH (2 × 10 ml) is then added and the reaction mixture is heated to 70 °C for 1.5 h.

The reaction mixture is then cooled to 55 °C and propionic acid (20.6 ml) is added. Concentrated phosphoric acid (6.5 ml) is gradually added, maintaining the temperature below 65 °C. The mixture is then kept at 70 °C for 30 min, allowed to cool to room temperature over 1 h, and then stirred for a further 1 h. The reaction slurry is filtered, and the filter cake is washed with EtOH (4 × 15 ml), H_2O (5 × 8 ml), and CH_3CN (2 × 3 ml), and dried *in vacuo*. The yield is 4.66 g (79%) of a colorless crystalline solid.

IR (FT-IR, solid): $\tilde{\nu}$ (cm^{-1}) = 2642, 2359, 2233, 1653, 1496, 1332, 1233, 1109, 960, 922, 889, 844, 584.

3.3.4.2	*	**4-(5-Hydroxymethyl-2-mercaptoimidazol-1-ylmethyl)benzonitrile** [1]



A slurry of the ammonium salt **3.3.4.1** (4.07 g, 17.7 mmol), potassium thiocyanate (2.58 g, 26.6 mmol), and dihydroxyacetone dimer (1.75 g, 9.7 mmol) in CH_3CN/H_2O (93 : 7, 18 ml) and acetic acid (2.0 ml) is stirred for 18 h at 55 °C.

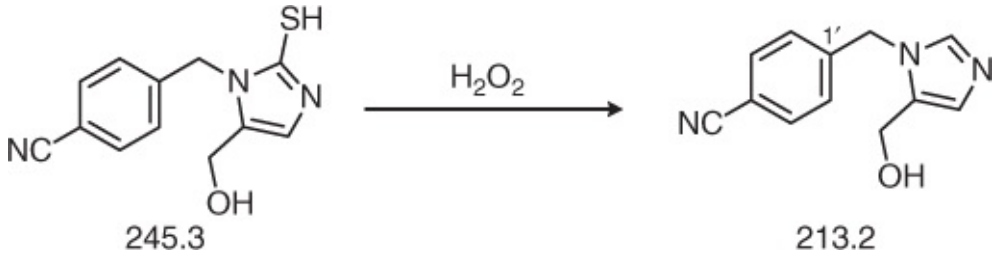
The reaction mixture is then cooled to room temperature and the precipitate formed is filtered off, washed with CH_3CN (17 ml), H_2O (35 ml), and EtOAc (17 ml), and dried *in vacuo* to give 3.31 g (76%) of a light-tan solid.

IR (FT-IR, solid): $\tilde{\nu}$ (cm^{-1}) = 3042, 2925, 2360, 2222, 1606, 1488, 1292, 1024, 815, 631, 521.

^{1}H NMR (300 MHz, [D_6]DMSO): δ (ppm) = 12.24 (s, 1H, SH), 7.79 (d, *J* = 8.5 Hz, 2H, Ar–H), 7.36 (d, *J* = 8.5 Hz, 2H, Ar–H), 6.90 (s, 1H, 4-H), 5.37 (s, 2H, CH_2–Ar), 5.23 (s_{br}, 1H, OH), 4.15 (s, 2H, C*H_2*–OH).

^{13}C NMR (75 MHz, [D_6]DMSO): δ (ppm) = 162.7 (C-2), 142.8 (C-1′), 132.3, 130.2, 127.7, 118.7 (C-4, C-5, C-2′, C-3′, C-5′, C-6′), 113.1 (CN), 109.9 (C-4′), 53.1, 46.3 (2 × CH_2).

3.3.4.3	*	**4-(5-Hydroxymethylimidazol-1-ylmethyl)benzonitrile** [1]



A 35% aqueous solution of H_2O_2 (3.72 g, 38.3 mmol) is added dropwise to a stirred solution of the mercapto compound **3.3.4.2** (2.85 g, 11.6 mmol) in acetic acid (5.5 ml) and H_2O (2.5 ml), with the temperature being maintained between 30 and 40 °C (cooling with an ice bath). The resulting yellow-orange solution is

stirred for 30 min at 40 °C and then cooled to room temperature.

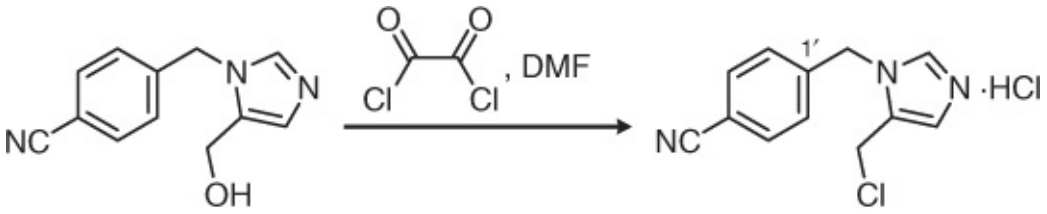
The reaction is quenched by the addition of 10% aqueous sodium sulfite (2 ml), and the mixture is treated with activated charcoal (0.2 g) and stirred for 30 min. The slurry is filtered and the filtrate is basified to pH 9 with 25% aqueous ammonia (approximately 11 ml) at 20 °C. The resulting slurry is stirred for 30 min and filtered. The solid is washed with H_2O (2 × 15 ml) and H_2O/MeOH (2 : 1, 15 ml), and dried *in vacuo*. The yield is 1.75 g (71%) of a brown solid, mp 163–164 °C.

IR (FT-IR, solid): $\tilde{\nu}$ (cm^{-1}) = 3122, 3057, 2836, 2745, 2359, 2232, 1698, 1495, 1326, 1247, 1105, 1027, 831, 780, 660, 556.

^{1}H NMR (300 MHz, [D_6]DMSO): δ (ppm) = 7.81 (s, 1H, 2-H), 7.71 (d, *J* = 8.5 Hz, 2H, Ar–H), 7.29 (d, *J* = 8.5 Hz, 2H, Ar–H), 6.85 (s, 1H, 4-H), 5.34 (s, 2H, Ar–CH_2), 5.11 (s_{br}, 1H, OH), 4.29 (s, 2H, C*H*$_2$–OH).

^{13}C NMR (75 MHz, [D_6]DMSO): δ (ppm) = 143.4 (C-1′), 138.6, 132.5 (C-2, C-5), 131.6, 127.7, 127.6 (C-4, C-2′, C-3′, C-5′, C-6′), 118.6 (*C*N), 110.3 (C-4′), 52.7, 47.1 (2 × CH_2).

3.3.4.4	**	**4-(5-Chloromethylimidazol-1-ylmethyl)benzonitrile HCl Salt** [1]



213.2 268.1

Oxalyl chloride (1.52 g, 12.0 mmol) is slowly added to a stirred solution of DMF (1.75 g, 24.0 mmol) in CH_3CN (20 ml), maintaining the temperature below 10 °C (cooling with an ice bath). The white slurry containing the “Vilsmeier reagent” is slowly added to a stirred suspension of the hydroxymethyl compound **3.3.4.3** (2.02 g, 9.47 mmol) in CH_3CN (15 ml), keeping the temperature below 6 °C (cooling with an ice bath). Finally, further CH_3CN (5 ml) is added and the reaction mixture is warmed to room temperature and stirred for 3 h.

The slurry is then cooled to 0 °C and stirred for 1 h. After filtration, the solid is

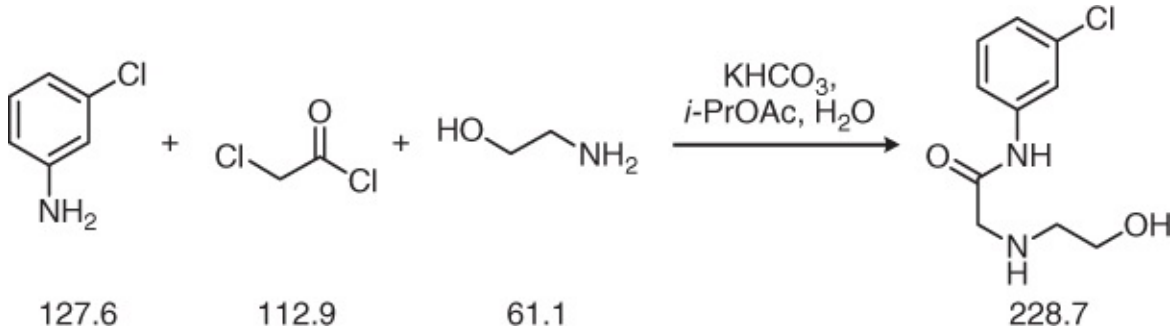
washed with ice-cold CH_3CN (8 ml) and dried *in vacuo* to give 2.20 g (80%) of a light-tan solid; mp 204–206 °C.

IR (FT-IR, solid): $\tilde{\nu}$ (cm^{-1}) = 3004, 2814, 2231, 1459, 1319, 820, 765, 684, 548.

^{1}H NMR (300 MHz, [D_6]DMSO): δ (ppm) = 9.41 (d, *J* = 1.2 Hz, 1H, 2-H), 7.88 (d, *J* = 8.5 Hz, 2H, Ar–H), 7.88 (s, 1H, 4-H), 7.54 (d, *J* = 8.5 Hz, 2H, Ar–H), 5.68 (s, 2H, Ar–CH_2), 4.92 (s, 2H, CH_2–Cl).

^{13}C NMR (75 MHz, [D_6]DMSO): δ (ppm) = 139.7, 137.7, 132.8 (C-2, C-5, C-1′), 130.1, 128.8 (C-2′, C-3′, C-5′, C-6′), 120.8 (C-4), 118.5 (CN), 111.3 (C-4′), 49.0, 33.1 (2 × CH_2).

3.3.4.5	**	***N*-(3-Chlorophenyl)-2-(2-hydroxyethylamino)acetamide** [1]



Chloroacetyl chloride (3.58 g, 31.7 mmol) is added dropwise to a stirred biphasic mixture of 3-chloroaniline (3.00 g, 23.5 mmol) in isopropyl acetate (23 ml) and potassium hydrogencarbonate (3.91 g) in H_2O (16 ml) at below 10 °C. The organic phase is separated and treated with ethanolamine (4.7 ml, 31.7 mmol), and the resulting mixture is heated to 60 °C for 1 h.

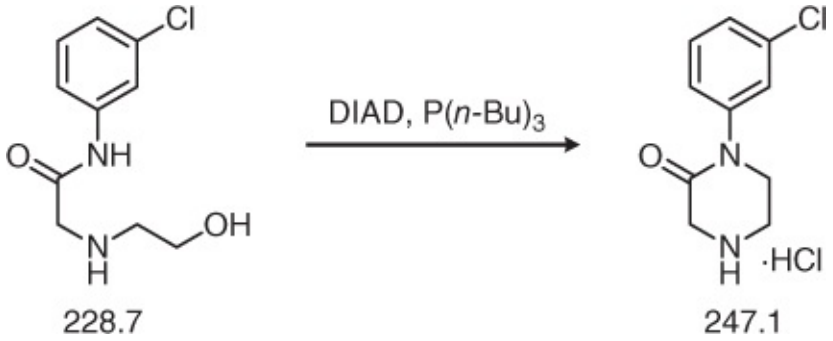
After the addition of water (7 ml), the organic phase is separated and cooled to 5 °C over 1 h. A crystalline precipitate is formed, which is collected by filtration, washed with isopropyl acetate (2 × 5 ml), and dried *in vacuo*. The yield is 3.69 g (69%) of colorless crystals, mp 99–101 °C.

IR (FT-IR, solid): $\tilde{\nu}$ (cm^{-1}) = 3310, 3057, 2930, 2873, 1683, 1593, 1542, 1418, 1056, 770, 679.

^{1}H NMR (300 MHz, [D_6]DMSO): δ (ppm) = 10.1 (s_{br}, 1H, C(O)NH), 7.84 (dd, *J* = 2.1, 2.1 Hz, 1H, Ar–H), 7.51 (ddd, *J* = 8.1, 2.1, 0.9 Hz, 1H, Ar–H), 7.32 (dd, *J* = 8.1, 8.1 Hz, 1H, Ar–H), 7.10 (ddd, *J* = 8.1, 2.1, 0.9 Hz, 1H, Ar–H), 4.62 (s_{br}, 1H, OH), 3.46 (t, *J* = 5.5 Hz, 2H, CH_2CH_2OH), 3.29 (s, 2H, $C(O)CH_2$), 2.60 (t, *J* = 5.5 Hz, 2H, CH_2CH_2OH).

^{13}C NMR (75 MHz, [D_6]DMSO): δ (ppm) = 171.0 (C=O), 140.2, 133.1, 130.4, 123.0, 118.7, 117.6 (6 × Ar–C), 60.4, 52.8, 51.6 (3 × CH_2).

3.3.4.6	**	**1-(3-Chlorophenyl)piperazin-2-one HCl** [1]



228.7 247.1

DIAD (7.20 g, 35.6 mmol) is added dropwise to a stirred solution of tri-*n*-butylphosphine (90%) (8.00 g, 35.6 mmol) in EtOAc (15 ml), keeping the temperature below 0 °C (cooling with an ice/salt bath). Stirring is continued for 30 min at 0 °C, and then the resulting yellow solution is added dropwise over 1 h to a stirred slurry of the amide **3.3.4.5** (6.00 g, 26.2 mmol) in EtOAc (35 ml), maintaining the temperature below 5 °C. The solution is warmed to room temperature over 1 h, then to 40 °C, whereupon 3.55 M anhydrous ethanolic HCl (7.3 ml, 26.2 mmol, note) is added over 1 h.

The resulting slurry is cooled to 0 °C within 1 h; the deposited hydrochloride is collected by filtration, washed with ice-cold EtOAc (2 × 10 ml), and dried *in vacuo* to yield 4.40 g (68%) of a colorless crystalline solid; mp 230–232 °C.

IR (FT-IR, solid): $\tilde{\nu}$ (cm^{-1}) = 3052, 2646, 1655, 1590, 1494, 1406, 1333, 889, 785, 695, 513.

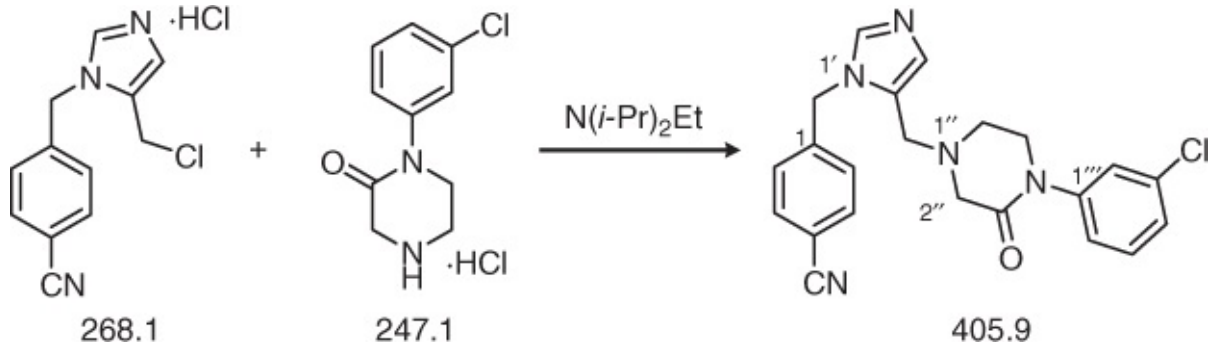
^{1}H NMR (300 MHz, [D_6]DMSO): δ (ppm) = 10.1 (s_{br}, 2H, NH_2^+), 7.47 (dd, *J* = 2.1, 2.1 Hz, 1H, Ar–H), 7.44 (m_c, 1H, Ar–H), 7.38 (ddd, *J* = 8.1, 2.1, 0.9 Hz, 1H, Ar–H), 7.31 (ddd, *J* = 8.1, 2.1, 0.9 Hz, 1H, Ar–H), 3.91 (t, *J* = 5.7

Hz, 2H, CH_2), 3.83 (s, 2H, C(O)CH_2), 3.50 (t, *J* = 5.7 Hz, 2H, CH_2).

^{13}C NMR (75 MHz, [D_6]DMSO): δ (ppm) = 162.1 (C=O), 142.7, 132.9, 130.7, 127.0, 126.0 (6 × Ar–C), 46.1, 44.9, 39.9 (3 × CH_2).

Note: The ethanolic HCl is prepared by passing gaseous hydrogen chloride (16.6 g, 455 mmol, lecture bottle) into anhydrous EtOH (128.1 ml) with stirring and ice-cooling.

3.3.4.7	*	**4-{5-[4-(3-Chlorophenyl)-3-oxo-piperazin-1-ylmethyl]imidazol-1-ylmethyl}benzonitrile** [1]



268.1 247.1 405.9

A mixture of the salts **3.3.4.4** (990 mg, 3.70 mmol) and **3.3.4.6** (890 mg, 3.60 mmol) in CH_3CN (5 ml) and ethyldiisopropylamine (1.85 ml) is stirred for 30 h at 0 °C.

H_2O (15 ml) is then added to give a light-brown precipitate, which is collected by filtration (note). It is washed with CH_3CN/H_2O (1 : 5; 6 ml) and CH_3CN/H_2O (1 : 9; 2 × 5 ml) and dried *in vacuo* to afford 1.06 g (73%) of the desired product; mp 140–141 °C.

IR (solid): $\tilde{\nu}$ (cm^{-1}) = 2812, 2230, 1651, 1423, 1338, 1320, 1105, 1077, 820, 783, 698, 663, 550.

^{1}H NMR (300 MHz, [D_6]DMSO): δ (ppm) = 7.83 (s, 1H, 2″-H), 7.79 (d, *J* = 8.2 Hz, 2H, Ar–H), 7.40 (dd, *J* = 8.1, 8.1 Hz, 1H, Ar–H), 7.35 (dd, *J* = 1.9 Hz, 1H, Ar–H), 7.30 (ddd, *J* = 8.1, 1.9, 1.0 Hz, 1H, Ar–H), 7.28 (d, *J* = 8.2 Hz, 2H, Ar–H), 7.20 (ddd, *J* = 8.1, 1.9, 1.0 Hz, 1H, Ar–H), 6.92 (s, 1H, C-4′), 5.39 (s, 2H, Ar–CH_2), 3.44 (s, 2H, C-5′-CH_2N), 3.32 (t, *J* = 5.4 Hz, 2H,

5″-H), 3.02 (s, 2H, 2″-H_2), 2.60 (t, *J* = 5.4 Hz, 2H, 6″-H).

^{13}C NMR (75 MHz, [D_6]DMSO): δ (ppm) = 165.7 (C(O)N), 144.0, 142.3, 139.5, 132.8, 132.3, 130.3, 129.4, 127.5, 126.8, 126.2, 125.6, 124.0 (14 × Ar–C), 118.6 (CN), 110.0 (C-4), 56.7, 49.2, 48.8, 48.1, 47.3 (5 × CH_2).

Note: If the product does not precipitate, it can be extracted with CH_2Cl_2 and purified after removal of the solvent by column chromatography (SiO_2; CH_2Cl_2/MeOH, 95 : 5, R_f = 0.33).

References

1. (a) Maligres, P.E., Waters, M.S., Weissman, S.A., McWilliams, J.C., Lewis, S., Cowen, J., Reamer, R.A., Volante, R.P., Reider, P.J., and Askin, D. (2003) *J. Heterocycl. Chem.*, **40**, 229–241;For an overview on farnesyltransferase inhibitors, see: (b) Bell, I.M. (2004) *J. Med. Chem.*, **47**, 1869–1878;Recently, structurally simple FTPase inhibitors have been shown to arrest the growth of malaria parasites: (c) Glenn, M.P., Chang, S.-Y., Hucke, O., Verlinde, C.L.M.J., Rivas, K., Hornéy, C., Yokoyama, K., Buckner, F.S., Pendyala, P.R., Chakrabarti, D., Gelb, M., Van Voorhis, W.C., Sebti, S.M., and Hamilton, A.D. (2005) *Angew. Chem.*, **117**, 4981–4984; *Angew. Chem. Int. Ed.*, (2005), **44**, 4903–4906.

2. Eicher, Th., Hauptmann, S., and Speicher, A. (2012) *The Chemistry of Heterocycles*, 3rd edn, Wiley-VCH Verlag GmbH, Weinheim, p. 224.

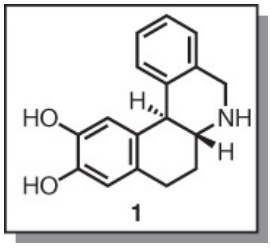
3. The Delepine reaction is useful for the preparation of benzylamines from benzyl halides, cf. Smith, M.B. (2013) *March's Advanced Organic Chemistry*, 7th edn, John Wiley & Sons, Inc., New York, p. 483.

4. 4-Cyanobenzyl bromide (**4**) is available commercially or can be prepared by NBS bromination of 4-cyanotoluene: (a) Wen, L., Li, M., and Schlenoff, J.B. (1997) *J. Am. Chem. Soc.*, **33**, 7726–7733;(b) *Organikum* (2001) 21st edn, Wiley-VCH Verlag GmbH, Weinheim, p. 205.

5. Hughes, D.L. (1992) *Org. React.*, **42**, 335–656.

6. Mitsunobu reaction in catalytic fashion: But, T.Y.S. and Toy, P.H. (2006) *J. Am. Chem. Soc.*, **128**, 9636–9637.

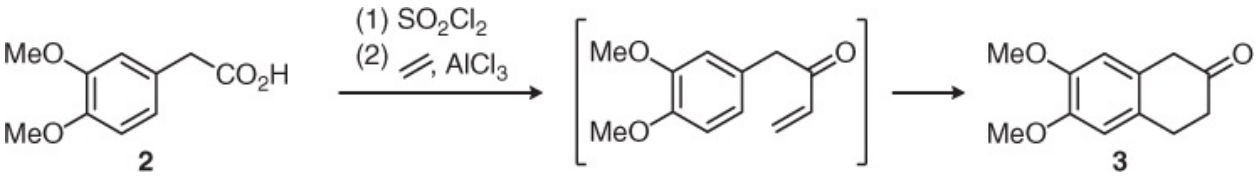
3.3.5 (±)-Dihydrexidine

	***Topics:***	• Synthesis of a dopamine agonist • Iodination (S_EAr)

		• Esterification, catalytic hydrogenation • Heck reaction • Dieckmann cyclization • Ester hydrolysis, Krapcho cleavage of a β-keto ester • Enamine formation with a primary amine and subsequent Nacylation • Photocyclization of an enamide • Reduction R–CO–NH_2 → R–CH_2–NH_2 by diborane • Catalytic debenzylation, demethylation with HBr

(a) General

(±)-Dihydrexidine (**1**, *trans*-10,11-dihydroxy-5,6,6a,7,8,12b-hexahydrobenzo[*a*]phenanthridine) is a highly potent and selective agonist of the dopamine D_1 receptor [1, 2]. For its synthesis, 6,7-dimethoxy-2-tetralone (**3**) is a suitable substrate, which can be prepared by several methods [1]. The most widely used procedure is based on a Friedel–Crafts reaction of the acid chloride of (3,4-dimethoxyphenyl)acetic acid (**2**) with ethylene followed by cyclization in the presence of $AlCl_3$ [3]:

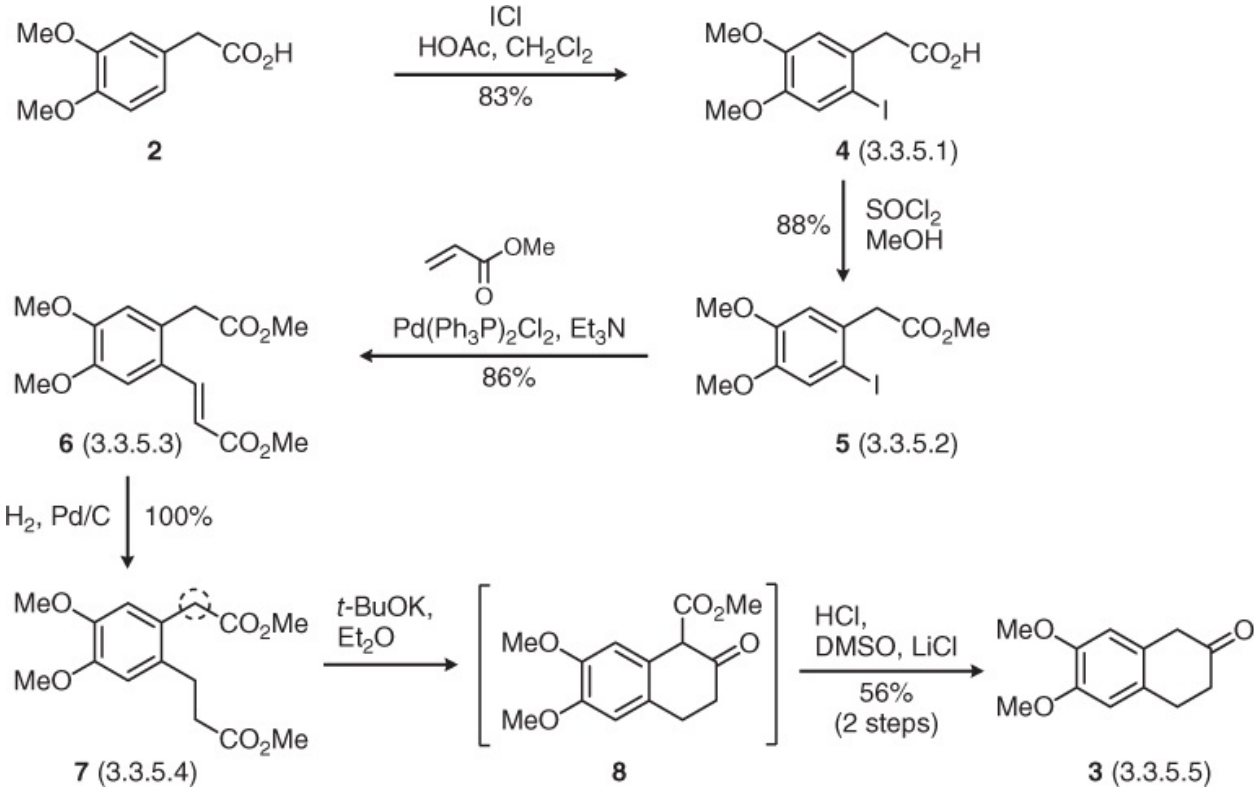


However, this approach suffers from preparative difficulties and a modest overall yield. Here, a new synthesis of the β-tetralone **3** starting from **2** is described [4], which raises the overall yield to 35%.

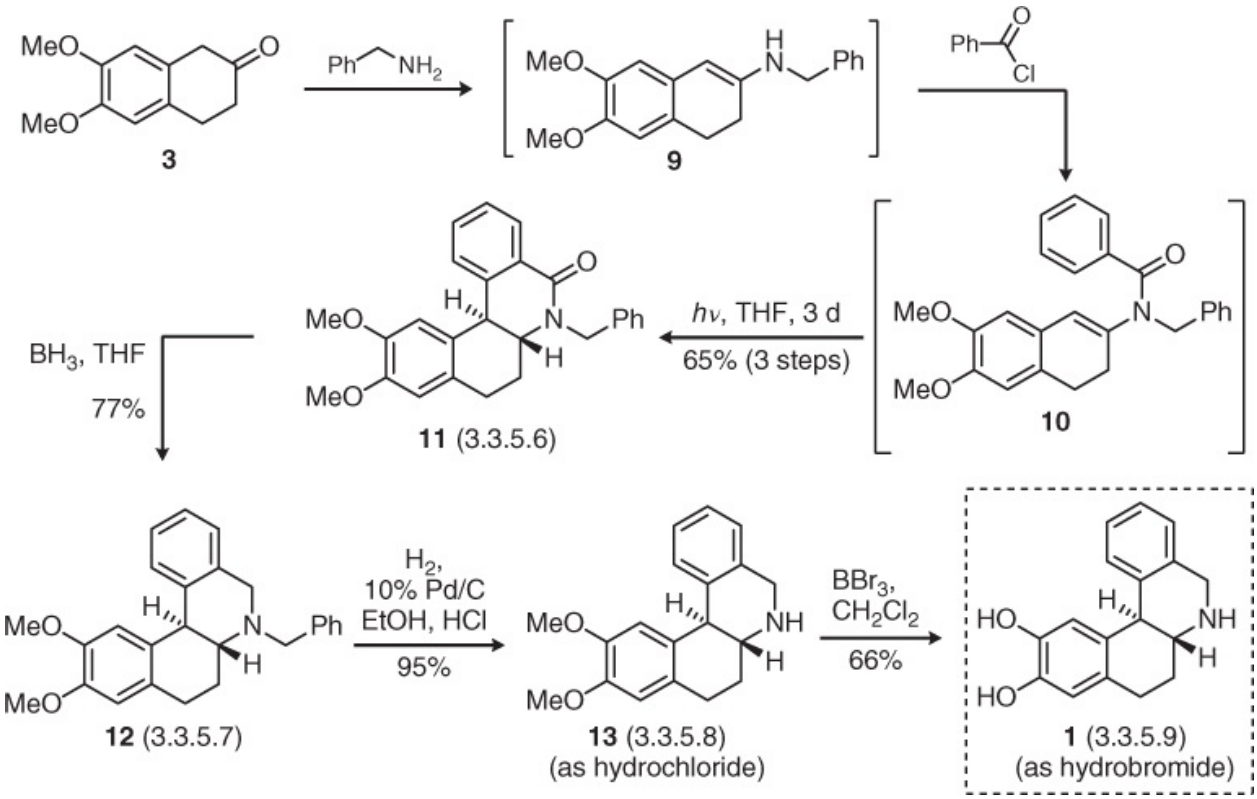
(b) Synthesis of 1

In the first part of the synthesis, (3,4-dimethoxyphenyl)acetic acid (**2**) is chemoselectively iodinated with iodine monochloride to give the iodo acid **4**, which is esterified by reaction with $SOCl_2$ in MeOH to afford the methyl ester **5** [4]. Heck reaction (cf. Section 1.6.1) of **5** with methyl acrylate in the presence of

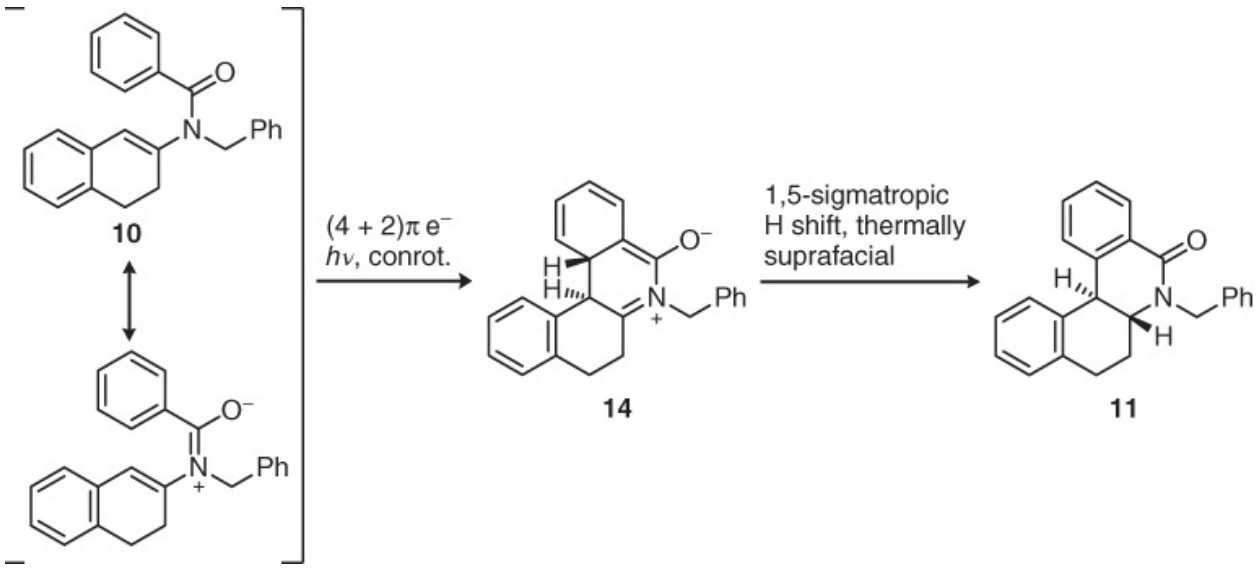
NEt_3 and dichlorobis(triphenylphosphine)palladium(II) – a highly stable and low-cost Pd(II) catalyst, which is transformed *in situ* into the required Pd(0) catalyst $Pd(PPh_3)_2$ – affords the cinnamate **6** in 86% yield. This is catalytically hydrogenated over Pd/C to yield the propionate **7** in an overall yield of 62% over four steps from **2**. The subsequent Dieckmann cyclization of the diester **7** using KO*t*-Bu proceeds chemoselectively because of the higher acidity of the benzylic CH_2–CO_2R group and leads to the β-keto ester **8**. Removal of the ester moiety in **8** with H_2O/DMSO/LiCl according to the Krapcho method [5] leads to the desired tetralone **3**. It can be purified by column chromatography on polyamide or via its bisulfite adduct [4]:



In the second part of the synthesis, the β-tetralone **3** is reacted with benzylamine to give the enamine **9**, which is Nacylated with benzoyl chloride. Without isolation, the resulting enamide **10** is irradiated in THF solution to give the tetracyclic lactam **11** as the product of a photocyclization (cf. Section 1.8.2):



Since the relative stereochemistry of the hydrogen atoms at the B/C ring junction in the cyclization product **11** was shown to be trans [1], a plausible interpretation of the formation of **11** might be a photochemically allowed conrotatory 6π-electrocyclization of **10** to give **14** followed by a thermal suprafacial 1,5-sigmatropic hydrogen shift leading to **11** [6].



Finally, the lactam **11** is reduced by diborane in THF to give the tertiary amine

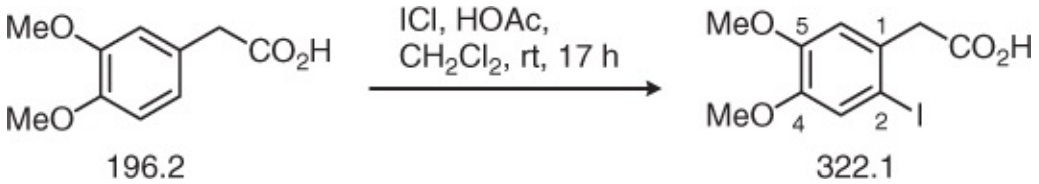
12, which is subjected to N-deprotection by catalytic debenzylation with H_2 over Pd/C in EtOH/HCl and to O-deprotection by demethylation with BBr_3 in CH_2Cl_2 to afford **1** via **13**. For reasons of crystallizability, the final product *trans*-**1** is isolated as its hydrobromide.

Thus, the target molecule **1** is obtained in 5 steps from **3** in an overall yield of 31% or in 11 steps from **2** in an overall yield of 11%.

It should be noted that the originally described demethylation of **13** with HBr gives only low yields.

(c) Experimental Procedures for the Synthesis of 1

3.3.5.1	**	**(2-Iodo-4,5-dimethoxyphenyl)acetic acid** [4]



196.2 322.1

Iodine monochloride (87.8 g, 540 mmol) is added dropwise over 3 h to a stirred solution of (3,4-dimethoxyphenyl)acetic acid (100 g, 510 mmol) in anhydrous CH_2Cl_2 (850 ml) and glacial acetic acid (100 ml) at room temperature under an argon atmosphere. Stirring is continued for 17 h.

The reaction is then quenched by the addition of saturated aqueous sodium thiosulfate solution (400 ml). The organic layer is separated, washed with saturated aqueous sodium thiosulfate solution (2 × 400 ml) and with aqueous HCl (2 M, 1 × 400 ml), dried over $MgSO_4$, and filtered. Any precipitate of the product in the separatory funnel is dissolved by adding some CH_2Cl_2. The solvent is removed *in vacuo*, the residue is suspended in Et_2O (500 ml), and the suspension is stirred for 30 min. The iodo acid is obtained as a white solid by filtration; 137 g (83%), mp 165–166 °C, R_f = 0.44 (*n*-pentane/EtOAc, 1 : 1).

UV (CH_3CN): λ_{max} (nm) (log ε) = 285 (3.462), 239 (4.082), 211 (4.579).

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3546, 3334, 3006, 2938, 2592, 1708, 1507, 1463, 1384, 1325, 1166, 1019, 860.

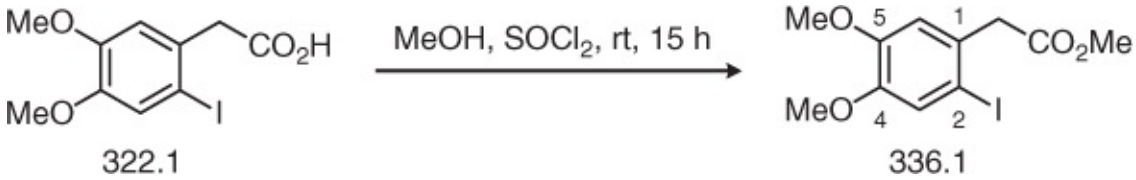
^{1}H NMR (300 MHz, [D_6]acetone): δ (ppm) = 7.33 (s, 1H, 3-H), 7.08 (s, 1H,

6-H), 3.85 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 3.77 (s, 2H, CH_2).

^{13}C NMR (76 MHz, [D_6]acetone): δ (ppm) = 171.2 (CO_2H), 150.0 (C-5), 149.3 (C-4), 131.1 (C-2), 122.0 (C-6), 114.6 (C-3), 88.80 (C-1), 55.79 (C-5–OCH_3), 55.54 (C-4–OCH_3), 45.03 (CH_2).

MS (EI, 70 eV): *m*/*z* (%) = 322 (100) $[M]^+$, 277 (72) $[M-CO_2H]^+$, 195 (44) $[M-I]^+$, 150 (11) $[M-CO_2H-I]^+$.

3.3.5.2	*	**(2-Iodo-4,5-dimethoxyphenyl)acetic acid methyl ester** [4]



322.1 336.1

Thionyl chloride (60 ml) is added dropwise over 3 h to a stirred solution of the iodo acid **3.3.5.1** (110 g, 342 mmol) in anhydrous MeOH (800 ml) at room temperature under argon atmosphere. Stirring is continued for 15 h at the same temperature.

Thereafter, the solvent is removed *in vacuo*, and the residue is dissolved in CH_2Cl_2 (400 ml) and treated with saturated aqueous $NaHCO_3$ solution (100 ml). After stirring for 15 min at room temperature, the organic layer is separated and subsequently washed with saturated aqueous $NaHCO_3$ solution (2 × 200 ml), H_2O (200 ml) and brine (200 ml). The organic layer is dried over $MgSO_4$ and filtered, and the solvent is removed *in vacuo*. Recrystallization of the residue from EtOAc/*n*-hexane affords the methyl ester as white needles; 101 g (88%), mp 77–78 °C, R_f = 0.27 (*n*-pentane/Et_2O, 2 : 1).

UV (CH_3CN): λ_{max} (nm) (log ε) = 285 (3.468), 239 (4.090), 211 (4.574).

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3079, 2992, 2934, 1722, 1507, 1437, 1329, 1218, 1165, 1029.

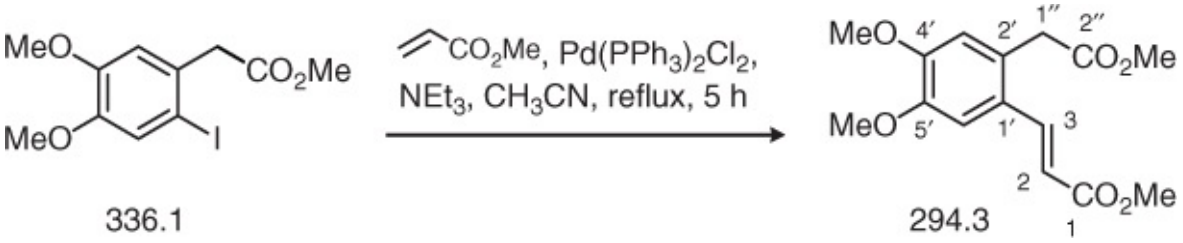
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.21 (s, 1H, 3-H), 6.79 (s, 1H, 6-H), 3.83 (s, 6H, 2 × OCH_3), 3.72 (s, 2H, CH_2), 3.70 (s, 3H, CO_2CH_3).

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 171.1 (CO_2CH_3), 149.2 (C-5),

148.5 (C-4), 129.8 (C-2), 121.4 (C-6), 113.1 (C-3), 88.73 (C-1), 56.03 (C-5–OCH_3), 55.82 (C-4–OCH_3), 52.06 (CO_2CH_3), 45.43 (CH_2).

MS (EI, 70 eV): *m*/*z* (%) = 336 (100) $[M]^+$, 277 (92) $[M-CO_2CH_3]^+$, 209 (83) $[M-I]^+$, 150 (10) $[M-CO_2CH_3-I]^+$.

3.3.5.3	**	**(*E*)-3-(4,5-Dimethoxy-2-methoxycarbonylmethyl-phenyl)acrylic acid methyl ester** [4]



336.1 294.3

A solution of the methyl ester **3.3.5.2** (80.0 g, 248 mmol), methyl acrylate (86.0 ml, 82.0 g, 953 mmol), and NEt_3 (100 ml, 72.6 g, 718 mmol) in anhydrous CH_3CN (300 ml) is thoroughly deoxygenated by bubbling an argon stream through it for 45 min, and then dichlorobis(triphenylphosphine)palladium(II) (1.00 g, 1.42 mmol, 0.6 mol%) is added. The reaction mixture is heated to reflux for 5 h.

The solvent is then removed *in vacuo*, and the residue is taken up in EtOAc (1000 ml). The solution is washed with H_2O (400 ml), aqueous HCl (2 M, 2 × 400 ml), and again H_2O (400 ml). The organic layer is dried over $MgSO_4$ and filtered, and the solvent is removed *in vacuo* to a volume of 300 ml. After addition of charcoal (1.0 g), the mixture is heated to boiling for decolorization. The mixture is filtered and the solvent is removed *in vacuo*. Crystallization of the residue from EtOH (200 ml) affords the acrylic ester as colorless needles; 62.7 g (86%), mp 96–97 °C, R_f = 0.45 (*n*-pentane/EtOAc, 7 : 3).

UV (CH_3CN): λ_{max} (nm) (log ε) = 327 (4.187), 296 (4.158), 238 (4.066), 219 (4.160).

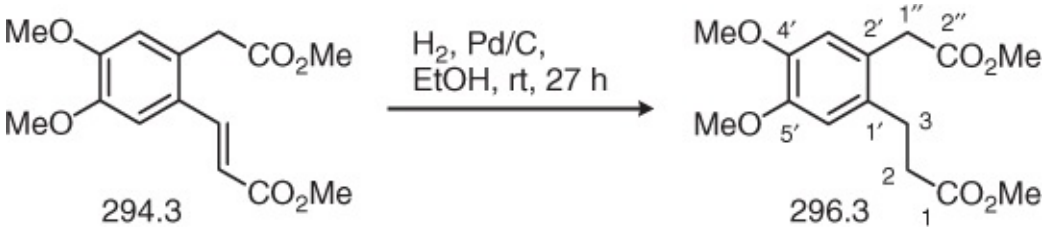
IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3082, 2998, 2953, 1730, 1603, 1516, 1428, 1272, 1095, 1001, 860.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.87 (d, *J* = 15.8 Hz, 1H, 3-H), 7.07 (s, 1H, 6′-H), 6.73 (s, 1H, 3′-H), 6.28 (d, *J* = 15.8 Hz, 1H, 2-H), 3.88 (s, 6H, 2 × OCH_3), 3.78 (s, 3H, 2-CO_2CH_3), 3.72 (s, 2H, 1″-H_2), 3.68 (s, 3H, 1″-CO_2CH_3).

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 171.4 (C-1), 167.3 (C-2″), 150.7 (C-5′), 148.4 (C-4′), 141.3 (C-3′), 127.2 (C-2′), 125.9 (C-1′), 117.4 (C-2), 113.4 (C-3), 108.8 (C-6′), 55.89 (C-4′–OCH_3), 55.84 (C-5′–OCH_3), 52.14 (C-2–CO_2CH_3), 51.59 (C-1″–CO_2CH_3), 37.93 (C-1″).

MS (EI, 70 eV): *m*/*z* (%) = 294 (100) $[M]^+$, 262 (21) $[M-OCH_3-H]^+$, 234 (30) $[M-CO_2CH_3-H]^+$, 221 (22) $[M-CHCO_2CH_3-H]^+$, 203 (50) $[M-CO_2CH_3-OCH_3-H]^+$, 175 (51) $[M-CO_2CH_3-CO_2CH_3-H]^+$, 161 (17) $[M-CO_2CH_3-CO_2CH_3-CH_3]^+$, 59 (18) $[CO_2CH_3]^+$.

3.3.5.4	**	**3-(4,5-Dimethoxy-2-methoxycarbonylmethyl-phenyl)propionic acid methyl ester** [4]



The acrylic ester **3.3.5.3** (50.0 g, 170 mmol) is dissolved in hot EtOH (1000 ml), and 10% palladium on charcoal (5.00 g) is added. The flask is flushed with hydrogen for 30 min, and hydrogenation is carried out at ambient pressure until hydrogen uptake ceases (approximately 27 h).

The suspension is then filtered through a pad of Celite® (approximately 1 cm), which is subsequently washed with Et_2O (1000 ml). The solvent is removed *in vacuo* to afford the product as a colorless oil in quantitative yield; 50.3 g (100%), R_f = 0.45 (*n*-pentane/EtOAc, 7 : 3).

UV (CH_3CN): λ_{max} (nm) (log ε) = 284 (3.527), 233 (3.957), 203 (4.671).

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3449, 2998, 2953, 2849, 1736, 1610, 1521, 1437,

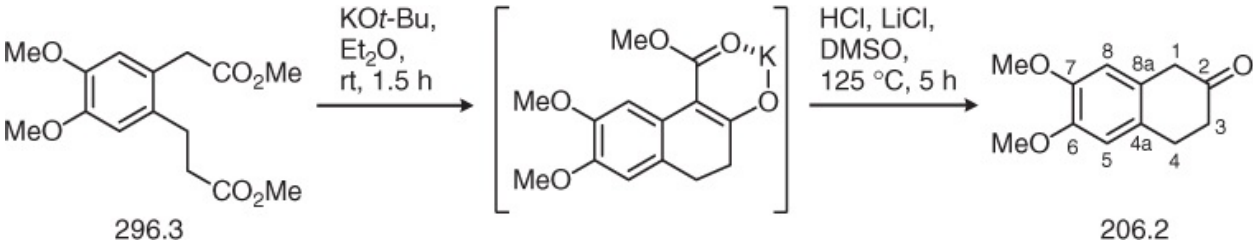
1276, 1162, 1099, 1013.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 6.71 (s, 1H, 3′-H), 6.69 (s, 1H, 6′-H), 3.84 (s, 6H, 2 × OCH_3), 3.68 (s, 3H, 1″-CO_2CH_3), 3.66 (s, 3H, 2-CO_2CH_3), 3.60 (s, 2H, 1″-H_2), 2.90 (t, *J* = 7.9 Hz, 2H, 3-H_2), 2.57 (t, *J* = 7.9 Hz, 2H, 2-H_2).

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 173.3 (C-1), 172.2 (C-2″), 148.2 (C-5′), 147.4 (C-4′), 131.3 (C-1′), 124.0 (C-2′), 113.5 (C-6′), 112.3 (C-3′), 55.86 (C-4′–O*C*H_3), 55.82 (C-5′–O*C*H_3), 52.03 (C-1″–CO_2*C*H_3), 51.61 (C-2–CO_2*C*H_3), 37.87 (C-1″), 35.34 (C-2), 27.68 (C-3).

MS (EI, 70 eV): *m*/*z* (%) = 296 (100) $[M]^+$, 264 (56) $[M-OCH_3-H]^+$, 237 (47) $[M-CO_2CH_3]^+$, 223 (27) $[M-CH_2CO_2CH_3]^+$, 165 (51) $[M-CO_2CH_3-CH_2CO_2\ CH_3+H]^+$.

3.3.5.5	**	**6,7-Dimethoxy-3,4-dihydro-1*H*-naphthalen-2-one (6,7-dimethoxy-β-tetralone)** [4]



A solution of the propionic ester **3.3.5.4** (45.7 g, 154 mmol) in anhydrous Et_2O (500 ml) is added dropwise to a well-stirred suspension of KO*t*-Bu (19.0 g, 170 mmol) in Et_2O (1000 ml) over 1.5 h at room temperature under an argon atmosphere. Stirring is continued for 1 h, and then the resulting suspension is filtered and the filter cake is washed with Et_2O (500 ml). The potassium enolate thus collected is dried in high vacuum and is obtained in quantitative yield.

A solution of the potassium salt (10.0 g, 33.1 mmol) and anhydrous LiCl (1.68 g, 39.7 mmol) in DMSO (23 ml) is deoxygenated by bubbling an argon stream through it for 15 min, and then concentrated HCl (3.30 ml, 40.0 mmol) is rapidly added with stirring. The flask is placed in an oil bath, preheated to 125 °C, and stirring is continued at this temperature for 5 h.

After cooling, the reaction mixture is diluted with EtOAc (500 ml), the organic layer is washed with H_2O (3 × 200 ml), dried over $MgSO_4$ and filtered, and the solvent is removed *in vacuo*. The residue is purified by column chromatography on polyamide (15% EtOAc/*n*-pentane) and then recrystallized from EtOAc/*n*-hexane to afford the β-tetralone as a white solid; 3.81 g (56%), mp 85–86 °C; R_f = 0.45 (*n*-pentane/EtOAc, 7 : 3).

UV (CH_3CN): λ_{max} (nm) (log ε) = 285 (3.571), 202 (4.597).

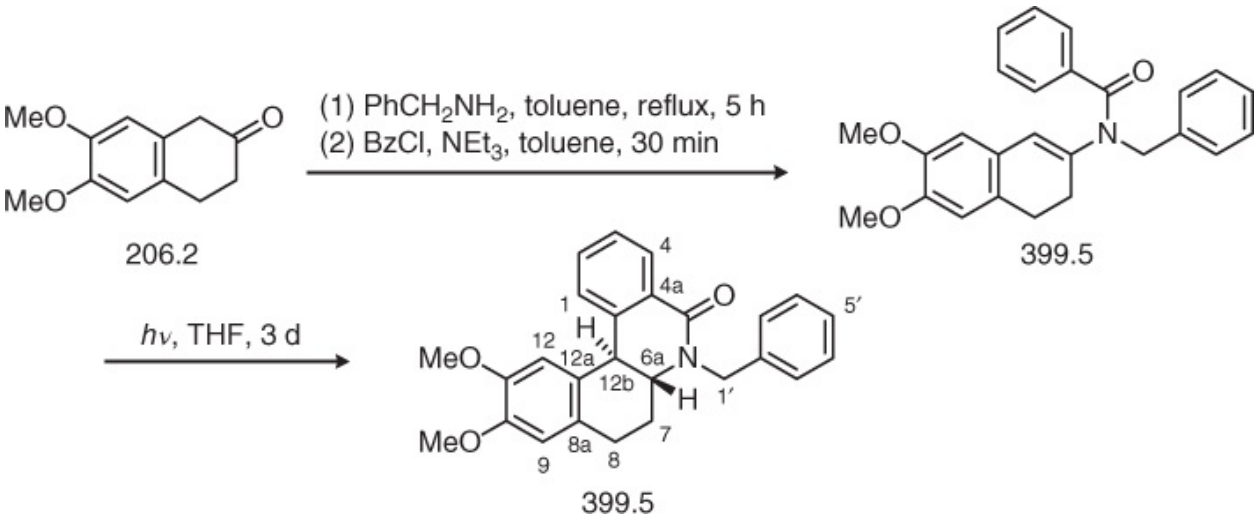
IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3014, 2998, 2958, 2851, 1717, 1515, 1462, 1346, 1248, 1113, 880.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 6.74 (s, 1H, 8-H), 6.62 (s, 1H, 5-H), 3.88 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.51 (s, 2H, 1-H_2), 3.00 (t, *J* = 6.7 Hz, 2H, 4-H_2), 2.55 (t, *J* = 6.7 Hz, 2H, 3-H_2).

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 210.8 (C-2), 147.9 (C-7), 147.7 (C-6), 128.4 (C-4a), 125.0 (C-8a), 111.3 (C-8), 111.1 (C-5), 56.03 (2 × OCH_3), 44.20 (C-1), 38.58 (C-3), 28.11 (C-4).

MS (EI, 70 eV): *m*/*z* (%) = 206 (100) $[M]^+$, 164 (40) $[M-C_2H_2O]^+$.

3.3.5.6	**	***trans*-6-Benzyl-10,11-dimethoxy-5,6,6a,7,8,12b-hexahydrobenzo[*a*]- phenanthridin-5-one** [1]



A solution of the tetralone **3.3.5.5** (1.03 g, 5.00 mmol) and benzylamine (0.56 g,

5.23 mmol) in toluene (20 ml) is heated to reflux for 5 h under an argon atmosphere with continuous removal of H_2O using a Dean–Stark trap. The solution is cooled to about 80 °C, and benzoyl chloride (0.77 g, 5.48 mmol) and triethylamine (0.56 g, 5.53 mmol) are added dropwise. The resulting mixture is stirred at room temperature for 2 h.

The solvent is then removed *in vacuo*, the residue is dissolved in CH_2Cl_2 (100 ml), and washed with H_2O (50 ml). The aqueous layer is extracted with CH_2Cl_2 (50 ml), the combined organic phases are dried over Na_2SO_4 and filtered, and the solvent is removed *in vacuo*. Column chromatography on silica gel yields the crude enamide as a yellow solid (2.01 g). Small amounts of remaining 6,7-dimethoxy-β-tetralone do not interfere with the next step.

To remove the remaining 6,7-dimethoxy-β-tetralone, sodium borohydride (50 mg) is added to a solution of the crude product in EtOH (50 ml). The mixture is stirred for 30 min at 50 °C, the EtOH is removed *in vacuo*, and CH_2Cl_2 (100 ml) and H_2O (30 ml) are added. The organic layer is separated, dried over Na_2SO_4 and filtered, and the solvent is removed *in vacuo*. The residue is dissolved in THF (60 ml) and irradiated for 3 days with a 300-W high-pressure mercury lamp in a ring reactor.

The product is purified by column chromatography on silica gel (*n*-pentane/EtOAc 3 : 1) and recrystallized from Et_2O/*n*-pentane to give the phenanthridin-5-one as colorless needles; 1.29 g (65% over three steps), mp 191–195 °C, R_f = 0.16 (*n*-pentane/EtOAc 3 : 1).

UV (CH_3CN): λ_{max} (nm) (log ε) = 282.0 (3.76), 200.0 (4.88).

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 2934, 1655, 1514, 1460, 1403, 1261, 1115, 1023, 742.

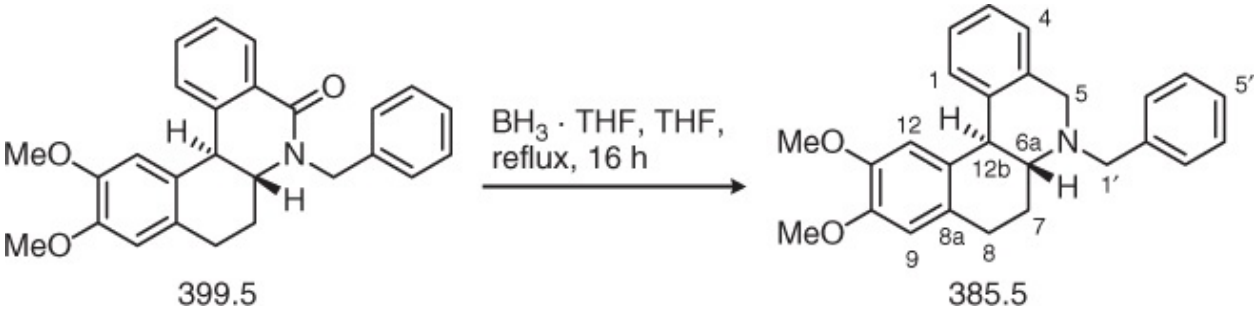
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.20 (m, 1H, Ar–H), 7.53 (m, 1H, Ar–H), 7.49–7.39 (m, 2H, 2 × Ar–H), 7.32–7.19 (m, 5H, 5 × Ar–H), 6.92 (s, 1H, Ar–H), 6.63 (s, 1H, Ar–H), 5.34 (d, *J* = 15.9 Hz, 1H, 1′-H_b), 4.78 (d, *J* = 15.9 Hz, 1H, 1′-H_a), 4.36 (d, *J* = 11.4 Hz, 1H, 12b-H), 3.89, 3.87 (2s, 6H, OCH_3), 3.78 (m_c, 1H, 6a-H), 2.67 (m_c, 2H, 8-H_2), 2.26 (m_c, 1H, 7-H_b), 1.75 (m_c, 1H, 7-H_a).

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 166.2 (C-5), 147.6, 146.8, 141.5, 138.5, 131.2, 129.4, 123.6 (C-4a, C-2′, C-8a, C-10, C-11, C-12a, C-12c),

130.9, 129.1, 128.6, 126.8, 126.5, 122.8 (C-1, C-2, C-3, C-4, C-3′, C-4′, C-5′, C-6′, C-7′), 112.7, 111.7 (C-9, C-12), 59.99 (C-6a), 56.03 (OCH_3), 55.76 (OCH_3), 45.84 (C-12b), 45.06 (C-1′), 29.09 (C-8), 26.20 (C-7).

MS (ESI): *m*/*z* (%) = 821.0 (100) $[2M+Na]^+$, 1219.6 (74) $[3M+Na]^+$, 422.2 (15) $[M+Na]^+$.

3.3.5.7	**	***trans*-6-Benzyl-10,11-dimethoxy-5,6,6a,7,8,12b-hexahydrobenzo[*a*]- phenanthridine** [1]



A solution of borane THF complex in THF (1 M, 5.50 ml, 5.50 mmol) is slowly added to a stirred ice-cold solution of the phenanthridin-5-one **3.3.5.6** (734 mg, 1.84 mmol) in anhydrous THF (60 ml), and then the reaction mixture is heated to reflux for 16 h.

After cooling to room temperature, H_2O (6 ml) is slowly added and the solvent is evaporated under reduced pressure. The residue is dissolved in toluene (30 ml), methanesulfonic acid (0.6 ml) is added, and the resulting mixture is heated to 70 °C for 1 h. The mixture is then diluted with H_2O (25 ml) and the aqueous layer is separated. The organic layer is extracted with aqueous HCl (6 M, 4 × 30 ml) and the combined aqueous phases are cooled in an ice bath and slowly basified with concentrated NH_4OH (120 ml). The free base is extracted with CH_2Cl_2 (3 × 50 ml) and the combined organic phases are dried over $MgSO_4$, filtered, and the solvent is removed *in vacuo* to afford the *N*-benzylphenanthridine as a yellow solid; 545 mg (77%), mp (HCl salt) 230–232 °C, R_f = 0.43 (*n*-pentane/EtOAc, 2 : 1).

UV (CH_3CN): λ_{max} (nm) (log ε) = 286.5 (3.614), 194.5 (4.890), 192.5 (4.898).

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3442, 3006, 2944, 2854, 1608, 1514, 1463, 1347,

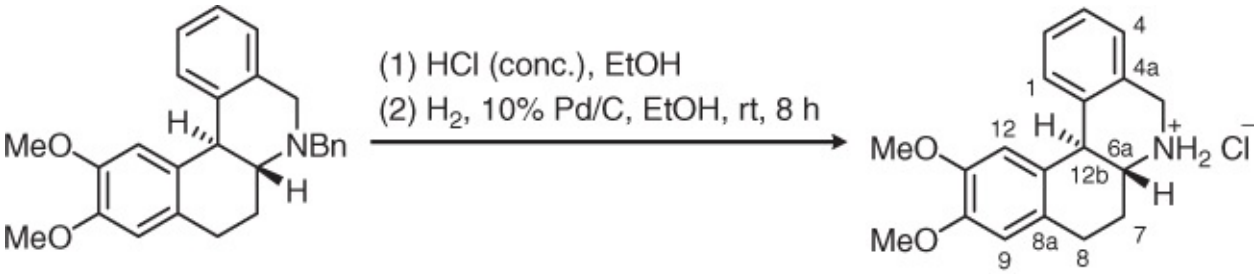
1257, 1236, 1195, 1125, 1087, 1014, 874, 765, 701.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.44–7.08 (m, 9H, 1-H, 2-H, 3-H, 4-H, 3′-H, 4′-H, 5′-H, 6′-H, 7′-H), 6.89 (s, 1H, 12-H), 6.73 (s, 1H, 9-H), 4.06 (d, *J* = 10.6 Hz, 1H, 12b-H), 3.89 (s, 3H, OCH_3), 3.95–3.82 (m, 2H, 5-H_b, 1′-H_b), 3.78 (s, 3H, OCH_3), 3.52 (d, *J* = 15.2 Hz, 1H, 1′-H_a), 3.29 (d, *J* = 13.3 Hz, 1H, 5-H_a), 2.86 (m_c, 2H, 8-H_2), 2.35 (m_c, 1H, 6a-H), 2.22 (m_c, 1H, 7-H_b), 2.03 to 1.86 (m, 1H, 7-H_a).

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 147.2, 146.7, 139.5, 137.6, 136.0, 130.5, 129.7 (C-4a, C-8a, C-10, C-11, C-12a, C-12c, C-2′), 129.0 (C-3′, C-7′), 128.3 (C-4′, C-6′), 127.2, 127.0, 126.6, 126.3, 126.0 (C-1, C-2, C-3, C-4, C-5′), 111.7, 110.9 (C-9, C-12), 65.30 (C-6a), 57.70 (C-5), 56.03 (OCH_3), 55.93 (OCH_3), 53.37 (C-1′), 43.43 (C-12b), 28.11 (C-8), 27.59 (C-7).

MS (ESI): *m*/*z* (%) = 386 (100) $[M+H]^+$.

3.3.5.8	**	***trans*-10,11-Dimethoxy-5,6,6a,7,8,12b-hexahydrobenzo[*a*] phenanthridine hydrochloride** [1]



385.5 331.8

A suspension of the *N*-benzylphenanthridine **3.3.5.7** (392 mg, 1.02 mmol) in EtOH (100 ml) is carefully acidified with concentrated HCl (0.40 ml), and then the solvent is removed *in vacuo*. The residue is dissolved in EtOH (80 ml), 10% Pd/C catalyst (100 mg) is added, and the mixture is shaken at room temperature under hydrogen (3.5 bar) for 8 h.

After removal of the catalyst by filtration, the solvent is removed *in vacuo*. The residue is recrystallized from CH_3CN/MeOH to afford the hydrochloride as light-yellow crystalline solid; 320 mg (95%), mp 238–239 °C, R_f = 0.62 (CH_2Cl_2/MeOH, 4 : 1).

UV (MeOH): λ_{max} (nm) (log ε) = 285.0 (3.585), 204.5 (4.687).

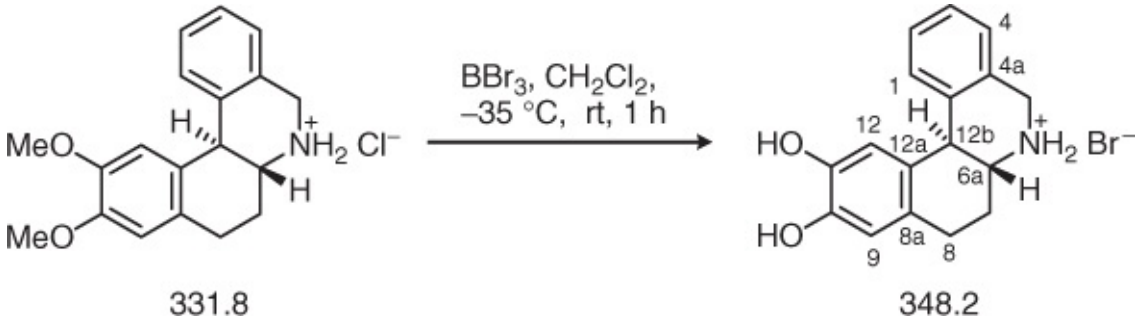
IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3420, 2937, 2775, 1607, 1515, 1446, 1205, 1128, 1092, 1038, 871, 750.

^{1}H NMR (300 MHz, [D_6]DMSO): δ (ppm) = 10.0 (s_{br}, 2H, NH_2), 7.45–7.25 (m, 4H, 1-H, 2-H, 3-H, 4-H), 6.87, 6.84 (2s, 2H, 9-H, 12-H), 4.36 (s, 2H, 5-H_2), 4.26 (d, *J* = 10.9 Hz, 1H, 12b-H), 3.75 (s, 3H, OCH_3), 3.68 (s, 3H, OCH_3), 2.95 (m_c, 1H, 6a-H), 2.88–2.69 (m, 2H, 8-H_2), 2.28–2.14 (m, 1H, 7-H_b), 2.08–1.90 (m, 1H, 7-H_a).

^{13}C NMR (76 MHz, [D_6]DMSO): δ (ppm) = 147.6, 146.7, 137.2, 130.5, 129.5 (C-8a, C-10, C-11, C-12a, C-12c), 127.8, 127.6, 126.8, 125.2 (C-1, C-2, C-3, C-4), 124.9 (C-4a), 112.6, 112.0 (C-9, C-12), 56.55 (C-6a), 55.63 (OCH_3), 55.52 (OCH_3), 43.47 (C-5), 40.60 (C-12b), 26.89 (C-8), 25.20 (C-7).

MS (ESI): *m*/*z* (%) = 296 (100) $[M-Cl]^+$.

3.3.5.9	**	***trans*-10,11-Dihydroxy-5,6,6a,7,8,12b-hexahydrobenzo[*a*]phenanthridine hydrobromide** [1]



331.8 348.2

The phenanthridine hydrochloride **3.3.5.8** (83.0 mg, 0.25 mmol) is taken up in saturated aqueous $NaHCO_3$ solution (10 ml) and the liberated free amine is extracted with CH_2Cl_2 (3 × 10 ml). The combined organic phases are washed with brine, dried over Na_2SO_4 and filtered, and the solvent is removed *in vacuo*.

Boron tribromide (1 M in CH_2Cl_2, 0.75 ml, 0.75 mmol) is added dropwise to a solution of the residue (73.8 mg, 0.25 mmol) in CH_2Cl_2 (5 ml) at −35 °C. The mixture is stirred at room temperature for 1 h.

Et_2O (4 ml) and MeOH (0.1 ml) are then added, the solvents are removed *in vacuo*, and Et_2O is added to precipitate the crude product. Recrystallization from CH_3CN affords the desired (±)-dihydrexidine hydrobromide as yellow needles; 57 mg (66%), mp 185–186 °C, R_f = 0.10 (CH_2Cl_2/MeOH, 10 : 1).

UV (CH_3OH): λ_{max} (nm) (log ε) = 288.5 (3.55), 202.5 (4.63).

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3224, 2937, 1521, 1276, 750.

^{1}H NMR (300 MHz, [D_6]DMSO): δ (ppm) = 9.59 (s_{br}, 2H, NH_2), 9.38 (s_{br}, 2H, OH), 7.37 (m, 4H, Ar–H), 6.74 (s, 1H, Ar–H), 6.64 (s, 1H, Ar–H), 4.40 (s, 2H, 5-H_2), 4.19 (d, *J* = 10.8 Hz, 1H, 12b-H), 2.99 (m, 1H, 6a-H), 2.73 (m, 2H, 8-H_2), 2.19 (m, 1H, 7-H_b), 1.94 (m, 1H, 7-H_a).

^{13}C NMR (76 MHz, [D_6]DMSO): δ (ppm) = 144.0, 143.1, 136.3, 130.3, 127.7, 124.3 (C-4a, C-8a, C-10, C-11, C-12a, C-12c), 127.7, 127.5, 126.8, 126.2 (C-1, C-2, C-3, C-4), 115.9, 114.6 (C-9, C-12), 56.74 (C-6a), 43.99 (C-5), 40.30 (C-12b), 26.29 (C-8), 25.31 (C-7).

MS (ESI): *m*/*z* (%) = 268.1 (100) $[M+H]^+$.

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2. Knoerzer, T.A., Watts, V.J., Nichols, D.E., and Mailman, R.B. (1995) *J. Med. Chem.*, **38**, 3062–3070.

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4. Qandil, A.M., Miller, D.W., and Nichols, D.E. (1999) *Synthesis*, 2033–2035.

5. Kouvarakis, A. and Katerinopoulos, H.E. (1995) *Synth. Commun.*, **25**, 3035–3044; Krapcho cleavage leads to (formal) decarboxylation of β-keto esters, malonates, and cyanoacetates.

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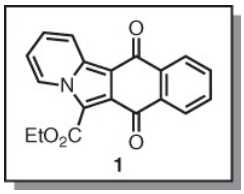
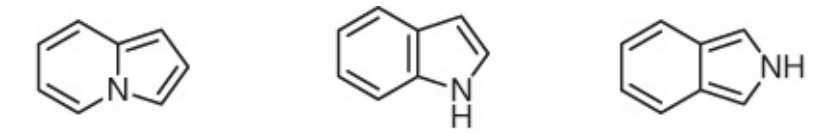
3.4 Condensed Heterocycles

3.4.1 6-Ethoxycarbonylnaphtho[2,3-*a*]indolizine-7,12-quinone

 1	***Topics:***	• Indolizine synthesis • N–CH–EWG-substituted pyridinium betaines as 1,3-dipoles in 1,3-dipolar cycloaddition • Chemoselective cleavage of *tert*-butyl esters • Formation of a cyclic dicarboxylic anhydride • Regioselective cleavage of an anhydride by a Grignard compound • Formation of a quinone by intramolecular Friedel–Crafts acylation

(a) General

Indolizine (**2**), one of the three benzopyrroles (**2–4**), constitutes the core structure of many naturally occurring alkaloids. The chemistry of indolizines is not as well known as that of indoles (**3**); however, it has attracted much interest in recent years [1, 2]. On the other hand, isoindoles (**4**) are usually less stable compounds because of their ortho-quinoid structure, though **4** can be isolated as colorless needles at low temperature.



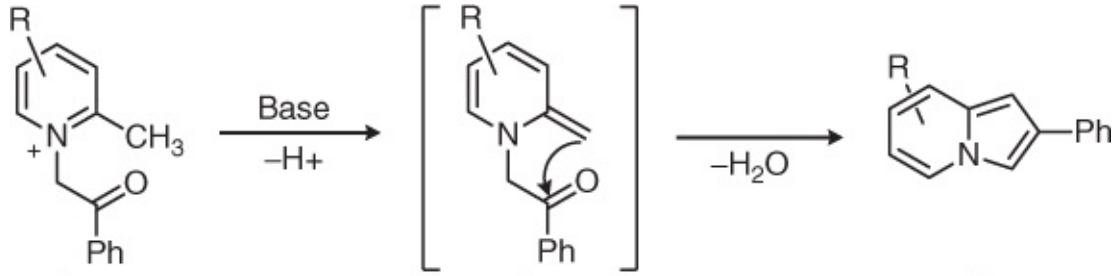
Indolizine
benzo[a]pyrrole
2

Indole
benzo[b]pyrrole
3

Isoindole
benzo[c]pyrrole
4

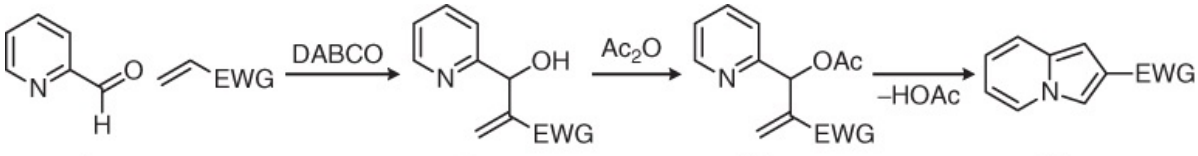
There are three important methods for the synthesis of indolizines:

1. 2-Methyl-*N*-phenacylpyridinium ions **5**, easily accessible from 2-picolines by alkylation, cyclize upon treatment with a base to give 2-phenylindolizines **7**. Evidently, of the two CH-acidic centers in **5**, the 2-methyl group is deprotonated selectively to provide the enamines **6** as intermediates, which lead to the indolizines **7** by intramolecular aldol condensation [3]:



5 **6** **7**

2. The Baylis–Hillman reaction (cf. **1.1.3.1**) of pyridine-2-carbaldehyde **8** with acceptor-substituted alkenes yields the adducts **9a**; the corresponding acetate derivatives **9b** lead to 2-acceptor-substituted indolizines **10** by a thermally induced intramolecular cyclization [4]:

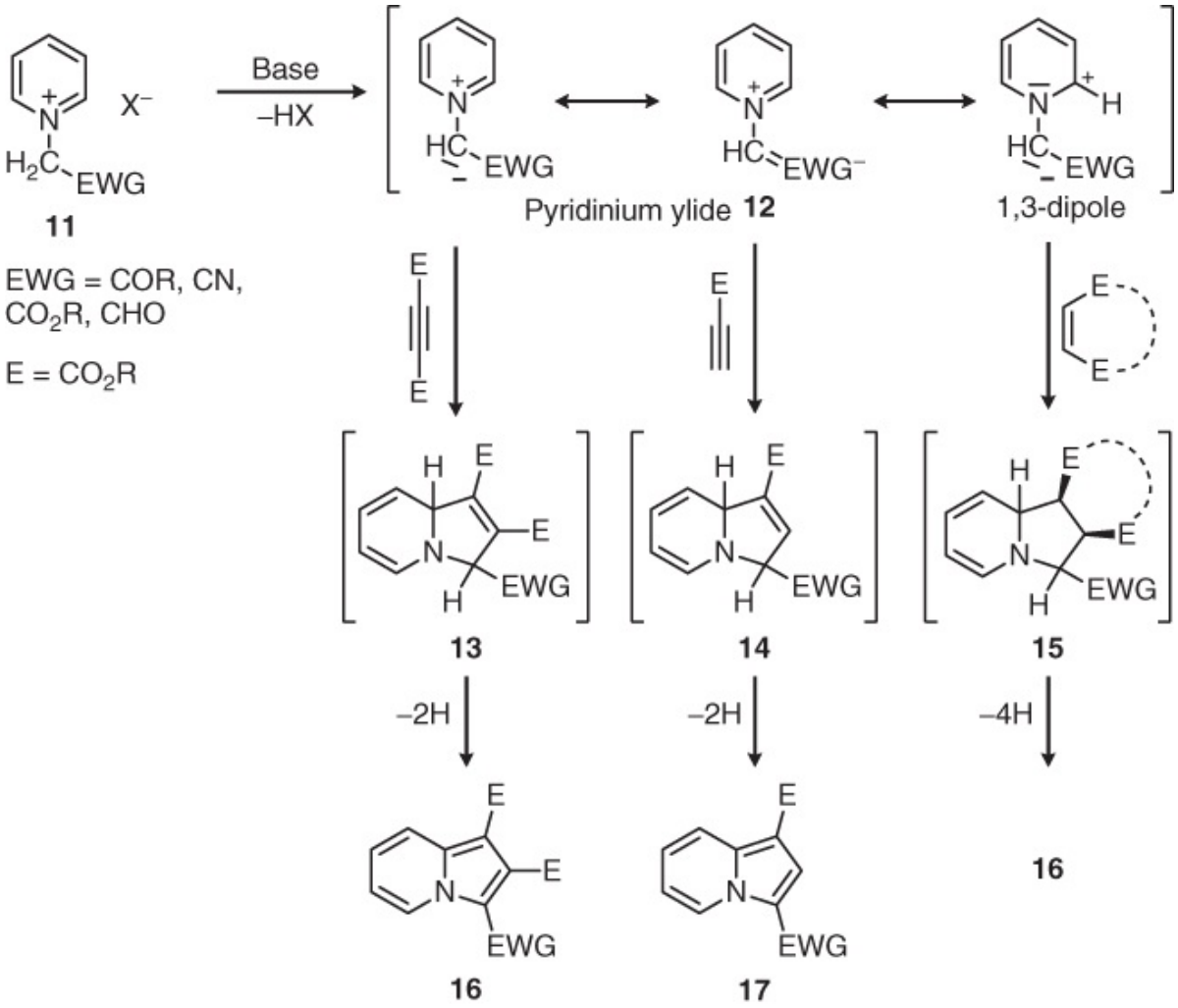


8 **9a** **9b** **10**

With only a few exceptions, methods (1) and (2) are restricted to the formation of 2-substituted indolizines and are therefore of limited scope and applicability.

3. The electron-withdrawing group (EWG)-CH-substituted pyridinium-*N*-betaines **12** undergo 1,3-dipolar cycloaddition with acetylene dicarboxylate, propiolate, or maleinate, or with electron-deficient alkenes as dipolarophiles. With alkynes, the cycloadducts (**13**/**14**) undergo spontaneous dehydrogenation to give indolizines, which are of the 1,2,3-trisubstituted

type **16** or (indicating a regioselective cycloaddition) of the 1,3-disubstituted type **17** [5–9]. With olefinic substrates, the presence of an oxidant for additional dehydrogenation of the primary cycloadducts (e.g., **15** → **16**) is required [10]:

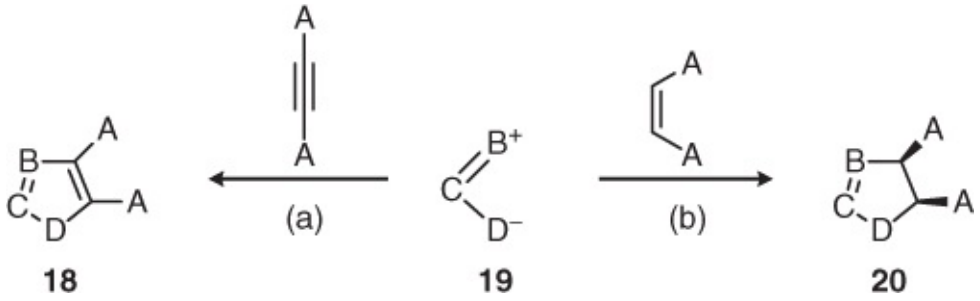


Since the pyridinium ylides **12** result from deprotonation of the corresponding *N*-alkylpyridinium ions **11**, cycloaddition is easily performed with **11**, the dipolarophile, and a base, preferentially in phase transfer catalysis (PTC) [5, 6] or microwave-assisted [9] multicomponent reaction (MCR) versions.

Here, method (3) is chosen for the preparation of the indolizine **1**.

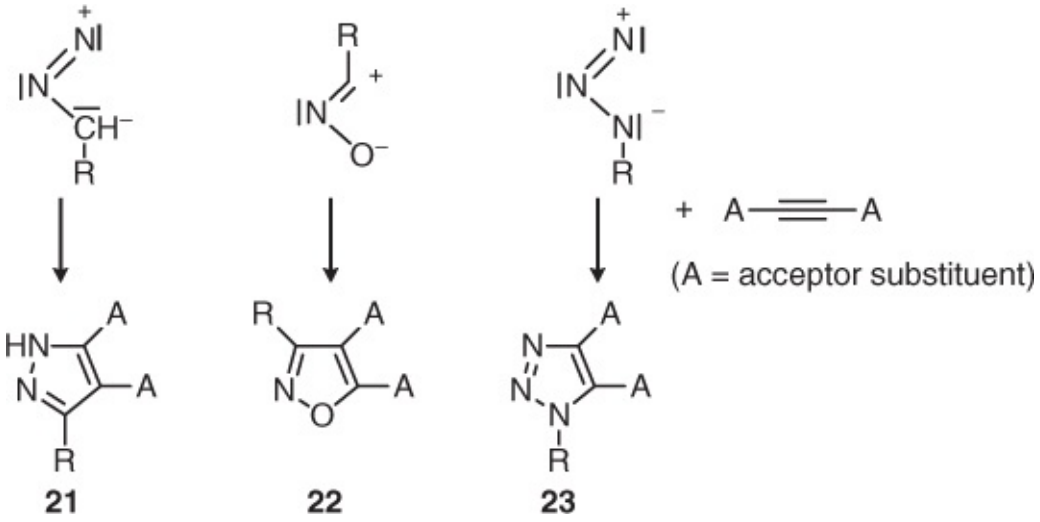
The 1,3-dipolar cycloaddition is a very versatile and effective method for the preparation of five-membered heterocycles [11]. In general, 1,3-dipolar cycloadditions proceed as concerted 6π-processes, in which a 1,3-dipole **19** (containing usually one or more nitrogen atoms) reacts with an electron-

acceptor-substituted alkyne (a) or alkene (b), that is

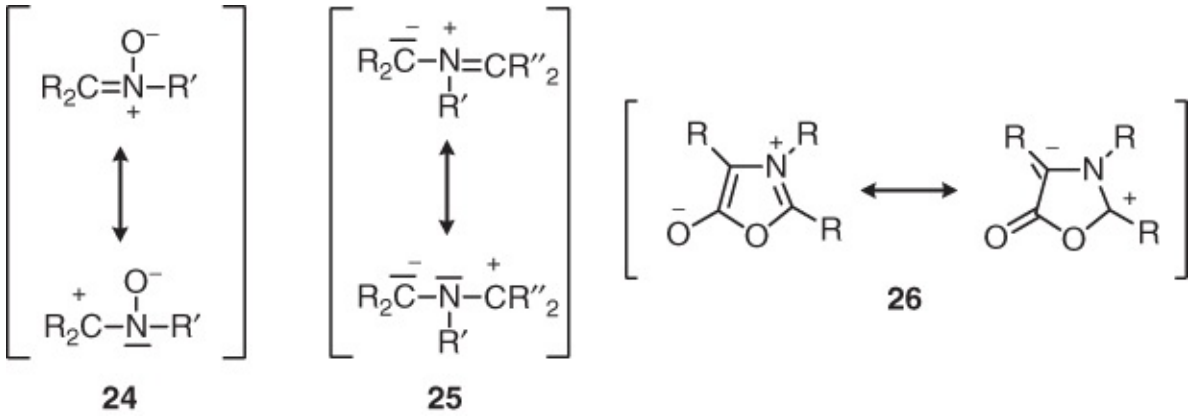


Electron-donor-substituted dipolarophiles can also be used, but they generally give lower yields. In case (a), aromatic azoles **18** are the products; in case (b), dihydroazoles **20** result, in which the alkene configuration is transferred to the sp[3] centers in the product, thus indicating that the cycloaddition proceeds in a stereoselective manner.

Classical examples of (a) are the formation of pyrazoles/1,2-oxazoles/1,2,3-triazoles (**21–23**) by 1,3-dipolar cycloaddition of diazoalkanes/nitrile oxides/azides to alkynes:



Other types of 1,3-dipoles are represented by nitrones **24**, azomethine ylides **25**, and mesoionic compounds **26**, which also undergo cycloaddition to olefinic and acetylenic dipolarophiles to allow the synthesis of a large number of different heterocyclic systems [12]:

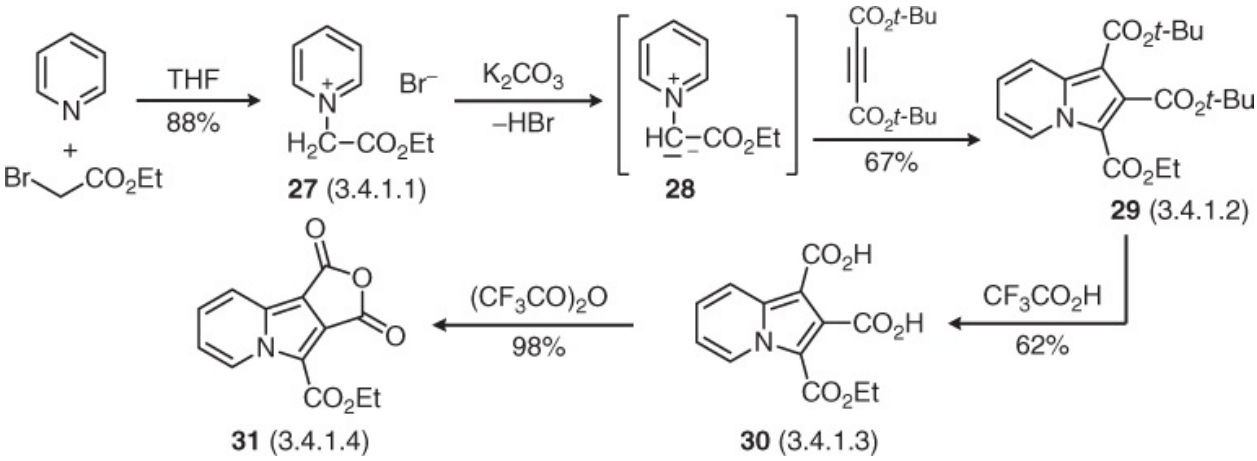


In this context, indolizine formation **12**→**16**/**17** can be classified as 1,3-dipolar cycloaddition with a dipole of the azomethine ylide type.

(b) Synthesis of 1

For the synthesis of **1** containing a quinone moiety, the indolizine-1,2,3-tricarboxylic acid monoester **30** was chosen as key intermediate. It was planned to prepare the quinone moiety in analogy with anthraquinone formation from phthalic anhydride via *o*-benzoylbenzoic acid [13].

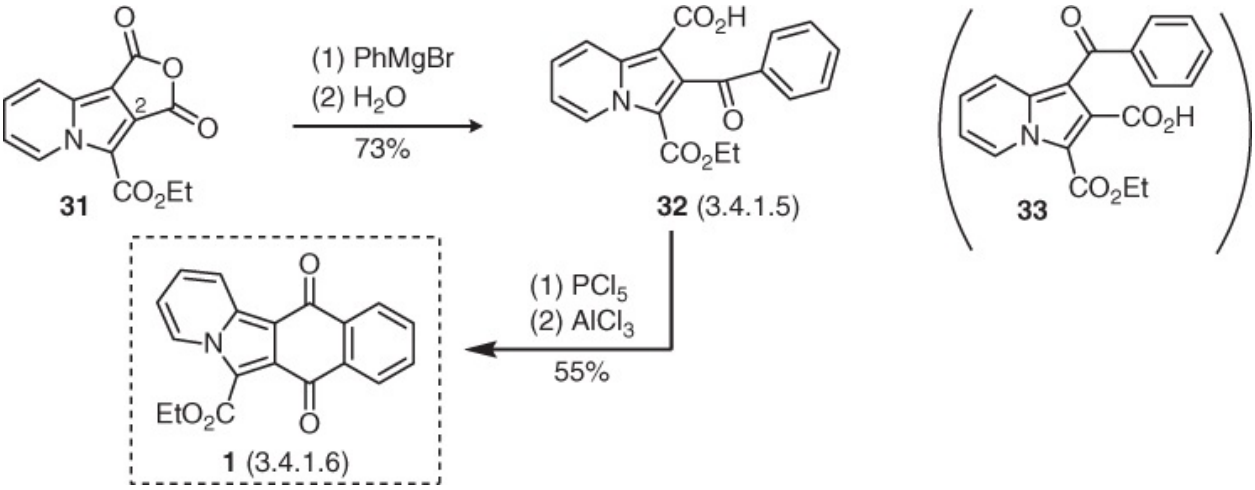
The synthesis of **1** [14] starts with the reaction of (*N*-ethoxycarbonylmethyl) pyridinium bromide (**27**), which is readily available from pyridine and ethyl bromoacetate [15], with di-*tert*-butyl acetylenedicarboxylate in the presence of K_2CO_3 as a base. Under these conditions, the indolizine-1,2,3-triester **29** is obtained by a 1,3-dipolar cycloaddition of the alkyne to the initially formed pyridinium ylide **28**:



Then, the *tert*-butyl ester groups in **29** are cleaved chemoselectively using CF_3CO_2H to give the dicarboxylic acid **30**, which is transformed into the

anhydride **31** on treatment with trifluoroacetic anhydride.

Reaction of the anhydride **31** with phenylmagnesium bromide in THF at −78 °C leads exclusively to the 2-benzoylindolizine-1-carboxylic acid **32**; thus, the regioisomeric acid **33** is not formed. The reason for this unexpected regioselectivity of anhydride opening (cf. Section 1.1.4) is not known. However, one can assume that a complexation of the Grignard reagent with the adjacent less reactive CO_2Et group favors attack at the carbonyl group at C-2.

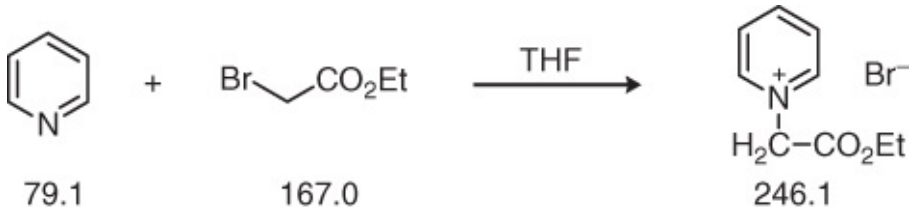


Finally, treatment of the carboxylic acid **32** with PCl_5 followed by $AlCl_3$ affords the quinone **1** by an intramolecular Friedel–Crafts acylation via the intermediately formed acid chloride.

Thus, the target molecule **1** is obtained from the pyridinium salt **27** in a six-step sequence in an overall yield of 16%.

(c) Experimental Procedures for the Synthesis of 1

3.4.1.1	*	***N*-(Ethoxycarbonylmethyl)pyridinium bromide** [15]



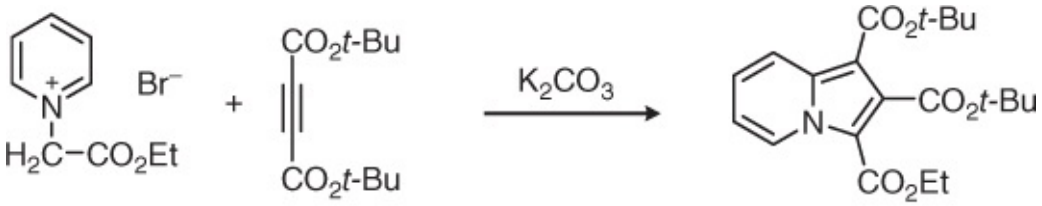
Ethyl bromoacetate (6.68 g, 45.0 mmol) is added dropwise to a stirred solution of anhydrous pyridine (3.56 g, 45.0 mmol) in anhydrous THF (200 ml), and the mixture is stirred at 25 °C for 12 h. The solvent is distilled off to give the crude product as a beige solid; 8.65 g (88%), mp 125–127 °C.

FT-IR: $\tilde{\nu}$ (cm^{-1}) = 1737.

^{1}H NMR (500 MHz, [D_6]DMSO): δ (ppm) = 9.09 (d, *J* = 6.6 Hz, 2H, Ar–H), 8.72 (t, *J* = 7.9 Hz, 1H, Ar–H), 8.25 (t, *J* = 7.9 Hz, 2H, Ar–H), 5.71 (s, 2H, N–CH_2), 4.24 (q, *J* = 7.3 Hz, 2H, C*H*$_2$$CH_3$), 1.25 (t, *J* = 7.3 Hz, 3H, CH_2C*H*$_3$).

^{13}C NMR (126 MHz, [D_6]DMSO): δ (ppm) = 166.4 (C = O), 146.8, 146.2, 127.8 (5 × Ar–C), 62.3 (N–CH_2), 60.3 (C*H*$_2$$CH_3$), 13.9 ($CH_2$*C*H$_3$).

3.4.1.2	**	**Di-*tert*-butyl 3-ethoxycarbonylindolizine-1,2-dicarboxylate** [14]



Anhydrous K_2CO_3 (7.28 g, 52.7 mmol) and di-*tert*-butyl acetylenedicarboxylate (7.91 g, 35.0 mmol) are added to a suspension of the pyridinium bromide **3.4.1.1** (8.61 g, 35.0 mmol) in anhydrous THF (340 ml) and the mixture is stirred at room temperature for 4 days.

The solid is then filtered off and the filtrate is concentrated *in vacuo* to give an oily residue, which is purified by column chromatography on SiO_2 (*n*-hexane/Et_2O, 10 : 1). The indolizine tricarboxylate is obtained as a yellow solid; 9.13 g (67%), R_f = 0.36 (*n*-hexane/Et_2O, 10 : 1), mp 124–126 °C.

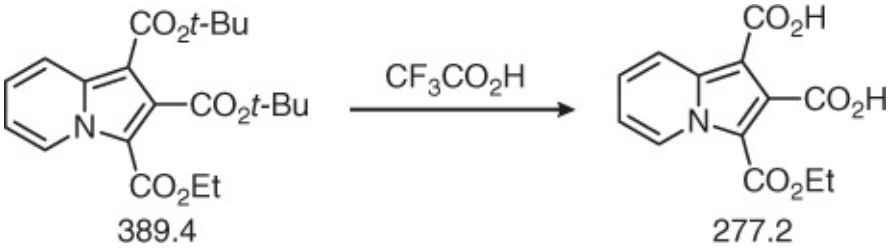
FT-IR: $\tilde{\nu}$ (cm^{-1}) = 1734, 1677.

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 9.55 (dt, *J* = 7.3, 1.0 Hz, 1H, Ar–H), 8.19 (dt, *J* = 9.1, 1.0 Hz, 1H, Ar–H), 7.28 (ddd, *J* = 9.1, 7.0, 1.2 Hz, 1H, Ar–H), 6.96 (dt, *J* = 7.0, 1.2 Hz, 1H, Ar–H), 4.42 (q, *J* = 7.0 Hz, 2H, OCH_2), 1.65 (s, 9H, $CO_2C(CH_3)_3$), 1.63 (s, 9H, $CO_2C(CH_3)_3$), 1.39 (t, *J* = 7.0 Hz, 3H, CH_3).

^{13}C NMR (126 MHz, [D_6]DMSO): δ (ppm) = 164.4, 162.1, 160.6 (3 ×

C=O), 137.0, 132.2, 127.9, 125.8, 120.1, 114.7, 111.7, 105.3 (8 × Ar–C), 82.4, 81.1 (2 × $CO_2C(CH_3)_3$), 60.7 (CH_2CH_3), 28.6, 28.3 (2 × $CO_2C(CH_3)_3$), 14.7 (CH_2CH_3).

3.4.1.3 * 3-Ethoxycarbonylindolizine-1,2-dicarboxylic acid [14]



389.4 277.2

Trifluoroacetic acid (15.7 g, 137 mmol) is added to a solution of the indolizine tricarboxylate **3.4.1.2** (5.35 g, 13.7 mmol) in CH_2Cl_2 (55 ml) and the mixture is stirred at room temperature overnight.

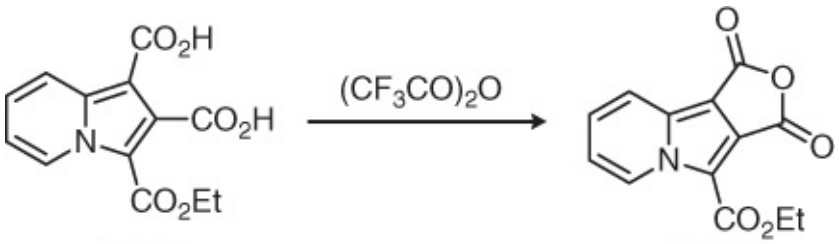
The orange-brown solid that separates is collected by filtration, washed with *n*-hexane (40 ml), and dried *in vacuo* to yield the monocarboxylate as a yellow solid; 2.35 g (62%), mp 207–208 °C.

FT-IR: $\tilde{\nu}$ (cm^{-1}) = 1701, 1658.

^{1}H NMR (500 MHz, [D_6]DMSO): δ (ppm) = 12.86 (s, 2H, 2 × CO_2H), 9.41 (dt, *J* = 7.0, 1.0 Hz, 1H, Ar–H), 8.28 (dt, *J* = 8.8, 1.2 Hz, 1H, Ar–H), 7.51 (ddd, *J* = 8.8, 6.7, 0.9 Hz, 1H, Ar–H), 7.23 (td, *J* = 7.0, 1.2 Hz, 1H, Ar–H), 4.31 (q, *J* = 7.0 Hz, 2H, CH_2CH_3), 1.28 (t, *J* = 7.0 Hz, 3H, CH_2CH_3).

^{13}C NMR (126 MHz, [D_6]DMSO): δ (ppm) = 166.0, 163.8, 159.7 (3 × C=O), 137.2, 132.2, 127.6, 127.1, 119.3, 115.7, 110.6, 102.5 (8 × Ar–C), 60.5 (CH_2CH_3), 13.9 (CH_2CH_3).

3.4.1.4 * 3-Ethoxycarbonylindolizine-1,2-dicarboxylic anhydride [14]



277.2 259.2

A suspension of the 1,2-dicarboxylic acid **3.4.1.3** (2.08 g, 7.50 mmol) in CH_2Cl_2 (25 ml) and trifluoroacetic anhydride (4.73 g, 22.5 mmol) is heated to reflux for 2 h.

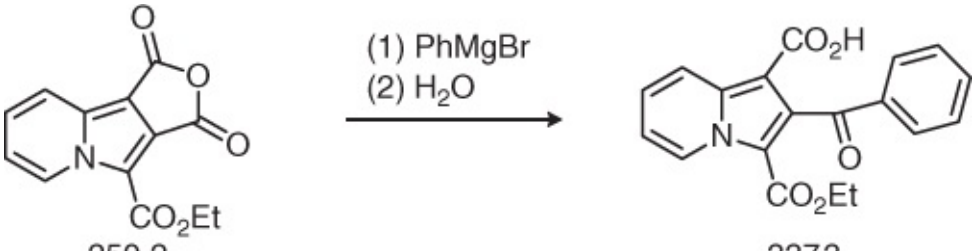
The solvent is then distilled off, and the yellow-green residue is suspended in *n*-hexane/Et_2O (1 : 1). The solid is collected by filtration and dried *in vacuo* to give the anhydride as a yellow solid; 1.91 g (98%), mp 167–168 °C.

FT-IR: $\tilde{\nu}$ (cm^{-1}) = 1828, 1764, 1693.

^{1}H NMR (500 MHz, [D_6]DMSO): δ (ppm) = 9.70 (d, *J* = 7.3 Hz, 1H, Ar–H), 7.98 (d, *J* = 9.1 Hz, 1H, Ar–H), 7.57 (t, *J* = 8.9 Hz, 1H, Ar–H), 7.26 (td, *J* = 8.0, 1.2 Hz, 1H, Ar–H), 4.50 (q, *J* = 7.0 Hz, 2H, C*H*$_2$CH$_3$), 1.50 (t, *J* = 7.0 Hz, 3H, CH$_2$C*H*$_3$).

^{13}C NMR (126 MHz, [D_6]DMSO): δ (ppm) = 159.3, 158.0, 157.4 (3 × C=O), 132.1, 129.6, 129.2, 128.4, 119.1, 117.5, 110.9, 109.5 (8 × Ar–C), 61.8 (C*H*$_2$CH$_3$), 14.2 (CH$_2$C*H*$_3$).

3.4.1.5	**	**2-Benzoyl-3-ethoxycarbonylindolizine-1-carboxylic acid** [14]



259.2 337.3

Phenylmagnesium bromide (15 ml, 15.0 mmol, 1.0 M solution in THF, Aldrich, note) is slowly added to the indolizine-1,2-dicarboxylic anhydride **3.4.1.4** (1.95 g, 7.50 mmol) in anhydrous THF (40 ml) at −78 °C, and the brown mixture is stirred for 15 min. The mixture is then allowed to warm to 0 °C and stirred for an

additional 30 min.

The reaction mixture is diluted with CH_2Cl_2 (100 ml) and subsequently acidified with 10% aqueous HCl, the organic layer is separated, and the aqueous layer is extracted with CH_2Cl_2 (3 × 150 ml). Insoluble material is filtered off. The combined organic layers are washed with H_2O (2 × 50 ml), dried over Na_2SO_4, and filtered, and the solvent is removed *in vacuo*. The brown solid is purified by column chromatography on silica gel ($CHCl_3$/MeOH, 50 : 1) to give the benzoylindolizine as a yellow solid; 1.85 g (73%), R_f = 0.17 ($CHCl_3$/MeOH, 50 : 1), mp 203–204 °C.

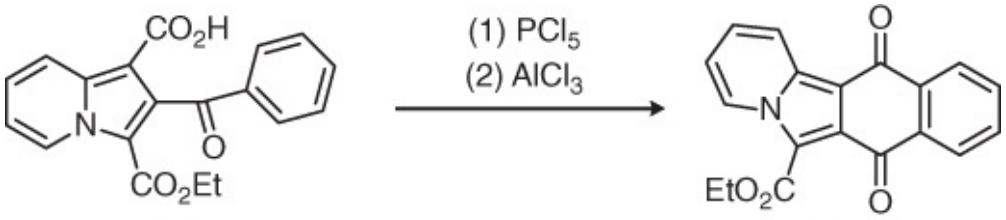
FT-IR: $\tilde{\nu}$ (cm^{-1}) = 1654, 1597.

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 9.61 (d, *J* = 7.3 Hz, 1H, Ar–H), 8.40 (d, *J* = 9.1 Hz, 1H, Ar–H), 7.85 (d, *J* = 7.3 Hz, 2H, Ar–H), 7.55 (t, *J* = 7.3 Hz, 1H, Ar–H), 7.45–7.39 (m, 3H, Ar–H), 7.09 (td, *J* = 6.9, 1.2 Hz, 1H, Ar–H), 4.08 (q, *J* = 7.3 Hz, 2H, C*H*$_2$CH$_3$), 0.86 (t, *J* = 7.3 Hz, 3H, CH$_2$C*H*$_3$).

^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) = 192.2, 168.2, 160.2 (3 × C=O), 139.0, 137.5, 137.4, 133.1, 129.3, 128.3, 128.2, 128.1, 127.3, 120.1, 115.5, 112.9 (14 × Ar), 60.8 (C*H*$_2$CH$_3$), 13.4 (CH$_2$C*H*$_3$).

Note: Phenylmagnesium bromide can be prepared by the standard procedure from bromobenzene and Mg turnings in THF.

3.4.1.6	**	**6-Ethoxycarbonylnaphtho[2,3-*a*]indolizine-7,12-quinone** [14]



337.3 319.3

A suspension of the carboxylic acid **3.4.1.5** (0.41 g, 1.23 mmol) and phosphorus pentachloride (1.29 g, 6.19 mmol) in 1,2-dichloroethane (10 ml) is stirred at room temperature overnight. Aluminum(III) chloride (0.83 g, 6.22 mmol) is then added to the red-colored solution and the mixture is heated at 50 °C for 2 h (color changes to green). Additional aluminum(III) chloride (0.33 g, 2.47 mmol)

is added and the mixture is heated at 50 °C for a further 2 h.

The mixture is then diluted with H_2O (15 ml) and extracted with CH_2Cl_2 (3 × 75 ml). The combined organic layers are washed with water, dried over Na_2SO_4, and filtered, and the solvent is removed *in vacuo*. The residue is purified by column chromatography (silica gel; *n*-hexane/EtOAc, 5 : 1) to give the indolizinequinone as an orange solid, 0.21 g (55%); R_f = 0.29 (*n*-hexane/EtOAc, 5 : 1), mp 151–152 °C.

FT-IR: $\tilde{\nu}$ (cm^{-1}) = 1691, 1670, 1640.

^{1}H NMR (500 MHz, [D_6]DMSO): δ (ppm) = 9.29 (dt, *J* = 7.3, 1.0 Hz, 1H, Ar–H), 8.63 (dt, *J* = 8.8, 1.1 Hz, 1H, Ar–H), 8.22 (m_c, 2H, Ar–H, Ar–H), 7.71 (m_c, 2H, Ar–H), 7.44 (ddd, *J* = 8.8, 6.9, 1.0 Hz, 1H, Ar–H), 7.10 (td, *J* = 6.9, 1.3 Hz, 1H, Ar–H), 4.56 (q, *J* = 6.9 Hz, 2H, C*H*$_2$CH$_3$), 1.54 (t, *J* = 7.0 Hz, 3H, CH$_2$C*H*$_3$).

^{13}C NMR (126 MHz, [D_6]DMSO): δ (ppm) = 180.2, 179.6, 161.3 (3 × C=O), 136.4, 135.5, 134.9, 133.4, 132.9, 128.0, 127.4, 127.5, 127.4, 126.1, 121.2, 117.1, 115.0, 112.3 (14 × Ar–C), 61.8 (C*H*$_2$CH$_3$), 14.2 (CH$_2$C*H*$_3$).

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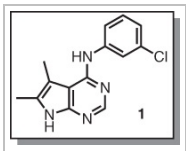
3.4.2 EGF-R-Pyrrolo[2,3-*d*]pyrimidine

	***Topics:***	• Technical heterocycle synthesis using domino and MCR processes • Formation of a 2-amino-3-cyanopyrrole by Dakin–West reaction of alanine und subsequent cyclocondensation with malonodinitrile

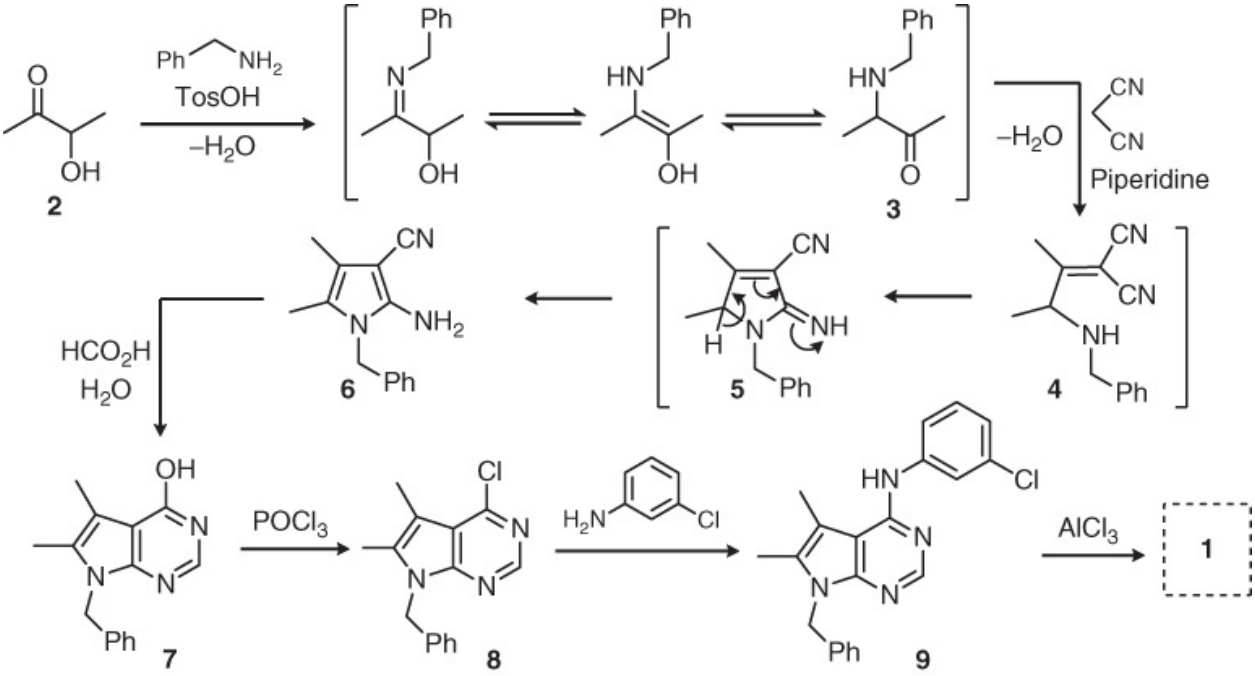
		• Pyrimidine formation by (modified) Remfry–Hull synthesis • Dimroth rearrangement

(a) General

Derivatives of pyrrolo[2,3-*d*]pyrimidine have been shown to bind to the epidermal growth factor receptor (EGF-R), causing inhibition of tyrosine kinase. By variation of the substitution pattern, the selectivity and the biological profile could be optimized, leading to target molecule **1**, which has attained development status as an antitumor agent [1].

To support further biological profiling as well as to supply the drug for initial clinical trials, the first laboratory synthesis had to be elaborated to a technical large-scale process.

The research synthesis was conducted along the following lines:



The α-hydroxy ketone **2** (acyloin) is first condensed with benzylamine in the presence of TosOH, and then with malonodinitrile in the presence of piperidine to give the *N*-benzyl-protected 2-amino-3-cyanopyrrole **6** (via the α-amino ketone **3** and **4** formed by Knoevenagel condensation of **3** with $CH_2(CN)_2$, which cyclizes to give **5**). A pyrimidine ring is then annelated to the pyrrole by a modified Remfry–Hull cyclocondensation [2] with aqueous formic acid (→**7**).

This is followed by replacement of the hydroxy group in **7** by a chloro substituent (**7** → **8**) and an S_NAr displacement of Cl by *m*-chloroaniline (**8** → **9**) to give the pyrrolopyrimidine **9**, *N*-debenzylation of which using $AlCl_3$ yields **1**.

However, several problems arose in scaling up the synthesis, necessitating alteration of the following steps:

1. The synthesis of **1** outlined above employs *N*-benzyl protection of the pyrrole moiety. However, removal of the benzyl group turned out to be technically difficult because of the requirement of a large excess of $AlCl_3$.
2. The pyrimidine formation in boiling formic acid raised safety concerns and also resulted in dark coloration of the product, which necessitated a cumbersome purification.
3. Low solubilities of the hydroxy and chloropyrimidine intermediates made it necessary to work in dilute solutions and to use a large excess of $POCl_3$.

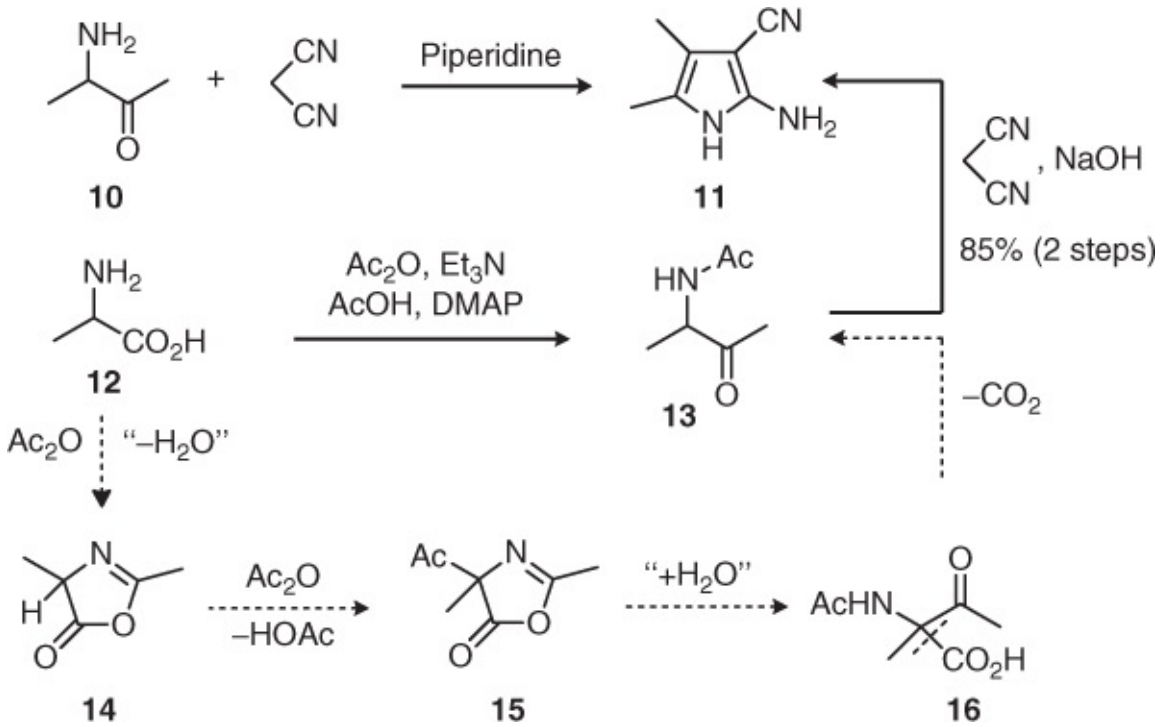
Therefore, for the technical synthesis of **1**, a slightly different approach has been developed.

1. It turned out to be favorable to still use a 2-amino-3-cyanopyrrole as key intermediate, but in the N-unprotected form **11**.
2. A simple one-step synthesis of **11** is known [3]; moreover, **11** is sufficiently stable to be handled.
3. For the formation of the pyrimidine moiety in **1**, formic acid was replaced by ethyl orthoformate as a suitable formic acid derivative.

The improved procedure [1] is presented in Section (b).

(b) Synthesis of 1

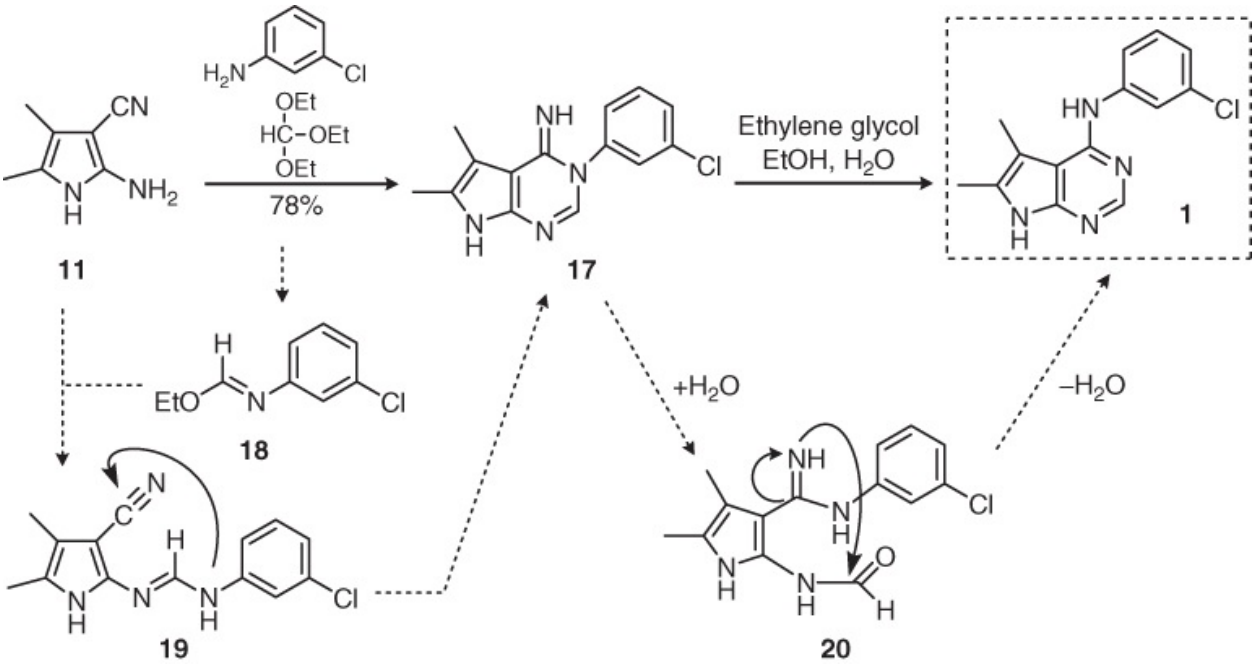
The key intermediate 2-amino-3-cyano-4,5-dimethylpyrrole (**11**) can be prepared [3] by cyclocondensation of 3-amino-2-butanone (**10**) and malonodinitrile in the presence of a base.



However, amino ketone **10** is unstable, and therefore it is replaced by the *N*-acetyl amino derivative **13**. The preparation of **13** by a Dakin–West reaction [4] of *rac*-alanine (**12**) can be efficiently combined with the reaction with malonodinitrile in a one-pot multicomponent process (MCR [5]) to afford the pyrrole **11** in high yield.

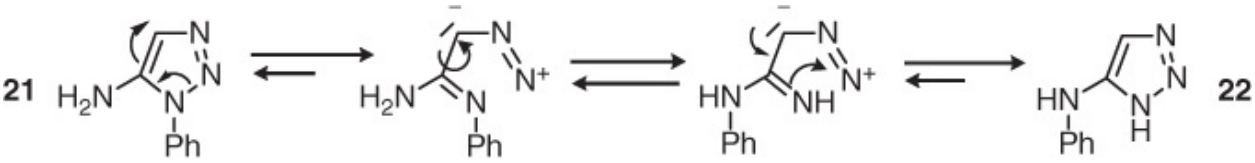
In the Dakin–West reaction, α-acylamino ketones (e.g., **13**) are produced from α-amino acids and acid anhydrides. As mechanistic investigations [6] have shown, azlactones (e.g., **14**) are formed initially, which subsequently undergo C-acylation at C-5 (**14** → **15**), ring-opening hydrolysis to a β-keto acid (**15** → **16**), and decarboxylation (**16** → **13**).

For the annelation of the pyrimidine part to the pyrrole **11**, a one-pot three-component cyclocondensation was developed, in which **11**, triethyl orthoformate (as formic acid equivalent), and *m*-chloroaniline reacted to yield the iminopyrrolopyrimidine **17**:



The formation of **17** can be rationalized by a domino process [7], in which an imidate **18** is first formed from the orthoester and *m*-chloroaniline; by reaction with the amino function of pyrrole **11** and prototropy, the imidate **18** is transformed into the amidine **19**, which cyclizes by intramolecular addition of the NH group to the nitrile function. Finally, the formed 4-imino-3-arylpyrimidine **17** isomerizes to **1** containing a 4-aminoaryl moiety on heating it in an ethylene glycol/H_2O mixture. The isomerization **17** → **1**, which can be referred to as a ***Dimroth-type rearrangement***, is not truly a rearrangement, but rather a hydrolysis – addition of H_2O and ring opening – to give the amidine **20**, which undergoes recyclization by addition of the imino group to the formyl group followed by elimination of water.

In general, in Dimroth rearrangements [8], isomerizing interconversions of heterocycles take place by ring opening and recyclization, leading to an exchange of an “inner” with an “outer” heteroatom. Another instructive example is the thermal rearrangement of 5-amino-1-phenyl-1,2,3-triazole (**21**) to 5-phenylamino-1,2,3-triazole (**22**):

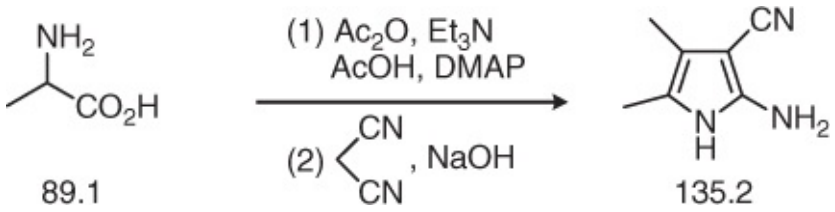


The new procedure led to an improvement in the preparation of **1** from the initial five-step laboratory synthesis to a three-step synthesis using multicomponent

domino processes to give **1** in 61% overall yield (based on *rac*-alanine (**12**)). Most importantly, the new approach could be employed on a large scale.

(c) Experimental Procedures for the Synthesis of 1

3.4.2.1	**	**2-Amino-3-cyano-4,5-dimethylpyrrole** [1]



A mixture of acetic anhydride (16.9 g, 165 mmol), acetic acid (2.26 g, 37.6 mmol), triethylamine (19.0 g, 188 mmol), and 4-(dimethylamino)pyridine (0.10 g, 0.75 mmol) is heated to 50 °C. Then D,L-alanine (6.79 g, 76.2 mmol) is added in small portions over 4 h with stirring, keeping the reaction temperature between 45 and 55 °C; stirring of the red-colored mixture is continued for 8 h at 50 °C.

Acetic anhydride, acetic acid, and triethylamine are then distilled off (15–20 mbar), gradually increasing the bath temperature up to 100 °C. The residue is cooled to room temperature and diluted with water (40 ml). Malonodinitrile (4.71 g, 71.3 mmol) is added, and the mixture is slowly poured into 30% aqueous NaOH solution (25 ml), keeping the temperature below 60 °C.

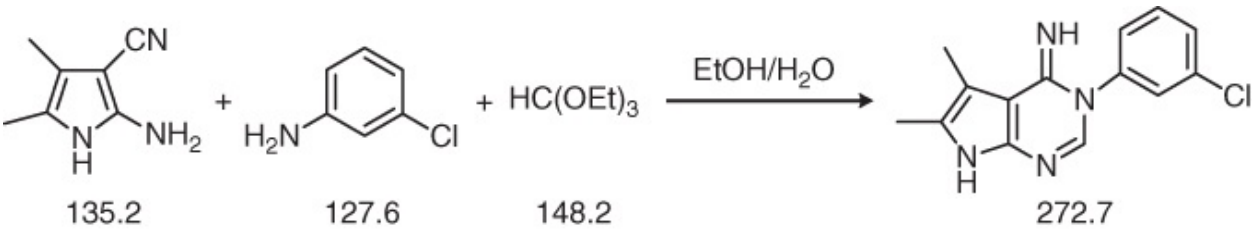
The mixture is cooled to 0 °C and the orange precipitate formed is filtered off, washed with water (45 ml), and dried *in vacuo* to give the pyrrole as a beige solid: 6.65 g (66%), mp 162–164 °C.

FT-IR (solid): $\tilde{\nu}$ (cm^{-1}) = 3408, 3279, 2188, 1636, 1581, 1498, 1440.

^{1}H NMR (300 MHz, [D_6]DMSO): δ (ppm) = 9.78 (s, 1H, NH), 5.30 (s, 2H, NH_2), 1.90 (s, 3H, CH_3), 1.81 (s, 3H, CH_3).

^{13}C NMR (75 MHz, [D_6]DMSO): δ (ppm) = 146.3 (C-2), 118.7, 115.0 (C-4, C-5), 111.0 (CN), 71.1 (C-3), 10.1, 9.4 (2 × CH_3).

3.4.2.2	**	**3-(3-Chlorophenyl)-5,6-dimethyl-4*H*-pyrrolo[2,3-*d*]pyrimidine-4-imine** [1]



A solution of triethyl orthoformate (2.34 g, 16.5 mmol) and 3-chloroaniline (2.68 g, 21.0 mmol) in anhydrous EtOH (15 ml) is acidified to pH 5–5.5 by adding 2–3 drops of acetic acid. The mixture is then heated to 50 °C, and aminocyanopyrrole **3.4.2.1** (2.03 g, 15.0 mmol) is added in small portions over 4 h, keeping the temperature at 45–50 °C. The mixture is then kept at 50 °C for a further 4 h and thereafter is left at room temperature for 8 h.

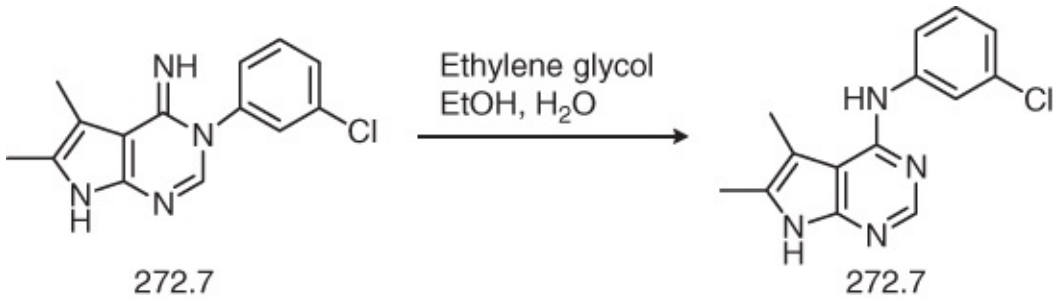
Water (1.5 ml) is then added, and the mixture is cooled to 0 °C and kept at this temperature for 30 min. The precipitate formed is filtered off, washed with EtOH/H_2O (4 : 1, 150 ml), and dried *in vacuo* to yield the pyrimidine imine as a yellow solid: 2.32 g (57%), mp 150–152 °C.

FT-IR (solid): $\tilde{\nu}$ (cm^{-1}) = 3259, 2201, 1664, 1594, 1523, 1499, 1328, 1285.

^{1}H NMR (300 MHz, [D_6]DMSO): δ (ppm) = 10.92 (s, 1H, NH), 10.21 (s, 1H, NH), 8.53 (s, 1H, 2-H), 7.33 to 7.02 (m, 4H, Ar–H), 2.05 (s, 3H, CH_3), 1.93 (s, 3H, CH_3).

^{13}C NMR (75 MHz, [D_6]DMSO): δ (ppm) = 147.8, 145.0, 141.7, 133.7, 130.8, 121.7, 120.2, 118.0, 113.8 (12 × Ar–C), 10.3, 9.4 (2 × CH_3).

3.4.2.3	*	**4-(3-Chlorophenyl)-5,6-dimethyl-7*H*-pyrrolo[2,3-*d*]pyrimidine (EGF-R-pyrrolo[2,3-*d*]pyrimidine)** [1]



A suspension of the pyrrolopyrimidine imine **3.4.2.2** (1.91 g, 7.00 mmol) in H_2O

(5 ml), EtOH (10 ml), and ethylene glycol (10 ml) is heated to 95 °C for 4 h.

After cooling the mixture to room temperature over 60 min, the precipitate formed is collected by filtration, washed with H_2O (40 ml), and dried *in vacuo* at 50 °C to yield the pyrrolopyrimidine as a yellow solid: 1.57 g (83%), mp 240–242 °C.

FT-IR (solid): $\tilde{\nu}$ (cm^{-1}) = 3445, 1607, 1595, 1447.

^{1}H NMR (300 MHz, [D_6]DMSO): δ (ppm) = 11.48 (s, 1H, NH), 8.18 (s, 1H, NH), 8.11 (s, 1H), 7.93 (s, 1H), 7.67 (d, *J* = 8.2 Hz, 1H, Ar–H), 7.30 (t, *J* = 8.2 Hz, 1H, Ar–H), 7.01 (d, *J* = 8.2 Hz, 1H, Ar–H), 2.39 (s, 3H, CH_3), 2.26 (s, 3H, CH_3).

^{13}C NMR (75 MHz, [D_6]DMSO): δ (ppm) = 152.6, 150.7, 149.3, 142.1, 132.7, 129.8, 129.3, 121.2, 119.6, 118.8, 104.8, 103.5 (12 × Ar–C), 10.7, 10.3 (2 × CH_3).

References

1. Fischer, R.W. and Misun, M. (2001) *Org. Process Res. Dev.*, **5**, 581–586.

2. Eicher, Th., Hauptmann, S., and Speicher, A. (2012) *The Chemistry of Heterocycles*, 3rd edn, Wiley-VCH Verlag GmbH, Weinheim, p. 468.

3. Gewald, K. (1961) *Z. Chem.*, **1**, 349.

4. Buchanan, G.L. (1988) *Chem. Soc. Rev.*, **17**, 91–109.

5. See: Zhu, J. and Bienayme, H. (2004) *Multicomponent Reactions*, Wiley-VCH Verlag GmbH, Weinheim.

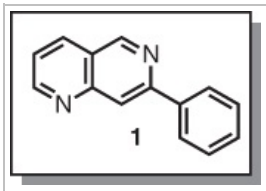
6. (a) Steglich, W., Höfle, G., and Prox, A. (1972) *Chem. Ber.*, **105**, 1718–1725; (b) Steglich, W. and Höfle, G. (1969) *Angew. Chem.*, **81**, 1001; *Angew. Chem., Int. Ed. Engl.*, (1969), **8**, 981.

7. (a) Tietze, L.F. (1996) *Chem. Rev.*, **96**, 115–136;(b) Tietze, L.F., Brasche, G., and Gericke, K. (2006) *Domino Reactions in Organic Synthesis*, Wiley-VCH Verlag GmbH, Weinheim;(c) Tietze, L.F. (ed.) (2014) *Domino Reactions – Concepts for Efficient Organic Synthesis*, Wiley-VCH Verlag GmbH,

Weinheim.

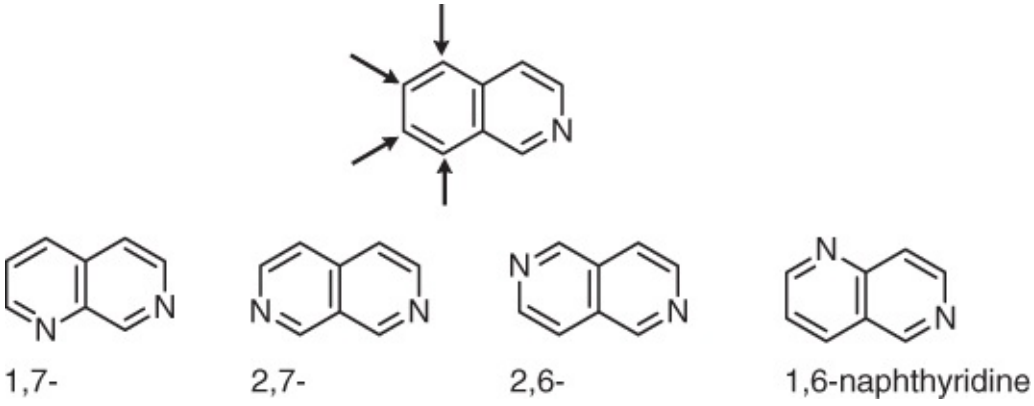
8. Eicher, Th., Hauptmann, S., and Speicher, A. (2012) *The Chemistry of Heterocycles*, 3rd edn, Wiley-VCH Verlag GmbH, Weinheim, p. 261 and 476.

3.4.3 7-Phenyl-1,6-naphthyridine

 1	***Topics:***	• Metalation of 2-bromopyridine • Formylation of a lithiopyridine • Sonogashira coupling • Larock isoquinoline synthesis, application to naphthyridine formation

(a) General

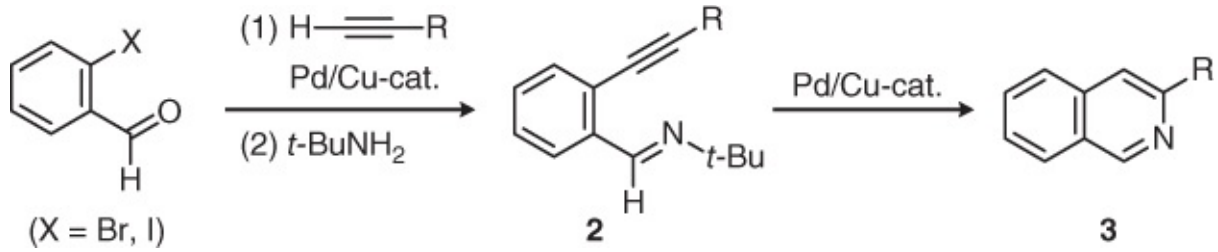
Naphthyridines (pyridopyridines) can be viewed as C–C condensation products of two pyridines. Of the six possible naphthyridines, four relate topologically to isoquinoline by replacement of a CH unit in the benzo part by a nitrogen atom:



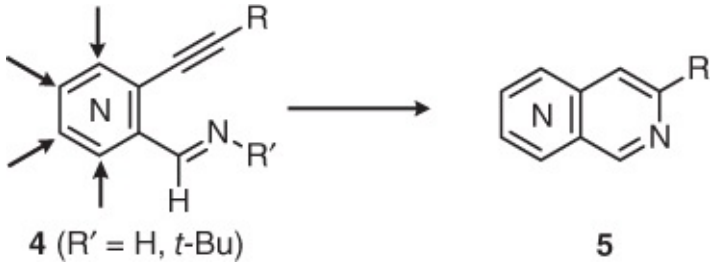
In principle, naphthyridines may be synthesized by applying the methods for quinoline or isoquinoline formation but starting with pyridine derivatives. However, since most of these (such as the Doebner–Miller and Bischler–Napieralski syntheses, cf. Sections 3.5.3 and 3.3.2) proceed through S_EAr cyclizations, adaptation to the electron-deficient pyridine system is limited [1].

In a novel method for isoquinoline synthesis [2], various 2-substituted

isoquinolines **3** have been synthesized by transition-metal-mediated cyclization of (2-ethynyl)benzaldimines **2**, which are easily accessible from 2-halogenobenzaldehydes [3] by Sonogashira cross-coupling reactions (Larock isoquinoline synthesis):



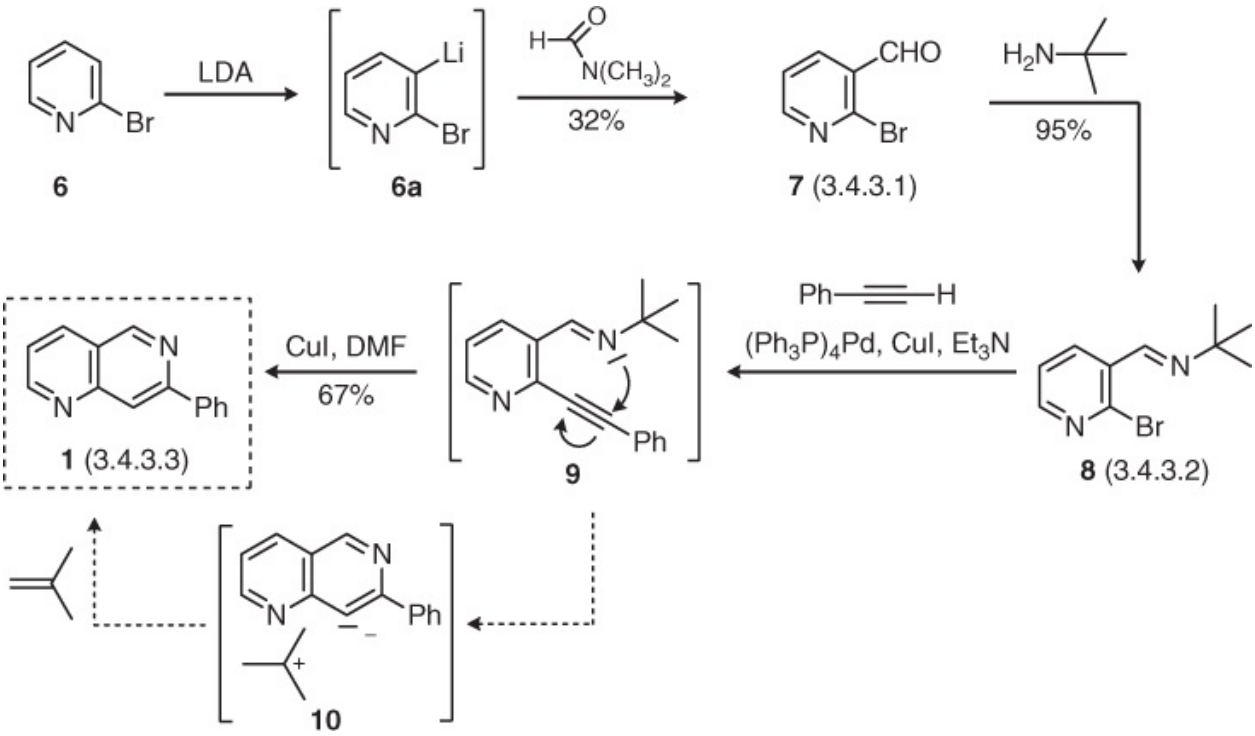
This versatile method (and a modified procedure [4] amenable to **4**, R′ = H) has been successfully applied for the construction of 1,6-, 1,7-, 2,6-, and 2,7-naphthyridines **5** by cyclization of imines derived from ethynylpyridinecarbaldehydes **4**:



Since the 7-substituted 1,6-naphthyridine structure of the target molecule **1** corresponds to **5**, the synthesis of **1** presented in Section (b) follows the described principle [2b].

(b) Synthesis of 1

As key intermediate for the synthesis of **1**, 2-bromopyridine-3-carbaldehyde (**7**) is used, which is prepared [4, 5] by metalation of 2-bromopyridine **6** at the 3-position with LDA [6] to give the 3-lithio-2-bromopyridine (**6a**), which is intercepted with DMF. The aldehyde **7** thus formed is transformed to the imine **8** by condensation with *tert*-butylamine:

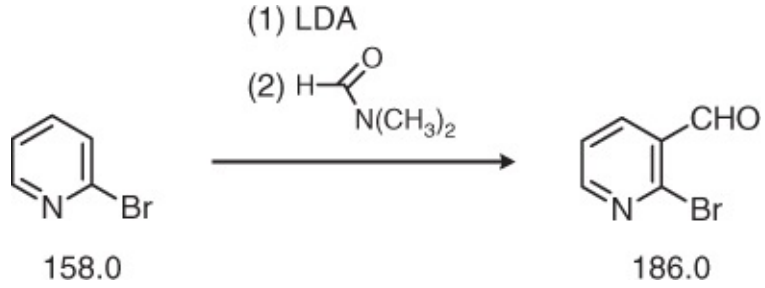


Sonogashira cross-coupling (cf. **1.7.3**) of **8** with phenylacetylene occurs readily by using the palladium catalyst $(Ph_3P)_4Pd$ in the presence of Cu(I) iodide and triethylamine. The thus formed (2-phenyl-ethynyl)pyridine-3-aldimine **9** is not isolated but cleanly undergoes cyclization to give the 7-phenyl-substituted 1,6-naphthyridine **1** upon thermal reaction with Cu(I) iodide in DMF. It can be assumed that the reaction proceeds by intramolecular nucleophilic addition of the imine function to the C≡C triple bond (→**10**) with loss of the *t*Bu group under formation of isobutene (**10**→**1**).

Thus, the target molecule **1** is prepared in a three-step sequence with an overall yield of 20% (based on 2-bromopyridine **6**).

(c) Experimental Procedures for the Synthesis of 1

3.4.3.1	**	**2-Bromopyridine-3-carbaldehyde** [4, 5]



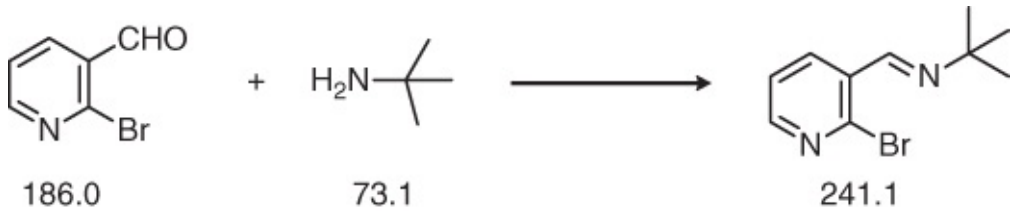
A solution of *n*-Butyllithium (4.30 ml, 1.6 M in hexane, 6.88 mmol) is added by means of a syringe to a solution of diisopropylamine (810 mg, 8.00 mmol) in anhydrous THF (20 ml) under an argon atmosphere at −78 °C, and stirring is continued for 60 min at this temperature. A solution of 2-bromopyridine (950 mg, 6.00 mmol) in anhydrous THF (5 ml) is then added dropwise, and stirring is continued for 4 h at −78 °C. Finally, DMF (2.0 ml, 26.0 mmol) is added at −78 °C. After 30 min at −78 °C, the reaction mixture is allowed to warm to room temperature, with stirring for additional 2 h.

A saturated aqueous NH_4Cl solution (50 ml) and Et_2O (50 ml) are added, the phases are separated, and the aqueous phase is extracted with Et_2O (2 × 40 ml). The combined organic layers are washed with brine (50 ml) and dried over $MgSO_4$, filtered, and the solvent is removed *in vacuo* to afford a brown oil, which is purified by flash chromatography (EtOAc/*n*-hexane, 1 : 10) to give colorless needles; 360 mg (32%), mp 70–71 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 10.36 (d, *J* = 0.8 Hz, 1H, CHO), 8.58 (dd, *J* = 4.6, 2.1 Hz, 1H, 6-H), 8.18 (dd, *J* = 7.6, 2.1 Hz, 1H, 4-H), 7.44 (ddd, *J* = 7.6, 4.6, 0.8 Hz, 1H, 5-H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 191.1 (CHO), 154.5, 145.4, 138.0, 130.6, 123.5 (5 × Ar–C).

3.4.3.2 * *N*-(2-Bromopyridin-3-ylmethylene)-*tert*-butylamine [2b]



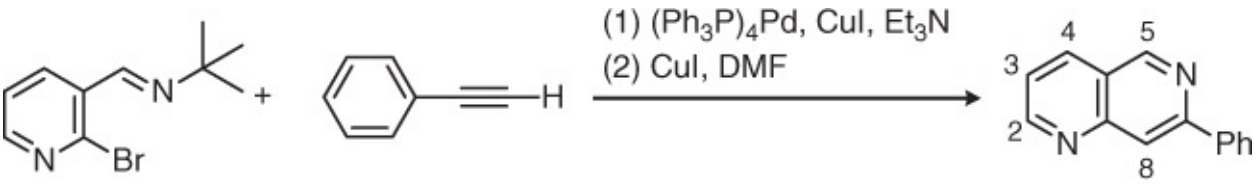
A mixture of the aldehyde **3.4.3.1** (200 mg, 1.08 mmol) and *tert*-butylamine (236 mg, 3.22 mmol) is stirred at room temperature for 15 h.

The excess amine is then removed *in vacuo*, H_2O (3 ml) is added, and the mixture is extracted with Et_2O (3 × 5 ml). The combined organic layers are dried over Na_2SO_4, filtered, and the solvent is removed *in vacuo* to afford the imine as a pale-yellow oil; 248 mg (95%).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.52 (d, *J* = 0.8 Hz, 1H, CH = N), 8.38 (dd, *J* = 4.5, 2.0 Hz, 1H, 6-H), 8.30 (dd, *J* = 7.5, 2.0 Hz, 1H, 4-H), 7.30 (ddd, *J* = 7.5, 4.5, 0.8 Hz, 1H, 5-H), 1.32 (s, 9H, $CO_2C(CH_3)_3$).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 153.2 (CH=N), 151.1, 143.9, 136.9, 132.9, 123.2 (5 × Ar–C), 58.44 ($CO_2C(CH_3)_3$), 29.56 ($CO_2C(CH_3)_3$).

3.4.3.3	**	**7-Phenyl-1,6-naphthyridine** [2b]



A mixture of triethylamine (2 ml), $(Ph_3P)_4Pd$ (11.5 mg, 0.01 mmol, note 1), the imine **3.4.3.2** (121 mg, 0.5 mmol), phenylacetylene (62.0 mg, 0.60 mmol), and CuI (2 mg, 0.01 mmol) is heated at 55 °C for 3 h under an argon atmosphere. The reaction is monitored by TLC (SiO_2; *n*-hexane/EtOAc, note 2).

The reaction mixture is then cooled and diluted with Et_2O (2 ml). The mixture is filtered, the filter cake is washed with Et_2O (5 ml), and the combined filtrates and washings are concentrated under reduced pressure. The residue is dissolved in DMF (5 ml), and CuI (10 mg, 0.05 mmol) is added. The mixture is heated at 100 °C for 15 h under an argon atmosphere.

The reaction mixture is then cooled, diluted with Et_2O (25 ml), washed with saturated aqueous NH_4Cl solution (30 ml), dried over Na_2SO_4, and filtered. The solvent is removed *in vacuo* and the residue is purified by chromatography on silica gel (*n*-hexane/EtOAc, 1 : 1) to afford the naphthyridine as a colorless solid; 70 mg (67%), R_f = 0.21 (*n*-hexane/EtOAc, 1 : 1), mp 135–136 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 9.35 (d, *J* = 0.7 Hz, 1H, 5-H), 9.10 (dd, *J* = 4.3, 1.8 Hz, 1H, 2-H), 8.35 (s_{br}, 1H, 8-H), 8.30 (ddd, *J* = 8.3, 1.8, 0.7 Hz, 1H, 4-H), 8.22–8.15 (m, 2H, Ph–H), 7.53 (m_c, 2H, Ph–H), 7.48 (dd, *J* = 8.3, 4.3 Hz, 1H, 3-H), 7.45 (m_c, 1H, Ph–H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 155.3, 155.1, 152.7, 151.4, 138.9, 135.6, 129.2, 128.9, 127.2, 122.7, 122.2, 117.8 (14 × Ar–C).

Notes:

1. As in the original literature [2b], $(Ph_3P)_2PdCl_2$ can also be used as Pd catalyst.
2. It should be noted that the cyclization may already occur to some extent during the Sonogashira reaction.

References

1. (a) Stanforth, J.P. (1996) in *Comprehensive Heterocyclic Chemistry*, (eds A.R. Katritzky, C.W. Rees, and E.F.V. Scriven), vol. 7, Pergamon, Oxford, p. 527;for a review on advances in the chemistry of naphthyridines, see: (b) Litvinov, V.P. (2006) *Adv. Heterocycl. Chem.*, **91**, 189–300.

2. (a) Roesch, K.R. and Larock, R.C. (1998) *J. Org. Chem.*, **63**, 5306–5307;(b) Roesch, K.R. and Larock, R.C. (2002) *J. Org. Chem.*, **67**, 86–94.

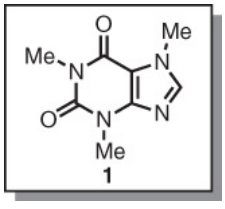
3. It should be mentioned that reaction of *o*-halogenobenzaldehydes and *di*substituted alkynes in the presence of a Pd(0) catalyst leads to 2,3-disubstituted indenones: Larock, R.C. and Doty, M.J. (1993) *J. Org. Chem.*, **58**, 4579–4583.

4. Numata, A., Kondo, Y., and Sakamoto, T. (1999) *Synthesis*, 306–311.

5. Bracher, F. (1993) *J. Heterocycl. Chem.*, **30**, 157–159.

6. For the relative acidities of pyridines, see: Eicher, Th., Hauptmann, S., and Speicher, A. (2012) *The Chemistry of Heterocycles*, 3rd edn, Wiley-VCH Verlag GmbH, Weinheim, p. 353.

3.4.4 Caffeine



1

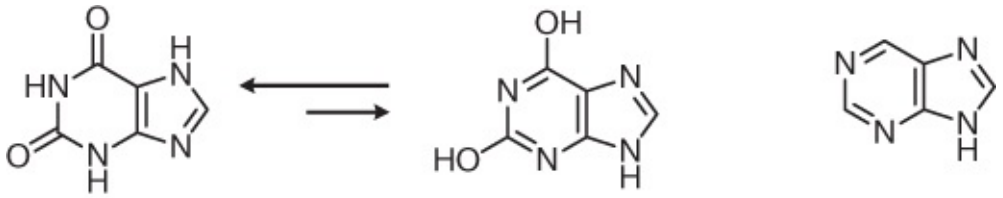
Topics:

- Cyanoacetylation of a urea derivative
- Ring closure of an (*N*-cyanoacetyl)urea to a 4-aminouracil

		• Traube synthesis of a purine derivative according to the Bredereck modification

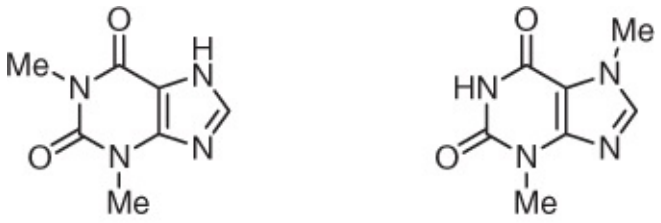
(a) General

Caffeine (**1**, 1,3,7-trimethylxanthine) is a derivative of xanthine (**2**), which exists as an equilibrium between the imide **2a** and the energetically less favored lactim **2b**. The underlying heterocycle is purine (**3**).



2a **2b** **3**

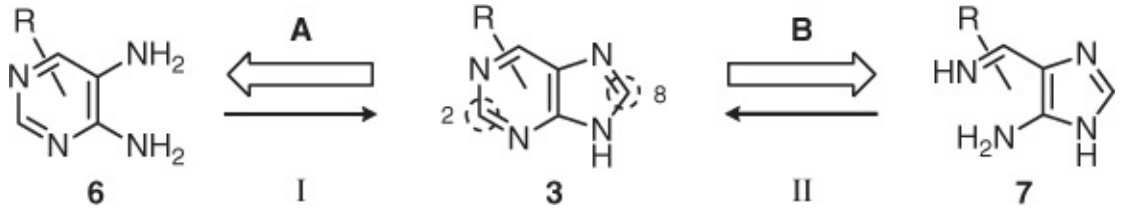
Other alkaloids of the xanthine type are theophylline (**4**) and theobromine (**5**):



4 **5**

Caffeine occurs in coffee beans and tea leaves; it exhibits stimulating effects on the central nervous system and is used therapeutically as an analeptic [1].

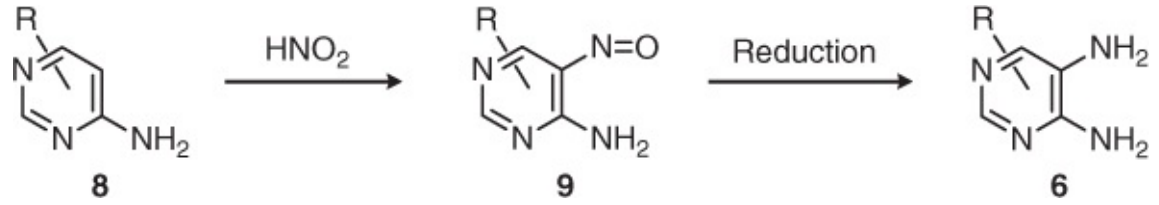
Two different retrosyntheses of purine (**3**), that is, A and B, have to be considered, according to the heterocyclic substrates **6** and **7** used as starting materials.



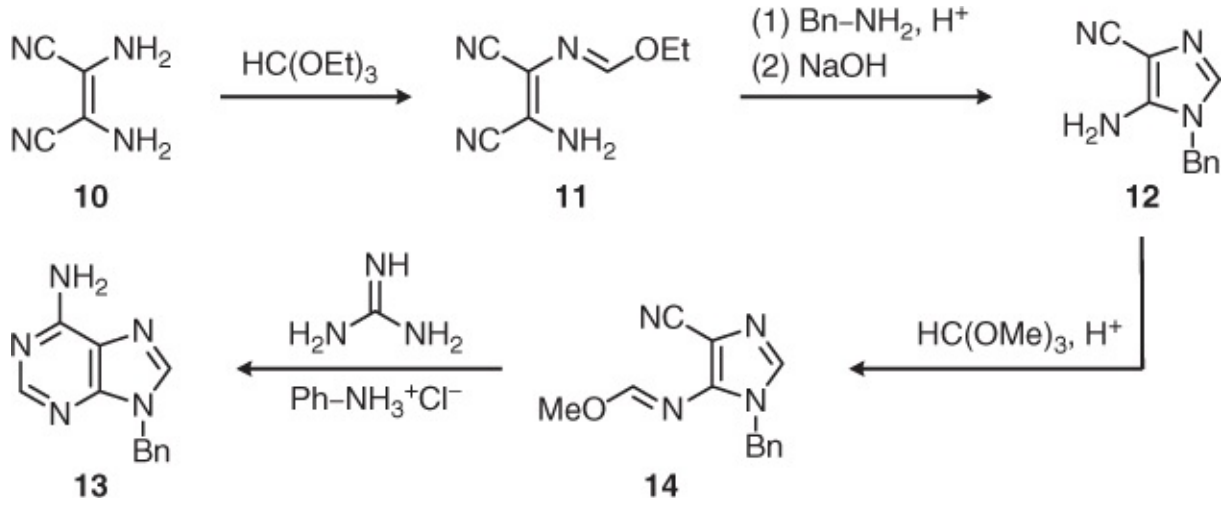
6 I **3** II **7**

It should be stressed that carbon atoms C-2 and C-8 in purine (**3**) are at the oxidation level of formic acid. Thus, the standard method for purine formation is the classical Traube synthesis [2], in which, according to strategy **I**, 4,5-diaminopyrimidines of type **6** are subjected to cyclocondensation with formic acid or a formic acid derivative (formamide, formamidine, orthoformates, etc.).

The 4,5-diaminopyrimidines **6** are generally obtained from 4-aminopyrimidines **8** by nitrosation and reduction of the intermediately formed 5-nitroso compounds **9**:

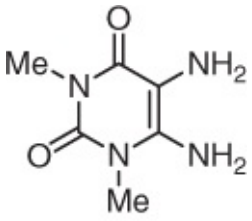


On the other hand, according to strategy **II**, 4,5-disubstituted imidazoles of type **7** can also be used as substrates. However, this approach has only limited scope. A recent and instructive example of the use of strategy **II** is the synthesis of 9-benzyladenine (**13**) [3]:



5-Amino-1-benzyl-4-cyanoimidazole (**12**), readily available from diaminomaleodinitrile (**10**) via the imidate **11** and cyclization with benzylamine, is transformed into the formimidate **14** by reaction with trimethyl orthoformate; **14** undergoes cyclocondensation with guanidine to give the adenine derivative **13**.

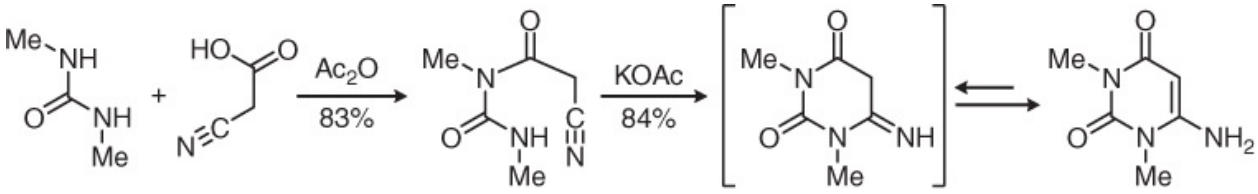
The synthesis of caffeine, however, was performed using the Traube method (**I**), which requires 4,5-diaminouracil **15** as intermediate and which is described in detail in Section (b).



15

(b) Synthesis of 1

N,*N*′-Dimethylurea (**16**) is acylated with cyanoacetic acid in the presence of acetic anhydride, probably via formation of its mixed anhydride with acetic acid. The formed *N*-(cyanoacetyl)urea **17** readily cyclizes in an aqueous medium in the presence of potassium acetate as a base to provide the 4-aminouracil **19**:

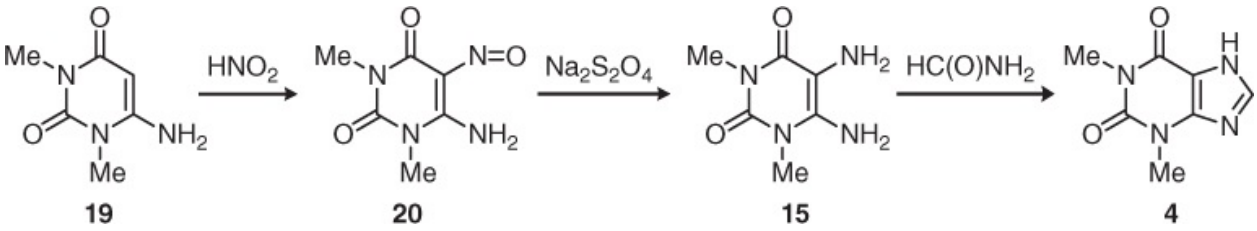


16 17 18 19

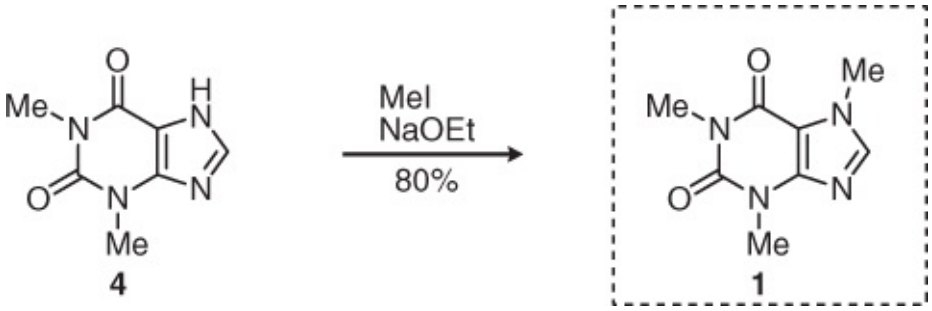
This two-step procedure formally represents the basic principle of the Pinner synthesis of pyrimidine derivatives, which consists of the cyclocondensation of a 1,3-bis-electrophile (here: cyanoacetic acid) with an N–C–N system (here: a urea) (cf. Section 3.3.3).

In the cyclization step, nucleophilic addition of the urea nitrogen to the nitrile function leads to the imine **18** as intermediate, which tautomerizes to **19** containing a more stable enamide moiety.

To attach the imidazole ring to the uracil system, **19** is first nitrosated at the 5-position. The nitroso compound is then reduced, and the 4,5-diaminouracil **15** thus obtained is cyclocondensed with formic acid. This sequence can be carried out in a stepwise manner [4], but from a preparative point of view it is advantageous to perform it as a one-pot procedure (Bredereck protocol [5]), using formamide as solvent for the nitrosation with HNO_2 (→**20**) and reduction with $Na_2S_2O_4$ (→**15**). The formamide used as solvent then reacts with **15** to give the xanthine derivative theophylline (**4**).



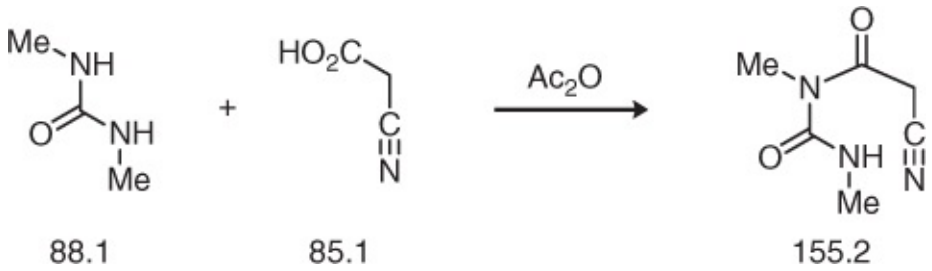
Using this approach, **4** is obtained in 55% yield (over three steps). For the synthesis of caffeine (**1**), theophylline (**4**) is methylated at N-7 by reaction with methyl iodide in the presence of sodium ethoxide.



In this way, the target molecule **1** is synthesized in a four-step sequence with an overall yield of 30% (based on **16**) [6].

(c) Experimental Procedures for the Synthesis of 1

3.4.4.1	*	***N*-Cyanoacetyl-*N,N′*-dimethylurea** [7]



A solution of *N,N′*-dimethylurea (30.0 g, 0.34 mol) and cyanoacetic acid (30.0 g, 0.35 mol) in acetic anhydride (60 ml, note 1) is heated at 100–110 °C (external temperature) for 1.5 h.

The excess acetic anhydride is then distilled off *in vacuo* (∼100 mbar) and the remaining dark-brown oil is dissolved in an EtOH/Et_2O mixture (60 ml/20 ml). After keeping the solution at 5 °C for 2 h (refrigerator), the yellowish crystals that are formed (note 2) are filtered off and washed with Et_2O (2 × 5 ml). The filtrate is concentrated to approximately 40 ml, Et_2O (40 ml) is added, and the solution is kept in a refrigerator for 12 h to give another crop of crystals. The

total yield is 44.0 g (83%), mp 77–79 °C. Recrystallization from acetone/Et_2O (1 : 2) gives yellowish cubes, mp 82–83 °C, R_f = 0.60 (AcOEt).

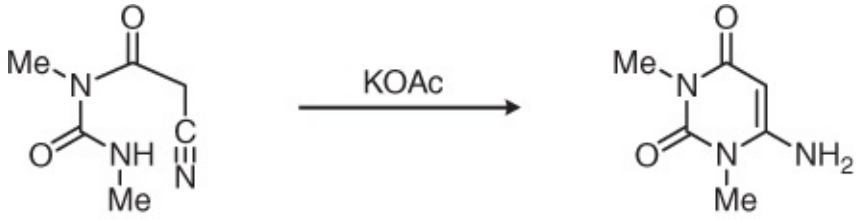
IR (film): $\tilde{\nu}$ (cm^{-1}) = 3300, 2260, 1700, 1670.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.20 (s_{br}, 1H, NH; exchangeable with D_2O), 3.77 (s, 2H, CH_2), 3.25 (s, 3H, NCH_3), 2.77 (d, *J* = 4.5 Hz, 3H, NHC*H*$_3$).

Notes:

1. Acetic anhydride should be freshly distilled before use, bp_{760} 139–140 °C.
2. It is recommended that crystallization be induced by scratching with a glass rod.

3.4.4.2 * 4-Amino-1,3-dimethyluracil [8]



155.2 155.2

Cyanoacetylurea **3.4.4.1** (31.0 g, 0.20 mol) is added portionwise to a stirred solution of potassium acetate (7.50 g, 76.4 mmol) in water (250 ml) at room temperature. The mixture is heated to reflux. The solid goes into solution and then the product begins to crystallize; heating is continued for 30 min.

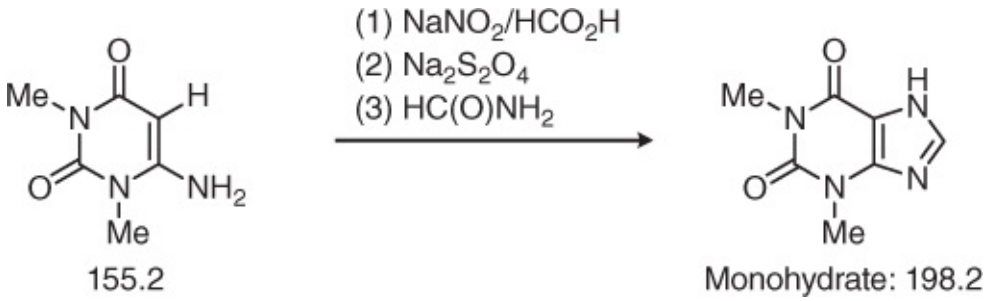
After cooling to room temperature, the mixture is kept in a refrigerator for 12 h. The crystals that are formed are collected by filtration and washed with ice-cold water. The filtrate is concentrated to approximately one-third of its original volume, whereupon another crop of crystals is obtained. The total yield of the aminouracil is 26.0 g (84%) as faintly yellow needles, mp 296–297 °C. Recrystallization from H_2O with the addition of decolorizing charcoal yields colorless needles; mp 299–300 °C, R_f = 0.70 (EtOH).

IR (film): $\tilde{\nu}$ (cm^{-1}) = 3410, 3360, 3240, 1650, 1575.

^{1}H NMR (300 MHz, [D_6]DMSO): δ (ppm) = 6.79 (s, 2H, NH_2; exchangeable with D_2O), 4.73 (s, 1H, 5-H), 3.29, 3.12 (s, 2 × 3H, 2 × NCH_3).

Derivative: **4-Amino-5-nitroso-1,3-dimethyluracil** [4]: Formic acid (2.0 ml) is added dropwise to a stirred solution of uracil **3.4.4.2** (2.00 g, 12.9 mmol) and $NaNO_2$ (0.89 g, 12.9 mmol) in hot H_2O (40 ml). Crystals of the nitroso compound are formed immediately. The mixture is kept at 0 °C for 4 h and then the crystals are collected by filtration, washed with ice-cold water, and dried over P_4O_{10} *in vacuo*; 2.37 g (100%) of red-violet crystals, mp 260–261 °C (dec.), R_f = 0.70 (EtOH).

3.4.4.3	**	**Theophylline (1,3-dimethylxanthine)** [5]



A stirred solution of the aminouracil **3.4.4.2** (23.3 g, 0.15 mol) and sodium nitrite (14.7 g, 0.15 mol) in formamide (120 ml) is heated to 60 °C (internal temperature). With vigorous stirring, formic acid (24.0 ml) is added dropwise over 10 min; the 5-nitroso compound separates as a red-violet precipitate (cf. **3.4.4.2**, *derivative*).

The suspension is then heated to 100 °C and sodium dithionite (4.66 g, 26.8 mmol) is added in small portions over a period of 10 min with stirring; the internal temperature increases to 130–140 °C and a yellow solution is obtained. When the addition of the reducing agent is complete, the reaction mixture is heated to 180–200 °C and kept at this temperature for 30 min.

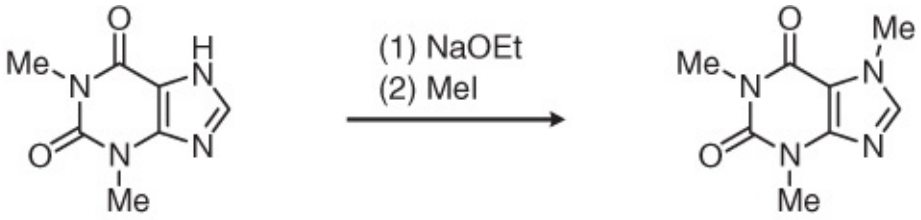
On cooling to room temperature, the product precipitates in part; it is collected by filtration and washed with water (3 × 20 ml). The combined filtrate and washings are diluted with H_2O (approximately 300 ml) and extracted with $CHCl_3$ (3 × 100 ml). The organic extracts are combined, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to obtain a further crop of the product. The

combined fractions of crude product are recrystallized from EtOH/H_2O (1 : 1), and theophylline monohydrate is obtained as a faintly yellow, microcrystalline powder; 16.2 g (55%), mp 272–273 °C, R_f = 0.60 (EtOH).

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3140, 1710, 1665.

^{1}H NMR (300 MHz, [D_6]DMSO): δ (ppm) = 13.35 (s_{br}, 1H, NH; exchangeable with D_2O), 7.73 (s, 1H, 8-H), 3.54, 3.34 (2 × s, 2 × 3H, 2 × NCH_3).

3.4.4.4 ** Caffeine (1,3,7-trimethylxanthine) [4]



Sodium (0.60 g, 26.0 mmol) is added in small pieces to anhydrous EtOH (40 ml). Theophylline monohydrate **3.4.4.3** (3.60 g, 18.2 mmol) is added to the thus obtained solution of NaOEt. The suspension is then heated to reflux with stirring for 1.5 h; after cooling to room temperature, a solution of methyl iodide (1.90 ml, 30.0 mmol; Caution: carcinogenic!) in anhydrous EtOH (10 ml) is added dropwise with stirring over a period of 30 min. During the addition of methyl iodide, the external temperature should be kept at 50–55 °C. A suspension results, which is stirred at 50–55 °C for 3–4 h.

The solvent is then removed *in vacuo*; the colorless residue is taken up in H_2O (50 ml) and the aqueous solution is extracted with CH_2Cl_2 (10 × 50 ml). The combined extracts are dried over $MgSO_4$, and filtered, and the solvent is removed *in vacuo*. Caffeine is obtained as a colorless to faintly ochre-colored microcrystalline powder (without water of crystallization); 2.82 g (80%), mp 227–228 °C. Recrystallization from EtOH/H_2O (1 : 1) raises the mp to 234–235 °C (monohydrate); TLC (SiO_2; EtOAc): R_f = 0.30.

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 1695, 1655.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.50 (s, 1H, 8-H), 3.99 (s, 3H, N-7-CH_3), 3.58, 3.40 (s, 3H, N-1/N-3-CH_3)

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4. Traube, W. (1900) *Ber. Dtsch. Chem. Ges.*, **33**, 3035.

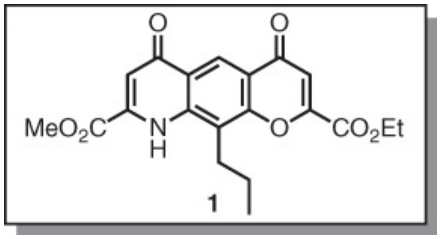
5. Bredereck, H., Gompper, R., Schuh, H.G.V., and Theilig, G. (1959) *Angew. Chem.*, **71**, 753.

6. It should be noted that caffeine has been prepared in a novel six-step sequence starting from uracil: Zajac, M.A., Zakrzewski, A.G., Kowal, M.G., and Narayan, S. (2003) *Synth. Commun.*, **33**, 3291.

7. Baum, F. (1908) *Ber. Dtsch. Chem. Ges.*, **41**, 525.

8. Baum, F. (1908) *Ber. Dtsch. Chem. Ges.*, **41**, 532.

3.4.5 Nedocromil Analogon



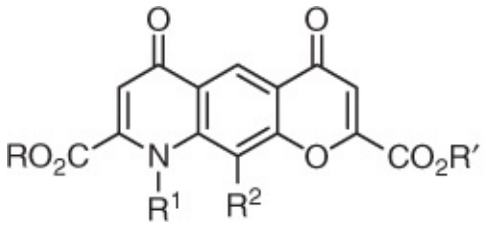
Topics:

- Formation of a chromone derivative
- Formation of a 4-quinolone derivative
- Claisen rearrangement of an aryl allyl ether
- Michael addition to dimethyl

		acetylenedicarboxylate • Catalytic hydrogenation of a C=C bond • Nacylation and deacylation • Ester hydrolysis

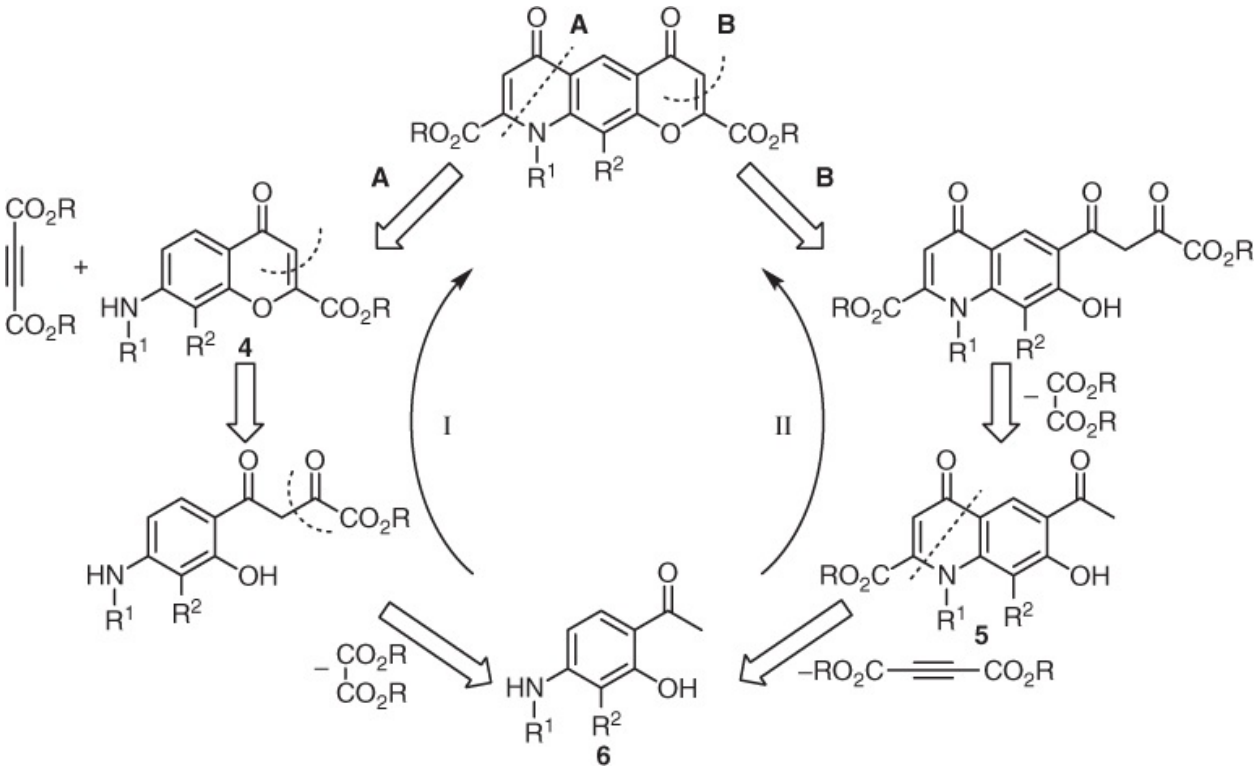
(a) General

A number of pyranoquinoline dicarboxylic acids of types **2**/**3** are pharmaceutically relevant as anti-allergics for the topical treatment of asthma. Among them, nedocromil (**3**, used as its Na salt) shows the strongest therapeutic effects [1]:



1: R^1 = H, R^2 = Pr, R = Me, R′ = Et
2: R^1 = H, R^2 = Pr, R = R′ = H
3: R^1 = Et, R^2 = Pr, R = R′ = H

Retrosynthesis of the linear condensed heterotricyclic compounds **1–3** can be conducted in two directions starting with disconnection either **A** at the quinolone site or **B** at the chromone site, thus proceeding via either the chromone **4** or the quinolone **5**:



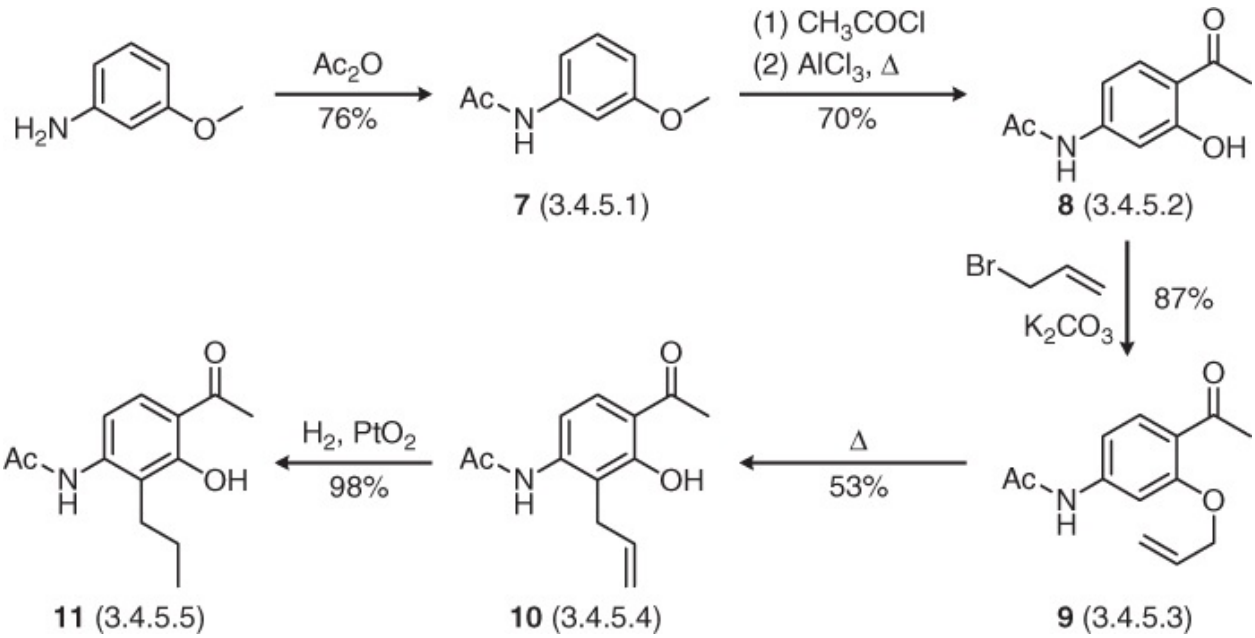
Both retroanalytical pathways lead to the substrate **6**.

The substrate **6** (R^1 = H, R^2 = Pr) required for the synthesis of **1** or **2** – in contrast to the substrate **6** (R^1 = Et, R^2 = Pr) for the synthesis of **3** – is accessible from inexpensive starting materials. Therefore, the preparation of the nedocromil analogon **1** [2] is described here, as presented in Section (b). As can be seen from the retrosynthesis according to strategy **I**, the chromone part of **1** is formed first and this is followed by annelation of the 4-quinolone moiety. This has the advantage that the protection/deprotection steps required can be kept to a minimum.

(b) Synthesis of 1

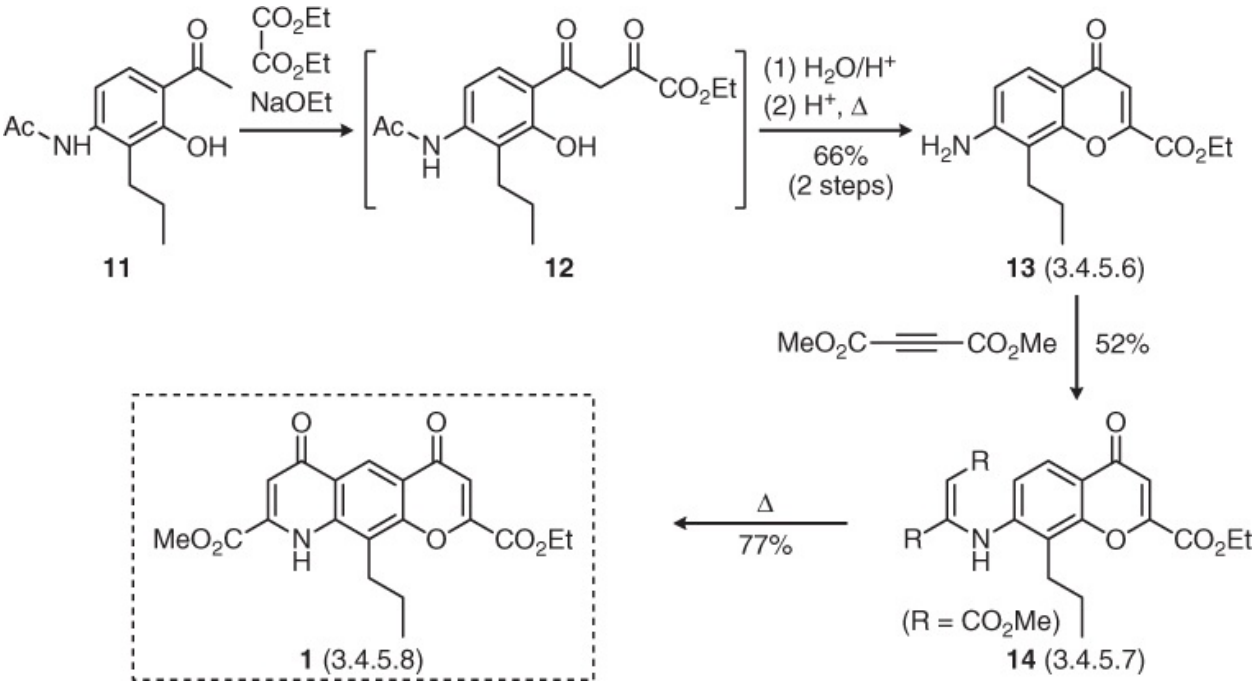
For the formation of chromones and flavones, 2-hydroxyacetophenones are preferentially used as starting materials [3]. Therefore, for the synthesis of **1**, a 2-hydroxyacetophenone of type **6** is employed, which bears a propyl substituent in the 3-position and a protected amino group in the 4-position; it is prepared by conventional means starting from *m*-anisidine. Acetylation of *m*-anisidine using acetic anhydride gives the N-acetylated product **7** [4], which is subjected to $AlCl_3$-catalyzed Friedel–Crafts acylation with acetyl chloride and concomitant cleavage of the methyl ether to yield 4-acetylamino-2-hydroxyacetophenone (**8**) [5]. The phenolic OH group in **8** is then transformed to the *O*-allyl ether **9**, which

isomerizes to the C-3-allyl phenol **10** upon thermolysis by [3,3]-sigmatropic Claisen rearrangement [6]. Finally, the 3-allyl group is subjected to catalytic hydrogenation to produce the desired 4-acetylamino-2-hydroxy-3-propylacetophenone (**11**):

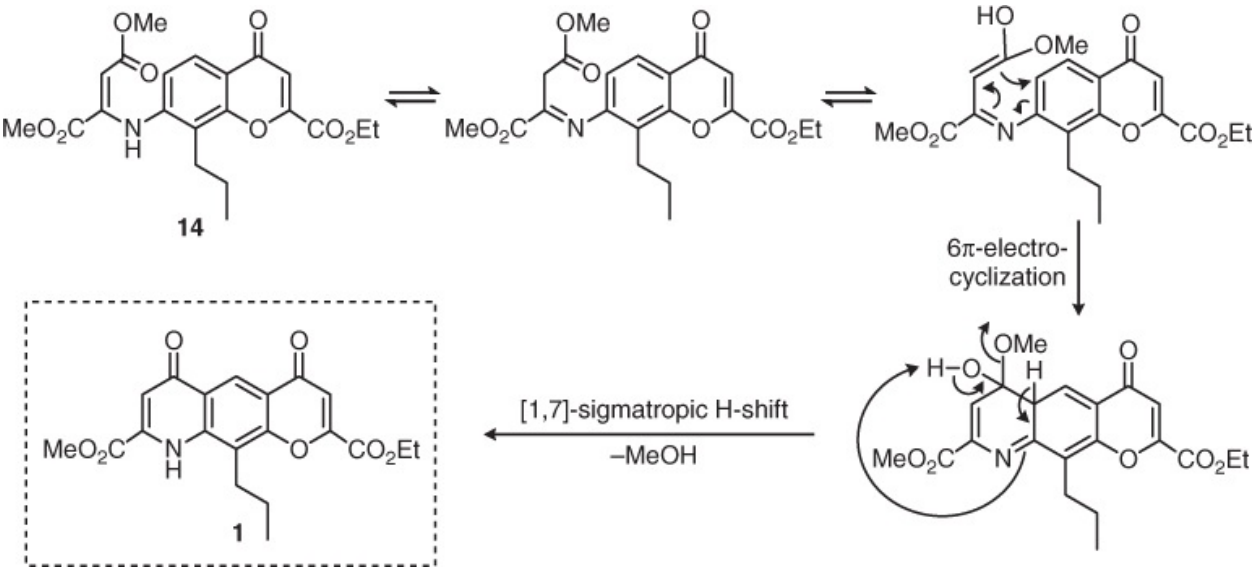


For the formation of the chromone moiety, the 2-hydroxyacetophenone **11** is reacted with diethyl oxalate in the presence of sodium ethoxide. The initially formed product of the Claisen condensation, the β-keto ester **12**, is not isolated, but is directly cyclized by treatment with acid to give the chromone carboxylic ester **13**. In addition, the *N*-acetyl group is removed under the reaction conditions.

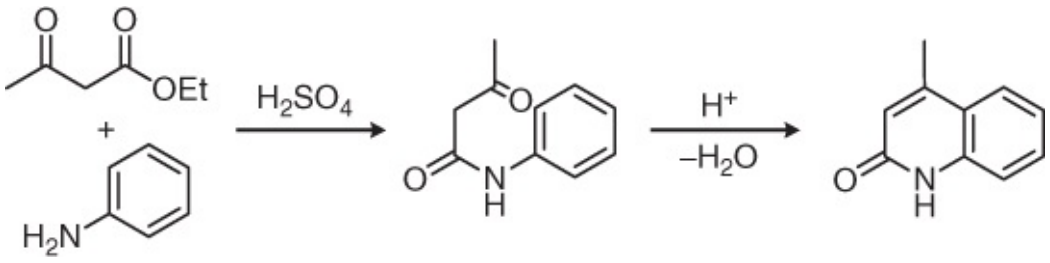
Annelation of the 4-quinolone moiety to the chromonone **13** is achieved in a two-step sequence. First, the β-enamino ester **14** is formed by Michael addition of the NH_2 function in **13** to dimethyl acetylenedicarboxylate, and then **14** is cyclized to afford the 4-quinolone diester **1** by heating it in diphenyl ether.



The thermal cyclization of β-anilinoacrylic esters (like **14**) to give 4-quinolones is referred to as the ***Conrad–Limpach synthesis*** [7]; as a noncatalyzed thermal process, it is likely to proceed as a conrotatory 6π-electrocyclization, as formulated for the transformation **14** → **1**:



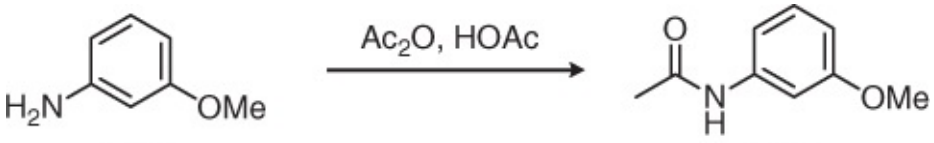
In contrast, the formation of 2-quinolones by cyclization of β-keto anilides is catalyzed by strong acids (Knorr synthesis [7]) and is interpreted as an S_EAr process, as shown in the following example:



Using the described procedure, the target molecule **1** is obtained by a linear nine-step sequence in an overall yield of 6% (based on *m*-anisidine).

(c) Experimental Procedures for the Synthesis of 1

3.4.5.1	*	***N*-(3-Methoxyphenyl)acetamide** [4]



123.2 165.2

Acetic anhydride (30.0 ml, 0.32 mol) (note) is added dropwise to a stirred solution of *m*-anisidine (30.0 g, 0.24 mol) in glacial acetic acid (30 ml) at 0 °C. The solution is stirred for 15 h at room temperature and then poured onto crushed ice (150 g) in water (150 ml).

A precipitate forms, which is collected by filtration, washed with water, and dried *in vacuo* (50 °C/20–30 mbar) over $CaCl_2$ to give a colorless solid; 30.7 g (76%), mp 78–79 °C, TLC (SiO_2; 5% MeOH in CH_2Cl_2): R_f = 0.36.

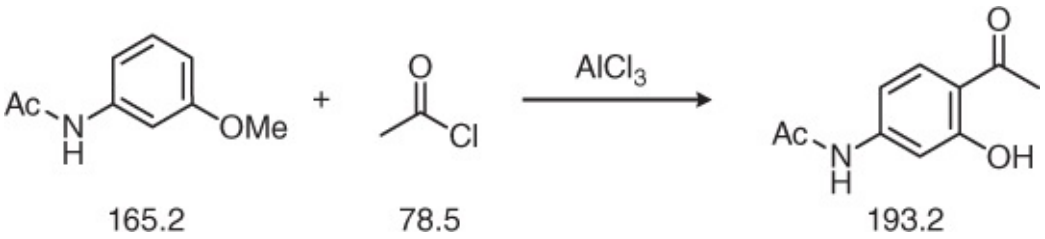
FT-IR (solid): $\tilde{\nu}$ (cm^{-1}) = 3255, 2843, 1662, 1601, 1482, 1415, 1280, 1152, 1048, 858, 761.

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.63 (s_{br}, 1H, NH), 7.27 (m_c, 1H, Ar–H), 7.19 (t, *J* = 8.0 Hz, 1H, Ar–H), 6.98 (dd, *J* = 7.9 Hz, 1H, Ar–H), 6.65 (dd, *J* = 8.2, 2.0 Hz, 1H, Ar–H), 3.77 (s, 3H, OCH_3), 2.15 (s, 3H, CH_3CO).

^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) = 168.6 (CH_3CO), 160.1 (C-3), 139.2 (C-1), 129.6 (C-5), 112.1, 110.0, 105.8 (C-2, C-4, C-6), 55.3 (OCH_3), 24.6 (CH_3CON).

Note: Acetic anhydride has to be distilled before use, bp_{760} 140–141 °C.

3.4.5.2	**	**4-Acetylamino-2-hydroxyacetophenone** [5]



Acetyl chloride (4.72 g, 4.30 ml, 60.0 mmol) (note 1) is added dropwise to a stirred solution of the acetamide **3.4.5.1** (4.00 g, 24.2 mmol) in anhydrous 1,2-dichloroethane (20 ml) under an argon atmosphere. After complete addition, the solution is cooled to 0 °C and, with vigorous stirring, anhydrous $AlCl_3$ (10.2 g, 76.0 mmol) (note 2) is added at such a rate that the internal temperature is kept below 15 °C. After complete addition, the dark reaction mixture is heated under reflux for 2 h (release of HCl gas), and then allowed to cool to room temperature.

The viscous brown oil obtained is poured onto crushed ice (∼100 g), and the resulting mixture is stirred for 30 min. The yellow precipitate is collected, washed with water, dried *in vacuo* (50 °C/20–30 mbar), and recrystallized from cyclohexane/EtOAc (2 : 1, 140 ml). The insoluble material is filtered from the hot suspension; 3.30 g (70%) of a light-yellow crystalline solid, mp 138–140 °C.

FT-IR (solid): $\tilde{\nu}$ (cm^{-1}) = 3179, 3105, 3045, 1602, 1407, 1362, 1250, 788.

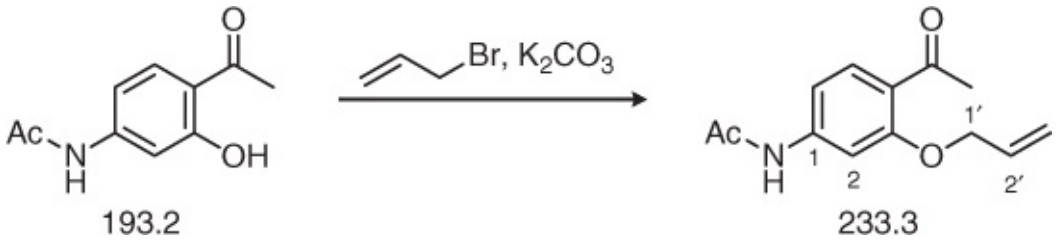
^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 12.47 (s, 1H, OH), 7.67 (d, *J* = 8.5 Hz, 1H, Ar–H), 7.57 (s_{br}, 1H, NH), 7.17 (dd, *J* = 8.5, 1.6 Hz, 1H, Ar–H), 7.08 (d, *J* = 1.6 Hz, 1H, Ar–H), 2.58 (s, 3H, CH_3COAr), 2.21 (s, 3H, CH_3CON).

^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) = 203.0 ($CH_3\mathit{C}OAr$), 168.7 ($CH_3\mathit{C}ON$), 163.8 (C-3), 145.0 (C-1), 132.1 (C-5), 116.2, 110.3, 107.2 (C-2, C-4, C-6), 26.4 ($\mathit{C}H_3COAr$), 24.9 (CH_3CON).

Notes:

1. Acetyl chloride has to be distilled before use, bp_{760} 51–52 °C.
2. It is recommended that the addition is performed under constant inert gas flow.

3.4.5.3	*	***N*-[4-Acetyl-3-(2-propenyloxy)phenyl]acetamide** [2]



193.2 233.3

Allyl bromide (2.14 g, 1.53 ml, 17.7 mmol) is added dropwise to a stirred suspension of the hydroxyacetophenone **3.4.5.2** (2.44 g, 12.6 mmol) and potassium carbonate (note 1) (2.70 g, 19.5 mmol) in anhydrous DMF (25 ml). The yellow reaction mixture is stirred at room temperature for 5 h.

It is then poured into water (100 ml), and the resulting aqueous mixture is extracted with EtOAc (5 × 30 ml). The combined organic extracts are washed with 10% aqueous NaOH (3 × 30 ml) and H_2O (3 × 30 ml), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The yellow residue is dried *in vacuo* (50 °C/20–30 mbar); 2.56 g (87%) (note 2), mp 107–108 °C, TLC (SiO_2; EtOAc/hexane, 4 : 1): R_f = 0.50.

FT-IR (solid): $\tilde{\nu}$ (cm^{-1}) = 3319, 1697, 1586, 1263, 1187, 931, 830.

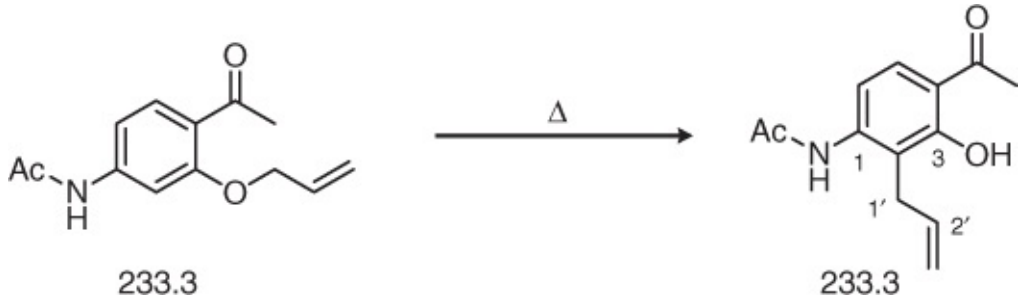
^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.98 (s_{br}, 1H, NH), 7.74–7.75 (m, 2H, 2 × Ar–H), 6.77 (dd, *J* = 8.5, 1.9 Hz, 1H, Ar–H), 6.06 (m_c, 1H, 2′-H), 5.43 (dt, *J* = 17.3, 1.6 Hz, 1H, 3′-H_A), 5.32 (dt, *J* = 10.4, 1.6 Hz, 1H, 3′-H_B), 4.63 (ddd, *J* = 5.7, 1.3, 1.6 Hz, 2H, 1′-H_2), 2.63 (s, 3H, CH_3COAr), 2.20 (s, 3H, CH_3CON).

^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) = 198.5 (CH_3COAr), 169.0 (CH_3CON), 159.5 (C-3), 143.4 (C-1), 132.4 (C-5), 131.4 (C-2′), 123.5 (C-4), 118.6 (C-3′), 111.0, 103.8 (C-2, C-6), 69.6 (C-1′), 32.1 (CH_3COAr), 24.8 (CH_3CON).

Notes:

1. It is recommended that K_2CO_3 is dried for 24 h at 80 °C.
2. The product can be used in the next step without further purification.

3.4.5.4 * *N*-[4-Acetyl-3-hydroxy-2-(2-propenyl)phenyl]acetamide [2]



233.3 233.3

A solution of the aryl allyl ether **3.4.5.3** (12.2 g, 52.3 mmol) in *N*,*N*-dimethylaniline (60 ml) is heated under reflux (230 °C external temperature) for 4 h.

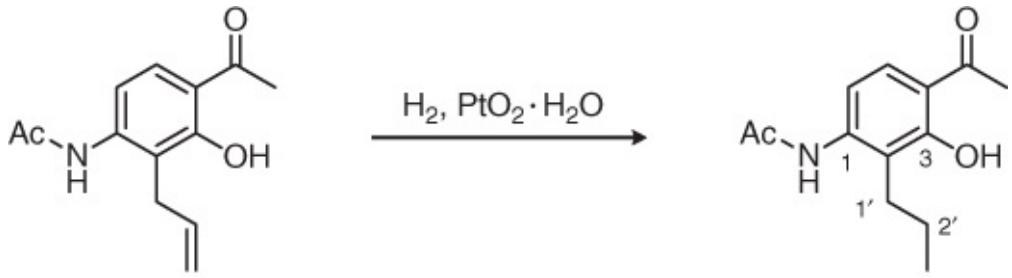
The solution is slowly cooled to ambient temperature, and the precipitate formed is collected by filtration, washed with petroleum ether (bp 40–60 °C, ∼250 ml), and dried *in vacuo* (50 °C/20–30 mbar) to give a crystalline grey solid; 6.49 g (53%), mp 177–179 °C, TLC (SiO_2; EtOAc/hexane, 4 : 1): R_f = 0.66.

FT-IR (solid): $\tilde{\nu}$ (cm^{-1}) = 3256, 3002, 1659, 1625, 1515, 1355, 1276, 810, 668.

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 12.91 (s, 1H, OH), 7.73 (s_{br}, 1H, Ar–H), 7.65 (d, *J* = 8.8 Hz, 1H, Ar–H), 7.50 (s_{br}, 1H, NH), 5.94 (ddt, *J* = 6.0, 17.3, 10.1 Hz, 1H, 2′-H), 5.19 (dt, *J* = 10.1 Hz, 1H, 3′-H_A), 5.13 (dt, *J* = 17.3 Hz, 1H, 3′-H_B), 3.51 (ddd, *J* = 6.0, 1.6 Hz, 2H, 1′-H_2), 2.60 (s, 3H, CH_3COAr), 2.17 (s, 3H, CH_3CON).

^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) = 203.6 (CH_3*C*OAr), 168.4 (CH_3*C*ON), 161.0 (C-3), 143.7 (C-1), 135.5 (C-5), 130.0 (C-2′), 116.2, 116.1 (C-2, C-4, C-3′), 112.1 (C-6), 27.8 (C-1′), 26.5 (*C*H_3COAr), 24.8 (*C*H_3CON).

3.4.5.5 * *N*-[4-Acetyl-3-hydroxy-2-propylphenyl]acetamide [2]



233.3 235.3

The acetophenone **3.4.5.4** (7.32 g, 31.4 mmol) is dissolved in glacial acetic acid (200 ml) and hydrogenated at about 3 bar H_2 pressure and room temperature using $PtO_2 \cdot H_2O$ (∼50 mg) as catalyst. The H_2 uptake is complete after 14 h.

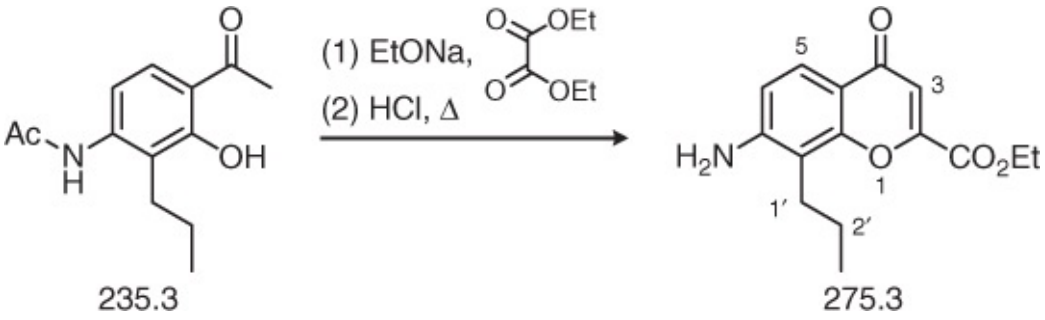
The reaction mixture is then moderately heated to redissolve the suspended product, and the catalyst is removed from the warm solution by filtration. The filtrate is concentrated and the residue is dried *in vacuo* (50 °C/20–30 mbar) over $CaCl_2$; 7.23 g (98%), mp 190–191 °C, TLC (SiO_2; EtOAc/hexane, 4 : 1): R_f = 0.40.

FT-IR (solid): $\tilde{\nu}$ (cm^{-1}) = 3294, 2958, 2871, 1659, 1625, 1512, 1362, 1278, 1110, 807, 666.

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 12.8 (s_{br}, 1H, OH), 7.68 (s_{br}, 1H, Ar–H), 7.59 (d, *J* = 8.8 Hz, 1H, Ar–H), 7.30 (s_{br}, 1H, NH), 2.62 (t, *J* = 7.5 Hz, 2H, 1′-H_2), 2.59 (s, 3H, CH_3COAr), 2.23 (s, 3H, CH_3CON), 1.56 (sextet, *J* = 7.5 Hz, 2H, 2′-H_2), 0.99 (t, *J* = 7.5 Hz, 3H, 3′-H_3).

^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) = 203.7 (CH_3*C*OAr), 168.5 (CH_3*C*ON), 161.4 (C-3), 142.4 C-1), 129.2, 119.4, 116.1, 112.4 (C-2, C-4, C-5, C-6), 26.5 (*C*H_3COAr), 25.5 (*C*H_3CON), 24.9 (C-1′), 21.8 (C-2′), 14.2 (C-3′).

3.4.5.6	**	**Ethyl 7-amino-4-oxo-8-propyl-4*H*-1-benzopyran-2-carboxylate** [2]



Sodium (1.00 g, 4.25 mmol) is added under inert gas atmosphere in small pieces to anhydrous EtOH (25 ml). A suspension of the acetophenone **3.4.5.5** (2.00 g, 8.50 mmol) and diethyl oxalate (3.05 g, 20.8 mmol) in anhydrous EtOH (60 ml) is then added to the thus formed solution of EtONa with intense stirring. The yellow solution is heated under reflux for 2 h and then stirred for 1 h at room temperature.

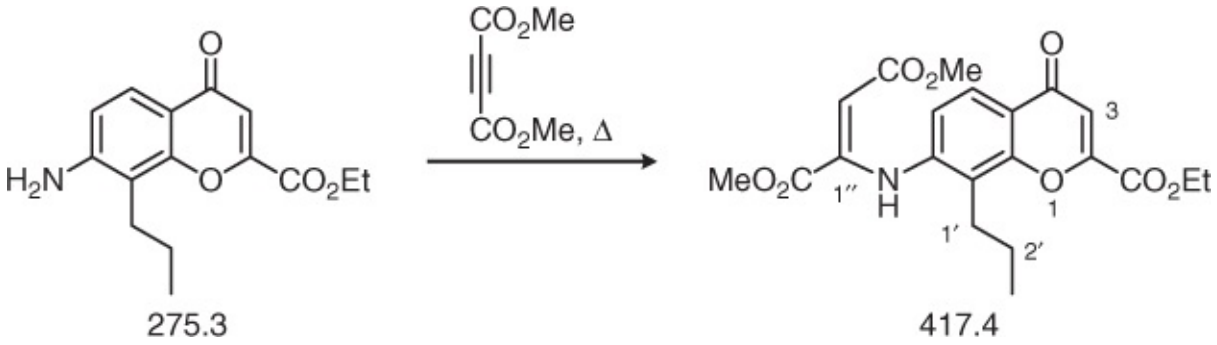
The mixture is poured into water (100 ml), and acidified with 7% aqueous HCl until a yellow precipitate appears. The mixture is extracted with CH_2Cl_2 (5 × 50 ml). The combined extracts are washed with brine (3 × 50 ml), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue is suspended in anhydrous EtOH (30 ml) containing concentrated HCl (0.3 ml). The reaction mixture is heated under reflux for 15 h.

It is then poured into water (100 ml) and the resulting mixture is extracted with EtOAc (5 × 80 ml). The combined organic extracts are washed with water (4 × 80 ml), dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give a dark-colored sticky gum. On triturating with a small amount of petroleum ether (bp 40–60 °C), the product is obtained as a dark-yellow solid; 1.54 g (66%), mp 86–89 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.90 (d, *J* = 8.6 Hz, 1H, Ar–H), 7.04 (s, 1H, Ar–H), 6.87 (d, *J* = 8.6 Hz, 1H, Ar–H), 4.43 (q, *J* = 7.3 Hz, 2H, OCH_2), 2.82 (t, *J* = 7.5 Hz, 2H, 1′-H_2), 1.68 (sextet, *J* = 7.4 Hz, 2H, 2′-H_2), 1.43 (t, *J* = 7.4 Hz, 3H, OCH_2CH_3), 1.03 (t, *J* = 7.4 Hz, 3H, 3′-H_3).

^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) = 178.0 (C-4), 160.8 (CO_2Et), 155.7 (C-2), 151.6, 148.4 (C-7, C-8a), 124.5, 117.4, 115.4, 114.3 (C-3, C-4a, C-5, C-6, C-8), 62.6 (OCH_2CH_3), 25.9 (C-3′), 21.4 (C-2′), 14.2, 14.1 (C-3′, OCH_2CH_3).

3.4.5.7	*	**(*Z*)-Dimethyl *N*-[2-(ethoxycarbonyl)-4-oxo-8-propyl-4*H*-1-benzopyran-7-yl]-2-amino-2-butene-1,4-dioate** [2]



A solution of the amine **3.4.5.6** (1.10 g, 4.00 mmol) and dimethyl acetylenedicarboxylate (0.66 g, 4.70 mmol) in anhydrous EtOH (5 ml) is heated under reflux for 17 h.

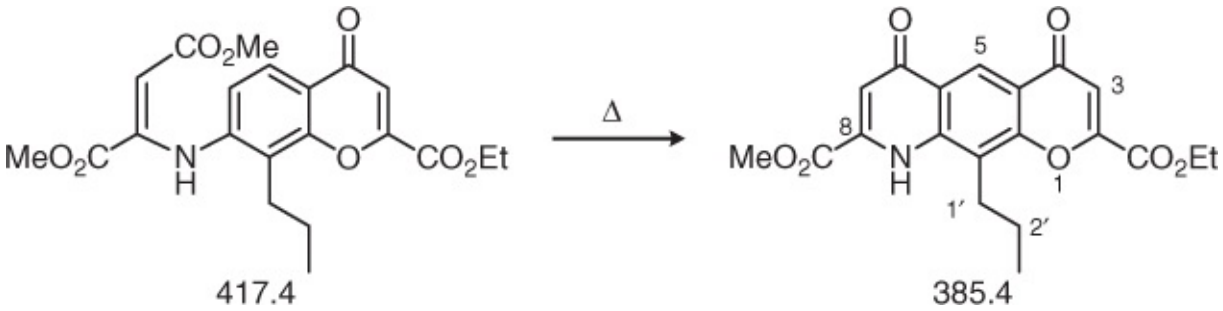
On cooling (refrigerator) the product precipitates; it is collected by filtration and dried *in vacuo* to give a yellow solid; 860 mg (52%), mp 138–139 °C.

FT-IR (solid): $\tilde{\nu}$ (cm^{-1}) = 3438, 3387, 3095, 2960, 1725, 1660, 1642, 1593, 1338.

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 9.86 (s_{br}, 1H, NH), 7.93 (d, *J* = 8.5 Hz, 1H, Ar–H), 7.07 (s, 1H, Ar–H), 6.75 (d, *J* = 8.5 Hz, 1H, Ar–H), 5.67 (s, 1H, 2″-H), 4.43 (q, *J* = 6.9 Hz, 2H, OCH_2CH_3), 3.79, 3.71 (2 × s, 2 × 3H, 2 × CO_2CH_3), 3.00 (t, *J* = 7.3 Hz, 2H, 1′–H_2), 1.77 (sextet, *J* = 7.3 Hz, 2H, 2′–H_2), 1.44 (t, *J* = 6.9 Hz, 3H, OCH_2CH_3). 1.07 (t, *J* = 7.3 Hz, 3H, 3′–H_3).

^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) = 178.2 (C-4), 169.7, 164.2, 160.6 (2 × CO_2CH_3, $CO_2CH_2CH_3$), 155.0, 152.2 (C-2, C-8a), 146.6, 144.4 (C-7, C-1″), 123.6, 122.3, 120.7, 118.5, 114.4 (C-3, C-4a, C-5, C-6, C-8), 97.8 (C-2″), 62.8 ($CO_2CH_2CH_3$) (OCH_2CH_3), 53.0, 51.6 (2 × CO_2CH_3), 26.5 (C-1′), 22.1 (C-2′), 14.1, 14.0 (C-3′, OCH_2CH_3).

3.4.5.8	*	**2-Ethyl 8-methyl 6,9-dihydro-4,6-dioxo-10-propyl-4*H*-pyrano[3,2-*g*]quinoline-2,8-dicarboxylate** [2]



The triester **3.4.5.7** (500 mg, 1.20 mmol) is added in one portion to refluxing diphenyl ether (12.5 ml) with stirring, and the mixture is heated for 10 min.

The solution is cooled, poured into petroleum ether (bp 60–80 °C, 50 ml), and the precipitated product is collected and dried *in vacuo* over P_2O_5.

Recrystallization from EtOAc affords the diester as a yellow solid; 355 mg (77%), mp 177–178 °C.

FT-IR (solid): $\tilde{\nu}$ (cm^{-1}) = 3370, 3094, 2870, 2577, 2465, 1740, 1731, 1637, 1614.

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 9.00 (s, 1H, Ar–H), 8.95 (s_{br}, 1H, NH), 7.05 (s, 1H, Ar–H), 6.87 (s, 1H, Ar–H), 4.49 (q, *J* = 7.3 Hz, 2H, $CO_2CH_2CH_3$), 4.08 (s, 3H, CO_2CH_3), 3.13 (t, *J* = 7.6 Hz, 2H, 1′-H_2), 1.81 (sextet, *J* = 7.6 Hz, 2H, 2′-H_2), 1.47 (t, *J* = 7.3 Hz, 3H, $CO_2CH_2CH_3$), 1.0 (t, *J* = 7.6 Hz, 3H, 3′-H_3).

^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) = 179.5, 178.0 (C-4, C-6), 163.3, 163.3, 155.0, 152.3, 140.6, 136.9 (C-2, C-8, C-9a, C-10a, CO_2Et, CO_2Me), 124.4, 123.6, 120.7, 118.4, 114.0, 111.4 (C-3, C-4a, C-5, C-5a, C-7, C-10), 63.0 ($CO_2CH_2CH_3$), 54.2 (CO_2CH_3), 25.7 (C-3′), 22.1 (C-2′), 14.1 ($CO_2CH_2CH_3$, C-3′).

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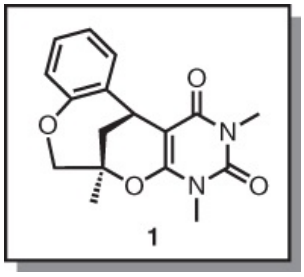
3.4.6 High-Pressure Reaction



Topics:

- Mesylation of a primary homoallylic alcohol
- Nucleophilic substitution (Williamson ether synthesis)
- Knoevenagel condensation
- Intramolecular hetero-Diels–Alder reaction under high pressure

(a) General

The reaction rate and the equilibrium position of many chemical transformations can be strongly enhanced by applying high pressure, usually in the range up to 1.5 GPa (15 kbar) (pressure units: 1 kbar = 100 MPa = 0.1 GPa = 14503.8 psi =986.92 atm) [1]. Of synthetic value is the application of high pressure to transformations with a large negative volume of activation ($\Delta V^{\ddagger}$), since this will

increase the reaction rate, allowing the process to be run at a lower temperature; examples include Diels–Alder reactions, 1,3-dipolar cycloadditions, [2 + 2]-cycloadditions, sigmatropic rearrangements, and radical polymerizations (Table 3.1).

Table 3.1 Typical $\Delta V^{\ddagger}$ values of organic reactions.

	$\Delta V^{\ddagger}$ ($cm^3\ mol^{-1}$)
Free-radical bond cleavage	0 to 13
S_N2 reaction	0 to −20
Formation of acetals	−5 to −10
Claisen, Cope rearrangements	−8 to −15
Free-radical polymerization	−10 to −25
Diels–Alder reaction	−25 to −50
[2 + 2]-Cycloaddition	−35 to −50

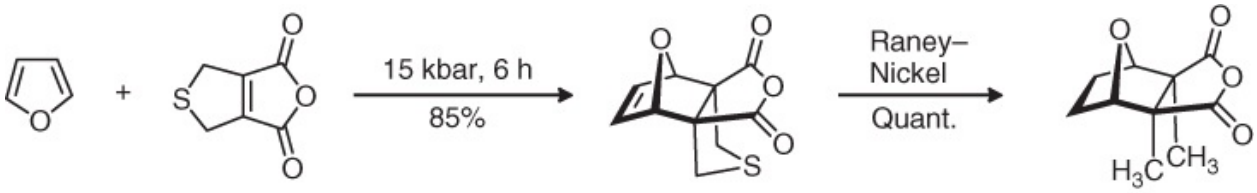
Mathematical correlations between the reaction rate and applied pressure for different values of volume of activation are indicated in Table 3.2.

Table 3.2 Influence of pressure on rates of reaction at 25 °C.

$k(p)/k(0.1\ MPa) = \exp[-\Delta V^{\ddagger}/RT(p-1)]$				
	$\Delta\Delta V^{\ddagger}$ ($cm^3\ mol^{-1}$)			
Pressure (MPa)	+10	−10	−20	−30
100	0.67	1.5	2.2	3.4
300	0.30	3.4	11	38
500	0.13	7.5	56	420
700	0.06	17	280	4 800
1 000	0.02	56	3 200	180 000

Theoretically, a transformation with a $\Delta V^{\ddagger}$ of −30 $cm^3\ mol^{-1}$ can be accelerated by a factor of 2.0×10^6 at 1.5 GPa compared to the reaction at atmospheric pressure; however, the calculated rates are usually accurate for pressures only up to 0.2 GPa. At higher pressures, the influence of increasing viscosity on dynamic effects must be taken into consideration, which would lead to a retardation of any given process [2, 3].

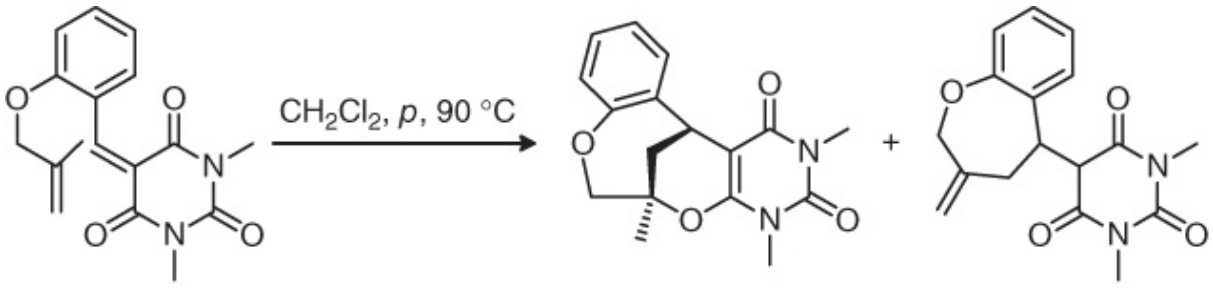
One of the first examples of the usefulness of the application of high pressure was the total synthesis of (±)-cantharidin (**5**, an ingredient of Spanish Fly) by Dauben and coworkers [4], using a Diels–Alder reaction of **2** and **3** to give **4**. The reaction does not take place at ambient pressure. Compound **4** can be transformed into (±)-cantharidin by hydrogenation using Raney nickel as catalyst.



2 **3** **4** **5**

Besides increasing the reaction rate, high pressure can also be employed to improve the chemo, regio, diastereo, and/or enantioselectivity of a chemical transformation [5, 6]. This can be attributed to a temperature effect on transformations for which there is a large difference in reaction enthalpies for the pathways leading to the different isomers. Thus, lowering the temperature usually has a strong effect on the observed selectivity. On the other hand, pure pressure effects on selectivity are also known. The latter are observed for reactions with a pronounced $\Delta\Delta V^{\ddagger}$ value of the different reaction channels leading to the isomers. A $\Delta\Delta V^{\ddagger}$ value of 10 $cm^3\ mol^{-1}$ at 1000 MPa corresponds to an isomer ratio of C_1/C_2 = 1 : 56.6 in the product mixture.

An example of a change in the mechanism of a chemoselective reaction upon the application of high pressure is the transformation of the benzylidene-1,3-dicarbonyl compound **6** into **1** by way of an intramolecular hetero-Diels–Alder reaction and to **7** by way of an intramolecular ene reaction (L. F. Tietze, C. Ott, unpublished results). At 110 °C and 100 MPa in CH_2Cl_2, a ratio of **1**/**7** of 11 : 1 was observed, whereas at 90 °C and 550 MPa the ratio was found to be 76.3 : 1. Thus, higher pressure and lower temperature favor the formation of cycloadduct **1**. The $\Delta\Delta V^{\ddagger}$ value amounts to $-(10.7 \pm 1.9)\ cm^3\ mol^{-1}$ and the $\Delta\Delta H^{\ddagger}$ value to $-(32.4 \pm 7.2)\ kJ\ mol^{-1}$.



6 1 7

$\Delta\Delta V^{\ddagger} = -(10.7 \pm 1.9)$ cm^3 mol^{-1}

$\Delta\Delta H^{\ddagger} = -(32.4 \pm 7.2)$ kJ mol^{-1}

Pressure (MPa)	Selectivity (**1**:**7**)
75	19.5:1
100	23.5:1
320	40.7:1
550	76.3:1

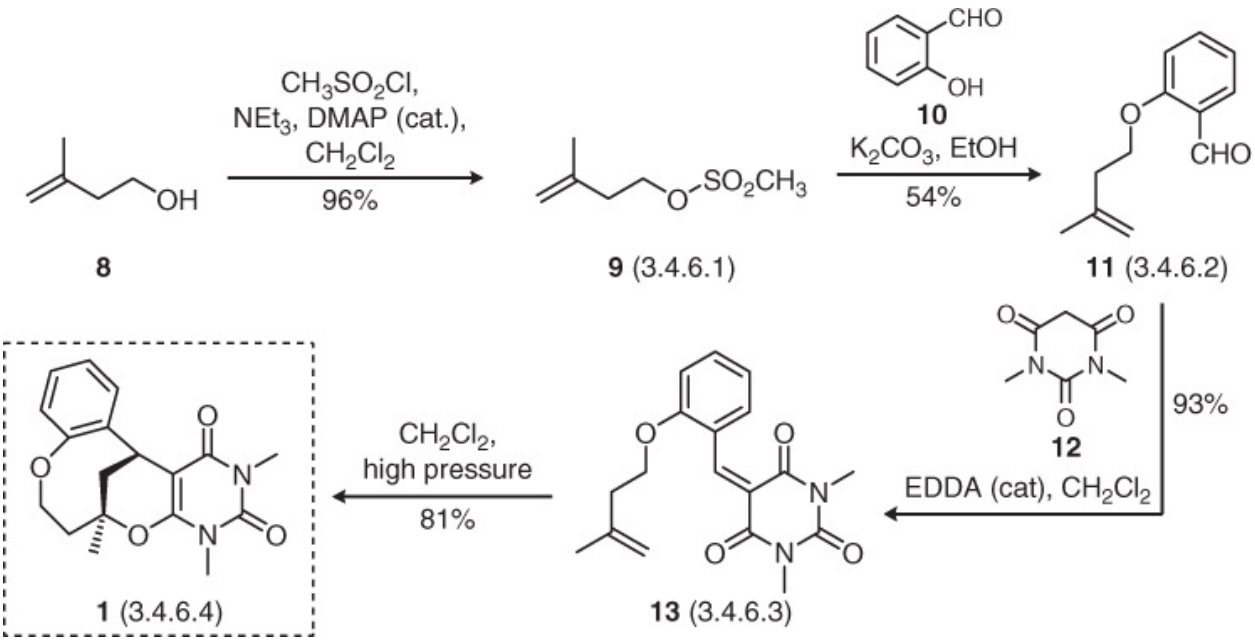
Influence of pressure on the chemoselectivity of the reaction of **6** in CH_2Cl_2 at 90 °C.

The large difference between the volumes of activation for the two reaction pathways can be correlated with the intrinsic contribution of $\Delta V^{\ddagger}$ for the formation of a covalent bond. In the Diels–Alder reaction to give **1**, two single bonds are formed, whereas in the ene reaction to give **7**, only one single bond (a C–H bond is not counted) is produced. It should also be noted that the $\Delta\Delta V^{\ddagger}$ value strongly depends on the solvent.

(b) Synthesis of 1

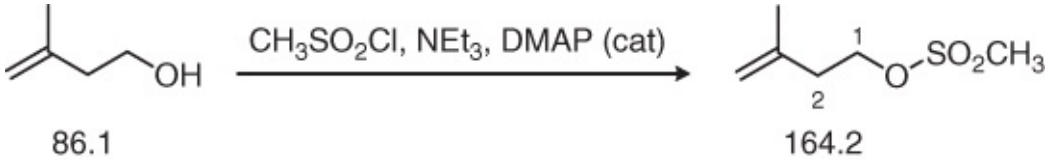
The precursor **13** for the hetero-Diels–Alder reaction is prepared in three steps starting from the commercially available homoallyl alcohol **8**.

Mesylation of **8** gives the sulfonate **9**, which is used for Oalkylation of salicylaldehyde (**10**) to afford the ether **11** in an S_N process. Knoevenagel condensation of **11** with *N*,*N*-dimethylbarbituric acid (**12**) in the presence of a catalytic amount of ethylene diammonium diacetate (EDDA) leads to the benzylidene compound **13**. Intramolecular hetero-Diels–Alder reaction of **13** is carried out under a pressure of 9 kbar and leads to the cycloadduct **1** as the main product.



(c) Experimental Procedures for the Synthesis of 1

3.4.6.1	**	**3-Methyl-3-butenyl-methanesulfonate** [7]



NEt_3 (7.08 g, 70.0 mmol) and a catalytic amount of DMAP are added to a stirred solution of 3-methyl-3-buten-1-ol (5.17 g, 60.0 mmol) in CH_2Cl_2 (120 ml) at 0 °C. Stirring is continued for 15 min, methanesulfonyl chloride (7.56 g, 66.0 mmol) is then added dropwise, and stirring is continued for 2 h at 0 °C.

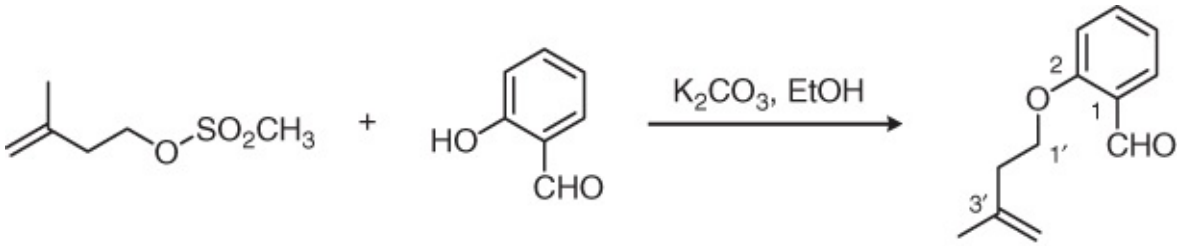
The reaction is then quenched by the addition of H_2O (150 ml); the organic layer is separated and the aqueous phase is extracted with CH_2Cl_2 (3 × 50 ml). The combined organic layers are washed with saturated aqueous NH_4Cl solution (100 ml), saturated aqueous $NaHCO_3$ solution (100 ml), and brine (100 ml), dried over Na_2SO_4, and filtered. The solvent is removed *in vacuo* and the residue is purified by column chromatography (*t*-BuOMe/petroleum ether, 1 : 3) to yield the sulfonate; 9.45 g (96%) (*note*), R_f = 0.25 (*t*-BuOMe/petroleum ether, 1 : 1).

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 2972, 2942, 2920, 1652, 1354, 1174.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 4.85 (m_c, 1H, 4-H), 4.77 (m_c, 1H, 4-H), 4.30 (t, *J* = 7.0 Hz, 2H, 1-H_2), 2.99 (s, 3H, S–CH_3), 2.44 (t, *J* = 7.0 Hz, 2H, 2-H_2), 1.75 (s, 3H, 3-CH_3).

Note: The product MUST be stored in the refrigerator and used within 1 week.

3.4.6.2	**	**2-(3-Methyl-3-butenyloxy)-benzaldehyde** [7]



164.2 122.1 190.2

A stirred suspension of salicylaldehyde (2.50 g, 20.5 mmol), anhydrous K_2CO_3 (3.11 g, 22.5 mmol), and the mesylate **3.4.6.1** (3.03 g, 18.4 mmol) in anhydrous EtOH (40 ml) is heated under reflux for 6 h.

The dark-yellow reaction mixture is then concentrated *in vacuo*, and H_2O (60 ml) is added. The aqueous phase is extracted with Et_2O (3 × 50 ml). The combined organic layers are washed with aqueous NaOH (2 M, 50 ml) and brine (50 ml), dried over Na_2SO_4, filtered, and the solvent is removed *in vacuo* to provide a yellow oil. After column chromatography (*t*-BuOMe/petroleum ether, 1 : 20), the Oalkylated salicylaldehyde is obtained; 1.88 g (54%), R_f = 0.41 (*t*-BuOMe/petroleum ether, 1 : 10).

UV (CH_3CN): λ_{max} (nm) (log ϵ) = 318 (3.6752), 251 (3.9983), 215 (4.3349).

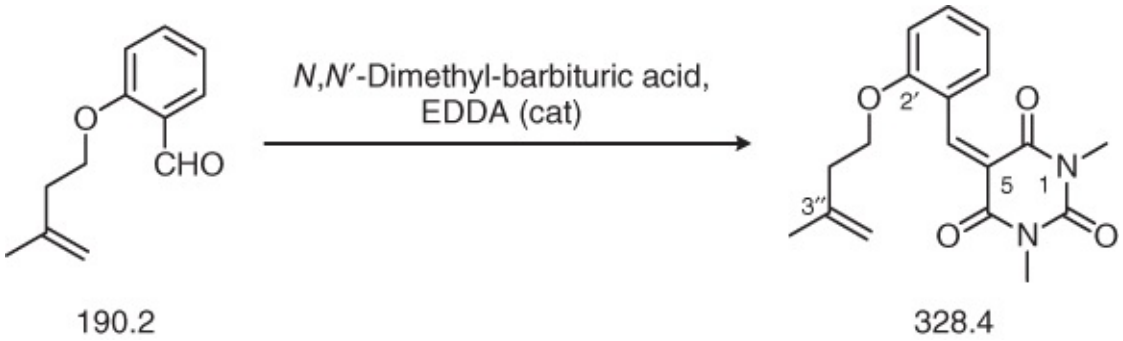
IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3042, 2970, 2940, 2882, 1690, 1600, 1458.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 10.47 (d, *J* = 0.8 Hz, 1H, CHO), 7.81 (dd, *J* = 7.7, 1.5 Hz, 1H, 6-H), 7.55–7.48 (m, 1H, 4-H), 7.03–6.93 (m, 2H, 3-H, 5-H), 4.87–4.77 (m, 2H, 4′-H_2), 4.18 (t, *J* = 6.6 Hz, 2H, 1′-H_2), 2.54 (t, *J* = 6.6 Hz, 2H, 2′-H_2), 1.79 (s, 3H, 3′-CH_3).

MS (EI, 70 eV): *m*/*z* (%) = 190 (11) $[M]^+$, 122 (100) $[M-C_5H_8]^+$, 69 (68)

$[C_5H_9]^+$, 41 (89) $[C_3H_5]^+$.

3.4.6.3	*	**5-[2-(3-Methyl-3-butenyloxy)-benzylidene]-1,3-dimethyl-pyrimidine-2,4,6-trione** [7]



190.2 328.4

The aldehyde **3.4.6.2** (1.00 g, 5.27 mmol) is added to a mixture of *N*,*N*-dimethylbarbituric acid (0.78 g, 5.00 mmol) and EDDA (10.0 mg, 0.056 mmol) in anhydrous CH_2Cl_2 (40 ml), and the reaction mixture is stirred for 4 h at room temperature.

After evaporation of the solvent under reduced pressure, the resulting yellow oil crystallizes at −20 °C. Recrystallization from MeOH affords the pyrimidine-2,4,6-trione as yellow crystals; 1.53 g (93%), mp 128–129 °C, R_f = 0.28 (*t*-BuOMe/petroleum ether, 1 : 3).

UV (CH_3CN): λ_{max} (nm) (log ε) = 373 (4.0078), 315 (3.8353), 245 (4.0054), 221 (4.0440).

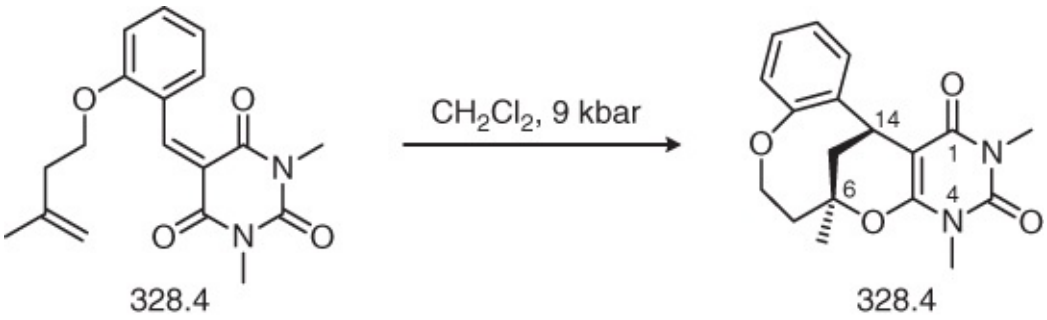
IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3046, 2966, 2942, 1666, 1574, 1462.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.92 (s, 1H, α-H), 8.05 (dd, *J* = 7.9, 1.6 Hz, 1H, 6′-H), 7.48 (m_c, 1H, 4′-H), 7.07–6.91 (m, 2H, 3′-, 5′-H), 4.84 (dd, *J* = 12.0, 1.6 Hz, 2H, 4″-H_2), 4.18 (t, *J* = 6.7 Hz, 2H, 1″-H), 3.43, 3.36 (2 × s, 2 × 3H, 2 × N–CH_3), 2.55 (t, *J* = 6.7 Hz, 2H, 2″-H_2), 1.82 (s, 3H, 3″-CH_3).

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 162.5 (C=O), 160.4 (C=O), 122.3 (C-2′), 119.7 (C-5′), 117.2 (C-5), 112.5 (C-4″), 111.3 (C-3′), 67.1 (C-1″), 37.1 (C-2″), 28.9, 28.3 (2 × N–CH_3), 22.7 (C-3″).

MS (70 eV): *m*/*z* (%) = 328 (10) $[M]^+$, 243 (100) $[M-OC_5H_9]^+$, 41 (43) $[C_3H_5]^+$.

3.4.6.4	**	**(6*R*,14*S*)-(±)-6,14-Methano-2,4,6-trimethyl-6,7,8,14-tetrahydro-4*H*-5,9-dioxa-2,4-diaza-dibenzo[*a*,*d*]cyclodecene-1,3-dione** [7]



A solution of the benzylidene compound **3.4.6.3** (55.0 mg, 0.17 mmol) in CH_2Cl_2 (4 ml) is placed in a Teflon tube, one end of which is closed. The tube is sealed under argon (heating pliers), placed in a high-pressure device, and kept for 20 h at 9 kbar and 70 °C.

The tube is then opened, the solvent is removed *in vacuo*, and the remaining yellow-orange oil is purified by flash chromatography (EtOAc) to yield the title compound; 44.6 mg (81%), mp 160–161 °C, R_f = 0.49 (EtOAc).

UV (CH_3CN): λ_{max} (nm) (log ϵ) = 226 (3.9800).

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3016, 2966, 2930, 1700, 1646, 1634, 1612, 1456.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.51 (d_{br}, *J* = 8.0 Hz, 1H, 13-H), 7.22–7.08 (m, 2H, 11-H, 12-H), 6.90 (dd, *J* = 8.0, 1.5 Hz, 1H, 10-H), 4.25–4.08 (m, 2H, 8-H_{eq}, 14-H), 4.00 (dt, *J* = 12.0, 4.5 Hz, 1H, 8-H_{ax}), 3.41 (s, 3H, N–CH_3), 3.29 (s, 3H, N–CH_3), 2.39 (s_{br}, 1H, 7-H_{eq}), 2.13 (dd, *J* = 15.0, 6.0 Hz, 1H, 15-H), 1.97 (dd, *J* = 10.0, 4.5 Hz, 1H, 7-H_{ax}), 1.88 (dt, *J* = 15.0, 4.5 Hz, 1H, 15-H), 1.56 (s, 3H, 6-CH_3).

^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) = 162.6 (C-1), 156.5 (C-9a), 154.4 (C-4a), 151.1 (C-3), 136.7 (C-13a), 130.9 (C-13), 128.6 (C-11), 125.2 (C-12), 122.8 (C-10), 89.9 (C-14a), 82.2 (C-6), 69.4 (C-8), 41.2 (C-7), 37.7 (C-15), 32.8 (6-CH_3), 31.8 (C-14), 28.6 (N–CH_3), 27.9 (N–CH_3).

MS (70 eV): *m*/*z* (%) = 328 (100) $[M]^+$, 243 (51) $[M-OC_5H_9]^+$, 69 (8) $[C_5H_9]^+$, 41 (10) $[C_3H_5]^+$.

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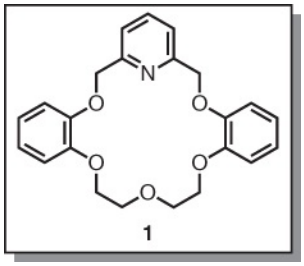
3.5 Other Heterocyclic Systems, Heterocyclic Dyes

3.5.1 Dibenzopyridino[18]crown-6



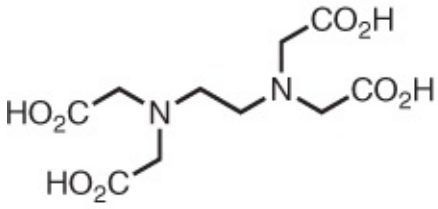
1

Topics:

- Synthesis of a crown ether
- Alkyl chlorides from alcohols and $SOCl_2$
- Monoalkylation of a bisphenol
- Carboxylic esters by alcoholysis of carboxylic acid chlorides
- Reduction of an ester to give a primary alcohol
- Formation of a macrocycle by cycloalkylation of a bisphenol with a bishalide
- Use of the Ziegler–Ruggli high-dilution principle

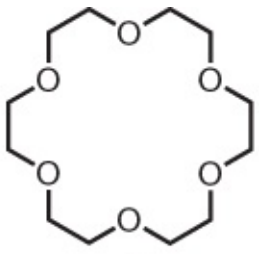
(a) General

Podands, coronands, and cryptands are ring-open, cyclic, and bi(poly)cyclic receptor molecules, respectively (e.g., **2–4**), which bind other molecules or ions by electrostatic, van der Waals, coordinative, or donor–acceptor interactions in a "host–guest" relationship according to basic features of supramolecular chemistry [1]:



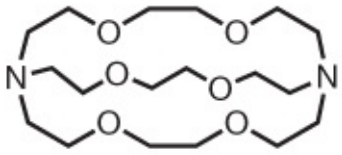
2
EDTA

(a podand)



3
[18]-crown-6

(a coronand)



4
Bicyclo[8.8.8]-1,10-diaza hexaoxahexacosane
(a cryptand)

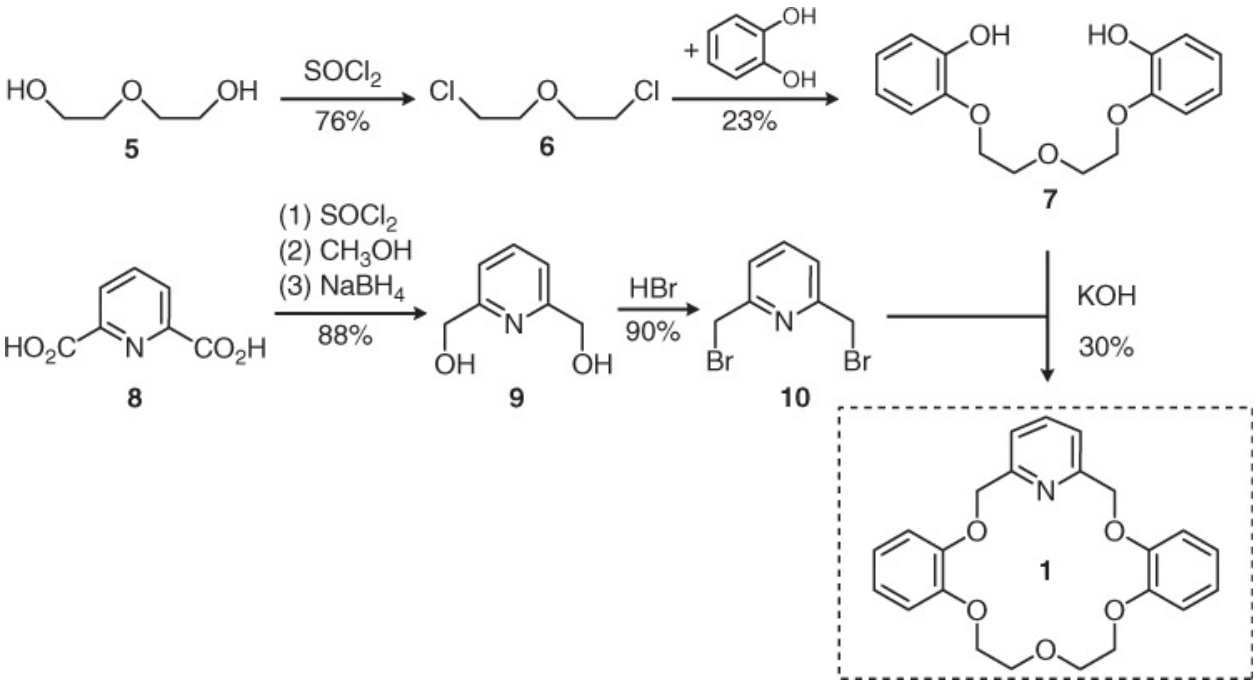
Macrocyclic polyethers of type **3**, usually named *crown ethers* [2], and their

analogs containing sulfur or nitrogen atoms instead of oxygen atoms, exhibit unusual potentiality and specificity in the complexation of cations through ion–dipole interactions. For example, in the presence of the crown ether **3**, $KMnO_4$ shows solubility in benzene due to the formation of a stable **3**·[K^+] complex, thus allowing oxidations with $KMnO_4$ in an organic medium that would otherwise be impossible. Many other applications of crown-ether complexation with cations are known in preparative chemistry, for example, use in phase-transfer catalysis, acceleration of S_N reactions, and enhancement of ester hydrolysis, among others [2].

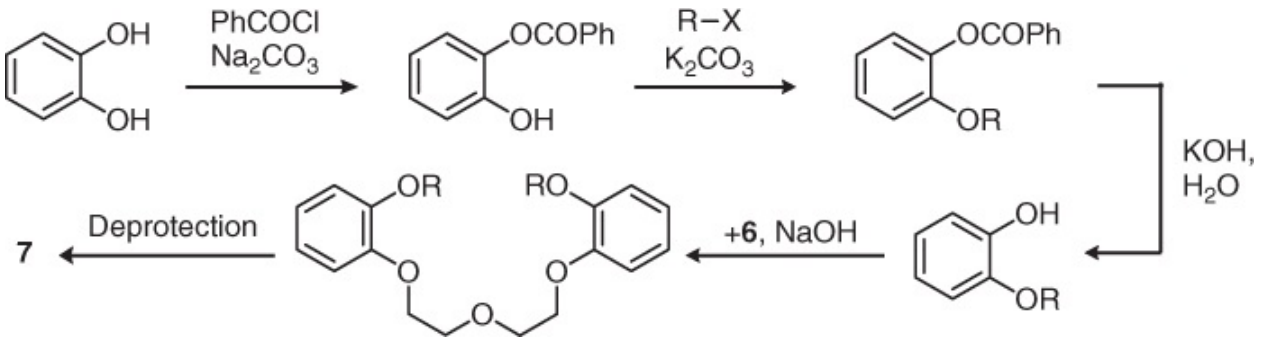
The target molecule **1** is a crown ether in which one oxygen atom is replaced by a nitrogen atom. The compound can be traced back to [18]crown-6 (**3**) by exchanging one CH_2–O–CH_2 moiety by pyridine and two lateral O–CH_2–CH_2–O groups by catechol. Its synthesis utilizing typical reactions of crown ether synthesis is described in detail in Section (b).

(b) Synthesis of 1

For the synthesis of **1**, a convergent approach [3] (F. Vögtle, private communication, 1981) is used. First, the separate synthesis of the two building blocks **7** and **10** is performed. Then, an intramolecular bisalkylation of the heterobenzylic bishalide **10** and the bisphenol **7** is carried out to give **1**, applying the high-dilution principle of Ziegler/Ruggli [4].



Building block **7** is prepared by way of a two-step procedure starting from diethylene glycol (**5**). By reaction with thionyl chloride, the OH groups of **5** are replaced by chloro substituents to yield 1,5-dichloro-3-oxapentane **6**. S_N reactions at both electrophilic sites of **6** with two molecules of catechol then lead to the bisphenol **7**. The yield of the alkylation step **6** → **7** is rather low; however, the substrates for the formation of **7** are inexpensive and the product can be easily separated. It might be possible to improve the yields by the use of monoprotected catechol, but this would prolong the synthesis of **7** by four steps [5]:



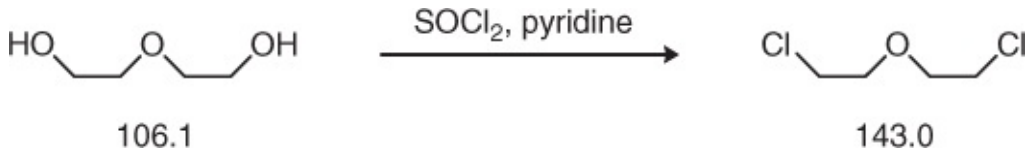
Building block **10** (2,6-bis(bromomethyl)pyridine) is prepared starting from pyridine-2,6-dicarboxylic acid (**8**) by esterification (alcoholysis of the acid chloride of **8**), reduction of the ester with sodium borohydride to 2,6-bis(hydroxymethyl)pyridine (**9**), and reaction of **9** with HBr.

The final step is the combination of the two building blocks **7** and **10** in a cycloalkylation reaction using a benzene/DMF/EtOH/H_2O mixture in the presence of KOH as a base to give the macrocycle **1** in 30% yield after chromatographic purification. The product forms a well-defined crystalline 1 : 1 complex with KSCN, showing K^+ ion specificity, as expected for an analog of the crown ether **3**.

Thus, the synthesis of the target molecule **1** can be performed in six steps, where the building block **7** is obtained in two steps in 17% yield and the building block **10** is obtained in three steps in 72% yield. The combination of **7** and **10** is accomplished in 30% yield.

(c) Experimental Procedures for the Synthesis of 1[4]

3.5.1.1	*	**1,5-Dichloro-3-oxapentane** [3]

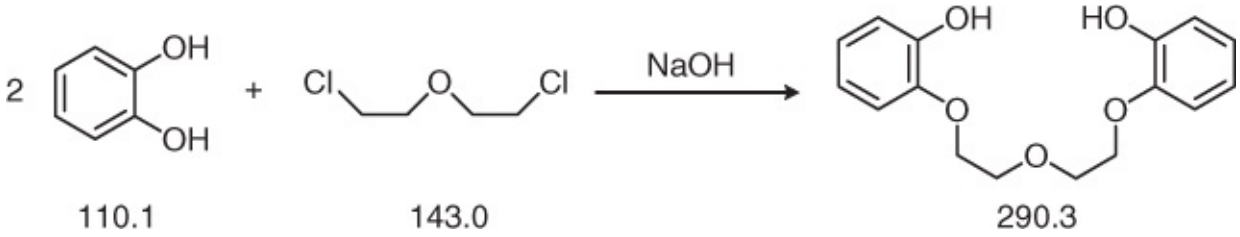


A stirred solution of diethylene glycol (106 g, 1.00 mol), benzene (900 ml; Caution: carcinogenic!), and pyridine (180 ml) is heated to 86 °C. Thionyl chloride (264 g, 1.40 mol, approximately 162 ml) is then added dropwise, and stirring is continued for 16 h at 86 °C.

The solution is then cooled to room temperature, and a mixture of concentrated HCl (50 ml) and H_2O (200 ml) is added dropwise over 15 min. The phases are separated, the aqueous phase is extracted several times with benzene, and the combined organic phases are washed with ice-cold brine, dried over Na_2SO_4, and filtered. The solvent is removed and the residue is distilled *in vacuo* to give the product as a colorless oil; 100 g (70%), bp_{11} 60–62 °C, n^{20}_D = 1.4570.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.81 (dt, *J* = 6.0, 0.9 Hz, 4H, 2 × 2-H_2), 3.66 (dt, *J* = 6.0, 0.9 Hz, 4H, 2 × 1-H_2).

3.5.1.2	*	**1,5-Bis(2-hydroxyphenoxy)-3-oxapentane** [3]

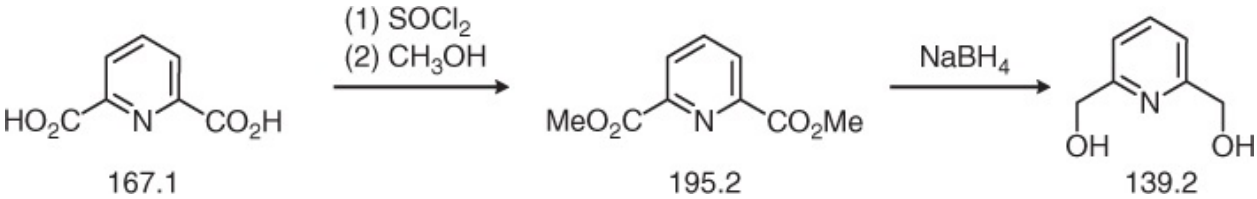


1,5-Dichloro-3-oxapentane **3.5.2.1** (32.8 g, 229 mmol) is added in one portion to a solution of catechol (55.0 g, 500 mol) and NaOH (20.0 g, 500 mol) in water (500 ml) under a nitrogen atmosphere. The biphasic system is vigorously stirred to form an emulsion and then heated under reflux for 24 h with stirring.

The mixture is then acidified with concentrated HCl and concentrated *in vacuo*. The dark-brown, tar-like residue is triturated with hot MeOH (500 ml) and filtered to remove salts. The MeOH extract is concentrated to approximately one-fourth of its original volume, giving an impure precipitate mixed with brown particles. Two recrystallizations of the crude product from MeOH give colorless crystals; 32.0 g (48%), mp 86–88 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.54 (s, 2H, OH), 7.12 to 6.72 (m, 8H, Ar–H), 4.32 to 4.09 (m, 4H, 2 × CH_2), 4.02 to 3.79 (m, 4H, 2 × CH_2).

3.5.1.3 * 2,6-Bis(hydroxymethyl)pyridine [3]



167.1 195.2 139.2

a. A stirred solution of pyridine-2,6-dicarboxylic acid (31.0 g, 186 mmol) in thionyl chloride (200 ml) is heated under reflux for 10 h. Excess $SOCl_2$ is then distilled off, and the residue (acid chloride) is cooled in an ice bath; anhydrous MeOH (250 ml) is added dropwise with stirring. The resulting solution is heated under reflux for 30 min.

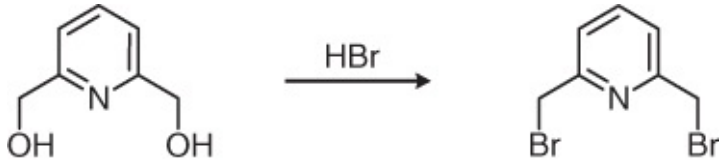
   The MeOH is partially distilled off (150 ml), and the remaining solution is cooled in an ice bath to allow crystallization of the formed methyl diester of pyridine-2,6-dicarboxylic acid. The solid is collected by filtration and washed with ice-cold MeOH; 34.6 g (95%), mp 115–120 °C. The product is sufficiently pure to be used in the next step; the pure product has mp 120–121 °C (from MeOH).

b. Sodium borohydride (26.0 g, 688 mmol) is added portionwise over 15 min to a stirred suspension of the methyl diester prepared in (a) (29.0 g, 149 mmol) in anhydrous EtOH (400 ml) with ice cooling. The mixture is stirred for 1 h at 0 °C; the ice bath is then removed and an exothermic reaction starts, which brings the solution to reflux. The solution is stirred at room temperature for 3 h and heated under reflux for 10 h.

   The solvent is then distilled off *in vacuo*, the residue is dissolved in acetone (100 ml), the solution is filtered, and the filtrate is concentrated *in vacuo*. The residue is taken up in saturated aqueous K_2CO_3 solution (100 ml), and the mixture is heated on a steam bath for 1 h. Continuous extraction of the mixture with chloroform for 10 h followed by evaporation of the solvent *in vacuo* gives 19.3 g (93%) of the diol, mp 112–114 °C (the pure product has mp 114–115 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.71 (t, *J* = 7.6 Hz, 4-H), 7.22 (d, *J* = 6.0 Hz, 2H, 3-H, 5-H), 4.79 (s, 4H, 2 × CH_2), 3.22 (s, 2H, OH).

3.5.1.4 * 2,6-Bis(bromomethyl)pyridine [3]



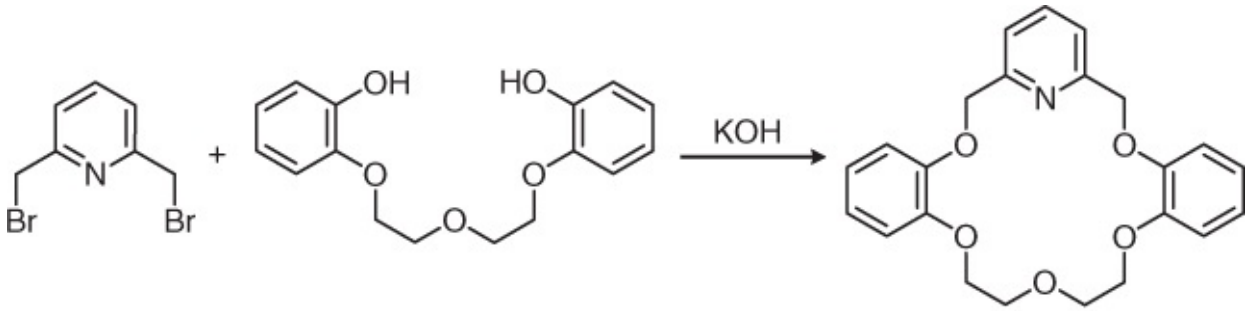
139.2 264.9

2,6-Bis(hydroxymethyl)pyridine **3.5.2.3** (30.0 g, 216 mmol) is dissolved in 48% hydrobromic acid (300 ml) with stirring, and the solution is heated under reflux for 2 h.

The mixture is neutralized with concentrated aqueous NaOH solution, keeping the temperature at 0 °C (dry ice cooling bath), and a colorless precipitate forms. The amorphous residue is collected by filtration, washed with H_2O, and dried over P_4O_{10} *in vacuo*. Recrystallization from petroleum ether (50–70 °C, approximately 750 ml) gives colorless needles of the dibromide; 46.6 g (82%), R_f = 0.37 (EtOAc), mp 86–89 °C (Caution: the product is a lachrymator!).

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.73 (t, *J* = 7.8 Hz, 1H, 4-H), 7.40 (d, *J* = 7.8 Hz, 2H, 3-H, 5-H), 4.56 (s, 4H, 2 × CH_2).

3.5.1.5 * Dibenzopyridino[18]crown-6 [3]



264.9 290.3 393.4

A solution of the dibromide **3.5.2.4** (4.3 g, 20.0 mmol) in benzene (250 ml,

Caution: carcinogenic!), a solution of the bisphenol **3.5.2.2** (5.81 g, 20.0 mmol) in DMF (250 ml), and a solution of KOH (3.24 g, 40.0 mmol) in an ethanol/water mixture 50 : 1 (250 ml) are simultaneously added dropwise with stirring to refluxing *n*-butanol (1000 ml) over a period of 8–10 h. After the addition is complete, the solution is heated under reflux for an additional 2 h.

The solvents are then removed *in vacuo*, and the stirred oily residue is triturated with H_2O to remove DMF. The solidified crude product is taken up in hot $CHCl_3$, the solution is filtered, the filtrate is dried over $MgSO_4$, and filtered. The solvent is removed *in vacuo*, and the residue is purified by chromatography on basic aluminum oxide (CH_2Cl_2; the product migrates ahead of a yellow fraction). The solvent is removed *in vacuo* and the residue is recrystallized from EtOAc/*n*-hexane to yield the crown ether as colorless crystals; 2.28 g (30%), mp 131–132 °C (dec.) (note).

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 1600, 1510, 1255, 1130, 1055, 1010.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.76 (t, *J* = 7.8 Hz, 1H, 4-H), 7.45 (d, *J* = 7.8 Hz, 2H, 3-H, 5-H), 7.40–6.89 (m, 8H, 2′-H, 3′-H, 4′-H, 5′-H), 5.18 (s, 4H, 2 × CH_2), 4.21–4.03 (m, 4H, 1″-H), 3.86 (t, *J* = 4.5 Hz, 4H, 2″-H).

Note: The crown ether can be characterized as its 1 : 1 complex with KSCN according to Ref. [3], colorless platelets, mp 212–213 °C.

References

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2. Pedersen, C.J. (1988) *Angew. Chem.*, **100**, 1053–1059; *Angew. Chem., Int. Ed. Engl.*, (1988), **27**, 1021–1027.

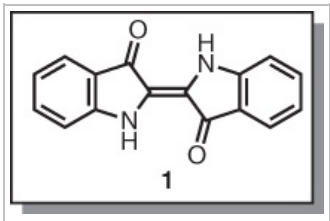
3. (a) Weber, E. and Vögtle, F. (1976) *Chem. Ber.*, **10**, 1803–1831;(b) Weber, E. and Vögtle, F. (1980) *Angew. Chem.*, **92**, 1067–1068; *Angew. Chem., Int. Ed.*

Engl., (1980), **19**, 1030–1031.

4. (a) Vögtle, F. (1972) *Chem. Ztg.*, **96**, 396–403;(b) Rossa, L. and Vögtle, F. (1983) *Top. Curr. Chem.*, **113**, 1–86.

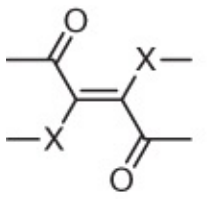
5. In analogy to the synthesis of guaiacol: Tietze, L.F. and Eicher, Th. (1991) *Reaktionen und Synthesen im Organisch-chemischen Praktikum und Forschungslaboratorium*, 2nd edn, Georg Thieme Verlag, Stuttgart, p. 409.

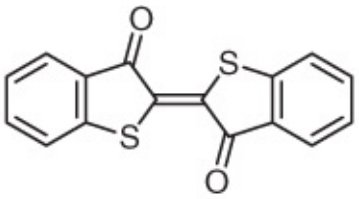
3.5.2 Indigo

 1	***Topics:***	• Nitroaldol addition (Henry reaction) • Oxidative dimerization of a 3*H*-indol-3-one precursor to indigo

(a) General

Indigo (**1**) and other members of the group of indigoid vat dyes, for example, thioindigo (**3**), possess a doubly-cross-conjugated, twofold donor–acceptor substituted olefinic double bond **2** (X = NH, S) as the chromophoric system:


2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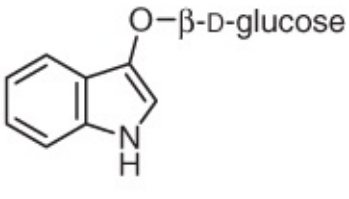
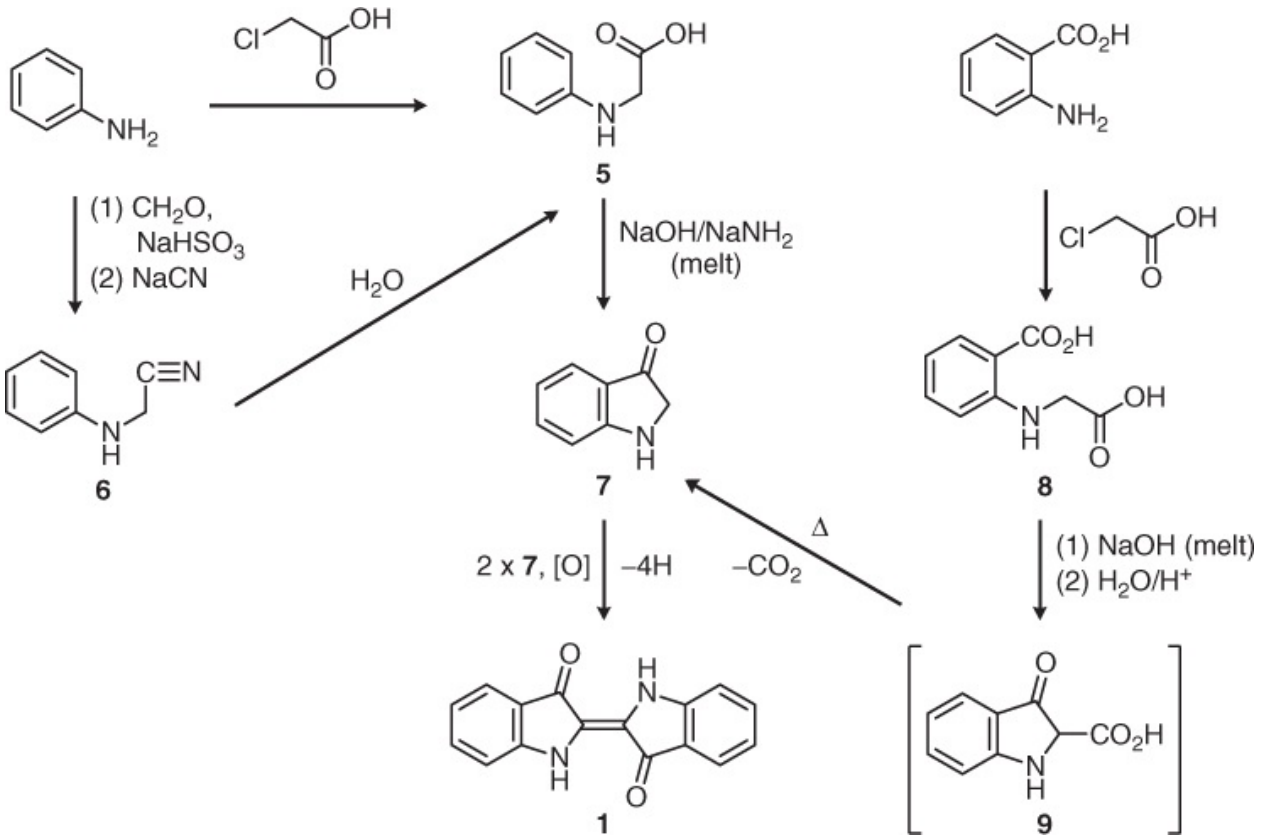


4

Since antiquity, indigo has been obtained from indican (**4**) by enzymatic hydrolysis to give indoxyl (**7**), which undergoes oxidative dimerization (**7** → **1**). Indican (**4**) is the β-glucoside of indoxyl (**7**) found in the tropical indigo plant (*Indigofera tinctoria*) and in European woad (*Isatis tinctoria*; dyer's woad). However, since the beginning of the last century, indigo of natural origin has been completely replaced by indigo produced by industrial synthesis [1–3]:



The technically relevant syntheses of indigo [1] start either from aniline or from anthranilic acid. In the first Heumann synthesis, aniline is N-alkylated by chloroacetic acid to give *N*-phenylglycine (**5**), which is cyclized to indoxyl (**7**) in an $NaOH/NaNH_2$ melt. Alternatively (and with higher yields), *N*-phenylglycine is synthesized by alkaline hydrolysis of *N*-phenylglycinonitrile (**6**), which is obtained by reaction of aniline with formaldehyde/$NaHSO_3$ followed by NaCN.

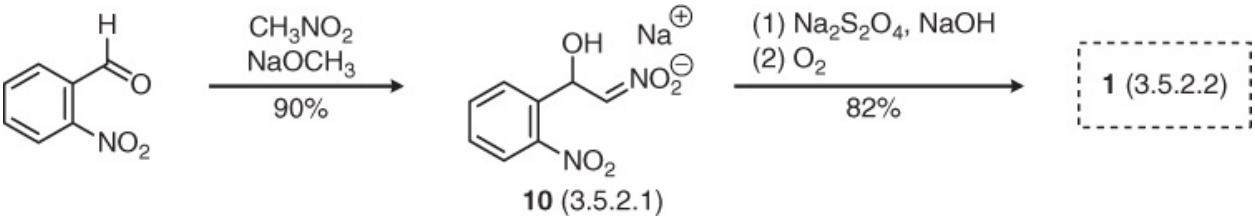
In the second Heumann synthesis, *N*-phenylglycine-*o*-carboxylic acid (**8**), accessible from anthranilic acid and chloroacetic acid, cyclizes in an alkali melt to give indoxyl-2-carboxylic acid (**9**), thermal decarboxylation of which also yields indoxyl (**7**). As the final step in these syntheses, indoxyl is oxidized by aerial oxygen to afford indigo (**1**).

For the laboratory synthesis of indigo, a preparatively more convenient procedure [4] that avoids the high-temperature alkali melt formation of indoxyl is presented in Section (b).

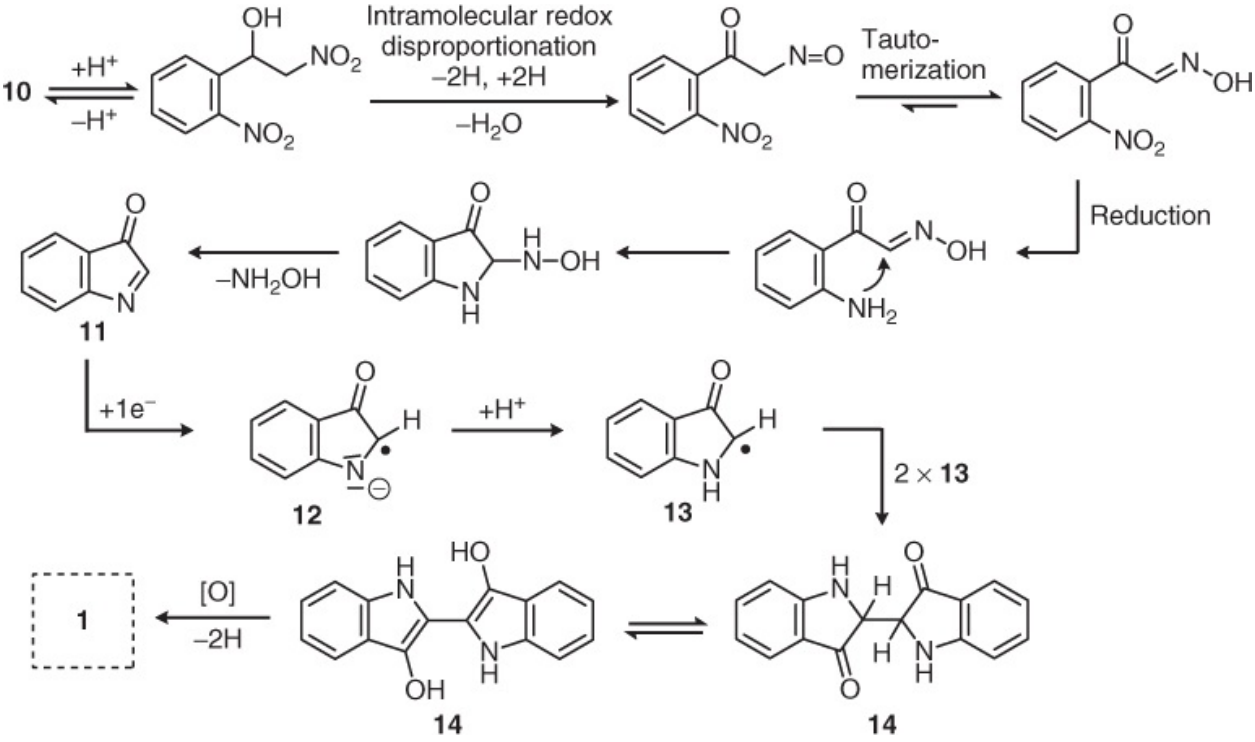
(b) Synthesis of 1

The substrate for the synthesis of **1** [4] is *o*-nitrobenzaldehyde, which is subjected to an aldol addition with nitromethane (Henry reaction) in the presence

of sodium methoxide to give the nitroaldol, which is isolated as the sodium salt **10**. On reduction of this nitronate salt with sodium dithionite in aqueous NaOH and subsequent oxidation with air, indigo (**1**) is obtained in high yield as a blue crystalline powder:



The mechanism of this indigo formation (**10** → **1**) remains speculative.



It has been assumed [5] that the elusive 3*H*-indol-3-one (**11**) is the primary intermediate, from which an SET process via radical anion **12** and radical **13** followed by dimerization may lead to the leuco form of indigo, **14**. This is finally dehydrogenated by aerial oxygen to give indigo (**1**). The sequence **13** → **14** → **1** corresponds to indigo formation from indoxyl (**7**) [6].

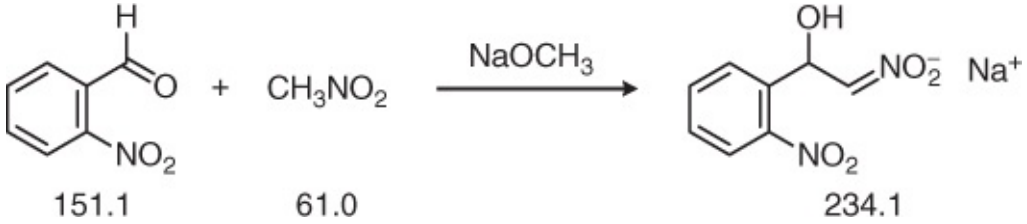
The proposed intermediacy of 3*H*-indol-3-one (**11**) might be rationalized by a working hypothesis that includes intramolecular redox disproportionation [7] of the nitronate **10** (or of the hydroxynitro compound obtained by protonation), tautomerization of the resulting α-nitroso ketone to afford an α-oximino ketone, reduction of $NO_2 \rightarrow NH_2$, and eliminative cyclization to form the indolone

system.

According to the described procedure, the target molecule is prepared in two steps in an overall yield of 73% (based on *o*-nitrobenzaldehyde).

(c) Experimental Procedures for the Synthesis of 1[5]

3.5.2.1	*	1-(*o*-Nitrophenyl)-2-nitroethanol, Na salt

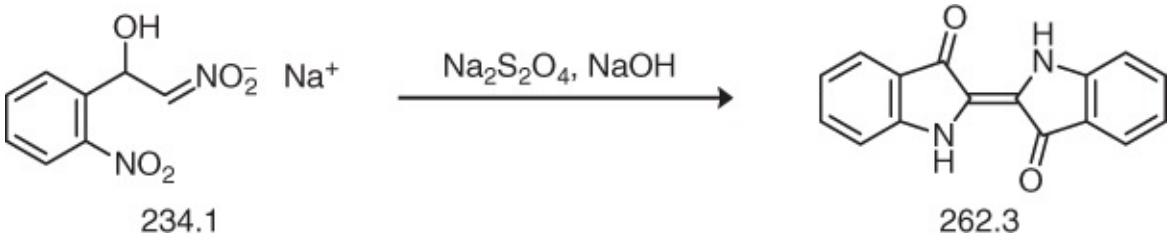


A solution of sodium methoxide is first prepared by portionwise addition of sodium (1.80 g, 78.3 mmol) to anhydrous MeOH (30 ml). This solution is then added dropwise over 20 min to a stirred solution of *o*-nitrobenzaldehyde (10.0 g, 66.2 mmol) and anhydrous nitromethane (4.60 g, 75.4 mmol) in MeOH (50 ml) at 0–5 °C. Toward the end of the addition, the yellow product crystallizes. The mixture is left at 0 °C for 15 h and can be used directly for the next step.

The nitronate salt is isolated by filtration, washed with MeOH (2 × 10 ml) and Et_2O (3 × 1 ml), and finally dried *in vacuo* over P_4O_{10}; 14.0 g (90%), yellow, air-sensitive powder.

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3120, 1570, 1530, 1345.

3.5.2.2	*	Indigo



The product from **3.5.2.1** (note) is dissolved in water (200 ml), aqueous NaOH (2 M, 60 ml) is added, and the yellow solution is cooled to 6 °C. With vigorous stirring, sodium dithionite (33.6 g, 193 mmol) is added in small portions at such a rate that the temperature remains well below 15 °C; the addition time is

approximately 15 min. The solution rapidly darkens and indigo precipitates as a blue-black solid. When the dithionite addition is complete, air is rapidly bubbled through the reaction mixture for approximately 30 min.

The solid is collected by filtration, and washed with water until alkaline-free, and then with EtOH (3 × 20 ml), and Et_2O (3 × 20 ml). The product is dried at 120 °C for 3 h to give a dark-blue crystalline powder with a metallic sheen; 7.13 g (82%) of indigo, mp 390–393 °C (dec.).

UV/Vis (DMSO): λ_{max} (nm)/(log ε) = 619 (4.20), 287 (4.41) [8].

Note: When the reaction mixture of **3.5.3.1** is used directly, the methanol is removed *in vacuo* at 25 °C and the residue is dissolved in water (200 ml).

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5. (a) Gosteli, J. (1977) *Helv. Chim. Acta*, **60**, 1980–1983;(b) Hiremath, S.P. and Hooper, M. (1978) *Adv. Heterocycl. Chem.*, **22**, 123–181.

6. Eicher, Th., Hauptmann, S., and Speicher, A. (2012) *The Chemistry of Heterocycles*, 3rd edn, Wiley-VCH Verlag GmbH, Weinheim, p. 146.

7. A long-known example of such an intramolecular redox reaction is the formation of anthranilic acid from *o*-nitrotoluene in NaOH/EtOH: Hauptmann, S. (1988) *Organische Chemie*, 2nd edn, VEB Verlag, Leipzig, p. 510.

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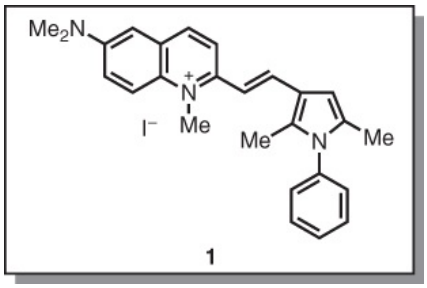
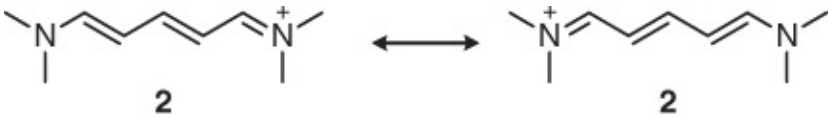
3.5.3 Pyrvinium Iodide

 1	***Topics:***	• Synthesis of an unsymmetrical cyanine dye • Paal–Knorr synthesis of a pyrrole derivative • Doebner–Miller synthesis of a quinoline derivative • Aldol condensation with C–H-acidic substituted heterocycles • Vilsmeier reaction of a hetarene

(a) General

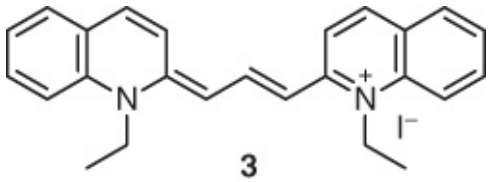
The pyrvinium salt **1** (6-dimethylamino-2-[2-(2,5-dimethyl-1-phenyl-3-pyrrolyl)vinyl]-1-methyl-quinolinium iodide) is used pharmaceutically in the form of the pamoate (also called ***embonate***) as an anthelmintic [1]. It is structurally related to the cyanine dyes, which represent an important class of dyestuffs and are technically relevant as sensitizers in color photography [2].

Cyanine dyes contain as chromophore a polymethine chain with an odd number of methine CH groups, which bears at its terminal positions an (uncharged) amino nitrogen and a (charged) iminium nitrogen, thus allowing symmetrical charge delocalization over the chain, as exemplified in the case of the pentamethine cyanine system **2**:



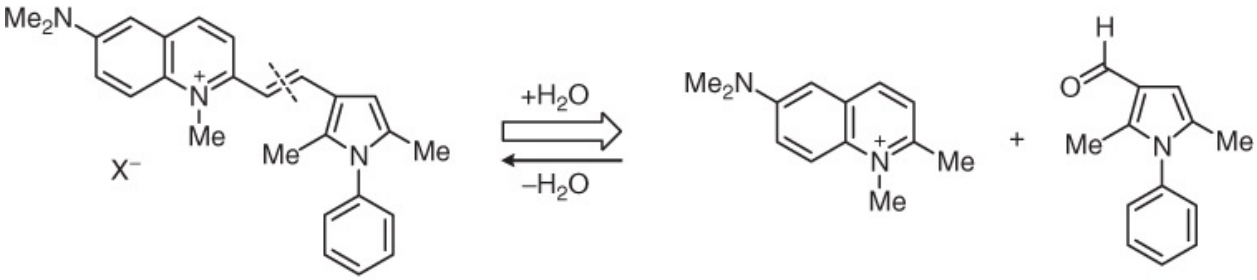
2 2

The terminal nitrogens can be incorporated into heterocycles, thus giving rise to cyanine dyes with heterocyclic end groups, which can be arranged symmetrically (as in **3**) or unsymmetrically (as in **1**); both cyanine systems **1** and **3** contain a pentamethine cyanine structural unit.



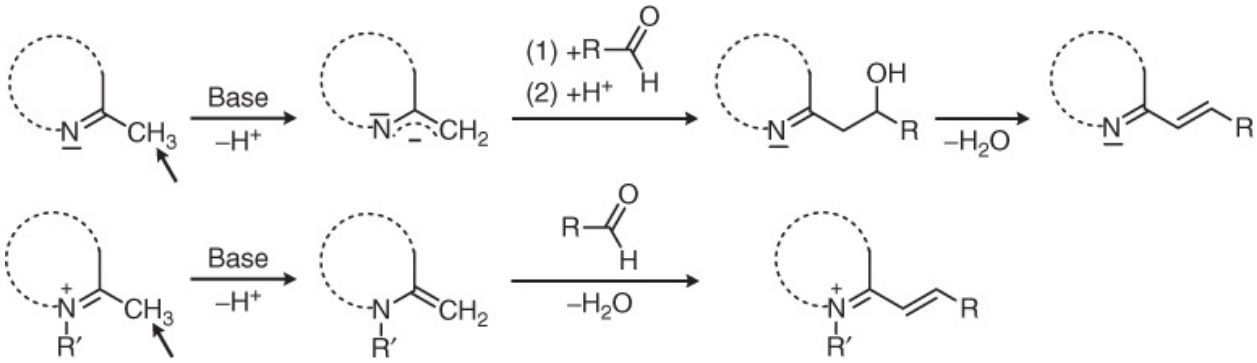
3

For the retrosynthesis of the target molecule **1**, the CH=CH group connecting the two heterocyclic moieties is of strategic relevance, since its disconnection according to a retroaldol mode leads to the two building blocks **4** and **5**. Thus, **1** should be accessible by an aldol condensation of **4** and **5**.



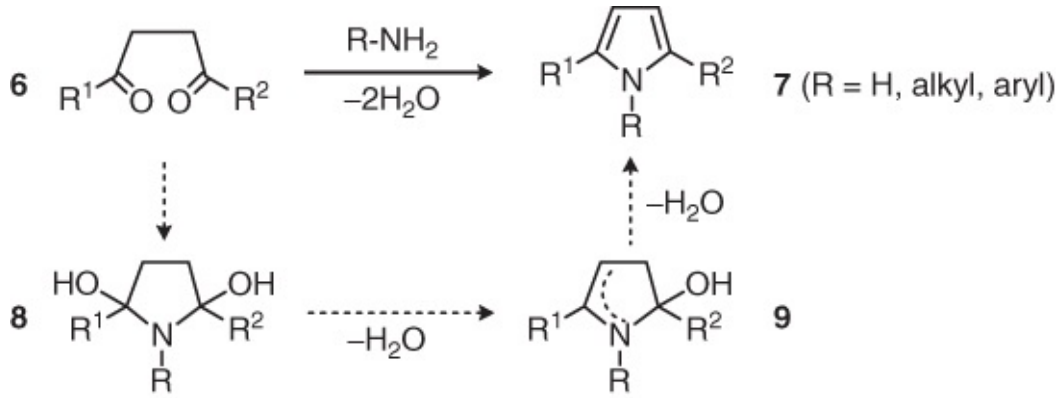
1 4 5

The basis for the retroanalytical approach is the well-known CH acidity of heterobenzylic C–H bonds, preferentially of CH_3 groups. The CH acidity is strongly enhanced by the N-quaternation. Thus, methyl groups in the 2-and/or 4-position of azines and benzazines [3] can be deprotonated with a base to give a carbanion, which can undergo C–C bond-forming transformations such as alkylations, acylations, or aldol reactions, for example:



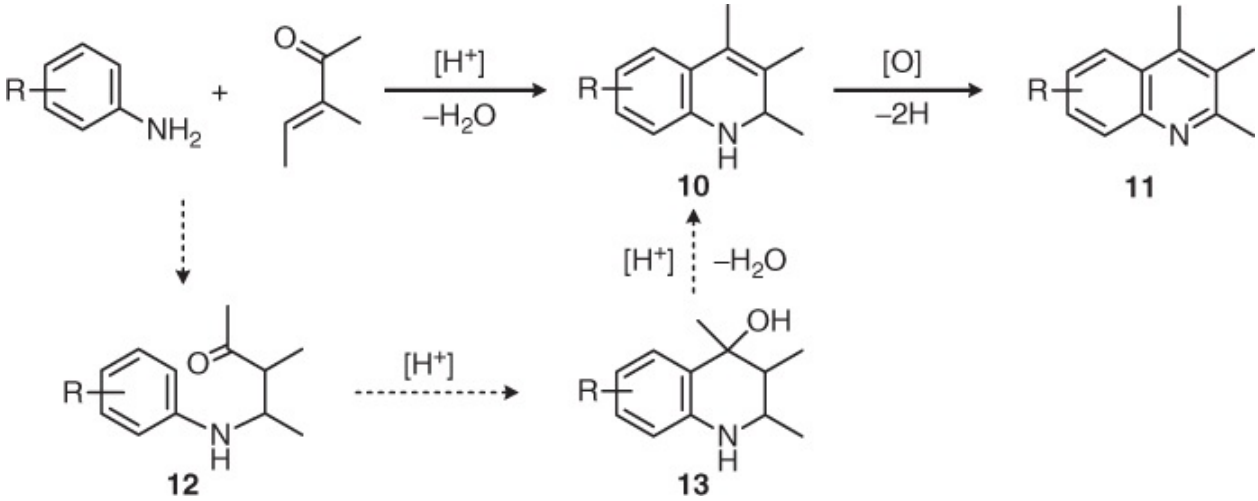
For the synthesis of the two building blocks **4** and **5**, two universally applicable methods of heterocycle synthesis are applied, namely the Paal–Knorr synthesis of pyrroles and the Doebner–Miller synthesis of quinolines [4].

In the Paal–Knorr synthesis, 1,4-dicarbonyl compounds **6** are cyclocondensed with ammonia or primary amines, thus producing 2,5-disubstituted pyrroles **7**:



The initial reaction step leads to twofold hemiaminals **8**, which give the pyrroles **7** by stepwise H_2O elimination via imine (R = H) or enamine (R ≠ H) intermediates **9** [5].

In the Doebner–Miller synthesis, primary arylamines with an unsubstituted ortho position are reacted with α,β-unsaturated carbonyl compounds in the presence of a proton acid and an oxidant (nitroarene, As_2O_5, etc.)[6] to give quinoline derivatives **11**:



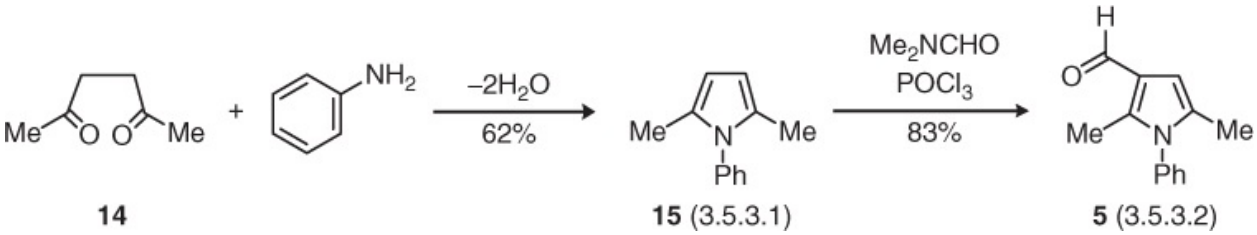
For this synthesis, a complex multistep sequence has been established, which includes Michael addition of the arylamine to the enone system (→**12**), ring closure of intermediate **12** by H^+-catalyzed intramolecular hydroxyalkylation (→**13**), and dehydration leading to a 1,2-dihydroquinoline **10**, which is dehydrogenated (by the oxidant) to give the quinoline **11**.

(b) Synthesis of 1

Based on the retrosynthetic considerations in Section (a), a convergent approach for the construction of **1** is presented, in which the building blocks **4** and **5** are

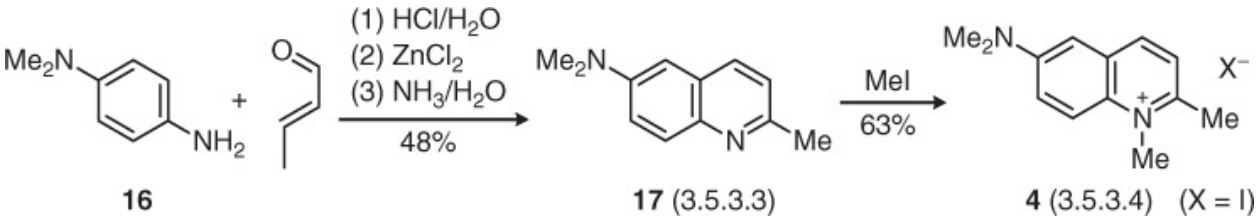
first prepared separately.

The synthesis of pyrrolecarbaldehyde **5** starts with the cyclocondensation of hexane-2,5-dione (**14**) with aniline according to the Paal–Knorr procedure to give the pyrrole **15**. Introduction of an aldehyde function at the 3-position of the activated heterocycle is achieved by means of Vilsmeier formylation (→**5**):



14 **15** (3.5.3.1) **5** (3.5.3.2)

The synthesis of the quaternized quinaldinium salt **4** follows the pattern of the Doebner–Miller method. *p*-(Dimethylamino)aniline (**16**) is cyclocondensed with crotonaldehyde in 6 N aqueous hydrochloric acid in the presence of $ZnCl_2$ to give the 2-methylquinoline **17**:

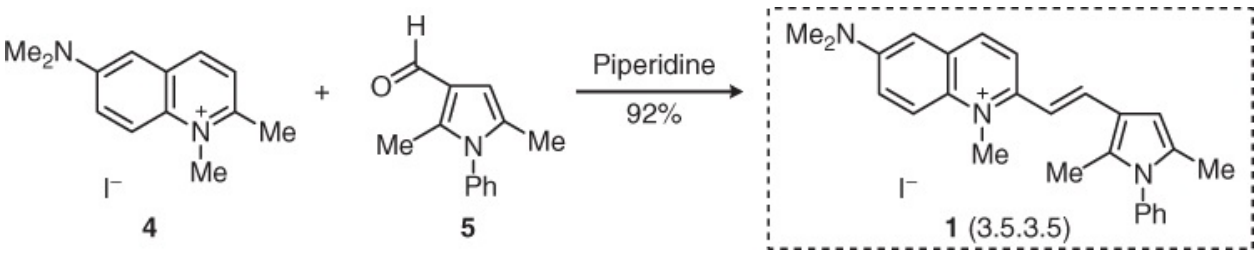


16 **17** (3.5.3.3) **4** (3.5.3.4) (X = I)

In this variant of the Doebner–Miller synthesis, a Zn complex of the cyclization product **17** is isolated first, which is then decomposed using ammonia. In this way, a process that is usually accompanied by side reactions can be greatly improved.

The quinaldine **17** is transformed to the quaternary salt **4** (X = I) by alkylation with methyl iodide. Initially, a mixture of products methylated at the azine nitrogen and at the $(CH_3)_2N$ group results; however, the product isomerizes thermally to the *N*-methylquinaldinium salt (**4**, X = I) [6].

Finally, the building blocks **4** and **5** are combined by aldol condensation in the presence of piperidine as base to provide pyrvinium iodide (**1**):

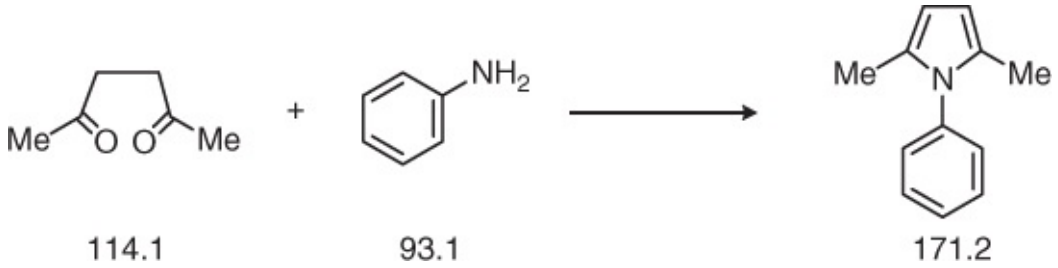


4 **5** **1** (3.5.3.5)

Thus, the target molecule **1** is obtained in a convergent synthesis in one step in 92% yield from **4** and **5**, which are formed in two steps each in yields of 51% and 30%, respectively.

(c) Experimental Procedures for the Synthesis of 1

3.5.3.1 * 2,5-Dimethyl-1-phenylpyrrole [7]



114.1 93.1 171.2

Aniline (27.9 g, 0.30 mol) (note 1) and hexane-2,5-dione (34.2 g, 0.30 mol) are heated under reflux for 1 h.

The reaction mixture is then cooled to room temperature, and poured into a mixture of H_2O (100 ml) and concentrated HCl (10 ml). The precipitate is collected by suction filtration, washed with iced water, and recrystallized from a mixture of MeOH (150 ml) and H_2O (15 ml) (note 2). The product is obtained as colorless crystals; 31.8 g (62%), mp 50–51 °C, TLC (cyclohexane): R_f = 0.75.

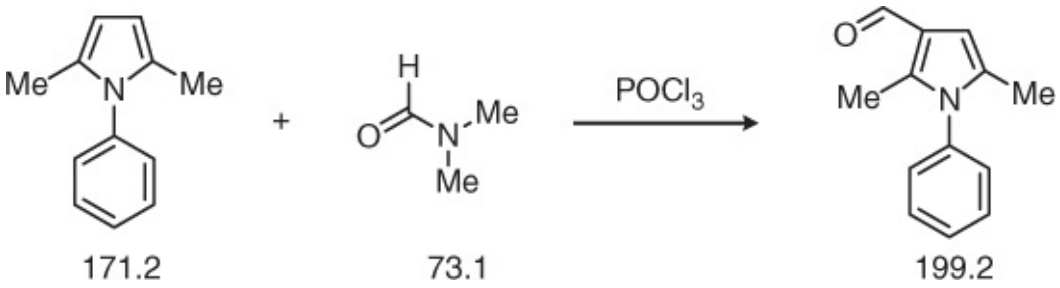
IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 1595, 1490, 1400, 1315.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.62–7.11 (m, 5H, phenyl-H), 5.93 (s, 2H, 3-H, 4-H), 1.98 (s, 6H, 2 × CH_3).

Notes:

1. Aniline (bp_{20} 84–85 °C) has to be distilled before use.
2. If the product separates as an oil on cooling, it has to be redissolved by the addition of a small amount of MeOH (approximately 3 ml).

3.5.3.2 * 2,5-Dimethyl-1-phenylpyrrole-3-carbaldehyde [8]



171.2 73.1 199.2

The pyrrole **3.5.3.1** (25.0 g, 146 mmol) and anhydrous DMF (16.0 g, 219 mmol) are dissolved in anhydrous toluene (100 ml). With vigorous stirring, $POCl_3$ (27.0 g, 219 mmol) (note) is added dropwise over 30 min. The temperature of the solution rises to approximately 80 °C, and a dark color develops. When the addition of $POCl_3$ is complete, the solution is heated with stirring to 100 °C for 6 h.

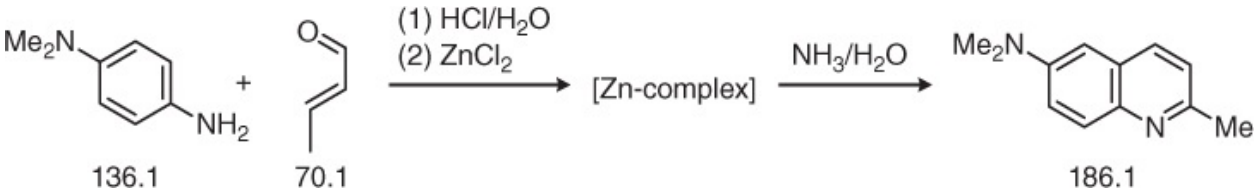
The reaction mixture is then cooled to room temperature, poured into saturated aqueous NaOAc solution (300 ml), and the resulting mixture is vigorously stirred for 30 min. The organic layer is separated and the aqueous layer is extracted with toluene (2 × 200 ml). The organic layers are combined and washed successively with 10% aqueous Na_2CO_3 solution (200 ml) and H_2O (200 ml). The toluene is distilled off *in vacuo*, and the residue is purified by fractionating distillation *in vacuo*. The pyrrole carbaldehyde is obtained as a yellowish oil, which solidifies on cooling; 24.0 g (83%), bp_{12} 190–191 °C, mp 90–91 °C; TLC (Et_2O): R_f = 0.70.

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 1650, 1600, 1540.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 9.88 (s, 1H, CHO), 7.62–7.10 (m, 5H, phenyl-H), 6.39 (d, J = 1.2 Hz, 1H, 4-H), 2.28 (s, 3H, CH_3), 1.99 (d, J = 1.2 Hz, 3H, CH_3).

Note: $POCl_3$ is a lachrymator and should be handled only in a hood; it has to be distilled before use (bp_{760} 105–106 °C).

3.5.3.3	*	**6-Dimethylamino-2-methylquinoline** [7]



A solution of *p*-(dimethylamino)aniline (35.0 g, 257 mmol) in aqueous HCl (6 N, 130 ml) is heated to reflux. With intense stirring, crotonaldehyde (25.0 g, 357 mmol) is added dropwise over 30 min. When the addition is complete, the dark solution is heated to reflux for 1 h.

The reaction mixture is cooled to room temperature and extracted with Et_2O (100 ml) to remove undissolved dark impurities; anhydrous zinc chloride (35.4 g, 0.26 mol) is added to the clear brown-red solution, and then concentrated NH_3 is added with stirring until the pH of the solution reaches 5–5.5. An orange-red zinc complex of the product (note 1) is formed, which crystallizes. It is collected by suction filtration, suspended in isopropanol (200 ml), and the suspension is stirred for 5 min. After filtration, the Zn complex is washed with isopropanol (in portions of 50 ml) until the washings are only faintly colored; the product is then washed with Et_2O (100 ml) and air-dried.

The Zn complex is decomposed by portionwise addition to concentrated aqueous NH_3 (150 ml), and the quinoline derivative formed is extracted with CH_2Cl_2 (4 × 200 ml). The CH_2Cl_2 extracts are combined, dried over K_2CO_3, filtered, and the solvent is distilled off; the residue (approximately 28 g) is then fractionated *in vacuo*. The quinoline derivative is obtained as a yellow oil, which solidifies on cooling (note 2); 23.0 g (48%), $bp_{0.01}$ 120–121 °C, mp 92–93 °C; TLC (Et_2O): R_f = 0.50.

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 1630, 1605, 1515.

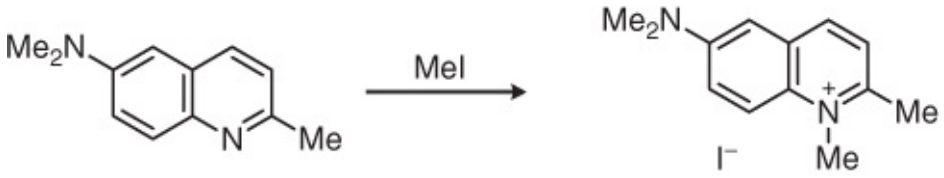
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.91 (d, *J* = 3.0 Hz, 1H, 3-H), 7.81 (d, *J* = 3.0Hz, 1H, 4-H), 7.31 (dd, *J* = 8.5, 3.0 Hz, 1H, 7-H), 7.13 (d, *J* = 8.5 Hz, 1H, 8-H), 6.78 (d, *J* = 3.0 Hz, 1H, 5-H), 3.03 (s, 6H, $N(CH_3)_2$), 2.66 (s, 3H, CH_3).

Notes:

1. The complex contains $ZnCl_2$ and two molecules of the quinoline [7].
2. The product is air-sensitive. Cleavage of the Zn complex should be

rapid, the distillation should be performed under a N_2 atmosphere, and the product should be kept in a refrigerator under N_2. Because of the sensitivity of the quinoline, the next step (alkylation) should follow immediately.

3.5.3.4 * 6-Dimethylamino-1,2-dimethylquinolinium iodide [7]



186.3 328.2

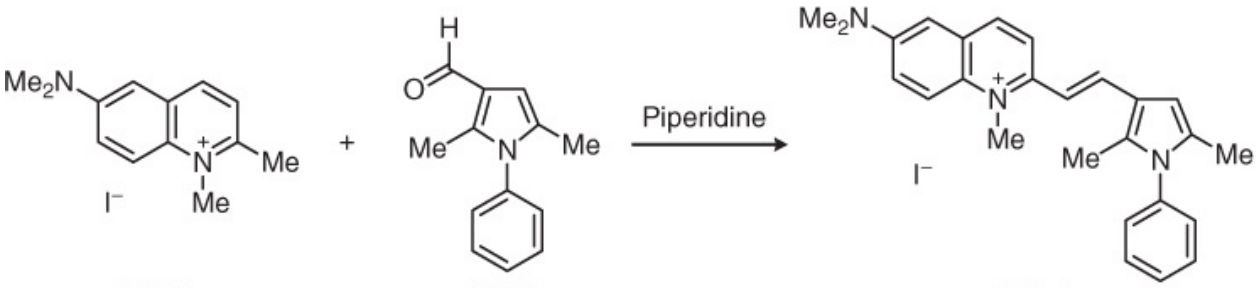
A solution of the quinoline derivative **3.5.3.3** (22.0 g, 118 mmol) and methyl iodide (33.5 g, 236 mmol; Caution: carcinogenic!) in anhydrous isopropanol (130 ml) is heated under reflux for 2 h with stirring. Orange-red crystals of the quinolinium salt are formed.

The reaction mixture is then cooled to room temperature, and the crystals formed are collected by filtration, washed with ice-cold isopropanol, and air-dried: 34.4 g (89%), mp 253–258 °C. For purification, the crude product is heated to 200–210 °C (external temperature) for 10–15 min; the product must attain a dark color. After cooling to room temperature, the crystals are dissolved in boiling H_2O (approximately 220 ml) and the hot solution is filtered. On cooling to room temperature, the product crystallizes in brown-red needles, which are collected by suction filtration, washed with H_2O, and dried *in vacuo* over P_4O_{10}; 24.5 g (63%), mp 265–267 °C.

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3050, 2940, 1625, 1610, 1525.

^{1}H NMR (300 MHz, [D_6]DMSO): δ (ppm) = 8.73 (d, *J* = 8.1 Hz, 1H, 3-H), 8.30 (d, *J* = 8.1 Hz, 1H, 4-H), 7.85 (d, *J* = 8.0 Hz, 1H, 8-H), 7.68 (dd, *J* = 8.0, 2.9 Hz, 1H, 7-H), 7.23 (d, *J* = 2.9 Hz, 1H, 5-H), 4.40 (s, 3H, $^+$N–CH_3), 3.14 (s, 6H, $N(CH_3)_2$), 3.03 (s, 3H, CH_3).

3.5.3.5 * Pyrvinium iodide [6]



328.2 199.2 509.1

Freshly distilled piperidine (2.20 g, bp_{760} 105–106 °C) is added to a stirred solution of **3.5.3.4** (8.80 g, 26.8 mmol) and the pyrrole carbaldehyde **3.5.3.2** (5.34 g, 26.8 mmol) in anhydrous MeOH (100 ml). On heating to reflux, the solution becomes intensely red, and after some minutes the product precipitates as red crystals. Heating to reflux is continued for 30 min.

The reaction mixture is cooled to room temperature, and the product is collected by suction filtration, washed with MeOH, and dried over P_4O_{10} *in vacuo*; 12.5 g (92%), reddish-brown crystalline powder, mp 286–287 °C.

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 1620, 1575, 1530.

^{1}H NMR (300 MHz, [D_6]DMSO): δ (ppm) = 8.45–6.90 (m, 12H, arom. H + vinyl H), 6.50 (s, 1H, pyrrole 4-H), 4.40 (s, 3H, $^+N–CH_3$), 3.20 (s, 6H, $N(CH_3)_2$), 2.25, 2.08 (2 × s, 2 × 3H, CH_3).

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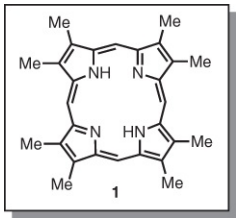
3.5.4 2,3,7,8,12,13,17,18-Octamethylporphyrin

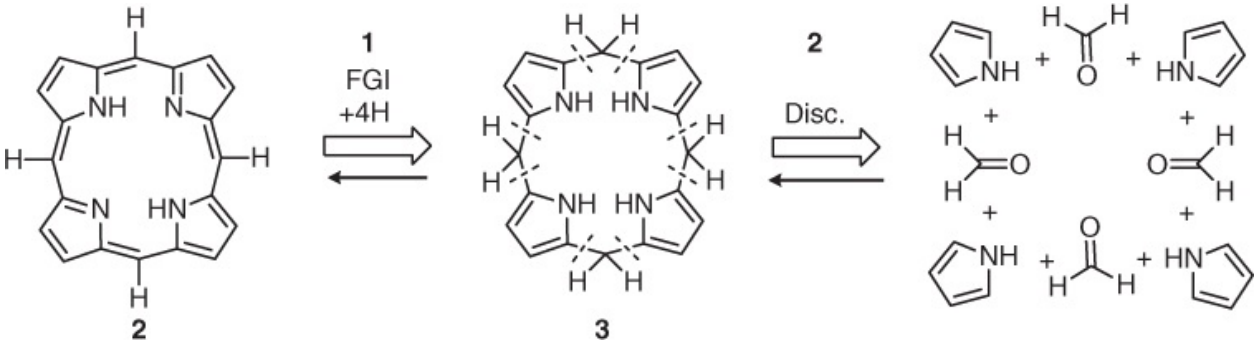


Topic:

- Synthesis of a symmetrically substituted porphyrin by oxidative cyclotetramerization of a pyrrole with an aldehyde

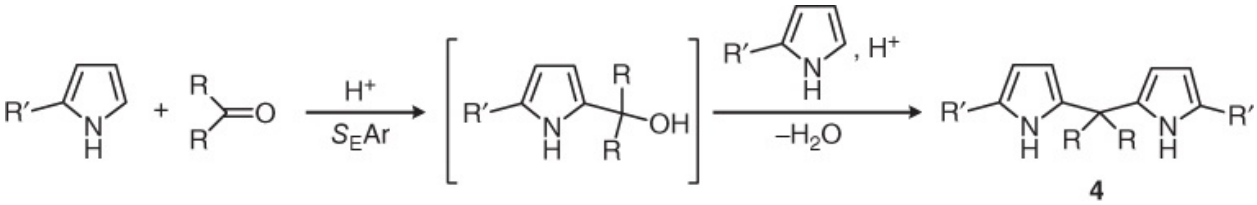
(a) General

Porphyrin (**2**) is the parent compound of the natural product family of tetrapyrroles (e.g., hemine, chlorophyll). In porphyrin, four pyrrole-derived units are linked together at their two α-positions by four methine (sp^2-C) bridges. They form a planar C_{20} macroheterocycle with a conjugated delocalized aromatic π-system of 18 π-electrons ($4n + 2$ with $n = 4$; altogether there are 22 π-electrons) [1].



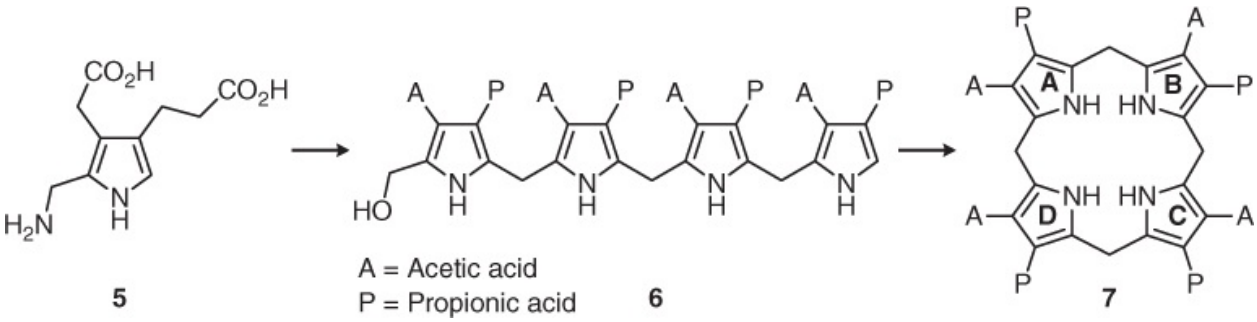
Among the numerous approaches for the synthesis of porphyrins [2], the simplest and most straightforward strategy stems from the following retroanalytical considerations: (i) in a reductive FGI, the four sp^2 methine bridges of **2** can be transformed into sp^3 methane bridges as in **3** (porphyrinogen), and (ii) successive disconnection of the methane bridges leads to four molecules of pyrrole and four molecules of formaldehyde.

The retrosynthesis step (ii) is based on the reversal of the well-known formation of dipyrrolylmethanes **4** by H^+-catalyzed hydroxyalkylation/alkylation of pyrroles with free α-positions by carbonyl compounds, which is one of the most important electrophilic reactions of pyrroles [3]:



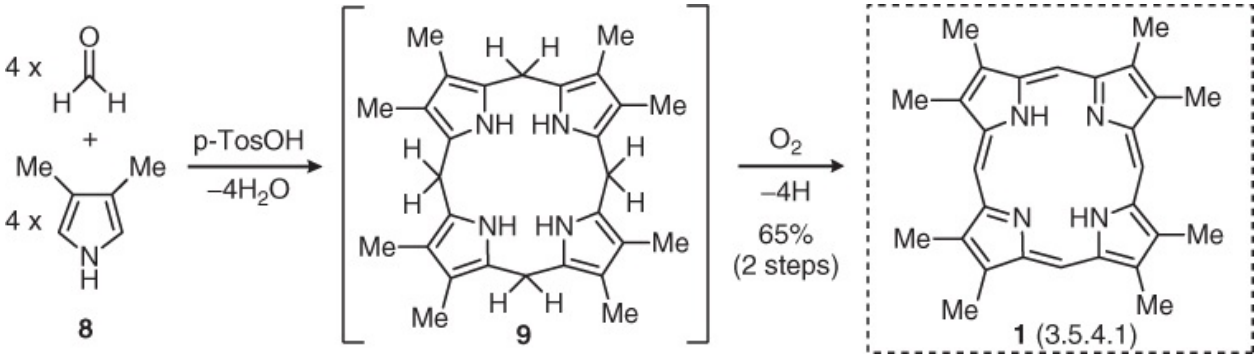
Accordingly, as shown in Section (b), the cyclotetramerization of pyrrole or pyrroles with identical substituents at C-3 and C-4 with aldehydes in the presence of a proton acid or Lewis acid followed by dehydrogenation represents the method of choice for the synthesis of symmetrically substituted porphyrins such as **1**; it has been realized for pyrrole and aryl aldehydes [4] as well as for 3,4-dialkyl-pyrroles and formaldehyde or aryl aldehydes [5–7].

The procedure corresponds very well with the biosynthesis of natural tetrapyrroles starting from the pyrrole derivative porphobilinogen (**5**) [8]. In an enzymatic linear condensation, the acyclic tetramer hydroxymethylbilane **6** is formed, which cyclizes to give uroporphyrinogen III (**7**) with inversion of ring D [9]. Compound **7** is the substrate of other pigments essential to life, such as the hemes, chlorophylls, corrins, and factor 43 [10].



(b) Synthesis of 1

3,4-Dimethylpyrrole (**8**, cf. Section 3.2.2) is subjected to cyclotetramerization with formaldehyde in the presence of *p*-toluenesulfonic acid as catalyst in benzene solution. The octamethylporphyrinogen **9** initially formed by azeotropic removal of H_2O is not isolated but is dehydrogenated *in situ* by reaction with oxygen to give the octamethylporphyrin (**1**) in a one-pot procedure[7]



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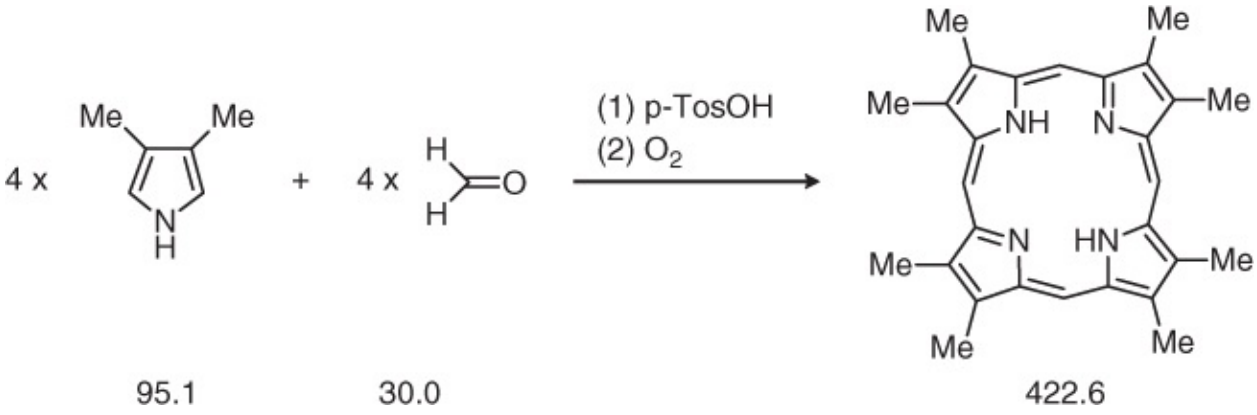
(c) Experimental Procedure for the Synthesis of 1

3.5.4.1	**	**2,3,7,8,12,13,17,18-Octamethylporphyrin** [7, 8]



Under a nitrogen atmosphere, a 500-ml round-bottomed flask, wrapped with aluminum foil (for light protection) and equipped with a Dean–Stark trap and a reflux condenser, is charged with 3,4-dimethyl-pyrrole (cf. Section 3.2.2; 0.77 g, 8.10 mmol), benzene (300 ml, Caution: carcinogenic!), aqueous formaldehyde solution (37%, 0.73 ml, 8.9 mmol, Caution!), and *p*-toluenesulfonic acid (0.03 g, 1.7 mmol). The mixture is heated to reflux with stirring and removal of water for 8 h.

The brown reaction mixture is then cooled to room temperature, and oxygen is bubbled through it (frit) at room temperature for 12 h with stirring to give a

black suspension.

The solvent is then evaporated *in vacuo*, and the residue is washed with $CHCl_3$ (5 ml) and MeOH (5 ml) and dried *in vacuo* to afford an amorphous, purple-black powder; 0.52 g (61%) (note).

^{1}H NMR ($CDCl_3/CF_3CO_2H$, 400 MHz): δ (ppm) = 10.57 (s, 4H, methine-CH), 3.55 (s, 24H, 8 × CH_3) (note).

^{13}C NMR ($CDCl_3/CF_3CO_2H$, 400 MHz): δ (ppm) = 142.1 (pyrroleC_α), 138.7 (pyrroleC_β), 98.3 (methine-CH), 11.9 (CH_3).

Note: The product is insoluble in most common solvents; however, it can be recrystallized from nitrobenzene [7]. It is also soluble in $CHCl_3$ on addition of a small amount of TFA, producing a deep purple-red color by formation of the porphyrin dication [2]. For NMR measurements, a solution of 7 mg of the above product in 1 ml of $CDCl_3$ and two drops of TFA is used. According to ^{1}H NMR, the product is of >98% purity.

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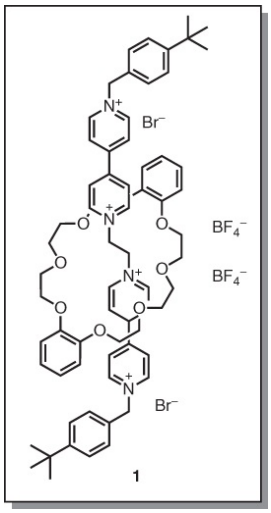
3.5.5 Synthesis of a Rotaxane



Topics:

- Preparation of a rotaxane consisting of a crown ether and a blocked linear bis(4,4′-dipyridylium)ethane unit
- Crown ethers
- Dipyridylium salts
- Electrostatic interactions
- π–π Stacking

(a) General

Rather unusual types of compounds are the catenanes [1], consisting of two

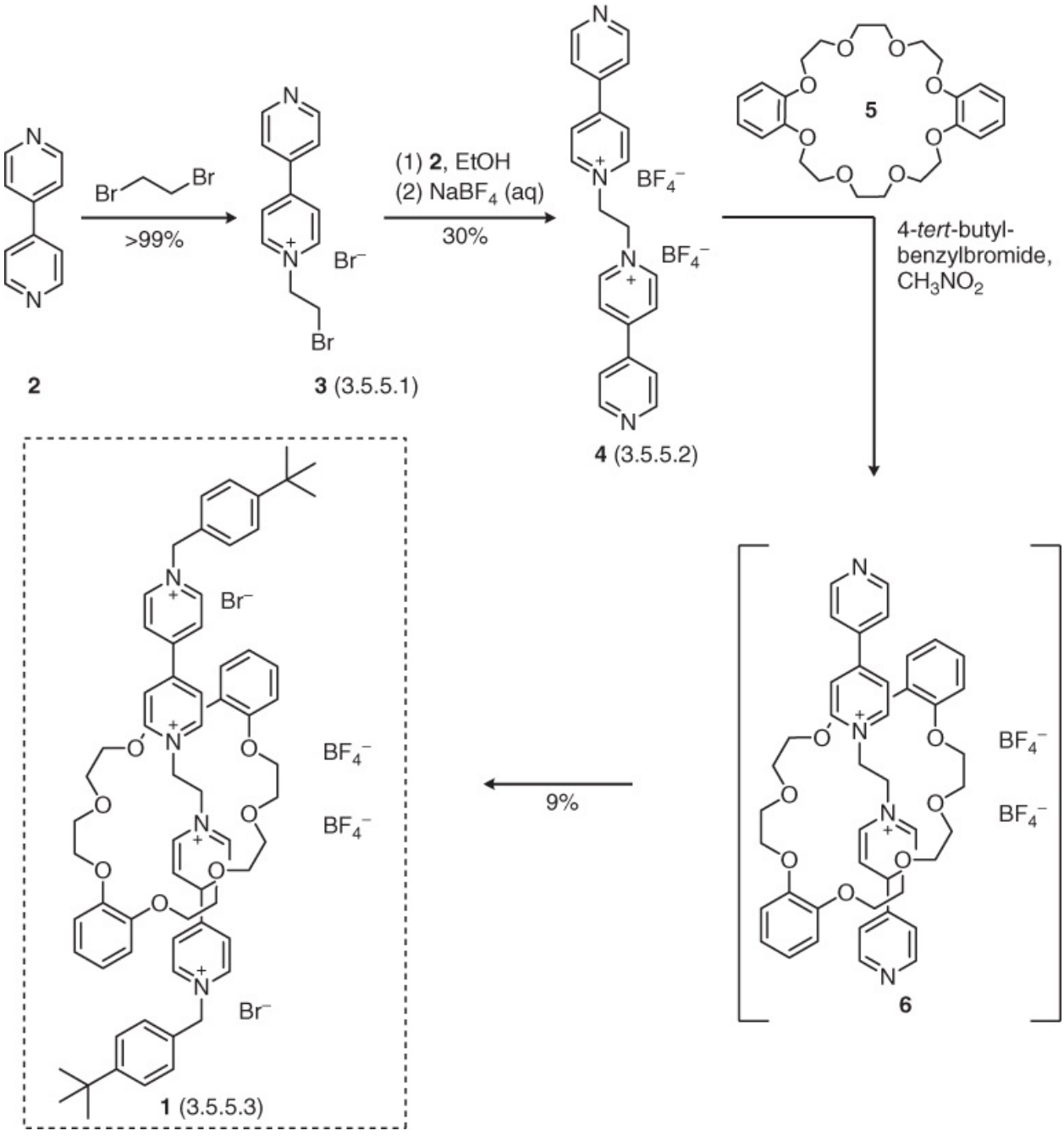
interlocking rings, and the rotaxanes [2], which consist of an assembly of one ring and a dumbbell. The striking feature of these substances is the fact that the two parts of the molecules are not connected to each other by a covalent bond, but by a so-called mechanical bond, which in the case of the catenanes is also a topological bond. Cleavage of catenanes requires breaking of one of the two rings, whereas in the case of rotaxanes a deformation of one of the two parts is necessary to dissociate the ring from the dumbbell, which is normally prevented from unthreading by large stoppers at its two ends.

General structures of a catenane (left) and a rotaxane (right).

Such compounds, especially the rotaxanes, have attracted much attention in recent years because of their photophysical and electronic properties as well as their dynamic behavior [3]; thus, rotaxanes can be considered as wheels. This allows the design of molecular motors [4] with an axle rotating inside a stator. For a long time it was thought that the wheel and molecular motors were inventions of humankind, but recently it has been demonstrated that nature also exploits this type of concept in ATP synthases [5]. These enzymes generate ATP from ADP and are responsible for the supply of chemical energy in all living organisms.

In the early work in this area, the synthesis of catenanes and rotaxanes completely depended on statistical approaches leading to the desired compounds usually in only very low yields [6]. Nowadays, directed and template methods are used. In the case of rotaxanes, in the directed method a pre-rotaxane is synthesized, in which the cyclic part and the dumbbell are linked together. Cleavage of the connections between the two parts then leads to the rotaxanes. The most efficient method – the template method, of which one example is described in the following – uses noncovalent interactions (ionic, van der Waals, hydrogen bonding, π–π stacking, metal–ligand interactions) to assemble a pre-rotaxane, which is then transformed into the rotaxane by blocking the ends of the linear axle to avoid its slipping out.

(b) Synthesis of 1

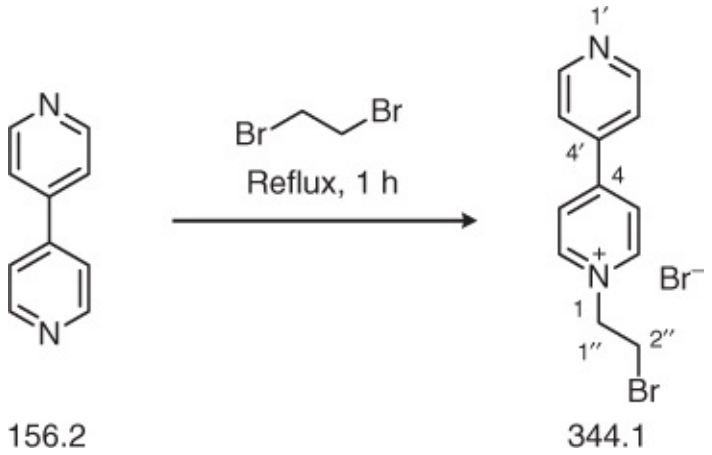


Stoddart and coworkers have shown that ortho-and meta-substituted crown ethers of appropriate size are excellent receptors for bipyridinium dications [7]. As noncovalent binding forces, electrostatic interactions and π–π stacking can be assumed. Based on this preorganization, Wisner [8] prepared the rotaxane **1** using the dipyridinium salt **4** and the crown ether **5**. First, a pre-rotaxane **6** is formed by insertion of **4** into the crown ether **5**; then, **6** is stabilized by blocking the ends of the dipyridinium system through alkylation with 4-*tert*-butyl-benzyl bromide. The success of the reaction can be recognized from a strong

bathochromic effect on the UV/vis absorbance of **1** compared to that of **4**. The obtained yields are moderate, but the procedure is simple and illustrative.

(c) Experimental Procedures for the Synthesis of 1

3.5.5.1	*	**1-(2-Bromoethyl)-[4,4′]bipyridyl-1-ium bromide** [8]



156.2 344.1

A stirred solution of 4,4′-dipyridyl (5.00 g, 32.0 mmol) in 1,2-dibromoethane (86.9 g, 463 mmol, 40.0 ml) is heated to reflux for 1 h.

After cooling to room temperature, the resulting salt is filtered off, washed with Et_2O, and dried *in vacuo* to yield the bromide as a beige solid; 10.9 g (99%).

UV (MeOH): λ_{max} (nm) (log ε) = 267.5 (4.27), 201.0 (4.40).

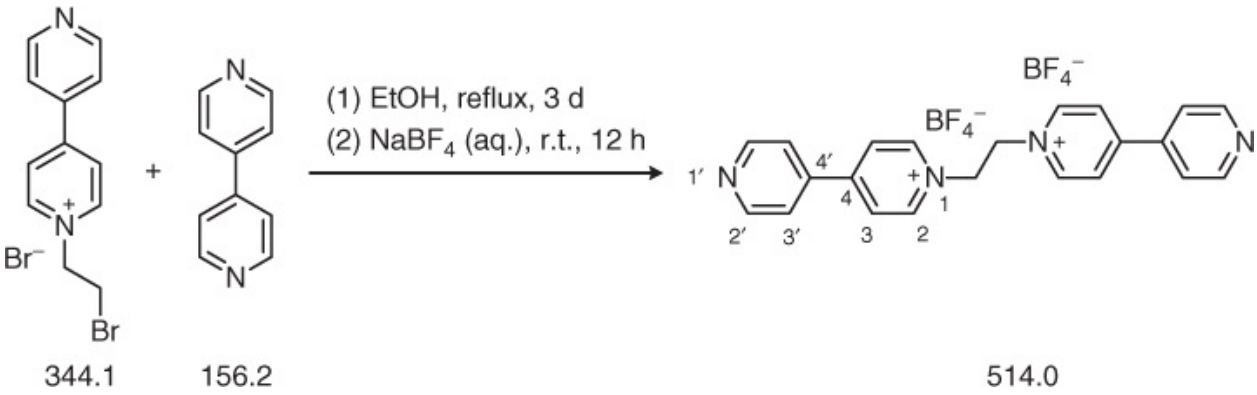
IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 2999, 1643, 1599, 1548, 1531, 1494, 1469, 1409, 1366, 1225, 1175, 1071, 995, 889, 814, 748, 714, 661, 477.

^{1}H NMR (300 MHz, D_2O): δ (ppm) = 9.09 (d, *J* = 1.9, 5.2 Hz, 2H, 2-H), 8.84 (dd, *J* = 1.9, 4.7 Hz, 2H, 2′-H), 8.51 (dd, *J* = 1.9, 5.2 Hz, 2H, 3-H), 7.98 (dd, *J* = 1.9, 4.7 Hz, 2H, 3′-H), 5.17 (t, *J* = 5.6 Hz, 2H, 2″-H), 4.11 (t, *J* = 5.6 Hz, 2H, 1″-H).

^{13}C NMR (50 MHz, D_2O/MeOH): δ (ppm) = 155.7 (C-4), 151.0 (C-2), 146.1 (C-2′), 143.5 (C-4′), 127.1 (C-3), 123.5 (C-3′), 62.7 (C-2″), 31.2 (C-1″).

MS (ESI): *m*/*z* (%) = 265.1 (53) $[(M - Br)]^+$, 263.0 (52) $[(M - Br)]^+$, 184.3 (13) $[(M - 2Br)]^+$, 183.2 (100) $[(M - 2Br)]^+$.

3.5.5.2	**	**1,2-Di-(4,4′-dipyridylium tetrafluoroborate)-ethane** [8]

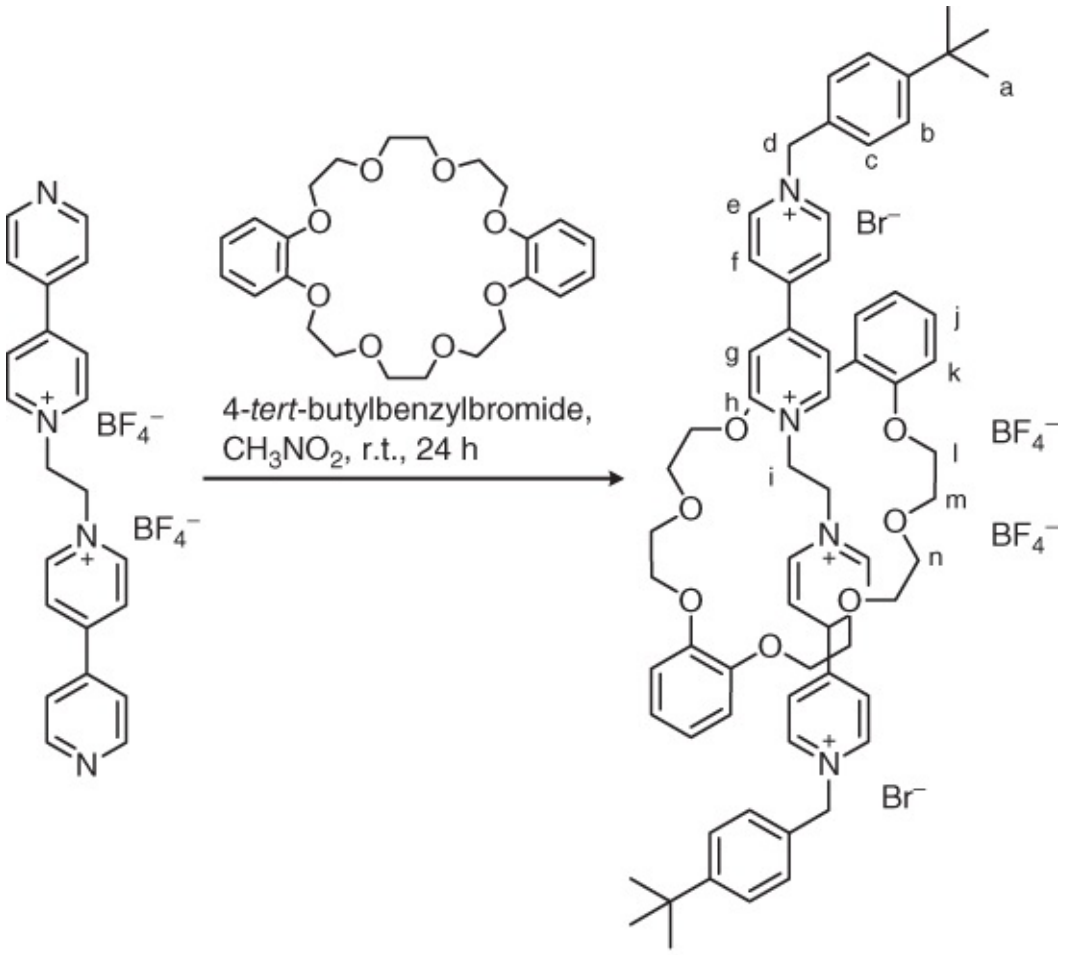


A solution of the bromide **3.5.5.1** (640 mg, 1.86 mmol) and 4,4′-dipyridyl (1.30 g, 8.32 mmol) in anhydrous EtOH (50 ml) is heated to reflux for 3 days.

After cooling to room temperature, the precipitate formed is filtered off, dried *in vacuo*, and dissolved in boiling H_2O (3 ml). Saturated aqueous sodium tetrafluoroborate solution is added dropwise to the boiling solution. The mixture is left at room temperature for 12 h, whereupon the dipyridium salt is obtained as a beige solid, which is collected by filtration; 287 mg (30%).

^{1}H NMR (300 MHz, D_2O): δ (ppm) = 9.20 (d, *J* = 7.2 Hz, 4H, 2-H), 9.01 (dd, *J* = 1.5, 5.3 Hz, 4H, 2′-H), 8.65 (d, *J* = 7.2 Hz, 4H, 3-H), 8.36 (dd, *J* = 1.5, 4.9 Hz, 4H, 3′-H), 5.56 (s, 4H, 2 × CH_2).

3.5.5.3	***	**Rotaxane**[8]



514.0 1416.8

A solution of the dipyridinium salt **3.5.5.2** (50 mg, 97 µmol) and dibenzo-24-crown-8 (131 mg, 0.292 mmol) in nitromethane (5.00 ml) is stirred for 30 min at room temperature; 4-(*tert*-butyl)benzyl bromide (133 mg, 0.58 mmol) is then added dropwise over 10 min and stirring is continued for 24 h.

The resulting mixture is then filtered, the filtrate is concentrated *in vacuo*, and the residue is recrystallized from CH_2Cl_2/Et_2O. The rotaxane is obtained as a dark-red solid; 12.8 mg (9%).

^{1}H NMR (300 MHz, [D_6]DMSO): δ (ppm) = 9.45 (d, *J* = 6.8 Hz, 4H, h), 9.20 (d, *J* = 6.8 Hz, 4H, e), 8.59 (d, *J* = 6.8 Hz, 4H, g), 8.48 (d, *J* = 6.8 Hz, 4H, f), 7.60 (m_c, 8H, b, c), 6.63 (dd, *J* = 3.4, 5.7 Hz, 4H, k), 6.21 (dd, *J* = 3.4, 6.2 Hz, 4H, j), 5.93 (s, 4H, d), 5.48 (s, 4H, i), 4.01–3.90 (m, 24H, l, m, n), 1.28 (s, 18H, *t*Bu).

^{13}C NMR (126 MHz, [D_6]DMSO): δ (ppm) = 146.2 (e), 145.4 (h), 126.5 (f),

128.6, 125.8 (b, c), 125.5 (g), 120.7 (j), 112.2 (k), 70.3, 69.9, 67.4 (l, m, n), 63.3 (d), 57.9 (i), 30.9 (a).

MS (ESI-HRMS): calcd.: 628.30900 [$(M + 2BF_4)^{2+}$]; found: 628.30919 [$(M + 2BF_4)^{2+}$].

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8. Loeb, S.J., and Wisner, J.A. (1998) *Chem. Commun.*, 2757–2758.

[1] U. Schöllkopf, D. Hoppe, private communication, 1981.

[2] Thioindoxyls are the precursors of the thioindigo dyes, which are formed by their oxidative dimerization [1].

[3] The described mechanism of pyrimidine formation is simplified. In reality, it is more complicated [1] and involves H^+-catalyzed orthoester–imino ester–amidine equilibria, in which the symmetrical amidine Ar–NH–CH=N–Ar is likely to play a central role. The equilibria are driven to the product side by removal of **1** from the solution due to its low solubility and not by thermodynamic factors.

[4] F. Vögtle, private communication, 1981.

[5] Modification of the method reported in Ref. [4].

[6] Originally, for the reaction of anilines and acrolein to give 2,3,4-unsubstituted quinolines the name “Skraup synthesis” and for the reaction of anilines and crotonaldehyde to give quinaldines the name “Doebner–Miller synthesis” was used. Today, the reaction of enones with arylamines in general is listed as “Doebner–Miller synthesis”.

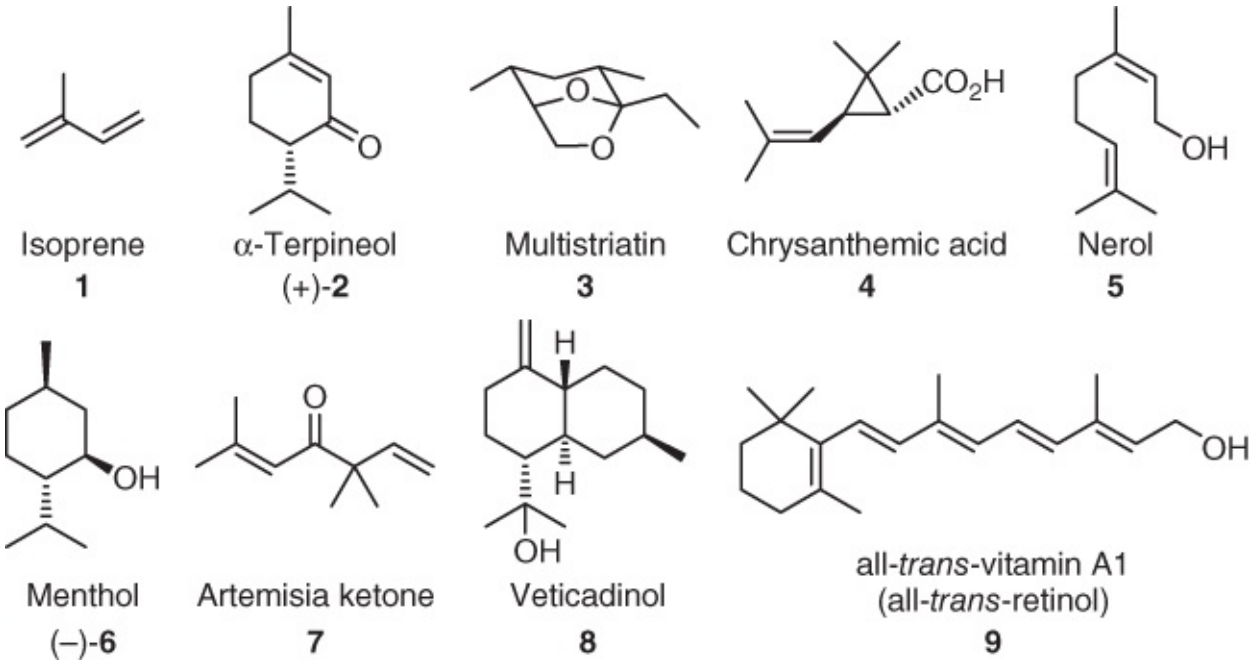
[7] The synthesis of **1** by cyclotetramerization of 3,4-dimethylpyrrole with formaldehyde described in Ref. [7] was modified, adapting the conditions used in Ref. [6] for the preparation of the corresponding octaethylporphyrin.

[8] Modification of the procedure given in Ref. [8].

Chapter 4
Selected Natural Products

4.1 Isoprenoids

The terpenes are a huge group of natural products, which can be formally deduced from the hydrocarbon isoprene (**1**). According to the number of carbon atoms, which is always a multiple of 5 (=isoprene), one distinguishes between monoterpenes (C_{10}), sesquiterpenes (C_{15}), diterpenes (C_{20}), sesterterpenes (C_{25}), triterpenes (C_{30}), and tetraterpenes (C_{40}), as well as polyterpenes [1]. In this book, syntheses of the following monoterpenes are described: α-terpineol (**2**) (Section 1.7.5), *trans*-chrysanthemic acid (**4**) (Section 5.3.1), nerol (**5**) (Section 4.1.1), (−)-menthol (**6**) (Section 4.1.2), and artemisia ketone (**7**) (Section 4.1.3). In addition, preparations of the sesquiterpene veticadinol (**8**) (Section 4.1.4) and the diterpene all-*trans*-vitamin A (**9**) (Section 4.1.5) are also presented.

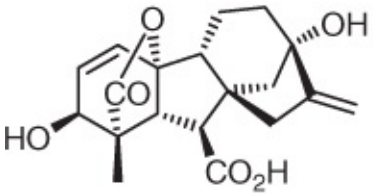


To date, nearly 50 000 different terpenes have been isolated from natural sources as primary ingredients of the essential oils of many types of flowers and plants. Some terpenes are also found in animals, where they act, for example, as pheromones, such as multistriatin (**3**), and in marine organisms, where they are commonly highly halogenated. A large amount of terpenes are emitted from conifers (over 1 000 000 000 tons per annum), which sometimes leads to the

development of a haze in summertime, as in the Smoky Mountains in the United States. Terpenes can form linear chains and cyclic compounds of different sizes, as well as annelated and bridged compounds. In 1910, Professor Otto Wallach of the Georg-August-University in Göttingen was awarded the Nobel Prize for his excellent work in this field.

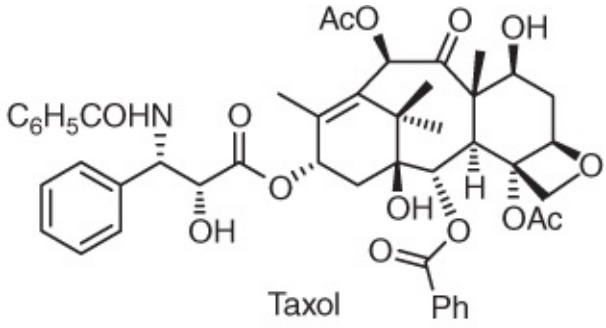
Monoterpenes and sesquiterpenes are mostly used as fragrances in perfumery [2]. There are several important diterpenes, such as the plant growth factor gibberellic acid (**10**), the anticancer agent taxol (**11**) [3], and the sight purpur retinal (**9**, CHO instead of CH_2OH). A notable triterpene is the tetracyclic compound lanosterol (**12**), the precursor of steroids [4–7] in animals.

Important tetraterpenes are the acyclic lycopene, the dye of tomatoes, and the carotenes. The best known polyterpene is natural rubber, in which all double bonds are of (*Z*)-configuration. Moreover, many compounds found in nature are degradation products of terpenes, such as β-ionone (**13**) (cf. Section 1.5.3), which is formed by oxidative cleavage of a tetraterpene.



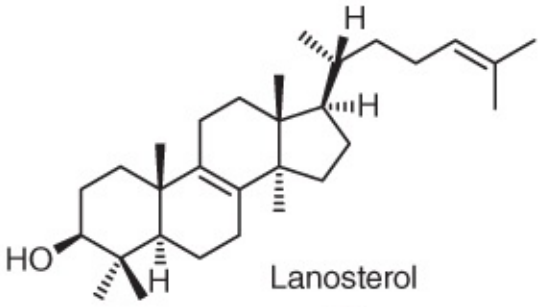
Gibberellic acid GA_3

10



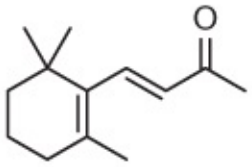
Taxol

11



Lanosterol

12



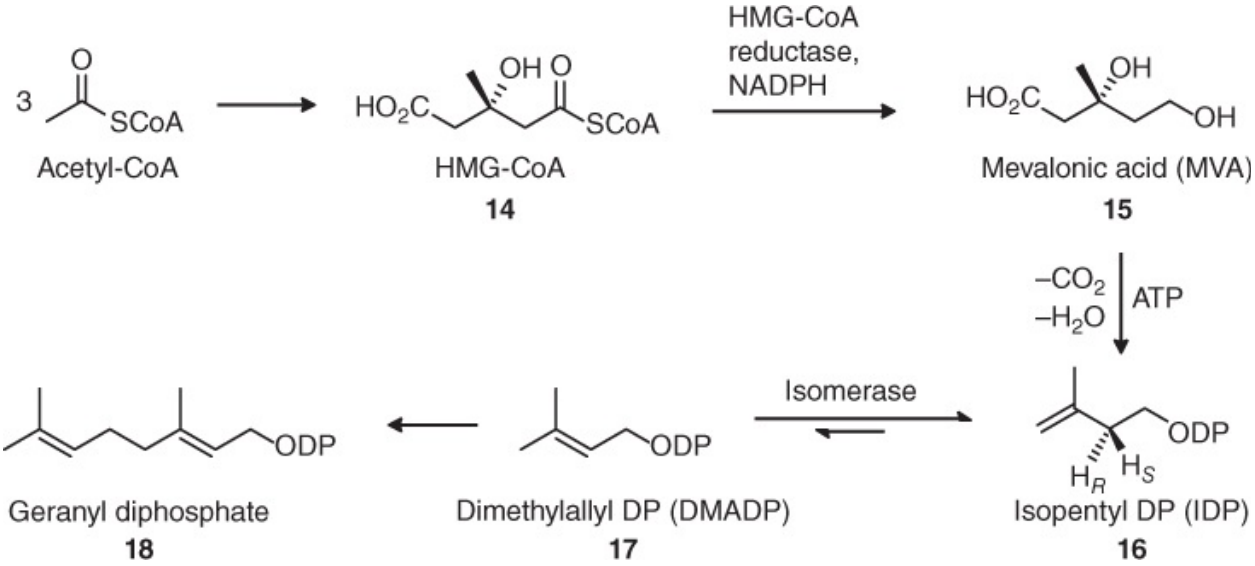
β-Ionone

13

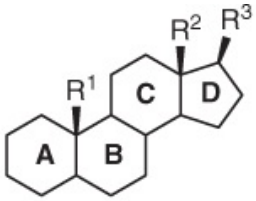
Terpenes are biosynthesized from acetyl-CoA via 3-hydroxy-3-methylglutaryl-CoA (**14**) (HMG-CoA) and mevalonic acid (**15**) (MVA) to afford isopentenyl diphosphate (**16**) (IDP) and dimethylallyl diphosphate (**17**) (DMADP), which undergo a head-to-tail condensation to give the monoterpene geranyl diphosphate (**18**), the mevalonate pathway [7]. This is the natural substrate for nearly all other terpenes. However, in a few cases, a head-to-head connection

also takes place. This type of condensation is found in the biosynthesis of chrysanthemic acid (**4**) (Section 5.3.1) [8] and in a way also in that of artemisia ketone (**7**) (Section 4.1.3).

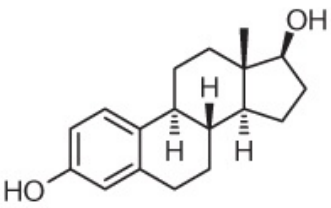
Recently, it has been shown that in some bacteria and plastids of plants another pathway is operative (2-methyl-D-erythritol-4-phosphate (MEP) pathway), which starts from a C_4-sugar, MEP, to again give IDP and DMADP [9].



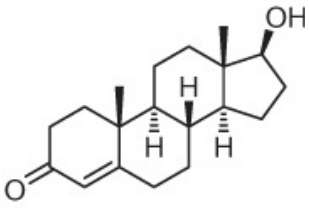
Closely related to the terpenes are the steroids, since they are formed from lanosterol (**12**) in animals as well as in fungi, and from cycloartenol (**24**) in plants as well as in algae. They all contain a perhydrogenated a cyclopenta[*c*]phenanthrene carbon skeleton **19**.



19



Estradiol
20



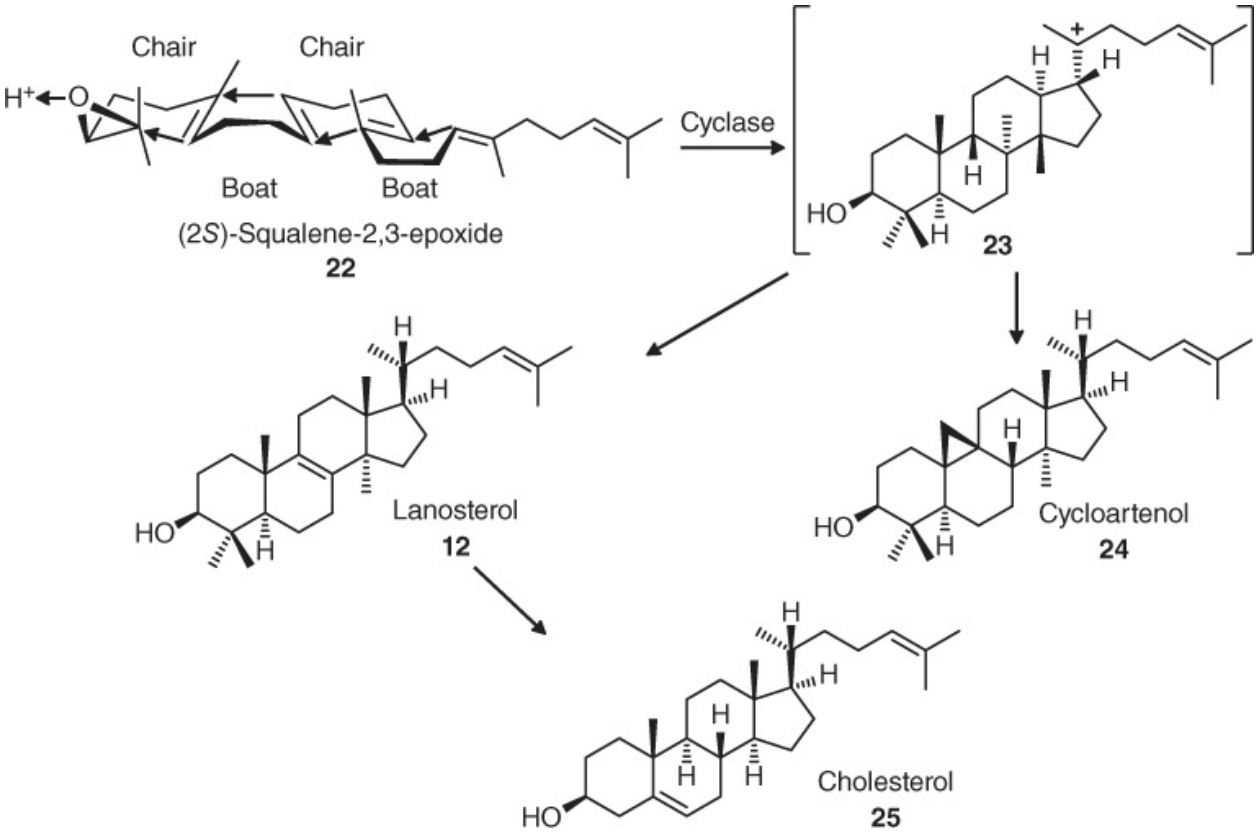
Testosterone
21

Fundamental skeleton	R^1	R^2	R^3
Gonane	H	H	H
Estrane	H	CH_3	H
Androstane	CH_3	CH_3	H
Pregnane	CH_3	CH_3	CH_3

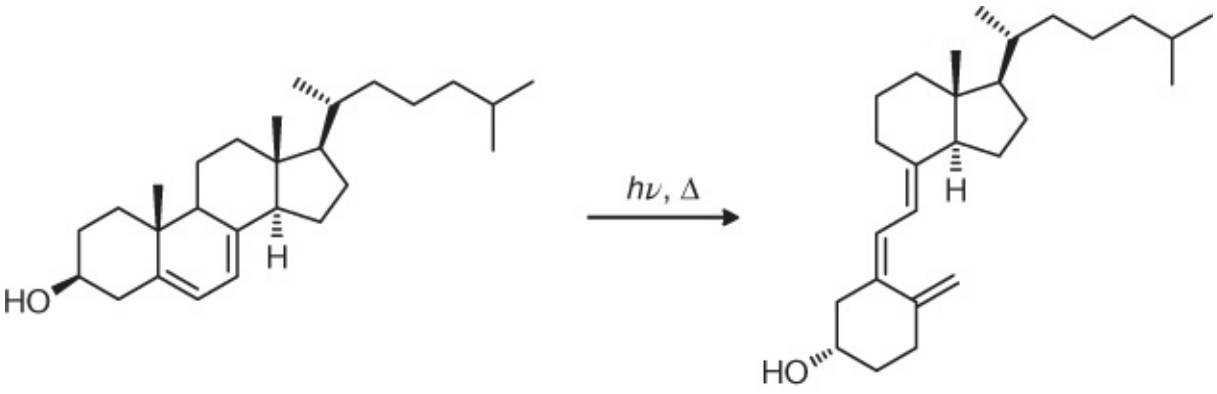
Because of their pronounced biological activity as hormones such as estradiol

(**20**) and testosterone (**21**), the steroids are by far the best investigated group of natural products. They are formed in nature from the acyclic triterpene squalene by cyclization of its epoxide **22** to give either lanosterol (**12**) or cycloartenol (**24**) via the intermediate carbocation **23** [4].

In animals, lanosterol (**12**) is transformed into cholesterol (**25**), which is the principal animal steroid. It is present in the membranes of all animal cells and, furthermore, is the precursor for the formation of other steroid hormones.



Vitamin D (**27**) is also a steroid derivative formed from steroid **26** by an interesting photochemical ring-opening of the cyclohexadiene moiety followed by a thermal 1,7-sigmatropic hydrogen shift [5]. In 1928, Prof. A. Windaus of the Georg-August-University in Göttingen was awarded the Nobel Prize for his outstanding work on vitamin D.



Provitamin D_3
26

Cholecaliferol (Vitamin D_3)
27

References

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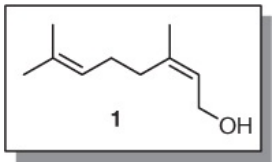
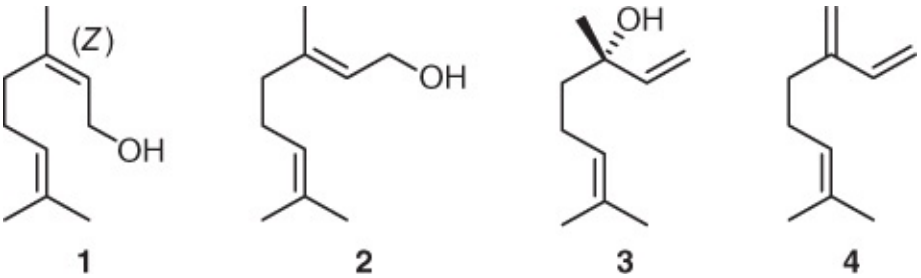
4.1.1 Nerol

	***Topics:***	• Synthesis of a monoterpene alcohol • Stereoselective dimerization (telomerization) of isoprene induced by LDA • Transformation of a tertiary allylamine to an allyl chloride • Crown ether-catalyzed S_N reaction • Saponification of a carboxylic ester

(a) General

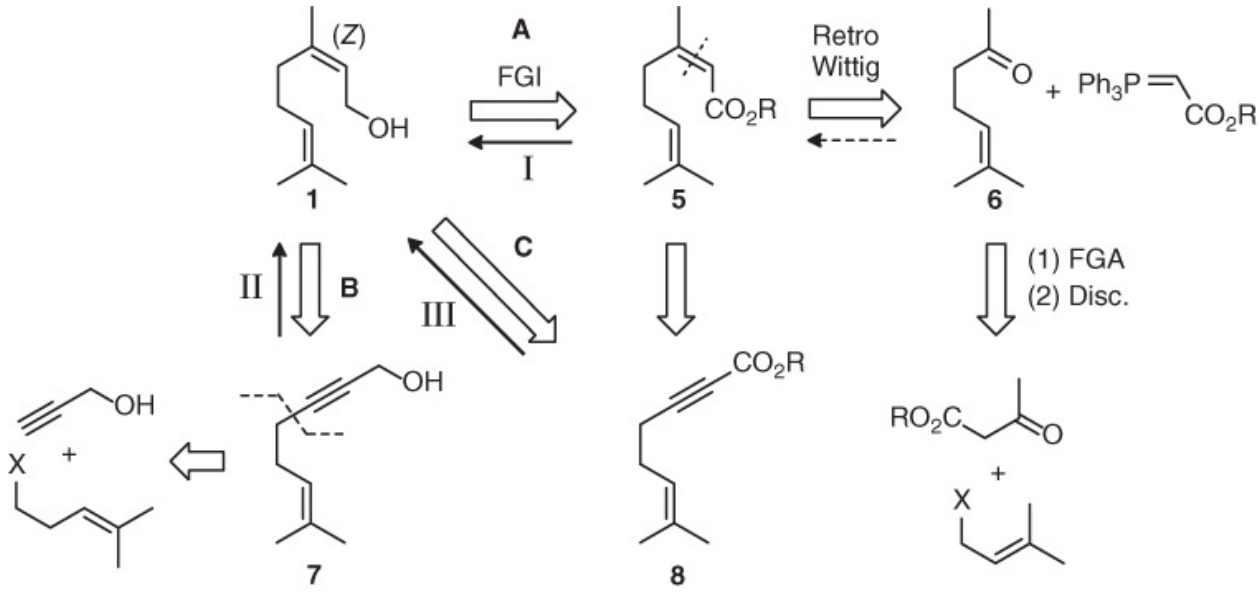
Nerol, (2*Z*)-3,7-dimethylocta-2,6-dien-1-ol (**1**), and its (2*E*)-stereoisomer geraniol (**2**) belong to the group of unsaturated acyclic monoterpene alcohols most widespread in nature. Nerol (**1**) and geraniol (**2**) are found as free alcohols and in esterified form in palmarosa oil and geranium oil; nerol (**1**) is also found in the etheric oil of the straw flower *Helichrysum italicum* (*Helichrysum angustifolium*, Asteraceae). Together with the allyl-isomeric linalool (**3**), geraniol (**2**) and nerol (**1**) are used in perfumery and cosmetics [1]. Nerol (**1**) is technically produced along with geraniol (**2**) and linalool (**3**) from β-pinene via myrcene (**4**) [2].



1 **2** **3** **4**

Geranyl and neryl diphosphates are important intermediates in the biosynthesis of acyclic and cyclic monoterpenes according to the mevalonate pathway [3].

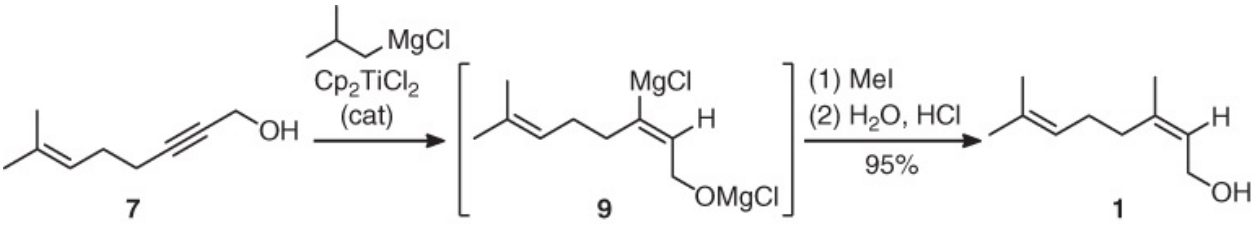
For the chemical synthesis of nerol (**1**), several retrosynthetic approaches are possible:



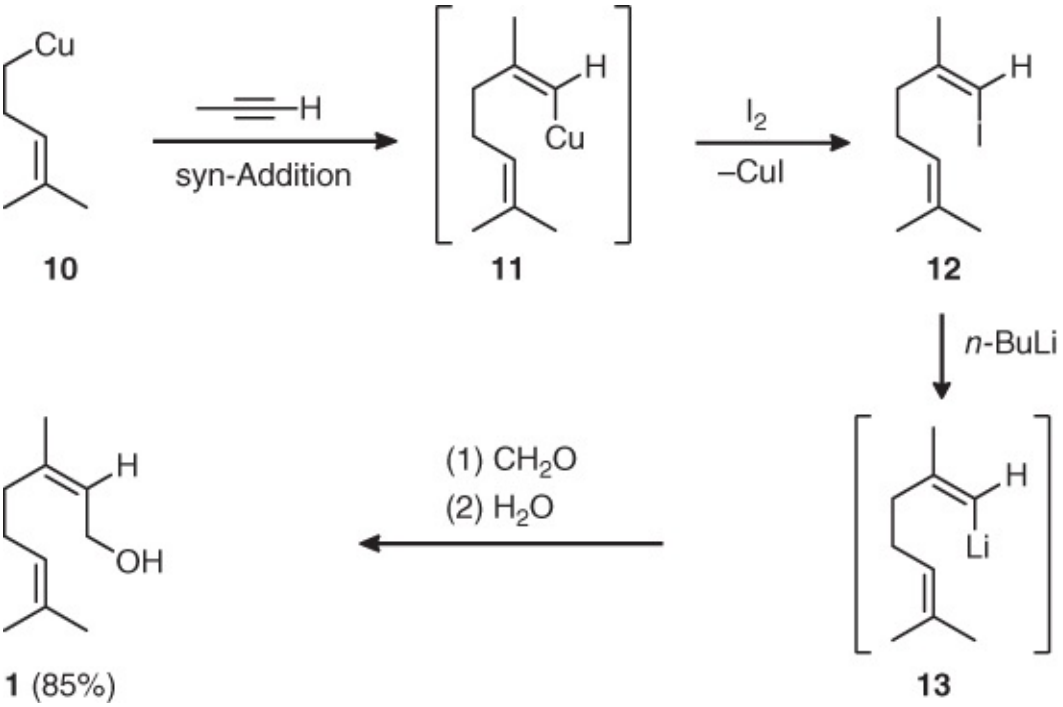
Following strategy **A**, the functional group interconversion (FGI) of the alcohol moiety leads to the α,β-unsaturated ester **5**, which is then disconnected at the C-2/C-3 double bond by a retro-Wittig reaction to methylheptenone **6** and a P-ylide. Ketone **6** is further disconnected to give acetoacetate and a prenyl halide. The synthesis of ketone **6** by alkylation of acetoacetate followed by "ketone cleavage" of the alkylated β-keto ester is straightforward [4], but the carbonyl olefination of **6**, for example, by the Wittig–Horner method [5], leads to (*E*)/(*Z*) mixtures of the unsaturated ester **5** and thus lacks the stereoselectivity required for a concise synthesis of **1**.

According to strategy **B**, the alkyne **7** is a good precursor of **1** since the addition of an organometallic M–CH_3 species (M = metal) allows (*Z*)-stereoselective construction of nerol (**1**). Similar considerations (**C**) would lead to the acetylenic ester **8**, its transformation to **5** by syn-addition of an M–CH_3 species, such as a cuprate [6], and finally reduction of the (*Z*)-α,β-unsaturated ester moiety in **5** to give nerol (**1**). In fact, strategy **B** serves as a basis for several stereoselective syntheses of nerol (**1**) [7], as shown by the following examples.

Treatment of the propargylic alcohol **7** with isobutyl-MgCl catalyzed by Cp_2TiCl_2 leads to hydromagnesiation of the triple bond, which proceeds readily in a syn manner and leads regioselectively to the vinylmagnesium compound **9**; its C-methylation by CH_3I with retention of configuration followed by hydrolysis gives nerol (**1**) in high yield [8].



Likewise, addition of the alkenylcopper reagent **10** to propyne occurs with complete syn selectivity at low temperature to yield the vinylcopper intermediate **11**, which is trapped as the vinyl iodide **12** by reaction with iodine and transformed to the vinyllithium compound **13** by halogen–metal exchange with *n*-BuLi; since the double-bond configuration is preserved in the transmetallation sequence (**11** → **12** → **13**), addition of **13** to formaldehyde and subsequent hydrolysis leads to nerol (**1**) [9]:

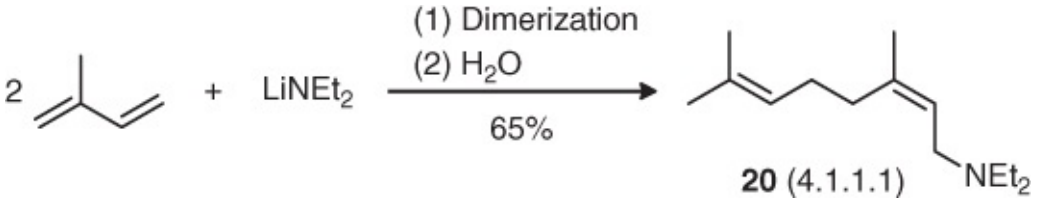


While the syn addition of alkyl cuprates to acetylenic esters of type **8** is documented in numerous examples [10], the transformation of **8** to afford **5** followed by reduction to give nerol (**1**) has not yet been realized. This is probably due to the instability of **5**, since (*Z*)-α,β-unsaturated esters easily isomerize to give the corresponding (*E*)-compounds.

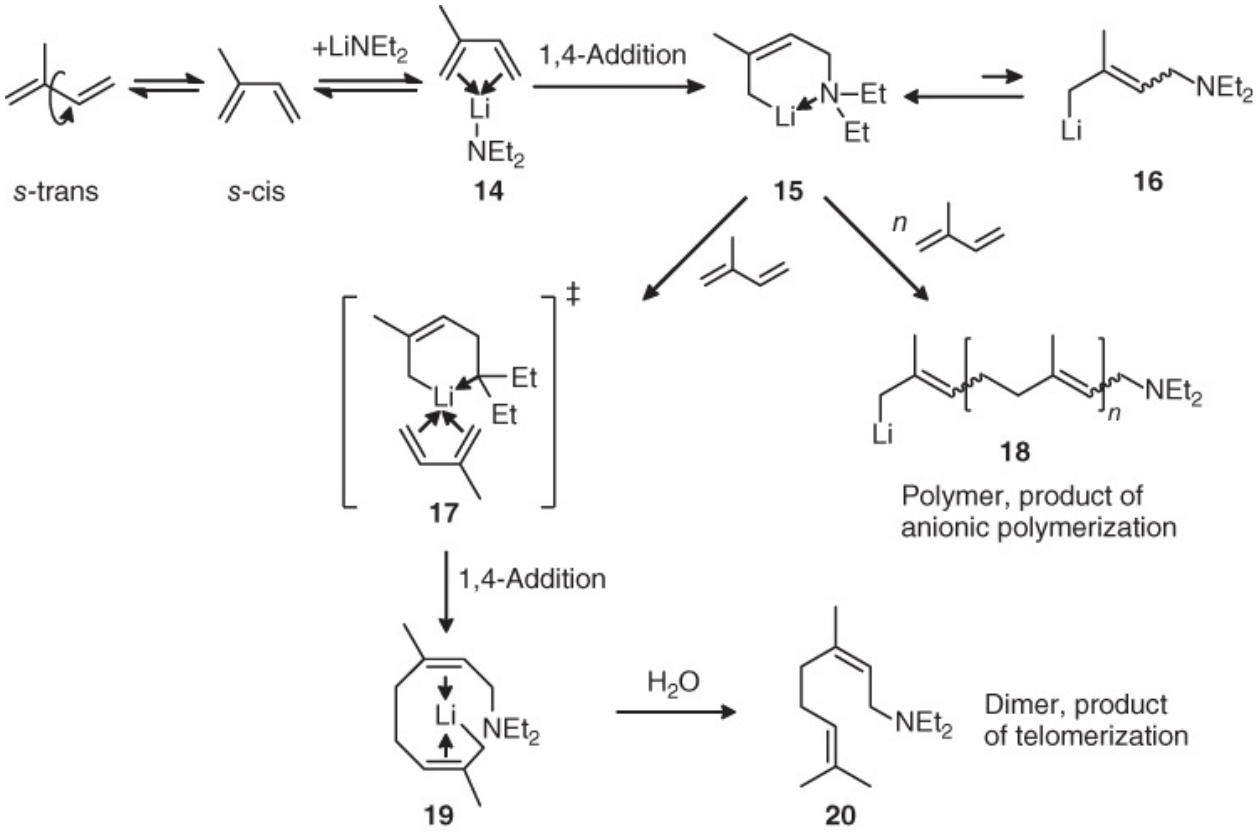
For reasons of preparative viability, the synthesis of nerol (**1**) described here follows the reaction principle of lithium diethylamide (LDA)-induced stereoselective telomerization of isoprene.

(b) Synthesis of (1)

Reaction of isoprene with LDA in anhydrous benzene leads to *N*,*N*-diethylnerylamine (**20**) in 65% yield after hydrolytic work-up [11]. LDA effects head-to-tail coupling of two isoprene units in analogy to the biosynthesis of isoprenoids [2], but directs this process to proceed stereoselectively in a (*Z*)-manner with respect to the C-2/C-3 double bond formed in product **20**:



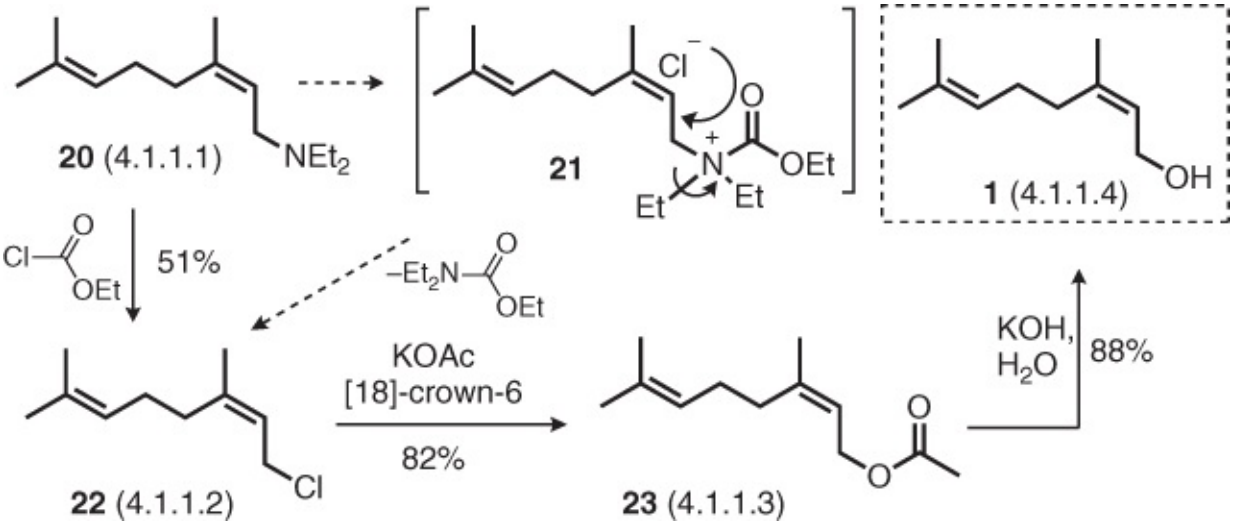
This remarkable dimerization (telomerization, cf. Section **1.8.1**) is favored over the expected anionic polymerization of the 1,3-diene (isoprene → polymer **18**). It can be rationalized on the basis of the following mechanisms [11]:



Initially, the 1,4-addition of LDA to isoprene might be facilitated by the formation of a preorientated metal complex **14** by π-coordination of the *s*-cis conformer of the conjugated diene to lithium. This leads to an allyllithium intermediate **15**, and the nonpolar reaction medium (benzene) favors

intramolecular Li coordination with the amine donor function, as in **15** with a (*Z*)-configuration at the C-2/C-3 double bond. Addition of a second isoprene unit proceeds via π-coordination to the Li center of **15** in a highly ordered transition state **17**. The Li complex **19** results as the product of this second 1,4-addition, which is probably stabilized by internal N-and π-coordination, leading to nerylamine (**20**) on hydrolysis.

Nerylamine (**20**) is transformed into nerol (**1**). First, the amine function is replaced by a chloro substituent by reacting **20** with ethyl chloroformate to give the allylic chloride **22**. This substitution is generally applicable to tertiary allylic amines [12]. It is assumed to occur via N-acylation (**20** → **21**) and elimination of a urethane moiety by attack of chloride at the allylic ammonium position, providing the chloride **22**.

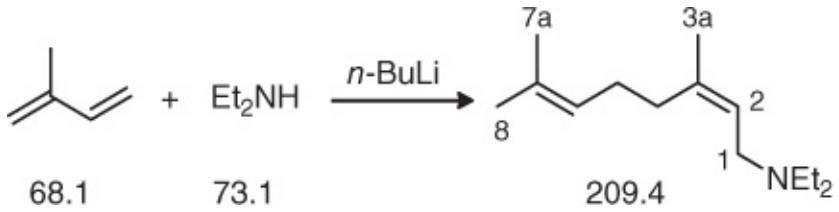


Finally, the chloride **22** is subjected to an S_N displacement in the presence of a crown ether to increase the nucleophilicity of the anion (cf. Section 3.5.3) using KOAc. The resulting allylic acetate **23**, which is formed without allylic inversion, is saponified with aqueous KOH to provide nerol (**1**).

Thus, the target molecule **1** is obtained by a four-step sequence in an overall yield of 24% based on isoprene.

(c) Experimental Procedures for the Synthesis of 1

4.1.1.1	***	***N*,*N*-Diethylnerylamine** [11]



Under an argon atmosphere, isoprene (34.1 g, 500 mmol) and diethylamine (7.31 g, 100 mmol) are dissolved in anhydrous benzene (40 ml) (Caution: carcinogenic!) in a 250-ml three-necked round-bottomed flask, fitted with a reflux condenser and an inert gas inlet. *n*-BuLi (0.75 M in *n*-hexane, 27.0 ml, 20 mmol) is added with stirring, and the solution is heated to 51 °C for 30 h. During this time, a precipitate is formed, which redissolves after several hours of stirring and the solution becomes yellow as the internal temperature rises to 67 °C.

The solution is then cooled, EtOH (20 ml) is added dropwise, and the resulting solution is washed with H_2O (70 ml). The aqueous phase is saturated with NaCl and extracted with benzene (3 × 50 ml). The combined organic phases are washed with brine (50 ml), dried over Na_2SO_4, and filtered, and the solvent is removed *in vacuo*. The residue is distilled to give the product as a colorless oil; 13.5 g (65%), bp_{19} 135–138 °C, n^{20}_D = 1.4669.

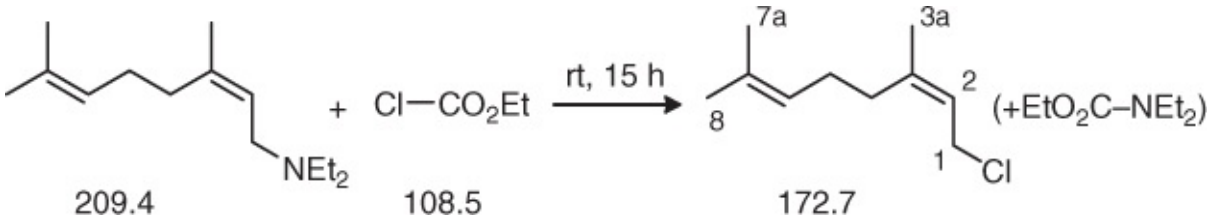
IR (NaCl): $\tilde{\nu}$ (cm^{-1}) = 2960, 2920, 2865, 2800, 1670.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 5.25 (t, *J* = 6.8 Hz, 1H, 6-H), 5.06–5.15 (m, 1H, 2-H), 3.04 (dd, *J* = 6.8, 1.2 Hz, 2H, 1-H_2), 2.49 (q, *J* = 7.2 Hz, 4H, 2 × NC$\underline{H}_2$$CH_3$), 2.05 (d, *J* = 3.2 Hz, 4H, 4-H_2, 5-H_2), 1.70–1.73 (m, 3H, 3a-H_3), 1.67 (s, 3H, 8-H_3), 1.60 (s, 3H, 7a-H_3), 0.99 (t, *J* = 7.2 Hz, 6H, 2 × $NCH_2C\underline{H}_3$).

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 137.7 (C-3), 131.7 (C-7), 124.1 (C-2), 122.7 (C-6), 50.4 (C-1), 46.6 (2 × $\underline{C}H_2CH_3$), 32.2 (C-4), 26.5 (C-5), 25.7 (C-8), 23.5 (C-3a), 17.6 (C-7a), 11.8 (2 × $CH_2\underline{C}H_3$).

Note: Isoprene (bp 34–35 °C) and diethylamine (bp 56–57 °C, dried over KOH) are distilled before use.

4.1.1.2	*	**Neryl chloride** [13]



N,*N*-Diethylnerylamine (cf. **4.1.1.1**) (11.5 g, 55.2 mmol) is added dropwise to ethyl chloroformate (11.9 g, 110 mmol) (note 1) at 0 °C (inner temperature) over a period of 15 min. The mixture is stirred at room temperature for 15 h as the amine odor changes to a fruity one.

The product is distilled directly from the reaction mixture under reduced pressure; the excess ethyl chloroformate distils first at room temperature (Caution: foaming!), followed by *N*,*N*-diethylethoxyformamide (bp_{15} 67–73 °C, 7.50 g) and neryl chloride as a colorless oil; 5.37 g (note 2), bp_{15} 98–99 °C, n^{20}_D = 1.4728.

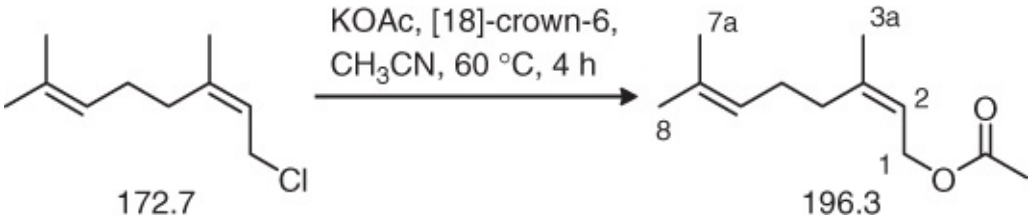
IR (film): $\tilde{\nu}$ (cm^{-1}) = 1665, 675.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 5.43 (t, *J* = 8.1 Hz, 1H, 2-H), 5.04–5.14 (m, 1H, 6-H), 4.06 (dd, *J* = 8.1, 0.7 Hz, 2H, 1-H_2), 2.07–2.12 (m, 4H, 4-H_2, 5-H_2), 1.78–1.80 (m, 3H, 3a-H_3), 1.67 (s, 3H, 8-H_3), 1.59 (s, 3H, 7a-H_3).

Notes:

1. Ethyl chloroformate has to be distilled before use, bp 94–95 °C.
2. According to ^{1}H NMR, the neryl chloride obtained is 90% pure, corresponding to a 51% yield. The contaminating $Et_2N–CO_2Et$ can be removed by spinning-band distillation; however, it does not interfere with the following reaction.

4.1.1.3 * **Neryl acetate** [13]



Potassium acetate (dried over P_4O_{10} under vacuum; 2.93 g, 30.0 mmol) is added

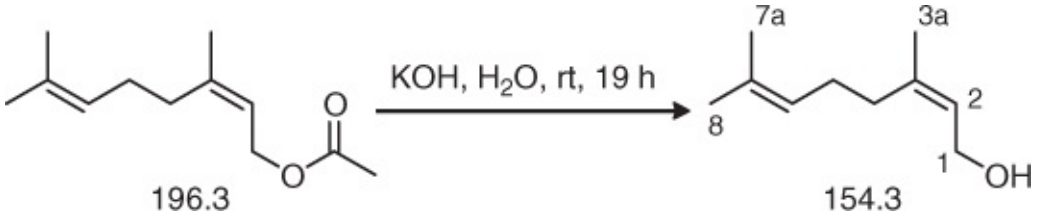
to a solution of neryl chloride (cf. **4.1.1.2**) (4.41 g, 32.2 mmol) and [18]-crown-6 (0.53 g, 2.00 mmol) in anhydrous CH_3CN (25 ml) and the mixture is stirred for 4 h at 60 °C.

The mixture is then cooled to room temperature and filtered, and the solvent is removed *in vacuo*. The brown residue is distilled *in vacuo* in a microdistillation apparatus. The product is 90% pure with a contamination of $Et_2N–CO_2Et$ (^{1}H NMR); 4.15 g (82%), bp_{15} 119–122 °C, n^{20}_D = 1.4602.

IR (film): $\tilde{\nu}$ (cm^{-1}) = 1740, 1230, 1020.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 5.34–5.39 (m, 1H, 5-H), 5.08–5.12 (m, 1H, 9-H), 4.55–4.58 (dd, *J* = 7.3, 0.8 Hz, 2H, 4-H_2), 2.09–2.11 (m, 4H, 7-H_2, 8-H_2), 2.05 (s, 3H, 1-H_3), 1.77–1.78 (m, 3H, 6a-H_3), 1.69 (s, 3H, 11-H_3), 1.61 (s, 3H, 10a-H_3).

4.1.1.4	*	**Nerol (3,7-dimethylocta-2(*Z*)-6-dien-1-ol)** [13]



Neryl acetate (cf. **4.1.1.3**) (3.55 g, 16.0 mmol) is dissolved in methanolic KOH (1.50 g, 27.0 mmol of KOH in 10.7 ml of MeOH). The solution is stirred at room temperature for 19 h, whereupon potassium acetate precipitates.

H_2O (40 ml) is then added and the mixture is extracted with $CHCl_3$ (1 × 40 ml, then 3 × 25 ml). The combined organic phases are washed with H_2O (30 ml), dried over Na_2SO_4, and filtered, and the solvent is removed at atmospheric pressure. The yellow oily residue is fractionally distilled *in vacuo* to give nerol as a colorless oil; 2.28 g, bp_{15} 111–113 °C, n^{20}_D = 1.4730.

The product is 95% pure (^{1}H NMR) (still contaminated with $Et_2N–CO_2Et$), which corresponds to a yield of 88%. The product shows a *Z*/*E* ratio of 99.5 : 0.5 and is pure as indicated by thin-layer chromatography (TLC) (SiO_2; CH_2Cl_2) with R_f = 0.90 for nerol (as compared to R_f = 0.65 for geraniol) (note).

IR (NaCl): $\tilde{\nu}$ (cm^{-1}) = 3320, 1675, 1000.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 5.38–5.51 (m, 1H, 2-H), 5.06–5.17 (m, 1H, 6-H), 4.10 (dd, *J* = 7.2, 0.9 Hz, 2H, 1-H_2), 2.01–2.18 (m, 4H, 4-H_2, 5-H_2), 1.74–1.79 (m, 3H, 3a-H_3), 1.70 (s, 3H, 8-H_3), 1.62 (s, 3H, 7a-H_3), 1.38 (s_{br}, 1H, OH).

Note: Crystalline derivatives of nerol are the tetrabromide, mp 118–119 °C, and the diphenylurethane, mp 52–53 °C. Compare with the corresponding derivatives of geraniol: the tetrabromide, mp 70–71 °C, and the diphenylurethane, mp 81–82 °C.

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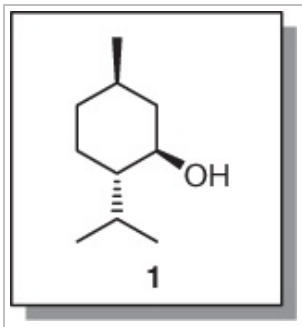
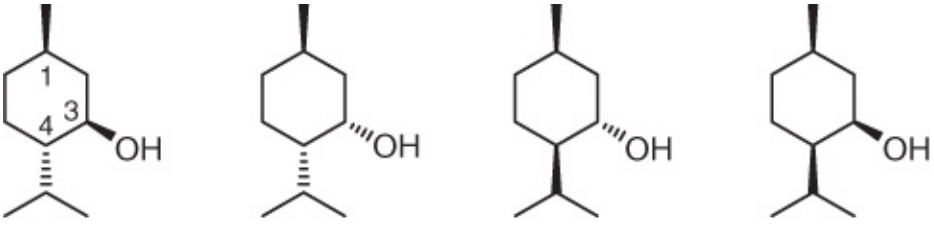
4.1.2 (−)-Menthol

 **1**	***Topics:***	• Lewis acid-mediated ene reaction • Catalytic hydrogenation of an olefinic double bond

(a) General

(−)-Menthol ((1*R*,3*R*,4*S*)-4-isopropyl-1-methylcyclohexan-3-ol or (1*R*,3*R*,4*S*)-*p*-menthan-3-ol) (**1**) possesses three defined stereogenic centers within its cyclohexane core. It is one of the eight possible stereoisomers with this skeleton, of which four occur in nature ((−)-menthol (**1**), (+)-neomenthol (**2**), (+)-isomenthol (**3**), and (+)-neoisomenthol (**4**)) [1]:



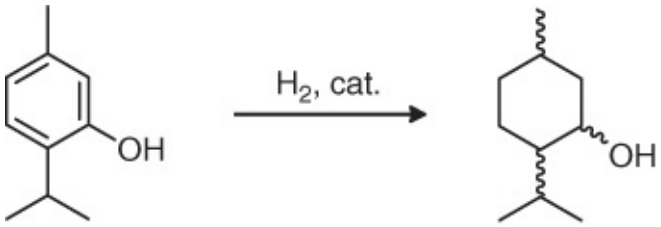
1 (1*R*,2*R*,4*S*) **2** (1*R*,3*S*,4*S*) **3** (1*R*,3*S*,4*R*) **4** (1*R*,1*R*,4*R*)

(−)-Menthol (**1**) is widespread in nature as the main component of peppermint and cornmint oils, which are obtained from the species *Mentha piperita* and

Mentha arvensis in free and esterified forms (e.g., acetate, isovalerate). (−)-Menthol (**1**) is used as a cooling and refreshing ingredient in cigarettes, cosmetics, toothpastes, sweets, and medicines [2].

In the industrial production of (−)-menthol (**1**), isolation from natural sources competes with partial or total synthesis. Among the numerous syntheses [3], two methods are worth mentioning.

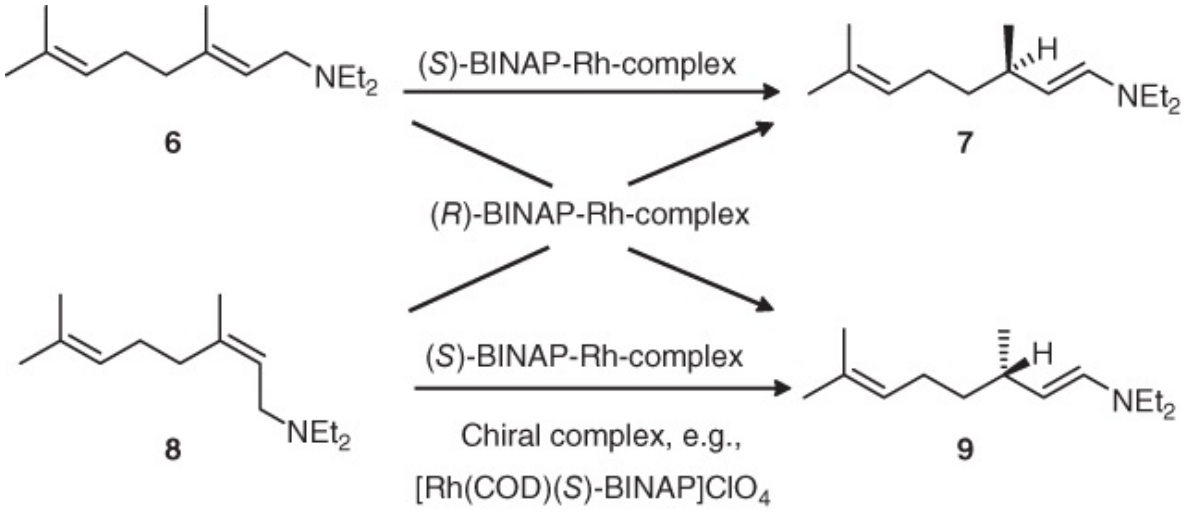
1. (−)-Menthol has been synthesized by catalytic hydrogenation of thymol (**5**) [2]:



5

This process yields a mixture of the four possible diastereomers in various ratios, from which *rac*-menthol is separated by fractional distillation and resolved into its enantiomers by selective crystallization of the benzoates.

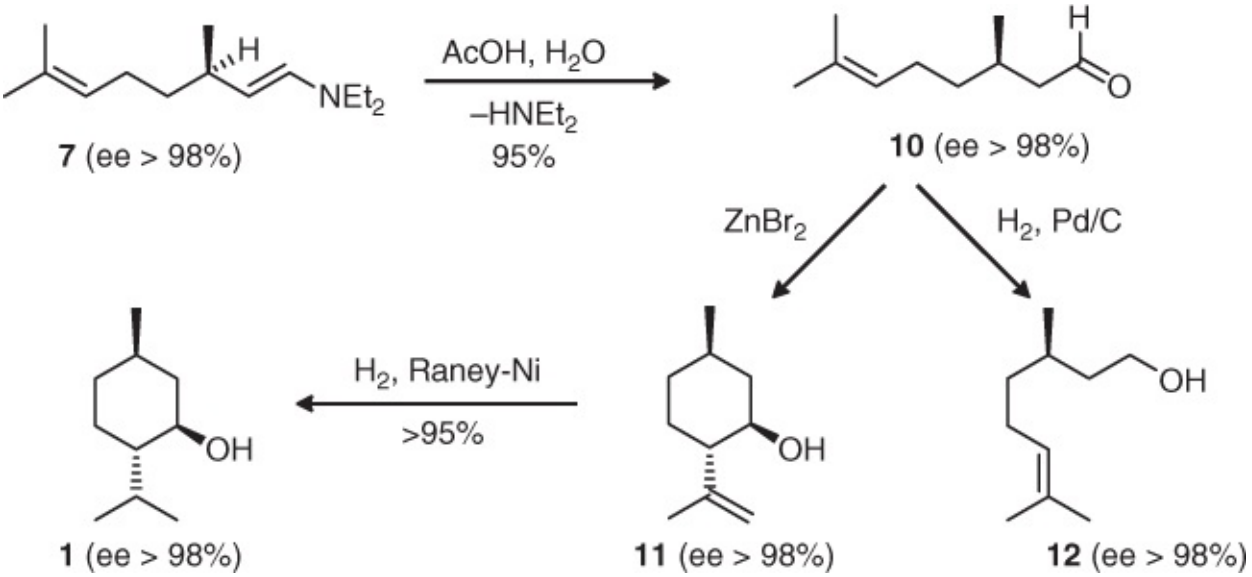
2. (−)-Menthol is obtained on an industrial scale (Takasago) [4] by an enantioselective asymmetric hydrogen shift of *N*,*N*-diethylgeranylamine (**6**) catalyzed by a chiral rhodium(I)-(*S*)-BINAP complex to give the (*E*)-enamine **7** of (*R*)-citronellal:



Interestingly, *N*,*N*-diethylnerylamine (**8**) (cf. **4.2.2.1**) can also serve as a substrate for the formation of **7** if the Rh-(*R*)-BINAP complex is used as catalyst, while the enantiomeric enamine **9** arises from **6** by catalysis with the Rh-(*R*)-

BINAP complex and from **8** by catalysis with the Rh-(*S*)-BINAP complex. The origin of the enantioselection has been discussed in detail in terms of chiral recognition caused by the chiral Rh-BINAP complexes [3–5].

The chiral enamine **7** is hydrolyzed in an acidic medium ($AcOH/H_2O$) to give (*R*)-citronellal (**10**). This is then subjected to a Lewis acid-catalyzed intramolecular carbonyl ene reaction (see Section (b)), which proceeds stereoselectively to form (−)-isopulegol (**11**). Hydrogenation of **11** then leads to the desired (−)-menthol with >98% ee. Alternatively, (*R*)-citronellol (**12**) can be obtained from the aldehyde **10** by catalytic hydrogenation [4].

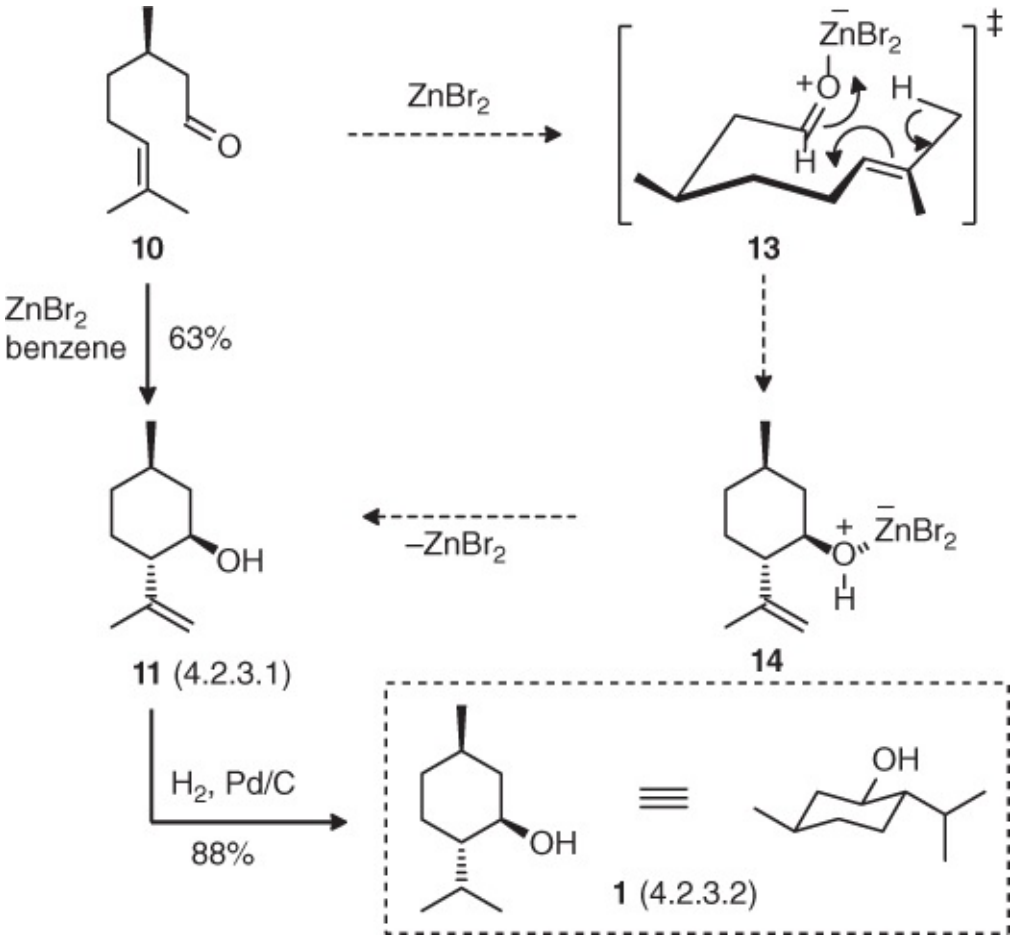


In the Takasago process, all transformations are reported to occur with high chemical yields (95–100%) and excellent enantioselectivities (>98% ee).

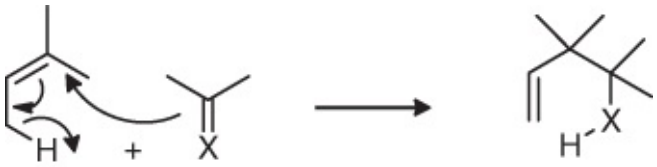
Since the chiral Rh complexes applied for the enantioselective H-shift in **6** to give **7** are expensive, only the subsequent transformations of the technical synthesis of (−)-menthol are presented in Section (b).

(b) Synthesis of 1

In the first step, (*R*)-citronellal (**10**) is cyclized to (−)-isopulegol (**11**) in benzene solution at 5–10 °C in the presence of $ZnBr_2$. It can be assumed that an oxenium ion is initially formed by coordination of the Lewis acid to the carbonyl moiety. This then undergoes a carbonyl ene reaction via a chair-like transition state **13**, with an equatorial orientation of the methyl group controlling the stereochemistry of the newly formed stereogenic centers in **11**.



Ene reactions take place between olefines bearing an allylic hydrogen and an "enophile" which is either a second olefin bearing one or two electron-withdrawing groups or a carbonyl moiety. "All-carbon" ene reactions usually follow a concerted mechanism as pericyclic reactions, whereas carbonyl ene reactions proceed via a carbocation as an intermediate in a two-step mechanism [6]. In cases in which transfer of chirality or high stereoselection in product formation is observed, a highly ordered transition state can be assumed.



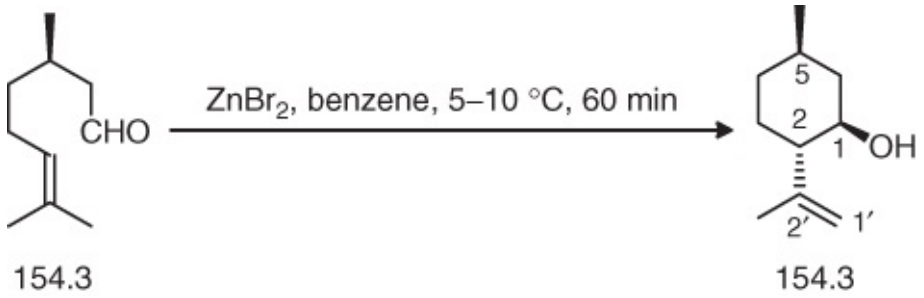
X = CR_2 : ene reaction

X = O : carbonyl ene reaction

In the second step, (−)-isopulegol (**11**, cf. **4.1.2.1**) is subjected to catalytic hydrogenation to yield (−)-menthol (**1**) in high yield (88%) and with high enantiomeric purity (>98% ee).

(c) Experimental Procedures for the Synthesis of 1

4.1.2.1	*	**Isopulegol** [7]



$ZnBr_2$ (219 mg, 972 µmol) is added portionwise to a stirred solution of (*R*)-citronellal (150 mg, 972 µmol) in anhydrous benzene (2 ml) (Caution: carcinogenic!) at 5 °C under an argon atmosphere, and stirring is continued at 5–10 °C for 60 min.

After filtration, the $ZnBr_2$ is rinsed with Et_2O (10 ml), and the filtrate is washed with H_2O (10 ml) and saturated aqueous $NaHCO_3$ solution (10 ml), dried over Na_2SO_4, and filtered. The solvent is removed *in vacuo* and the crude product is purified by flash column chromatography on silica gel (*n*-pentane/Et_2O, 10 : 1) to afford (−)-isopulegol as colorless oil; 94.5 mg (63%), $bp_{2.6}$ 50–60 °C; n^{20}_D = 1.4695; $[\alpha]^{20}_D$ = −18.8 (*c* = 1.0, $CHCl_3$), R_f = 0.51 (Et_2O/*n*-pentane, 1 : 1).

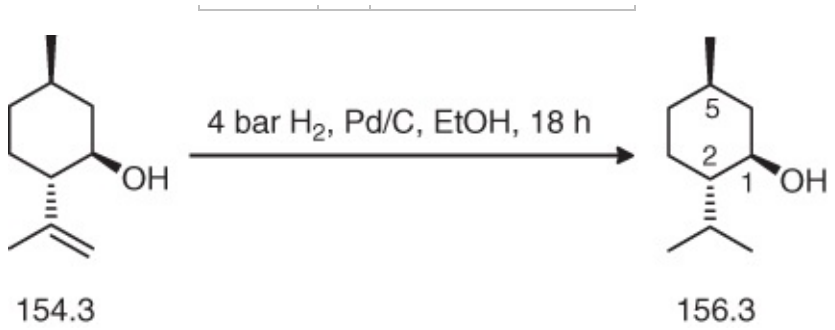
IR (NaCl): $\tilde{\nu}$ (cm^{-1}) = 2923, 1645, 1455, 1095, 1027, 886, 846.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 4.90 (s, 1H, 1′-H_a), 4.86 (s, 1H, 1′-H_b), 3.47 (td, *J* = 10.4, 4.3 Hz, 1H, 1-H), 2.04 (m_c, 1H, 2-H), 1.94–1.84 (m, 2H, alkylCH_2), 1.71 (s, 3H, 2′-CH_3), 1.70–1.63 (m, 2H, alkylCH_2), 1.59–1.42 (m, 1H, 5-H), 1.40–1.24 (m, 2H, alkylCH_2), 0.95 (d, *J* = 6.6 Hz, 3H, 5-CH_3).

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 146.6 (C-2′), 112.9 (C-1′), 70.3 (C-1), 54.1 (C-2), 42.6 (C-6), 34.3 (C-4), 31.4 (C-5), 29.6 (C-3), 22.2 (5-CH_3), 19.2 (C-3′).

MS (EI, 200 eV): *m*/*z* (%) = 154.2 (40) $[M]^+$.

4.1.2.2	**	**(−)-Menthol** [7]



A mixture of isopulegol (cf. **4.1.2.1**) (702 mg, 4.55 mmol) and 10% Pd on charcoal (200 mg) in EtOH (45 ml) is shaken for 18 h at 20 °C under an atmosphere of hydrogen (4 bar) (Caution!).

The catalyst is then filtered off by passing the mixture through a pad of Celite®, which is subsequently rinsed with EtOH (50 ml). Evaporation of the solvent *in vacuo* and purification of the crude product by flash column chromatography on silica gel (*n*-pentane/EtOAc (ethyl acetate), 9 : 1) affords (−)-menthol as colorless solid; 627 mg (88%), mp 40–41 °C, $[\alpha]^{20}_{D}$ = −37.1 (*c* = 2.7, EtOH); R_f = 0.51 (Et_2O/*n*-pentane, 1 : 1).

IR (NaCl): $\tilde{\nu}$ (cm^{-1}) = 2954, 1455, 1045, 1025.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.41 (td, *J* = 10.6, 4.4 Hz, 1H, 1-H), 2.17 (sept of d, *J* = 7.2, 2.8 Hz, 1H, C<u>H</u>$(CH_3)_2$), 1.96 (m_c, 1H, 5-H), 1.71–1.57 (m, 2H), 1.51–1.34 (m, 2H), 1.16–1.06 (m, 1H), 1.05–0.95 (m, 1H), 0.93 (d, *J* = 4.7 Hz, 3H, CH(C<u>H</u>$_3)_2$), 0.90 (s, 3H, 5-CH_3), 0.81 (d, *J* = 4.4 Hz, 3H, CH(C<u>H</u>$_3)_2$).

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 71.5 (C-1), 50.1 (C-2), 45.0 (C-6), 34.5 (C-4), 31.6 (C-5), 25.8 (<u>C</u>H$(CH_3)_2$), 23.1 (C-3), 22.2 (5-CH_3), 21.0, 16.1 (CH(<u>C</u>H$_3)_2$).

MS (EI, 200 eV): *m*/*z* (%) = 156.2 (2) $[M]^+$.

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1. Steglich, W., Fugmann, B., and Lang-Fugmann, S. (eds) (1997) *Römpp Lexikon Naturstoffe*, Georg Thieme Verlag, Stuttgart, p. 392.

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Wiley-VCH Verlag GmbH, Weinheim, p. 100.

3. For an instructive overview on menthol synthesis, see: Nicolaou, K.C. and Sorensen, E.J. (eds) (1996) in *Classics in Total Synthesis*, Wiley-VCH Verlag GmbH, Weinheim, p. 343; see also: Schäfer, B. (2013) *Chem. Unserer Zeit*, **47**, 174–182.

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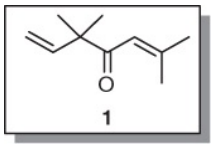
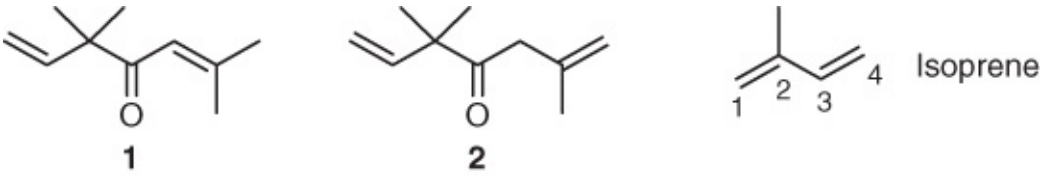
7. (a) Tani, K., Yamagata, T., Akutagawa, S., Kumobayashi, H., Taketomi, T., Takaya, H., Miyashita, A., Noyori, R., and Otsuka, S. (1984) *J. Am. Chem. Soc.*, **106**, 5208–5217;(b) Nakatani, Y. and Kawashima, K. (1978) *Synthesis*, **2**, 147–148.

4.1.3 Artemisia Ketone

 1	***Topics:***	• Synthesis of a monoterpene ketone • Formation of an acid chloride from a carboxylic acid • Formation of an allylsilane from an allyl Grignard compound and trimethylchlorosilane • Acylation of an allylsilane with C–Si cleavage and allylic inversion

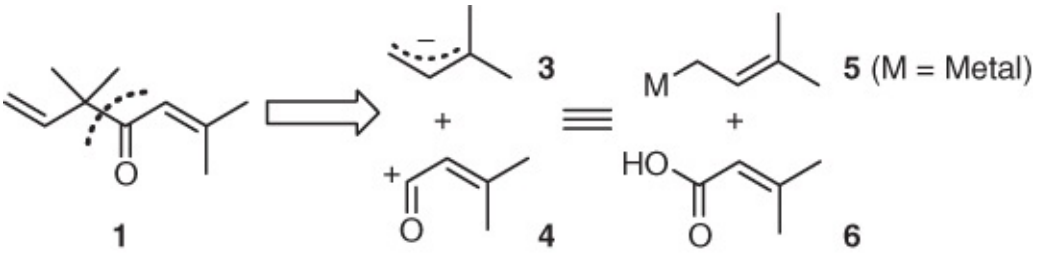
(a) General

Artemisia ketone (**1**, 3,3,6-trimethyl-1,5-heptadien-4-one) has been isolated from the etheric oils of *Artemisia annua* (mugwort) and *Santolina chamaecyparissus* (lavender cotton), which contain mixtures of **1** and its isomer **2** (*iso* artemisia ketone). In terms of the biological activity of **1**, no practical application is known [1].



As a C_{10} monoterpene ketone, the structure of **1** can be deduced from two isoprene C_5 units. In contrast to the usual head-to-tail orientation (C-1 to C-4) derived from the mevalonate pathway of terpene biogenesis (cf. Section 4.2.2), the two building blocks of **1** are in a C-2/C-4 alignment.

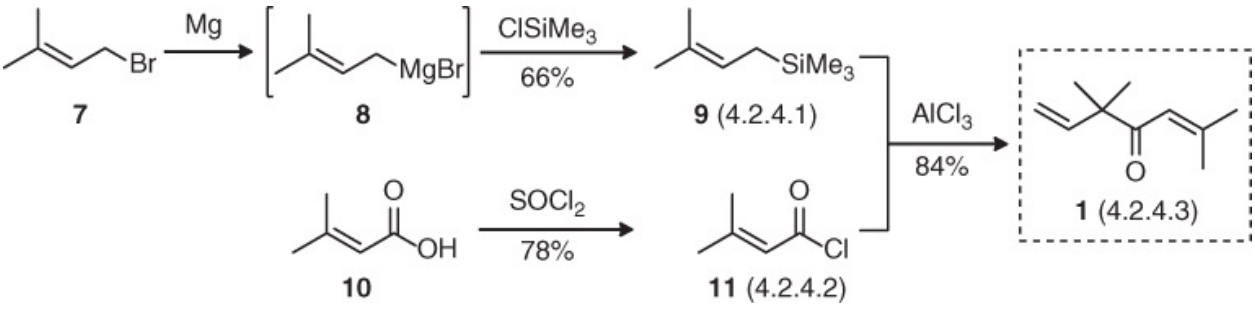
Retrosynthesis of **1** offers disconnection at the sp^3 site of the carbonyl group, leading to synthons **3** and **4**, which can be assigned to a β,β-dimethylallyl organometallic and β,β-dimethylacrylic acid (**5**/**6**).



Synthesis of **1** is problematic according to this retroanalytical concept using regioselective acylation of the metalorganic compound **5** with the acid **6**, because the electrophilic attack has to occur at the sterically more hindered site of an appropriate allyl organometallic derivative **5**. As shown in Section (b), the use of an allylsilane [2] offers an elegant solution to this problem, allowing the desired acylation to proceed with complete allylic inversion.

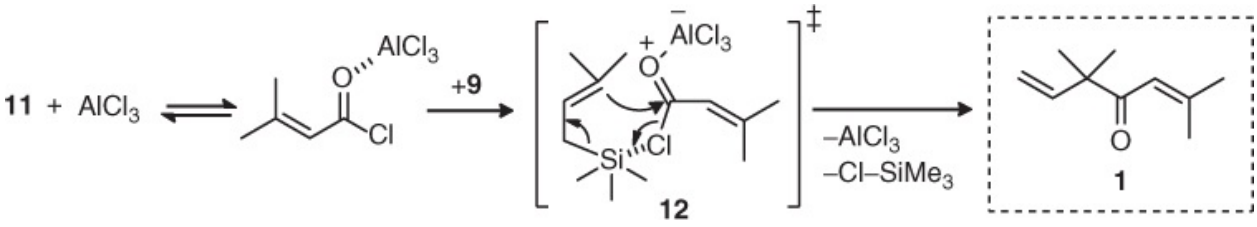
(b) Synthesis of 1

The required (β,β-dimethylallyl)silane **9** is prepared by coupling of the Grignard compound **8**, prepared from prenyl bromide (**7**), with trimethylchlorosilane [3]. The electrophilic attack of Me_3SiCl takes place at the CH_2 site of the allyl Grignard compound **8** bearing the covalent C–Mg bond.



The acid chloride **11** is prepared from senecioic acid (**10**) by treatment with thionyl chloride.

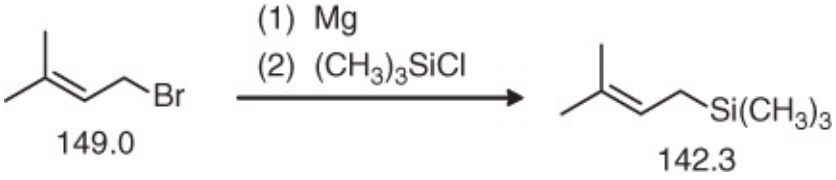
In the last step, allylsilane **9** is reacted with acid chloride **11** in the presence of $AlCl_3$. As evidenced by the structure of the product **1**, the electrophilic acylation of **9** proceeds in a different mode compared to the reaction of **8** → **9** because of allylic inversion accompanied with C–Si cleavage. It can be assumed that the acylation process (**9** → **1**) involves a cyclic transition state **12**, which (i) is preceded by complexation of $AlCl_3$ at the C=O group of the acid chloride **11** and (ii) is likely to be favored by gaining the high Si–Cl bond energy after C–Si cleavage:



Thus, a three-step convergent synthesis of **1** provides the target molecule in an overall yield of 55% (based on senecic acid (**10**)).

(c) Experimental Procedures for the Synthesis of 1

4.1.3.1	**	**1-Trimethylsilyl-3-methyl-2-butene** [4]



Magnesium turnings (14.6 g, 0.60 mol) in anhydrous tetrahydrofuran (THF) (160 ml) are treated with one crystal of iodine and prenyl bromide (1 g). As soon as the formation of the Grignard reagent starts (disappearance of the iodine color), the mixture is cooled in an ice bath and a solution of prenyl bromide (29.8 g, 0.20 mol, total amount including the initial 1 g) and trimethylchlorosilane (20.6 g, 0.19 mol) in anhydrous THF (60 ml) is added dropwise over 40 min. When the addition is complete, stirring is continued for 30 min at 0 °C and for 15 h at room temperature.

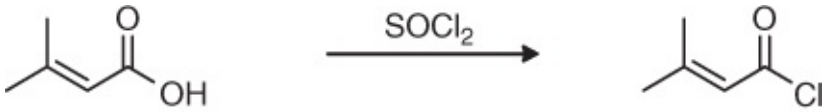
The excess magnesium is then removed by filtration, the filtrate is cooled to −20 °C, and a saturated aqueous NH_4Cl solution (150 ml) is slowly added dropwise. The phases are separated, the aqueous phase is extracted with Et_2O (50 ml), and

the combined organic phases are dried over Na_2SO_4 and filtered. The solvents are removed *in vacuo* and the residue is fractionally distilled to give the product as a colorless oil; 17.7 g (66%), bp_{300} 100–101 °C; n^{20}_D = 1.4308.

IR (film): $\tilde{\nu}$ (cm^{-1}) = 1675 (weak, C=C), 1250, 865.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 5.09 (t_{br}, *J* = 8.5 Hz, 1H, =CH), 1.67, 1.53 (2 × s_{br}, 2 × 3H, 2 × =C–CH_3), 1.36 (d, *J* = 8.5 Hz, 2H, =C–CH_2), 0.05 (s, 9H, $Si(CH_3)_3$).

4.1.3.2 * Senecyl chloride (3,3-dimethylacryloyl chloride) [5]



100.1 118.6

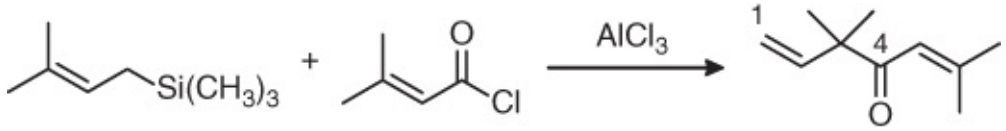
A mixture of senecioic acid (3,3-dimethylacrylic acid, 50.0 g, 0.50 mol), thionyl chloride (89.2 g, 0.75 mol), and anhydrous *N*,*N*-dimethylformamide (DMF) (1 drop) is heated under reflux until the initially vigorous gas evolution (Caution: SO_2 and HCl are formed!) ceases (approximately 2 h).

The excess thionyl chloride is then removed *in vacuo* (hood!), and the residue is distilled *in vacuo* to give the acid chloride as a colorless oil; 64.1 g (78%), bp_{13} 52–53 °C.

IR (film): $\tilde{\nu}$ (cm^{-1}) = 1765, 1730, 1600.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 6.05 (sept, *J* = 1.5 Hz, 1H, =C–H), 2.14, 1.97 (2 × d, *J* = 1.5 Hz, 2 × 3H, 2 × =C–CH_3).

4.1.3.3 ** Artemisia ketone (3,3,6-trimethylhepta-1,5-dien-4-one) [3]



142.3 118.6 152.2

3,3-Dimethylacryloyl chloride (cf. **4.1.3.2**) (5.93 g, 50.0 mmol) is added to

anhydrous aluminum chloride (6.67 g, 50.0 mmol) in anhydrous CH_2Cl_2 (25 ml) at 0 °C. This solution is added dropwise over 30 min to a solution of the allylsilane (cf. **4.1.3.1**) (7.83 g, 55.0 mmol) in CH_2Cl_2 (50 ml) at −65 °C and stirring is continued for 10 min.

The reaction mixture is then poured into a vigorously stirred mixture of NH_4Cl (30 g) and crushed ice (100 g). The phases are separated, the aqueous phase is extracted with CH_2Cl_2 (2 × 50 ml), and the combined organic phases are dried over Na_2SO_4 and filtered. The solvent is removed *in vacuo* and the residue is fractionally distilled *in vacuo* to give the product as a colorless oil with an aromatic odor; 6.35 g (84%), bp_{20} 80–81 °C, n^{20}_D = 1.4670.

IR (film): $\tilde{\nu}$ (cm^{-1}) = 3090, 1670, 1635.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 6.18 (s_{br}, 1H, 5-H), 5.94–4.91 (m, 3H, 1-H_2, 2-H), 2.10, 1.89 (2 × s, 2 × 3H, 2 × 6-CH_3), 1.18 (2 × 3H, 2 × 3-CH_3).

Note: The following derivatives may be prepared:

1. the 2,4-dinitrophenylhydrazone, mp 66–67 °C;
2. the semicarbazone, mp 71–72 °C.

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1. Steglich, W., Fugmann, B., and Lang-Fugmann, S. (eds) (1997) *Römpp Lexikon Naturstoffe*, Georg Thieme Verlag, Stuttgart, p. 58.

2. (a) Hosomi, A. (1988) *Acc. Chem. Res.*, **21**, 200–206;(b) Mayr, H. and Patz, M. (1994) *Angew. Chem.*, **106**, 990–1010; *Angew. Chem. Int. Ed. Engl.*, (1994), **33**, 938–957.

3. Pillot, J.P., Dunogues, J., and Calas, R. (1976) *Tetrahedron Lett.*, **17**, 1871–1872.

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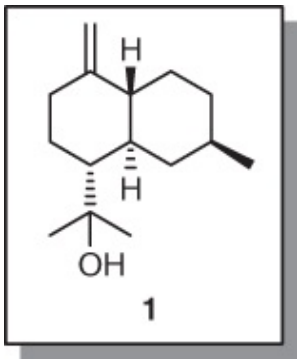
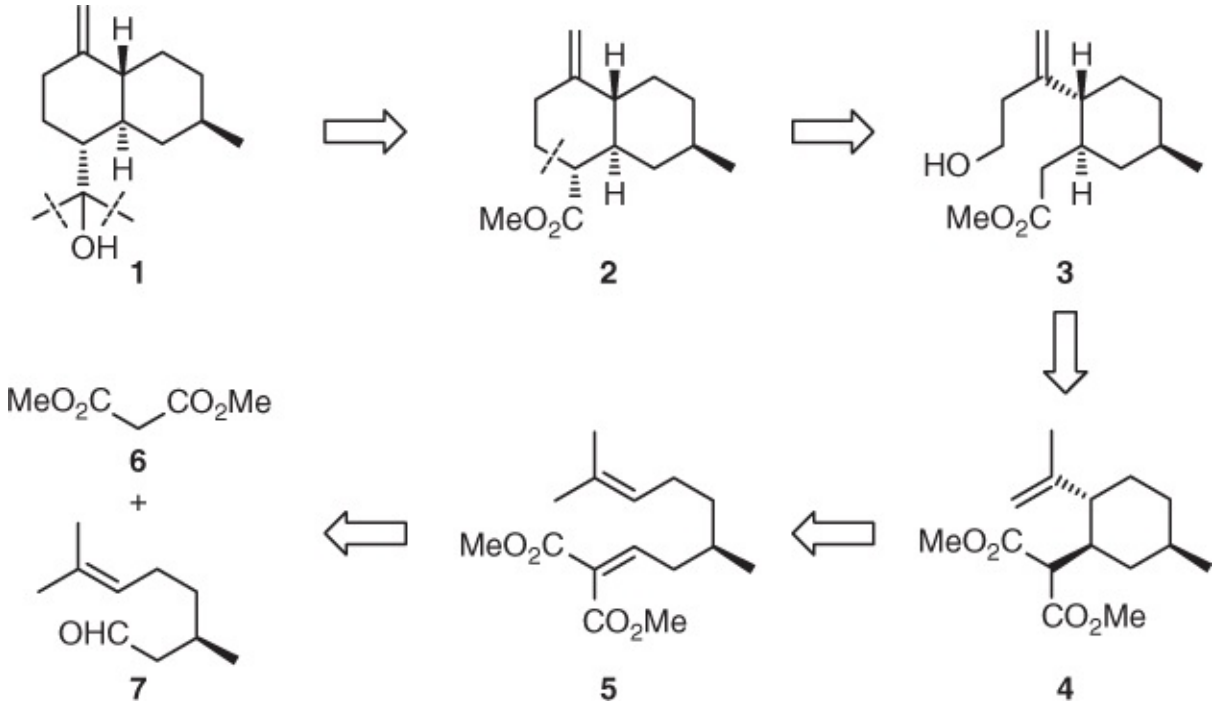
4.1.4 Veticadinol

 1	***Topics:***	• Synthesis of the sesquiterpene veticadinol • Knoevenagel condensation • Lewis acid-mediated intramolecular ene reaction • Krapcho decarboxylation • Prins reaction (oxa-ene reaction) • Tosylation and nucleophilic substitution • Intramolecular alkylation • Grignard reaction

(a) General

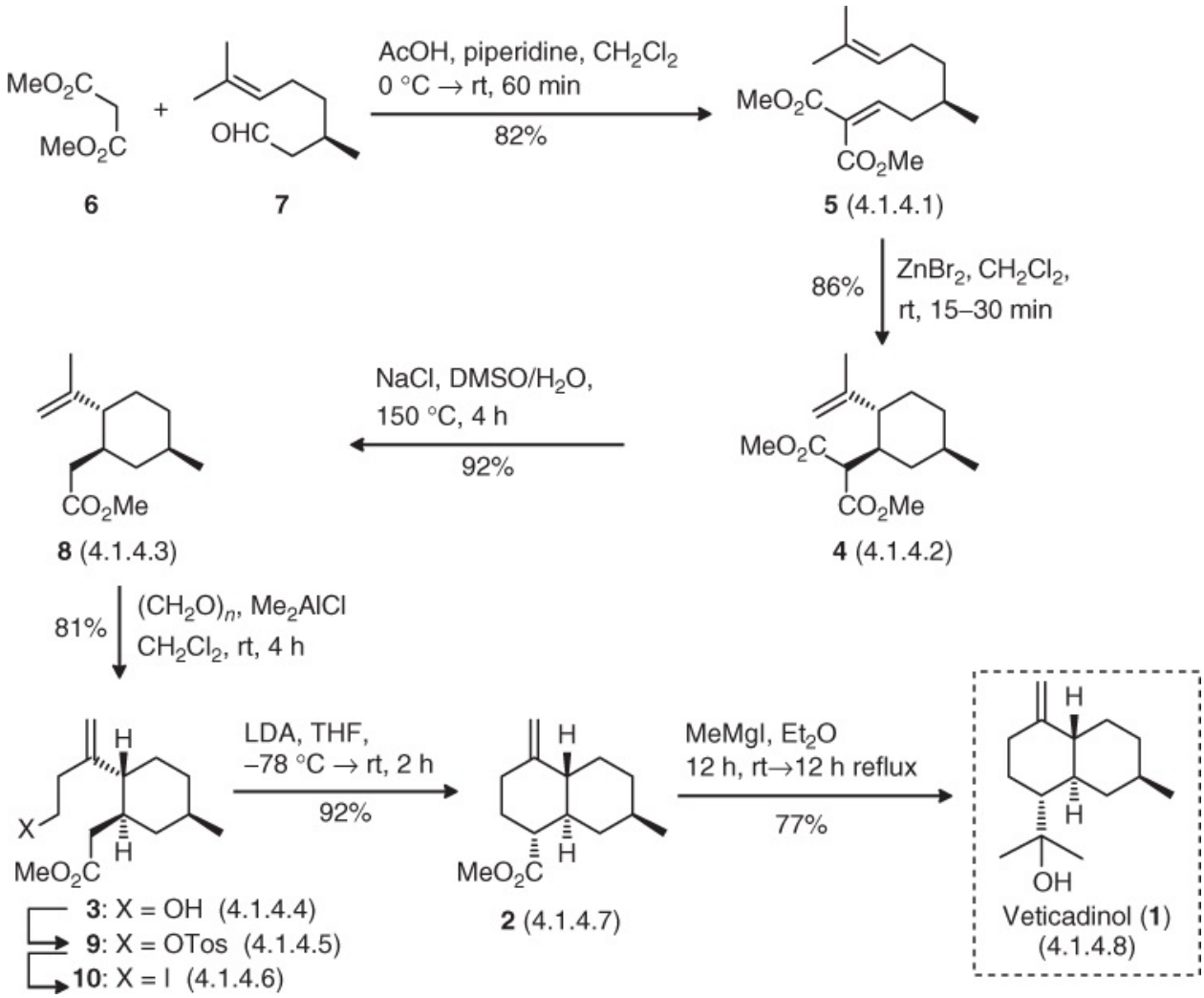
Veticadinol (**1**) is a natural product belonging to the sesquiterpene family [1], which is formed in nature from MVA. It was first obtained as a mixture with other terpenes from vetiver oil in 1961 [2] from the roots of the grass *Vetiveria zizanioides* by steam distillation. Several synthetic methods have been published, although, again, they only led to product mixtures. The first stereoselective synthesis providing veticadinol in eight steps and 33% overall yield starting from (*R*)-citronellal (**7**) and dimethyl malonate (**6**) was developed by Tietze and coworkers in 1988 [3].

Retrosynthetic analysis of **1** leads to the ester **2**. Addition of methylmagnesium iodide to compound **2** provides the tertiary alcohol moiety of **1** [4]. Cleavage of the decalin skeleton leads to alcohol **3**, which in the synthetic approach can be alkylated with the ester enolate after activation as the iodide. The central retrosynthetic steps are the retro-Prins reaction (**3** → **4**) and the retro-ene reaction to give **5**. This is easily accessible by a Knoevenagel condensation of aldehyde **7** and dimethyl malonate (**6**).



(b) Synthesis of 1

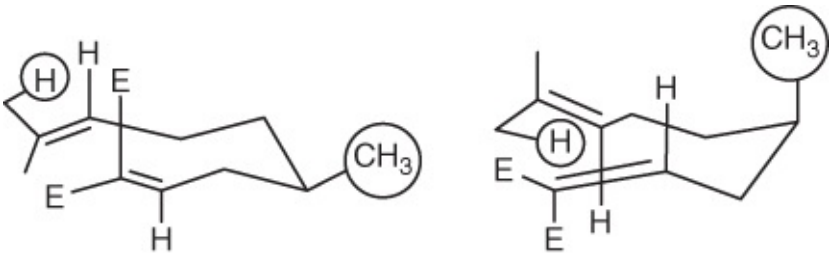
Citronellal (**7**) (ee = 97%) is used for the Knoevenagel condensation [5] with dimethyl malonate in the presence of piperidinium acetate to give the alkylidene-1,3-dicarboxylate **5** in 82% yield. The key step in the synthesis of veticadinol (**1**) is the subsequent Lewis acid-mediated intramolecular ene reaction of **5** [6]. The *trans*-1,2-disubstituted cyclohexane **4** is obtained in 86% yield with excellent selectivity (simple and induced diastereoselectivity). Thereafter, one of the ester moieties in **4** is removed using NaCl in dimethyl sulfoxide (DMSO) at 150 °C (Krapcho reaction) [7]. In this one-pot transformation, the methyl ester is first cleaved by nucleophilic substitution at the methyl group to the corresponding acid, which then undergoes decarboxylation to yield **8**. Esters are usually cleaved by aqueous hydrolysis. However, in this case, only low yields are obtained.



The next step in the synthesis of **1** is an oxa-ene reaction (Prins reaction) using formaldehyde and dimethylaluminum chloride [8]. This reaction is not a concerted transformation like the normal ene reaction, but proceeds stepwise via a carbocation. For the ring closure to decalin **2**, the alcohol moiety in **3** is first transformed into the corresponding tosylate **9** by reaction with TosCl; **9** is then subjected to nucleophilic substitution using sodium iodide in acetone to give the iodide **10** in 87% yield over the two steps. Intramolecular alkylation of **10** using LDA for the formation of the ester enolate then leads to **2** in 92% yield. The final step is a twofold Grignard reaction of the ester moiety in **2** with MeMgI to afford the desired veticadinol (**1**) in 77% yield. Thus, starting from malonate and almost enantiopure citronellal, veticadinol (**1**) is prepared in eight steps in 33% overall yield.

As already mentioned, the ene reaction of **5** to **4** proceeds with high simple and induced diastereoselectivity. For this transformation, a chair-like transition state

(K-1), with an equatorial orientation of the methyl group is proposed. The conformation of the alkylchain is controlled by a 1,3-allylic strain because of the two triply substituted double bonds [9] being responsible for the selective formation of the product with a trans orientation of its 1,2-substituents.



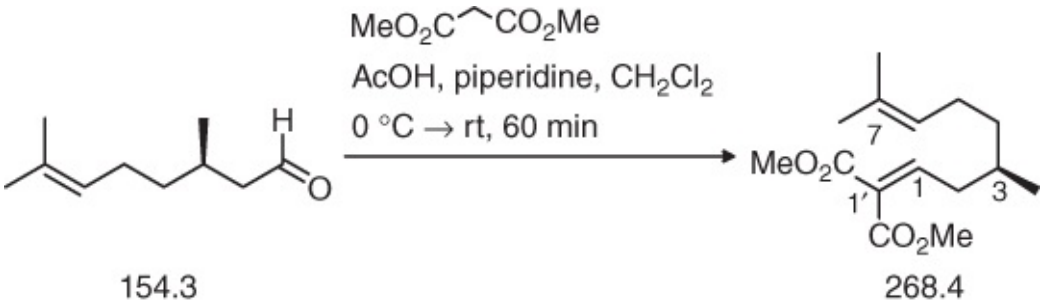
Because of the two electron-withdrawing groups at the enophile, its lowest unoccupied molecular orbital (LUMO) energy is decreased, which leads to a reduction in the activation energy [10]. In presence of an equimolar amount of Lewis acid $ZnBr_2$, which further lowers the LUMO energy of the enophile by complexation to the CO groups of the ester moieties, the reaction takes place at room temperature. The ene reaction is a pericyclic transformation, which proceeds in a concerted manner without any intermediates. It resembles a Diels–Alder reaction; however, its activation energy is usually higher since it involves cleavage of a C–H bond.

Formation of the *trans*-1,2-disubstituted cyclohexane moiety (simple diastereoselectivity) proceeds with dr > 99.1 : 0.9, while the orientation of the methyl group with respect to the two newly formed stereogenic centers is 96.6 : 3.4 (induced diastereoselectivity). This corresponds well with the *A*-value of a methyl group at a cyclohexane ring of 12.1 kJ mol^{-1}. Thus, a reaction via transition state K-2 is disfavored as a result of the axial orientation of the methyl group. The selectivity and yield of the ene reaction of **5** can be further improved by using a catalytic amount of $FeCl_3$ supported on Al_2O_3 (10 mol%) at −78 °C, obtaining **4** with an induced dr = 98.82 : 1.18 and 94% yield [11].

For comparison, it is interesting to note that the ene reaction is performed with a substrate bearing only one ester group at the enophile moiety. In this case, the reaction temperature required is much higher and a 1 : 1 mixture of the *cis*- and *trans*-1,2-disubstituted cyclohexanes is obtained in low yields.

(c) Experimental Procedures for the Synthesis of 1

4.1.4.1	**	**(3*R*)-2-(3,7-Dimethyloct-6-enylidene)-malonic acid dimethyl ester** [3]



Acetic acid (60.1 mg, 1.00 mmol) and piperidine (85.2 mg, 1.00 mmol) are added dropwise to a stirred solution of (*R*)-citronellal (1.54 g, 10.0 mmol) and dimethyl malonate (1.45 g, 11.0 mmol) in CH_2Cl_2 (5.00 ml) at 0 °C. After allowing the reaction to proceed at room temperature for 45 min, further aliquots of acetic acid (60.1 mg, 1.00 mmol) and piperidine (85.2 mg, 1.00 mmol) are added and the mixture is stirred for another 15 min.

The solvent is removed *in vacuo*, the residue is dissolved in Et_2O (50 ml), and the obtained solution is washed with H_2O (2 × 10 ml). The combined aqueous layers are extracted with Et_2O (2 × 10 ml). The combined organic layers are washed with saturated aqueous $NaHCO_3$ solution (10 ml), H_2O (10 ml), and brine (10 ml), dried over Na_2SO_4, filtered, and the solvent is removed *in vacuo*. The residue is purified by chromatography on silica gel with petroleum ether/acetone (8 : 2) to afford the product as colorless, air-sensitive oil; 2.20 g (82%), $[\alpha]^{20}_D = -8.2$ (*c* = 1, CH_3CN), $R_f = 0.51$ (Et_2O/*n*-hexane, 1 : 1).

UV (CH_3CN): λ_{max} (nm) (log ϵ) = 210 (4.13).

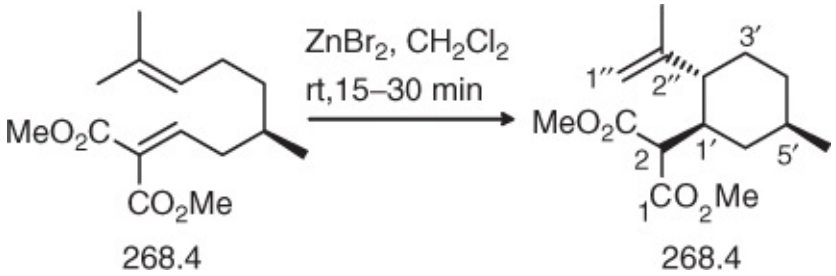
IR (NaCl): $\tilde{\nu}$ (cm^{-1}) = 2960, 2920, 2860, 1730, 1645, 1435, 1375, 1260, 1225, 1060.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.03 (t, *J* = 8.0 Hz, 1H, 1-H), 5.04 (tsept, *J* = 7.0, 1.4 Hz, 1H, 6-H), 3.79 (s, 3H, CO_2CH_3), 3.75 (s, 3H, CO_2CH_3), 2.28 (ddd, *J* = 14.8, 7.6, 5.7 Hz, 1H, 2-H_A), 2.12 (dt, *J* = 15.7, 7.9 Hz, 1H, 2-H_B), 2.03–1.84 (m, 2H, 5-H_2), 1.65 (s, 3H, 7-CH_3), 1.64 (t, *J* = 6.8 Hz, 1H, 3-H), 1.56 (s, 3H, 7-CH_3), 1.39–1.25 (m, 1H, 4-H_A), 1.25–1.09 (m, 1H, 4-H_B), 0.89 (d, *J* = 6.6 Hz, 3H, 3-CH_3).

^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) = 166.1, 164.5 (2 × $\underline{C}O_2CH_3$), 149.6 (C-1), 131.7 (C-7), 128.7 (C-1′), 124.4 (C-6), 52.4, 52.3 (2 × $CO_2\underline{C}H_3$), 37.0 (C-2), 36.9 (C-4), 32.6 (C-3), 25.8 (C-5), 25.6 (7-CH_3), 19.7 (3-CH_3), 17.8 (C-8).

MS (EI, 70 eV): *m*/*z* (%) = 268 (1) $[M]^+$, 237 (2) $[M-CH_3O]^+$, 236 (3) $[M-CH_3OH]^+$, 209 (2) $[M-C_2H_3O_2]^+$, 208 (5) $[M-C_2H_4O_2]^+$, 204 (16) $[M-2CH_3OH]^+$, 136 (47) $[C_{10}H_{16}]^+$, 121 (24) $[136-CH_3]^+$, 109 (23) $[C_8H_{13}]^+$, 69 (57) $[C_5H_9]^+$, 67 (19) $[C_5H_7]^+$, 59 (17) $[C_2H_3O_2]^+$, 55 (29) $[C_4H_7]^+$, 41 (100) $[C_3H_5]^+$.

4.1.4.2	**	**(1*R*,2*R*,5*R*)-2-[(2-Isopropenyl-5-methyl)-cyclohex-1-yl]-malonic acid dimethyl ester** [3]



The dimethyl ester (cf. **4.1.4.1**) (2.10 g, 7.84 mmol) is added dropwise to a stirred suspension of zinc bromide (1.17 g, 8.04 mmol, dried *in vacuo*) in CH_2Cl_2 (20 ml) at room temperature. The reaction is monitored by TLC until complete conversion is observed (15–30 min).

The solvent is removed *in vacuo*, the residue is dissolved in Et_2O (40 ml), the solution is washed with H_2O (2 × 10 ml), and the combined aqueous layers are extracted with Et_2O (3 × 10 ml). The combined organic layers are washed with saturated aqueous $NaHCO_3$ solution (10 ml) and brine (10 ml), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue is purified by chromatography on silica gel with Et_2O/petroleum ether (1 : 4) as eluent to afford the product; 1.72 g (86%), $bp_{0.5}$ 128–129 °C, $[\alpha]^{20}_D = -31.5$ (*c* = 1, CH_3CN), R_f = 0.56 (Et_2O/*n*-hexane, 1 : 1).

IR (NaCl): $\tilde{\nu}$ (cm^{-1}) = 3065, 2950, 2920, 2860, 1750, 1735, 1645, 1435,

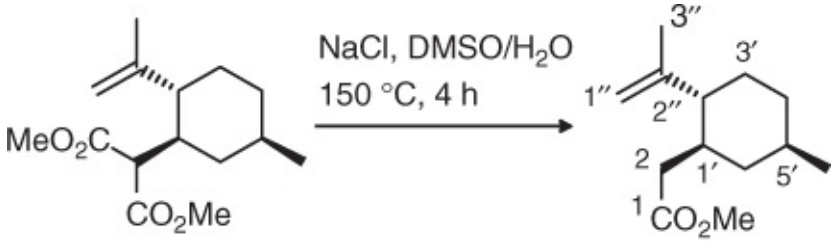
1155, 1035, 1020, 895.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 4.76–4.73 (m, 1H, 1″-H_A), 4.70–4.67 (m, 1H, 1″-H_B), 3.67 (s, 6H, 2 × CO_2CH_3), 3.56 (d, *J* = 3.4 Hz, 1H, 2-H), 2.08 (tt, *J* = 11.5, 3.4 Hz, 1H, 1′-H), 2.01 (td, *J* = 11.1, 3.5 Hz, 1H, 2′-H), 1.61 (s, 3H, 2″-CH_3), 1.76–1.58 (m, 3H), 1.46–1.26 (m, 2H), 1.14–0.86 (m, 2H) (3′-H_2, 4′-H_2, 5′-H, 6′-H_2) 0.91 (d, *J* = 6.5 Hz, 3H, 5′-CH_3).

^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) = 170.1, 169.0 (C-1, C-3), 147.5 (C-2″), 112.3 (C-1″), 53.21 (C-2), 52.19, 51.80 (2 × $CO_2\underline{C}H_3$), 48.6 (C-2′), 39.88 (C-1′), 36.5 (C-6′), 34.6 (C-4′), 32.7 (C-5′), 32.3 (C-3′), 22.5 (5′-CH_3), 18.9 (C-3″).

MS (EI, 70 eV): *m*/*z* (%) = 268 (4) $[M]^+$, 250 (1) $[M-H_2O]^+$, 237 (3) $[M-CH_3O]^+$, 236 (3) $[M-CH_3OH]^+$, 209 (3) $[M-C_2H_3O_2]^+$, 208 (7) $[M-C_2H_4O_2]^+$, 137 (19) $[C_{10}H_{17}]^+$, 136 (100) $[C_{10}H_{16}]^+$, 132 (16) $[C_5H_8O_4]^+$, 121 (35) $[C_9H_{13}]^+$, 107 (41) $[C_8H_{11}]^+$, 94 (14) $[C_7H_{10}]^+$, 93 (34) $[C_7H_9]^+$, 79 (21) $[C_6H_7]^+$, 59 (10) $[C_2H_3O_2]^+$.

4.1.4.3	*	**(1*R*,2*R*,5*R*)-[(2-Isopropenyl-5-methyl)cyclohex-1-yl]-acetic acid methyl ester** [3]



268.4 210.3

Sodium chloride (454 mg, 7.77 mmol) and water (430 mg, 23.9 mmol) are added to a solution of the dimethyl malonate derivative (cf. **4.1.4.2**) (1.60 g, 5.97 mmol) in DMSO (9 ml). The mixture is then heated to 150 °C for a period of 4 h.

After cooling to room temperature, the mixture is diluted with H_2O (30 ml) and extracted with petroleum ether (6 × 15 ml). The combined organic layers are washed with brine, dried over Na_2SO_4, and filtered, and the solvent is removed

in vacuo. The residue is purified by chromatography on silica gel using Et_2O/petroleum ether (1 : 9) as eluent to afford the product; 1.15 g (92%), $[\alpha]^{20}_D$ = −24.3 (*c* = 1, CH_3CN), R_f = 0.53 (Et_2O/*n*-hexane, 1 : 1).

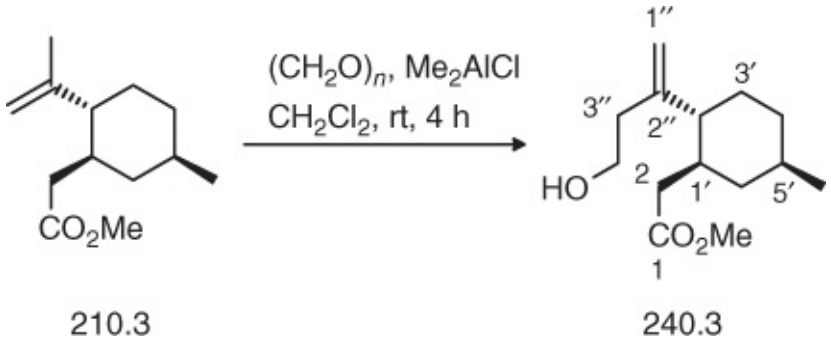
IR (NaCl): $\tilde{\nu}$ (cm^{-1}) = 3070, 2950, 2920, 2860, 1740, 1645, 1435, 1375, 1160, 890.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 4.72–4.67 (m, 2H, 1″-H_2), 3.61 (s, 3H, OCH_3), 2.47–2.33 (m, 1H, 2-H_A), 1.66 (s, 3H, 3″-H_3), 1.91–1.54 (m, 5H), 1.46–1.28 (m, 3H), 1.00–0.86 (m, 1H) (2-H_B, 1′-H, 2′-H, 3′-H_2, 4′-H_2, 5′-H, 6′-H_{eq}), 0.84 (d, *J* = 6.5 Hz, 3H, 5′-CH_3), 0.72–0.58 (m, 1H, 6′-H_{ax}).

^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) = 174.1 (C-1), 148.3 (C-2″), 111.8 (C-1″), 51.6, 51.4 (C-2′, OCH_3), 41.3 (C-2), 39.5 (C-6′), 36.5 (C-1′), 35.0 (C-4′), 32.5 (C-5′), 32.2 (C-3′), 22.7 (5′-CH_3), 19.0 (C-3″).

MS (EI, 70 eV): *m*/*z* (%) = 210 (19) $[M]^+$, 195 (3) $[M-CH_3]^+$, 179 (13) $[M-CH_3O]^+$, 178 (19) $[M-CH_3OH]^+$, 137 (57) $[C_{10}H_{17}]^+$, 136 (100) $[C_{10}H_{16}]^+$, 121 (41) $[136-CH_3]^+$, 107 (54) $[C_8H_{11}]^+$, 95 (53) $[C_7H_{11}]^+$, 81 (68) $[C_6H_9]^+$, 67 (45), $[C_5H_7]^+$, 55 (45), $[C_4H_7]^+$, 43 (30) $[C_3H_7]^+$, 41 (95) $[C_3H_5]^+$.

4.1.4.4	**	**(1*R*,2*R*,5*R*)-2-{[2-(4-Hydroxy-1-buten-2-yl)-5-methyl]-cyclohex-1-yl}-acetic acid methyl ester** [3]



210.3 240.3

A 1 M solution of dimethylaluminum chloride in *n*-hexane (6.67 ml, 6.67 mmol) is added dropwise to a stirred solution of the methyl ester (cf. **4.1.4.3**) (1.00 g, 4.76 mmol) and paraformaldehyde (129 mg, 4.29 mmol) in CH_2Cl_2 (14 ml) at 0

°C. After stirring for 2 h at room temperature, additional paraformaldehyde (129 mg, 4.29 mmol) is slowly added and the mixture is stirred for a further 2 h.

Et_2O (10 ml) and saturated aqueous NaH_2PO_4 solution (5 ml) are then added. The white precipitate formed is dissolved by dropwise addition of 10% aqueous HCl, the organic layer is separated, and the aqueous layer is extracted with Et_2O (3 × 10 ml). The combined organic layers are washed with brine, dried over Na_2SO_4, and filtered. The solvent is removed *in vacuo*, and purification of the residue by column chromatography on silica gel using Et_2O/petroleum ether (1 : 1) affords the hydroxy ester as a colorless oil; 929 mg (81%), $[\alpha]^{20}_D = -38.4$ (*c* = 1.0, CH_3CN), $R_f = 0.19$ (Et_2O/*n*-hexane, 1 : 1).

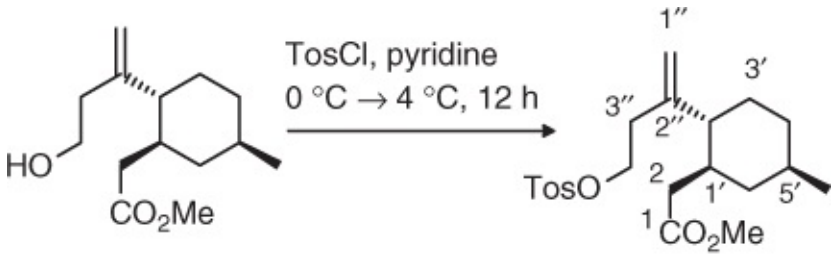
IR (NaCl): $\tilde{\nu}$ (cm^{-1}) = 3390, 3060, 2940, 2910, 2850, 1735, 1635, 1435, 1360, 1155, 1030, 885.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 4.90–4.87 (m, 1H, 1″-H_A), 4.86–4.83 (m, 1H, 1″-H_B), 3.73 (t, *J* = 6.2 Hz, 2H, 4″-H_2), 3.63 (s, 3H, OCH_3), 2.49–2.39 (m, 1H), 2.24 (t, *J* = 6.2 Hz, 2H, 3″-H_2), 2.00–1.20 (m, 9H), 1.00–0.83 (m, 1H) (2-H_2, 1′-H, 2′-H, 3′-H_2, 4′-H_2, 5′-H, 6′-H_{eq}, OH), 0.87 (d, *J* = 6.5 Hz, 3H, 5′-CH_3), 0.70 (q, *J* = 12.0, 1H, 6′-H_{ax}).

^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) = 174.1 (C-1), 149.1 (C-2″), 111.7 (C-1″), 60.9 (C-4″), 51.5, 50.6 (C-2′, OCH_3) 41.5 (C-2), 39.5 (C-6′), 37.3 (C-1′,C-3″), 35.1 (C-4′), 33.4 (C-3′), 32.5 (C-5′), 22.6 (5′-CH_3).

MS (EI, 70 eV): *m*/*z* (%) = 240 (0.1) $[M]^+$, 222 (20) $[M-H_2O]^+$, 210 (100) $[M-CH_2O]^+$, 178 (33) $[210-CH_3OH]^+$, 167 (36) $[M-C_3H_5O_2]^+$, 137 (49) $[C_{10}H_{17}]^+$, 136 (90) $[C_{10}H_{16}]^+$, 121 (53) $[136-CH_3]^+$, 41 (61) $[C_3H_5]^+$.

4.1.4.5	**	**(1*R*,2*R*,5*R*)-2-{[2-(4-*p*-Toluenesulfonyloxy-1-buten-2-yl)-5-methyl]-cyclohex-1-yl}-acetic acid methyl ester** [3]



240.3 394.5

A solution of the hydroxy ester (cf. **4.1.4.4**) (800 mg, 3.33 mmol) in pyridine (1.05 g, 13.3 mmol) is cooled to 0 °C and *p*-toluenesulfonyl chloride (630 mg, 3.33 mmol) is added. The mixture is stirred at 0 °C for 1 h and at 4 °C overnight.

It is then partitioned between ice-cold aqueous HCl (2 M, 50 ml) and ice-cold Et_2O (20 ml). The aqueous layer is extracted with Et_2O (3 × 20 ml). The combined organic layers are washed with aqueous HCl (2 M) to completely remove the pyridine, then washed with saturated aqueous $NaHCO_3$ solution (10 ml) and brine (10 ml), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting crude product can be used for subsequent reactions without further purification. Analytically pure samples are prepared by chromatography on silica gel using Et_2O/petroleum ether (1 : 4) as eluent to afford the tosylate; 1.22 g (93%), $[\alpha]^{20}_D = -19.6$ (*c* = 1, CH_3CN); $R_f = 0.44$ (Et_2O/*n*-hexane, 1 : 1).

UV (CH_3CN): λ_{max} (nm) (log ϵ) = 273 (2.76), 267 (2.81), 262 (2.81), 255 (2.76), 225 (4.11).

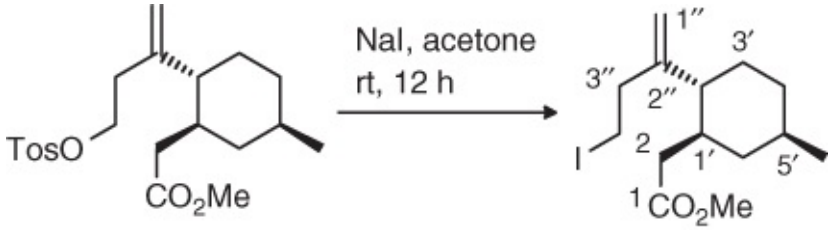
IR (NaCl): $\tilde{\nu}$ (cm^{-1}) = 3060, 3020, 2940, 2920, 2850, 1735, 1640, 1595, 1360, 1190, 1175, 965, 905, 815, 770, 660.

^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) = 7.88–7.32 (m, 4H, Ar–H), 4.87 (s, 1H, 1″-H), 4.74 (m_c, 1H, 1″-H), 4.13 (t, *J* = 7.0 Hz, 2H, 4″-H), 3.64 (s, 3H, OCH_3), 2.46 (s, 3H, Ar–H), 2.38 (m_c, 1H), 2.32 (tm, *J* = 7.0 Hz, 2H, 3″-H), 1.94–1.27 (m, 7H), 1.20 (dqm, *J* = 13.0, 3.0 Hz, 1H), 0.98–0.78 (m, 1H), 0.86 (d, *J* = 6.5 Hz, 3H, 5′-CH_3), 0.66 (dt, *J* = 13.0, 11.5 Hz, 1H, 6′-H_{ax}).

^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) = 173.5 (C-1), 146.9 (C-2″), 144.8, 133.2 (Ar–C), 129.9, 127.9, 112.3 (C-1″), 68.83 (C-4″), 51.26, 50.50 (C-2′, OCH_3), 41.13 (C-2), 39.12 (C-6′), 36.89 (C-1′), 34.87 (C-4′), 32.80, 32.59 (C-3′, C-3″), 32.23 (C-5′), 22.43 (5′-CH_3), 21.57 (Ar–CH_3).

MS (EI, 70 eV): *m*/*z* (%) = 394 $[M]^+$, 363 (3) $[M-CH_3O]^+$, 362 (3) $[M-CH_3OH]^+$, 334 (3) $[M-CH_3OH + CO]^+$, 222 (47) $[C_{14}H_{22}O_2]^+$, 193 (35) $[222-CH_3O]^+$, 148 (84) $[222-C_3H_6O_2]^+$, 91 (61) $[C_7H_7]^+$, 74 (100) $[C_3H_6O_2]^+$, 41 (37) $[C_3H_5]^+$.

4.1.4.6	**	**(1*R*,2*R*,5*R*)-2-{[2-(4-Iodo-1-buten-2-yl)-5-methyl]-cyclohex-1-yl}-acetic acid methyl ester** [3]



394.5 350.2

Sodium iodide (2.09 g, 13.9 mmol) is added to a solution of the tosylate (cf. **4.1.4.5**) (1.10 g, 2.78 mmol) in acetone (11.0 ml) at room temperature. The reaction mixture is stirred for 12 h at room temperature.

Sodium tosylate is then removed by filtration and the filtrate is partitioned between petroleum ether (20 ml) and H_2O (10 ml). The organic layer is dried over Na_2SO_4, filtered, and the solvent is removed *in vacuo* (rotary evaporator bath temperature: 20 °C). The crude product can be used for subsequent reactions without further purification. Analytically pure samples are prepared by chromatography on silica gel using Et_2O/petroleum ether (1 : 7) as eluent to afford the iodo ester, which decomposes easily giving rise to a red color; 919 mg (94%), $[\alpha]^{20}_D$ = −30.7 (*c* = 1, CH_3CN), R_f = 0.55 (Et_2O/*n*-hexane, 1 : 1).

UV (CH_3CN): λ_{max} (nm) (log ϵ) = 252 (2.83).

IR (NaCl): $\tilde{\nu}$ (cm^{-1}) = 3060, 2940, 2910, 2850, 1735, 1640, 1430, 1360, 1155, 895.

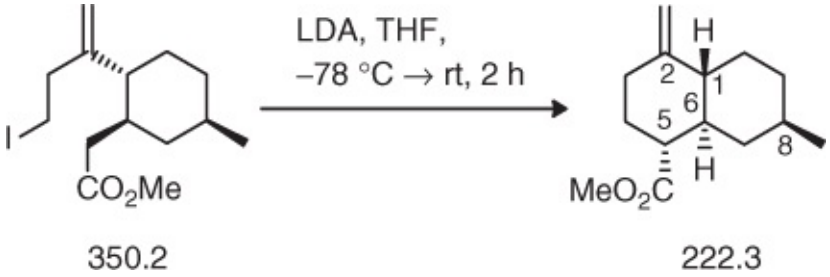
^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) = 4.92 (s, 1H, 1″-H), 4.84 (m_c, 1H, 1″-H), 3.65 (s, 3H, OCH_3), 3.24 (tm, *J* = 7.5 Hz, 2H, 4″-H), 2.54 (tm, *J* = 7.5 Hz, 2H, 3″-H), 2.50 (m_c, 1H), 2.00–1.16 (m, 8H), 0.88 (d, *J* = 6.5 Hz, 3H,

5′-CH_3), 1.04–0.80 (m, 1H), 0.70 (dt, *J* = 13.0, 11.5 Hz, 1H, 6′-H_{ax}).

^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) = 173.6 (C-1), 151.0 (C-2″), 111.5 (C-1″), 51.32, 50.07 (C-2′, OCH_3), 41.18 (C-2), 39.23 (C-6′), 38.53 (C-3″), 37.13 (C-1′), 34.99 (C-4′), 33.28 (C-3′), 32.22 (C-5′), 22.45 (5′-CH_3), 3.07 (C-4″).

MS (EI, 70 eV): *m*/*z* (%) = 319 (5) $[M-CH_3O]^+$, 276 (2) $[M-C_3H_6O_2]^+$, 223 (61) $[M-I]^+$, 149 (80) $[M-C_3H_6IO_2]^+$, 93 (100), 81 (61) $[C_6H_9]^+$, 74 (67) $[C_3H_6O_2]^+$, 67 (41) $[C_5H_7]^+$, 55 (68) $[C_4H_7]^+$, 41 (80) $[C_3H_5]^+$.

4.1.4.7	**	**(1*R*,5*R*,6*R*,8*R*)-8-Methyl-2-methylene-bicyclo[4.4.0]decane-5-carboxylic acid methyl ester** [3]



350.2 222.3

A solution of *n*-butyllithium in *n*-hexane (1.6 M, 2.15 ml, 3.43 mmol) is added to a solution of diisopropylamine (389 mg, 3.84 mmol) in THF (29 ml) at 0 °C. After stirring for 5 min, the mixture is cooled to −78 °C. A solution of the iodo ester (cf. **4.1.4.6**) (800 mg, 2.29 mmol) in THF (2.0 ml) is added dropwise with stirring over 15 min. The mixture is allowed to warm to room temperature over a period of 2 h.

Saturated aqueous NH_4Cl solution (2.5 ml) is then added, and the mixture is diluted with petroleum ether (60 ml). The organic phase is washed with H_2O (20 ml) and brine (20 ml), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by chromatography on silica gel using Et_2O/petroleum ether (1 : 1) as eluent affords the product; 466 mg (92%), $[\alpha]^{20}_D$ = −10.4 (*c* = 1, CH_3CN), R_f = 0.57 (Et_2O/*n*-hexane, 1 : 1).

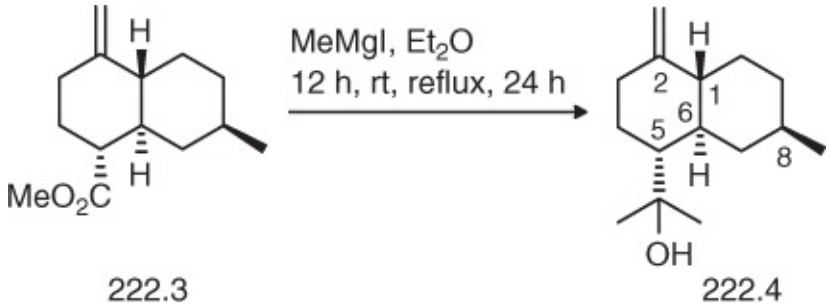
IR (NaCl): $\tilde{\nu}$ (cm^{-1}) = 3090, 3000, 2930, 2875, 2850, 1740, 1650, 1435, 1370, 1160, 895.

^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) = 4.71 (m_c, 1H, C=CH_2), 4.61 (m_c, 1H, C=CH_2), 3.69 (s, 3H, OCH_3), 2.47–2.33 (m, 1H), 2.24 (ddd, *J* = 12.3, 11.0, 3.5 Hz, 1H, 5-H_{ax}), 2.10 (dddm, *J* = 14.0, 4.5, 3.0 Hz, 1H, 3-H_{eq}), 2.03–1.19 (m, 9H), 1.09–0.84 (m, 1H), 0.87 (d, *J* = 6.5 Hz, 3H, 8-CH_3), 0.74 (q, *J* = 12.0 Hz, 1H, 7-H_{ax}).

^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) = 175.8 (5 C-α), 150.6 (C-2), 105.2 (2 C-α), 51.3 (OCH_3), 50.5 (C-5), 45.2, 45.0 (C-1, C-6), 40.7 (C-7), 35.5 (C-3), 34.7 (C-9), 32.1 (C-8), 31.4 (C-4), 28.7 (C-10), 22.5 (8-CH_3).

MS (EI, 70 eV): *m*/*z* (%) = 222 (17) $[M]^+$, 207 (2) $[M-CH_3]^+$, 193 (7) $[M-C_2H_5]^+$, 191 (7) $[M-CH_3O]^+$, 190 (9) $[M-CH_3OH]^+$, 163 (70) $[M-C_2H_3O_2]^+$, 162 (100) $[M-CH_3OH + CO]^+$, 148 (13) $[163-CH_3]^+$, 147 (20) $[162-CH_3]^+$, 107 (35) $[C_8H_{11}]^+$, 95 (46) $[C_7H_{11}]^+$, 93 (34) $[C_7H_9]^+$, 81 (46) $[C_6H_9]^+$, 79 (38) $[C_6H_7]^+$.

4.1.4.8	**	**(1*R*,5*R*,6*R*,8*R*)-5-(2-Hydroxyisopropyl)-8-methyl-2-methylene-bicyclo[4.4.0]decane (veticadinol)** [3]



222.3 222.4

A solution of the ester (cf. **4.1.4.7**) (350 mg, 1.58 mmol) in Et_2O (8 ml) is added dropwise to a stirred solution of methylmagnesium iodine, prepared by reaction of methyl iodide (741 mg, 5.22 mmol) and magnesium (115 mg, 4.73 mmol) in anhydrous Et_2O (16 ml). The mixture is stirred for 12 h at room temperature and thereafter for 12 h at reflux temperature.

After cooling, the mixture is carefully poured into a saturated NH_4Cl solution (10 ml) and the aqueous layer is extracted with Et_2O (5 × 5 ml). The combined organic layers are washed with H_2O (10 ml) and brine (10 ml), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by chromatography on

silica gel using Et_2O/petroleum ether (1 : 4) as eluent affords veticadinol as a solid; 270 mg (77%), mp 84–85 °C, $[\alpha]^{20}_D$ = +11.8 (*c* = 1.0, CH_3CN), R_f = 0.10 (Et_2O/*n*-hexane, 1 : 1).

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3330, 3100, 3000, 2980, 2960, 2940, 2880, 1650, 1460, 1382, 1372, 1160, 1140, 892, 885.

^{1}H NMR (200 MHz, C_6D_6): δ (ppm) = 4.78 (m_c, 1H, C=CH_2), 4.71 (m_c, 1H, C=CH_2), 2.57 (dddm, *J* = 13.0, 6.0, 3.0 Hz, 1H, 7-H_{eq}), 2.32 (dtm, *J* = 13.0, 3.5 Hz, 1H, 3-H_{eq}), 2.01 (dm, *J* = 12.5 Hz, 1H, 3-H_{ax}), 1.92 (dq, *J* = 12.5, 3.0 Hz, 1H, 10-H_{eq}), 1.78–1.60 (m, 2H, 4-H_{eq}, 9-H_{eq}), 1.52 (tm, *J* = 11.0 Hz, 1H, 1-H_{ax}), 1.33 (dq, *J* = 12.0, 3.5 Hz, 1H, 10-H_{ax}), 1.00 (s, 3H, 5-C-α-CH_3), 0.96 (s, 3H, 5 C-α-CH_3), 0.94 (d, 3H, 8-CH_3), 1.40–0.84 (m, 5H, 4-H_{ax}, 5-H_{ax}, 6-H_{ax}, 8-H_{ax}, 9-H_{ax}), 0.74 (dt, *J* = 13.0, 11.0 Hz, 1H, 7 H_{ax}), 0.70 (s, 1H, OH).

^{13}C NMR (50 MHz, C_6D_6): δ (ppm) = 152.7 (C-2), 103.9 (2 C-α), 73.6 (5 C-α), 53.4 (C-5), 46.8 (C-6), 46.0 (C-1), 42.4 (C-7), 37.0 (C-3), 34.9 (C-9), 33.0 (C-8), 31.8 (5 C-β), 31.3 (C-4), 29.8 (C-10), 24.6 (5 C-β), 23.3 (8-CH_3).

MS (EI, 70 eV): *m*/*z* (%) = 222 (0.04) $[M]^+$, 204 (28) $[M-H_2O]^+$, 164 (33) $[M-C_3H_6O]^+$, 149 (43) $[164-CH_3]^+$, 135 (21) $[C_{10}H_{15}]^+$, 121 (23) $[C_9H_{13}]^+$, 93 (21) $[C_7H_9]^+$, 81 (22) $[C_6H_9]^+$, 59 (100) $[C_3H_7O]^+$.

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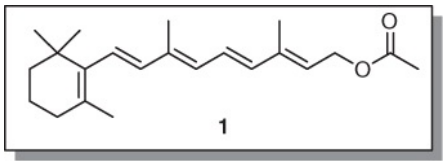
4.1.5 all-*trans*-Vitamin A acetate



1

Topics:

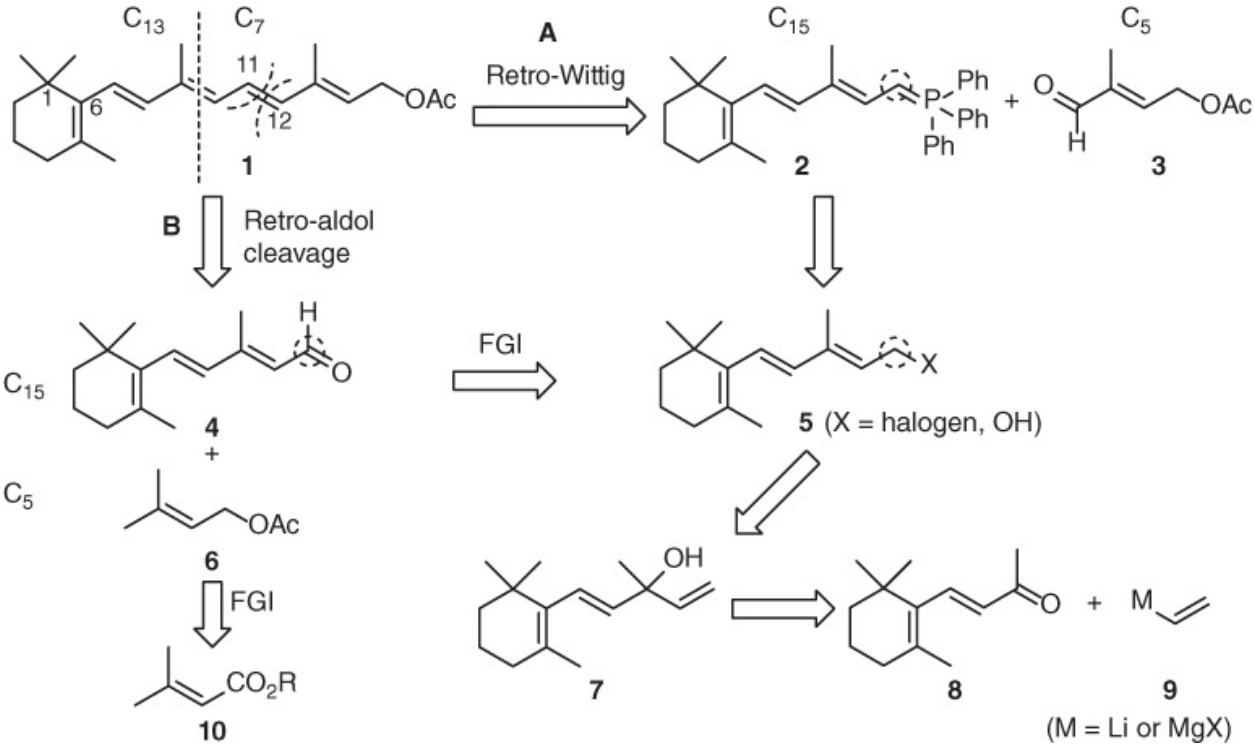
- Synthesis of a diterpene-derived polyene ester
- Carbonyl olefinations according to Wittig and Horner reactions
- Formation of phosphonium salts
- Reduction of esters to primary alcohols

(a) General

The name “vitamin A” refers to a number of monocyclic C_{20}-diterpenes (retinoids), in which a trimethylcyclohexene unit is combined with a terminally functionalized polyene side chain. The most prominent member, the polyene alcohol retinol (vitamin A_1), exclusively occurs in animal tissues and is stored, for example, in the liver in the form of esters of higher fatty acids (e.g., palmitic acid). Retinol plays a number of roles in the organism, the most important being growth, development, differentiation of epithelial tissue, reproduction, and vision [1].

Retinol is almost exclusively manufactured in the form of the more stable esters, mainly the acetate **1**, but also as propionate and palmitate. Vitamin A is produced (i) by isolation from natural sources or (ii) in increasing amounts by synthesis on an industrial scale. The target molecule of most syntheses is retinol acetate (**1**).

For a retrosynthetic approach to **1**, two restrictions prove to be useful. First, it should be considered that β-ionone (**8**, cf. **1.5.3.5**) is the key intermediate in almost all syntheses. Second, C–C disconnections in the remaining polyene side chain should focus on the C=C double bonds and, therefore, on the retro-transformations of carbonyl olefination and/or aldol-type condensation reactions.

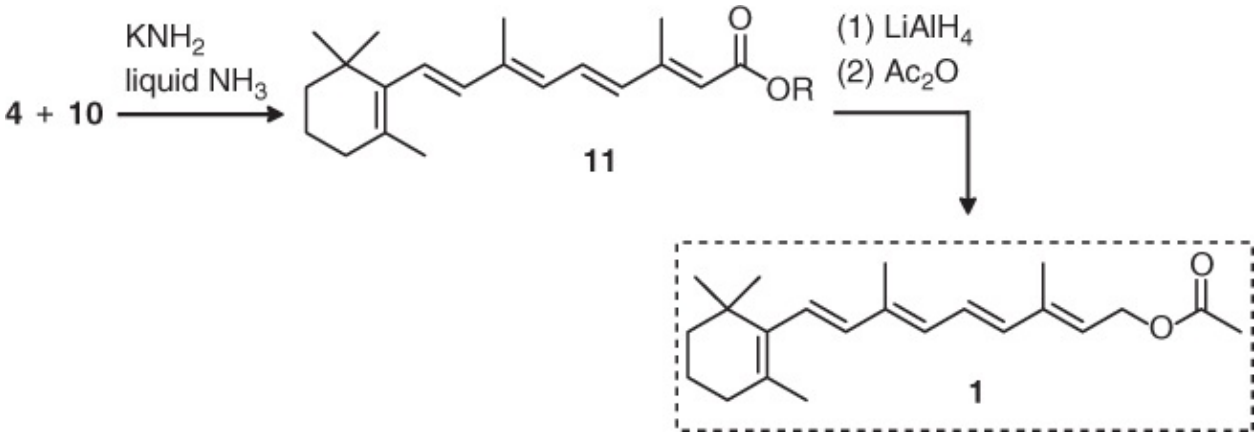


Since C_2-elongation at the carbonyl group of the β-ionone C_{13} unit is simple (**8** → **7**), disconnection at the C-11/C-12 double bond in **1** is most attractive (C_{20} →

C_{15} + C_5) and gives rise to a retro-Wittig mode **A** (with the olefination components ylide **2** and aldehyde **3**) and to a retro-aldol reaction **B** with the condensation components aldehyde **4** and acetate **6**, of which the latter is accessible from ester **10**. Ylide **2** and aldehyde **4** can be deduced from the common intermediate **5**, allylic rearrangement of which leads to the isomeric C_{15} alcohol **7**, which is the product of addition of, for example, a vinyl Grignard compound **9** (M = MgX) to β-ionone (**8**). Educt **10** is an ester of senecioic acid, while aldehyde **3** has been the subject of an earlier synthesis (cf. **1.1.1.3**).

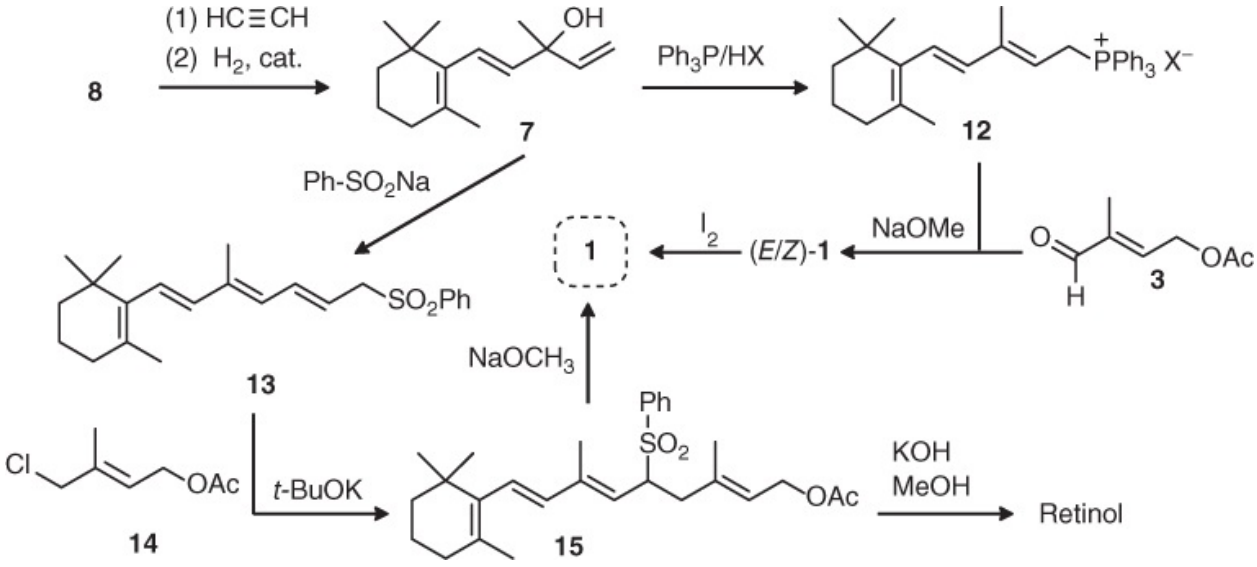
From these retroanalytical considerations, two of the industrial syntheses of **1** documented in the literature [1, 2] can be deduced.

In the Sumitomo synthesis [3], aldol condensation of aldehyde **4** with 3-methyl-2-butenoic ester **10** using KNH_2 in liquid NH_3 produces the all-*trans* retinoic ester **11**, reduction of which with $LiAlH_4$ and subsequent acetylation yields **1**:

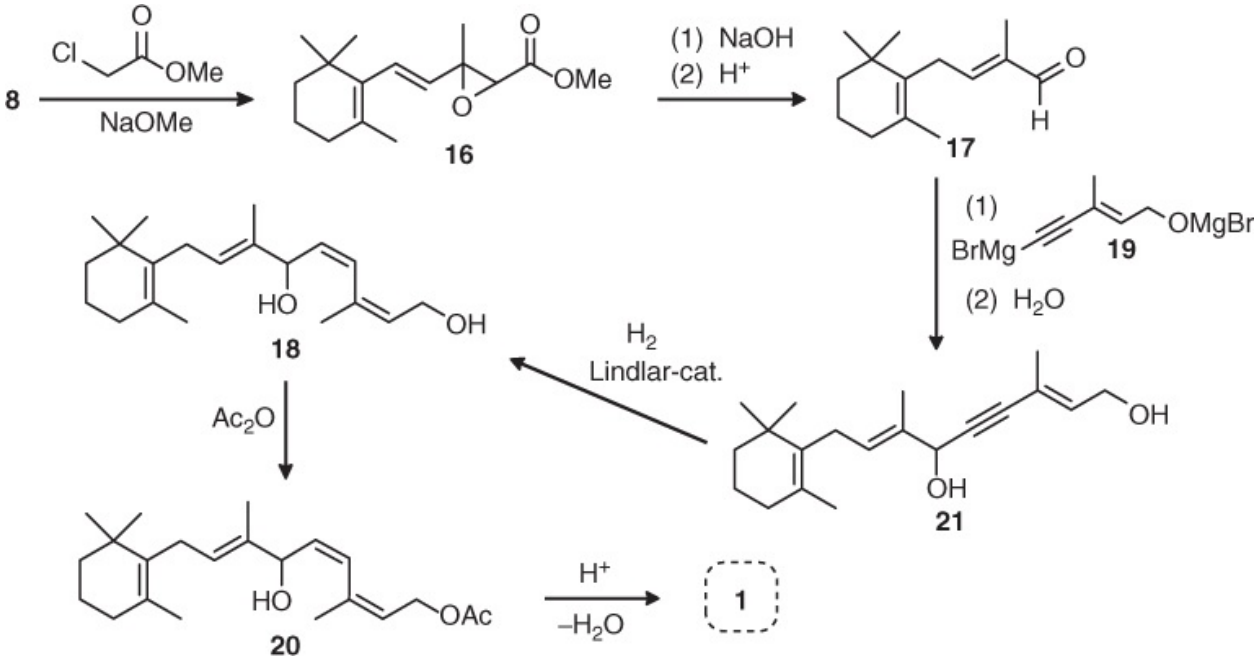


In the BASF synthesis [4], β-ionone (**8**) is transformed to vinyl-β-ionol (**7**) by ethynylation with acetylene followed by partial hydrogenation. Treatment of **7** with Ph_3P/HX provides the C_{15} phosphonium salt **12**, the key building block for the synthesis of retinoids [4]. Wittig reaction with the aldehyde **3** leads to a 70 : 30 mixture of C-11-(*E*)/(*Z*)-isomers, which is transformed to the all-*trans* acetate **1** by treatment with iodine.

In the Rhône-Poulenc synthesis [5], the starting material is the allyl phenyl sulfone **13** obtained from vinyl-β-ionol (**7**) and sodium phenylsulfinate. Sulfone **13** is deprotonated at the α-position and alkylated with the allylic halide **14** (a precursor of aldehyde **3**, cf. **1.1.1.2**) to give **15**. Finally, the acetate **1** or free retinol can be obtained from **15** by base-induced elimination of sulfinate:



The conceptually different approach of Hoffmann-La Roche [6] starts with the C_{14}-building block **17**, which is obtained from β-ionone (**8**) via **16** by a Darzens synthesis. Aldehyde **17** is then converted to the C_{20}-alkyne diol **21** by Grignard reaction with the bis-MgBr derivative **19** of 3-methyl-2-penten-4-yn-1-ol (accessible from methyl vinyl ketone by ethynylation and H^+-catalyzed allylic rearrangement). cis-Stereoselective partial hydrogenation using a Lindlar catalyst to give the (*E*)/(*Z*)-diol **18**, acetylation of the primary hydroxyl function (→**20**), and subsequent acid-induced dehydration with double-bond isomerization lead to **1**:



It should be noted that syntheses of the polyene chain by formation of C(sp^2)–C(sp^2) single bonds by means of Heck reactions are also known [7].

(b) Synthesis of 1

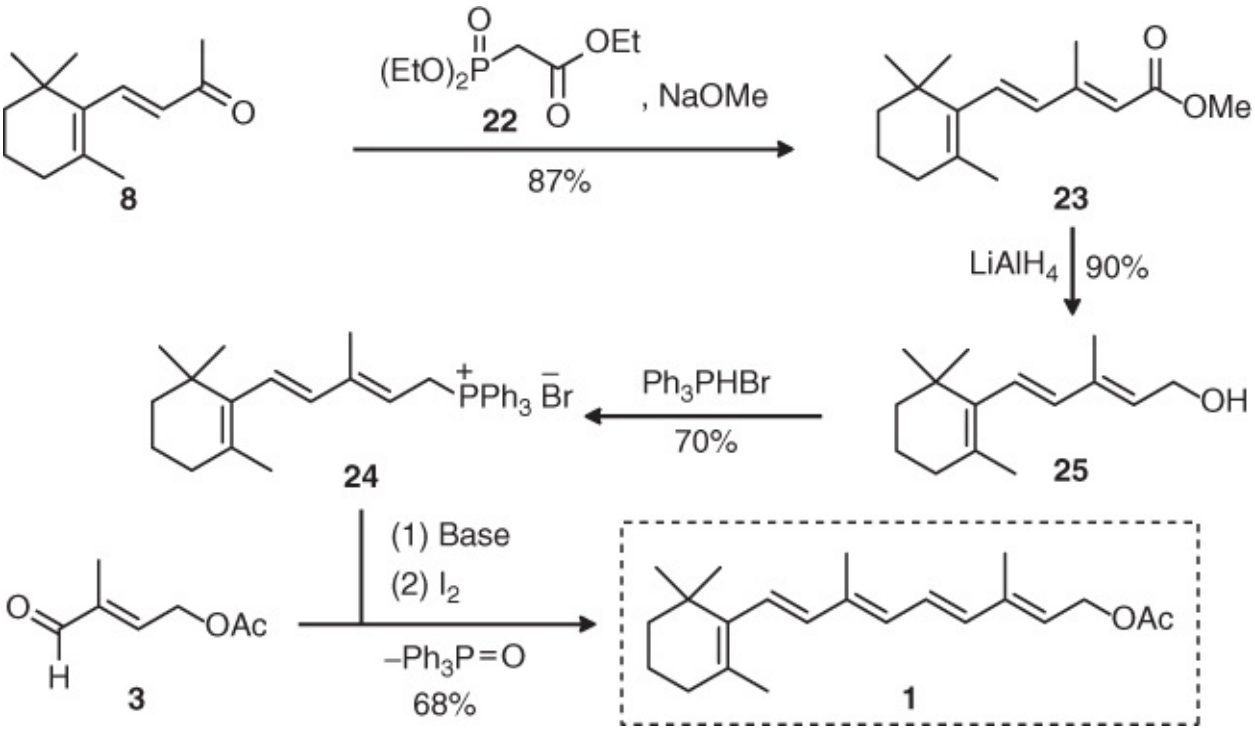
For the synthesis of vitamin A acetate **1**, a laboratory procedure is presented, which is based on the retrosynthesis according to **A** and which contains elements of the industrial synthesis developed by BASF [4]. Thus, β-ionone (**8**) is olefinated with diethyl (ethoxycarbonyl)methylphosphonate (**22**) in the presence of $NaOCH_3$ in a Wittig–Horner reaction (P–O-activated carbonyl olefination, cf. Section 1.1.7) with concomitant transesterification to give methyl β-ionylidene acetate (**23**).

The ester **23** is reduced using $LiAlH_4$ to give β-ionylidene ethanol **25**, which is converted into the C_{15}-phosphonium bromide **24** by reaction with triphenylphosphonium hydrobromide.

Thereafter, phosphonium salt **24** is deprotonated to provide (*in situ*) the ylide **2**, which is combined in a Wittig reaction with the aldehyde **3** (cf. **1.1.1.3**) to give a mixture of (*E*)- and (*Z*)-retinol acetates under elimination of Ph_3PO. Isomerization with iodine subsequently leads to the all-*trans*-configured retinol acetate **1**.

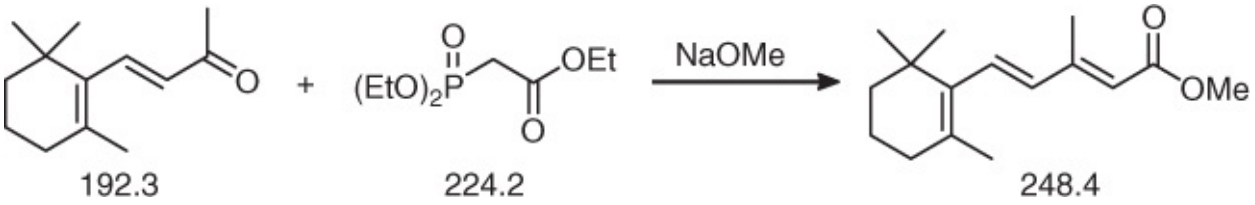
For the deprotonation of **24**, two specific methods are used, namely (i) base-free ylide formation with an oxirane (1,2-butene oxide) as HX acceptor and (ii) ylide formation in a two-phase system with aqueous NaOH/CH_2Cl_2.

The synthesis of β-ionone **8** (cf. **1.5.3.5**) as the starting material for the preparation of the C_{15}-salt **24** requires five steps starting from acetoacetate (overall yield 29%), and the transformation of **8** into **24** needs additional three steps with 55% yield. Since the aldehyde **3** is prepared in three steps with 48% yield, the described synthesis of vitamin A acetate synthesis requires 12 steps and has an overall yield of 8%.



(c) Experimental Procedures for the Synthesis of 1

4.1.5.1	**	**Methyl β-ionylidene acetate** [8]



A solution of NaOMe (prepared from sodium (3.68 g, 160 mmol) in anhydrous MeOH (80 ml)) is slowly added dropwise to a stirred solution of β-ionone (Section 1.5.3) (30.0 g, 156 mmol) and diethyl (ethoxycarbonyl)methylphosphonate (36.0 g, 160 mmol) in anhydrous benzene (80 ml; Caution: carcinogenic!) at room temperature. Stirring is continued at 40 °C for 15 min.

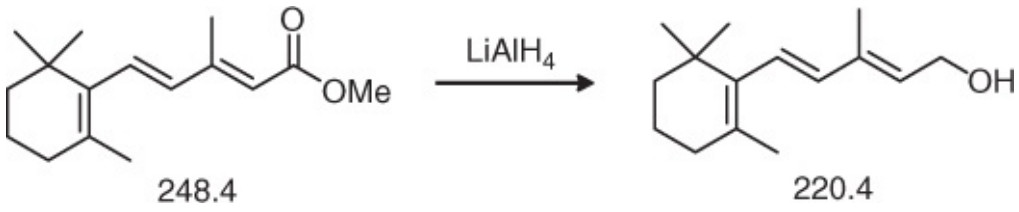
The solution is then poured onto ice (300 g) and extracted with Et_2O (3 × 100 ml). The combined organic phases are washed with H_2O (2 × 200 ml), dried over Na_2SO_4, and filtered. The solvent is removed *in vacuo* and the residue is fractionally distilled to give the product as a light yellow oil; 34.6 g (89%), $bp_{0.3}$ 118–120 °C.

IR (film): $\tilde{\nu}$ (cm^{-1}) = 1715, 1610, 1235, 1135.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 6.52, 6.08 (2 × d, *J* = 16.1 Hz, 1H, CH=CH), 5.77 (m, 1H, 2-H), 3.72 (s, 3H, OCH_3), 2.35 (s, 3H, =C–CH_3), 2.21–1.83 (m, 2H, allyl-CH_2), 1.70 (s, 3H, =C–CH_3), 1.62–1.14 (m, 4H, CH_2–CH_2), 1.02 (s, 6H, C($C\underline{H}_3$)$_2$).

Note: As a derivative, β-ionylidene acetic acid, mp 124–125 °C, can be easily prepared by saponification (KOH in methanol, 24 h, room temperature).

4.1.5.2 ** β-Ionylidene-ethanol [8]



A solution of β-ionylidene acetate (cf. **4.1.5.1**) (20.0 g, 80.0 mmol) in anhydrous Et_2O (80 ml) is added dropwise to a stirred suspension of $LiAlH_4$ (3.40 g, 90.0 mmol) in anhydrous Et_2O (60 ml) at 0 °C over 30 min. Stirring is continued at 0 °C for 1 h (note).

A mixture of MeOH/H_2O (9 : 1; 20 ml) is slowly dropped into the solution with stirring, followed by aqueous NH_4Cl solution (10%). During the addition, external cooling with ice is necessary. The phases are separated and the aqueous phase is extracted with Et_2O (3 × 100 ml). The combined organic phases are washed with H_2O (50 ml), dried over Na_2SO_4, and filtered. The solvent is removed *in vacuo* and the residue is fractionally distilled to give the product as a nearly colorless oil; 17.0 g (90%), $bp_{0.3}$ 140–145 °C, n^{20}_D = 1.5390.

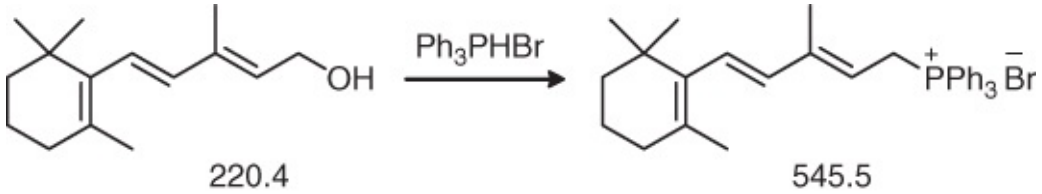
IR (film): $\tilde{\nu}$ (cm^{-1}) = 3320 (br, OH), 1460, 1010, 980.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 6.09 (s, 2H, vinyl-H), 5.73 (t, *J* = 7 Hz, 1H, vinyl-H), 4.29 (d, *J* = 7 Hz, 2H, HO–$C\underline{H}_2$), 2.10–1.85 (m, 2H, allyl-CH_2), 1.91 (s, 1H, OH), 1.86, 1.70 (2 × s, 3H, =C–CH_3), 1.60–1.21 (m, 4H,

CH_2–CH_2), 1.02 (s, 6H, $C(CH_3)_2$).

Note: The progress of the reaction can be followed via TLC (SiO_2; CH_2Cl_2).

4.1.5.3	*	**(β-Ionylidene-ethyl)triphenylphosphonium bromide** [9]



220.4 545.5

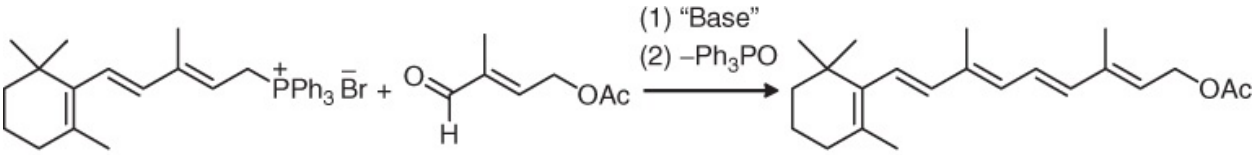
β-Ionylidene-ethanol (cf. **4.1.5.2**) (11.0 g, 50.0 mmol) and triphenylphosphonium hydrobromide (17.1 g, 50.0 mmol) in MeOH (200 ml) are stirred at room temperature for 48 h. During this time, the phosphonium dissolves and the solution turns yellow.

The solvent is then evaporated *in vacuo*, and the yellow crystalline residue is dissolved in a minimum volume of acetone. Addition of Et_2O and scratching with a glass rod cause the C_{15}-salt to crystallize as pale-yellow prisms; 18.2–18.8 g (67–69%), mp 151–153 °C.

IR (film): $\tilde{\nu}$ (cm^{-1}) = 1435, 1110, 745, 720, 685.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.80 (m, 15H, Ar), 6.00 (s, 2H, vinyl-H), 5.52–5.10 (m, 1H, vinyl-H), 4.75 (dd, J_{HP} = 15 Hz, J = 8 Hz, 2H, P–CH_2), 2.23–1.79 (m, 2H, allyl-CH_2), 1.63, 1.47 (2 × s, 3H, =C–CH_3), 1.58–1.14 (m, 4H, CH_2–CH_2), 0.97 (s, 6H, $C(CH_3)_2$).

4.1.5.4	**	**all-*trans*-Vitamin A acetate** [9, 10][1)]



545.5 142.2 328.5

Method 1

The C_{15}-salt (cf. **4.1.5.3**) (12.5 g, 23.0 mmol) is dissolved in anhydrous DMF

(50 ml) under a nitrogen atmosphere[1] and the solution is cooled to 0 °C. The C_5-aldehyde (cf. **1.1.1.3**) (4.00 g, 28.0 mmol) is added with stirring, and then 1,2-butene oxide (4.18 g, 58.0 mmol) is added dropwise. The mixture is stirred for 16 h at room temperature and for 4 h at 60 °C.

Petroleum ether (100 ml, 40–60 °C fraction) is added and the solution is poured into ice-cold 20% aqueous H_2SO_4 (150 ml). The organic phase is separated and the aqueous phase is extracted with petroleum ether (2 × 100 ml). The combined organic phases are dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude retinol acetate is obtained as yellow oil; 5.52 g (73%).

The UV spectrum (UV (EtOH): λ_{max} (log ϵ) = 327 nm (4.54)) indicates a 68 : 32 mixture of the **11**(*E*)/**11**(*Z*) isomers. The UV spectrum of the pure **11**(*Z*)-isomer shows λ_{max} (log ϵ) = 327 nm (4.70).

Isomerization

The crude product (5.00 g) is dissolved in *n*-pentane (10 ml), iodine (2.5 mg) is added, and the solution is left for 2 h in the dark at room temperature.

The solution is then diluted with *n*-pentane (100 ml), washed sequentially with dilute aqueous $Na_2S_2O_3$ solution and H_2O, dried over Na_2SO_4, filtered, and concentrated *in vacuo*.

The residue contains only all-*trans*-retinol acetate (**UV** (EtOH): λ_{max} (log ϵ) = 327 nm (4.67)), 0.98 g (93%). The product can be crystallized from *n*-hexane (at −20 to −30 °C) or MeOH/EtOAc (2 : 1) (at −20 °C) to give yellow prisms, mp 58–59 °C.

Method 2

A solution of the C_5-aldehyde (cf. **1.1.1.3**) (0.52 g, 3.60 mmol) in CH_2Cl_2 (200 ml) is layered with aqueous NaOH (2 M, 200 ml). A solution of the C_{15}-salt (cf. **4.1.5.3**) (1.96 g, 3.60 mmol) in CH_2Cl_2 (200 ml) is added dropwise under vigorous stirring. The organic phase acquires a red color; the mixture is stirred for 30 min at room temperature.

The organic phase is separated and washed with H_2O until the aqueous washings are neutral. The CH_2Cl_2 phase is dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude oily product (0.82 g, 69%) is crystallized by triturating with *n*-hexane at −20 to −30 °C to give yellow prisms, mp 57–59 °C. According to

the UV spectrum (**UV** (EtOH): λ_{max} (log ϵ) = 327 nm (4.67)), the product consists of 94% all-*trans*-retinol acetate.

UV (EtOH): λ_{max} (log ϵ) = 327 nm (4.69); 98% all-*trans* retinol acetate.

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 1730 (C=O), 1220, 1020, 980, 950.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 6.65 (dd, *J* = 15, 11 Hz, H, 11-H), 6.27 (d, *J* = 15 Hz, 1H, 12-H), 6.12 (d, *J* = 16 Hz, 2H, 7-H, 8-H), 6.09 (d, *J* = 11 Hz, 1H, 10-H), 5.61 (t, *J* = 7 Hz, 1H, vinyl-H), 4.70 (d, *J* = 7 Hz, 2H, allyl–CH_2), 2.07–1.82 (m, 2H, allyl–CH_2), 1.95, 1.89, 1.70 (3 × s, 3 × 3H, 9-CH_3, 13-CH_3, 5-CH_3), 1.64–1.12 (4H, CH_2–CH_2), 1.03 (s, 6H, $C(CH_3)_2$).

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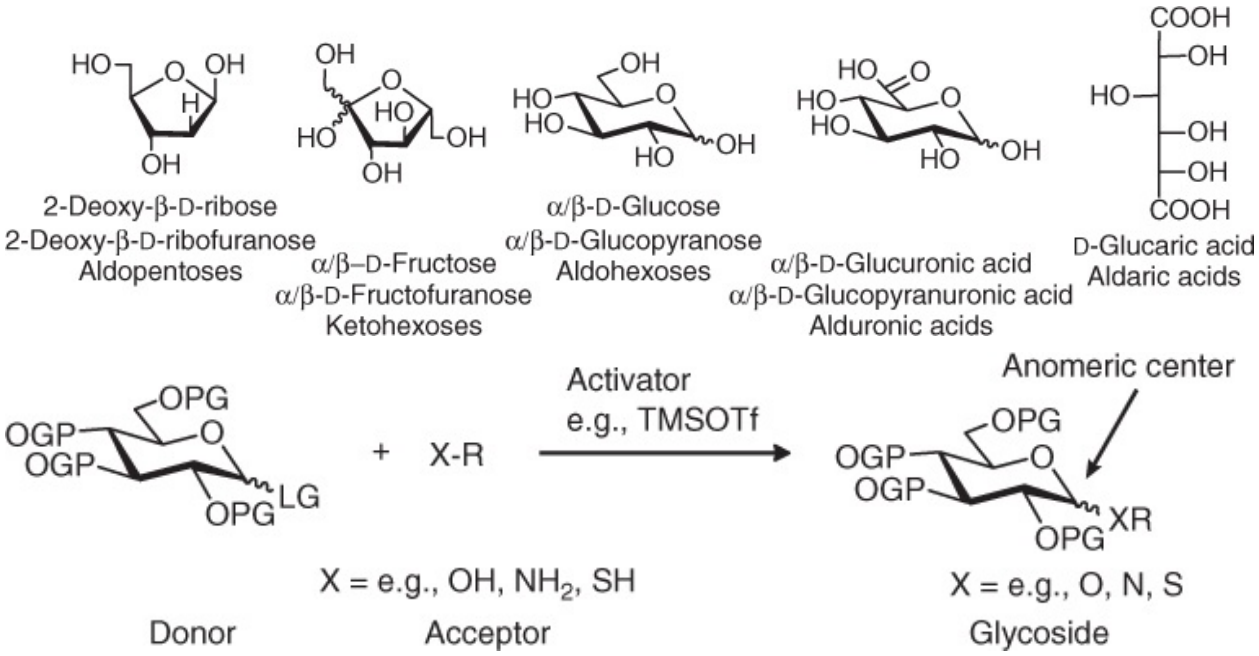
4.2 Carbohydrates

Introduction

Carbohydrates are the most widely distributed natural products, representing about two-thirds of the annually renewable biomass [1]. The majority exists in the form of simple or complex oligo-and polysaccharides in the supporting tissue of plants, microbial cell walls, mammalian membranes, and in the casings of insects and the shells of crabs. Carbohydrates play a role in many biological processes, such as cell recognition [2], signal transduction [3], oncogenesis [4], bacterial infection, and probably even in Alzheimer's disease [5]. In addition, carbohydrates are valuable substrates in organic synthesis.

Monosaccharides, the building blocks of oligo-and polysaccharides, as well as glycosides, are polyhydroxy aldehydes (aldoses) or polyhydroxy ketones (ketoses) of different lengths and with defined stereochemistry at the stereogenic centers. The diversity is further increased by replacing hydroxyl groups by amino functionalities (amino sugars), hydrogen (deoxy sugars), or other groups. Aldopentoses such as 2-deoxyribose and ketohexoses such as fructose usually exist as THFs, while aldohexoses such as glucose contain a tetrahydropyran moiety, both having a hemiacetal functionality. Further important derivatives of monosaccharides are the cyclic uronic acids, such as glucuronic acid, and the acyclic aldaric acids, such as glucaric acid, and sugar alcohols such as glucitol.



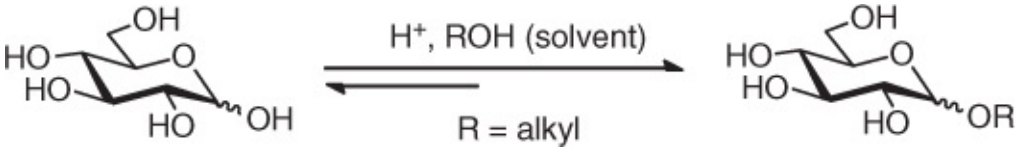
Among the reactions of carbohydrates, two transformations are most commonly encountered, namely the introduction of protecting groups at the hydroxyl groups, and the stereoselective formation of acetals of the hemiacetal moiety (glycosylation or glycosidation). For the glycosylation step, two building blocks are needed: the glycosyl donor and the glycosyl acceptor. Under activation (e.g., trimethylsilyl trifluoromethanesulfonate (TMSOTf), $BF_3 \cdot OEt_2$), these two building blocks react to form a glycoside.

It is important to bear in mind that the protecting groups have a great influence not only on the reactivity in the glycosylation step but also on the stereochemistry (α or β) of the reaction. Many glycosylation methods have been developed that allow stereoselective acetal formation at the anomeric centers of carbohydrates as donor molecules. They react with an alcohol, a phenol, or another sugar moiety with a free hydroxyl group or with other acceptor molecules (e.g., amines (glycosylamines), thiols (thioglycosides), or nucleophilic carbon (C-glycosides)).

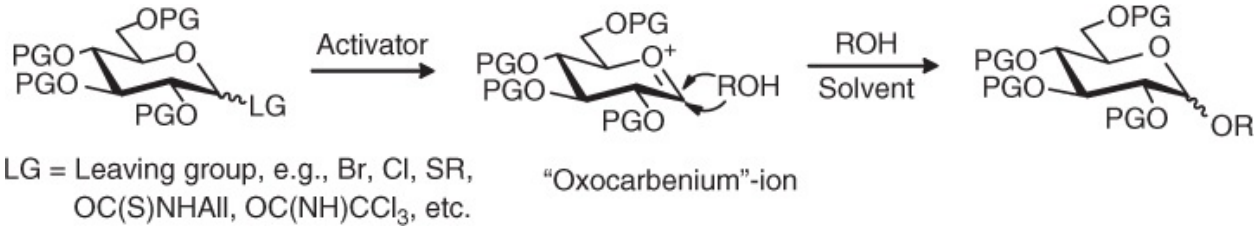
The first glycosylation reactions were reported by Arthur Michael in 1879, followed by Emil Fischer (1893), as well as Wilhelm Koenigs and Eduard Knorr (1901) in the field of *O*-glycosides [6].

Fischer-type glycosylation, in which a monosaccharide is reacted with an alcohol in the presence of a catalytic amount of a strong acid, does not require any protecting group on the carbohydrate moiety. However, this method is severely limited by the need for a large excess of the alcohol (often used as the solvent) and does not permit stereoselective glycosylation. The procedure is used

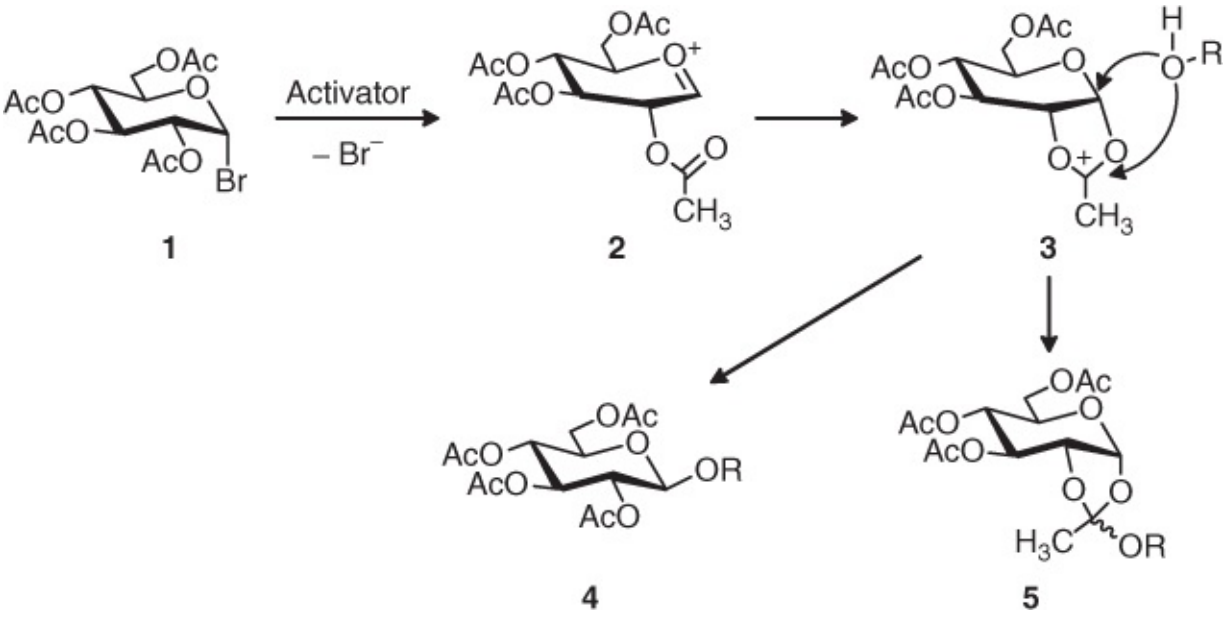
solvent) and does not permit stereoselective glycosylation. The procedure is used nowadays on a multi-ton scale for the synthesis of alkyl glucosides of dodecanol as important biocompatible tensides.



The most important and versatile stereoselective glycosylation methods of today are the Koenigs–Knorr reaction [6] using acyl-protected glycosyl halides, most often the bromides, and the Schmidt procedure employing a trichloroacetimidate moiety at the anomeric center of the glycosyl donor. However, thioglycosides, *N*-allylthiocarbamates [7a], phosphites [7b], 1,2-anhydro sugars [7c,d], trimethylsilyl (TMS)-glycosides [7e], and several other sugar derivatives have also been used as donors [7f]. In addition, enzymes can also be employed for glycosylations [8].



In the Koenigs–Knorr procedure for example, the 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**1**) is reacted with silver or mercury salts as an activator, which abstracts the halide to give an oxocarbenium cation **2**. This is attacked by the neighboring acetyl group to form a new carbocation **3**, which then reacts with an alcohol from the β-side in a 1,2-trans mode to give the β-glucoside **4**. The corresponding mannose derivative therefore provides the α-mannoside. As side products, orthoesters such as **5** may be formed by attack of the alcohol at the cationic center of the 1,3-dioxolane ring in **3**. Orthoesters themselves can also be applied as donors in glycosylations.



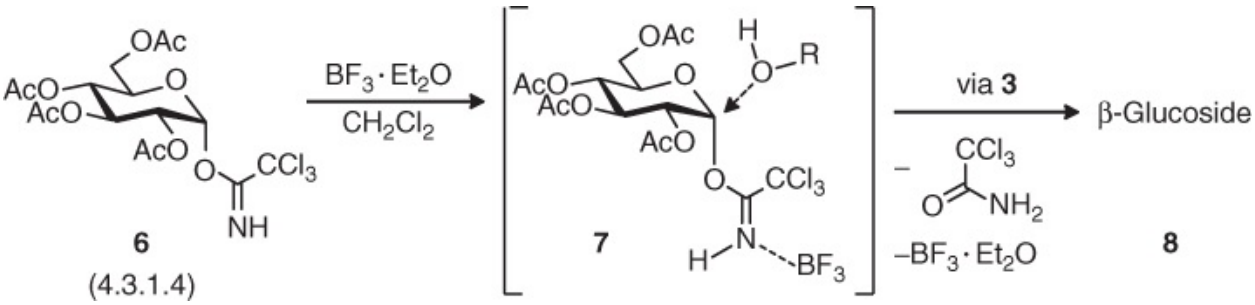
For stereoselective glycosylation using the Koenigs–Knorr procedure, an acyl protecting group must be present at C-2. However, the reactivity of the compounds is decreased compared to alkylated or benzylated sugars. A comparative study, for example, of thiogalactosides, showed an increasing reactivity with different substituents at C-2 in the order: $–N_3$ < $–OCOCH_2Cl$ < –NPhth < –OBz < –OAc < –OBn.

In glycosylations, a peracetylated donor proved to be 1189 times less reactive than the corresponding perbenzylated compound, but because of the lack of a neighboring group effect, the transformation of the latter compound resulted in the formation of a mixture of α-and β-galactosides. Comparing different sugar types, a reactivity order of fucose > galactose > glucose > mannose was found [9].

The Schmidt glycosylation using α-or β-glucosyl trichloroacetimidates **6** bearing an acetoxy group at C-2 [10] follows a similar route as described for the Koenigs–Knorr reaction. After activation with a catalytic amount of the Lewis acid $BF_3 \cdot Et_2O$, the intermediate **7** is formed which usually reacts to give the cation **3**, which then undergoes an attack of the alcohol from the β-side. If one uses α-or β-glucosyl trichloroacetimidates with benzyl protecting groups, the reaction proceeds in a different way. Under mild Lewis acid catalysis, for example, using $BF_3 \cdot Et_2O$, the β-imidate leads to the α-glucoside, whereas the α-imidate affords the β-glucoside in a type of S_N2 reaction. In contrast, with strong Lewis acids such as TMSOTf, the α-glucoside is usually predominately obtained. Similar results are found for other monosaccharides. An exception is

D-mannose with an axially positioned hydroxyl group at C-2, from which the α-mannosides can always be obtained with very good selectivity, but the selective formation of β-mannosides is difficult because of the anomeric effect [11].

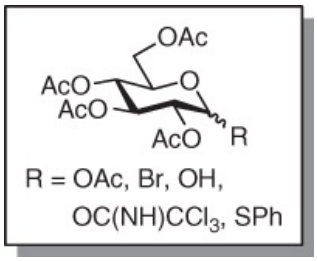
A special feature in glycosylation chemistry is the nitrile effect. Thus, when a glycosylation is performed in the presence of a nitrile such as acetonitrile using, for example, gluco-trichloroacetimidates with nonparticipating protecting groups at C-2, β-selectivity is observed. It is proposed that in these reactions an α-glucopyranosyl nitrilium ion is formed, which is attacked by the alcohol with inversion of configuration. The great advantage of the glycosyl trichloroacetimidates is their higher stability compared to the halides and the possibility of preparing the α-and β-glycosyl trichloroacetimidates in a largely selective manner by judicious choice of the base used and the reaction time (see **4.2.1.4**).



In carbohydrate chemistry, there are no universal tools for all types of glycosylation problems. To find the right procedure for a given synthetic problem is not an easy task and one has to apply different conditions. The German carbohydrate chemist Paulsen [12] wrote in his review in *Angewandte Chemie* in 1982 about the state of the art of chemical oligosaccharide synthesis:

“Although we have now learned to synthesize oligosaccharides, it should be emphasized that each oligosaccharide synthesis remains an independent problem, whose resolution requires considerable systematic research and a good deal of know-how. There are no universal reaction conditions for oligosaccharides.” Despite significant advances in the last 20 years, Paulsen's statement has largely remained true.

4.2.1 Synthesis of Glucosyl Donors



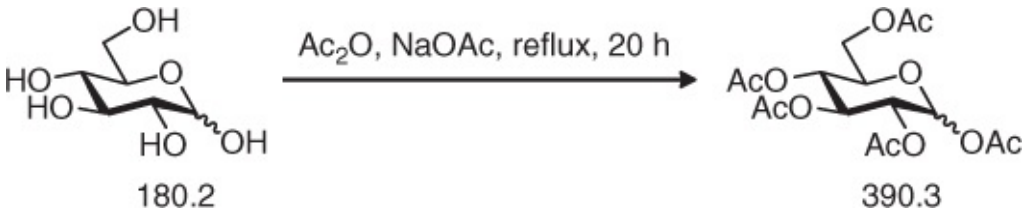
Topics:

- Acetylation of free sugars
- Displacement of the 1-*O*-acetyl group with thiols or bromide
- Anomeric deprotection
- Introduction of a trichloroacetimidate moiety

(a) Acetylation of D-Glucose

Many methods are available for the synthesis of peracetylated carbohydrates. Most commonly, the sugar is treated with acetic anhydride in the presence of NaOAc [13]. One can also use pyridine instead of NaOAc or a mixture of acetic anhydride, acetyl chloride, and a small amount of dimethylaminopyridine (DMAP). Acidic conditions can also be employed, such as the reaction with acetic anhydride in the presence of perchloric acid [14]. Depending on the method and the reaction temperature, one can partly control the ratio of the resulting peracetylated α/β-pyranose and α/β-furanose mixture.

4.2.1.1	*	**1,2,3,4,6-Penta-*O*-acetyl-α/β-D-glucopyranose**



A suspension of D-glucose (5.00 g, 27.8 mmol) and freshly fused, powdered NaOAc (0.46 g, 5.55 mmol) in acetic anhydride (20 ml, 21.7 g, 213 mmol) is vigorously stirred under reflux for 1.5 h. EtOH (4.5 ml) is then added and stirring is continued for 30 min.

The solution is poured into iced water (~50 ml) and diluted with *n*-pentane/CH_2Cl_2 (2 : 1; 150 ml), and the phases are separated. The organic layer is washed with iced water (50 ml), saturated $NaHCO_3$ solution (4 × 50 ml), and ice-cold brine (50 ml). The resulting solution is dried over Na_2SO_4 and the

solvents are removed *in vacuo*. The pure β-compound can be separated by crystallization from EtOH; 10.7 g (99%), α-compound: R_f = 0.58 (EtOAc/*n*-pentane, 1 : 1); β-compound: mp 130–131 °C, $[\alpha]^{20}_D$ = +4.2 (*c* = 1.0, $CHCl_3$), R_f = 0.58 (EtOAc/*n*-pentane, 1 : 1).

α-Compound:

IR (KBr) (α/β): $\tilde{\nu}$ (cm^{-1}) = 2968, 1746, 1370, 1224, 1038, 912.

^{1}H NMR (300 MHz, $CDCl_3$) (from α/β mixture): δ (ppm) = 6.33 (d, *J* = 3.7 Hz, 1H, 1-H), 5.46 (dd, *J* = 9.9, 9.8 Hz, 1H, 3-H), 5.11, 5.12 (2 × m_c, 2H, 2-H, 4-H), 4.27 (dd, *J* = 11.0, 4.2 Hz, 1H, 6_b-H), 4.13, 4.10 (m, 2H, 5-H, 6_a-H), 2.17, 2.08, 2.03, 2.01, 2.00 (5 × s, 5 × 3H, 5 × $OC(O)CH_3$).

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 170.5, 170.2, 169.3, 169.6, 168.7 (5 × $O\underline{C}(O)CH_3$), 89.0 (C-1), 69.8, 69.1, 67.8 (C-2, C-3, C-4, C-5), 61.4 (C-6), 20.8, 20.8, 20.7, 20.5, 20.4 (5 × $OC(O)\underline{C}H_3$).

MS (ESI): *m*/*z* (%) = 802.6 (10) $[2M + Na]^+$, 413.0 (100) $[M+Na]^+$.

β-Compound:

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 5.72 (d, *J* = 8.2 Hz, 1H, 1-H), 5.48, 5.26 (2 × m_c, 2H, 3-H, 4-H), 5.12 (dd, *J* = 9.2, 8.2 Hz, 1H, 2-H), 4.30 (dd, *J* = 12.5, 4.5 Hz, 1H, 6_b-H), 4.11 (dd, *J* = 12.5, 2.2 Hz, 1H, 6_a-H), 3.85 (ddd, *J* = 9.9, 4.4, 2.2 Hz, 1H, 5-H), 2.12, 2.09, 2.04, 2.02 (5 × s, 5 × 3H, $OC(O)CH_3$).

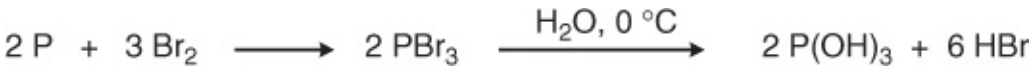
^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 170.5, 170.0, 169.3, 169.2, 168.9 (5 × $O\underline{C}(O)CH_3$), 91.7 (C-1), 72.7 (C-5), 72.7 (C-3), 70.2 (C-2), 67.7 (C-4), 61.4 (C-6), 20.8, 20.7, 20.6, 20.5 (5 × $OC(O)\underline{C}H_3$).

MS (ESI): *m*/*z* (%) = 802.6 (10) $[2M + Na]^+$, 413.0 (100) $[M+Na]^+$.

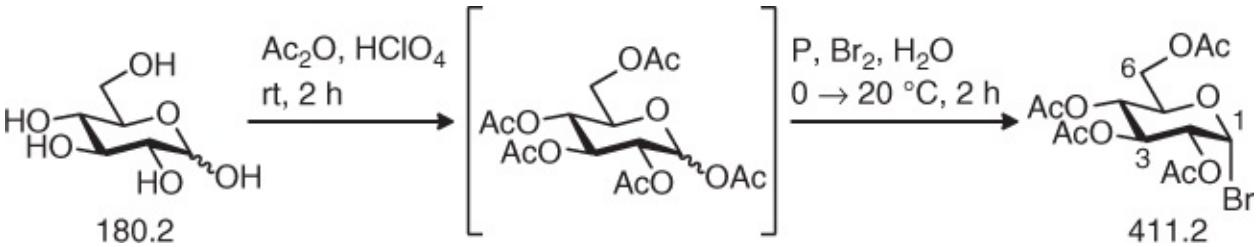
(b) Bromination of D-Glucose

The normal protocol for the generation of glycosyl bromides is the reaction of a 1-*O*-acyl-glycoside with 30% HBr solution in glacial acetic acid and CH_2Cl_2 as solvent. Other procedures start from the 1-hydroxy derivatives and use oxalyl

bromide or bromotrimethylsilane (TMSBr) in CH_2Cl_2. The method presented here is a two-step, one-pot procedure, in which the free sugar is first peracetylated and then brominated at C-1 with HBr generated *in situ* by reaction of PBr_3 with H_2O. In general, only the α-bromides are obtained because of the well-known anomeric effect [15].



4.2.1.2	**	**2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl bromide** [13]



D-Glucose (10.0 g, 55.4 mmol) is added in small portions over 30 min to a stirred mixture of acetic anhydride (40 ml, 43.5 g, 426 mmol) and perchloric acid (0.24 ml) at such a rate that the temperature does not exceed 40 °C. After 2 h, amorphous red phosphorus (3.00 g, 96.9 mmol) is added and the mixture is cooled to 0 °C. At this temperature, bromine (18.0 g, 5.80 ml, 113 mmol) is slowly dropped into the mixture, immediately followed by H_2O (3.62 ml, 200 mmol) over 15 min. A local rise of the internal temperature should be avoided; stirring is continued at room temperature for 2.5 h.

The solution is then diluted with CH_2Cl_2/*n*-pentane (1 : 2; 100 ml) and poured into iced water (150 ml). The mixture is extracted with CH_2Cl_2/*n*-pentane (1 : 2; 2 × 50 ml). The combined organic layers are filtered (removal of phosphorus), washed with saturated ice-cold $NaHCO_3$ solution (2 × 80 ml) (Caution: vigorous evolution of carbon dioxide!), iced water (80 ml), and ice-cold brine (80 ml), dried over Na_2SO_4, and filtered. Activated charcoal (500 mg) and $NaHCO_3$ (25 mg) are added, and the mixture is stirred at room temperature for 1 h. After filtration through Celite and removal of the solvents *in vacuo*, a yellow oil is obtained, which is recrystallized from absolute Et_2O to afford the bromide as white needles; 18.8 g (83%), mp 88–89 °C, $[\alpha]^{20}_D$ = +195 (*c* = 3.0, $CHCl_3$), R_f = 0.69 (EtOAc/*n*-pentane, 1 : 1).

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 2964, 1745, 1384, 1229, 1112, 1041, 923, 555, 486.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 6.62 (d, *J* = 4.0 Hz, 1H, 1-H), 5.56 (t, *J* = 9.8 Hz, 1H, 4-H), 5.17 (dd, *J* = 10.1, 9.6 Hz, 1H, 3-H), 4.84 (dd, *J* = 10.0, 4.0 Hz, 1H, 2-H), 4.34 (dd, *J* = 13.1, 3.2 Hz, 1H, 6_b-H), 4.30 (ddd, *J* = 9.8, 3.9, 1.4 Hz, 1H, 5-H), 4.13 (m, 1H, 6_a-H), 2.11, 2.10, 2.06, 2.04 (4 × s, 4 × 3H, 4 × $OC(O)CH_3$).

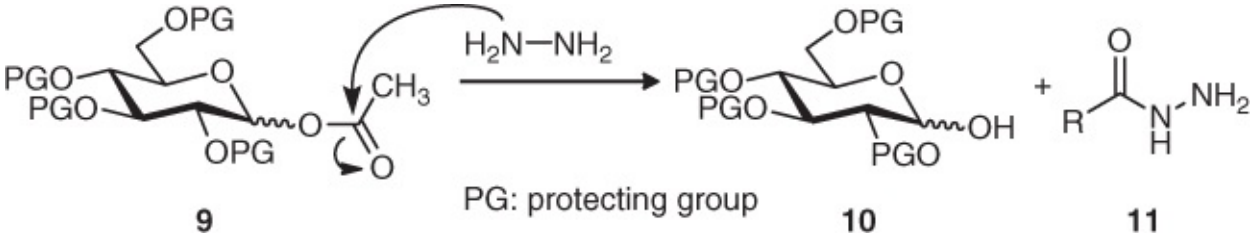
^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 170.5, 169.8, 169.7, 169.4 (4 × $O\underline{C}(O)CH_3$), 86.5 (C-1), 72.1 (C-2), 70.6 (C-3), 70.1 (C-5), 67.1 (C-4), 60.9 (C-6), 20.6, 20.6, 20.6, 20.5 (4 × $OC(O)\underline{C}H_3$).

MS (ESI): *m*/*z* (%) = 434.9 (57) $[M+Na]^+$.

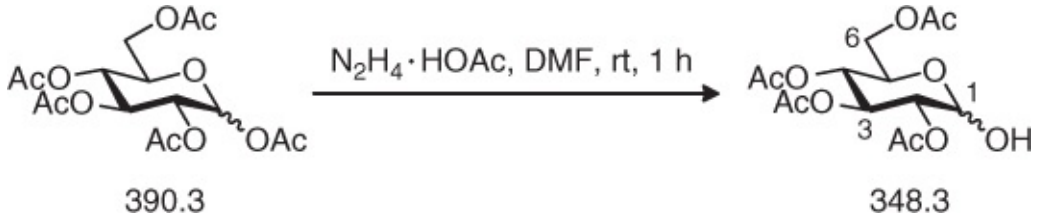
(c) Anomeric Deprotection

A common problem in carbohydrate chemistry is the selective deprotection of the anomeric center in the presence of similar hydroxyl group protection. In general, this is due to the higher reactivity of the anomeric center, which corresponds to a derivative of a hemiacetal. In the case of an acyl protecting group, the standard reagent for deprotection is hydrazinium acetate, whereas for the cleavage of a 1-*O*-methyl group strong acids such as H_2SO_4 can be used.

Hydrazine attacks the carbonyl group of the 1-*O*-acyl-protected carbohydrate **9** to give the corresponding carbohydrate **10** with a free anomeric center.



4.2.1.3	*	**2,3,4,6-Tetra-*O*-acetyl-α/β-D-glucopyranose** [14]



A solution of the pentaacetate (cf. **4.2.1.1**) (5.00 g, 12.8 mmol) and hydrazinium acetate (1.47 g, 16.0 mmol) (Caution: carcinogenic!) in DMF (55 ml) is stirred

for 60 min at room temperature.

The reaction mixture is then diluted with EtOAc (340 ml), and washed with iced water (120 ml), cold brine (120 ml), cold saturated aqueous $NaHCO_3$ solution (2 × 120 ml), and again with iced water (120 ml). The solution is dried over Na_2SO_4, and filtered. The solvent is removed *in vacuo* to afford the D-glucopyranose as a white foam, which solidifies under high vacuum; 3.92 g (88%), R_f = 0.19 (EtOAc/*n*-pentane, 1 : 2).

^{1}H NMR (300 MHz, $CDCl_3$) (from α/β-mixture, 2 : 3): δ (ppm) = 5.54 (dd, *J* = 10.0, 9.7 Hz, 1H, 3_α-H), 5.47 (d, *J* = 3.4 Hz, 1H, 1_α-H), 5.26 (t, *J* = 9.5 Hz, 1H, 3_β-H), 5.10, 5.09 (2 × t, *J* = 9.7 Hz, 2H, $4_{\alpha+\beta}$-H), 4.92 (dd, *J* = 9.9, 3.5 Hz, 1H, 2_α-H), 4.91 (dd, *J* = 9.6, 8.0 Hz, 1H, 2_β-H), 4.76 (d, *J* = 8.0 Hz, 1H, 1_β-H), 4.27, 4.16 (m, 5H, 5_α-H, $6_{\alpha+\beta}$-H_2), 4.07 (s_{br}, 1H, OH_β), 3.80 (s_{br}, 1H, OH_α), 3.77 (ddd, *J* = 10.1, 4.8, 2.4 Hz, 1H, 5_β-H), 2.11, 2.10, 2.05, 2.04, 2.03 (4 × s, 4 × 6H, $OC(O)CH_3$).

α-Compound:

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 170.8, 170.2, 170.1, 169.6 (4 × $O\underline{C}(O)CH_3$), 90.0 (C-1), 71.0 (C-2), 69.8 (C-3), 68.4 (C-4), 67.1 (C-5), 61.9 (C-6), 20.7, 20.6, 20.6, 20.5 (4 × $OC(O)\underline{C}H_3$).

β-Compound:

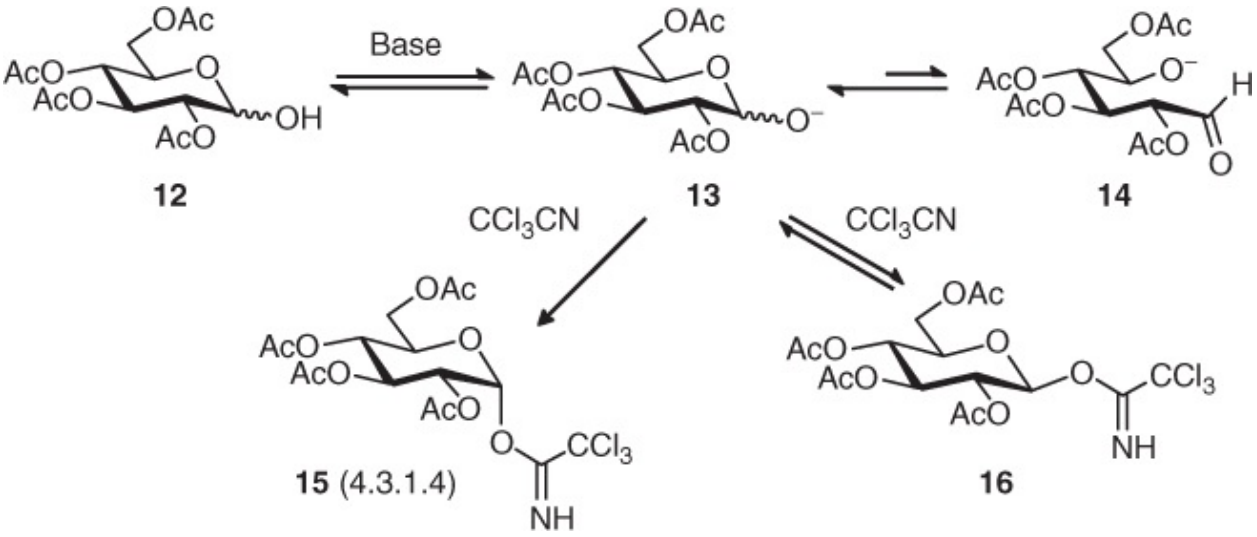
^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 170.8, 170.2, 169.5 (4 × $O\underline{C}(O)CH_3$), 95.4 (C-1), 73.1 (C-2), 72.2 (C-3), 71.9 (C-5), 68.3 (C-4), 61.9 (C-6), 20.7, 20.7, 20.5 (4 × $OC(O)\underline{C}H_3$).

MS (ESI): *m*/*z* (%) = 1088.4 (51) $[3M + 2Na]^+$, 718.7 (100) $[2M + Na]^+$, 371.1 (70) $[M+Na]^+$.

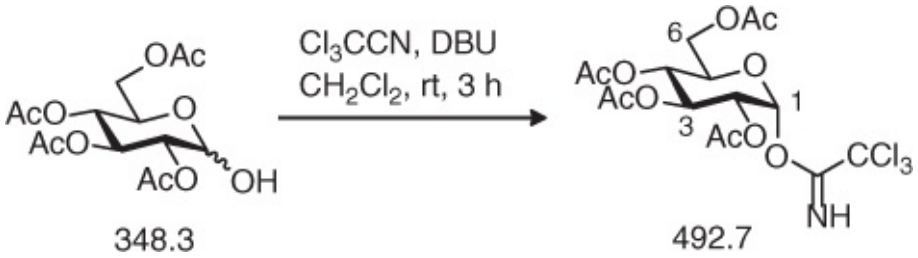
(d) Synthesis of Glycosyl Trichloroacetimidates

Glycosyl trichloroacetimidates are donors in glycosylation reactions. They are prepared from the corresponding 1-hydroxy derivatives **12**, which are deprotonated by a base before treatment with trichloroacetonitrile to give the desired product. The choice of base and the reaction time have a high influence

on the preferred formation of the α-or β-anomer. Under kinetic control using weak bases, the β-anomer **15** is formed predominately, whereas a long reaction time and strong bases such as NaH lead to the α-anomer **6** as the thermodynamically more stable compound via re-anomerization of the less stable β-anomer **15** [10b].



4.2.1.4	***	**2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl trichloroacetimidate** [16]



A mixture of D-glucopyranose tetraacetate (cf. **4.2.1.3**) (1.74 g, 5.00 mmol), trichloroacetonitrile (14.4 g, 10.2 ml, 100 mmol), and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (0.38 g, 0.38 ml, 2.50 mmol) in CH_2Cl_2 (30 ml) is stirred at room temperature for 3 h.

It is then concentrated under reduced pressure at <30 °C. The residue is purified by column filtration through silica gel with *n*-pentane/EtOAc (3 : 1; containing 2.5% of NEt_3) to afford the trichloroacetimidate as colorless (or slightly yellow) oil. For further purification, the product can be crystallized from Et_2O/*n*-pentane to give a colorless solid; 1.70 g (69%), mp 153–154 °C, $[\alpha]^{20}_D$ = +8.1 (*c* = 1.0, $CHCl_3$), R_f = 0.73 (EtOAc/*n*-pentane, 1 : 1).

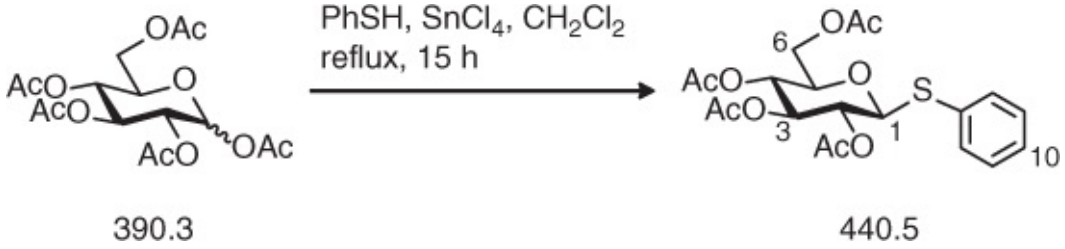
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.70 (s_{br}, 1H, NH), 6.57 (d, *J* = 3.7 Hz, 1H, 1-H), 5.57 (t, *J* = 9.8 Hz, 1H, 4-H), 5.19 (dd, *J* = 10.0, 9.8 Hz, 1H, 3-H), 5.14 (dd, *J* = 10.2, 3.7 Hz, 1H, 2-H), 4.28 (dd, *J* = 12.1, 4.0 Hz, 1H, 6_b-H), 4.22 (ddd, *J* = 10.2, 4.1, 1.8 Hz, 1H, 5-H), 4.13 (dd, *J* = 12.1, 2.0 Hz, 1H, 6_a-H), 2.08, 2.06, 2.04, 2.02 (4 × s, 12H, 4 × $OC(O)CH_3$).

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 170.6, 170.0, 169.9, 169.5 (4 × $O\underline{C}(O)CH_3$), 160.8 (CCl_3), 92.9 (C-1), 69.9, 69.7, 69.6, 67.7 (C-2, C-3, C-4, C-5), 61.3 (C-6), 20.6, 20.6, 20.4 (4 × $OC(O)\underline{C}H_3$).

(e) Synthesis of Thioglycosides

The most widely used approach for the synthesis of thioglycosides is the condensation of a 1-*O*-acyl-protected sugar with a thiol under Lewis acid catalysis, usually with $BF_3 \cdot Et_2O$, $SnCl_4$, or $ZnCl_2$. After coordination of the Lewis acid to the carbonyl oxygen of the anomeric acetyl group, it is displaced by the added thiol, such as thiophenol.

4.2.1.5	**	**Phenyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside** [17]



390.3 440.5

Thiophenol (6.72 g, 6.26 ml, 61.0 mmol) and tin(IV)chloride (9.25 g, 4.15 ml, 35.5 mmol) are slowly added to a stirred solution of D-glucose pentaacetate **4.2.1.1** (19.8 g, 50.8 mmol) in CH_2Cl_2 (100 ml) at room temperature. The reaction mixture is heated under reflux for 16 h.

It is then cooled to room temperature and quenched by the addition of saturated $NaHCO_3$ solution (250 ml) (Caution: strong odor and formation of carbon dioxide!). CH_2Cl_2 (75 ml) and *n*-pentane (350 ml) are then added. The aqueous layer is separated and extracted with *n*-pentane/CH_2Cl_2 (2 : 1; 2 × 150 ml). The combined organic layers are washed with brine, dried over Na_2SO_4, and filtered. The solvents are removed *in vacuo* to provide a white solid. The crude material is recrystallized from EtOAc/*n*-pentane to afford the thioglucopyranoside as

white needles; 16.1 g (72%), mp 122–123 °C, $[\alpha]^{20}_{D}$ = +17.1 (*c* = 1.0, $CHCl_3$), R_f = 0.57 (EtOAc/*n*-pentane, 1 : 1).

UV (CH_3CN): λ_{max} (nm) (log ϵ) = 246 (0.193).

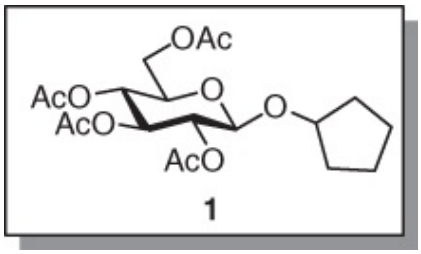
IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 2949, 1746, 1226, 1089, 1043, 913, 745.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.18–7.54 (m, 5H, Ar), 5.23 (t, *J* = 9.3 Hz, 1H, 3-H), 5.05 (m, 1H, 4-H), 4.98 (dd, *J* = 10.0, 9.4 Hz, 1H, 2-H), 4.72 (d, *J* = 10.1 Hz, 1H, 1-H), 4.24 (dd, *J* = 12.5, 5.1 Hz, 1H, 6_b-H), 4.18 (dd, *J* = 12.4, 2.9 Hz, 1H, 6_a-H), 3.74 (ddd, *J* = 10.1, 4.8, 2.8 Hz, 1H, 5-H), 2.10, 2.09, 2.03, 2.00 (4 × s, 4 × 3H, 4 × $OC(O)CH_3$).

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 170.5, 170.1, 169.4, 169.2 (4 × $OC(O)CH_3$), 133.1 (C-8, C-12), 131.6 (C-7), 128.9 (C-9, C-11), 128.4 (C-10), 85.7 (C-1), 75.7 (C-5), 73.9 (C-3), 69.9 (C-2), 68.1 (C-4), 62.1 (C-6), 20.7, 20.6 (4 × $OC(O)CH_3$).

MS (ESI): *m*/*z* (%) = 902.7 (50) $[2M + Na]^+$, 463.1 (100) $[M+Na]^+$.

4.2.2 Glycosylations of Glucosyl Donors with Cyclopentanol



1

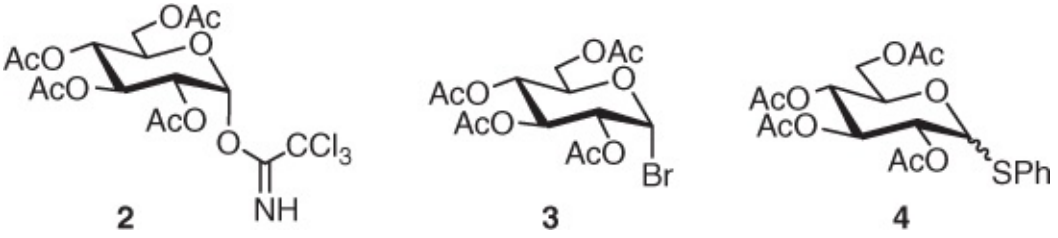
Topics:

- Glycosylation with trichloroacetimidates
- Koenigs–Knorr glycosylation
- Glycosylation with thioglycosides

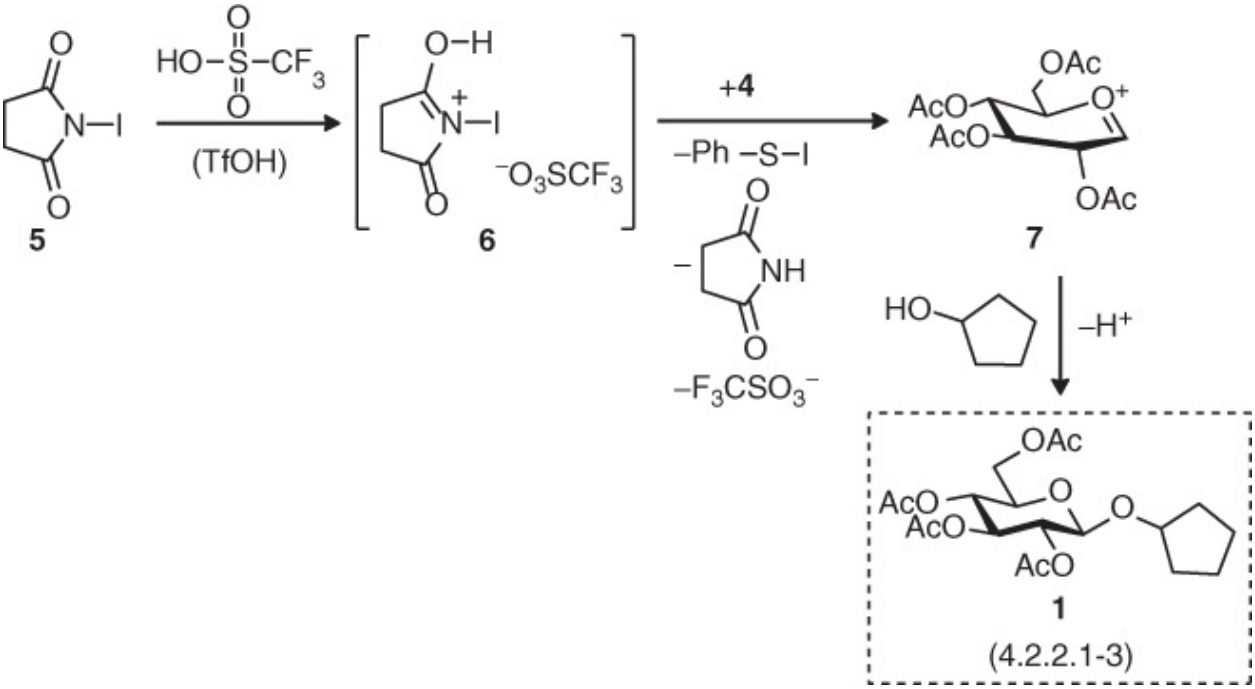
(a) General

In this section, β-glycoside formations employing cyclopentanol as the alcohol component and several types of *O*-acetyl-protected glycosyl donors, such as the

trichloroacetimidate **2**, the bromide **3**, and the thioglycoside **4**, are described.



While glycosylations with **2** and **3** have already been described in detail in the introductory section, for the condensation of the 1-thio-β-D-glucopyranoside **4**, the following aspects are relevant:



Activation of thioglycosides is usually achieved by the addition of halonium or formal methyl cations. Besides the use of iodonium-*sym*-dicollidine perchlorate [18a] (IDCP), MeI, and dimethyl-(methylthio)sulfonium triflate (DMTST) [19b], a mixture of *N*-iodosuccinimide **5** (NIS) [19c] and trifluoromethanesulfonic acid (TfOH) is most commonly applied. The acid serves to generate an iodonium cation **6**, which attacks the sulfur atom in the thioglycoside to give oxocarbenium ion **7** (see above) and iodo-thiophenol (I–S–Ph). The subsequent attack of the nucleophilic alcohol corresponds to the Koenigs–Knorr reaction and the stereochemistry is once again influenced by the protecting group at C-2.

4.2.2.1	***	**Cyclopentyl-2,3,4,6-tetraacetyl-β-D-glucopyranoside I** [19]

A mixture of the trichloroacetimidate (cf. **4.2.1.4**) (160 mg, 0.32 mmol), cyclopentanol (32 µl, 30.0 mg, 0.36 mmol), and powdered 4 Å molecular sieves (200 mg) in CH_2Cl_2 (1.5 ml) is stirred at room temperature for 30 min. The solution is then cooled to −10 °C, boron trifluoride etherate (10.3 µl, 11.5 mg, 0.08 mmol) in CH_2Cl_2 (0.5 ml) is added dropwise, and stirring is continued for 1 h.

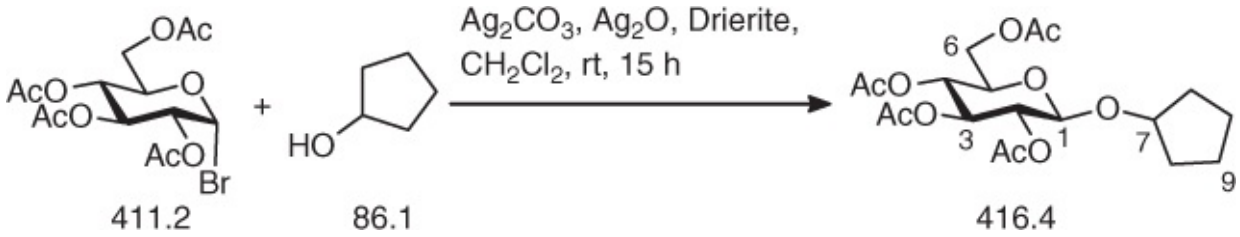
Thereafter, the reaction is terminated by adding NEt_3 (50 µl). The solvent is removed under reduced pressure and the residue is purified by column chromatography on silica gel (7 g) with *n*-pentane/EtOAc (3 : 1) as eluent to provide the β-glucoside as a white solid; 98 mg (73%), mp 118–120 °C, $[\alpha]^{20}_D$ = −34.2 (*c* = 1.0, $CHCl_3$), R_f = 0.71 (EtOAc/*n*-pentane, 1 : 1).

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 5.21 (t, *J* = 9.6 Hz, 1H, 3-H), 5.07 (t, *J* = 9.6 Hz, 1H, 4-H), 4.94 (dd, *J* = 9.6, 8.0 Hz, 1H, 2-H), 4.53 (d, *J* = 8.0 Hz, 1H, 1-H), 4.28 (m, 1H, 7-H), 4.27 (dd, *J* = 12.2, 4.9 Hz, 1H, 6_b-H), 4.13 (dd, *J* = 12.2, 2.5 Hz, 1H, 6_a-H), 3.69 (ddd, *J* = 9.9, 4.9, 2.5 Hz, 1H, 5-H), 2.09, 2.04, 2.03, 2.01 (4 × s, 4 × 3H, 4 × $OC(O)CH_3$), 1.45–1.83 (m, 8H, cyclopentyl-H).

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 170.7, 170.3, 169.4, 169.2 (4 × $OC(O)CH_3$), 99.5 (C-1), 81.5 (C-7), 72.8 (C-3), 71.7 (C-5), 71.4 (C-2), 68.5 (C-4), 62.1 (C-6), 33.1, 32.1 (C-8, C-11), 23.3, 23.0 (C-9, C-10), 20.7, 20.6, 20.6 (4 × $OC(O)CH_3$).

MS (ESI): *m*/*z* (%) = 854.8 (39) $[2M + Na]^+$, 439.2 (100) $[M+Na]^+$.

4.2.2.2	**	**Cyclopentyl-2,3,4,6-tetraacetyl-β-D-glucopyranoside II** [19]



Under exclusion of light, silver(I) oxide (295 mg, 1.27 mmol) and silver(I) carbonate (68 mg, 0.25 mmol) are added to a stirred solution of the D-glucopyranosyl bromide (cf. **4.2.1.2**) (133 mg, 0.32 mmol) and cyclopentanol (32 µl, 30.0 mg, 0.36 mmol) in CH_2Cl_2 (10 ml) containing Drierite (540 mg), and the mixture is stirred at room temperature for 15 h.

After filtration through Celite, the solvent is removed under reduced pressure and the residue is purified by column chromatography on silica gel with *n*-pentane/EtOAc (3 : 1) as eluent to give the desired β-glucoside (77 mg, 57%) along with a trace of the α-glucoside (<2 mg, 1%); mp 118–120 °C, $[\alpha]^{20}_D$ = −34.2 (*c* = 1.0, $CHCl_3$), R_f = 0.71 (EtOAc/*n*-pentane, 1 : 1).

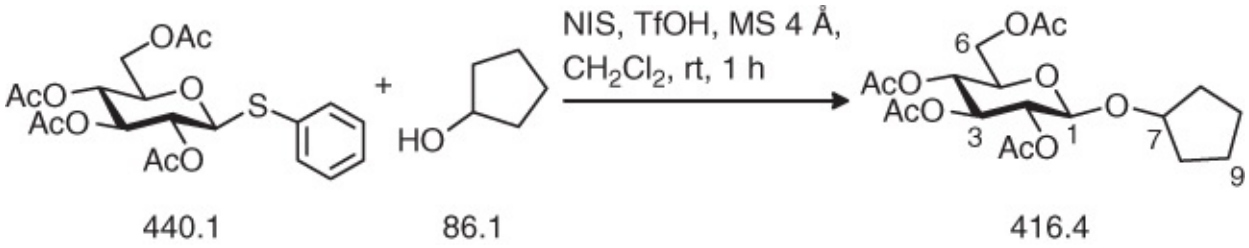
For spectroscopic data of the β-glucoside, see **4.3.2.1**.

α-Glucoside (*second product*):

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 5.46 (t, *J* = 10.0 Hz, 1H, 3-H), 5.16 (d, *J* = 3.8 Hz, 1H, 1-H), 5.04 (t, *J* = 9.9 Hz, 1H, 4-H), 4.81 (dd, *J* = 10.2, 3.8 Hz, 1H, 2-H), 4.27 (dd, *J* = 12.3, 4.7 Hz, 1H,6_b-H), 4.18 (m, 1H, 7-H), 4.10 (dd, *J* = 12.2, 2.0 Hz, 1H, 6_a-H), 2.02, 2.04, 2.05, 2.10 (4 × s, 4 × 3H, 4 × $OC(O)CH_3$), 1.49–1.81 (m, 8H, cyclopentyl-H).

^{13}C NMR (151 MHz, $CDCl_3$): δ (ppm) = 170.7, 170.2, 169.6 (4 × $OC(O)CH_3$), 94.3 (C-1), 80.2 (C-7), 71.0, 70.3, 68.7, 67.2 (C-2, C-3, C-4, C-5), 62.0 (C-6), 32.9, 31.8 (C-8, C-11), 23.3, 23.0 (C-9, C-10), 20.7, 20.7, 20.6 (4 × $OC(O)CH_3$).

4.2.2.3	***	**Cyclopentyl-2,3,4,6-tetraacetyl-β-D-glucopyranoside III** [20]



Thio-β-D-glucopyranoside (cf. **4.2.1.5**) (143 mg, 0.32 mmol), cyclopentanol (32 µl, 30 mg, 0.36 mmol), and NIS (77 mg, 0.34 mmol) are dissolved in CH_2Cl_2 (2.5 ml) containing powdered 4 Å molecular sieves (200 mg) and the mixture is stirred at room temperature for 1 h. Trifluoromethanesulfonic acid (6 µl, 10 mg, 70 µmol) in CH_2Cl_2 (0.5 ml) is then added dropwise and stirring is continued for 30 min.

A mixture of *n*-pentane/CH_2Cl_2 (3 : 1; 20 ml) is then added and the resulting mixture is transferred to a separatory funnel. The solution is washed with iced water (5 ml), 10% aqueous sodium thiosulfate solution (5 ml), saturated aqueous $NaHCO_3$ solution (5 ml), and cold brine (5 ml). The organic layer is dried over Na_2SO_4, filtered, and the solvent is removed *in vacuo*. Column chromatography on silica gel with *n*-pentane/EtOAc (3 : 1) as eluent affords the desired β-glucoside (66 mg, 49%), which contains a small amount of the α-compound (∼2%); β-glucoside: mp 118–120 °C, $[\alpha]^{20}_D = -34.2$ (*c* = 1.0, $CHCl_3$), $R_f = 0.71$ (EtOAc/*n*-pentane, 1 : 1); α-glucoside (by-product): $R_f = 0.73$ (EtOAc/*n*-pentane, 1 : 1).

For spectroscopic data, see **4.2.2.1** and **4.2.2.2**.

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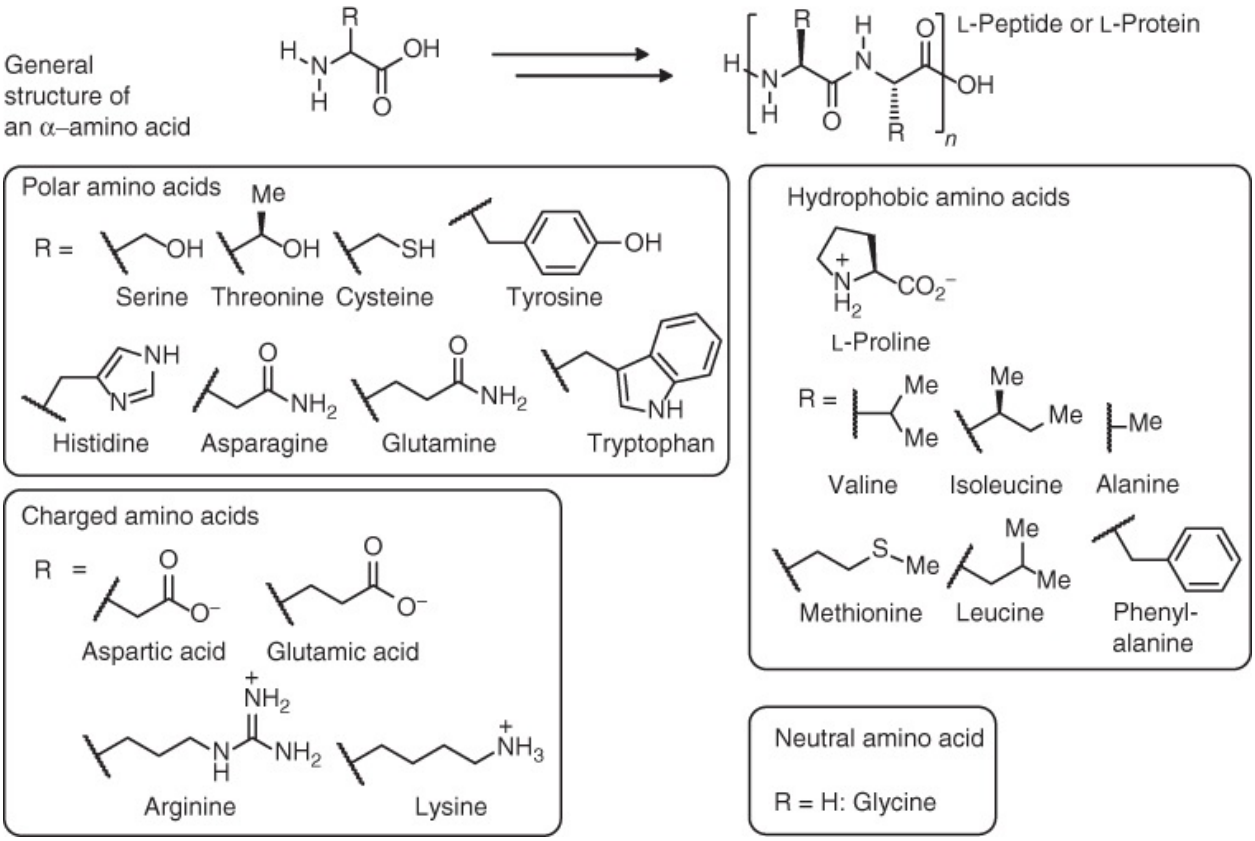
4.3 Amino Acids and Peptides

Introduction

Amino acids represent a class of organic compounds containing an amino group and a carboxylic acid functionality. The structural diversity of amino acids originates from two elements. On one hand, the two functional groups can be separated by one sp^3 C atom (as in α-amino acids) or by a larger number (e.g., two C atoms in β-amino acids). On the other hand, a large variety of different side chains are known (as exemplified below for an α-amino acid) that provide diverse functionalities and properties (classified as hydrophobic, polar, or charged amino acids).



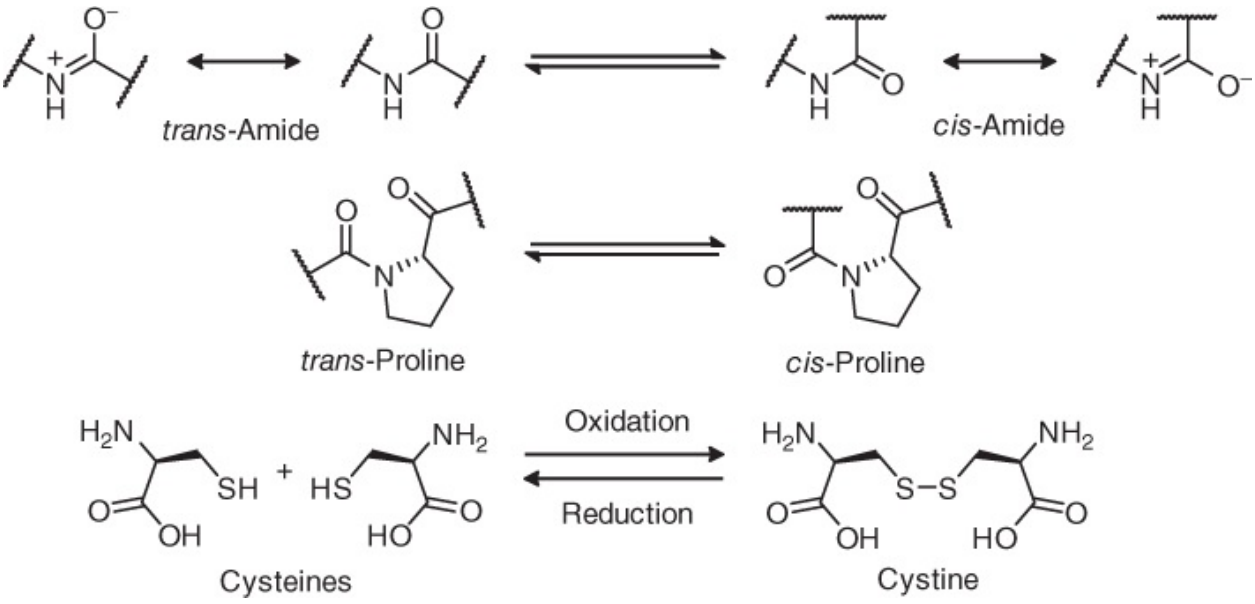
Amino acids are among the most important building blocks in nature – since they constitute the macromolecular structures of peptides and proteins – that play a central role as functional molecules in biological processes.

Peptides are linear oligomers consisting of two or more amino acids linked by amide bonds with an overall length of up to 50 monomeric units. They are heavily involved in essential biochemical and physiological processes as well as functioning, for example, as hormones, as neurotransmitters, and in receptor-mediated signal transduction [1–3].

Furthermore, peptides participate in immunological processes, in cell–cell communication, in the regulation of biochemical processes, and in immune response, to name only a few. The central role of peptides in biological processes has also prompted exceptional interest in the synthesis of peptides and peptide analogs by pharmacologists and chemists. With respect to their primary structure, proteins differ from peptides only in their length (>50 amino acids). Longer polyamide chains are folded into secondary structures such as α-helices, β-strands, or turns. These secondary elements are further arranged in a three-dimensional architecture [4]. Folding allows proteins to be functional in manifold manner. They can act as biological scaffolds, as is the case in collagen, keratin, or silk fibers. Moreover, they are essential for the enormous variety of

enzymes, and serve as regulators and facilitate transport, mechanical motion, and storage function. Proteins are able to acquire and process sensory impulses, and are essential in the immune system as well as for the expression of genetic information. The structural and functional diversity of peptides and proteins in biological processes usually originates from just 20 “standard” proteinogenic amino acids (specified by the genetic code). The sequential order of amino acids, the oligomer length, and especially the folding into three-dimensional structures are responsible for the functional variety. Natural peptides and proteins normally contain α-amino acids with L-configuration. The amino acids can be classified with respect to their side-chain polarity and recognition potential. Hydrophobic amino acids have an aliphatic (alanine, valine, leucine, isoleucine, proline, methionine) or aromatic (phenylalanine) side chain. They are typically found in nonpolar environments, like the inner regions of proteins or transmembrane protein domains, and often provide Van der Waals interactions.

Among the proteinogenic amino acids, proline is the only representative that features a secondary instead of a primary amino group resulting in unique structural properties (see below). The amino acids serine, threonine, cysteine, asparagine, glutamine, tyrosine, histidine, and tryptophan are equipped with more polar side chains and display a pronounced hydrogen-bonding ability. Aromatic side chains also often provide π–π stacking. Finally, there are positively (lysine, arginine) and negatively charged amino acids (aspartic acid, glutamic acid) with hydrogen-bonding ability and potential for Coulomb attraction. Charged amino acids are often found directed towards aqueous environment.



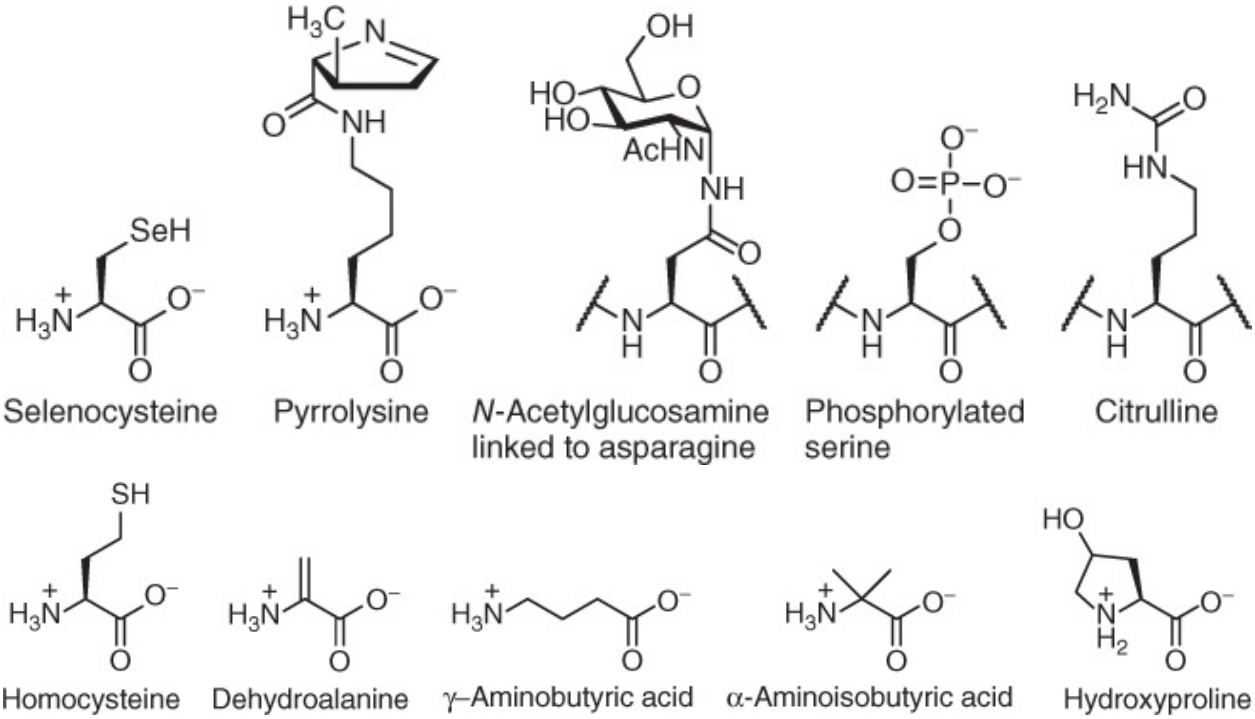
The general structure and especially the flexibility of peptides and proteins are

The general structure and especially the flexibility of peptides and proteins are greatly influenced by the nature of the amide bond, providing a partial double bond character. This phenomenon is most likely illustrated by the two typical resonance forms, which suggest an estimated double bond contribution of about 40% resulting in a significant planarity of the amide group and the residues attached to the N atom. Since the trans compared to the corresponding cis geometry is much more favorable for amides derived from primary amines, most peptide bonds exclusively result in trans isomers.

Two amino acids should be especially highlighted with regard to their roles in the folding and dynamics of three-dimensional protein structures. First, proline is the only cyclic proteinogenic amino acid with a secondary amine forming the peptide bond. The cyclic side chain of proline induces conformational restriction to the peptide backbone, making this amino acid favorable in turn structures and as the starting point of α-helices, but it is also known to disrupt other secondary structures. As a consequence of the side-chain cycle formed with the amide nitrogen, hydrogen bonding is lost and cis/trans isomerization of the amide bond is facilitated. Whereas most peptide bonds are nearly exclusively found as trans isomers, peptides with proline as well as N-alkylated amino acids (see Sections 4.3.1 and 4.3.2) show significant amounts of the cis isomer. For example, the polymer obtained from the glycine–proline–hydroxyproline repeating unit provides the collagen triple-helix coiled-coil structure, one of the most important fibrous structural proteins. Second, two cysteine side chains can be oxidized to form a disulfide bridge called ***cystine***. Through cystine formation in a protein chain, sequentially distant positions become covalently linked. Furthermore, the conformational flexibility of a protein is greatly restricted by the formation of disulfide bridges.

In addition to the 20 “standard” proteinogenic amino acids, numerous “nonstandard” amino acids are also found in nature [5]. Selenocysteine and pyrrolysine complete the group of the 22 proteinogenic amino acids, but these two are termed ***nonstandard*** proteinogenic amino acids. This is due to the fact that they are encoded via variant codons in combination with a characteristic mRNA, since both the UGA and UAG codons are normally referred to as ***opal*** and ***amber*** stop codons. Moreover, amino acids with D-configuration are available by isomerization from all naturally occurring L-amino acids. Enzymatic modifications of proteins after translation also lead to non-proteinogenic amino acids. Well-known post-translational modifications are functionalizations with recognition elements such as carbohydrates or lipids. For example, phosphorylation of serine is used to regulate enzymes by switching

enzymatic activity “on” or “off” or to influence receptor fitting. Methylation of arginine or lysine is similarly used to regulate biochemical processes. Post-translational functional group conversions also provide further amino acids, such as citrulline generated from arginine.

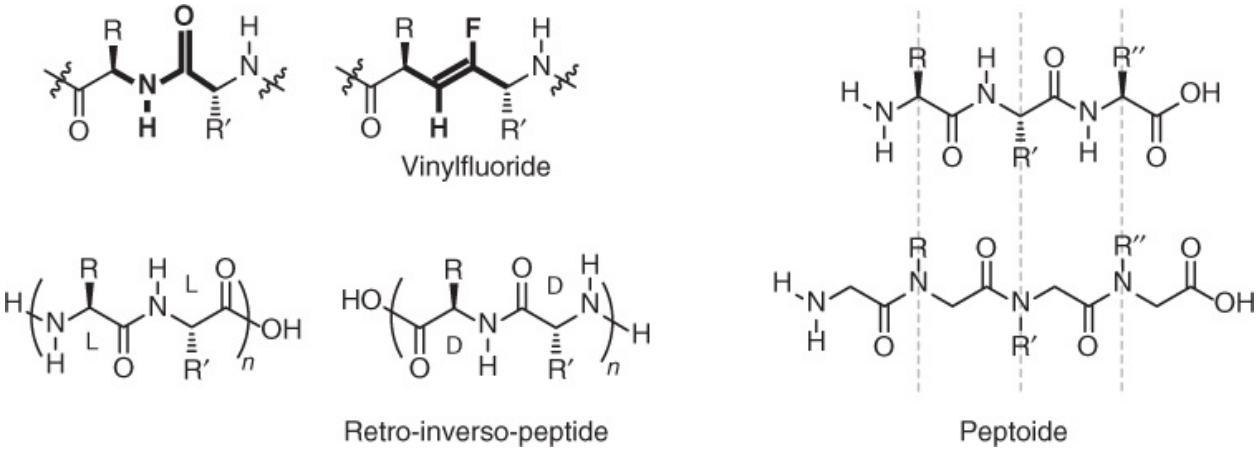


Additional post-translational modifications at the protein level are the formation of disulfide bridges and the cutting and shortening of peptide chains (as known, e.g., from the insulin biosynthesis pathway). Moreover, other “nonstandard” amino acids found in nature directly result from metabolism or catabolism; examples are ornithine, homocysteine, dehydroalanine, the inhibitory neurotransmitter γ-aminobutyric acid, α-aminoisobutyric acid, and hydroxyproline.

Nonchiral β-amino acids such as β-alanine also exist in nature. Therefore, extensive research is focused on the synthesis of a huge variety of β-amino acids derived by homologation of proteinogenic α-amino acids or β-amino acids containing artificial side chains [6]. The peptide world derived from β-amino acids (see Section 4.4.8) is of special interest since it is possible to mimic the secondary structures known from α-peptides in combination with enormously increased metabolic and conformational stability. Various helices as well as sheet and turn structures are obtained with even short sequences based on rational design including the substitution pattern and the configuration of side chains in α-or β-positions. As an additional benefit, the β-peptide series provides

the possibility to establish well-defined structural properties, such as directionality and magnitude of the overall helical dipole.

The synthesis of artificial amino acids with cofactor side chains, functional groups, or specific recognition elements is of great pharmacological relevance (see Section 4.4.1). In addition, modification of the peptide chain, the so-called backbone, is of value to generate function, to increase recognition as well as bioavailability, and to obtain metabolic stability. Among the numerous possible derivatizations, in here only the replacement of the peptide bond by isomorphous vinyl fluorides, the retro-inverso peptides, and the peptoides, with side chains linked to the amide N-atoms, should be mentioned. For the retro-inverso peptides, simultaneous inversion of strand orientation and configuration of all amino acids provides the maintenance of the spatial orientation of side chains [7].



The following sections deal with the preparation of enantiomerically pure amino acids as well as the chemical synthesis of peptides on solid supports [8, 9].

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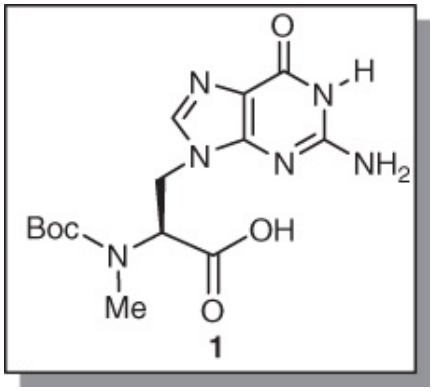
4.3.1 *N*-Boc-*N*-methyl-(*S*)-alanyl nucleo amino acid



1

Topics:

- Mitsunobu lactonization
- N-methylation of α-amino acids
- Serine lactone opening with nucleophiles
- Nucleophilic aromatic substitution
- *N*-Boc protection

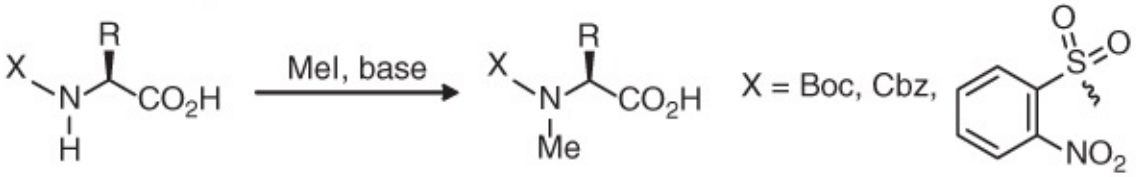
(a) General

N-Methyl-α-amino acids are common components of natural products such as cyclosporine, dolastatins, and didemnins, which show a wide range of biological effects [1]. Thus, antibiotic, anticancer, antiviral, and immunosuppressive activities have been reported for N-methylated peptides and proteins [2]. N-Methylation of amino acids, peptides, or proteins has a major impact on pharmacological parameters such as lipophilicity, bioavailability, proteolytic

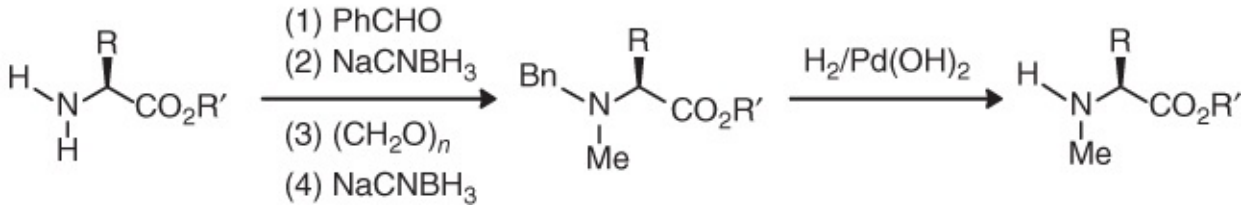
stability, and conformational rigidity, because, *inter alia*, the potential for hydrogen bond formation is usually lost and the amide bond of N-methylated amino acids is more prone to cis/trans isomerization [3]. Both parameters strongly influence the overall backbone conformation of peptides and proteins containing N-methylated amino acids.

For a long time, the synthesis of N-methylated amino acids was quite severely restricted because of the harsh reaction conditions of the known synthetic procedures, which were likely to cause racemization [4]. Moreover, these procedures were limited to amino acids without any additional nucleophilic functional groups. However, quite recently new general methods for the synthesis of N-methylated α-amino acids have been developed [5–9]. In the following, the hitherto established general strategies are presented:

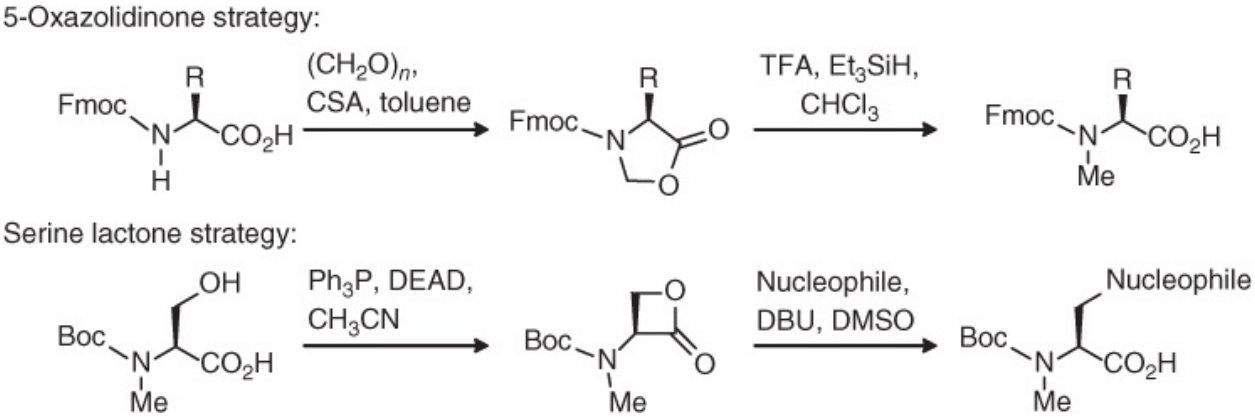
Direct-N-methylation:



Reductive amination:



Direct N-methylation can be performed by nucleophilic substitution of Nprotected α-amino acids and α-amino esters with, for example, MeI [4]; in addition, treatment with diazomethane is possible [5]. To avoid strongly basic conditions, the Nprotection can be combined with N-activation using the *o*-nitrobenzenesulfonyl (*o*-NBS) group [10] to also allow the synthesis of *N*-methylamino acids with acidic or basic side chains that can be directly applied to fluorenyl-9-methoxycarbonyl (Fmoc) solid-phase peptide synthesis (SPPS) [6]. Basic N-methylated amino acids can be obtained without side-chain protection by successive reductive amination of the amino acids, first using benzaldehyde/cyanoborohydride and then paraformaldehyde/cyanoborohydride [7].



A third strategy is based on conversion of Fmoc-protected amino acids into 5-oxazolidinones using paraformaldehyde under acidic conditions [8]; reductive opening with triethylsilane and trifluoroacetic acid (TFA) then provides N-methylated amino acids. Another method is based on serine lactone, which is readily available from *tert*-butyloxycarbonyl (Boc)-protected *N*-methyl serine [9] under Mitsunobu conditions [11]. Starting from this substrate, various N-methylated amino acids can be obtained by introducing the respective side chain by nucleophilic opening of the lactone moiety. This method is especially valuable for the preparation of non-proteogenic amino acids, such as the alanyl nucleo amino acids, which contain a nucleobase covalently linked at the β-position [12].

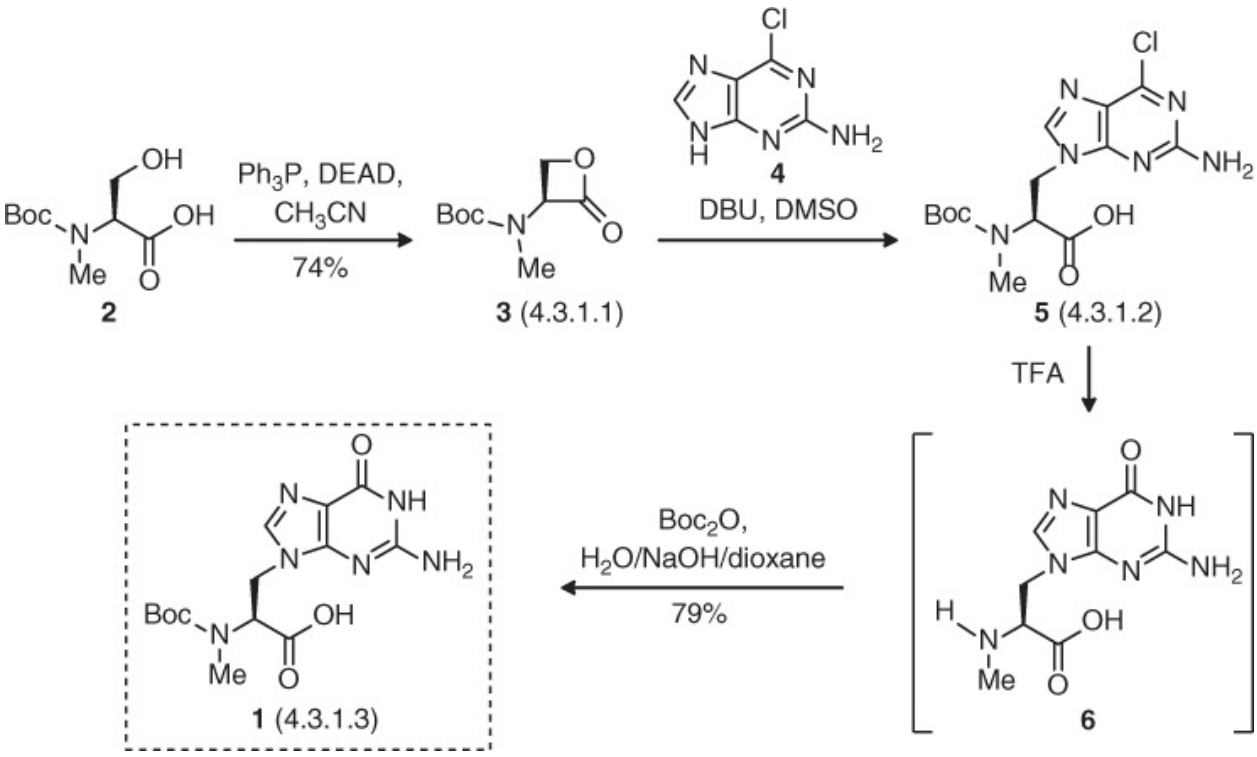
Some of the described methylation strategies can also be applied for the synthesis of N-methylated peptides or proteins directly on solid support [6, 13].

(b) Synthesis of 1

Starting from commercially available *N*-Boc-*N*-methyl serine (**2**), the serine lactone **3** can be obtained under Mitsunobu conditions in analogy to the Boc-serine lactone formation described by Vederas [11].

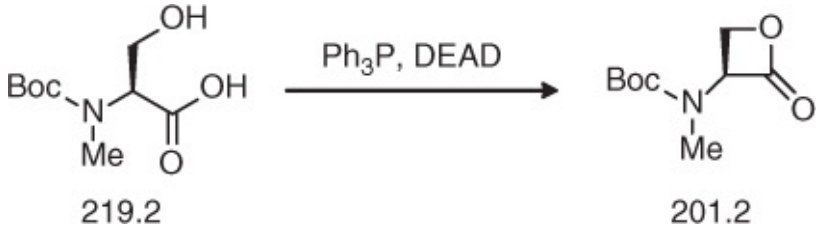
As also known from serine lactone, the *N*-methyl derivative **3** can be opened by various nucleophiles to yield amino acids with the nucleophile covalently linked at the β-position in the amino acid chain. The introduction of nucleobases is especially interesting because of their recognition potential [12]. However, purines are difficult nucleophiles because of competitive nucleophilicity at positions N-7 and N-9, low solubility and nucleophilicity, as well as aggregation behavior. In order to obtain the guaninyl nucleo amino acid **1**, guanine itself cannot be used as the nucleophile; instead, 6-chloro-2-aminopurine **4** can be employed, providing much better nucleophilicity and regioselectivity. The compound **5** thus obtained is then treated with TFA to provide **6** by nucleophilic

aromatic substitution of the chloro substituent. However, under the strongly acidic reaction conditions used, the Boc protecting group is lost and needs to be reestablished with di-*tert*-butyl dicarboxylate to yield the target nucleo amino acid **1**. Using the described procedure, the nucleo amino acid **1** is available in three steps starting from *N*-Boc-*N*-methyl serine **2** in an overall yield of 45%. The otherwise comparable reaction with *N*-Boc-serine lactone gives an overall yield of only 21%, hence the use of the N-methylated substrate **3** results in a remarkable improvement in yield. The better result using **3** is mainly due to its lower polarity.



(c) Experimental Procedures for the Synthesis of 1

4.3.1.1	**	**(*S*)-*N*-Butoxycarbonyl-*N*-methyl-L-serine lactone** [9]



Diethylazodicarboxylate (DEAD) (3.58 ml, 23.0 mmol) is added to a stirred solution of triphenylphosphine (6.04 g, 23.0 mmol) in anhydrous CH_3CN (100

ml) at −40 °C over a period of 15 min. The reaction mixture is kept at this temperature for about 20 min. A suspension of Boc-*N*-methyl-L-serine (5.00 g, 22.8 mmol) in anhydrous CH_3CN (50 ml) is then added, and stirring is continued at −35 °C for 2 h and at room temperature for a further 5 h.

After purification by flash chromatography (180 g silica gel; EtOAc/hexane, 1 : 3), the product is obtained as a colorless solid: 3.37 g (74%), mp 30–35 °C, ee > 98%;

R_f (*n*-hexane/EtOAc, 3 : 1) = 0.37; $[\alpha]^{20}_D$ = −44 (*c* = 0.75, MeOH).

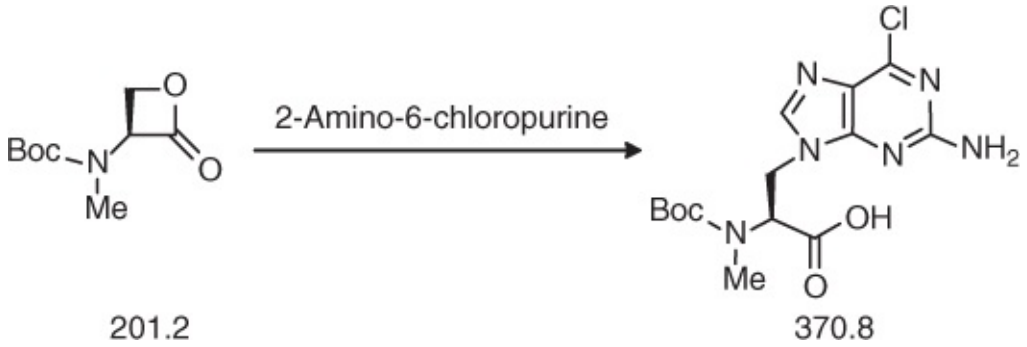
IR (film): $\tilde{\nu}$ (cm^{-1}) = 2980, 2935, 1833, 1762, 1697, 1482, 1455, 1401, 1370, 1352, 1329, 1302, 1254, 1111, 1051, 968, 941.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 4.43 (d, 2H, $C\underline{H}_2$), 2.98 (s, 3H, $C\underline{H}_3$), 1.47 (s, 9H, *t*-Bu).

^{13}C NMR (76 MHz, [D_6]DMSO): δ (ppm) = 77.2 (CO lactone), 77.0 (CO), 76.7 ($\underline{C}(CH_3)_3$), 64.4 (C-2), 58.7 (C-3), 30.3 (NCH_3), 27.8 ($C(\underline{C}H_3)_3$).

MS HRS: *m*/*z* = 224 $[M+Na]^+$.

4.3.1.2	***	**(*S*)-*N*-*tert*-Butoxycarbonyl-*N*-methyl-β-(2-amino-6-chloro-9-purinyl)-alanine** [9]



201.2 370.8

Under an argon atmosphere, DBU (513 µl, 3.43 mmol) is added to a suspension of 2-amino-6-chloropurine (688 mg, 4.06 mmol) in anhydrous DMSO (2.0 ml) and the mixture is stirred for 15 min. A solution of (*S*)-*N*-Boc-*N*-methyl-L-serine lactone (cf. **4.3.1.1**) (628 mg, 3.12 mmol) in anhydrous DMSO (2 ml) is then added over 15 min and the reaction mixture is kept at room temperature for 210 min.

The reaction is then quenched by the addition of AcOH (127 µl, 2.22 mmol) and the solvent is removed *in vacuo*. Purification of the residue by flash chromatography (SiO_2, EtOAc/MeOH 8 : 2, +0.2–1% AcOH) gives the desired nucleo amino acid as colorless solid; 889 mg (77%),

R_f (isopropanol/H_2O/AcOH, 5 : 2 : 1, saturated with NaCl) = 0.52; $[\alpha]^{20}_D$ = −109.3 (*c* = 0.30, DMSO).

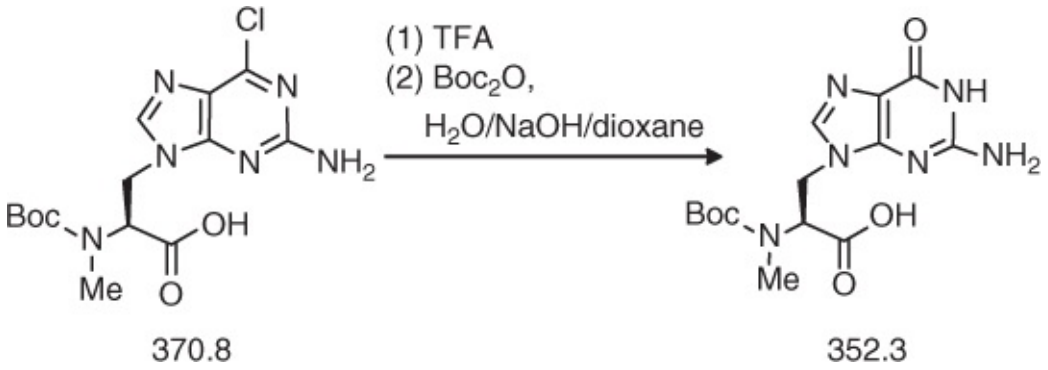
IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3347, 2977, 1693, 1616, 1565, 1520, 1469, 1393, 1368, 1155, 916, 785, 643.

^{1}H NMR (300 MHz, [D_6]DMSO): δ (ppm) = 8.01 (s, 1H, 8-H), 6.85 (s, 2H, NH_2), 4.89 (m, 2H, α-H, β-H), 4.45 (m, 1H, β-H), 2.74 (s, 0.5H, N–CH_3), 2.70 (s, 2.5H, N–CH_3), 1.20 (s, 1.5H, *t*-Bu), 1.06 (s, 7.5H, *t*-Bu).

^{13}C NMR (76 MHz, [D_6]DMSO): δ (ppm) = 170.2 (CO_2H), 160.0 (C-4), 155.0 (CONH), 154.2 (C-2), 149.5 (C-6), 142.3 (C-8), 123.2 (C-5), 78.8 ($\underline{C}(CH_3)$), 57.4 (α-C), 41.6 (NCH_3), 39.9 (β-C), 27.3 ($C(\underline{C}H_3)_3$).

MS HRS: *m*/*z* (%): 371.12 $[M+H]^+$.

4.3.1.3	**	**(*S*)-*N*-*tert*-Butoxycarbonyl-*N*-methyl-β-(9-guaninyl)-alanine** [9]



370.8 352.3

A solution of the amino acid **4.3.1.2** (869 mg, 2.34 mmol) in TFA/H_2O (3 : 1; 12 ml) is stirred at room temperature overnight. Toluene is then added and the mixture is concentrated to dryness. The formed guaninyl amino acid is dissolved in a mixture of H_2O/1 N NaOH/dioxane (1 : 1 : 2; 10 ml) and further 1 N NaOH is added to maintain a pH of 9.5. The reaction mixture is cooled to 0 °C, treated with di-*tert*-butyl dicarbonate (563 mg, 2.58 mmol), and kept for 45 min at 0 °C and for 60 h at room temperature. It is then adjusted to pH 6 by the addition of

ice-cold 1 N HCl. The solvents are removed *in vacuo*, the residue is purified by reversed phase (RP)-column chromatography (C-18) using MeOH (8%)/water to give the product as white solid; 522.6 mg (79%); mp > 198 °C (decomposition) (93% *ee*);

R_f (EtOAc/MeOH/H_2O/AcOH, 6 : 2 : 2 : 1, saturated with NaCl) = 0.69; $[\alpha]^{20}_D$ = −73.4 (*c* = 0.50, DMSO).

^{1}H NMR (300 MHz, [D_6]DMSO): δ (ppm) = 1.11 (s, 9H, *t*-Bu), 2.71 (s, 3H, CH_3N), 4.95 (m, 1H, β-H), 4.42 (dd, *J* = 14.5, 3.5 Hz, 1H, β-H), 4.59 (dd, *J* = 11.3, 3.9 Hz, 1H, α-H), 6.47 (s_{br}, 1H, N*H*Boc), 7.38 (s, 1H, 6-H).

^{13}C NMR (76 MHz, [D_6]DMSO): δ (ppm) = 171.2 (CO_2H), 155.2 (C-2), 154.2 (CONH), 151.2 (C-2), 137.2 (C-6), 116.5 (C-5), 77.8 ($\underline{C}(CH_3)_3$), 60.4 (α-C), 42.7 (β-C), 27.5 ($C\underline{C}H_3$), 27.9 ($C(\underline{C}H_3)_3$).

ESI MS: *m*/*z* (%): 704.8 $[2M + H]^+$ (20), 353.1 $[M+H]^+$ (100).

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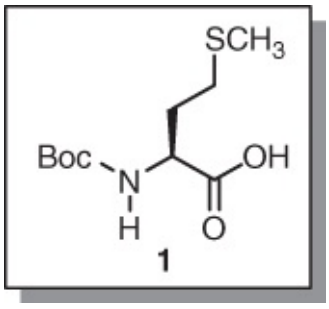
4.3.2 Amino Acid Resolution with Amino Acylase



1

Topics:

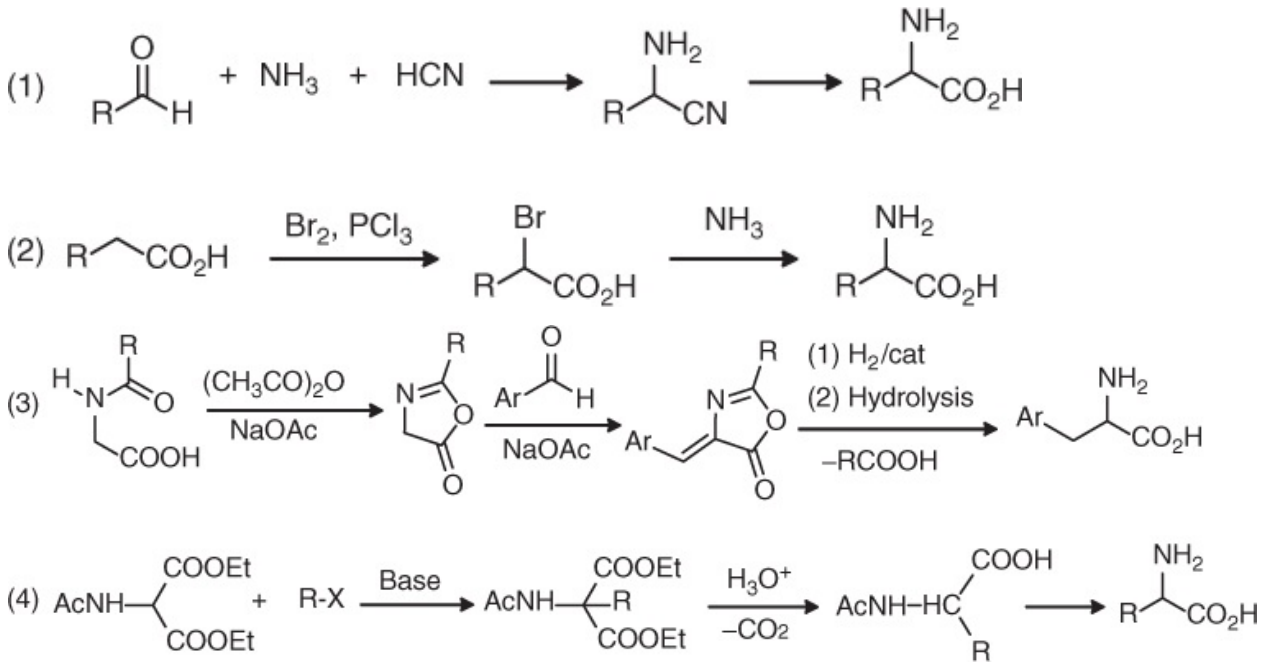
- Racemic amino acid synthesis
- Enzymatic reactions
- Kinetic resolution
- Boc-protected amino acids
- Ion-exchange chromatography

(a) General

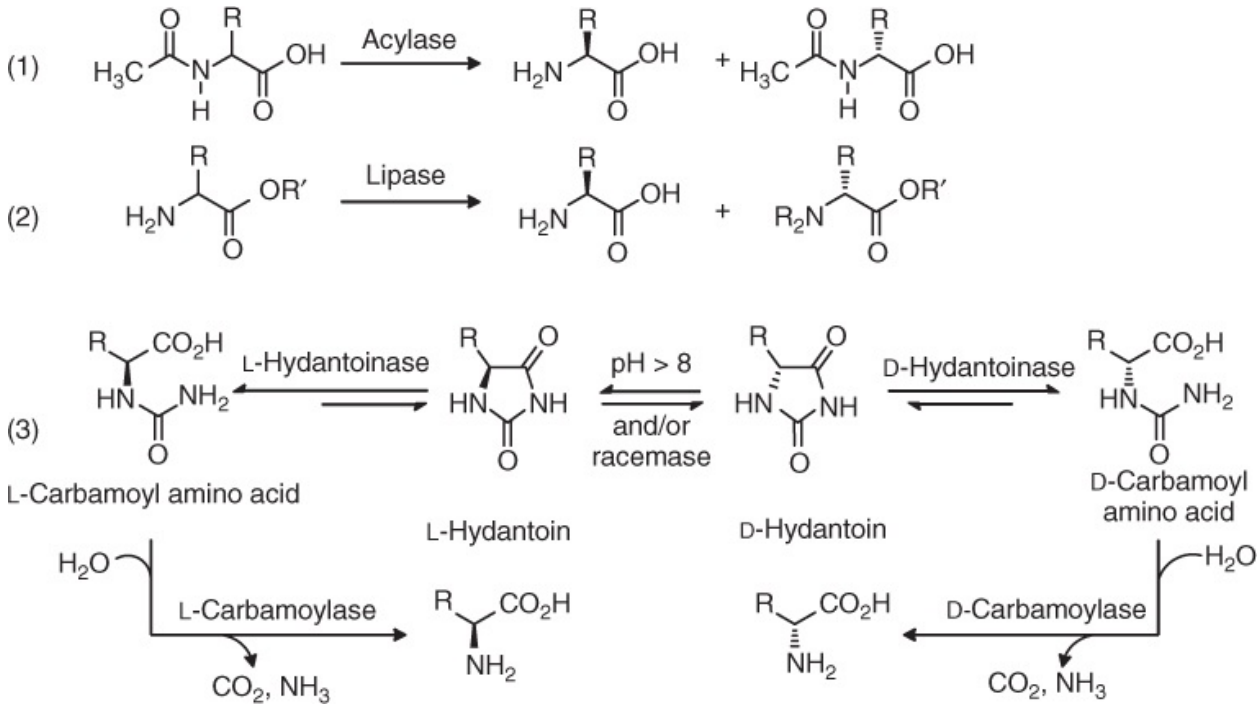
(a) General

For industrial and pharmacological purposes, there is a huge demand for the synthesis of enantiomerically pure amino acids. Proteinogenic amino acids are needed, for example, as sweeteners and food additives, and as regulating molecules and inhibitors in medicinal chemistry [1]. Moreover, there is a demand for labeled compounds as well as for modified and non-natural amino acids. The asymmetric synthesis of amino acids and derivatives is well established [2] and, in addition, resolution of racemic mixtures is still an inexpensive and competitive route for obtaining enantiopure amino acids. Co-crystallization with chiral nonracemic amines or acids is often used for resolution. Nevertheless, enzymatic resolution is competitive even on an industrial scale [3]. For such a kinetic resolution, the reaction rates for the two enantiomers must differ strongly, so that the enzyme selectively recognizes, for example, the L-amino acid, leaving the D-enantiomer unchanged. Enzymes typically used for this purpose are acylase, lipase, esterase, and aminase. After complete conversion of the L-amino acid, separation of the transformed L-amino acid from the remaining D-derivative is required, which is usually achieved by the precipitation of one of the compounds or by chromatography. Kinetic resolution is especially useful if both enantiomers are of interest. Otherwise, dynamic kinetic resolution might be a favorable method, combining the enzymatic conversion of amino acid derivatives with *in situ* racemization [4].

Prior to kinetic resolution, an efficient synthesis of the racemic mixture of the desired amino acid is required. Of the many contemporary methods, the following procedures are probably the most commonly used [5]. The Strecker synthesis (1) allows the introduction of highly diverse side chains by using various aldehydes, which are transformed into iminium ions and these, in turn, are treated with cyanide. The α-aminocyanide thus formed can be hydrolyzed to provide the amino acid. A second method is based on substitution of α-halogenated acids (2) with ammonia. In the Erlenmeyer azlactone synthesis (3), *N*-benzoylglycine is activated by acetic anhydride to self-condense to give an oxazolone. Further condensation with an aldehyde followed by hydration and hydrolysis provides the respective amino acid. Finally, acylamino malonic acid esters (4) are easily alkylated and the products can then be saponified and decarboxylated.

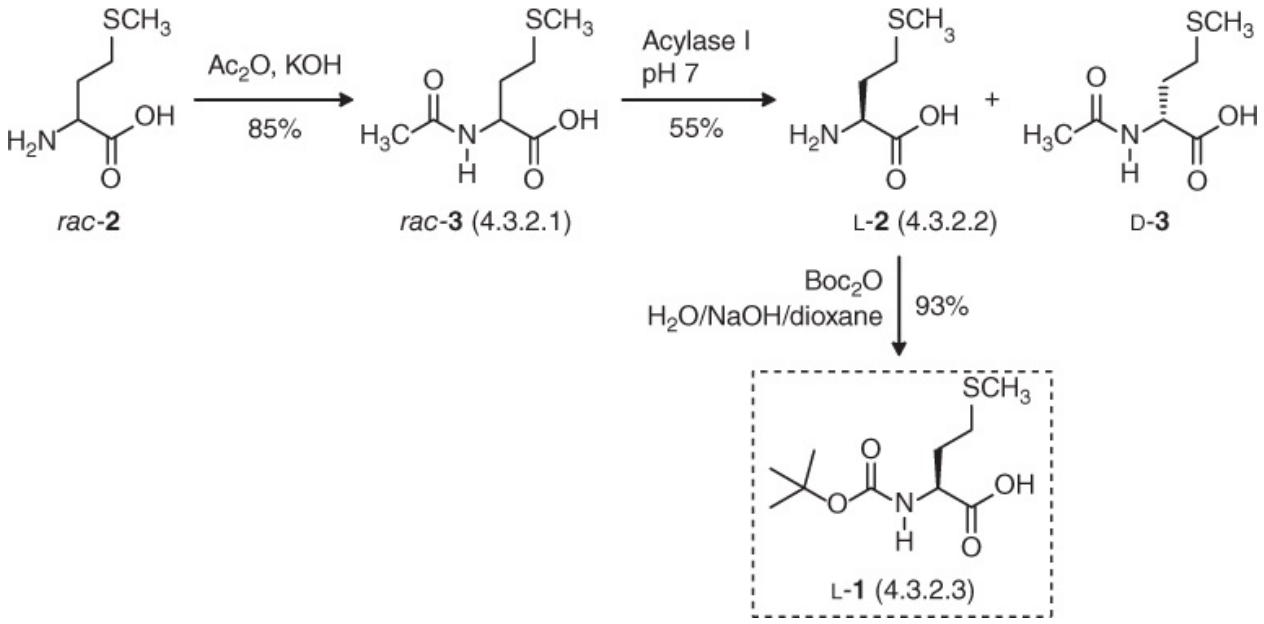


The following enzymatic transformations are usually applied for kinetic resolution of amino acids. (1) Acylase is used to cleave the amide bond in N-acylated amino acids. (2) Amino acid esters are saponified by lipases or esterases. In both cases, only L-amino acids are enzymatically recognized. Separation of the remaining D-amino acid derivative from the L-amino acid is required after 50% conversion is obtained. (3) Combination of the enzymes hydantoinase, carbamoylase, and racemase serves as an example of dynamic kinetic resolution of amino acids. Hydantoins are readily available, for example, by conversion of nonprotected amino acids with potassium cyanate. The respective hydantoinase is used to generate the enantiomerically pure *N*-carbamoyl amino acid, which is converted into the amino acid by carbamoylase. Using a racemase for isomerization of the hydantoins, overall complete conversion to a single enantiomer is obtained.



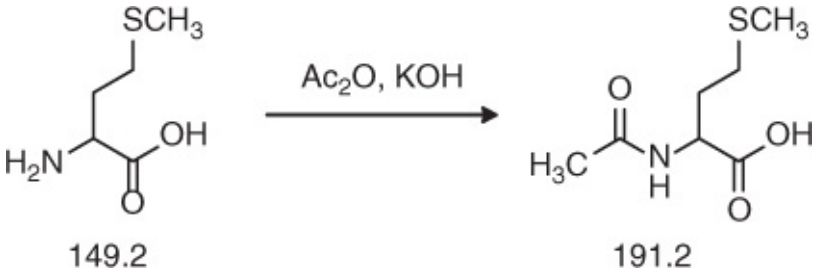
(b) Synthesis of Boc-Protected L-Methionine (1) by Kinetic Resolution

As an example of the enzymatic resolution of amino acids, the preparation of Boc-protected L-methionine (L-**1**) is described. Acylation of racemic methionine *rac*-**2** with acetic anhydride under basic conditions readily provides *rac*-**3**. This is then subjected to enzymatic conversion with acylase (from pork liver) in aqueous solution at neutral pH. It takes 2 days to fully convert L-**3** to give L-methionine (L-**2**) while D-**3** remains unaffected. To separate L-**2** from D-**3**, a cation exchanger is used to extract the liberated amino acid L-**2**. Finally, in order to use the amino acid in SPPS according to the Boc strategy, methionine is protected at the amino functionality using butoxycarbonyl anhydride under basic conditions following the standard procedure. Because of the polarity of L-**1** with a free carboxylic acid moiety, purification on reversed-phase silica gel (C18) is beneficial.



(c) Experimental Procedures for the Synthesis of L-1

4.3.2.1	*	***N*-Acetyl-*rac*-methionine** [6]



Acetic anhydride (50.0 ml, 54.0 g, 530 mmol) is added to a stirred solution of *rac*-methionine (20.0 g, 134 mmol) in 2 M aqueous KOH (70 ml) over 10 min. After stirring for a further 10 min at room temperature, H_2SO_4 (2 N, 70 ml) is added and the solution is concentrated *in vacuo* almost to dryness. The residue is extracted with boiling EtOAc, the organic solution is dried over Na_2SO_4 and filtered, and the solvent is removed *in vacuo*. Crystallization from EtOAc affords the product as colorless solid; 21.9 g (85%); mp 114–115 °C; R_f (EtOAc/MeOH/H_2O/AcOH, 10 : 1 : 1 : 0.5) = 0.53.

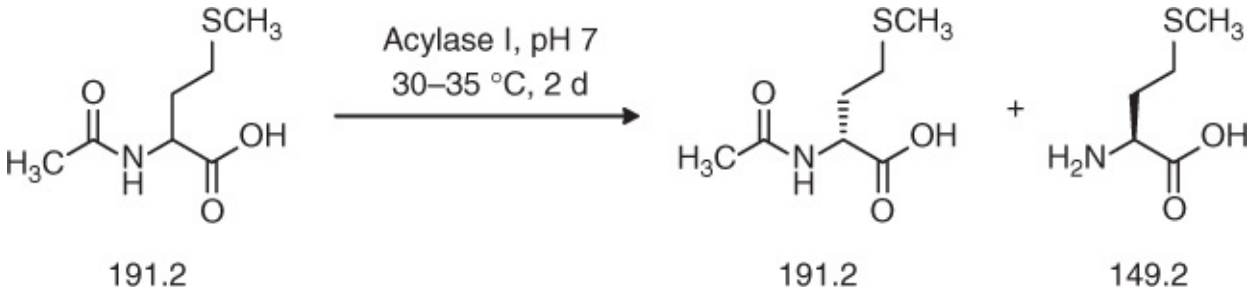
IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3343, 2967, 2918, 2594, 2461, 1694, 1621, 1561, 1446, 1423, 1377, 1339, 1322, 1256, 1235, 1190, 1117, 961, 799, 661, 593, 547.

^{1}H NMR (CD_3OD, 300 MHz): δ (ppm) = 4.52 (dd, *J* = 4.7, 9.6 Hz, 1H, α-CH), 2.63–2.45 (m, 2H, γ-CH_2), 2.08 (s, 3H, CH_3CO), 2.19–1.85 (m, 2H, β-CH_2), 1.98 (s, 3H, SCH_3).

^{13}C NMR (CD_3OD, 76 MHz): δ (ppm) = 175.2 (COOH), 173.5 (CONH), 157.2, 52.8 (α-C), 52.7, 32.1 (β-CH_2), 31.2 (γ-CH_2), 22.4 (CH_3CO), 15.2 (CH_3S).

EI HRMS: calcd. for $[M+H]^+$: 192.068 88; found: 192.06889.

4.3.2.2	**	**L-Methionine** [6]



191.2 191.2 149.2

In an Erlenmeyer flask, NaOH (1 N, 19 ml) is added to a solution of acetylmethionine (cf. **4.3.2.1**) (3.82 g, 20 mmol) in distilled H_2O (100 ml). The pH is adjusted to 7.2–7.5 by adding further NaOH or acetic acid as required. The overall volume is then made up to 200 ml with distilled H_2O. Acylase I (20–30 mg, from pork liver, Sigma, grade II, 500–1500 units mg^{-1}) is added and the mixture is kept at 30–35 °C for 2 days.

The reaction is then quenched by the addition of H_2SO_4 (2 N, 8 ml) and the mixture is filtered through Celite. A cation exchanger (Amberlyst 15, H^+-form, Fluka, 30 ml as a suspension in H_2O) is added, and the mixture is shaken for 2 min. The solution is tested for remaining methionine with ninhydrin. If necessary, an additional ion exchanger is added. The ion exchanger is then filtered off and washed with H_2O. An aqueous solution of ammonia diluted with further H_2O (1 : 9, 20–30 ml) is added to the ion exchanger until a pH of 8–9 is obtained. The ion exchanger is separated and washed with H_2O. The solution is adjusted to pH 6–7 with glacial AcOH and then concentrated to a volume of about 10 ml *in vacuo*. EtOH (100–200 ml) is then added until the amino acid precipitates. The product is filtered off and dried. The amino acid is obtained as

colorless solid; 820 mg (55%), mp 280 °C (dec.); $[\alpha]^{20}_{D}$ = +23.4 (*c* = 4.11, 5 M HCl).

UV (MeOH): λ_{max} (nm) = 287, 244, 204, 202.

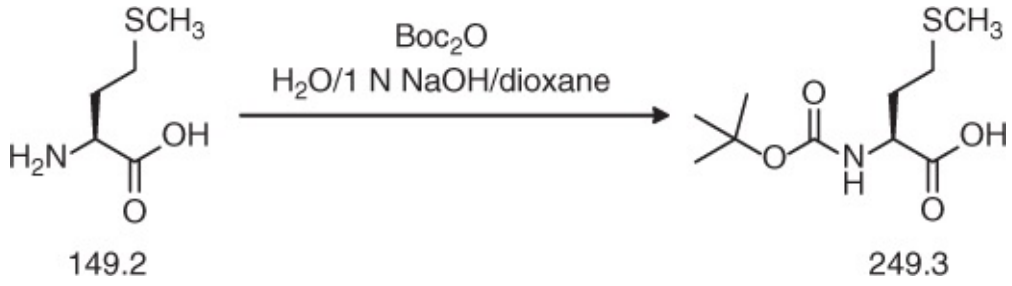
IR (KBr, pellet): $\tilde{\nu}$ (cm^{-1}) = 2945, 2915, 2724, 2615, 2319, 1656, 1609, 1580, 1515, 1445, 1414, 1340, 1315, 1276, 1220, 1161, 1080, 1046, 930, 878, 780, 719, 685, 553, 439.

^{1}H NMR (D_2O, 300 MHz): δ (ppm) = 3.93 (t, *J* = 6.55 Hz, 1H, α-CH), 2.72 (t, *J* = 7.71 Hz, 2H, γ-CH_2), 2.34–2.14 (m, 2H, β-CH_2), 2.21 (s, 3H, SCH_3).

^{13}C NMR (D_2O, 126 MHz): δ (ppm) = 175.1 (CO), 54.96 (CH), 30.7 (β-CH_2), 29.9 (γ-CH_2).

EI HRMS: calcd. for $C_5H_{11}NO_2S$: 149.0510; found: 149.0509.

4.3.2.3 * *N*-Boc-L-methionine [7]



L-Methionine (cf. **4.3.2.2**) (500 mg, 3.35 mmol) is dissolved in H_2O/1 N NaOH/dioxane (1 : 1 : 2; 24 ml) and the solution is cooled to 0 °C. Boc_2O (875 mg, 4.02 mmol) is added and the mixture is stirred for 45 min at 0 °C and for 24 h at room temperature. During the reaction, the pH is adjusted to 9–9.5 by adding further NaOH (1 N).

The reaction is quenched by adding HCl (1 N) until the pH is 6.5 and then the mixture is concentrated *in vacuo*. Purification of the residue by column chromatography on RP-18 (high-performance liquid chromatography (HPLC), H_2O, gradient MeOH 0 → 30%; 150 ml) and subsequent lyophilization gives the product as a colorless solid; 775 mg (93%); R_f = 0.59 (EtOAc/MeOH, 9 : 1, +0.5% AcOH); mp 46–48 °C; $[\alpha]^{20}_{D}$ = −22.5° (*c* = 0.5 in MeOH).

UV (CH_3CN): λ_{max} (nm) = 212.

IR (KBr, pellet): $\tilde{\nu}$ (cm^{-1}) = 3400, 2977, 2919, 1688, 1592, 1519, 1394, 1367, 1252, 1170, 1050, 1027, 860, 779.

^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 6.14 (d, *J* = 7.8 Hz, 1H, NH), 3.99 (m, 1H, α-CH), 2.52 (t, *J* = 7.4 Hz, 2H, γ-CH_2), 2.06 (s, 1H, CH_3S), 1.86 (m, 2H, β-CH_2), 1.42 (s, 9H, H_{Boc}).

^{13}C NMR ($CDCl_3$, 76 MHz): δ (ppm) = 179.3 (CO_2H), 156.7 (CONH), 79.6 ($\underline{C}(CH_3)_3$), 55.6 (CH), 32.2 (CH_2), 30.7 (CH_2), 28.5 ($C(\mathit{CH_3})_3$), 15.4 (CH_3S).

EI HRMS: calcd. for $C_{10}H_{19}NO_4S$ [M+Na^+]: 272.09270; found: 272.09285.

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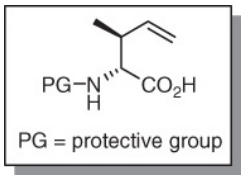
4. Schnell, B., Faber, K., and Kroutil, W. (2003) *Adv. Synth. Catal.*, **345**, 653–666.

5. Jones, J. (1992) *Amino Acid and Peptide Synthesis*, Oxford University Press, New York, pp. 8–12.

6. Moore, J.A. and Dalrymple, D.L. (1976) *Experimental Methods in Organic Chemistry*, 2nd edn, Saunders Company, Philadelphia, PA, pp. 253–258.

7. Bodanszky, M. and Bodanszky, A. (1995) *The Practice of Peptide Synthesis*, Springer, Berlin, pp. 15–18.

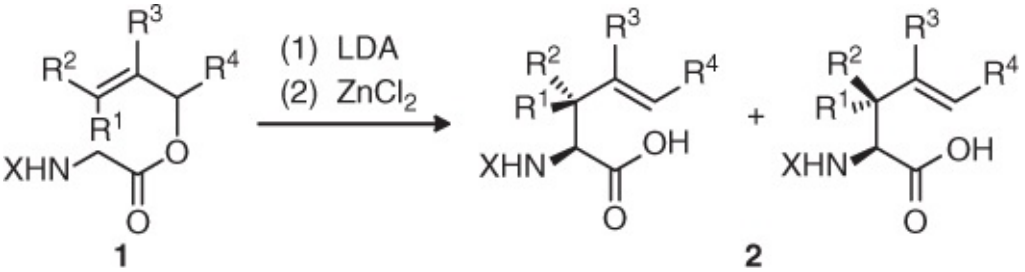
4.3.3 γ,δ-Unsaturated α-Amino Acids

	***Topics:***	• Synthesis of Nprotected γ,δ-unsaturated α-amino acids • (a) by [3,3]-sigmatropic rearrangement of chelate-bridged glycine ester enolates and • (b) by asymmetric glycine ester enolate Claisen rearrangement • Esterification of Z-and TFA-protected glycine • Z-and TFA-protection of glycine

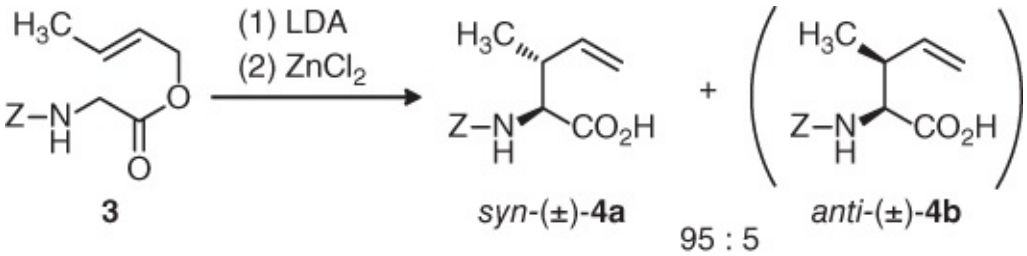
(a) General

γ,δ-Unsaturated α-amino acids have attracted considerable attention. Some of these unsaturated α-amino acids occur in nature, exhibit pronounced activities as, for example, antibiotics and enzyme inhibitors, and have proved useful for the synthesis of more complex compounds by functionalization of the double bond [1].

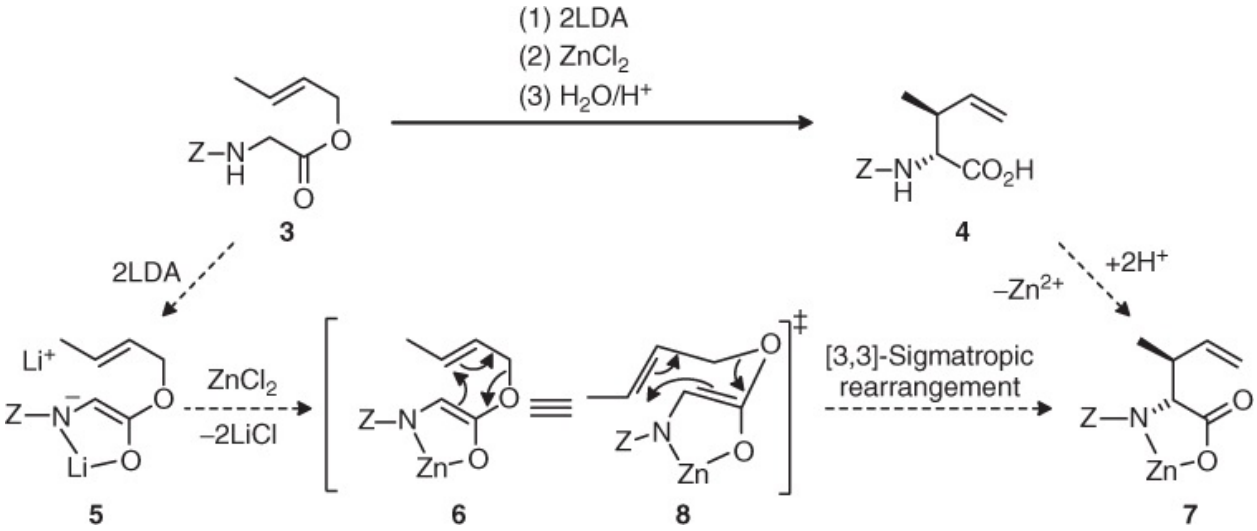
The method of choice for the synthesis of γ,δ-unsaturated α-amino acids is the [3,3]-sigmatropic rearrangement of the enolates of Nprotected glycine allyl esters **1** mediated by chelating metal salts, preferentially $ZnCl_2$, to give the diastereomeric C-allyl-α-amino acids **2** [1–3]:



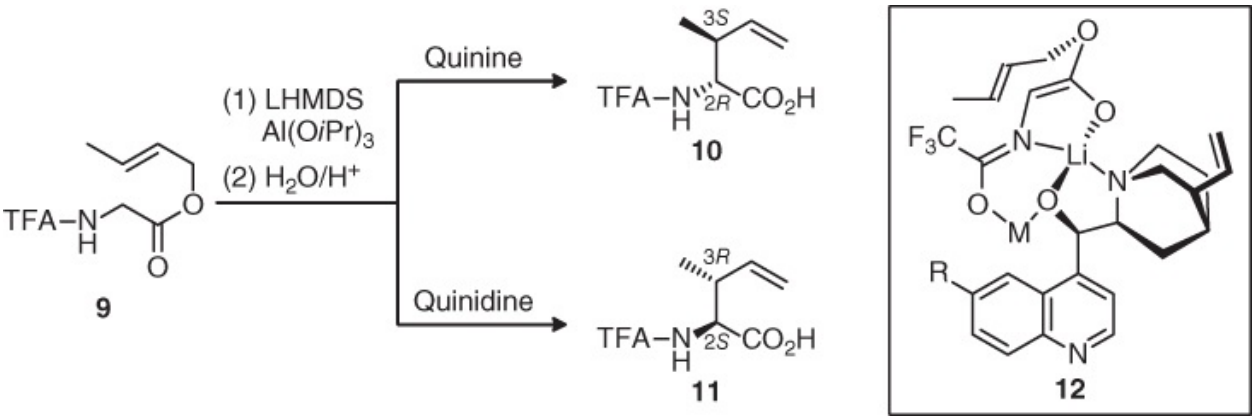
The allyl esters **1** show high diastereoselectivities (de = 93–96%) in this rearrangement, in which the formation of syn products from trans-substituted allyl esters and of anti products from cis-substituted allyl esters is generally favored. This is illustrated for the Z-protected crotyl ester **3** (as presented in Section (b)), which is rearranged to the acids **4a**/**4b** in a diastereomeric ratio of 95 : 5 in favor of the syn product **4a**:



As illustrated for the rearrangement **3** → **4**, a mechanism is proposed [1] in which a Zn-chelated ester enolate **6** (formed from the Li enolate **5** after α-deprotonation of the ester **3** with LDA) serves as the key intermediate. The Zn-enolate **6** is transformed in a Claisen-analogous [3,3]-sigmatropic process to a chelate-bridged (stabilized) carboxylate **7** via a chair-like transition state **8**, the highly ordered geometry of which is likely to account for the high syn diastereoselectivity observed:



When this glycine allyl ester enolate rearrangement is performed in the presence of a chiral ligand, the [3,3]-sigmatropic reaction proceeds in an asymmetric manner with high diastereo and enantio selectivity [4, 5]. As verified by the example in Section (b), the best results are obtained with electron-withdrawing Nprotecting groups (e.g., trifluoroacetyl), the isopropoxides of Mg and Al as metal components, and the cinchona alkaloids as chiral ligands. Interestingly, the use of quinine gives rise to formation of the (2*R*)-configured amino acid **10** from the TFA-protected glycine ester **9**, while quinidine provides the opposite enantiomer (**11**):



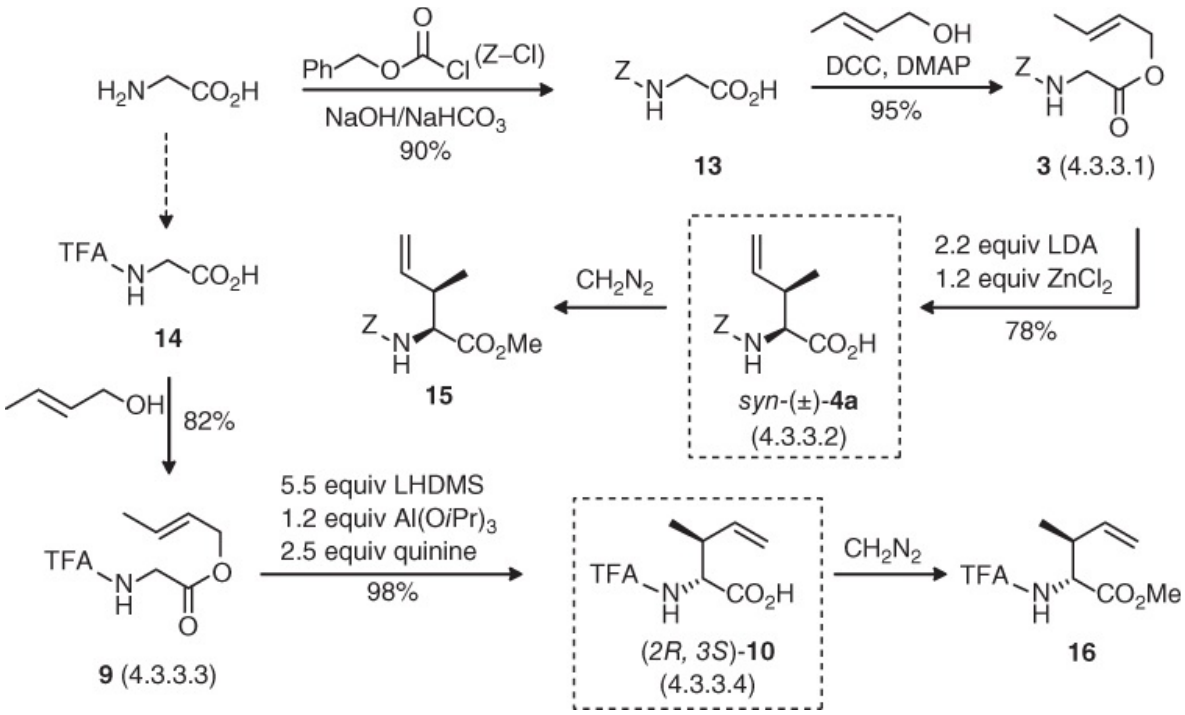
As a mechanistic rationale, a bimetallic complex **12** is postulated [4] to be formed with the bidentate ligand quinine (or quinidine, respectively), which coordinates to the lithium enolate. The incorporation of a second metal ion (Li^+, Al^{3+}, Mg^{2+}) should stabilize the complex **12** by imparting a rigid structure, in which one face of the enolate is shielded by the bicyclic substructure of the cinchona alkaloid, thus explaining the high stereoselectivity obtained.

(b) Syntheses of *syn*-(±)-4a and (2*R*,3*S*)-10

1. *Synthesis of syn*-(±)-**4a** [1]:

   N-(Benzoyloxycarbonyl)glycine (**13**) is prepared by acylation of glycine with benzyl chloroformate (Z-chloride) in the presence of a base, for example, NaOH [6]. The Z-protected glycine **13** is esterified with crotyl alcohol using the DCC (*N*,*N*′-dicyclohexyl carbodiimide)/DMAP method to give the Z-protected ester **3**.

   The crotyl ester **3** is treated with LDA in THF at −78 °C followed by anhydrous $ZnCl_2$. After hydrolysis with aqueous HCl, the acid **4** is obtained in 90% yield with a syn/anti ratio of 95 : 5 (determined by HPLC analysis of the readily available methyl ester **15**). Recrystallization from diethyl ether/petroleum ether affords the pure syn diastereomer *syn*-(±)-**4a** in 78% yield.



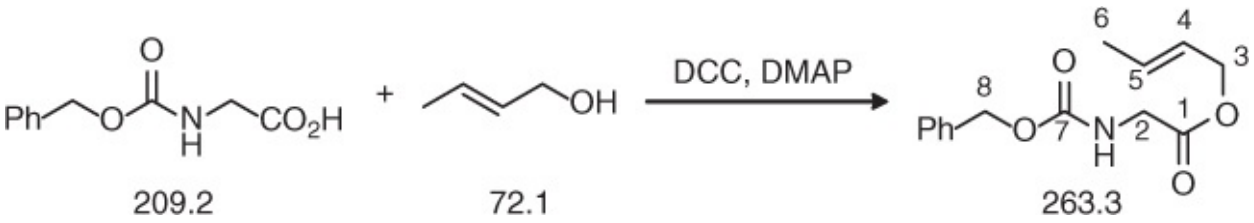
2. *Synthesis of* (*2R*,*3S*)-**10** [4, 5]:

   N-(Trifluoroacetyl)glycine (**14**) can be prepared by trifluoroacetylation of glycine with trifluoroacetic anhydride [7]. The trifluoroacetyl-protected glycine **14** is esterified with crotyl alcohol as above in (1) to give the ester **9**.

   The crotyl ester **9** is treated with excess lithium hexamethyldisilazide (Li-HMDS) in THF at −78 °C followed by Al(O*i*Pr)$_3$ and quinine. After hydrolytic work-up, the acid **10** is obtained in practically quantitative yield; for determination of the diastereomeric and enantiomeric ratios of the product, **10** may be converted to the methyl ester by reaction with diazomethane, which affords the (2*R*,3*S*) ester **16** in 98% yield with de = 98% and ee = 87%.

(c) Experimental Procedures for the Synthesis of *syn*-(±)-4a and (2*R*,3*S*)-10

4.3.3.1	**	***N*-(Benzyloxycarbonyl)glycine crotyl ester** [4]



a. *N*-(Benzyloxycarbonyl)glycine: Z-Glycine is available commercially or can be prepared according to Ref. [7] from glycine and Z-chloride; colorless prisms, mp 120–121 °C ($CHCl_3$).

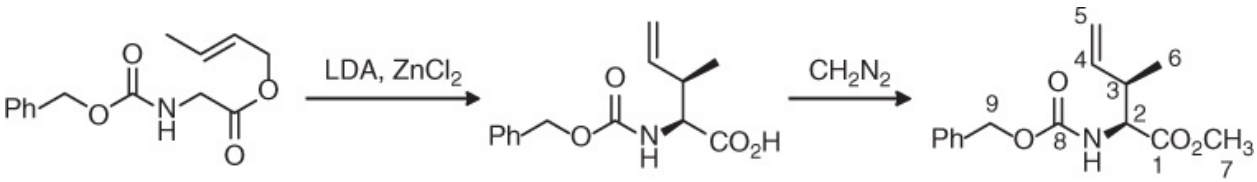
b. DCC (5.88 g, 28.5 mmol) and DMAP (375 mg, 3.0 mmol) are added to a solution of (*Z*)-crotyl alcohol (3.07 g, 28.5 mmol) in CH_2Cl_2 (90 ml) at 0 °C. The clear solution is cooled to −20 °C, and after 5 min Z-glycine (5.53 g, 28.5 mmol) is added with stirring. Stirring is continued for 12 h, during which the mixture is allowed to warm to room temperature.

The precipitate of dicyclohexylurea is filtered off and the filtrate is extracted with aqueous $KHSO_4$ solution (1 N), saturated aqueous $NaHCO_3$ solution, and brine (50 ml each). The organic phase is dried over Na_2SO_4 and filtered, and the solvent is removed *in vacuo*. The crude ester is purified by flash chromatography (SiO_2; petroleum ether/EtOAc, 7 : 3), yielding the product as colorless oil; 6.82 g (97%), R_f = 0.40 (petroleum ether/EtOAc, 7 : 3).

^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.30–7.35 (m, 5H, 5 × Ar–H), 5.80 (dq, *J* = 15.1, 5.7 Hz, 1H, 5-H), 5.55 (dt, *J* = 15.1, 6.9 Hz, 1H, 4-H), 5.36 (s_{br}, 1H, NH), 5.11 (s, 2H, 8-H), 4.56 (d, *J* = 5.7 Hz, 2H, 3-H), 3.96 (d, *J* = 5.5 Hz, 2H, 2-H), 1.72 (d, *J* = 6.9 Hz, 3H, 6-H).

^{13}C NMR ($CDCl_3$, 76 MHz): δ (ppm) = 169.8 (C-1), 156.2 (C-7), 136.3 (phenyl-C-1), 132.6 (C-5), 128.5 (phenyl-C), 128.1, 124.4 (C-4), 67.0 (C-8), 66.1 (C-3), 42.8 (C-2), 17.7 (C-6).

4.3.3.2	***	***syn*-(±)-*N*-(Benzyloxycarbonyl)-2-amino-3-methyl-4-pentenoic acid** [1]



A 1.65 M solution of *n*-butyllithium in *n*-hexane (20 ml, 33.0 mmol) is added to a stirred solution of diisopropylamine (5.60 g, 40.0 mmol) in anhydrous THF (30 ml) under an argon atmosphere at −20 °C. After 20 min at this temperature, the solution is cooled to −78 °C and a solution of the ester **4.3.3.1** (3.95 g 15.0 mmol) in THF (15 ml) is added dropwise. A solution of $ZnCl_2$ (2.32 g, 17.0 mmol; note) in THF (20 ml) is then added and the reaction mixture is allowed to warm to room temperature over 12 h.

The clear, faintly yellow solution is hydrolyzed by the addition of aqueous HCl (1 N, ice bath), the organic solvents are removed *in vacuo*, and the residue is dissolved in Et_2O (50 ml). The organic phase is washed with 1 N HCl (25 ml) and then extracted with 1 N aqueous NaOH (2 × 50 ml). The combined NaOH phases are acidified with concentrated HCl (ice bath), and the product is extracted with Et_2O (2 × 100 ml). The ethereal solution is dried over Na_2SO_4, filtered, and the solvent is removed *in vacuo*. The residue (3.55 g (90%), 95 : 5 mixture of diastereomers) is recrystallized from Et_2O/petroleum ether to give colorless needles; 3.08 g (78%), mp 81–82 °C; diastereomerically pure *syn*-(±) acid.

To determine the diastereomeric ratio and the enantiomeric purity, a small sample of the acid is treated with ethereal diazomethane solution [8], and the methyl ester formed is purified by flash chromatography on silica gel (quantitative yield) and examined by HPLC (Chiralcel OD-H, *n*-hexane/*i*PrOH, 85 : 15, 2 ml min^{-1}).

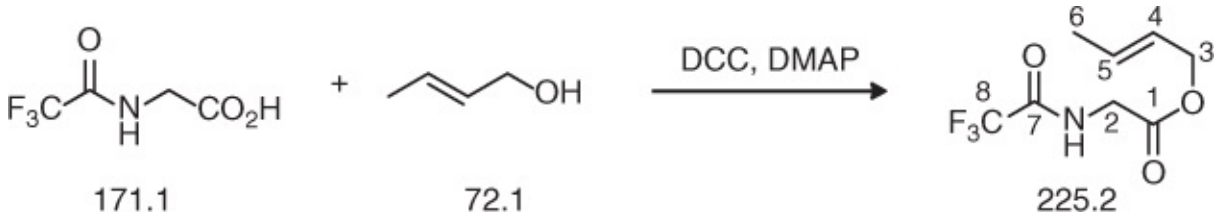
^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.28–7.40 (m, 5H, 5 × Ar–H), 5.68 (ddd, *J* = 17.1, 9.8, 1.4 Hz, 1H, 4-H), 5.28 (d, *J* = 8.4 Hz, 1H, NH), 5.08 (s, 2H, 9-H_2), 5.06 (dd, *J* = 9.8, 1.4 Hz, 1H, 5-H_A), 5.05 (dd, *J* = 17.1, 1.4 Hz, 1H, 5-H_B), 4.35 (dd, *J* = 9.0, 5.2 Hz, 1H, 2-H), 3.71 (s, 3H, 7-H_3), 2.64 (dd, *J* = 12.8, 6.7 Hz, 1H, 3-H), 1.03 (d, *J* = 7.0 Hz, 3H, 6-H_3).

^{13}C NMR ($CDCl_3$, 76 MHz): δ (ppm) = 171.8 (C-1), 155.9 (C-8), 138.4 (C-4), 136.2 (Ar–C-1), 128.5 (Ar–C), 128.1, 116.3 (C-5), 67.0 (C-7), 57.9 (C-

9), 52.0 (C-2), 40.8 (C-3), 16.4 (C-6).

Note: $ZnCl_2$ has to be dried *in vacuo* with a heat gun before use until it is in the form of a white powder.

4.3.3.3	*	***N*-(Trifluoroacetyl)glycine crotyl ester** [5]



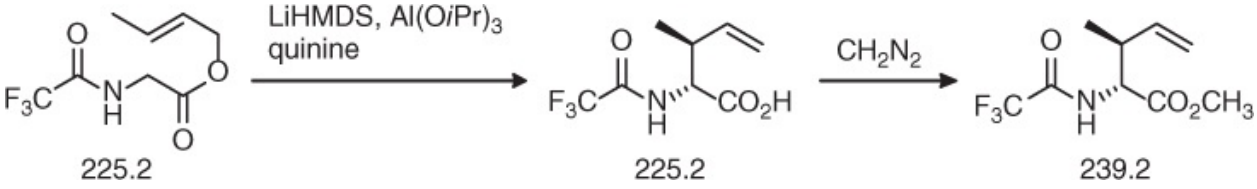
a. *N*-(Trifluoroacetyl)glycine: *N*-TFA-glycine is commercially available or can be prepared from glycine and trifluoroacetic anhydride [7]; colorless crystals, mp 118–119 °C (Et_2O/petroleum ether).

b. The esterification is performed according to the procedure used for **4.3.3.1** (b) with *N*-(trifluoroacetyl)glycine (7.58 g, 44.4 mmol), (*Z*)-crotyl alcohol (3.85 g, 53.3 mmol), DCC (10.1 g, 48.8 mmol), and DMAP (4.9 mmol). The crude product is purified by flash chromatography (SiO_2; petroleum ether/Et_2O, 4 : 1) and subsequent recrystallization from CH_2Cl_2/petroleum ether; 9.80 g (82%), colorless needles, mp 48–49 °C; R_f = 0.55 (petroleum ether/Et_2O, 4 : 1).

^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 6.96 (s_{br}, 1H, NH), 5.84 (dt, *J* = 17.4, 6.9 Hz, 1H, 4-H), 5.58 (dq, *J* = 17.4, 6.8 Hz, 1H, 5-H), 4.61 (d, *J* = 6.9 Hz, 2H, 3-H_2), 4.11 (d, *J* = 5.1 Hz, 2H, 2-H_2), 1.72 (d, *J* = 6.8 Hz, 3H, 6-H_3).

^{13}C NMR ($CDCl_3$, 76 MHz): δ (ppm) = 168.0 (C-1), 157.2 (q, *J* = 38.0 Hz, C-7), 133.0 (C-5), 124.0 (C-4), 115.6 (q, *J* = 286.5 Hz, C-8), 66.8 (C-3), 41.4 (C-2), 17.7 (C-6).

4.3.3.4	***	**(2*R*,3*S*)-3-Methyl-2-(trifluoroacetylamino)-4-pentenoic acid** [4]



A solution of LiHMDS is prepared by adding *n*-butyllithium (1.55 M in *n*-hexane, 1.6 ml, 2.5 mmol) to a stirred solution of hexamethyldisilazane (470 mg, 2.9 mmol) in anhydrous THF (1.5 ml) at −20 °C under an argon atmosphere. After stirring for 20 min, the freshly prepared LiHMDS solution is added dropwise to a solution of the ester **4.3.3.3** (124 mg, 0.55 mmol), $Al(OiPr)_3$ (114 mg, 0.55 mmol), and quinine (405 mg, 1.25 mmol) in anhydrous THF at −78 °C. The reaction mixture is allowed to warm up to room temperature over 12 h.

After dilution with Et_2O (50 ml), the reaction mixture is hydrolyzed by the addition of aqueous $KHSO_4$ solution (1 M, 25 ml). The organic layer is washed with aqueous $KHSO_4$ solution (1 M) and the product is extracted into saturated aqueous $NaHCO_3$ solution (3 × 25 ml). The combined basic extracts are subsequently acidified to pH 1 by the careful addition of solid $KHSO_4$ and then extracted with Et_2O (3 × 25 ml). The combined ethereal extracts are dried over Na_2SO_4, filtered, and the solvent is removed *in vacuo*.

To determine the enantiomeric and diastereomeric ratios, the residue (121 mg (98%)) is esterified with diazomethane [8]; 125 mg (98%), colorless oil, $[\alpha]^{20}_D$ = −54.4° (*c* = 2.0, $CHCl_3$), ee = 87%, de = 98% (GC on Chirasil-Val, 80 °C, isothermal).

^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 6.84 (s_{br}, 1H, NH), 5.65 (ddd, *J* = 17.1, 10.5, 6.9 Hz, 1H, C<u>H</u>=CH_2), 5.14 (dd, *J* = 10.5, 1.1 Hz, 1H, CH=C<u>H</u>$_2$), 5.09 (dd, *J* = 17.1, 1.1 Hz, 1H, CH=C<u>H</u>$_2$), 4.63 (dd, *J* = 8.5, 5.0 Hz, 1H, NCH), 3.77 (s, 3H, OCH_3), 2.73 (ddq, *J* = 8.5, 7.0, 6.9 Hz, C<u>H</u>CH_3), 1.09 (d, *J* = 7.0 Hz, 3H, CHC<u>H</u>$_3$).

^{13}C NMR ($CDCl_3$, 76 MHz): δ (ppm) = 170.3 (<u>C</u>O_2R), 156.6 (q, *J* = 38 Hz, CON), 137.3 (<u>C</u>HCH_2), 117.3 (CH<u>C</u>H$_2$), 115.6 (q, *J* = 287 Hz, CF_3), 52.6, 56.6 (2 × OCH_3), 40.6 (<u>C</u>HCH_3), 15.4 (CH<u>C</u>H$_3$).

For spectroscopic data of the anti diastereomer, see Ref. [5].

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2. For the transformation **1** → **2**, the Claisen–Ireland protocol via silyl ketene acetals Ireland, R.E., Mueller, R.H., and Willard, A.K. (1976) *J. Am. Chem. Soc.*, **98**, 2868–2877 has alternatively been used. The Kazmaier methodology [1] shows clear advantages in terms of reactivity and selectivity.

3. For applications of amino acid ester enolates in synthesis, see: (a) Kazmaier, U. and Zumpe, F.L. (2001) *Eur. J. Org. Chem.*, **2001**, 4067–4076;(b) Pohlmann, M., Kazmaier, U., and Lindner, T. (2004) *J. Org. Chem.*, **69**, 6909–6912.

4. Kazmaier, U. and Krebs, A. (1995) *Angew. Chem.*, **107**, 2213–2214; *Angew. Chem. Int. Ed. Engl.*, (1995) **34**, 2012–2013.

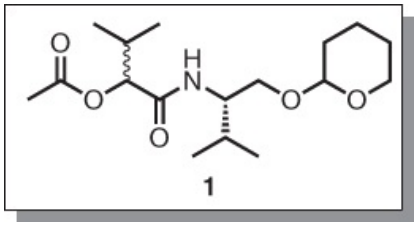
5. Kazmaier, U., Mues, H., and Krebs, A. (2002) *Chem. Eur. J.*, **8**, 1850–1855.

6. (a) Bergmann, M. and Zervas, L. (1932) *Chem. Ber.*, **65**, 1192;(b) for Z-protection of α-amino acids, see also: *Methoden der Organischen Chemie (Houben-Weyl)*, vol. 15/1, p. 47.

7. (a) Weygand, F. and Röpsch, A. (1959) *Chem. Ber.*, **92**, 2095;For alternative methods for trifluoroacetylation of α-amino acids, see: (b) *Methoden der Organischen Chemie (Houben-Weyl)*, vol. 15/1, p. 171.

8. Prepared according to *Organikum* (2001) 21st edn, Wiley-VCH Verlag GmbH, Weinheim, p. 647.

4.3.4 Passerini Hydroxyamide



1

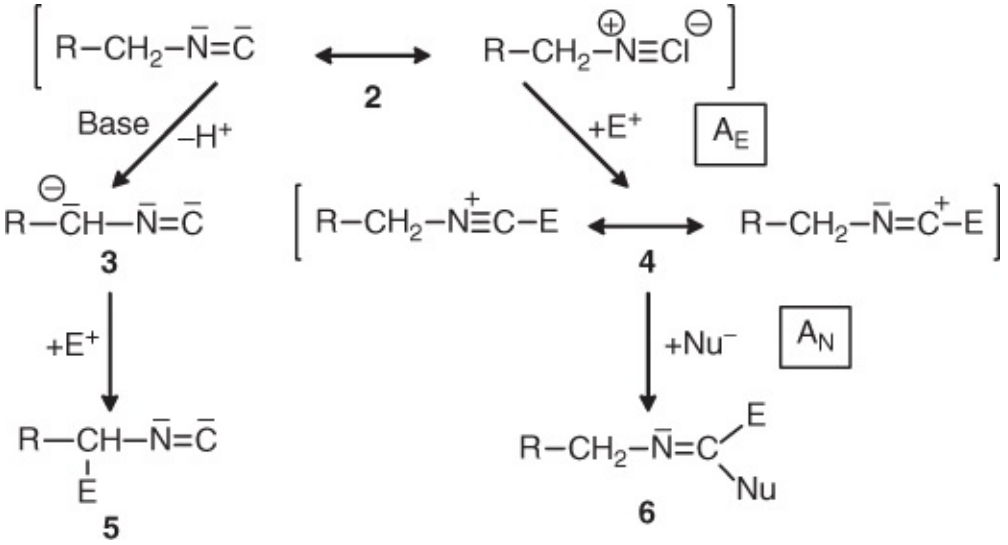
Topics:

- Chemoselective N-formylation of an amino alcohol
- OH protection by formation of a THP ether

		• Isonitrile formation from a primary *N*-formyl amine • Passerini reaction

(a) General

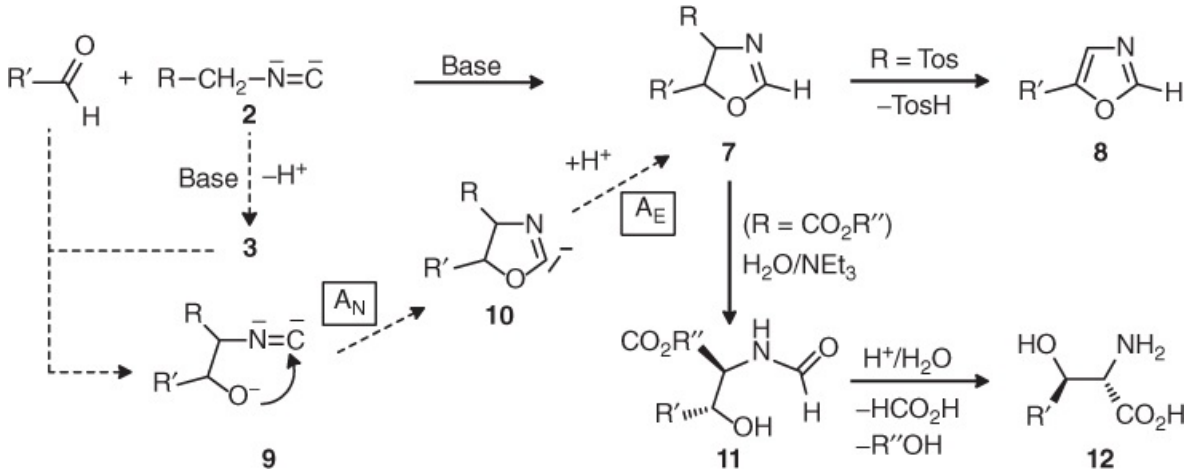
Isonitriles, such as **2**, show two basic modes of reactivity because of the specific electronic properties of the N=C group. First, they exhibit pronounced C–H acidity of the C–H bonds in the position α-to the N=C function, thus allowing their deprotonation by a base to give α-carbanions **3** (or metallation by Li organyls to give α-lithioisonitriles). This opens the possibility of attack by an electrophile, which corresponds to an overall α-substitution (→**5**). Second, isonitriles are susceptible to stepwise attack of nucleophiles *and* electrophiles at the terminal carbon atom of the N=C function, leading to the geminal introduction of two new substituents; if the electrophile adds first, nitrilium ions **4** are the primary intermediates (→**6**) [1].



These are the underlying principles of a number of synthetically useful reactions of isonitriles, as illustrated by the following examples.

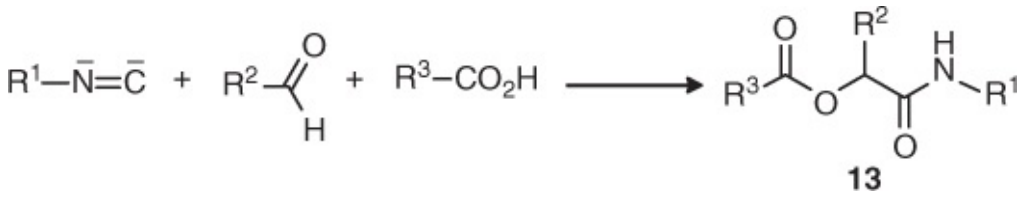
1. In the van Leusen synthesis of 1,3-oxazoles [2], the tosyl-substituted isonitrile **2** (R = Tos) (TosMIC) cyclocondenses with an aldehyde in the presence of a base to yield a 5-substituted 1,3-oxazole **8**. In the oxazole formation, the isonitrile group N=C has a threefold function: it facilitates α-deprotonation to give the carbanion **3**, which adds to the aldehyde C=O group to give intermediate **9**; then, it allows intramolecular interception of the nucleophilic center of **9** (A_N), leading to oxazoline **7** by protonation of

the 2-anion (A_E) formed in the ring-closure **9** → **10**; in the final base-induced elimination step, the oxazoline **7** is aromatized to afford the oxazole **8** by loss of sulfinic acid.

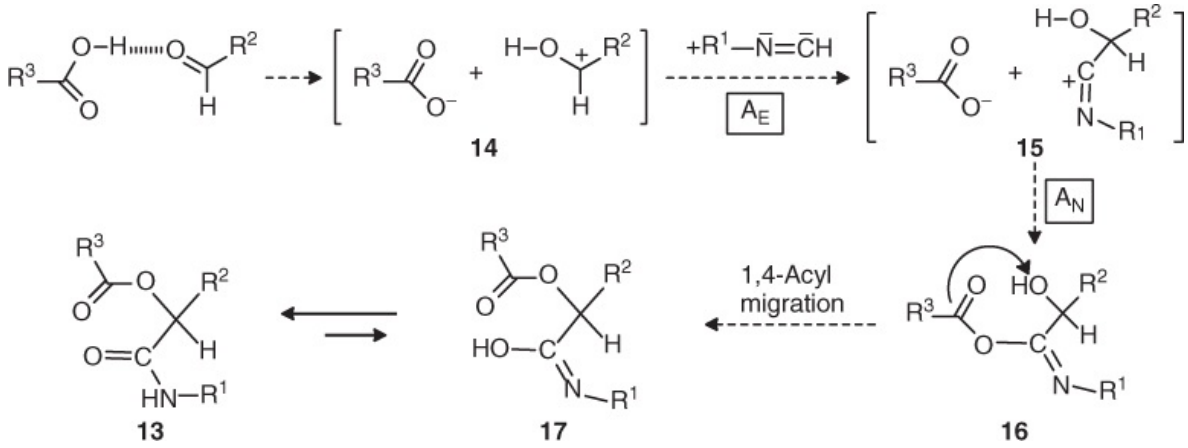


An analogous reaction is observed with the ester-substituted isocyanide **2** (R=CO_2R″) [3], in which the oxazoline **7** (with trans configuration of R and R′) can be isolated and transformed into β-hydroxy-α-amino acids **11**/**12** by hydrolysis.

2. In the Passerini reaction [1], isonitriles, aldehydes, and carboxylic acids react in a three-component process (MCR [4]) to give *O*-acylated α-hydroxyamides **13**:



The Passerini reaction is rationalized by the following mechanism [1]:



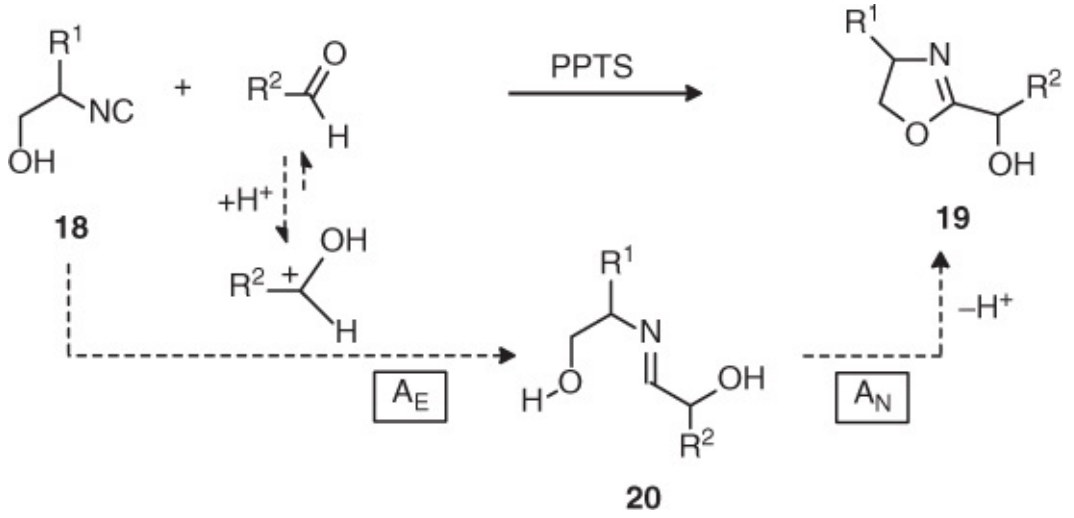
First, the aldehyde carbonyl group is activated by proton transfer from the carboxylic acid. The protonated carbonyl group then undergoes electrophilic addition (A_E) to the isonitrile carbon (**14** → **15**), which is followed by nucleophilic addition (A_N) of the carboxylate to the nitrilium ion in the ion pair **15**; 1,4-acyl migration in the *O*-acylimidate **16** (**16** → **17**) and tautomerization complete the sequence leading to product **13**.

The Passerini reaction can be extended to a four-component process by addition of ammonia or a primary amine (Ugi reaction, cf. Section 4.4.7).

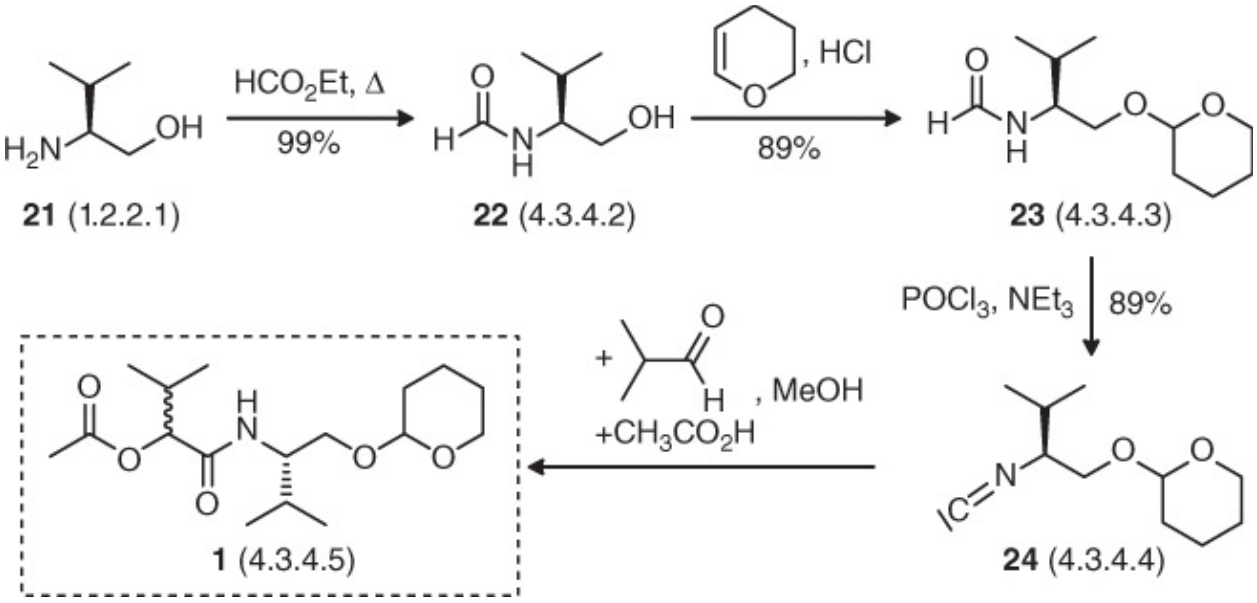
3. As a consequence of the mechanism of the Passerini reaction postulated in (2), β-hydroxy-isonitriles **18** and aldehydes lead to (2-hydroxyalkyl)oxazolines **19** on treatment with a weakly nucleophilic acid such as pyridinium *p*-toluenesulfonate (PPTS) [5]:

Apparently, the nitrilium ion **20**, resulting from addition of the protonated aldehyde to the N=C function, is intramolecularly trapped by interception of the β-hydroxy group and is thus cyclized to the oxazoline **19**.

Chiral oxazolines of type **19** are of interest as ligands for asymmetric synthesis [5]; the required chiral β-hydroxyisonitriles of type **18** can be conveniently obtained from enantiopure α-amino acids. Thus, the synthesis of a potential precursor and its utility in a Passerini reaction is presented in Section (b).

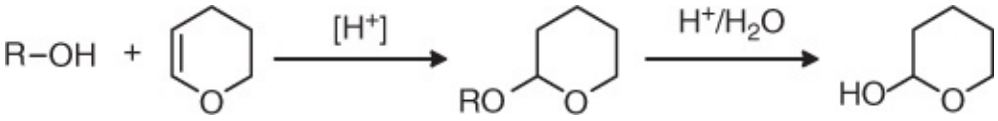


(b) Synthesis of 1



(*S*)-Valinol (**21**, 1.2.2.1) is chemoselectively N-formylated by reaction with ethyl formate to give (*S*)-*N*-(formyl)-valinol (**22**). Because of the conditions of the isonitrile-forming dehydration of the formylamino function in the next step, the free OH group in **22** requires protection; this is achieved by proton-catalyzed addition to dihydropyran (DHP), leading to the tetrahydropyranyl (THP) ether **23**.

As cyclic acetals, THP ethers are stable to bases, but are sensitive to hydrolysis even with dilute acids. Thus, OH functions in alcohols or phenols can be reversibly blocked by the THP protecting group [6]:

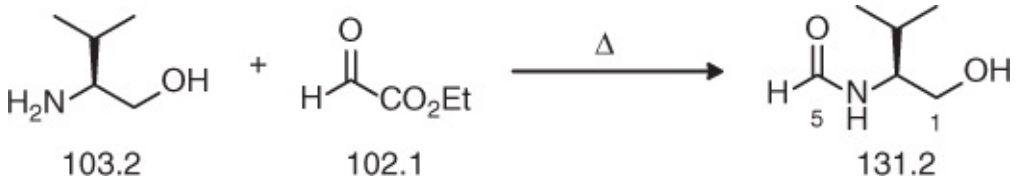


Accordingly, treatment of the THP ether **23** with $POCl_3$ in the presence of triethylamine cleanly affords the β-OH-protected chiral isonitrile **24**.

In the last step, the Passerini reaction is conducted as a three-component domino process with isonitrile **24**, isobutyraldehyde, and acetic acid to give the dihydroxyamide **1** as a mixture of diastereomers (see experimental section), in which the OH groups are protected as an acetate and a THP ether, respectively. Thus, the Passerini product **1** is obtained in a five-step sequence with an overall yield of 66% (based on L-valine).

(c) Experimental Procedures for the Synthesis of 1[2)]

4.3.4.1	*	**(2*S*)-(−)-(2-Formylamino)-3-methyl-1-butanol**



103.2 102.1 131.2

L-Valinol[2] (cf. **1.2.2.1**) (10.3 g, 0.10 mol) is dissolved in ethyl formate (9.66 g, 120 mmol) and the solution is heated under reflux for 2 h.

The excess formate is then removed *in vacuo* to leave the product as a colorless oil, which crystallizes on cooling or on treatment with Et_2O; 13.0 g (99%), mp 78–80 °C; $[\alpha]^{20}_D = -36.0$ (c = 1.00, $CHCl_3$), TLC (SiO_2; EtOAc/EtOH, 4 : 1): R_f = 0.49.

According to ^1H and ^{13}C NMR, the product consists of a 2 : 1 mixture of the *Z*/*E* rotamers.

(*Z*)-*Isomer*:

^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) = 8.19 (d, J = 1.9 Hz, 1H, 5-H), 6.53 (d, J = 6.3 Hz, 1H, NH), 3.78 (dddd, J = 9.9, 6.3, 6.3, 3.6 Hz, 1H, 2-H), 3.74 (t, J = 5.0 Hz, 1H, OH), 3.68–3.53 (m, 2H, 1-H), 1.85 (m, 1H, 3-H), 0.94, 0.91 (2 × d, J = 6.8 Hz, 6H, 4-H).

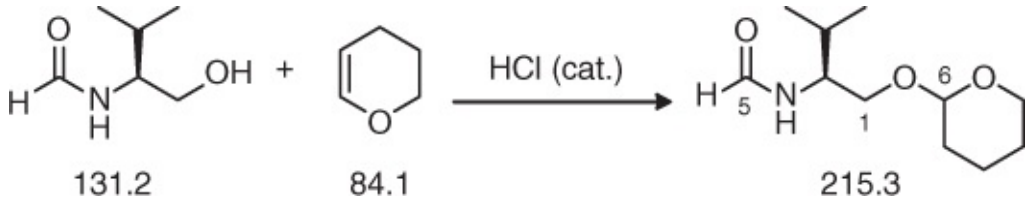
^{13}C NMR ($CDCl_3$, 126 MHz): δ (ppm) = 162.3 (d, C-5), 62.9 (t, C-1), 55.8 (d, C-2), 28.9 (d, C-3), 19.4 (2q, C-4), 18.6.

(*E*)-*Isomer*:

^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) = 7.95 (d, J = 11.8 Hz, 1H, 5-H), 6.85 (dd, J = 11.8, 7.8 Hz, 1H, NH), 4.04 (t, J = 5.6 Hz, 1H, OH), 3.68–3.53 (m, 2H, 1-H), 1.77 (m, 1H, 3-H), 3.10 (dddd, J = 10.1, 7.8, 6.6 Hz, 3.6 Hz, 1H, 2-H), 0.93, 0.89 (2 × d, J = 6.8 Hz, 6H, 4-H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ (ppm) = 165.8 (d, C-5), 63.2 (t, C-1), 60.8 (d, C-2), 29.3 (d, C-3), 19.6 (2 × q, C-4), 18.3.

4.3.4.2	*	**(2*S*)-(2-Formylamino)-3-methyl-1-tetrahydropyranyloxybutane**



Two drops of concentrated HCl are added to a stirred suspension of the alcohol **4.3.4.1** (5.91 g, 45.0 mmol) in DHP (6.15 g, 67.5 mmol) at 0 °C. The reaction mixture is allowed to slowly warm to room temperature over 12 h, as a clear solution is formed.

The mixture is then diluted with CH_2Cl_2 (50 ml), washed with saturated aqueous $NaHCO_3$ solution and brine, dried over Na_2SO_4, filtered, and the solvent is removed *in vacuo*. The residue is purified by chromatography on silica gel (EtOAc) to afford the THP ether as a colorless oil; 8.58 g (89%), 7 : 3 mixture of cis/trans rotamers.

(*Z*)-*Isomer*:

^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) = 8.20, 8.19 (2 × d, *J* = 1.4 Hz, 1H, 5-H), 5.94 (m, 1H, NH), 4.53, 4.49 (2 × m, 1H, 6-H), 3.94, 3.89 (2 × m, 1H, 2-H), 3.83 (dd, *J* = 10.2, 4.4 Hz, 1H, 1-H_a), 3.79 (m, 1H, 10-H_{eq}), 3.48 (m, 1H, 10-H_{ax}), 3.38 (2 × dd, *J* = 10.2, 3.8 Hz, 1H, 1-H_b), 1.90 (m, 1H, 3-H), 1.76 (m, 1H, 7-H_a), 1.67 (m, 1H, 7-H_b), 1.59–1.47 (m, 4H, 8-H, 9-H), 0.95, 0.93, 0.92, 0.91 (4 × d, *J* = 6.8 Hz, 6H, 4-H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ (ppm) = 160.85, 160.80 (2 × d, C-5), 99.8, 98.9 (2 × d, C-6), 68.1, 67.3 (2 × t, C-1), 62.9, 62.3 (2 × t, C-10), 52.9, 52.6 (2 × d, C-2), 30.6, 30.4 (2 × t, C-7), 29.4, 29.2 (2 × d, C-3), 25.3, 25.2 (2 × t, C-9), 19.4, 19.3 (2 × t, C-8), 19.8, 19.4, 18.9, 18.8 (4 × q, C-4).

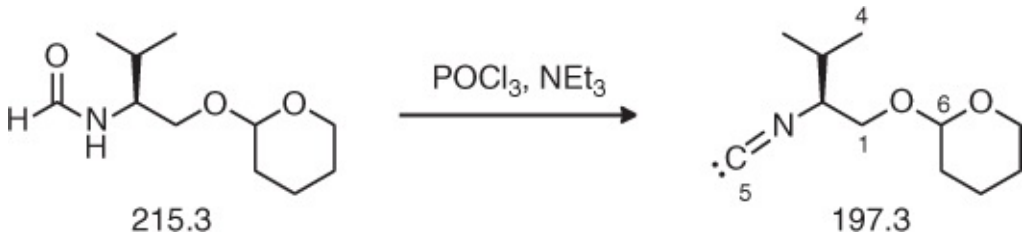
(*E*)-*Isomer*:

^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) = 8.03, 8.01 (2 × d, *J* = 11.9 Hz, 1H, 5-H), 6.11 (m, 1H, NH), 4.58, 4.53 (2 × m, 1H, 6-H), 3.79 (m, 1H, 10-H_{eq}), 3.69 (dd, *J* = 10.4, 4.0 Hz, 1H, 1-H_a), 3.57 (dd, *J* = 10.4, 3.8 Hz, 1H, 1-H_b), 3.48 (m, 1H, 10-H_{ax}), 3.23 (m, 1H, 2-H), 1.86 (m, 1H, 3-H), 1.76 (m, 1H, 7-H_a), 1.67 (m, 1H, 7-H_b), 1.59–1.46 (m, 4H, 8-H, 9-H), 0.96–0.90 (m, 6H, 4-

H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ (ppm) = 164.8, 164.6 (2 × d, C-5), 99.5, 98.4 (2 × d, C-6), 68.9, 68.2 (2 × t, C-1), 62.4, 61.8 (2 × t, C-10), 58.0, 57.8 (2 × d, C-2), 30.4, 30.3 (2 × t, C-7), 29.6, 29.5 (2 × d, C-3), 25.3, 25.2 (2 × t, C-9), 19.58, 19.55 (2 × t, C-8), 19.4, 18.9, 18.3, 18.1 (4 × q, C-4).

4.3.4.3	**	**(2*S*)-2-Isocyano-3-methyl-1-tetrahydropyranyloxybutane** (U. Kazmaier, M. Bauer, personal communication)



215.3 197.3

Triethylamine (10.5 ml, 75.0 mmol) is added to a stirred solution of the formamide **4.3.4.2** (6.45 g, 30.0 mmol) in anhydrous CH_2Cl_2 (30 ml) at 0 °C under N_2 atmosphere. Phosphoryl chloride (2.74 ml, 30.0 mmol) is then added at such a rate that the internal temperature does not exceed 5 °C. For completion of the reaction, stirring is continued at 0 °C for 1 h.

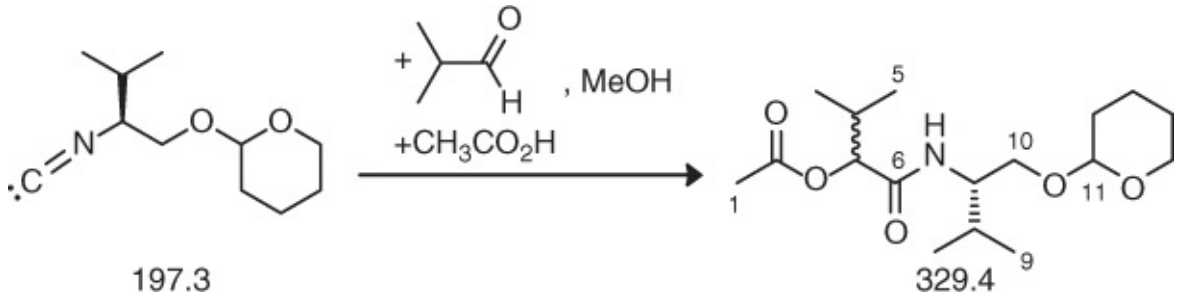
The reaction is then quenched by the dropwise addition of a solution of Na_2CO_3 (6.0 g) in water (24 ml) with stirring, during which the internal temperature is maintained at 26–28 °C (cooling with an ice bath as necessary). Thereafter, stirring is continued at room temperature for 30 min.

For work-up, water (60 ml) is added, and the aqueous phase is separated and extracted with CH_2Cl_2 (3 × 800 ml). The combined organic phases are washed with brine, dried over K_2CO_3, and filtered. The solvent is removed *in vacuo* and the residue is purified by chromatography on silica gel (EtOAc); 4.86 g (82%), faintly yellow liquid, TLC (Et_2O): R_f = 0.74.

^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) = 4.64 (t, *J* = 3.3 Hz, 1H, 6-H), 3.85 (m, 1H, 2-H), 3.85, 3.79 (2 × m, 1H, 10-H_{eq}), 3.60 (m, 1H, 1-H_a), 3.52 (m, 1H, 1-H_b), 3.52, 3.46 (2 × m, 1H, 10-H_{ax}), 1.96 (m, 1H, 3-H), 1.81 (m, 1H, 7-H_a), 1.71, (m, 1H, 7-H_b), 1.64–1.49 (m, 4H, 8-H, 9-H), 1.03, 1.03, 1.00, 1.00 (4 × d, *J* = 6.8 Hz, 6H, 4-H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ (ppm) = 156.5, 156.5 (2 × t, $J_{C–N}$ = 4.7 Hz, C-5), 99.4, 98.5 (2 × d, C-6), 67.9, 67.2 (2 × t, C-1), 62.3, 61.9 (2 × t, C-10), 61.0, 60.7 (2 × td, $J_{C–N}$ = 5.9 Hz, C-2), 30.4, 30.3 (2 × t, C-7), 28.9, 28.9 (2 × d, C-3), 25.3 (t, C-9), 19.6 (t, C-8), 19.2, 18.9, 17.0, 16.8 (4 × q, C-4).

4.3.4.4	*	**(2*S*)-2-[(3-Methyl-2-acetoxybutyryl)-amino]-3-methyl-1-tetrahydropyranyloxy-butane**



Acetic acid (693 µl, 12.0 mmol) is added to a stirred solution of the isonitrile **4.3.4.3** (1.19 g, 6.00 mmol) in MeOH (1.5 ml). Isobutyraldehyde (1.10 ml, 75.0 mmol) is then added, leading to an increase in the temperature of the reaction mixture. After the addition is complete, stirring is continued for 30 min at room temperature.

The reaction mixture is then concentrated *in vacuo*, the residue is dissolved in CH_2Cl_2 (45 ml), and this solution is washed with saturated aqueous $NaHCO_3$ solution. The aqueous phase is extracted with CH_2Cl_2 (3 × 30 ml), and the organic phases are combined, dried over Na_2SO_4, and filtered. The solvent is removed *in vacuo* and the residue is purified by chromatography on silica gel (*n*-hexane/EtOAc, 1 : 1). The Passerini product is obtained as a mixture of diastereomers; 1.54 g (78%), colorless oil, TLC (*n*-hexane/EtOAc, 1 : 1): R_f = 0.54.

^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) = 6.49, 6.39, 6.16, 6.11 (4 × d, *J* = 9.0, 9.3 Hz, 1H, NH), 4.97, 4.96, 4.96, 4.93 (4 × d, *J* = 4.6 Hz, 1H, 3-H), 4.46 (m, 1H, 11-H), 3.84–3.69 (m, 2H, 7-H, 15-H_{eq}), 3.44 (m, 1H, 15-H_{ax}), 3.76, 3.57, 3.52, 3.33, 3.27 (5 × m, 2H, 10-H), 2.22 (m, 1H, 4-H), 2.09, 2.09, 2.09, 2.08 (4 × s, 3H, 1-H), 1.85 (m, 1H, 8-H), 1.72 (m, 1H, 12-H_a), 1.63 (m, 1H, 12-H_b), 1.54–1.43 (m, 4H, 13-H, 14-H), 0.91–0.81 (m, 12H, 5-H, 9-H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ (ppm) = 169.6, 169.5, 169.5, 168.8, 168.7, 168.7 (6 × s, C-6, C-12), 99.6, 99.3, 98.9, 98.8 (4 × d, C-11), 78.4, 78.3 (2 × d, C-3), 68.5, 68.0, 67.2 (3 × t, C-10), 62.5, 62.2, 62.2, 62.2 (4 × d, C-15), 54.0, 53.8, 53.6, 53.4 (4 × d, C-7), 30.6, 30.5, 30.4, 30.4 (4 × t, C-12), 30.3, 30.2, 30.2, 30.2 (4 × d, C-4), 29.4, 29.4, 29.3, 29.2 (4 × d, C-8), 25.2, 25.2 (2 × t, C-14), 20.6 (q, C-1), 19.6–16.7 (m, C-5, C-9, C-13).

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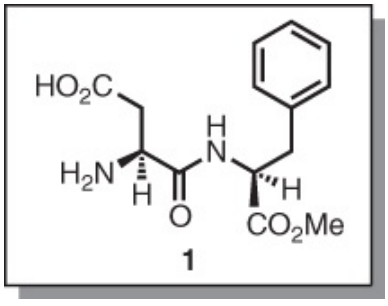
4.3.5 Aspartame



1

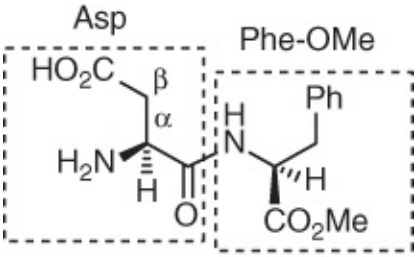
Topics:

- Synthesis of a dipeptide ester

		• N-Carboxybenzylation of an α-amino acid • Esterification of α-amino acids • Partial hydrolysis of an L-aspartic acid diester • Peptide formation using the DCC method • Catalytic debenzylation

(a) General

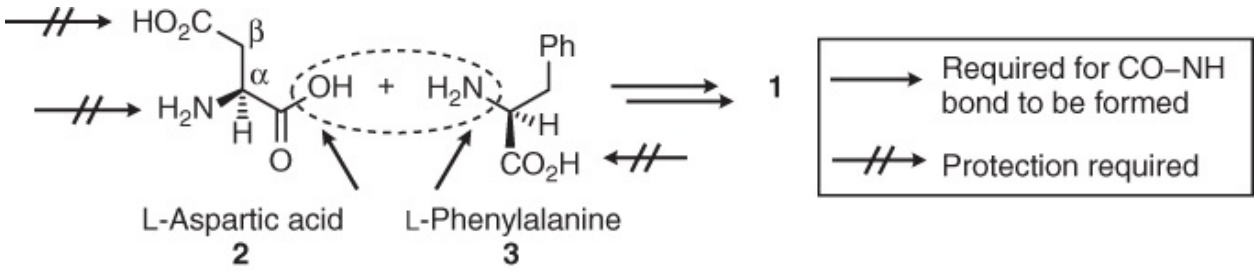
Aspartame (**1**, *N*-L-α-aspartyl-L-phenylalanine methyl ester; abridged nomenclature: H-Asp-Phe-OMe) is a dipeptide ester in which L-phenylalanine methyl ester is attached via its NH_2 group to the α-carboxyl function of L-aspartic acid:



1

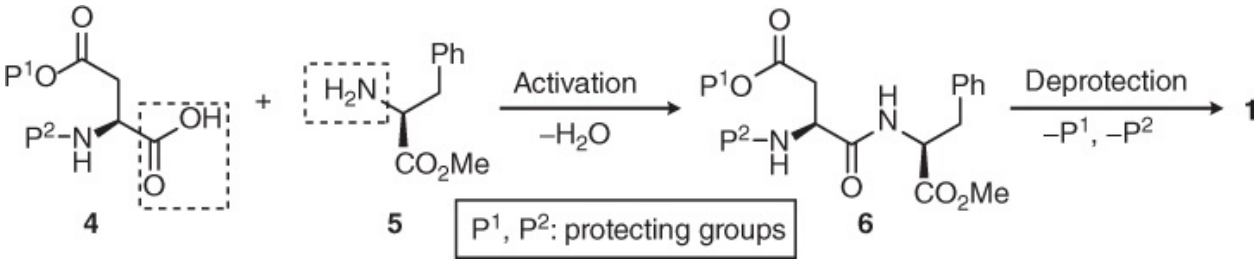
Aspartame **1** is used commercially as a sweetener [1]; it exhibits a very low nutritive value and a sweetness intensity that is 180–200 times higher than that of sucrose. Aspartame (**1**) is devoid of carcinogenicity, chronic toxicity, or teratogenicity [2].

The synthesis of aspartame is performed according to the fundamentals of peptide synthesis [3]. The key feature is the directed (chemoselective) formation of a CO–NH amide bond ("peptide bond") by condensation of bi-and trifunctional α-amino acids (here: **2**/**3**), which proceeds according to the following principles:

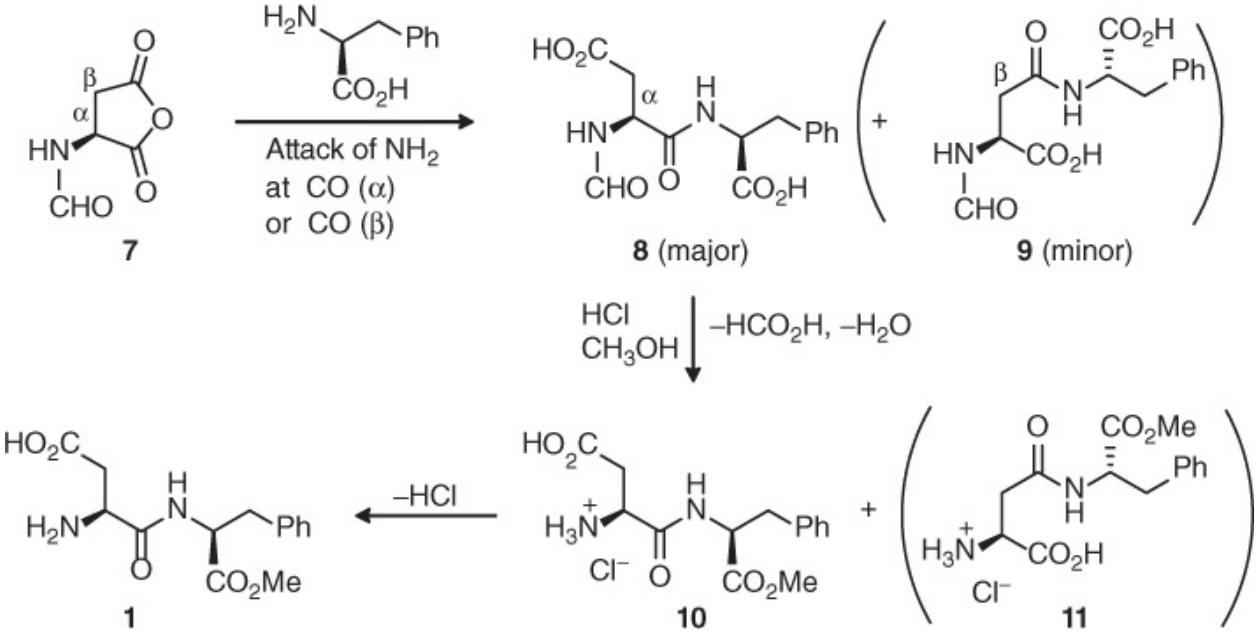


1. Directed peptide formation demands *protection* of NH_2 and CO_2H functions (as well as other functional groups) that do not participate in the peptide-bond-forming process. Commonly used protecting groups for NH_2 are Boc, Cbz (benzyloxycarbonyl), and Fmoc; for CO_2H, various ester groups are applied, often benzyl.
2. To facilitate amide formation between a CO_2H and an NH_2 group, a reaction that normally requires drastic conditions, the CO_2H group needs *activation*, in general by formation of a so-called active ester through the introduction of a good leaving group for nucleophilic attack of the amine function. Most commonly applied are the DCC, HOBt (1-hydroxy-benzotriazole), and anhydride methods.
3. After formation of the peptide bond, the protective groups have to be removed (*deprotection*) under reaction conditions that do not affect the amide functionality and do not lead to isomerization of the stereogenic centers.
4. The formation of peptide bonds using specific enzymes (proteases) represents a highly economical alternative to the above-mentioned strategy (1)–(3) since it can be performed with high selectivity and efficiency, *without* the use of protecting groups [4].

Using the first approach (1–3) for aspartame synthesis, L-aspartic acid has to be protected at the NH_2 and β-carboxyl groups, and then this bis-protected L-aspartic acid **4** has to be condensed with L-phenylalanine protected at the CO_2H group, preferentially as methyl ester **5**. Removal of the protecting groups P^1 and P^2 from the dipeptide ester **6** should then lead to aspartame **1**:



A synthesis of **1** following this strategy [5, 6] is presented in Section (b).

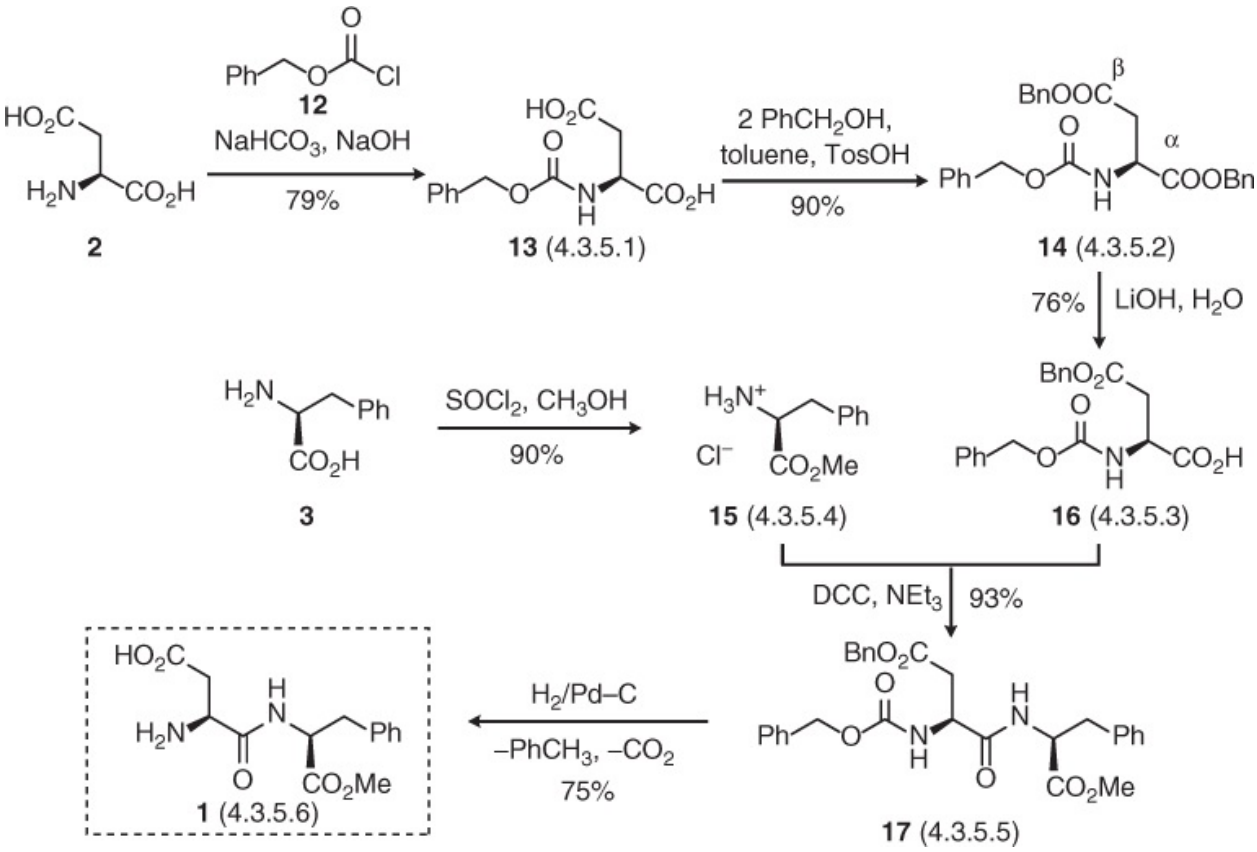


For an industrial synthesis of aspartame **1** [7], the anhydride **7** would be a very good starting material, since it represents an Nprotected and COOH-activated form of L-aspartic acid. However, it contains two C=O groups, which in the nucleophilic ring-opening with L-phenylalanine would lead to a mixture of *N*-formyl-α- and -β-aspartylphenylalanines **8** and **9**. Fortunately, the reaction can be directed toward the desired α-dipeptide by selecting an appropriate solvent. By treatment with HCl/MeOH, the formyl protecting group is removed and the CO_2H group of phenylalanine is selectively transformed into the methyl ester to give aspartame hydrochloride **10**, from which aspartame **1** is liberated by reaction with a base. The accompanying β-isomer **11** can be efficiently separated by fractional crystallization of the mixture of **10** and **11**.

Notably, in enzyme-catalyzed aspartame syntheses [1, 2], protected or unprotected L-aspartic anhydride or L-aspartic acid itself is linked directly to L-phenylalanine or its methyl ester.

(b) Synthesis of 1

L-Aspartic acid (**2**) is acylated at the NH_2 group using benzyloxycarbonyl chloride (**12**) in the presence of $NaOH/NaHCO_3$ (→**13**). The formed Nprotected aspartic acid **13** is then treated with benzyl alcohol in the presence of a catalytic amount of TosOH to yield dibenzyl *N*-benzyloxycarbonyl-L-aspartate (**14**) under azeotropic removal of H_2O:



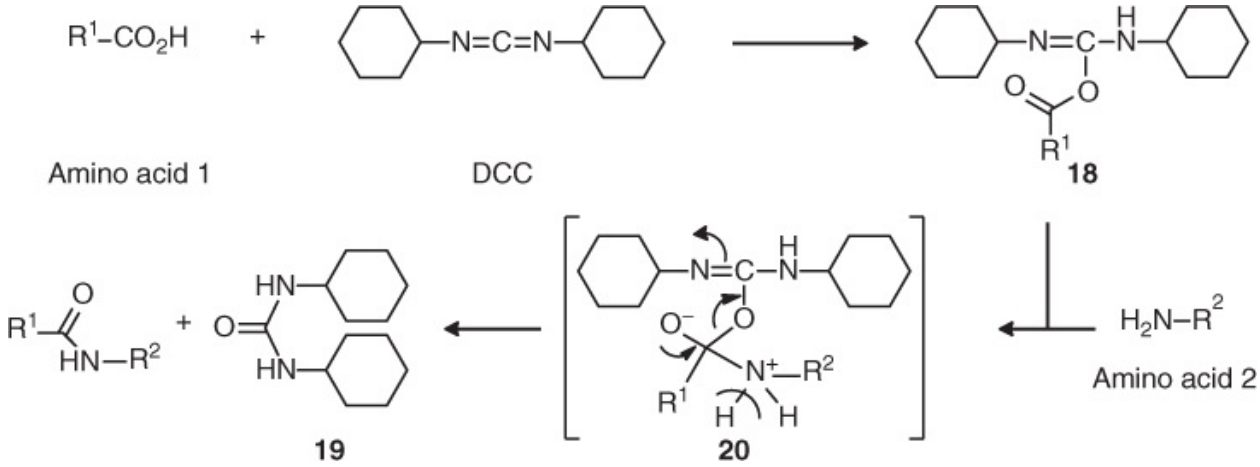
The dibenzyl ester **14** is subjected to partial alkaline hydrolysis ($LiOH/H_2O$) of the α-ester functionality, giving rise to the Nprotected L-aspartic acid β-benzyl ester **16**; the chemoselective saponification **14** → **16** (accelerated reaction of the α-ester vs the β-ester) might be due to an inductive effect of the amide moiety.

As the second substrate, the hydrochloride **15** of L-phenylalanine methyl ester is prepared by reaction of L-phenylalanine (**3**) with thionyl chloride in methanol (general method for the preparation of amino esters) [8].

The formation of the dipeptide of the protected aspartic acid derivative **16** and L-phenylalanine methyl ester hydrochloride **15** is then carried out using DCC and triethylamine to give the all-protected dipeptide ester **17** in almost quantitative yield.

The peptide bond of **17** is created in a complex reaction sequence. First, the NH_2

group of L-phenylalanine methyl ester (**5**) is liberated from the hydrochloride **15** by deprotonation with NEt_3. Second, the free α-CO_2H group of the precursor **16** is activated by addition to the heterocumulene moiety of DCC to afford the *O*-acyl isourea **18** as an "active ester." Third, by addition of the amino component **15** to the "active ester" **18**, an acyl transfer takes place in an S_Nt process (via **20**) with ensuing elimination of dicyclohexylurea (**19**) as leaving group, to give a CO–NH amide bond between the two reacting amino acid derivatives.

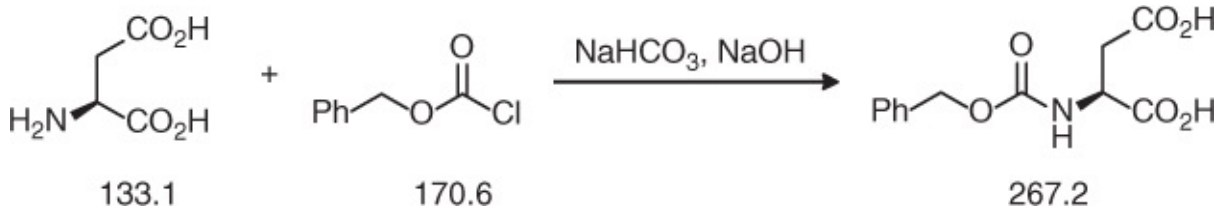


Finally, the protecting groups at the amino and the β-carboxylic acid moieties in the formed dipeptide ester **17** have to be removed. Deprotection at both NH_2 and CO_2H occurs concomitantly upon catalytic hydrogenation of **17**. Using Pd on charcoal, both functionalities undergo debenzylation with formation of toluene; carbon dioxide is additionally eliminated from the benzyloxycarbonyl group, to afford aspartame (**1**) in a clean-cut reaction.

Thus, the target molecule **1** is obtained in a six-step convergent synthesis, with respect to the five-step linear part in an overall yield of 37% (based on L-aspartic acid (**2**)).

(c) Experimental Procedures for the Synthesis of 1

4.3.5.1	**	***N*-Benzyloxycarbonyl-L-aspartic acid** [9]



Sodium hydrogencarbonate (67.2 g, 0.80 mol) is added portionwise to a stirred

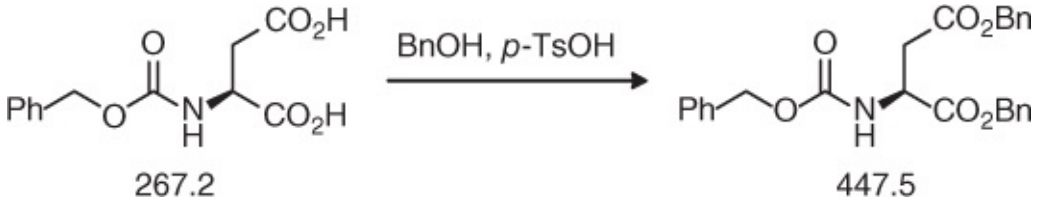
suspension of L-aspartic acid (53.2 g, 0.40 mol) in water (250 ml); after approximately 15 min, the amino acid would be dissolved. Thereafter, benzyloxycarbonyl chloride (75.0 g, 0.44 mol) and NaOH (2 N, 240 ml) are simultaneously added to the well-stirred solution, in such a proportion that the reaction mixture maintains a pH of 8–9 (control with indicator paper). After the addition is complete (approximately 4 h), stirring is continued for a further 1 h.

The reaction mixture is then acidified with concentrated HCl until pH 2 is reached. The (partially precipitated) product is extracted with EtOAc (3 × 200 ml), and the combined extracts are dried over Na_2SO_4 and filtered, and the solvent is removed *in vacuo*. The resulting oily residue is dissolved in EtOAc (150 ml), the solution is cooled to 0 °C, and *n*-hexane is slowly added with stirring until turbidity appears; stirring is continued for 15 min and further *n*-hexane (250 ml) is added. The precipitated (partially oily) product crystallizes completely on stirring; it is collected by suction filtration, washed with precooled *n*-hexane, and dried *in vacuo*. The yield is 84.0 g (79%), colorless crystals, mp 105–107 °C; the product can be recrystallized from EtOAc/*n*-hexane, mp 109–110 °C, TLC (SiO_2; Et_2O): R_f = 0.35, $[\alpha]^{20}_D$ = +9.25 (*c* = 2.0, HOAc).

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3340, 1710, 1540, 1420, 1280, 1200.

^{1}H NMR (300 MHz, [D_6]DMSO): δ (ppm) = 10.1 (s_{br}, 2H, CO_2H, exchangeable with D_2O), 7.35 (s, 5H, Ph–H), 6.43 (d, *J* = 9.1 Hz, 1H, NH, exchangeable with D_2O), 5.11 (s, 2H, Bn–CH_2), 4.62–4.43 (m, 1H, N–CH), 2.85 (d, *J* = 6.0 Hz, 2H, β-CH_2).

4.3.5.2 * Dibenzyl *N*-benzyloxycarbonyl-L-aspartate [5]



267.2 447.5

A solution of the Nprotected aspartic acid (Z-Asp-OH) (cf. **4.3.5.1**) (80.0 g, 0.30 mol), benzyl alcohol (360 ml; note 1), and *p*-toluenesulfonic acid (4.50 g) in anhydrous toluene (360 ml) is heated under reflux with stirring in an apparatus fitted with a Dean–Stark trap. The azeotropic distillation of H_2O should be

complete after 1 h (note 2).

Toluene is removed from the reaction mixture by distillation at 20 mbar, and then the excess benzyl alcohol is removed at 0.5 mbar. The oily residue is dissolved in Et_2O (150 ml) and the solution is cooled to −30 °C. With vigorous stirring, *n*-hexane is slowly added, whereupon the dibenzyl ester precipitates in crystalline form. The product is collected by filtration, washed with precooled *n*-hexane, and dried *in vacuo*; 120 g (90%), colorless crystals, mp 73–75 °C, TLC (CH_2Cl_2): R_f = 0.45 (note 3).

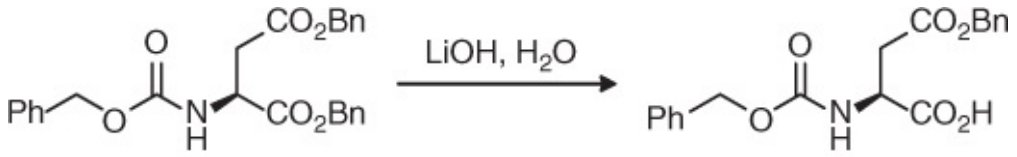
IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3360, 1745, 1705, 1420, 1355, 1220, 1195.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.30 (s, 15H, Ph–H), 5.82 (s_{br}, 1H, NH, exchangeable with D_2O), 5.12, 5.10, 5.05 (s, 2H, Bn–CH_2), 4.80–4.50 (m, 1H, α-CH), 2.98 (t, *J* = 5. Hz, 2H, β-CH_2).

Notes:

1. Benzyl alcohol has to be distilled before use, bp_{1013} 204–205 °C.
2. Theoretically, 10.8 ml of H_2O is expected to be formed.
3. The product thus obtained is sufficiently pure according to TLC and is used in the next step without further purification.

4.3.5.3 * *N*-Benzyloxycarbonyl-L-aspartic acid β-benzyl ester [5]



447.5 357.4

A solution of lithium hydroxide (2.55 g, 106 mmol) in H_2O (100 ml) is added dropwise over 30 min to a stirred solution of the diester **4.3.5.2** (45.0 g, 100 mmol) in a mixture of acetone (1.90 l) and H_2O (600 ml) at room temperature; stirring is then continued for 15 min.

After evaporation of the acetone under reduced pressure (bath temperature <40 °C), the remaining aqueous phase is extracted with Et_2O (3 × 100 ml) (note 1). The aqueous phase is then cooled to 0 °C and acidified by the addition of 6 N

aqueous HCl with stirring until pH 1 is reached. The oily precipitate of the product crystallizes on further stirring in the ice bath. The product is filtered off, washed with iced water, and dried *in vacuo* over P_4O_{10} to give 17.0 g of the monoester (76% based on transformed dibenzyl ester); colorless crystals, mp 97–99 °C, TLC (EtOH): R_f = 0.65 (note 2).

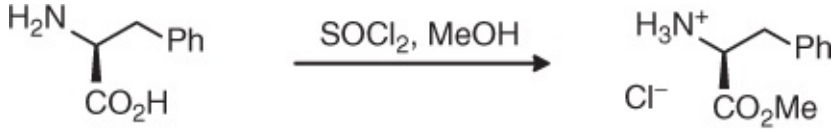
IR (KBr): $\tilde{\nu}$ (cm^{-1}) 3330, 1740, 1710, 1650, 1540, 1290, 1190.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.90 (s_{br}, H, CO_2H, exchangeable with D_2O), 7.35 (s, 10H, Ph–H), 5.87 (d, *J* 8.3 Hz, 1H, NH, exchangeable with D_2O), 5.15 (s, 4H, Bn–CH_2), 4.75 (q, *J* = 4.9 Hz, 1H, α-CH), 3.02 (t, *J* = 4.9 Hz, 2H, β-CH_2).

Notes:

1. The ethereal extract contains unreacted dibenzyl ester; work-up yields 17.0 g of the dibenzyl ester, mp 72–75 °C.
2. The product is practically pure according to TLC and can be used in the next step without further purification. Recrystallization from benzene gives colorless crystals of mp 106–108 °C, $[\alpha]_D^{20}$ = −13.1 (*c* = 1.0, in HOAc).

4.3.5.4 * L-**Phenylalanine methyl ester hydrochloride** [8]



165.2 215.7

Under N_2 atmosphere, anhydrous MeOH (175 ml) is cooled to −10 °C and thionyl chloride (19.6 g, 0.27 mol) (note 1) is added with vigorous stirring. Stirring is continued, and L-phenylalanine (36.3 g, 0.22 mol) is added portionwise. When the addition is complete, the mixture is heated under reflux for 2 h.

The excess MeOH is then removed *in vacuo*, the solid residue is dissolved in the minimum volume of boiling MeOH, and the solution is cooled to −10 °C. The hydrochloride of the product precipitates after slow addition of Et_2O with stirring. The salt is collected by suction filtration, washed with Et_2O, and dried

in vacuo over P_4O_{10}; 42.5 g (90%), colorless crystals, mp 158–159 °C (note 2).

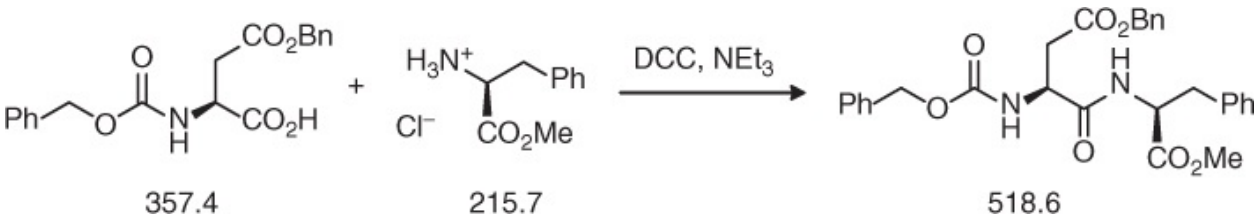
IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 1750, 1590, 1500, 1455, 1245.

^{1}H NMR (300 MHz, $CDCl_3$/[D_6]DMSO 1 : 1): δ (ppm) = 8.90 (s_{br}, 2H, NH_2, exchangeable with D_2O), 7.26 (s, 5H, Ph–H), 4.41–4.21 (m, 1H, CH), 3.69 (s, 3H, CO_2CH_3), 3.49–3.32 (m, 2H, CH_2).

Notes:

1. $SOCl_2$ has to be distilled prior to use, bp_{1013} 78–79 °C.
2. The hydrochloride is used in the next step without further purification.

4.3.5.5	**	**[*N*-Benzyloxycarbonyl-α-L-aspartyl(β-benzyl ester)]-L-phenylalanine methyl ester** [6]



The monoester **4.3.5.3** (13.9 g, 39.0 mmol) and the hydrochloride **4.3.5.4** (8.40 g, 0.39 mmol) are suspended in anhydrous CH_2Cl_2 (45 ml) and the suspension is cooled to 0 °C. Anhydrous triethylamine (3.96 g, 39.0 mmol) is added with stirring, followed, after 10 min, by DCC (8.82 g, 42.9 mmol). The reaction mixture is stirred for 1 h at 0 °C and for 12 h at room temperature.

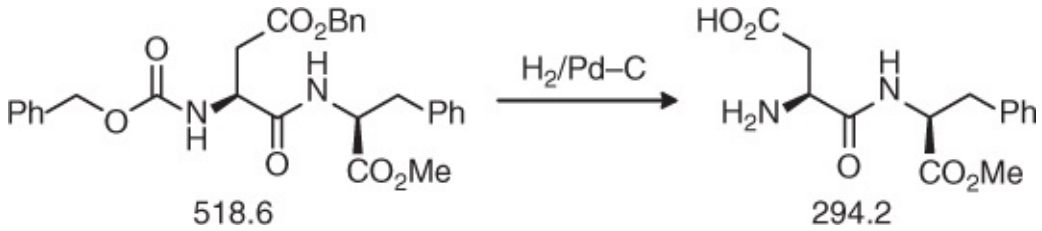
The precipitated dicyclohexylurea is then filtered off and washed with CH_2Cl_2. The combined filtrate and washings are washed successively with HCl (2 N, 60 ml), H_2O (60 ml), aqueous $NaHCO_3$ solution (60 ml), and H_2O (60 ml). The organic phase is then dried over $MgSO_4$ and filtered, and the solvent is removed *in vacuo*. The residue is recrystallized from EtOAc/petroleum ether (40–65 °C) to yield 18.9 g (93%) of the protected dipeptide as colorless crystals; mp 112–113 °C, TLC (EtOAc): R_f = 0.75.

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3310, 1740, 1720, 1650, 1535, 1265.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.40–6.80 (m, 15H, Ph–H), 5.11 (s,

4H, 2 × Bn–CH_2), 5.00–4.50 (m, 2H, Bn–CH_2), 3.68 (s, 3H, CO_2CH_3), 3.20–2.60 (m, 4H, β-CH_2).

4.3.5.6	**	L-**α-Aspartyl**-L-**phenylalanine methyl ester (aspartame)** [5]



A mixture of the protected dipeptide **4.3.5.5** (20.0 g, 38.6 mmol), glacial acetic acid (200 ml), water (10 ml), and 10% palladium on charcoal (1.00 g) is hydrogenated at room temperature at a hydrogen pressure of 3–4 bar for 4 h.

The catalyst is then filtered off (Caution: pyrophoric!) and the filtrate is concentrated to dryness *in vacuo*; toluene (10 ml) is added to remove residual H_2O and HOAc by azeotropic distillation *in vacuo*; this procedure is repeated three times. After dissolving the residue in boiling EtOH (approximately 80 ml), the solution is filtered and kept at 0 °C for crystallization. The product is filtered off, washed with a small amount of precooled EtOH, and dried *in vacuo*; 8.50 g (75%); fine, colorless needles with a sweet taste, mp 253–255 °C, TLC (MeOH): R_f = 0.55; $[\alpha]^{20}_D$ = −2.3 (*c* = 1.0 in 1 N HCl).

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3330, 1740, 1670, 1545, 1380, 1365, 1230, 700.

^{1}H NMR (300 MHz, [D_6]DMSO): δ (ppm) = 8.80 (s_{br}, 1H, CO–NH, exchangeable with D_2O), 7.22 (m, 5H, Ph–H), 5.30 (s_{br}, 2H, NH_2, exchangeable with D_2O), 4.54 (t, *J* = 7.0 Hz, 1H, α-aspartyl-CH), 3.60 (s, 3H, CO_2CH_3), 3.70–3.61 (m, H, phenylalaninyl-CH), 3.22–2.87 (m, 2H, Ph–CH_2), 2.60–2.23 (m, 2H, β-aspartyl-CH_2).

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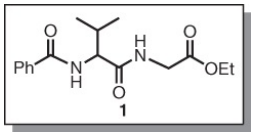
9. *Methoden der Organischen Chemie (Houben-Weyl)*, vol. 15/1, p. 321 and 349.

4.3.6 Ugi Dipeptide Ester

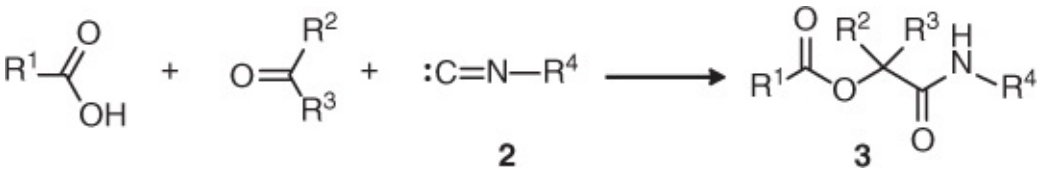
 1	***Topics:***	• One-pot peptide synthesis • Four-component Ugi reaction versus six-component Ugi reaction, combined with aminoacylal hydrolysis

(a) General

Many syntheses of acyclic, carbocyclic, and heterocyclic systems are conducted in the form of “multicomponent reactions” (MCRs) [1], thus creating complex molecules from several simple substrates efficiently and expeditiously in one process. Important examples of MCRs are the Passerini reaction and the Ugi reaction [2].

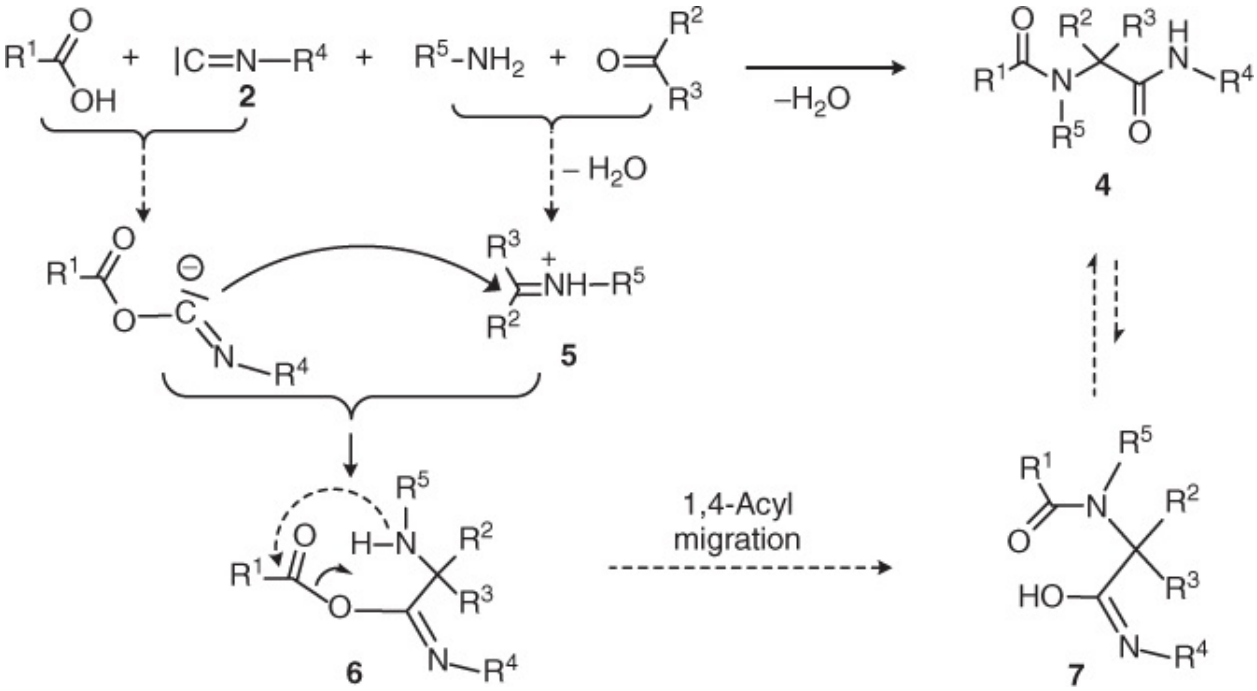
In the three-component Passerini reaction, isonitrile **2** is combined with a

carboxylic acid and an aldehyde (or a ketone) leading to an α-acyloxyamide **3** (cf. Section 4.3.3).

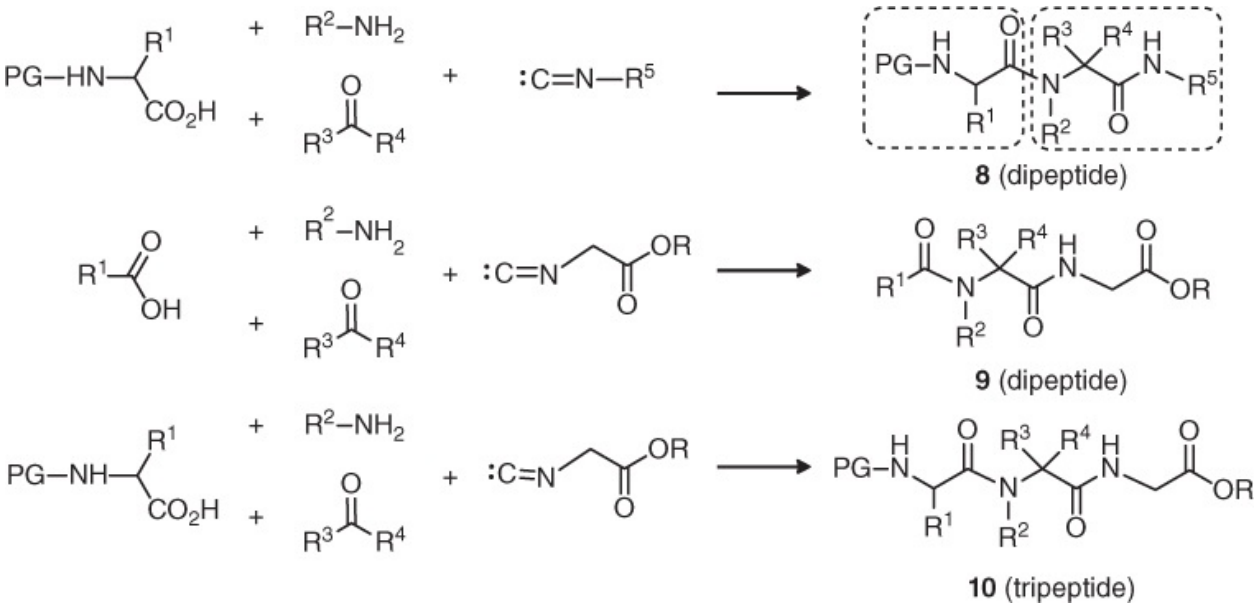


2 **3**

A very similar transformation is the four-component Ugi reaction, in which a mixture of an isonitrile, a carboxylic acid, an aldehyde (or ketone), and a primary amine (or ammonia) is reacted. The products are α-(*N*-acylamino)amides of type **4**:



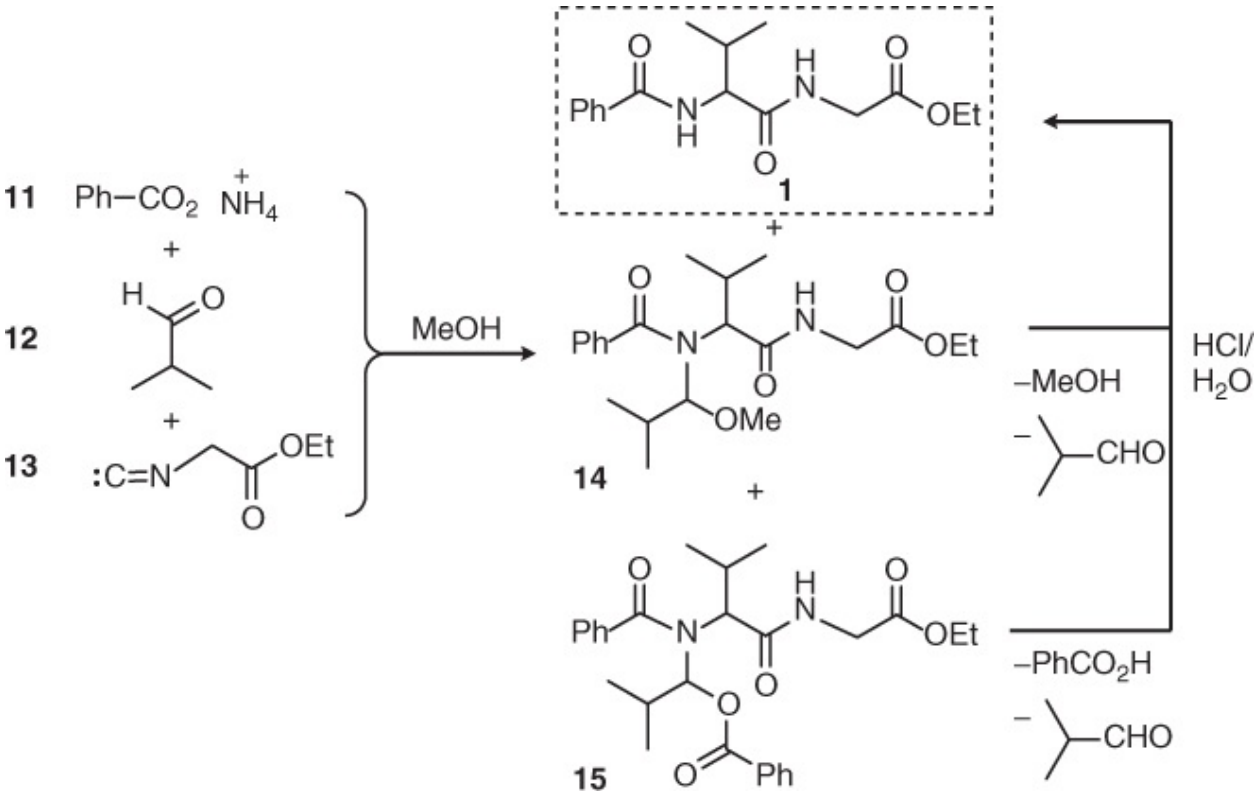
For the Ugi reaction, a mechanism analogous to that for the Passerini reaction is likely to be operative; in the crucial step, a protonated imine **5** – initially formed from the carbonyl compound, the amine (R-NH_2 or NH_3), and the proton of the carboxylic acid – serves as the electrophilic component (**5** → **6** → **7** → **4**). The four-component Ugi reaction has remarkable potential in peptide synthesis [3]. In particular, with Nprotected amino acids as acid components and isocyanoacetates as isonitrile components, a wide range of di-and tripeptidic fragments of types **8**/**9**/**10** are accessible [4]:



Since primary alkylamines are the preferred amino substrates, the formed peptidic systems **8–10** contain an "unnatural" N-alkylated peptide bond, –CO–NR–.

For the synthesis of NH peptides by the Ugi principle, ammonia has to be used. However, as shown in a recent investigation [5], the Ugi reaction with NH_3 takes a more complex course, although it may lead straightforwardly to the formation of Nprotected dipeptidic systems such as **1** under carefully controlled conditions, as presented in Section (b).

(b) Synthesis of 1

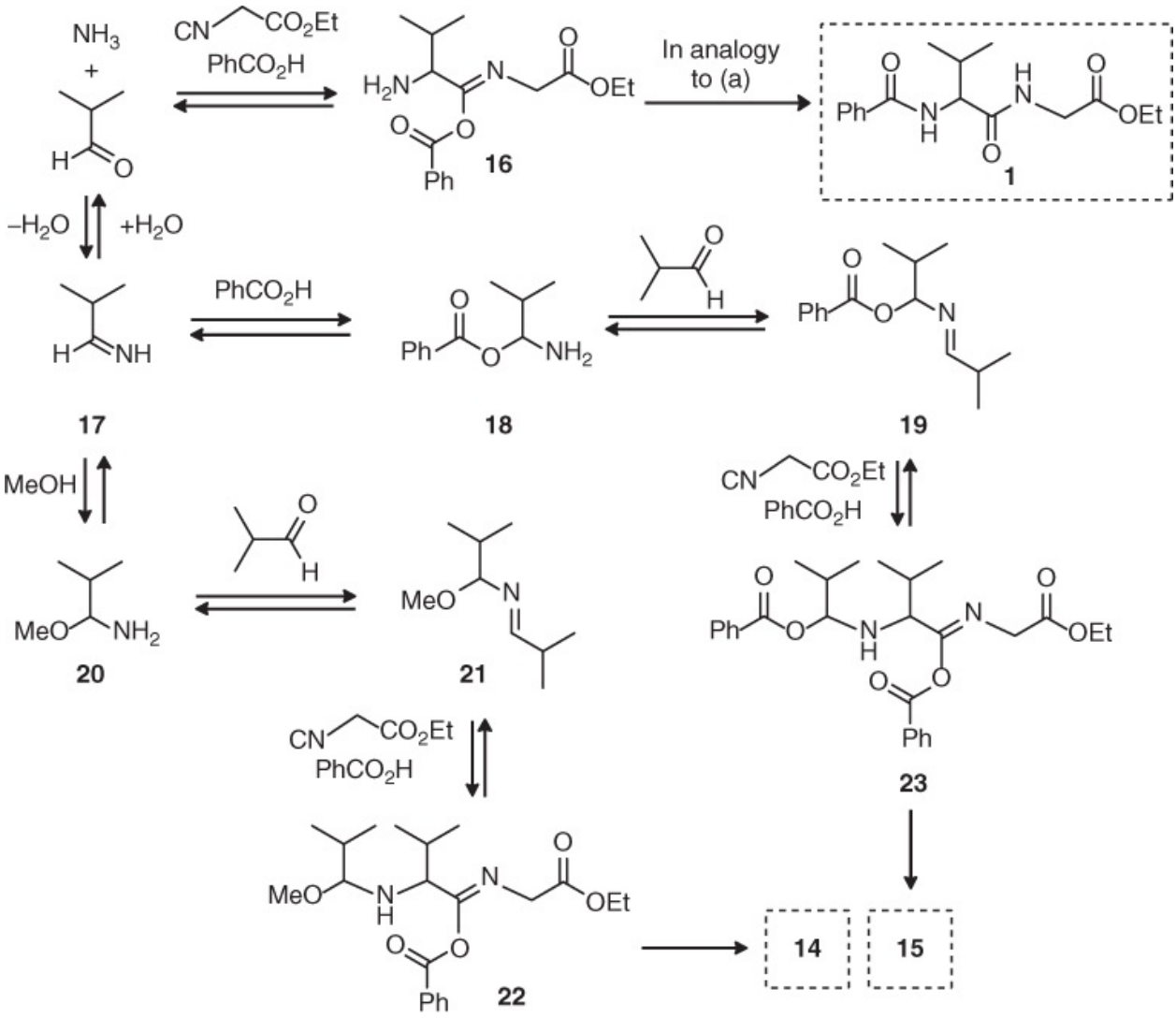


Reaction of ammonium benzoate (**11**, as a source of $PhCO_2H$ and NH_3), isobutyraldehyde (**12**), and ethyl isocyanoacetate (**13**, cf. **3.2.2.4**) in methanol as solvent leads to the dipeptide ester **1**, albeit only in low yield. The major products are the hemiaminals **14** and **15**, indicating that a six-component Ugi reaction with additional incorporation of a second aldehyde moiety together with CH_3OH (**14**), or with a second molecule of $PhCO_2H$ (**15**), is favored under these conditions[3]. The amounts of **14** and **15** are even increased by increasing the amount of aldehyde or benzoate; on the other hand, the formation of **14** can be suppressed by using a less nucleophilic solvent such as CF_3CH_2OH. Under optimized conditions (**11** : **12** : **13** = 4.4 : 2 : 1, MeOH as solvent), the aminoacylal **15** is the only six-component condensation product formed besides the four-component Ugi product **1** (ratio 3 : 4).

Selective hydrolysis of the aminoacylal function in **15** is accomplished by treatment with HCl/H_2O at room temperature to quantitatively afford the dipeptide ester **1**. Conveniently, the acidic hydrolysis can be performed directly after the multicomponent reaction (i.e., without separation of **1** and **15**) to give **1** in a total yield of 85%.

The following mechanism can be assumed for the sixfold coupling reaction [5]. In the first step, an imine **17** is formed, which obviously does not react directly

with the isonitrile (as proposed for the Ugi reaction in Section (a)), but with another nucleophile such as methanol or benzoate.



The resulting hemiaminal-type intermediates **18** and **20** can now incorporate a second aldehyde moiety to give the imines **19** and **21**. Addition of the isonitrile and the carboxylate generates the imidates **22** and **23**, which subsequently undergo rearrangement to the amides **14** and **15**.

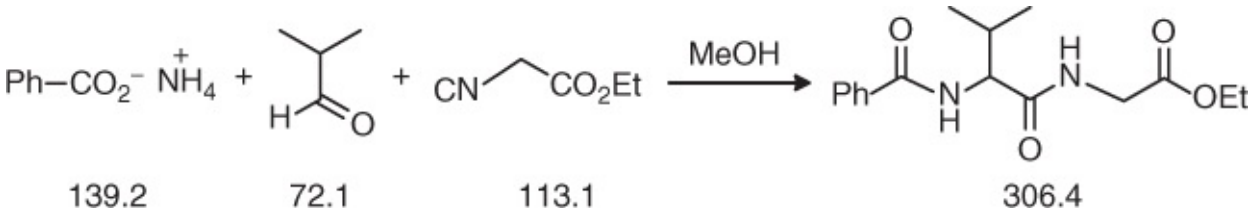
Thus, the polyfunctional (racemic) target molecule can be obtained by a four-component domino process in high yield (85%).

Synthesis of **1** (racemic or optically active) according to the classical linear strategy outlined in Section 4.3.2, namely preparation of Nprotected valine and of ethyl glycinate from the corresponding amino acids, peptide coupling of the free CO_2H and NH_2 functions, and removal of the protective groups, requires at

least four steps.

(c) Experimental Procedure for the Synthesis of 1

4.3.6.1	**	***rac*-*N*-(*N*-Benzoylvalinoyl) glycine ethyl ester (*N*-Bz-Val-Gly-OEt)** [5]



Isobutyraldehyde (8.03 ml, 88.0 mmol) is added to a solution of ammonium benzoate (5.56 g, 40.0 mmol) in MeOH (40 ml) at 0 °C. After stirring for 30 min, ethyl isocyanoacetate (2.16 g, 20.0 mmol; cf. Section 3.2.2) is added and the mixture is allowed to warm to room temperature over 12 h.

After evaporation of the solvent *in vacuo*, the residue is suspended in a mixture of H_2O and CH_3CN (30 ml each) and the suspension is acidified to pH 2 by dropwise addition of concentrated HCl and stirred at room temperature for 12 h.

The CH_3CN is then evaporated *in vacuo* and the resulting aqueous suspension is treated with H_2O and CH_2Cl_2 (approximately 50 ml each) until two clear layers are formed. The organic layer is separated, washed with saturated aqueous $NaHCO_3$ solution, dried over Na_2SO_4, and filtered, and the solvent is removed *in vacuo*. The solid residue is triturated with Et_2O (50 ml), collected by suction filtration, washed with Et_2O and *n*-hexane (10 ml each), and dried *in vacuo*; white powder, 5.20 g (85%), mp 163–164 °C; analytically pure, TLC (SiO_2; Et_2O): R_f = 0.31.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.48 (d, *J* = 8.0 Hz, 2H, Ph–H), 7.49 (d, *J* = 8.0 Hz, 1H, Ph–H), 7.40 (t, *J* = 8.0 Hz, 2H, Ph–H), 7.18 (m_c, 1H, NH), 7.08 (d, *J* = 8.8 Hz, 1H, NH), 4.61 (dd, *J* = 8.8, 7.2 Hz, 1H, NCHCO), 4.17 (q, *J* = 7.1 Hz, 2H, OCH_2), 4.12, 3.90 (2 × dd, *J* = 18.0, 5.2 Hz, 2 × 1H, N–CH_2), 2.23 (m_c, 1H, CH), 1.24 (t, *J* = 7.1 Hz, 3H, CH_3), 1.03, 1.01 (2 × d, *J* = 7.1 Hz, 6H, $(CH_3)_2$).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 171.7, 169.5, 167.5, 134.0, 131.7,

128.5, 127.1, 61.4, 58.7, 41.3, 31.3, 19.2, 18.4, 14.1.

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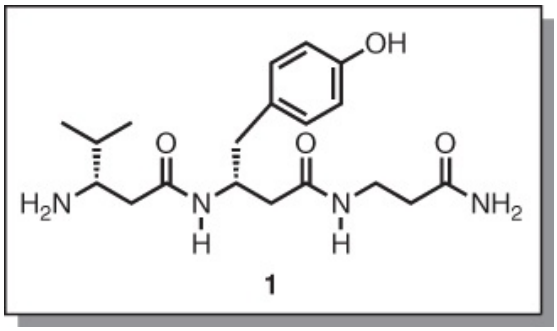
4.3.7 Solid-Phase Synthesis of β-Peptides



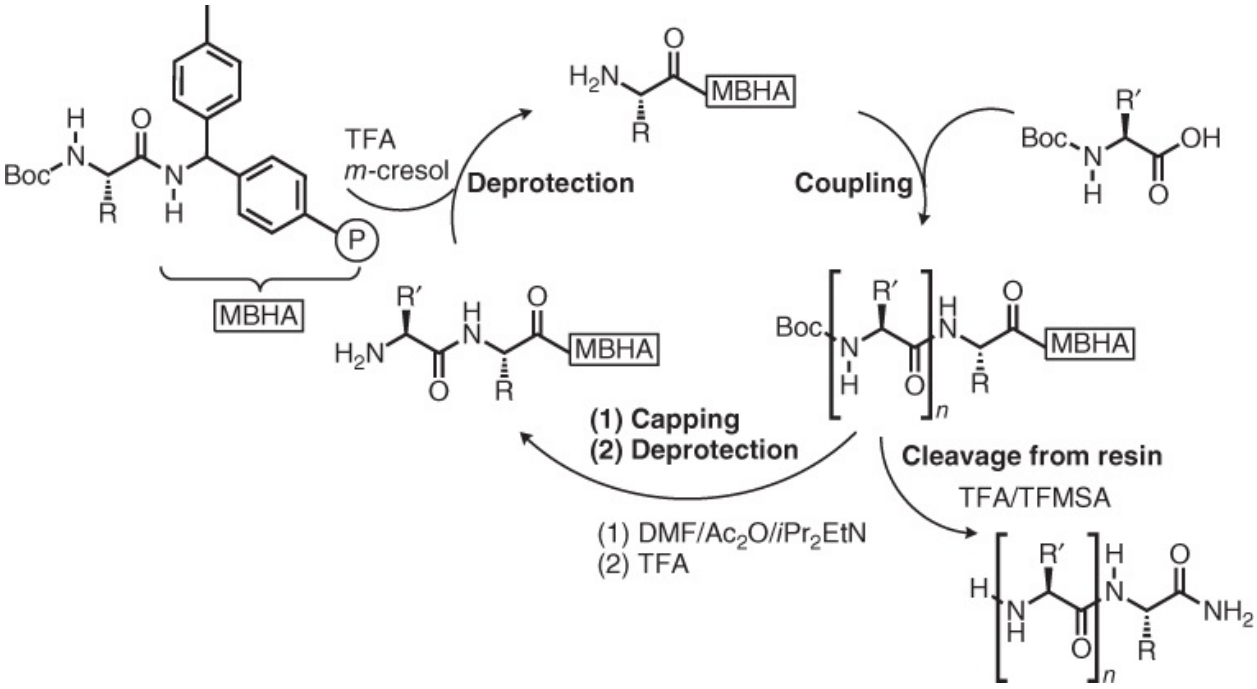
1

Topics:

- Solid-phase peptide synthesis (SPPS)
- Boc and Fmoc strategies
- Protective groups
- Peptide coupling reagents
- Solid supports
- β-Amino acids

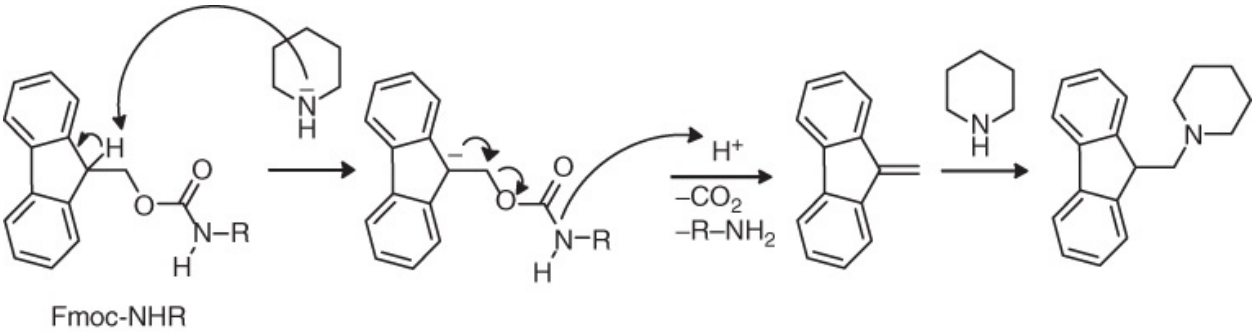
(a) General

Chemical synthesis is used to prepare a variety of small peptides, but proteins with 50–100 amino acids can also be obtained in this way. It is the only method in those cases in which the proteins are difficult to express in biological systems. Moreover, chemical synthesis of peptides and proteins is always necessary when non-natural amino acids are included and backbone modifications are made. Whereas peptide synthesis in solution is applied only in special cases and for very small peptides, SPPS, first proposed by Merrifield [1], has been developed into a mature automated procedure with coupling yields higher than 99.9% [2–4]. The synthesis is performed on a resin, which allows the use of an excess of reagents, gives high coupling yields, and permits fast purification. A flawless strategy for protecting the functional groups (permanent protecting groups) in the side chain, with individual solutions for the respective amino acids, is required. For chain elongation, which proceeds from the C-to the N-terminal end, temporary protection of the N-terminus (Boc or Fmoc strategy) is used, orthogonal with respect to the side-chain protection. This proceeds in combination with *in situ* C-terminal activation of the amino acid to be linked. The SPPS methods described in the literature mainly differ in their choice of resin, permanent and temporary protecting group strategies, and coupling reagents. A typical SPPS cycle is illustrated for the Boc strategy:



The resin loaded with the first amino acid is Boc-deprotected under acidic conditions. Coupling of the next Boc-protected amino acid takes place with *in situ* activation of the carboxylic acid by coupling reagents. Capping of

nonreacted oligomers with acetic anhydride facilitates oligomer separation at a later stage. By Boc deprotection, the synthesis cycle can be repeated until the desired peptide/protein length is reached. Cleavage from the resin is performed using HF (requiring careful handling) or, more conveniently, under strongly acidic conditions (mixture of TFA and trifluoromethanesulfonic acid (TfOH)), with simultaneous cleavage of all or most of the permanent side-chain protecting groups.

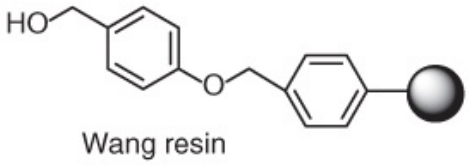


Fmoc-NHR

The SPPS cycle for the Fmoc strategy is broadly similar to that of the Boc procedure. Nevertheless, the Fmoc temporary protecting group for the N-terminus, as introduced by Carpino, allows deprotection under basic conditions (20% piperidine in DMF). Side-chain deprotection and cleavage from the resin is usually accomplished with TFA. Therefore, peptide formation using Fmoc chemistry involves milder cleavage conditions. Furthermore, the Fmoc group constitutes a chromophore, which facilitates monitoring of the progress of the synthesis.

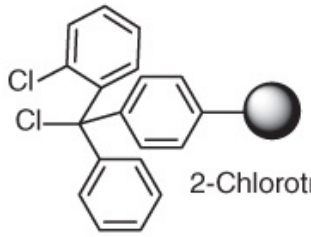
Most of the solid supports used for peptide synthesis are based on functionalized polystyrenes, which provide useful physical properties such as swelling, loading, and durability. They differ with respect to the linker, allowing various cleavage mechanisms and different functionalization at the C-terminus. Whereas the Merrifield, Wang, and 2-chlorotrityl resins provide a carboxylic acid moiety, cleavage from the 4-methylbenzhydrylamine (MBHA) resin results in the formation of an amide. Other resins are known that provide thioesters or esters, as exemplified by the 3-nitro-4-hydroxymethyl benzoyl linker.

Acidic cleavage to give C-terminal carboxylic acid



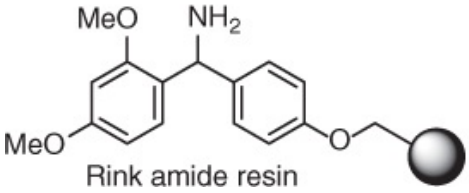
Wang resin

Mild acidic cleavage to give C-terminal carboxylic acid



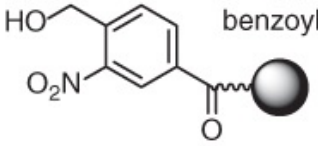
2-Chlorotrityl chloride resin

Acidolysis to give a C-terminal amide



Rink amide resin

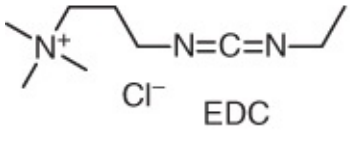
Base-cleavable linkers



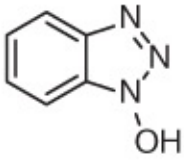
3-Nitro-4-hydroxymethyl benzoyl linker

The most critical aspect of SPPS concerns the permanent side-chain protecting groups. They need to be orthogonal to the respective temporary Boc or Fmoc protection used in the chain elongation and should usually be liberated concomitantly upon cleavage from the resin. On the other hand, for some applications, cleavage of the fully protected oligomer from the resin is required. Furthermore, side-chain protection is required for all nucleophiles that might otherwise interfere with chain elongation. The options, advantages, and disadvantages of the individual amino acid side-chain protection protocols are well documented and the different procedures well established [3].

Carbodiimide

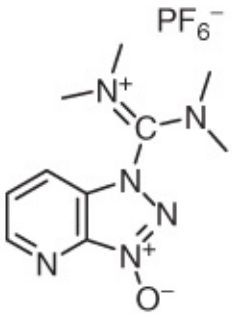


EDC



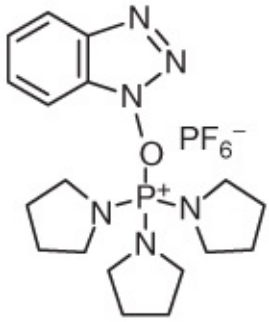
HOBt

Aminium salt



HATU

Phosphonium salt



PyBOP

The formation of the amide bond requires activation of the carboxylic acid moiety. In the case of difficult couplings, acid fluorides or active esters such as the pentafluorophenyl ester (OPfp) are applied. In most syntheses, *in situ* activation of the carboxylic acid is preferred. This is exemplified by carbodiimide (DIC, *N*,*N*′-diisopropylcarbodiimide) activation followed by treatment with HOBt to afford the active ester. Highly reactive coupling

reagents, which allow shorter coupling times, are the uronium salts *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HATU) and PyBOP. A major concern in all coupling reactions is the avoidance of racemization at Cα during active ester formation.

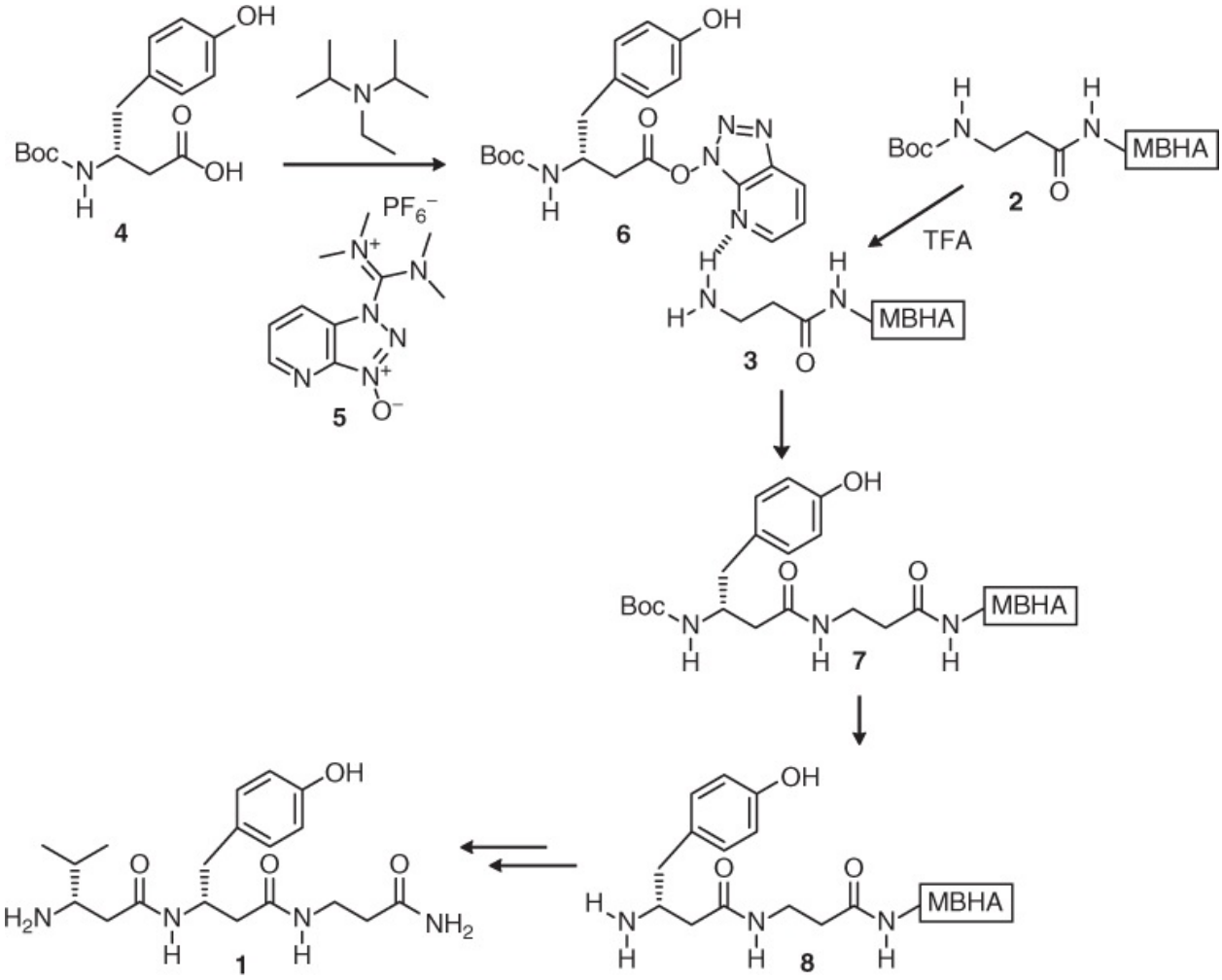
Oligomerization of β-amino acids by means of SPPS leads to β-peptides [5], which are of interest as mimics for α-peptide secondary structures since they provide much higher conformational stability even in short sequences of about six amino acids and are stable with respect to enzymatic degradation. Appropriate choice of the side-chain substituents at the α-and/or β-position in combination with the desired configuration allows the specific design of peptide secondary structures. Since manual and automated syntheses of α-peptides are comprehensively described in the literature, SPPS optimized for the preparation of β-peptides alone is described here.

(b) Synthesis of β-Peptides 1

β-Peptides can be prepared following the Fmoc [6] or Boc protocols [7]. A general method for the coupling of Boc-protected β-amino acids on an MBHA polystyrene solid support can be applied, which is closely related to the SPPS of α-peptides. A major difference, however, lies in the much higher tendency of β-peptides to form aggregates and secondary structures already on the solid support. Therefore, double coupling, higher temperatures, and a reactive coupling reagent are applied, HATU being used in the following synthesis. For β-amino acids with the side chain in the β-position, isomerization of the active esters is not a severe problem like in the α-peptide series since the proton at the stereogenic center is much less acidic.

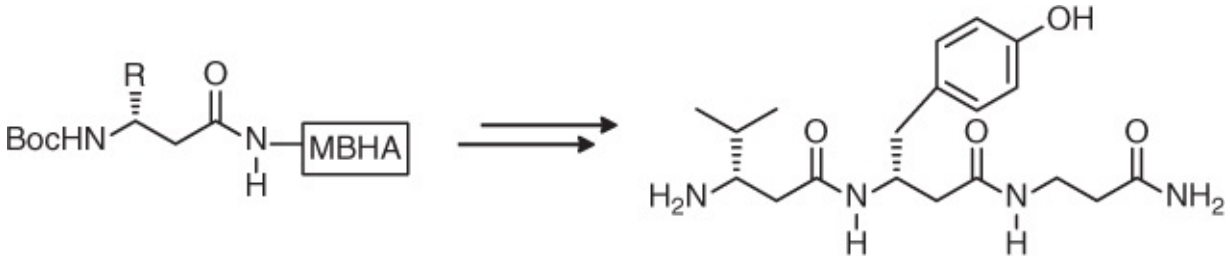
For the following synthesis of β-peptide **1**, the MBHA solid support is loaded with β-homoglycine (**2**), which is preferentially used at the C-terminus to avoid racemization. TFA-induced deprotection of the resin-bound amino acid yields amine **3**. The coupling step is initiated by activation of Boc-protected β-homotyrosine (**4**) by deprotonation with *N*,*N*-diisopropylethylamine (DIPEA) in conjunction with the coupling reagent HATU (**5**). It is likely that an acyloxy amidinium salt is formed as an intermediate, which immediately reacts with the benzotriazole derivative to give the active ester **6**. The nucleophilic amine is probably coordinated by hydrogen bonding to further improve amide formation. In the case of sterically demanding amino acids, the coupling is repeated to obtain higher coupling yields. The β-dipeptide **7** is elongated by successive deprotection and coupling cycles. The desired β-tripeptide is cleaved from the

resin under strongly acidic conditions. Oligomers with a length of four or more amino acids can be isolated by precipitation from cold diethyl ether. Since the tripeptide is too short to be precipitated in this way, the cleavage solution is concentrated *in vacuo* and the residue is directly purified by HPLC to yield the β-peptide **1** as the N-terminal amide.



(c) Experimental Procedure for the Synthesis of 1

4.3.7.1	***	**Manual solid-phase β-peptide synthesis** [8]



The β-tripeptide **1** is prepared in a small fritted glass column (10 ml) on an MBHA-polystyrene resin with a loading capacity of 0.62 mmol g^{-1}. The resin (48.5 mg) is used preloaded with *N*-Boc-β-homoglycine **2** (19.4 μmol homoglycine amide) and is first swollen by covering it with CH_2Cl_2 (2 ml) for 2 h. The solvent is then removed by a nitrogen flow, and the procedures described for deprotection, coupling, and capping are repeated for each coupling cycle:

1. *Deprotection*: The resin is treated with a TFA/*m*-cresol solution (95 : 5, 2 ml) for 3 min. This deprotection step is repeated, and then the resin is washed three times with CH_2Cl_2/DMF (1 : 1; 2 ml) and five times with pyridine (2 ml).
2. *Coupling*: Coupling of the β-amino acids is performed in an oven at 50 °C. First, the resin is treated with an excess of Boc-protected amino acid (for the synthesis of **1**, 37.3 mg β-homotyrosine for the first agent and 22.4 mg β-homovaline, 5 equiv, 97.0 μmol, for the second agent), which is activated by HATU (33.2 mg, 87.3 μmol, 4.5 equiv), 1-hydroxy-7-azabenzotriazole (HOAt) (194 μl, 97.0 μmol, 5 equiv of a 0.5 M solution in DMF), and DIPEA (46.6 μl, 272 μmol, 14 equiv) in DMF (400 μl). After gently agitating the resin for 1 h, the reaction mixture is drained.
3. *Capping*: Unreacted amines are acylated by treatment with a solution of DMF/Ac_2O/DIPEA (8 : 1 : 1; 2 ml) for 3 min. This capping step is repeated once more, and then the resin is washed with CH_2Cl_2/DMF (1 : 1; 2 ml).

   The deprotection, coupling, and capping steps are repeated according to the desired peptide. For the synthesis of **1**, after attachment of β-homovaline, the final deprotection step is performed with TFA (3 × 2 ml), and this is followed by washing with CH_2Cl_2 (5 × 2 ml) and drying of the resin *in vacuo*.
4. *Cleavage from the resin*: The resin is transferred into a small glass vessel and suspended in *m*-cresol/thioanisole/ethanedithiol (2 : 2 : 1; 500 μl). After stirring for 30 min at room temperature, TFA (2 ml) is added, and the mixture is cooled to −20 °C. Trifluoromethanesulfonic acid (TfOH) (200 μl) is added dropwise with stirring. The mixture is allowed to warm to room temperature over 1.5 h and stirring is continued for a further 2 h. The mixture is filtered through a fritted glass funnel, and the TFA is removed *in vacuo*.
5. *Purification*: The crude mixture is concentrated *in vacuo*, and the residue is dissolved in H_2O/acetonitrile and purified by HPLC on an RP C18 column

(150 × 10 mm, 4 μm, 80 Å, flow rate 3 ml min^{-1}) using the eluents (A) H_2O + 0.1% TFA and (B) CH_3CN/H_2O, 8 : 2, +0.1% TFA.

β-Peptide **1** is obtained with an HPLC gradient of 5–40% B in 30 min; t_R = 15.26 min.

EI HRMS: $C_{19}H_{30}N_4O_4$: calcd. for $[M+H^+]$: 379.233 98; found: 379.23408.

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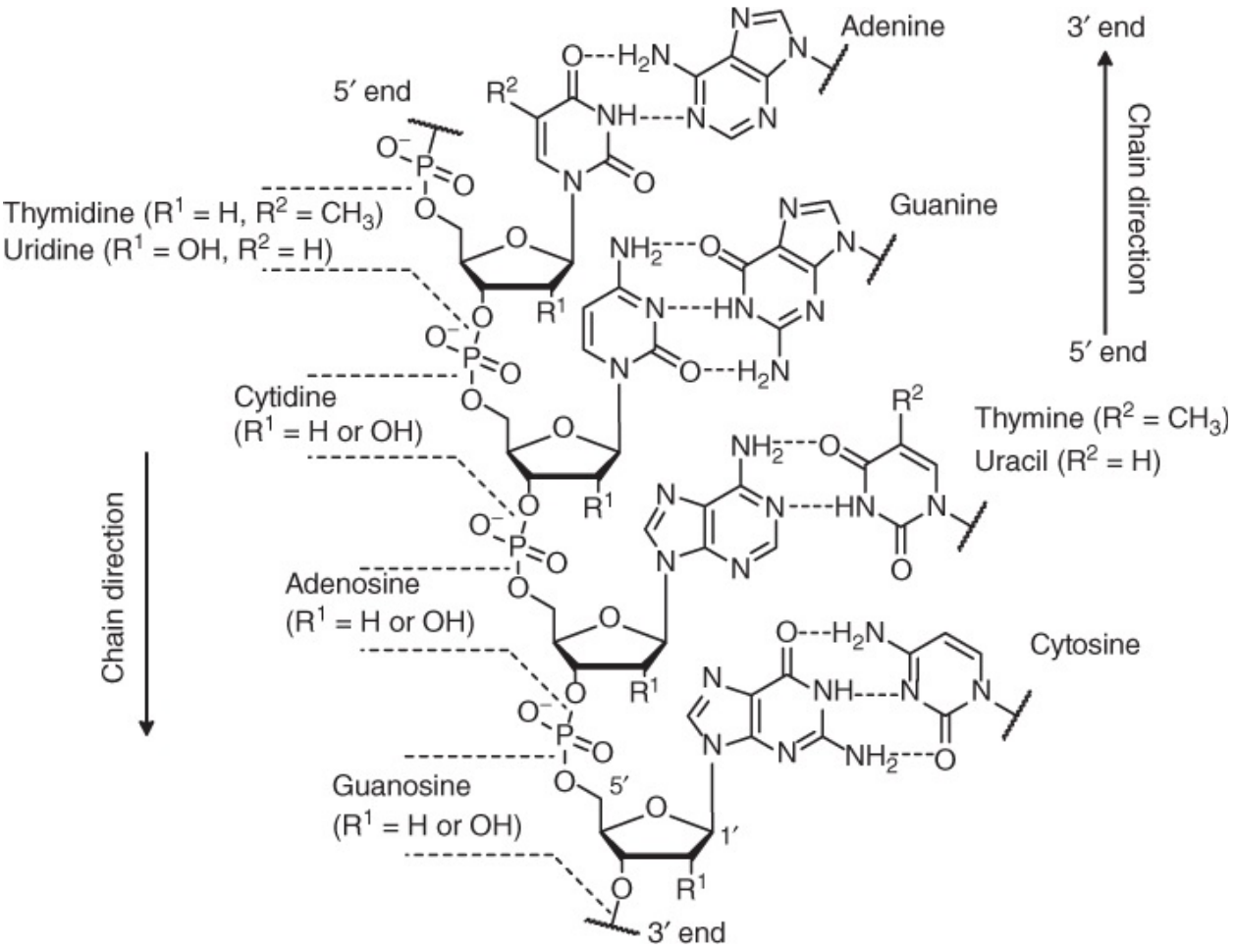
4.4 Nucleotides and Oligonucleotides

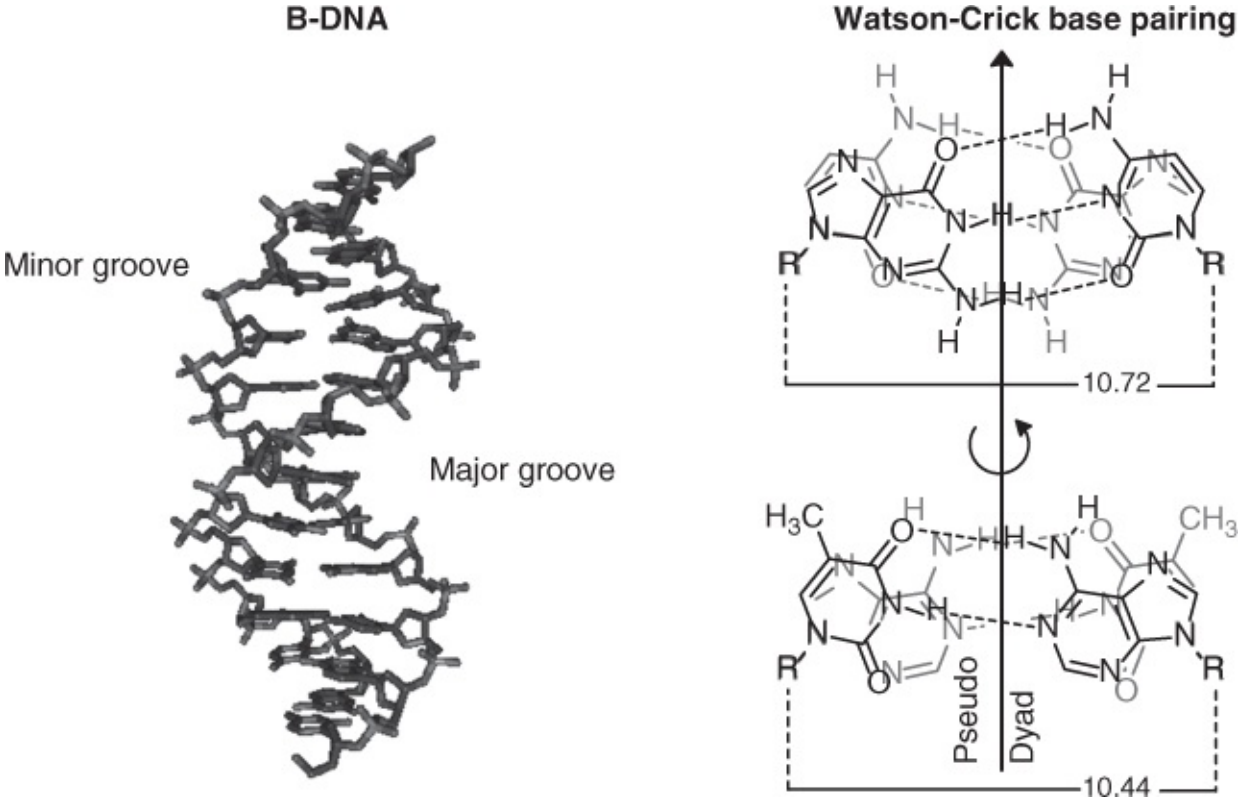
Introduction

The most important function of deoxyribonucleic acid (DNA) is the storage and

replication of information [1]. The complete instruction for the construction of cells and living organisms is coded in genes. Besides coding information, DNA also has structural and regulating functions. Genetic information is encoded in the sequential order of the four nucleobases adenine, guanine, cytosine (in DNA and RNA (ribonucleic acid)), and thymine (in DNA) or uracil (in RNA), which are linked together on a linear backbone polymer that consists of 2-deoxyribose (in DNA) or ribose (in RNA) units linked by phosphodiesters. The nucleobases can be classified in two subgroups purine (adenine and guanine) and pyrimidine (cytosine, thymine, and uracil) nucleobases. Nucleosides are the structural motifs consisting of a nucleobase bound to the anomeric center (C1′) of a deoxyribose or ribose sugar by a β-*N*-glycosidic bond yielding deoxyribonucleosides (in DNA) or ribonucleosides (in RNA). They are called *adenosine*, ***guanosine***, ***cytidine*** (in DNA and RNA), ***thymidine*** (in DNA), and ***uridine*** (in RNA). Nucleotides are the repeating units of a DNA or RNA polymer comprising deoxyribose or ribose, a phosphate group at the primary 5′-OH, and a purine or pyrimidine nucleobase attached to the sugar moiety (see above). Thus, a nucleotide can also be referred to as a ***nucleoside phosphate*** [2]. DNA polymers made from repeating nucleotides can reach an enormous length, for example, the largest human chromosome contains 220 million nucleotides.

For replication of information, the complementarity of nucleobase recognition is essential. Guanine is specifically recognized by cytosine (in DNA and RNA), forming three hydrogen bonds, whereas adenine and thymine (in DNA) or adenine and uracil (in RNA) provide the second base pair with only two hydrogen bonds, respectively. Both base pairs require an identical size and orientation of the deoxyribose linkages, regardless of purine–pyrimidine or pyrimidine–purine alignment. By this pseudosymmetry of Watson–Crick base pairing, it is ensured that all DNA sequences are possible without disturbing the overall helical structure [3]. The resulting helix topology, on the other hand, defines space and orientation of base pairs in DNA, allowing only the purine–pyrimidine combination and the Watson–Crick pairing mode. Of a number of alternative possibilities for hydrogen-bond recognition between nucleobases, the helix DNA topology leads to a restriction to the Watson–Crick mode and is, therefore, decisive for base pair complementarity and specific replication.

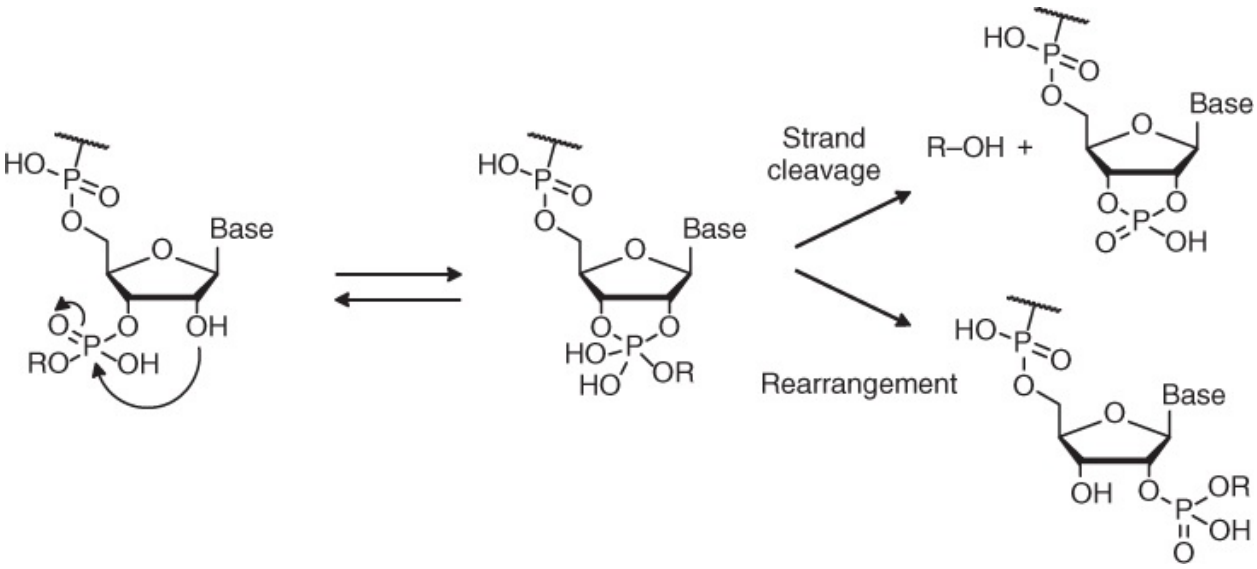

Adenine
3′ end
5′ end
Chain direction
5′ end
Thymidine (R^1 = H, R^2 = CH_3)
Uridine (R^1 = OH, R^2 = H)
Guanine
Cytidine
(R^1 = H or OH)
Thymine (R^2 = CH_3)
Uracil (R^2 = H)
Chain direction
Adenosine
(R^1 = H or OH)
Cytosine
Guanosine
(R^1 = H or OH)
3′ end



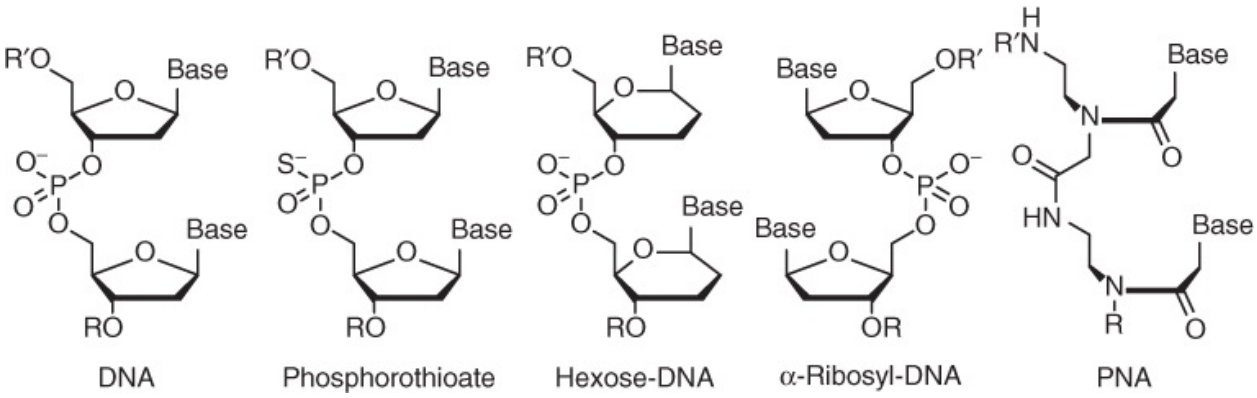
The antiparallel recognition of two complementary DNA strands leads to a right-handed double helix [4]. Besides specific hydrogen bonding between the nucleobases, aromatic stacking interactions and solvent effects contribute nearly equally to the overall stability of a DNA double strand. Stacking of nucleobases occurs with a preferred distance of 3.4 Å, which determines the overall helix structure. The DNA double helix provides a major groove and a smaller minor groove. Small molecules and proteins typically interact with DNA by specifically recognizing the respective hydrogen-bonding pattern of the nucleobase pairs in the grooves, intercalating between base pairs, or nonspecifically interacting with the negatively charged DNA backbone. Depending on the environment, DNA helices are able to adopt different conformations. The most prominent secondary structure is the B-form DNA double helix. However, there are also other left-handed helices, such as A, C, and D-DNA, which differ in the thickness of the helix, base pair stacking, and the size and depth of the grooves. In addition, for Z-DNA, a right-handed DNA double helix is also known. The different helix conformations provide an additional recognition motif besides base pair recognition, since there are proteins that require a specific DNA helix secondary structure for interaction and recognition. Furthermore, DNA double strands are highly dynamic structures that, for example, partially unwind, especially at their termini, where hydrogen bonds between base pairs are cleaved and reformed again. As a consequence of

interactions with small molecules, unwinding, bending, base flipping, or other conformational changes are regularly observed. The double helical structure is forced to be extended by repulsion between phosphodiester charges that are uniformly distributed over the helix. Selective charge neutralization at certain points, as provided by cations or cationic amino acids such as lysine or arginine, induces a bend in the DNA double helix. This kind of bending is an important mechanism with regard to the efficient packing of DNA in cells or viruses.

Besides DNA, there is another nucleic acid called ***ribonucleic acid*** which differs from DNA in that 2-deoxyribose is replaced by ribose as the sugar component and that thymine is replaced by uracil as one of the nucleobases, see above [5]. RNA plays an important role in the translation of genetic information from DNA into proteins. The transcription of the information from DNA into messenger RNA is followed by a transport of an RNA copy out of the nucleus as a source of information for further processing. Translation into proteins with the help of transfer RNA is the final step in translating the genetic code into an amino acid sequence in the ribosome, finally yielding proteins. With respect to the secondary structure, RNA oligomers form double strands like DNA, but in addition RNA can fold into a variety of motifs. The possibility of adopting various folded forms allows RNA to take over many biological functions and to act as artificial RNA-based enzymes called ***ribozymes***. The 2′-hydroxy group on the sugar moiety has an influence on the ribosyl conformation, thereby affecting the folding process, but it is also responsible for a significant decrease in the stability of RNA compared to DNA oligomers. Intramolecular attack of the 2′-OH on the neighboring phosphorus results in a phosphotriester that can be cleaved by the reverse reaction, by rearrangement to the 2′-linked RNA, or by strand cleavage leading to the cyclophosphate. The shorter lifetime of an RNA oligomer is important from the biological point of view because RNA molecules are intermediate transporters of information or function.



With the accessibility of DNA and RNA by organic synthesis, interest in modifications of oligonucleotides has also grown. Modified oligonucleotides with nuclease resistance and complementarity for a given oligonucleotide sequence are promising for diagnostic purposes as well as in *antigene* (interaction with the DNA double strand) or *antisense* (complementarity to an RNA single strand) therapies, blocking the complementary oligonucleotide sequence of interest and allowing genetic disorders to be translated to the protein level [6]. The recognition of double-stranded DNA by a third oligonucleotide strand is known to proceed in the major groove, especially by interaction with a purine-rich central strand by formation of specific hydrogen bonds on the so-called purine Hoogsteen face [7]. Based on the promising *antigene*/*antisense* idea, numerous DNA and RNA modifications have been investigated by varying the phosphodiester, the ribose moiety, or the nucleobase. As the first *antigene*/*antisense* therapeutics, phosphorothioates have been used in clinical trials [8]. In these compounds, one oxygen atom is replaced by sulfur atom. Hexose DNA is chosen as a representative of a modification in which an additional methylene group is introduced in the sugar moiety as compared to DNA [9]. This results in a six-membered sugar with a preferred chair conformation, which has consequences for the overall oligonucleotide topology. Many more conformationally constrained ribosyl derivatives have been investigated, especially with an emphasis on selective recognition of DNA and RNA, respectively.



Further modifications of DNA include α-ribosyl DNA, the enantiomer of naturally occurring DNA, and aminoethylglycine peptide nucleic acid (PNA), in which the ribosyl-phosphodiester backbone of DNA is completely substituted by a noncharged, nonchiral polyamide [10]. PNA oligomers are well suited to mimic DNA strands. DNA–PNA, RNA–PNA, and PNA–PNA double strands show high stability and structurally closely resemble the respective DNA–DNA or RNA–DNA double strands.

References

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9. Eschenmoser, A. and Dobler, M. (1992) 218–259. *Helv. Chim. Acta*, 75.

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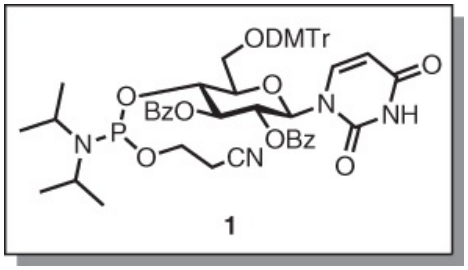
4.4.1 2′,3′-Dibenzoyl-6′-*O*-DMTr-β-D-glucopyranosyl-uracil 4′-*O*-phosphoramidite



1

Topics:

- Vorbrüggen and Hilbert–Johnson nucleosidation
- Phosphoramidite synthesis
- Solid-phase linkage of nucleosides
- Glucopyranosyl protection

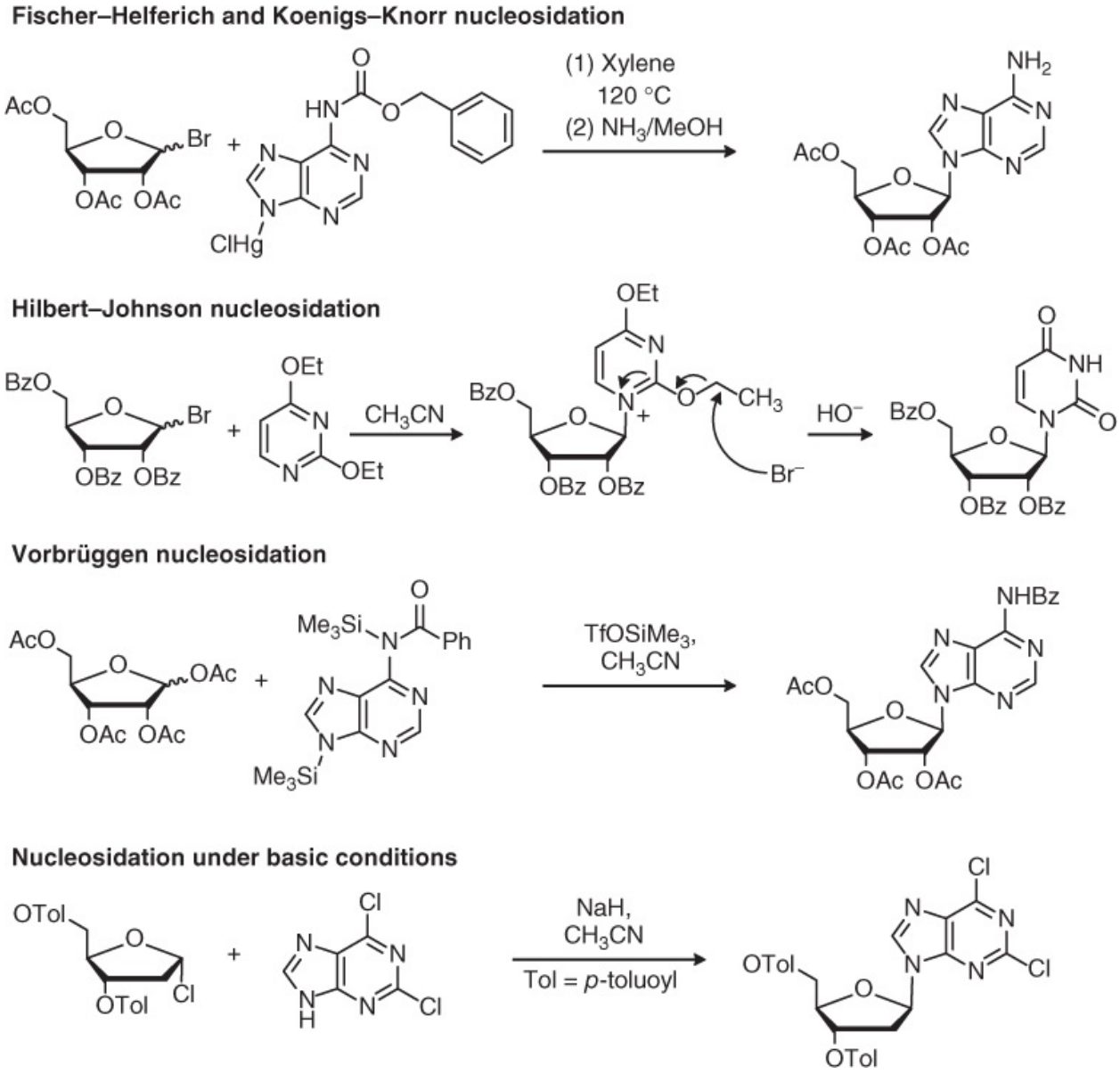
(a) General

Deoxyribosyl and ribosyl nucleotides with the canonical nucleobases guanine, adenine, cytosine, as well as thymine and uracil, respectively, are used for solid-phase DNA synthesis by the phosphoramidite strategy and are commercially available [1]. Nevertheless, the preparation of phosphoramidite building blocks, especially for the synthesis of oligonucleotides with nucleobase or sugar modifications, is still a major concern [2]. The key step in the formation of nucleosides and nucleotides is the nucleosidation reaction linking the nucleobase to the anomeric center of the sugar moiety [3]. Besides the nucleosidation reaction, nucleosides can be obtained by an alternative route building up the heterocycle in the presence of the sugar moiety.

General problems associated with the nucleosidation reaction are stereoselectivity and regioselectivity; on the other hand, poor nucleophilicity as well as simultaneous solubility of the nucleobases and sugar building blocks and low stability of the sugar donor are often troublesome. Nucleophilic addition of pyrimidines proceeds with low regioselectivity with respect to N-1 and N-3.

Purine nucleosides are formed in comparable amounts as the N-7 and N-9 regioisomers. Furthermore, the stereochemistry at the anomeric center is difficult to control. Neighboring group participation by an ester group in place of the hydroxyl group at C-2 can be used to direct the nucleophilic attack so that exclusively β-isomers are generated. Without neighboring group participation, the anomeric effect is not sufficient to provide α-anomeric products with reasonable selectivity; thus, the formed α/β-anomeric mixtures often need to be separated, which is not always an easy task.

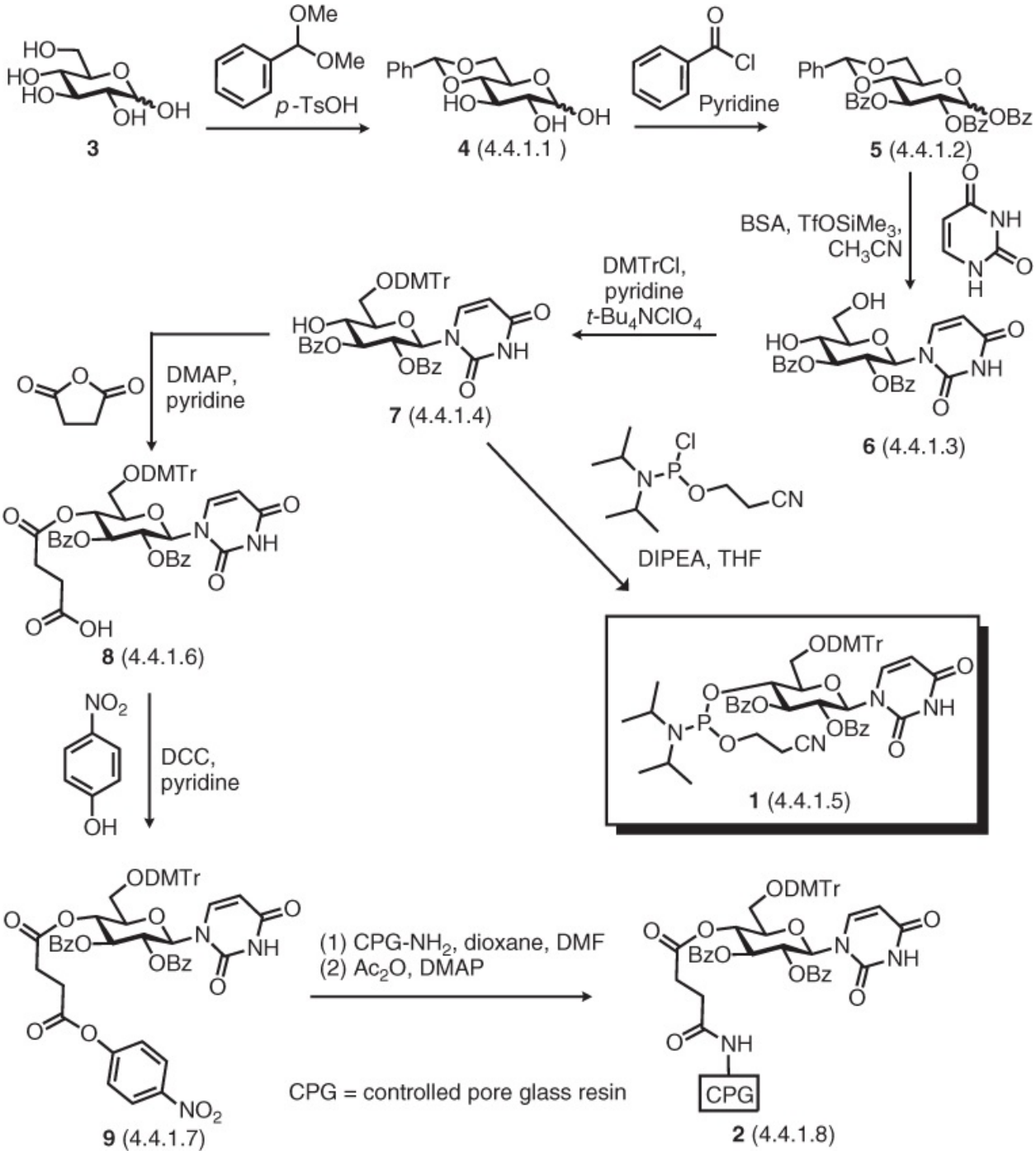
Four fundamentally different methods for nucleosidation reactions are known in the literature: (i) The Fischer–Helferich and Koenigs–Knorr procedures are based on Ag^{+} or Hg^{2+} heavy metal salts of the nucleobases substituting a halogen at the anomeric center. Low solubility of the nucleobase salts, fast hydrolysis of the ribosyl halogenides, and harsh reaction conditions limit the utility of these methods [4]. (ii) The Hilbert–Johnson nucleosidation employs alkylated nucleobases, which are sufficiently nucleophilic to substitute bromo sugars [5]. The generated quaternary salts offer a gentle means of introducing the nucleobase functionalities. (iii) The silyl version of the Hilbert–Johnson method is called *Vorbrüggen nucleosidation* [6]. Silylated nucleobases are used, which exhibit increased solubility. They are usually reacted with peracylated sugars in the presence of a strong Lewis acid such as $SnCl_4$ or $TfOSiMe_3$. The intermediately generated sugar halogenides or triflates are the true electrophiles, although there is a strong S_N1 contribution due to the possible formation of an intermediate oxocarbenium ion. The silyl groups on the nucleobase are cleaved during the coupling reaction. Silylation of the nucleobases is often performed *in situ* using hexamethyldisilazane with Me_3SiCl or *N*,*O*-bis(trimethylsilyl)acetamide (BSA). (iv) Finally, nucleosidation under basic conditions using NaH to deprotonate the nucleobase has been described by Kazimierczuk [7].



(b) Synthesis of 1

As an example of the synthesis of an artificial DNA analog, that of the glucopyranosyl phosphoramidite **1** is described, in which the monomeric unit for an oligonucleotide synthesis is generated on a solid support (cf. **4.4.1.2**). Furthermore, the preparation of a glucopyranosyl nucleoside linked to a controlled pore glass (CPG) support **2** is presented. In general, the well-documented synthesis protocols of ribosyl or deoxyribosyl phosphoramidites can be adapted to the preparation of glucopyranosyl nucleotides by applying harsher reaction conditions [8]. Starting from D-glucose (**3**), regioselective acetal protection is followed by benzoylation to give **5** via **4**. Nucleosidation of **5** with

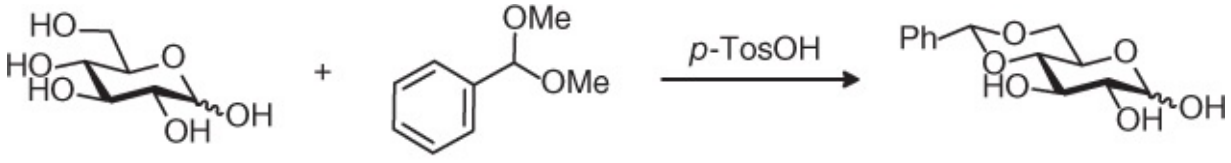
uracil under Vorbrüggen conditions is performed with bis(trimethylsilyl)acetamide (BSA) by *in situ* silylation under the assistance of $TfOSiMe_3$. The strongly acidic conditions simultaneously lead to acetal deprotection, resulting in the nucleoside **6**. The β-anomer of the N-1 regioisomer is obtained as the major isomer. The primary hydroxyl group of **6** is selectively protected as the 4,4′-dimethoxytrityl ether (DMTr) to form **7**, from which the phosphoramidite **1** is generated by nucleophilic substitution.



The CPG-bound nucleoside **2** is available from **7** by first using succinic anhydride to establish a linker that can be attached by DMAP activation. The resulting acid **8** is activated as *p*-nitrophenyl ester **9** and bound to the CPG resin as an amide. Finally, acylation of all remaining amino functionalities on the resin with acetic anhydride and DMAP is required as a capping step. The nucleoside-loaded CPG support **2** is used in solid-phase synthesis (cf. **4.4.2.1**).

(c) Experimental Procedures for the Synthesis of 1

4.4.1.1	*	**D-(4,6-Benzylidene)-glucose** [9]



180.2 152.2 268.3

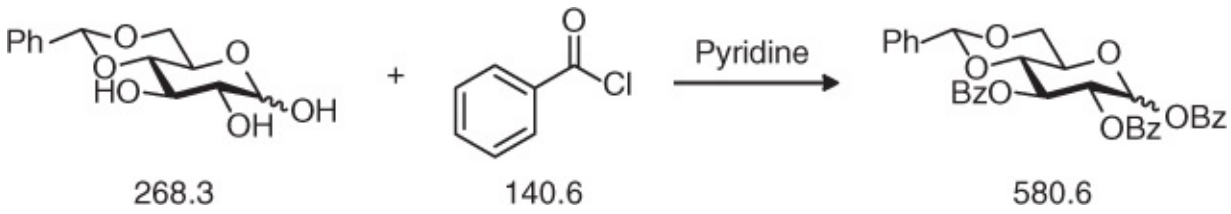
Benzaldehyde dimethyl acetal (3.31 ml, 22.2 mmol) is added to a suspension of D-glucose (2.00 g, 11.1 mmol) and *p*-toluenesulfonic acid (422 mg, 2.22 mmol, dried under high vacuum) in anhydrous DMF (32.0 ml) under an argon atmosphere. The mixture is heated until a solution is obtained, then stirred at room temperature for 2 h, after which Na_2CO_3 (5.00 g) is added. After stirring for 30 min, the solid is filtered off and washed with DMF. Evaporation of the solvent from the combined filtrate and washings is followed by flash chromatography (SiO_2, EtOAc). The light yellow oil obtained is dissolved in $CHCl_3$ (4.00 ml) and precipitated by the addition of ice-cold *n*-hexane (20.0 ml). The precipitate is crystallized (acetone/MeOH, 10 : 1) to give the product as a white solid; 1.82 g (61%); the ^{1}H NMR spectrum shows the existence of two anomers in the ratio α : β = 3 : 2; TLC (SiO_2; EtOAc/MeOH, 9 : 1): R_f = 0.58; $[\alpha]^{20}_D$ = −4.8 (*c* = 1.83, EtOH).

^{1}H NMR (300 MHz, CD_3OD): δ (ppm) = 7.43–7.56 (m, 2H, Ph), 7.25–7.38 (m, 3H, Ph), 5.56 (s, 1H, 7-H), 5.13 (d, 0.6H, *J* = 3.6 Hz, 1-H_α), 4.60 (d, 0.4H, *J* = 7.7 Hz, 1-H_β), 4.23 (dd, 0.4H, *J* = 11.3, 4.5 Hz, 6-H_β), 4.18 (dd, 0.6H, *J* = 9.9, 4.8 Hz, 6-H_α), 3.97 (dt, 0.6H, *J* = 11.8, 4.9 Hz, 5-H_α), 3.87 (t, 0.6H, *J* = 9.3 Hz), 3.58–3.81 (m, 1.4 H), 3.39–3.50 (m, 2H), 3.24 (dd, 0.4H, *J* = 8.8, 7.7 Hz, 2-H_β).

^{13}C NMR (50 MHz, CD_3OD): δ (ppm) = 139.6 (Ph), 139.5, 130.2 (Ph), 129.4, 127.9, 103.3 (C-7), 103.2, 99.2, 95.0, 83.4, 82.7, 77.5, 75.0, 74.7, 72.1, 70.5 (C-6), 70.0, 68.0, 63.8.

MS (FAB^+, 3-NOBA): *m*/*z* = 269 (100) $[M+H]^+$.

4.4.1.2 * D-(4,6-Benzylidene-1,2,3-tribenzoyl)-glucose [9]



Benzoyl chloride (4.28 g, 30.5 mmol) is added over 5 min to a stirred solution of benzylidene glucose (cf. **4.4.1.1**) (1.82 g, 6.77 mmol) in anhydrous pyridine (25.0 ml) at 0 °C under an argon atmosphere. The mixture is stirred for 2 h at room temperature, cooled to 0 °C, and the reaction is quenched by the addition of MeOH (2 ml). After almost complete removal of the solvent *in vacuo*, the residue is taken up in EtOAc (200 ml) and the solution obtained is extracted with saturated aqueous $NaHCO_3$ solution (100 ml) and brine (100 ml). The aqueous phases are re-extracted with EtOAc (100 ml), the combined organic phases are dried over Na_2SO_4 and filtered, and the solvent is removed *in vacuo*. Traces of pyridine are removed from the residue by co-evaporation with toluene (2 × 10 ml). Flash chromatography of the residue (SiO_2, *n*-hexane/EtOAc, 4 : 1) provides the product as a diastereomeric mixture of α : β = 0.56 : 0.44 (determined by ^{1}H NMR spectroscopy); 3.39 g (86%); TLC (SiO_2; EtOAc/hexane, 2 : 1): R_f = 0.64; $[\alpha]^{20}_D$ = −99.6 (*c* = 2.15, $CHCl_3$).

UV (EtOH): λ_{max} (log ϵ) = 230 nm (4.46).

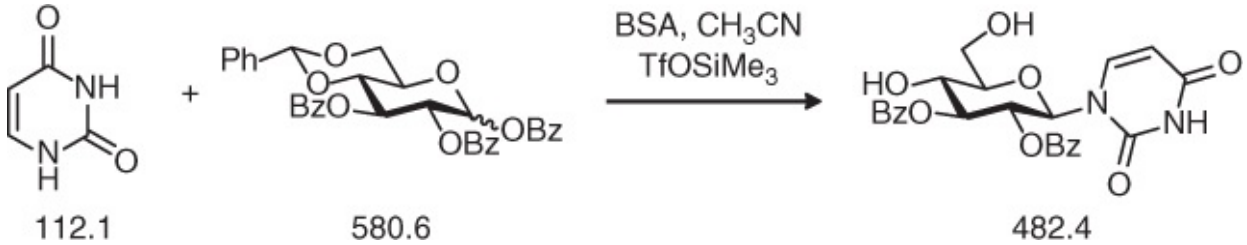
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.14 (m, 1H, Ar–H), 8.00 (m, 3H, Ar–H), 7.93 (m, 2H, Ar–H), 7.61 (m, 1H, Ar–H), 7.23–7.59 (m, 13H, Ar–H), 6.77 (d, 0.56H, *J* = 3.8 Hz, 1-H_α), 6.23 (d, 0.44H, *J* = 7.9 Hz, 1-H_β), 6.20 (t, 0.56H, *J* = 10.0 Hz, 3-H_α), 5.92 (t, 0.44H, *J* = 9.2 Hz, 2-H_β, 3-H_β), 5.80 (t, 0.44H, *J* = 7.9 Hz, 2-H_β, 3-H_β), 5.62 (dd, 0.56H, *J* = 10.0, 3.8 Hz, 2-H_α), 5.61 (s, 0.56H, 7-H_α), 5.58 (s, 0.44H, 7-H_β), 4.49 (dd, 0.44H, *J* = 9.4, 3.8

Hz, 6-H_β), 4.40 (dd, 0.56H, *J* = 10.3, 4.9 Hz, 6-Hα), 4.28 (dt, 0.56H, *J* = 9.9, 4.9 Hz, 5-H_α), 4.06 (t, 1H, *J* = 9.7 Hz, 4-H, 6-H), 4.95 (dt, 0.44H, *J* = 9.6, 4.3 Hz, 5-H_β), 3.88 (t, 1H, *J* = 10.1 Hz, 4-H, 6-H).

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 165.7, 165.5, 165.3, 164.6, 136.7, 133.9, 133.6, 133.5, 130.2, 130.1, 129.8, 129.6, 129.4, 129.3, 129.1, 128.9, 128.7, 128.6, 128.4, 128.2, 126.1, 101.7, 93.1, 90.5, 78.9, 78.6, 72.0, 71.5, 70.9, 69.6, 68.6 (C-6), 68.5, 67.4, 65.4.

MS (FAB^+, 3-NOBA): *m/z* = 581 (3) $[M+H]^+$, 580 (4) $[M]^+$, 579 (9) $[M-H]^+$, 475 (3) $[M-Bz]^+$.

4.4.1.3	***	**(2,3-Dibenzoyl-β-D-glucopyranosyl)-uracil** [9]



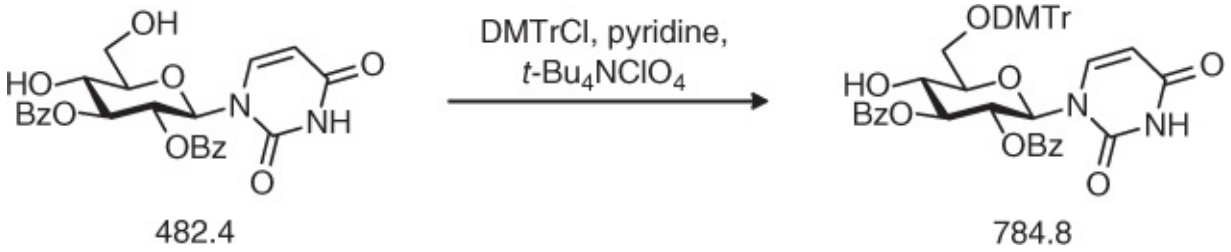
Bis(trimethylsilyl)acetamide (BSA) (7.34 ml, 30.0 mmol) is added to a stirred suspension of uracil (1.12 g, 10.0 mmol) and the glucose derivative **4.4.1.2** (6.39 g, 11.1 mmol) (both are dried overnight under high vacuum at room temperature) in anhydrous CH_3CN (30 ml) at room temperature under an argon atmosphere. Stirring is continued for 30 min at 100 °C until a homogeneous solution is obtained. After the addition of TMSOTf (3.63 ml, 20 mmol), the reaction mixture is stirred for 4.5 h at 100 °C, with an additional portion of TMSOTf (3.63 ml, 20.0 mmol) being added after 1 h. Thereafter, the solvent is removed *in vacuo*, the yellow oil obtained is dissolved in EtOAc (100 ml), and this solution is washed twice with a saturated aqueous $NaHCO_3$ solution and with brine (each 100 ml). The aqueous phases are re-extracted with EtOAc (100 ml), the combined organic phases are dried over Na_2SO_4, and filtered. Removal of the solvent and flash chromatography of the residue (SiO_2, EtOAc/hexane, 2 : 1) provides the desired nucleoside after crystallization from acetone; 3.03 g (63%); TLC (SiO_2; EtOAc): R_f = 0.40; mp 158 °C; $[\alpha]^{20}_D$ = 100.0 (*c* = 0.60, EtOH).

^{1}H NMR (300 MHz, [D_6]DMSO): δ (ppm) = 11.33 (s_{br}, 1H, NH), 7.97 (d, 1H, *J* = 8.2 Hz, 6-H), 7.88 (d, 2H, *J* = 7.1 Hz, Ar–H), 7.76 (d, 2H, *J* = 7.1 Hz, Ar–H), 7.58–7.63 (m, 2H, Ar–H), 7.42–7.50 (m, 4H, Ar–H), 6.10 (d, 1H, *J* = 9.0 Hz, 1′-H), 5.74 (m, 2H, 5-H, 4′-OH), 5.65 (t, 1H, *J* = 9.2 Hz, 3′-H), 5.53 (t, 1H, *J* = 9.3 Hz, 2′-H), 4.77 (t, 1H, *J* = 5.6 Hz, 6′-OH), 3.78–3.90 (m, 3H, 4′-H, 5′-H, 6′-H), 3.58 (m, 1H, 6′-H).

^{13}C NMR (100 MHz, [D_6]DMSO): δ (ppm) = 165.1, 164.6, 162.6 (C-4), 150.3 (C-2), 141.1 (C-6), 133.8 (Bz), 133.3, 129.4 (Bz), 129.1 (Bz), 129.0, 128.7, 128.5, 128.2 (Bz), 102.3 (C-5), 79.6 (C-1′), 79.3 (C-5′), 75.7 (C-3′), 71.2 (C-2′), 67.0 (C-4′), 60.5 (C-6′).

MS (FAB$^+$, 3-NOBA): *m*/*z* = 483 (17) $[M+H]^+$.

4.4.1.4	**	**(2,3-Dibenzoyl-6-*O*-(dimethoxytrityl)-β-D-glucopyranosyl)-uracil** [9]



482.4 784.8

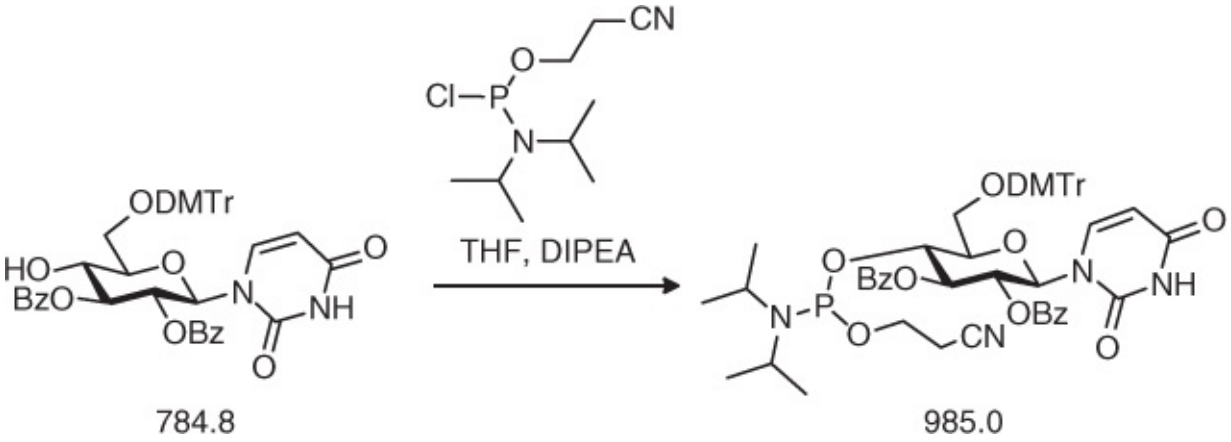
A mixture of the nucleoside **4.4.1.3** (2.00 g, 4.15 mmol), tetrabutylammonium perchlorate (1.70 g, 4.98 mmol), and 4,4′-Dimethoxytrityl chloride (1.69 g, 4.98 mmol) is dried under high vacuum at room temperature and then dissolved under an argon atmosphere in anhydrous pyridine (15.0 ml). The initially deep orange and later dark yellow solution is stirred for 90 min at room temperature. The reaction is then quenched by the addition of MeOH (2 ml), and stirring is continued for 10 min. The mixture is concentrated *in vacuo*, the residue is dissolved in EtOAc (50 ml), and the resulting solution is washed with a saturated aqueous $NaHCO_3$ solution and brine (each 2 × 50 ml). The combined aqueous phases are extracted with EtOAc (50 ml), the combined organic phases are dried over Na_2SO_4 and filtered, and the solvent is removed *in vacuo*. The residue is purified by flash column chromatography on silica gel (EtOAc/hexane, 2 : 3) to provide the desired nucleoside as a light yellow foam; 2.81 g (86%); TLC (SiO_2; EtOAc/hexane, 1 : 1): R_f = 0.30; mp 142 °C; $[\alpha]^{20}_D$ = 50.3 (*c* = 1.55, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.85 (s_{br}, 1H, NH), 7.93 (dd, *J* = 8.4, 1.3 Hz, 2H, Bz), 7.85 (dd, *J* = 8.4, 1.3 Hz, 2H, Bz), 7.39–7.60 (m, 5H, Bz, DMTr, 6-H), 7.21–7.37 (m, 11H, Bz, DMT), 6.82 (dd, *J* = 9.0, 1.2 Hz, 4H, DMTr), 6.07 (d, *J* = 9.3 Hz, 1H, 1′-H), 5.80 (d, *J* = 9.3 Hz, 1H, 5-H), 5.66 (t, *J* = 9.4 Hz, 1H, 3′-H), 5.50 (t, *J* = 9.5 Hz, 1H, 2′-H), 4.09 (t, *J* = 9.4 Hz, 1H, 4′-H), 3.85 (m, 1H, 5′-H), 3.77 (s, 6H, 2 × OCH_3), 3.49 (m, 2H, 6′-H), 3.22 (s_{br}, 1H, 4′-OH).

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 166.6, 165.5, 162.4, 158.7 (DMTr), 150.1 (C-2), 144.4 (DMT), 139.2 (C-6), 135.5, 133.8 (Bz), 133.6, 130.0, 129.9, 129.6, 129.2, 128.9, 128.4, 128.1, 128.0, 127.1, 113.3, 86.8 (DMTr), 80.6 (C-1′), 77.8, 76.0, 70.5, 70.1, 63.1 (C-6′), 55.2 (OCH_3).

MS (FAB$^+$, 3-NOBA): *m*/*z* = 785 (1) $[M+H]^+$, 784 (2) $[M]^+$.

4.4.1.5	***	**(2,3-Dibenzoyl-6-*O*-(dimethoxytrityl)-β-D-glucopyranosyl)-uracil 4-*O*-((2-cyanoethyl)-*N*,*N*-diisopropylamino-phosphoramidite)** [9]



DIPEA (663 µl, 3.82 mmol) and 2-cyanoethyl *N*,*N*-diisopropylchlorophosphoamidite (452 µl, 1.91 mmol) are successively added to a stirred solution of the nucleoside **4.4.1.4** (1.00 g, 1.27 mmol) in anhydrous THF (9 ml) under argon atmosphere. Stirring is continued for 2.5 h at room temperature. EtOAc (50 ml) is then added, and the reaction mixture is washed with a saturated aqueous $NaHCO_3$ solution (2 × 50 ml) and brine (2 × 50 ml). The aqueous phases are extracted with EtOAc (50 ml), the combined organic phases are dried over Na_2SO_4 and filtered, and the solvent is removed *in vacuo*. The residue is purified

by flash column chromatography on silica gel (EtOAc/hexane, 2 : 3). After removal of the solvent *in vacuo*, the oily product is dissolved in CH_2Cl_2 and the solvent is evaporated to give the desired phosphoramidite as a white foam (1 : 1 mixture of diastereomers); 1.09 g (87%); TLC (SiO_2; EtOAc/hexane, 2 : 3): $R_{f(1)}$ = 0.22, $R_{f(2)}$ = 0.28; $[\alpha]^{20}_D$ = 73.7 (*c* = 1.90, $CHCl_3$).

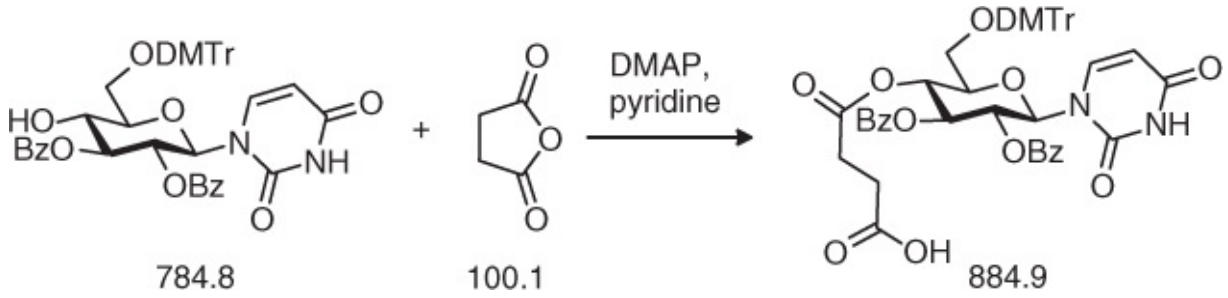
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.42 (s_{br}, 1H, NH), 7.99 (d, *J* = 8.5 Hz, 1H, Bz), 7.91 (d, *J* = 8.5 Hz, 1H, Bz), 7.89 (d, *J* = 8.5 Hz, 1H, Bz), 7.86 (d, *J* = 8.5 Hz, 1H, Bz), 7.62 (d, *J* = 8.2 Hz, 0.5H, 6-H), 7.56 (d, *J* = 8.2 Hz, 0.5H, 6-H), 7.45–7.54 (m, 3H, Bz), 7.41 (m, 1H, Bz), 6.78–6.85 (m, 4H, DMTr), 6.11 (d, *J* = 9.3 Hz, 0.5H, 1′-H), 6.09 (d, *J* = 9.3 Hz, 0.5H, 1′-H), 5.88 (d, *J* = 8.3 Hz, 0.5H, 5-H), 5.86 (d, *J* = 8.3 Hz, 0.5H, 5-H), 5.86 (t, *J* = 9.3 Hz, 0.5H, 3′-H), 5.81 (t, *J* = 9.3 Hz, 0.5H, 3′-H), 5.54 (t, *J* = 9.5 Hz, 0.5H, 2′-H), 5.42 (t, *J* = 9.5 Hz, 0.5H, 2′-H), 4.38 (q, *J* = 9.8 Hz, 0.5H, 4′-H), 4.18 (q, *J* = 9.8 Hz, 0.5H, 4′-H), 3.98 (dd, *J* = 9.7, 4.0 Hz, 0.5H, 5′-H), 3.87 (dd, *J* = 9.7, 2.0 Hz, 0.5H, 5′-H), 3.79 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.64 (t, *J* = 9.7 Hz, 1H, 6′-H), 3.49 (m, 0.5H, 6′-H), 3.41 (m, 0.5H, 6′-H), 3.35 (m, 2H, CH_2O), 3.29 (m, 1H, CH*i*-Pr), 3.20 (m, 1H, CH*i*-Pr), 2.25 (m, 1H, CH_2CN), 2.08 (m, 0.5H, CH_2CN), 2.02 (m, 0.5H, CH_2CN), 0.86–0.92 (m, 12H, CH_3*i*-Pr).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 165.5, 165.4, 162.2 (C-4), 158.6 (DMTr), 158.5, 150.0 (C-2), 144.8 (DMTr), 144.7, 139.5 (C-6), 139.4, 136.1, 135.9, 135.6, 133.7 (Bz), 133.2, 130.4, 130.3, 130.2, 130.0, 129.8, 129.7, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.8, 126.9, 117.3 (CN), 113.1 (DMTr), 103.4 (C5), 103.3, 86.3 (DMTr), 86.1, 80.7 (C-1′), 80.6, 78.8 (C-5′), 78.7, 75.2 (C-3′), 74.4, 70.9 (C-2′), 70.6, 70.5 (J_{CP} = 4.7 Hz, C-4′), 70.0 (J_{CP} = 6.6 Hz, C-4′), 63.2 (C-6′), 62.3 (C-6′), 57.7 (J_{CP} = 19.6 Hz, CH_2O), 57.6 (J_{CP} = 19.6 Hz, CH_2O), 55.2 (OCH_3), 43.0 (J_{CP} = 8.9 Hz, CH*i*-Pr), 42.9 (J_{CP} = 8.9 Hz, CH*i*-Pr), 24.4 (CH_3*i*-Pr), 24.3 (CH_3*i*-Pr), 24.2 (CH_3*i*-Pr), 19.9 (J_{CP} = 7.2 Hz, CH_2CN), 19.6 (J_{CP} = 7.6 Hz, CH_2CN).

^{31}P NMR (162 MHz, $CDCl_3$): δ (ppm) = 151.3, 150.0.

MS (FAB^+, 3-NOBA): 985 (0.4) $[M+H]^+$.

4.4.1.6	*	**(2,3-Dibenzoyl-6-*O*-(dimethoxytrityl)-β-D-glucopyranosyl)-uracil 4-*O*-(succinylacid)-ester** [9]



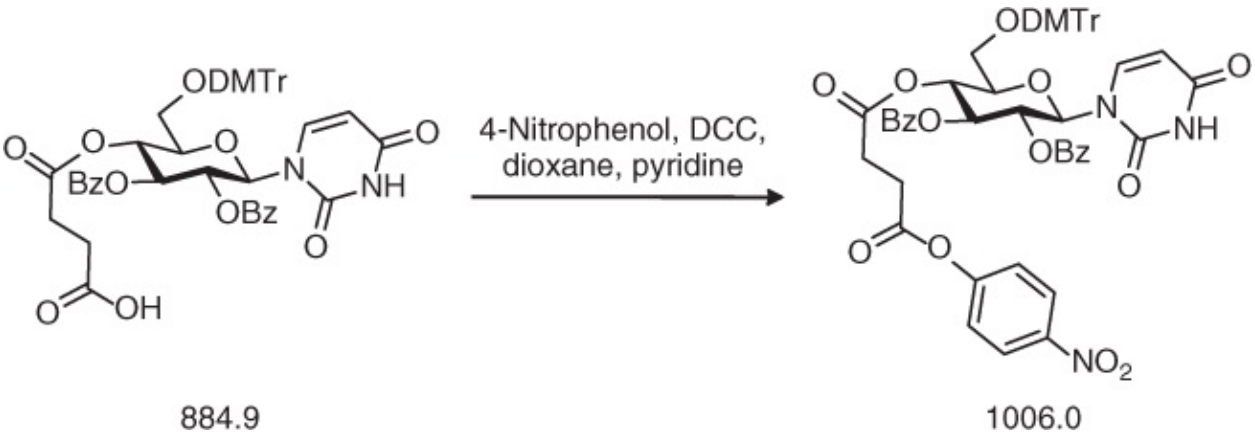
A solution of the nucleoside **4.4.1.5** (392 mg, 500 µmol), DMAP (73 mg, 0.60 mmol), and succinic anhydride (55 mg, 0.55 mmol) in anhydrous pyridine (4 ml) is stirred for 6 h at 60 °C. The pyridine is then distilled off *in vacuo* and any remaining pyridine is removed from the residue by co-evaporation with toluene (2 × 10 ml). The white foam is dissolved in CH_2Cl_2 (20 ml), and this solution is washed with a cooled solution of 10% aqueous citric acid (20 ml) and with H_2O (20 ml). The aqueous phases are extracted with CH_2Cl_2 (10 ml), the combined organic phases are dried over $MgSO_4$ and filtered, and the solvent is removed *in vacuo* to yield the product as a white foam; 442 mg (99%); TLC (SiO_2; EtOAc/hexane, 2 : 1): R_f = 0.31; mp 136 °C; $[\alpha]^{20}_D$ = 97.2 (*c* = 1.82, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.96 (s_{br}, 1H, NH), 7.84 (m, 4H, Bz), 7.57 (d, *J* = 8.3 Hz, 1H, 6-H), 7.42 (m, 4H, Bz, DMTr), 7.28 (m, 10H, Bz, DMTr), 7.19 (m, 1H, Bz, DMTr), 6.80 (dd, *J* = 9.0, 1.7 Hz, 4H, DMTr), 6.13 (d, *J* = 9.2 Hz, 1H, 1′-H), 5.86 (d, *J* = 8.2 Hz, 1H, 5-H), 5.82 (t, *J* = 9.7 Hz, 1H, 4′-H), 5.60 (t, *J* = 9.8 Hz, 1H, 2′-H, 3′-H), 5.55 (t, *J* = 9.5 Hz, 1H, 2′-H, 3′-H), 4.01 (d, *J* = 8.9 Hz, 1H, 5′-H), 3.75 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 3.40 (d, *J* = 9.3 Hz, 1H, 6′-H), 3.17 (dd, *J* = 10.9, 3.9 Hz, 1H, 6′-H), 2.28 (m, 4H, succinyl).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 175.6 (CO_2H), 170.4 (CO succinyl), 165.7 (CO), 165.3, 162.6 (C-4), 158.6 (DMTr), 150.1 (C-2), 144.2 (DMTr), 139.3 (C-6), 135.5, 135.4, 133.8 (Bz), 133.5, 130.1, 130.0, 129.8, 129.6, 128.6, 128.5, 128.4, 128.2, 128.0, 127.9, 127.0, 113.2 (DMTr), 103.6 (C-5), 86.3 (DMTr), 80.6 (C-1′), 76.5 (C-5′), 73.3 (C-3′), 70.6 (C-2′), 68.3 (C-4′), 63.5, 61.5 (C-6′), 55.2 (OCH_3), 28.8 (succinyl), 28.7.

MS (FAB$^-$, 3-NOBA): *m*/*z* = 884 (15) $[M]^-$, 883 (30) $[M-H]^-$.

4.4.1.7	*	**(2,3-Dibenzoyl-6-*O*-(dimethoxytrityl)-β-D-glucopyranosyl)-uracil 4-*O*-(succinylacid-4-nitrophenyl-ester)-ester** [9]



884.9 1006.0

A solution of Dicyclohexylcarbodiimide (DCC) (231 mg, 1.12 mol) in anhydrous dioxane (3.9 ml) is added to a stirred solution of the nucleoside **4.4.1.6** (382 mg, 432 µmol) and 4-nitrophenol (60 mg, 430 µmol) (dried overnight under high vacuum at room temperature before use) in anhydrous dioxane (2.5 ml) and anhydrous pyridine (178 µl) at room temperature under an argon atmosphere. After 2 h, the mixture is concentrated *in vacuo* and the residue is purified by flash chromatography on silica gel (EtOAc/hexane, 1 : 1). Evaporation of the solvent from the appropriate fraction and drying of the residue under high vacuum affords the desired active ester as a white solid, which is used directly for the next step; 355 mg (82%); TLC (SiO_2; EtOAc/*n*-hexane, 1 : 1): R_f = 0.33; mp 126 °C.

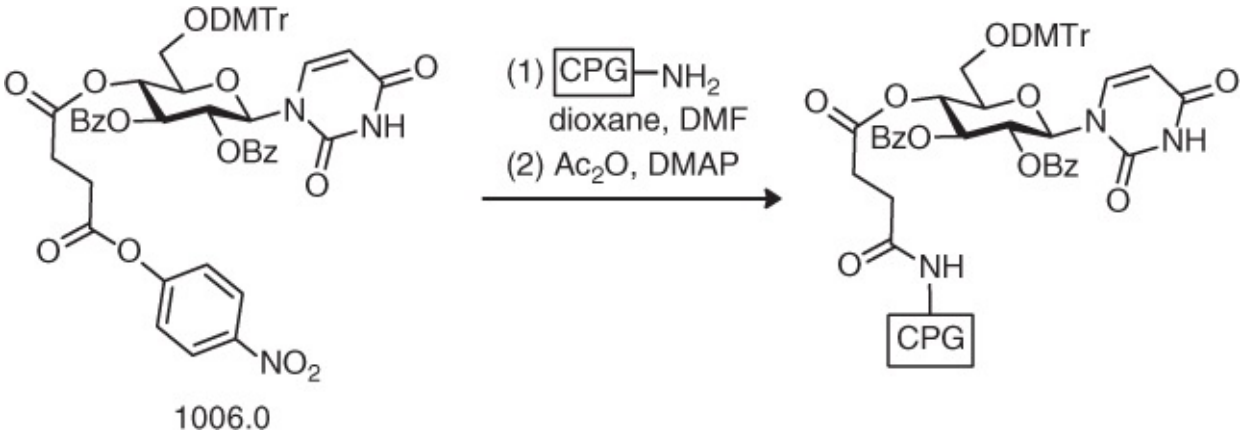
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.18 (s_{br}, 1H, NH), 8.13 (d, *J* = 9.2 Hz, 1H, NO_2Ph), 7.83–7.88 (m, 4H, Bz, DMTr), 7.52 (m, 1H, 6-H), 7.41–7.51 (m, 4H, Bz, DMTr), 7.20–7.36 (m, 13H, Bz, DMTr, NO_2Ph), 7.05 (d, *J* = 9.3 Hz, 1H, NO_2Ph), 6.80–6.84 (m, 4H, Bz, DMTr), 6.09 (dd, *J* = 11.7, 9.4 Hz, 1H, 1′-H), 5.87 (dd, *J* = 8.1, 5.4 Hz, 1H, 5-H), 5.79 (q, 1H, *J* = 9.7 Hz, 2′-H, 3′-H, 4′-H), 5.66 (dt, *J* = 9.9, 1.3 Hz, 1H, 2′-H, 3′-H, 4′-H), 5.57 (dq, *J* = 9.1, 3.2 Hz, 1H, 2′-H, 3′-H, 4′-H), 3.98 (m, 1H, 6′-H), 3.78 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 3.45 (dt, *J* = 10.9, 2.1 Hz, 1H, 6′-H), 3.20 (dt, 1H, *J* = 11.3, 4.0 Hz, 5′-H), 2.26–2.65 (m, 4H, succinyl).

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 171.4 (succinyl CO), 170.1, 165.6

(CO), 165.3, 161.9 (C-4), 158.6, 155.1, 153.8, 149.9 (C-2), 145.3 (DMTr), 144.4, 144.2, 139.1 (C-6), 139.0, 135.7, 135.6, 135.5, 135.3, 133.9, 133.4, 130.1, 130.0, 129.9, 129.8, 128.8, 128.7, 128.5, 128.4, 128.2, 128.0, 127.9, 127.0, 125.1, 122.2, 113.2 (DMTr), 103.6 (C-5), 86.4 (DMTr), 80.7 (C-1′), 76.5 (C-5′), 73.3 (C-3′), 70.5 (C-2′), 70.4, 68.6 (C-4′), 68.3, 61.5 (C-6′), 61.4, 55.2 (OCH_3), 32.6 (succinyl), 32.5, 30.7, 30.6.

MS (FAB^+, 3-NOBA): *m/z* = 1006 (0.2) $[M+H]^+$, 1005 (0.3) $[M]^+$.

4.4.1.8	**	**(2′,3′-Dibenzoyl-6′-*O*-(dimethoxytrityl)-β-D-glucopyranosyl)-uracil 4′-*O*-(succinylacid-CPG-amide)-ester** [9]



1006.0

Triethylamine (0.1 ml) and a solution of the active ester **4.4.1.7** (101 mg, 10 µmol) in anhydrous dioxane (0.5 ml) are added to a suspension of long-chain alkylamine CPG resin (500 mg) in anhydrous DMF (1.0 ml). The mixture is kept at room temperature with occasional shaking for 20 h. After filtration from the reaction mixture, the resin is washed with DMF, MeOH, and Et_2O. For the capping of unreacted amino functionalities, the resin is suspended in anhydrous pyridine (2.5 ml) containing DMAP (12.5 mg) and acetic anhydride (0.25 ml, 2.6 mmol), and the reaction flask is kept at room temperature for 30 min with occasional shaking. The reaction mixture is filtered, and the resin is washed with MeOH and Et_2O. After drying of the resin under high vacuum, the CPG-bound nucleoside **4.4.1.8** is obtained (540 mg). The loading of the resin is determined by deprotection of the resin-bound nucleoside **4.4.1.8** (1.7 mg) with dichloroacetic acid (5 ml, 2% in CH_2Cl_2). The absorption of 0.576 at λ = 503 nm corresponds to a loading of 24.2 µmol g^{-1}.

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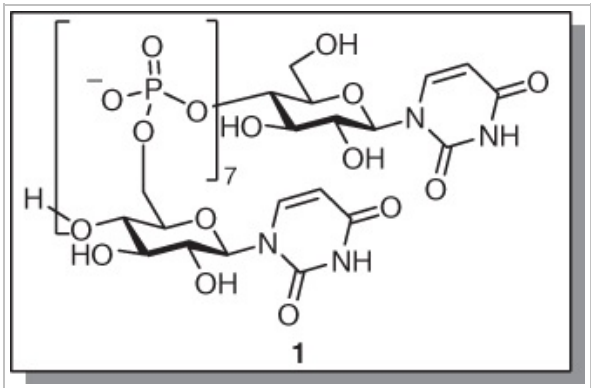
4.4.2 Solid-Phase Synthesis of Nucleic Acids



1

Topics:

- Solid-phase DNA synthesis
- Controlled pore glass (CPG) resin
- Phosphoramidite method

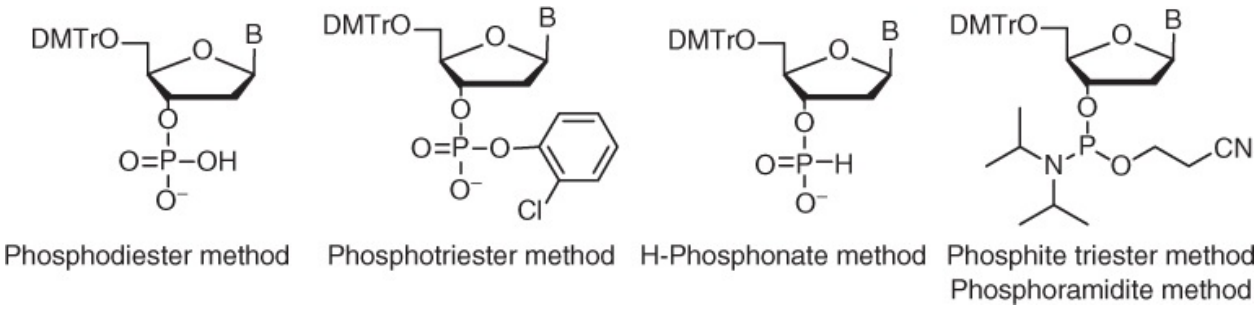
		• Protecting groups • RNA synthesis • Glucopyranosyl oligonucleotide

(a) General

The chemical synthesis of oligonucleotides started with the early work of Khorana [1] and has developed like SPPS into a well-established automated protocol [2]. The yields and procedures are well optimized, allowing the chemical preparation of DNA of length 150–200 nucleotides using automated synthesizers. Synthetically prepared DNA oligonucleotides have been used in biological applications, for example, as primers for DNA amplification or sequencing, as diagnostic tools, for *antisense* or *antigene* purposes targeting complementary sequences, to provide molecular architecture, and for the investigation of oligonucleotide recognition, manipulation, and interaction at the molecular level.

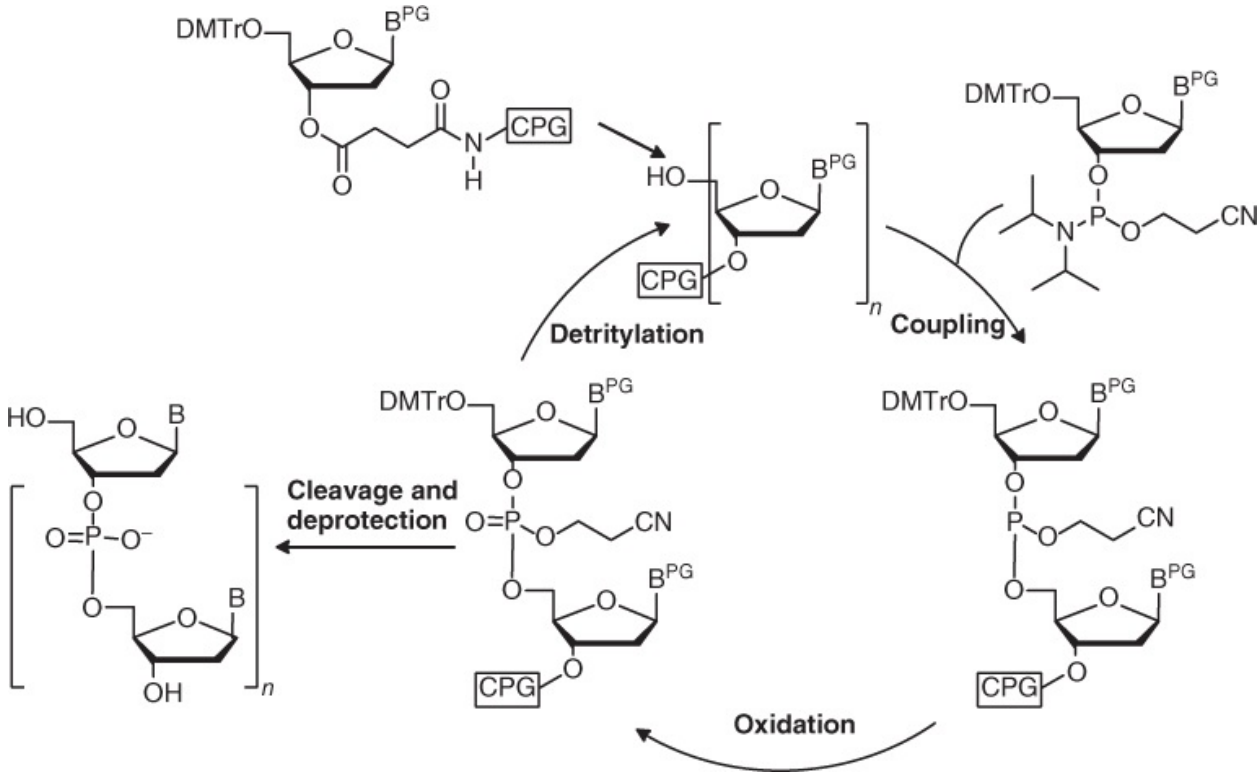
Oligonucleotides are synthesized on the inert resin CPG, which is functionalized with amines to immobilize the first nucleoside with a linker attached to the 3′-OH of the deoxyribosyl unit. The synthesis is performed from the 3′-end in the 5′-direction. General advantages of solid-phase synthesis, such as high yields by using an excess of reagents and easy removal of reagents and solvents, also apply for the synthesis of oligonucleotides.

Deprotection of the resin-bound nucleoside at 5′-OH is followed by nucleophilic coupling at the phosphorus of the next nucleotide. For the coupling process, four different strategies are used, which differ in the phosphorus group at the 3′-position of the nucleotide units: (i) In the phosphodiester method, a phosphorus monoester is coupled with the 5′-OH group activated by DCC [1]. This method suffers from long reaction times and severe side reactions. (ii) The phosphotriester method is based on a substitution at a phosphorus(V) diester anion [3], generating an aryl-protected phosphotriester after coupling. Because of the low stability of phosphotriesters, the potential for achieving longer chain lengths is limited.



(iii) In the phosphonate method, phosphorus(III) H-phosphonates are used [4]. This coupling method is especially valuable for DNA synthesis in solution and for the preparation of oligonucleotides modified at the phosphodiester. The additional oxidation step not only allows the introduction of oxygen but also, for example, the incorporation of sulfur to provide phosphorothioate DNA. Furthermore, the H-phosphonate starting materials are hydrolytically stable, making them easy to prepare and handle, especially with regard to water sensitivity. (iv) The phosphoramidite method (also called the ***phosphite triester method***), introduced by Caruthers [5], utilizes phosphorus(III) amidites. The automated DNA synthesis protocols in current use are based on phosphoramidite building blocks [6] and provide an extremely efficient coupling process with yields in excess of 99.8% and short reaction times. The 2-(cyanoethyl)-(diisopropylamino)phosphoramidites are most widely employed as monomeric units [7]. Phosphorus(III) provides an efficient electrophile and the diisopropylamine serves as a leaving group, while the cyanoethyl group is a convenient protecting group that is readily eliminated under basic conditions simultaneously with cleavage from the solid support as the final step of the oligomer synthesis.

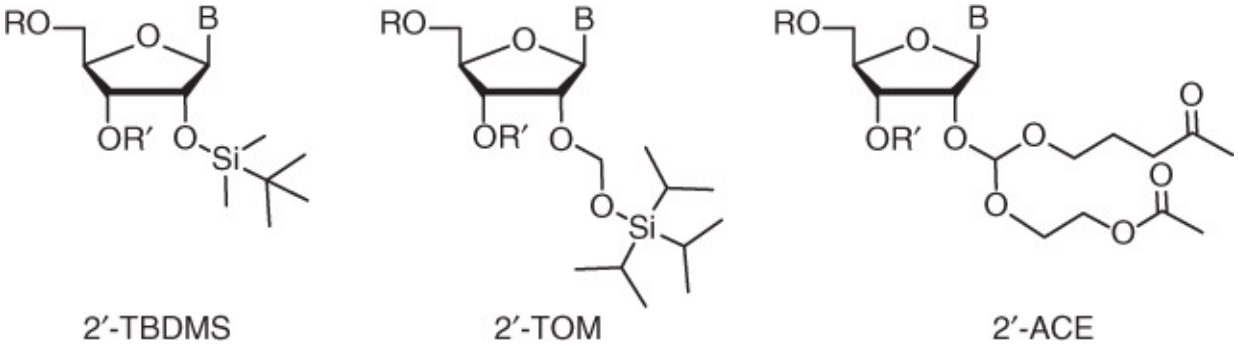
An efficient oligonucleotide synthesis is also dependent on finding an appropriate protecting group strategy. A temporary protecting group is required for the primary deoxyribosyl 5′-OH. For this, the DMTr group is suitable, which is cleaved under mild acidic conditions with 2% dichloroacetic acid; higher acidity would lead to cleavage of the nucleobases at the anomeric center. All permanent protecting groups are cleaved under basic conditions with aqueous ammonia, simultaneously liberating the oligomer from the solid support. Permanent protection is required for exocyclic amino functionalities of the nucleobases, which is usually provided by acylation. The phosphoramidite and phosphodiester are protected with the cyanoethyl group.



The phosphite triester reaction cycle starts with a nucleoside that is bound to the CPG resin. Deprotection provides the nucleophile, which reacts with the phosphoramidite that is activated with tetrazole. The phosphite linkage is stabilized by oxidation to the phosphate using aqueous iodine before the cycle can start again initiated by DMTr deprotection. As soon as the desired oligomer length is obtained, cleavage from the CPG resin is performed using aqueous ammonia, which also ensures complete deprotection of the nucleobases and the phosphodiesters. Usually, the oligomer is cleaved from the resin after DMTr deprotection. Nevertheless, purification can sometimes be improved by retaining the terminal DMTr group, thereby accepting an additional deprotection step. In most cases, reversed-phase or ion-exchange HPLC is used for purification, followed by a separation from salts on a small reversed-phase column.

Besides the classical synthesis of DNA oligonucleotides, the preparation of RNA and modified oligonucleotides is well established these days [2, 6]. For RNA synthesis, an additional permanent protecting group at the 2′-OH is required. The use of the *tert*-butyldimethylsilyl (TBDMS) group in RNA synthesis is limited with respect to the purity and length of the product, whereas the triisopropylsilyloxymethyl (TOM) group provides a coupling efficiency of more than 99% under standard DNA coupling conditions [8]. Further improvement of the coupling cycle has been obtained through acetoxy ethyl orthoester (ACE)

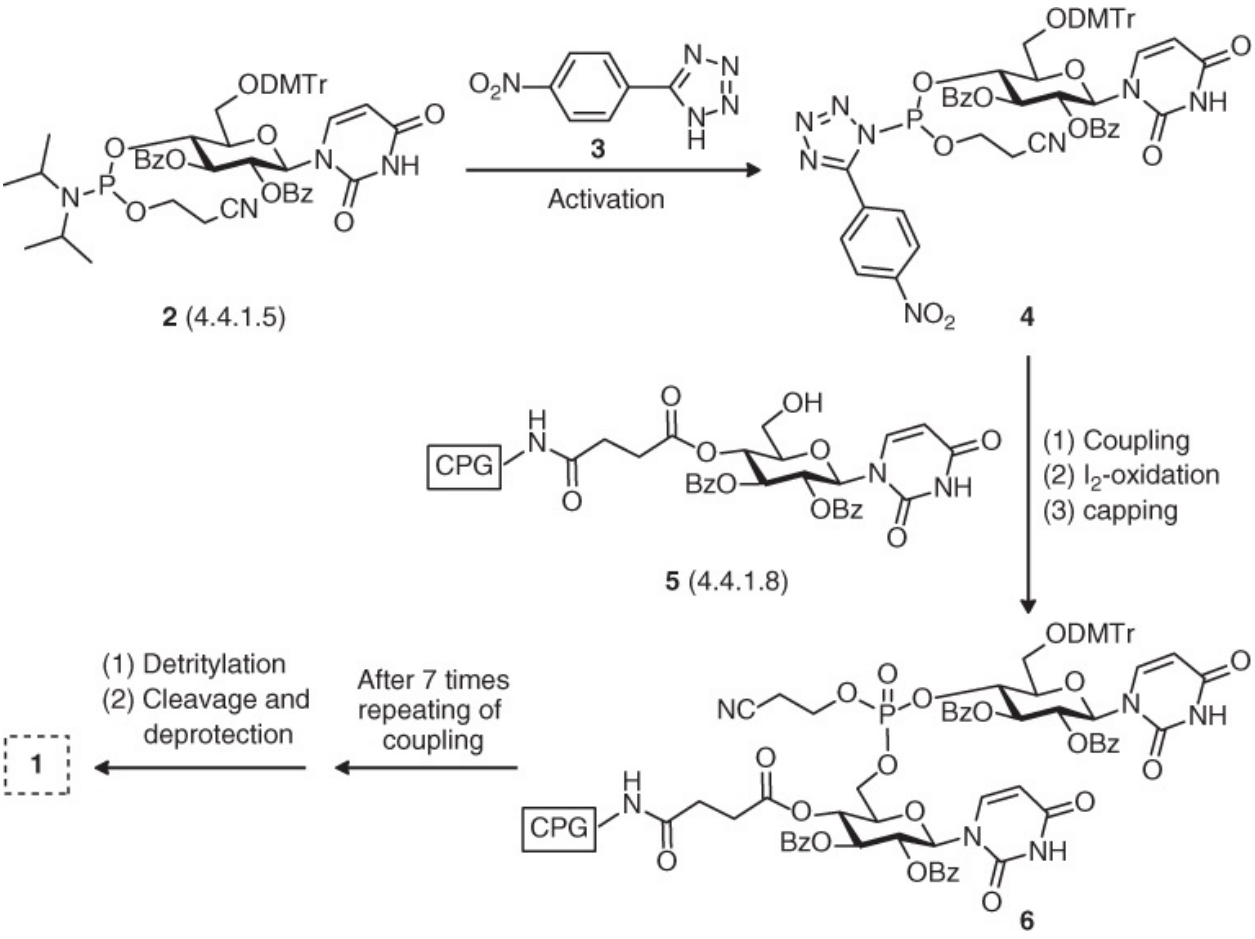
protection of 2′-OH, although this requires a silyl protecting group at 5′-OH [9].



(b) Synthesis of 1

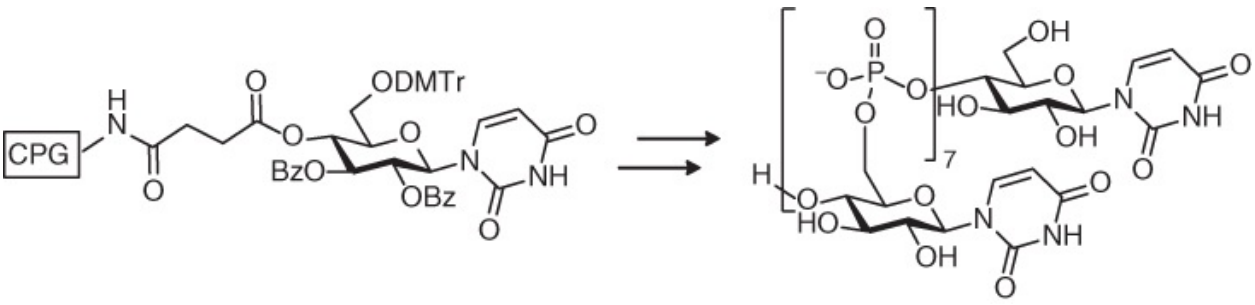
The solid-phase synthesis of DNA oligonucleotides is documented in great detail [2, 6]. Therefore, as an example of the synthesis of a non-natural oligonucleotide, the manual solid-phase synthesis of glucopyranosyl DNA **1** is described. This sugar-modified oligonucleotide can be obtained by repeated coupling of nucleoside **2** (cf. **4.4.1.5**) to the CPG-bound nucleoside **5** (cf. prepared from **4.4.1.8**). A glucopyranosyl oligomer is synthesized containing eight uracil nucleotides. Uracil does not need to be protected like the other nucleobases with functional groups of higher nucleophilicity.

Phosphoramidite **2** is activated with *p*-nitrophenyl tetrazole **3**, which substitutes the diisopropylamine moiety at the phosphorus(III). The resulting activated phosphoramidite **4** reacts in the coupling step with the solid-phase linked nucleoside **5**, which is obtained from nucleoside **4.4.1.8** by acidic deprotection of the DMTr group. 5-(*p*-Nitrophenyl)tetrazole (**3**) [10] is used as an equivalent of tetrazole with much higher reactivity, providing yields for each coupling step in excess of 96%, whereas tetrazole only provides about 75% yield. The coupling step is followed by phosphorus oxidation with aqueous iodine, and then unreacted alcohols are capped by acetylation, facilitating purification at a later stage. After DMTr deptrotection, the next cycle starts with coupling of phosphoramidite **2**, and this process is repeated until an octamer is reached. Finally, the last detritylation step is followed by cleavage from the resin with simultaneous deprotection of the nucleobases and of the cyanoethyl group at the phosphodiester by treatment with aqueous ammonia at high temperature.



(c) Experimental Procedure for the Synthesis of 1

4.4.2.1	***	**Manual solid-phase synthesis of glucopyranosyl-DNA** [11]



The glucopyranosyl DNA octamer **1** is prepared in a small fritted glass column using a CPG resin (25 mg) loaded with the uracil nucleoside **4.4.1.8** (25 µmol g^{-1}). The following procedure is repeated for each coupling cycle:

1. *Detritylation*: Dichloroacetic acid (2%, 5 ml) is added to the CPG-bound nucleoside or nucleic acid, respectively. After 5 min, the reagent is separated from the resin by filtration using nitrogen pressure, and then the resin is

washed with CH_2Cl_2 (5 ml) and Et_2O (5 ml). The solid support is dried in a nitrogen flow. The liquid phase resulting from deprotection is collected in order to determine the yield (>96%) by analysis of the $DMTr^+$ concentration, comparing successive coupling cycles.

2. *Coupling*: Phosphoramidite **4.4.1.5** (5.0 equiv) and *p*-nitrophenyl tetrazole (20 equiv) are added to the resin, which is then dried under high vacuum for 1 h. The glass column is flushed with argon, and then CH_3CN (150 µl) is added and the mixture is gently shaken for 1 h. Thereafter, the suspension is filtered, and the resin is washed with CH_3CN (5.0 ml) and THF (5.0 ml) and dried in a nitrogen flow.
3. *Oxidation*: The solid support is treated with a solution of iodine (0.1 mol) in THF/H_2O/2,6-lutidine 2 : 2 : 1 (5 ml) for 2 min. The suspension is then filtered and the resin is washed sequentially with THF/H_2O/2,6-lutidine (2 : 2 : 1; 5 ml), THF (5 ml), MeOH (5 ml), and Et_2O (5 ml).
4. *Capping*: Under an argon atmosphere, the resin is treated with a solution of DMAP (5.4%) in THF/2,6-lutidine/Ac_2O (10 : 1 : 1; 6 ml) for 5 min. The suspension is then filtered, and the resin is washed with THF (5 ml), MeOH (5 ml), and Et_2O (5 ml) and dried *in vacuo*.

   Steps (1)–(4) are repeated seven times until the desired oligomer length is obtained. A final detritylation step (1) is performed before basic cleavage.

5. *Deprotection and cleavage*: The resin-bound oligomer is suspended in concentrated aqueous ammonia (10 ml) for 16 h at 55 °C. After filtration and washing of the resin with H_2O, the combined aqueous filtrates are concentrated *in vacuo*. The residue is redissolved in H_2O (10 ml) and lyophilized.

The crude product can be purified by preparative HPLC on an ion-exchange column (Nucleogene DEAE 60-7) with the eluents: A: 20 mM K_2HPO_4/KH_2PO_4, pH 6, 20% CH_3CN, 80% H_2O, and 1 M KCl, B: 20 mM K_2HPO_4/KH_2PO_4, pH 6, 20% CH_3CN, 80% H_2O, gradient 10–50% B in 30 min, t_R = 18.6 min, or on an RP C-8 (Aquapore RP-300) column with the eluents: A: 0.1 M tetraethylammonium hydroxide, 0.1 M HOAc in H_2O, pH 7, B: 0.1 M tetraethylammonium hydroxide, 0.1 M HOAc in 20% H_2O, 80% CH_3CN, pH 7 gradient 5–20% B in 30 min, t_R = 15.1 min.

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[1] H. Pommer, A. Nürrenbach (1981) private communication.

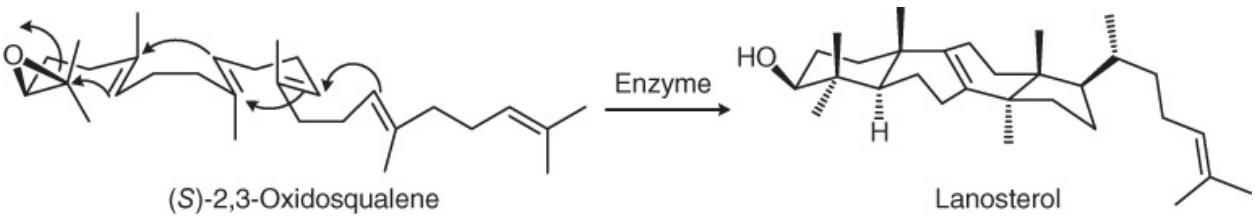
[2] U. Kazmaier, M. Bauer, personal communication.

[3] The six-component products **16** and **17** show interesting stereochemical features, cf. Ref. [5].

Chapter 5
Domino Reactions

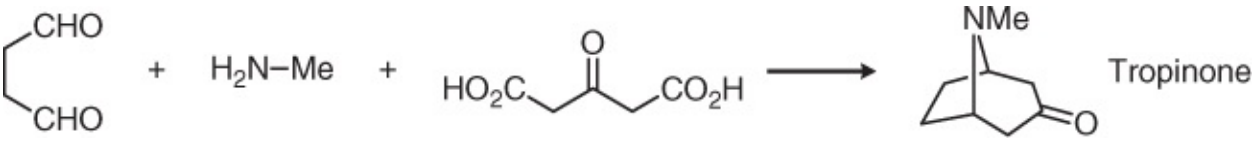
The synthesis of natural products, agrochemicals, drugs, consumables, and materials is a very important issue not only in academia but also in industry. The normal procedure for the synthesis of organic molecules in the last centuries has been the stepwise formation of individual bonds in the target molecules with work-up stages after each transformation. In contrast, modern synthesis management must seek procedures that allow the formation of several bonds, whether C–C, C–O, or C–N, in one process without the addition of any additional reagents or catalyst.

To meet these requirements, Tietze *et al.* [1] developed the domino concept and defined a domino reaction as a process in which two or more bond-forming reactions take place under identical reaction conditions, whereby the later transformations occur at the functionalities obtained in the earlier bond-forming reactions. Such an approach is highly advantageous from the ecological and economical stand points, since it saves time, reduces the amount of waste being formed, and is favorable to our resources and our environment. Moreover, using multicomponent domino processes, a multitude of different products can be formed; this is helpful in the development of bioactive compounds and valuable materials. Domino reactions are close to the ideal synthesis because they permit an effective reduction of the number of steps toward the final targets and give usually better yields than the stepwise procedures; furthermore, they show a good stereocontrol and atom efficiency. Thus, they allow the preparation of complex compounds from simple substrates in a very short and highly efficient way. A valuable criterion of the quality of a domino reaction is the increase of product complexity per process. Also, Nature uses this type of transformations. The best example is the biosynthesis of lanosterol from (*S*)-2,3-oxidosqualene [2], forming four rings and five new stereogenic centers.



The first domino reaction developed by chemists is the Mannich reaction in 1912

[3], and in the synthesis of tropinone [4] two Mannich reactions were used in one process.



These reactions are multicomponent domino processes; several syntheses of the heterocycles described in Chapter 3 belong to this group. For the classification of domino reactions, the mechanism of the characteristic bond-forming steps making up the process can be considered. For this purpose, cationic, anionic, radical, pericyclic, photochemical, transition-metal-catalyzed, oxidative and reductive, or enzymatic transformations are distinguished. Using this nomenclature, nucleophilic substitutions are counted as anionic processes, irrespective of whether a carbocation intermediate is formed, and nucleophilic additions to carbonyl groups with metal organic compounds such as MeLi, silyl enol ethers, or boron enolates are again counted as anionic transformations. Following this classification, we can establish a summary of possible combination of these reactions:

I. Transformation	II. Transformation	III. Transformation
Cationic	Cationic	Cationic
Anionic	Anionic	Anionic
Radical	Radical	Radical
Pericyclic	Pericyclic	Pericyclic
Photochemical	Photochemical	Photochemical
Transition metal	Transition metal	Transition metal
Oxidative or reductive	Oxidative or reductive	Oxidative or reductive
Enzymatic	Enzymatic	Enzymatic

The table shows 512 (8^3) different types of domino processes, but many of them have not yet been accomplished. The most common domino reactions are anionic transformations.

Domino reactions are very popular nowadays as shown by the multitude of publications [5] besides the work of Tietze.

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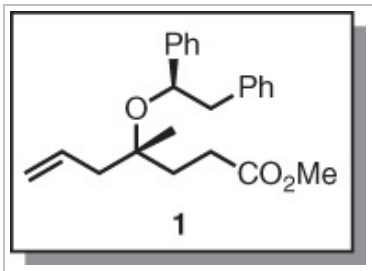
5.1 Domino Reactions in Synthetic Methodology

5.1.1 (*R*)-Methyl 4-[(*R*)-1,2-diphenylethoxy]-4-methylhept-6-enoate



1

Topics:

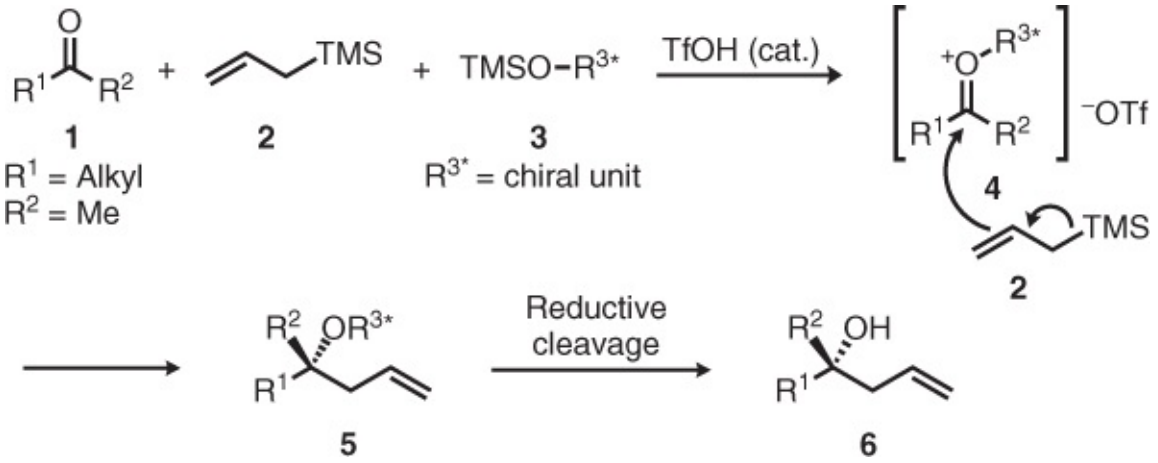
- Stereoselective allylation of ketones
- Synthesis of enantiopure tertiary allyl alcohols
- Domino reactions

(a) General

Allylations of aldehydes and ketones using allyl silanes, allyl stannanes, or allyl boronates are very important methods for the preparation of homoallylic alcohols [1]. The reactions can also be performed in an enantioselective way with high asymmetric induction if aldehydes are used as substrates. Otherwise, the stereoselective allylation of ketones such as alkyl methyl ketones is much

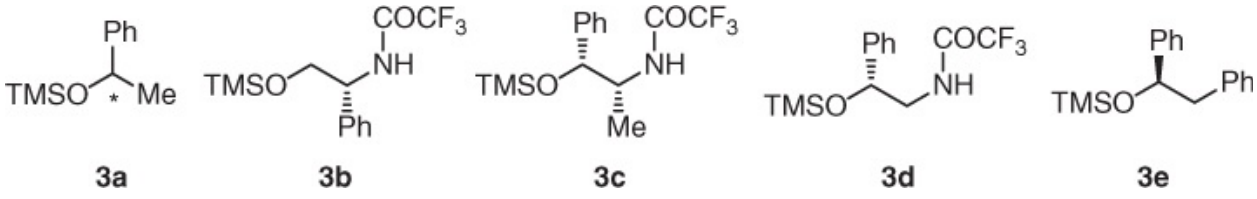
more difficult, and so far only one method exists for the transformation of aliphatic systems, which was developed by Tietze and coworkers [2, 3].

The following asymmetric allylation of alkyl methyl ketones can be regarded as a three-component domino reaction in which a ketone **1**, allyl trimethylsilane (**2**) as allylating reagent, and a chiral silyl ether **3** as the Oalkylating component react to give the homoallylic ether **5**. A catalytic amount of triflic acid is needed for the initiation of this multicomponent process.



The allylation proceeds via an intermediate carboxenium ion **4**, which is attacked by the allyl silane **2**. If a benzyl trimethylsilyl (TMS) ether **3** is used, the formed product **5** can be cleaved reductively to give the corresponding homoallylic tertiary alcohol **6**.

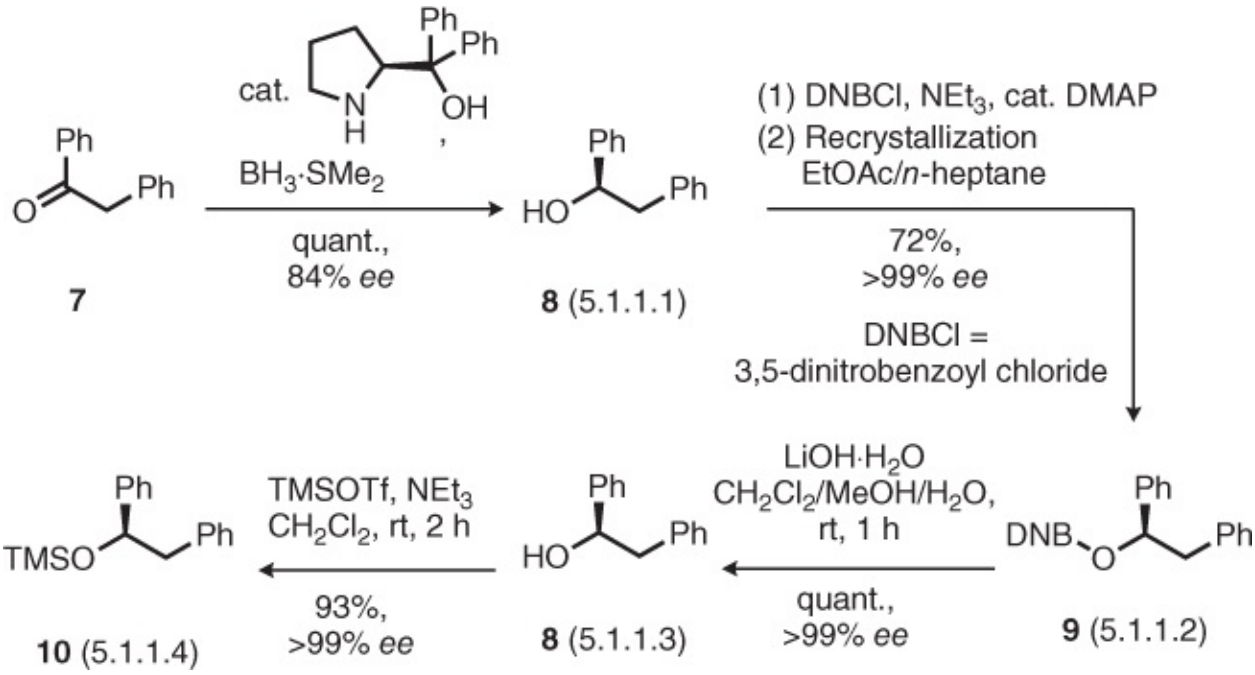
Chiral silyl ethers such as **3a** [4, 5] and **3b** [6] give only a very low selectivity of 1.8 : 1, whereas an excellent facial differentiation could be achieved with the norpseudoephedrine derivative **3c** [2], the mandelic acid derivative **3d** [3], and (*R*)-phenylbenzylcarbinol **3e** [7].



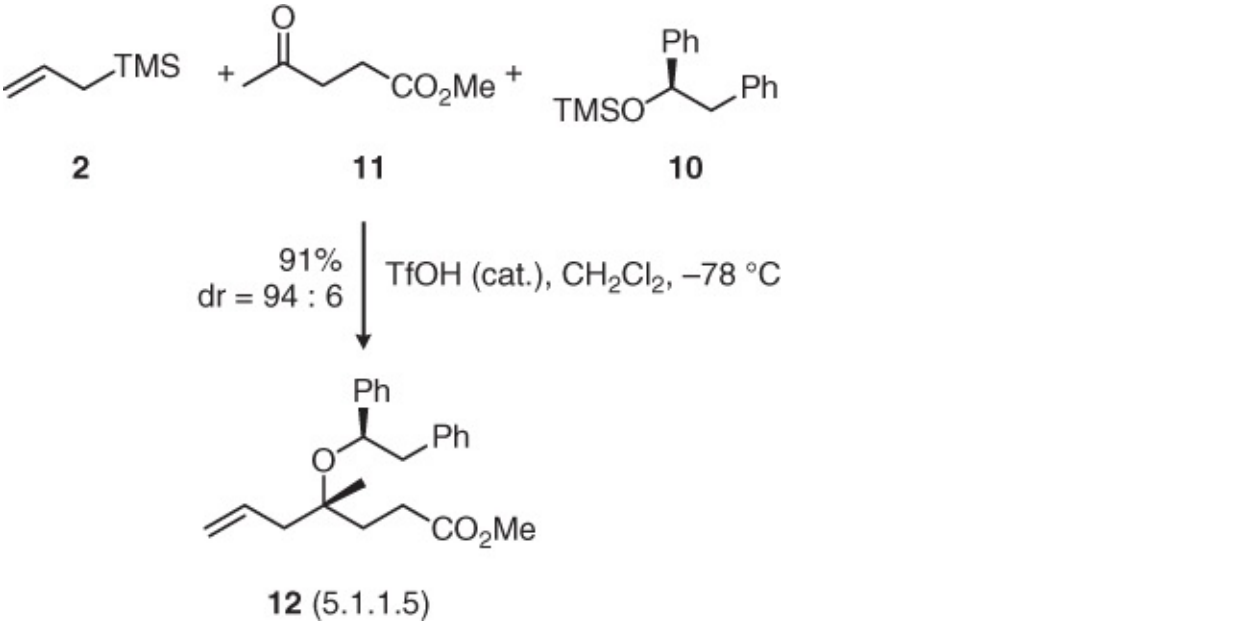
(b) Synthesis of 1

First, the chiral auxiliary **10** (= **3e**) is synthesized, which is derived from 1,2-diphenylethanone **7**. The enantioselective reduction of ketone **7** in quantitative yield could be performed with 84% ee, using catalytic amounts of chiral diphenylprolinol and $BH_3 \cdot SMe_2$ (**2.4.2.3**). The alcohol **8** is transformed into dinitrobenzoate **9** in 72% ee, and by recrystallization in >99% ee. Subsequent

removal of the protective group yielded alcohol **8** with >99% ee. The alcohol **8** is transferred into the TMS-ether **10**, which is used in the asymmetric allylation of **11** [7].

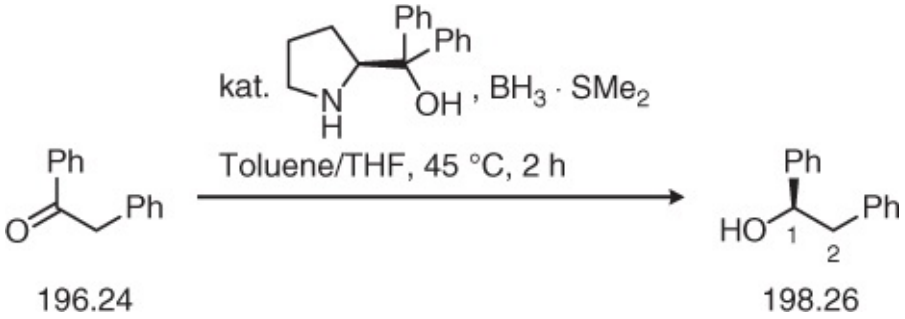


Methyl levulinate (**11**) is allylated with allyl trimethylsilane (**2**) in the presence of **10** and a catalytic amount of triflic acid in CH_2Cl_2 at −78 °C to afford the homoallylic ether (*R*,*R*)-**12** in 91% yield with a diastereomeric ratio of 94 : 6.



(c) Experimental Procedures for the Synthesis of 5

5.1.1.1	**	**(*R*)-1,2-Diphenylethanol (84% ee)** [7]



$BH_3{\cdot}SMe_2$ (12 ml of a 1 M solution in CH_2Cl_2, 12 mmol) is added at room temperature to a solution of diphenyl-L-prolinol **2.4.2.3** (265 mg, 1.00 mmol) in toluene (30 ml). To the resulting mixture, a solution of benzylphenylketone (2.0 g, 10 mmol) in THF (tetrahydrofuran) (10 ml) is added dropwise at 45 °C over a period of 1.5 h. After stirring for further 30 min at 45 °C, the reaction mixture is quenched by the addition of MeOH (2 ml).

The solution is washed with saturated aqueous NH_4Cl solution (20 ml), the aqueous layer is extracted with CH_2Cl_2 (3 × 50 ml), and the combined organic layers are washed with brine (20 ml), dried over Na_2SO_4, and filtered. The solvent is removed *in vacuo* to afford the crude alcohol as colorless solid; 2.1 g, (quantitative, 84% ee), R_f = 0.20 (EtOAc/*n*-pentane, 1 : 20).

UV (CH_3CN): λ_{max} (nm) (log ϵ) = 253 (2.5516), 258 (2.6105), 264 (2.5050).

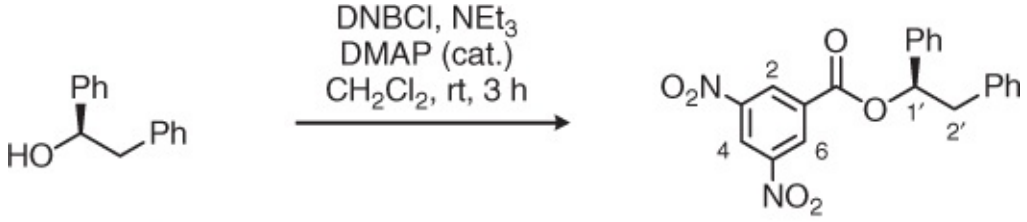
IR (film): $\tilde{\nu}$ (cm^{-1}) = 3294, 3026, 1495, 1453, 1316, 1273, 1071, 1039, 1026, 760, 742.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.18–7.40 (m, 10 × Ph–H), 4.92 (m_c, 1H, 1-H), 3.07 (dd, *J* = 13.5, 5.1 Hz, 1H, 2-H_a), 3.00 (dd, *J* = 13.5, 8.2 Hz, 1H, 2-H_b), 1.99 (d, *J* = 2.7 Hz, 1H, OH).

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 143.8 (Ph–C_i), 138.0 (Ph–C_i), 129.5 (2 × Ph–C), 128.5 (2 × Ph–C), 128.4 (2 × Ph–C), 127.6 (Ph–C), 126.6 (Ph–C), 125.9 (2 × Ph–C), 75.3 (C-1), 46.1 (C-2).

MS (EI, 70 eV): *m*/*z* (%) = 198 (3) $[M]^{+\bullet}$, 180 (23) $[M-H_2O]^{+\bullet}$, 107 (74) $[M-Bn]^+$, 92 (100) $[PhCH_3]^{+\bullet}$, 91 (29) $[Bn]^+$, 77 (24) $[Ph]^+$.

5.1.1.2	**	**(*R*)-1,2-Diphenylethyl 3,5-dinitrobenzoate** [7]



198.26 392.36

To a stirred solution of the crude alcohol **5.1.1.1** (2.1 g, 10 mmol, 84% ee), 3,5-dinitrobenzoyl chloride (3.0 g, 13 mmol), and DMAP (dimethylaminopyridine) (210 mg, 1.0 mmol) in CH_2Cl_2 (40 ml) is added dropwise NEt_3 (2.4 ml, 17 mmol) at 0 °C, and stirring is continued for 3 h at room temperature.

The solution is diluted with CH_2Cl_2 (100 ml) and washed with saturated aqueous $NaHCO_3$ (50 ml). The aqueous layer is extracted with CH_2Cl_2 (2 × 30 ml), and the combined organic layers are washed with brine (10 ml), dried over Na_2SO_4, and filtered. While removal of the solvent *in vacuo*, the crude product is instantly adsorbed on silica gel (9 g). Purification by flash chromatography (petroleum ether/CH_2Cl_2 2 : 1 → 1 : 2) affords the dinitrobenzoate as colorless solid; 3.8 g (95%, 84% ee), R_f = 0.40 (EtOAc/*n*-pentane, 1 : 20).

Recrystallization from EtOAc/*n*-heptane yields the dinitrobenzoate as an almost enantiopure compound (mp 107 °C); 2.9 g, (72%, >99% ee), $[\alpha]^{20}_D$ = +21.0 (*c* = 0.1, $CHCl_3$).

UV (CH_3CN): λ_{max} (nm) (log ϵ) = 208 (4.5501).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3087, 1729, 1628, 1543, 1455, 1341, 1272, 1164, 1074, 947.

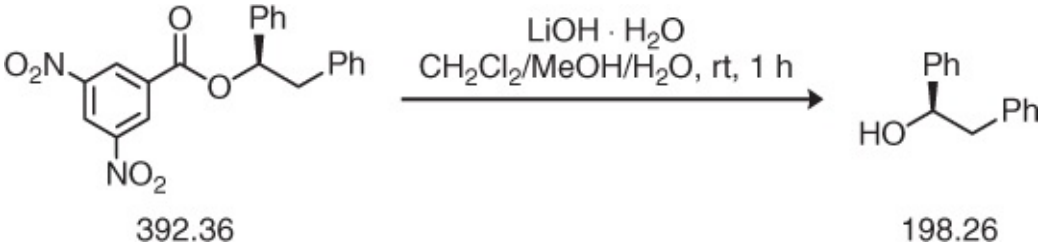
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 9.18 (t, *J* = 2.1 Hz, 1H, 4-H), 9.07 (d, *J* = 2.1 Hz, 2H, 2-H, 6-H), 7.15–7.42 (m, 10 × Ph–H), 6.22 (dd, *J* = 8.4, 5.7 Hz, 1H, 1′-H), 3.40 (dd, *J* = 14.0, 8.4 Hz, 1H, 2′-H_a), 3.00 (dd, *J* = 14.0, 5.7 Hz, 1H, 2′-H_b).

^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) = 161.6 (C=O), 148.6 (C-4), 138.7 (Ph–C_i), 136.3 (C-1), 134.0 (Ph–C_i), 129.4 (C-3, C-5), 129.3 (C-2, C-6), 129.3 (2 × Ph–C), 128.7 (2 × Ph–C), 128.5 (2 × Ph–C), 127.0 (Ph–C), 126.7

(2 × Ph–C), 122.3 (Ph–C), 75.3 (C-1′), 42.8 (C-2′).

MS (ESI, CH_3CN): *m/z* (%) = 410.1 (20) $[M+NH_4]^+$, 415.1 (17) $[M+Na]^+$, 431.0 (10) $[M+K]^+$, 807.2 (100) $[2M+Na]^+$.

5.1.1.3 * (*R*)-1,2-Diphenylethanol (>99% ee) [7]



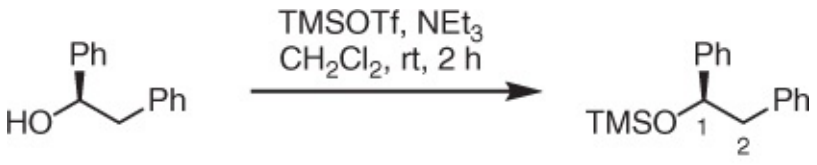
392.36 198.26

$LiOH \cdot H_2O$ (0.8 g, 19 mmol) is added to a solution of the dinitrobenzoate **5.1.1.2** (2.9 g, 7.4 mmol, >99% ee) in CH_2Cl_2/MeOH/H_2O 30 : 10 : 1 (8.2 ml) at room temperature, and the reaction mixture is stirred for 1 h.

The solution is diluted with CH_2Cl_2 (20 ml), washed with saturated aqueous $NaHCO_3$ solution (2 × 10 ml) and brine (5 ml), dried over Na_2SO_4, and filtered. The solvent is removed *in vacuo*, and the residue is purified by flash chromatography on silica gel (petroleum ether/EtOAc 20 : 1) to afford the alcohol as a colorless solid (mp 66 °C); 1.5 g (quantitative, >99% ee), $[\alpha]^{20}_D$ = −50.3 (*c* = 1, EtOH).

The spectra are identical with those of **5.1.1.1**.

5.1.1.4 ** (*R*)-(1,2-Diphenylethoxy)trimethylsilane [7]



198.26 270.44

TMSOTf (trimethylsilyl trifluoromethanesulfonate) (3.0 ml, 16.5 mmol) is added dropwise to a stirred solution of the alcohol **5.1.1.3** (1.5 g, 7.4 mmol, >99% ee), and then NEt_3 (5.7 ml, 39.0 mmol) in CH_2Cl_2 (80 ml) is added at 0 °C. After stirring for 2 h at room temperature, the reaction is quenched by the addition of a saturated aqueous $NaHCO_3$ solution (40 ml).

The aqueous layer is extracted with CH_2Cl_2 (2 × 30 ml). The combined organic

layers are washed with brine (10 ml), dried over Na_2SO_4, and filtered. The solvent is removed *in vacuo*, and the residue is purified by flash chromatography on silica gel (petroleum ether/MTBE (methyl *tert*-butyl ether) 80 : 1) to afford the silyl ether as colorless oil; 1.9 g (93%, >99% ee), R_f = 0.70 (EtOAc/*n*-pentane, 1 : 15), $[\alpha]^{20}_D$ = +27.0 (*c* = 1.0, $CHCl_3$).

UV (CH_3CN): λ_{max} (nm) (log ϵ) = 252 (2.5678), 258.0 (2.6450), 264.0 (2.5313).

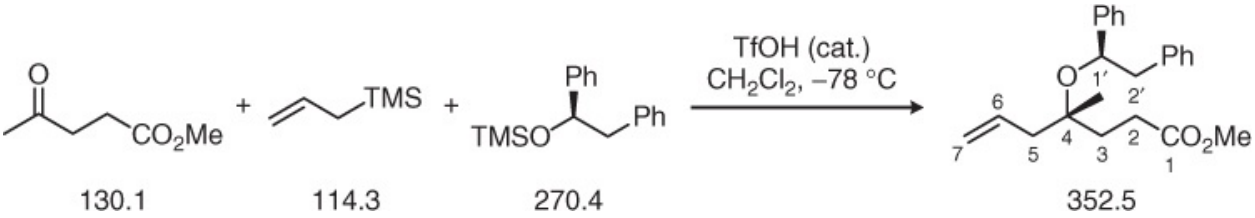
IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3028, 2954, 1495, 1453, 1250, 1088, 1066, 942, 835.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.09–7.31 (m, 10 × Ph–H), 4.74 (t, *J* = 6.5 Hz, 1H, 1-H), 2.89 (d, *J* = 6.5 Hz, 2H, 2-H), −0.16 (s, 9H, $SiMe_3$).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 144.9 (Ph–C_i), 139.0 (Ph–C_i), 129.8 (2 × Ph–C), 128.0 (2 × Ph–C), 127.9 (2 × Ph–C), 127.0 (Ph–C), 126.1 (Ph–C), 125.8 (2 × Ph–C), 76.4 (C-1), 47.5 (C-2), −0.3 ($SiMe_3$).

MS (EI, 70 eV): *m*/*z* (%) = 269.3 (2) $[M-H]^+$, 179.2 (100) $[M-TMS-H_2O]^+$, 73.1 (91) $[TMS]^+$.

5.1.1.5	***	**(*R*,*R*)-Methyl 4-(1,2-diphenylethoxy)-4-methylhept-6-enoate** [7]



Under an inert gas atmosphere, TfOH (60 µl, 0.3 mmol) is added to a solution of methyl levulinate (390 mg, 3.0 mmol), allyltrimethylsilane (**3**) (410 mg, 3.6 mmol), and auxiliary **5.1.1.4** (810 mg, 3.0 mmol) in CH_2Cl_2 (1.5 ml) at −78 °C. The reaction mixture is stirred for 14 h at −78 °C and then quenched by addition of NEt_3 (0.1 ml).

The solvent is removed *in vacuo*, and the residue purified by flash chromatography on silica gel (petroleum ether/*t*-BuOMe 50 : 1 → 20 : 1) to afford the homoallylic ether as colorless oil; 960 mg (91%, dr: 94 : 6), R_f = 0.15 (petroleum ether/MTBE, 30 : 1), $[\alpha]^{20}_D$ = +29.9 (*c* = 1, $CHCl_3$).

UV (CH_3CN): λ_{max} (nm) (log ϵ) = 253.0 (2.5510), 258.5 (2.6314), 264.0 (2.5107).

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3028, 1739, 1639, 1603, 1495, 1454, 1379, 1308, 1172, 1057, 916.

^{1}H NMR (300 MHz, $CDCl_3$): *main diastereomer:* δ (ppm) = 7.07–7.31 (m, 10 × Ph–H), 5.58 (ddt, *J* = 16.7, 10.4, 7.3 Hz, 1H, 6-H), 4.91–5.00 (m, 2H, 7-H_2), 4.62 (dd, *J* = 7.8, 5.4 Hz, 1H, 1′-H), 3.63 (s, 3H, OMe), 2.95 (dd, *J* = 13.2, 7.8 Hz, 1H, 2′-H_a), 2.83 (dd, *J* = 13.2, 5.4 Hz, 1H, 2′-H_b), 2.30 (ddd, *J* = 16.1, 9.6, 6.6 Hz, 1H, 2-H_a), 2.23 (ddd, *J* = 16.1, 9.3, 6.3 Hz, 1H, 2-H_b), 2.07 (dd, *J* = 13.9, 7.2 Hz, 1H, 5-H_a), 1.94 (dd, *J* = 13.9, 7.4 Hz, 1H, 5-H_b), 1.74 (ddd, *J* = 14.2, 9.3, 6.6 Hz, 1H, 3-H_a), 1.66 (ddd, *J* = 14.2, 9.6, 6.3 Hz, 1H, 3-H_b), 0.82 (s, 3H, 4-CH_3).

^{13}C NMR (126 MHz, $CDCl_3$): *main diastereomer:* δ (ppm) = 174.3 (C-1), 145.2 (Ph–C_i), 138.6 (Ph–C_i), 134.1 (C-6), 129.8 (2 × Ph–C), 127.9 (2 × Ph–C), 127.8 (2 × Ph–C), 126.8 (Ph–C), 126.2 (2 × Ph–C), 126.0 (Ph–C), 117.4 (C-7), 77.1 (C-4), 75.7 (C-1′), 51.4 (OCH_3), 46.9 (C-2′), 43.2 (C-5), 34.2 (C-3), 28.5 (C-2), 23.6 (4-CH_3).

MS (ESI, MeOH): *m*/*z* (%) = 370.2 (22) $[M+NH_4]^+$, 375.2 (100) $[M+Na]^+$.

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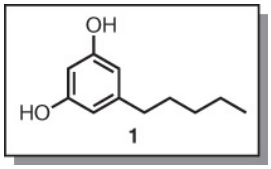
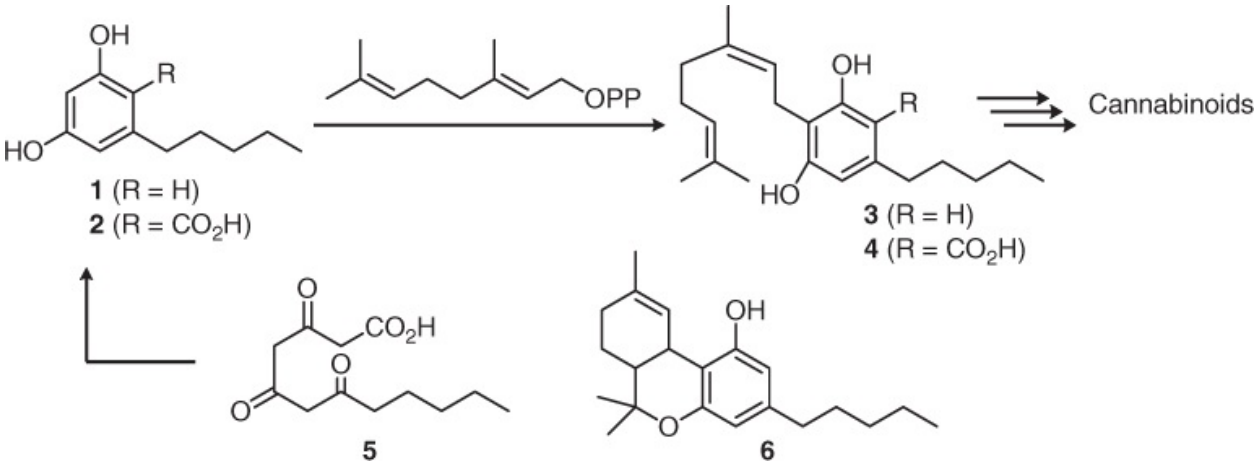
5.1.2 Olivetol

	***Topics:***	• Synthesis of a phenolic natural product (intermediate of cannabinoid biosynthesis) • Inter-and intramolecular aldol reaction • Domino process: Michael addition/intramolecular Claisen condensation • Ester cleavage and decarboxylation, aromatization of a cyclic 1,3-diketone

(a) General

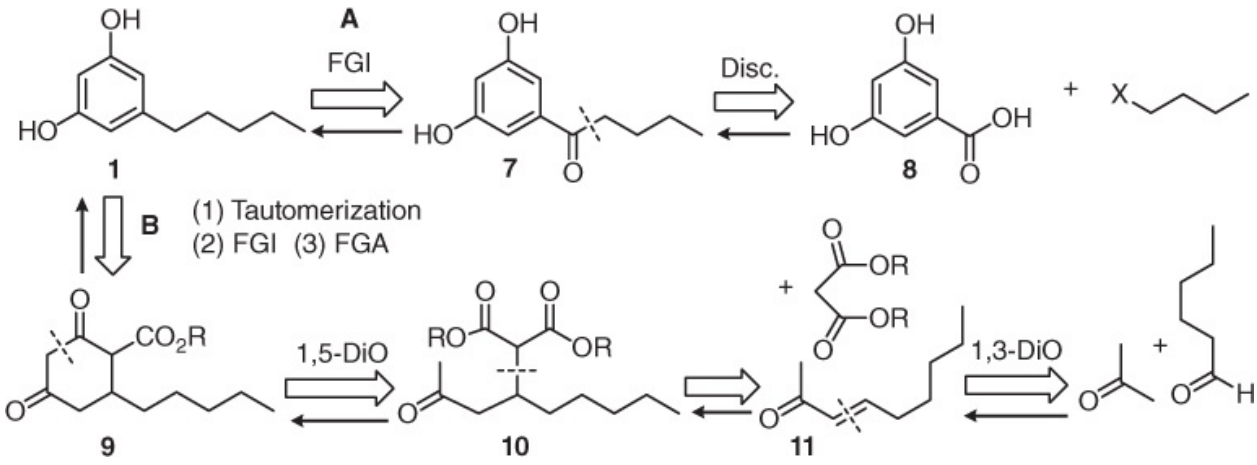
Olivetol (**1**) and the corresponding carboxylic acid **2** are intermediates in the biosynthesis of cannabinoids. They are likely to be formed from hexanoic acid, acetyl-CoA, and malonyl-CoA via the polyketide **5** [1]. After cyclocondensation, aromatization, and, in the case of **1,** decarboxylation, the resorcinol derivatives **1** and **2** are prenylated by geranyl diphosphate to give cannabigerol (**3**) and

cannabigerolic acid (**4**). Compound **3** is the biogenetic precursor of tetrahydrocannabinol (**6**), one of the active ingredients of cannabis. More recently, olivetol has been shown to be a building block in lichen constituents [2].



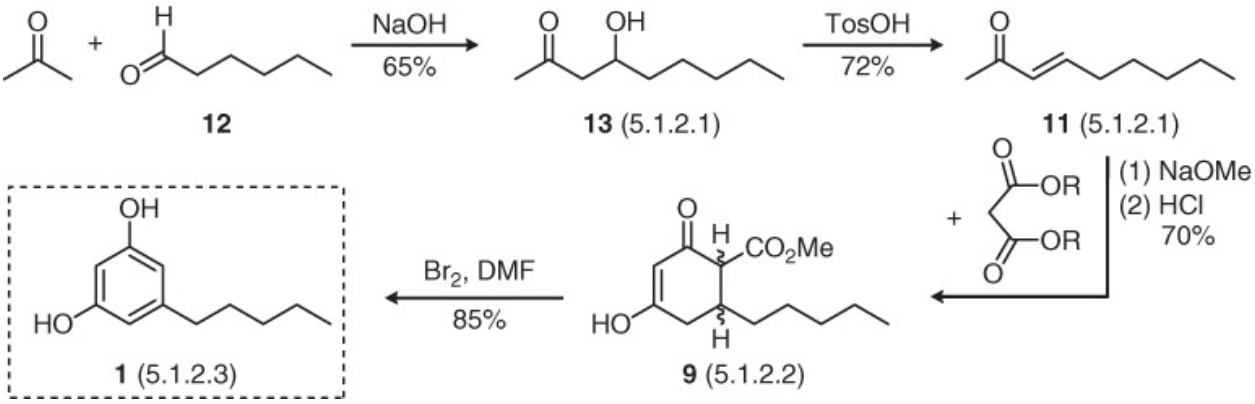
Retrosynthesis of olivetol **1** can be performed in two ways. In A, oxidation of the pentyl side chain in the benzylic position leads to the oxo compound **7**, which can be transformed to α-resorcylic acid **8**, an inexpensive substrate with the correct arrangement of phenolic hydroxyl groups, and a halobutane. A metalorganic species (X = Li or Mg) must be prepared from the halobutane for the reaction with **8**. Syntheses following a concept based on A have been reported in the literature [3].

Retrosynthetic analysis according to B leads to hexanal, acetone, and malonate via the intermediates **10** and **11**. This approach has been influenced by biosynthetic considerations and might be called a ***biomimetic synthesis***. Thus, in the synthesis of natural products, knowledge of the biosynthesis can be very helpful.



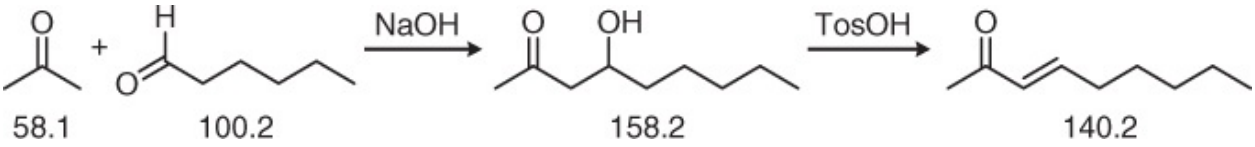
(b) Synthesis of 1

For the synthesis of **1** according to retroanalysis B, the base-induced aldol addition of acetone and hexanal (**12**) is used to give the β-hydroxy ketone **13**, which yields 3-nonen-2-one (**11**) by acid-catalyzed elimination of water. This α,β-unsaturated ketone is reacted with dimethyl malonate in the presence of NaOMe to yield the cyclic β-ketoester **9** in a base-catalyzed domino process consisting of an 1,4-addition of malonate to the enone (→**10**) followed by intramolecular Claisen condensation to afford the β-ketoester **9**. Reaction of **9** with bromine in DMF (*N*,*N*-dimethylformamide) yields olivetol (**1**) in a reaction cascade which includes bromination, elimination of HBr, tautomerization, ester cleavage, and decarboxylation:



(c) Experimental Procedures for the Synthesis of 1

5.1.2.1 | * | **3-Nonen-2-one** [4]



A solution of hexanal (distilled, bp_{760} 131–132 °C; 100 g, 1.00 mol) in acetone (175 ml) is added dropwise to a stirred mixture of acetone (175 ml) and sodium hydroxide (2.5 N, 50 ml) at 10–15 °C over 2.5 h. Stirring is continued at room temperature for 1 h.

The mixture is neutralized (pH 7) with ice-cold aqueous HCl (6 N), concentrated to a volume of approximately 150 ml, and extracted with Et_2O (3 × 60 ml). The combined extracts are washed with saturated aqueous $NaHCO_3$ solution (60 ml) and brine (60 ml). The organic layer is dried over Na_2SO_4, and filtered. The solvent is removed *in vacuo*, and the residue is distilled *in vacuo* to give 103 g

(65%) of the aldol adduct, bp_{10} 108–109 °C.

IR (film): $\tilde{\nu}$ (cm^{-1}) = 3450, 1710.

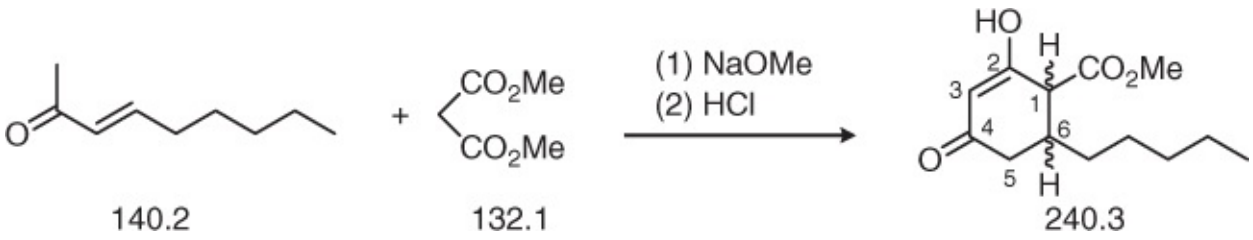
A mixture of the aldol adduct (95.0 g, 0.60 mol), *p*-toluenesulfonic acid (300 mg), and anhydrous Na_2SO_4 (40 g) in benzene (200 ml, Caution!) is heated under reflux for 1 h.

Na_2SO_4 is removed by filtration, and the organic phase is washed with a saturated $NaHCO_3$ solution (100 ml) and brine (100 ml), dried over Na_2SO_4, and filtered. The solvent is removed *in vacuo*, and the residue is distilled *in vacuo* over a small Vigreux column; yield 60.6 g (72%), bp_{10} 88–89 °C.

IR (film): $\tilde{\nu}$ (cm^{-1}) = 2970, 2940, 2880, 2870, 1685, 1630, 1360.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 6.83 (dt, *J* = 16.0, 7.0 Hz, 1H, 4-H), 6.06 (dt, *J* = 16.0, 1.5 Hz, 1H, 3-H), 2.20 (s, 3H, 1-H_3), 2.52–2.01 (m, 2H, 5-H_2), 1.68–1.13 (m, 6H, 6-H_2, 7-H_2, 8-H_2), 0.90 (t, *J* = 5.0 Hz, 3H, 9-H_3).

5.1.2.2 * Methyl 2-hydroxy-4-oxo-6-pentylcyclohex-2-ene-1-carboxylate [5]



140.2 132.1 240.3

Sodium (Caution! 8.10 g, 0.35 mol) is added in portions to anhydrous MeOH (200 ml, Hood! H_2 evolution!). After the sodium has completely dissolved, dimethyl malonate (52.8 g, 0.40 mol) is added with stirring and the mixture is heated to 60 °C. 3-Nonen-2-one **5.1.2.1** (42.1 g, 0.30 mol) is added dropwise over 30 min, and the solution is heated under reflux for 3 h.

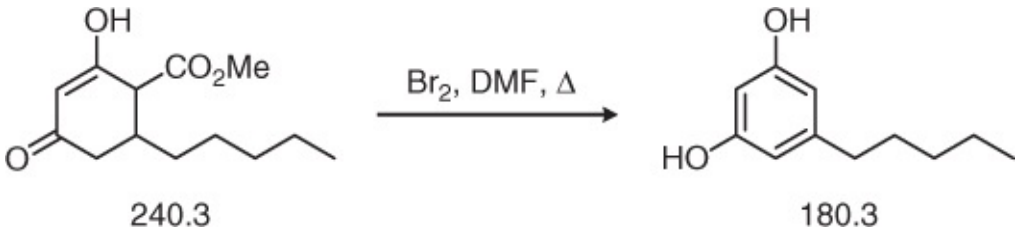
The solvent is then evaporated *in vacuo*, and the residue is dissolved in H_2O (250 ml). The aqueous solution is washed with $CHCl_3$ (3 × 50 ml, discard) and then acidified with concentrated HCl to pH 3–4. The precipitated oily solid is dissolved in $CHCl_3$ (200 ml), and the aqueous phase is extracted with $CHCl_3$ (3

× 50 ml). The combined organic phases are washed with brine, dried over $MgSO_4$, and filtered, and the solvent is removed *in vacuo*. The residue is recrystallized from a mixture of *n*-hexane/diisopropyl ether/isopropanol, 25 : 13 : 2 (150 ml), to give colorless needles; 50.5 g (70%), mp 98–100 °C.

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3300–2200, 1740, 1605, 1510, 1440, 1415, 1360.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 9.26 (s, 1H, OH), 5.50 (s, 1H, 3-H), 3.83 (s, 1.5H, OCH_3), 3.75 (s, 1.5H, OCH_3), 3.71–2.87 (m, 1H, 1-H), 2.76–2.29 (m, 2H, 5-H_2), 1.51–1.11 (m, 9H, 6-H, 4 × CH_2), 0.90 (t, *J* = 6 Hz, 3H, 5′-CH_3).

5.1.2.3 * 1,3-Dihydroxy-5-pentylbenzene (olivetol) [5]



Bromine (Caution: Hood! 7.50 g, 47.0 mmol, ∼2.40 ml) is added dropwise to a stirred solution of the methyl ester **5.1.2.2** (12.0 g, 50.0 mmol) in anhydrous dimethylformamide (30 ml) at 0 °C over a period of 90 min. The solution is slowly heated to 160 °C and stirred for 10 h at the same temperature. Evolution of carbon dioxide starts at approximately 100 °C.

The solution is cooled and concentrated *in vacuo* (approximately 100 °C/ 10 mbar). The residue is dissolved in H_2O (30 ml) and extracted with Et_2O (3 × 35 ml). The combined ethereal extracts are washed sequentially with H_2O (30 ml), 10% aqueous $NaHCO_3$ (2 × 20 ml), HOAc (2 M, 2 × 20 ml), and twice with brine, dried over Na_2SO_4, and filtered, and the solvent is removed *in vacuo*. The residue is distilled in a Kugelrohr to give a light-pink viscous oil that solidifies at 4 °C. It may be recrystallized from Et_2O; yield 7.22 g (85%), $bp_{0.01}$ 150 °C (oven temperature), mp 85–86 °C.

IR (film): $\tilde{\nu}$ (cm^{-1}) = 3600–2000, 1610, 1590.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 6.85 (s, 2H, OH), 6.25 (s_{br}, 3H, Ar–

H), 2.33 (t, J = 7.1 Hz, 2H, Ph–CH_2), 1.48–1.06 (m, 6H, 3 × CH_2), 0.83 (t, J = 6.0 Hz, 3H, CH_3).

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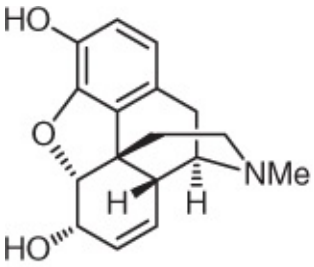
5.2 Domino Reactions in the Synthesis of Alkaloids

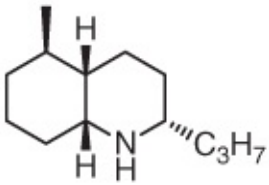
Alkaloids are nitrogen-containing natural products usually having a complex cyclic structure. Simple amines, amino acids, and proteins, as well as nucleosides and nucleic acids, which also contain nitrogen, are not included in this group [1]. However, heterocyclic compounds such as caffeine (cf. Section 3.4.4) are alkaloids. Originally, the term ***alkaloid*** was used for amines from plants, indicating that these compounds have a basic (=alkaline) character, but nowadays the definition has been broadened to also cover nonbasic nitrogen compounds such as ammonium salts and amides from all natural sources.

The vast majority of the over 20 000 known natural alkaloids have been isolated from plants, such as morphine (**1**) from *Papaver somniferum* [2], but alkaloids are also found in animals, for example, pumiliotoxin C (**2**) from the frog *Dendrobates pumilio* [3], and in mushrooms, for example, muscarine (**3**) from *Amanita muscaria* [4].



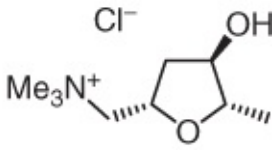
Morphine

1



Pumiliotoxin

2

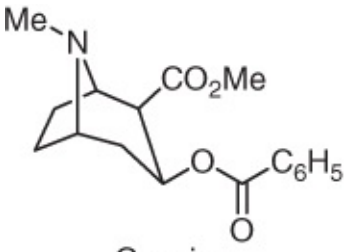


Muscarine

3

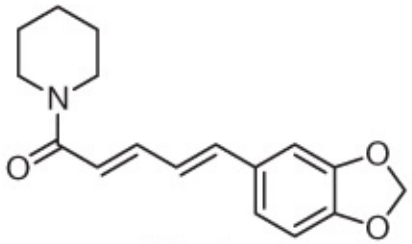
There are several ways of classifying alkaloids, either according to their origin, for example, ergot alkaloids, or according to their heterocyclic core structure, for example, indole alkaloids. However, the best classification of alkaloids is based on their biosynthesis. Despite a few exceptions [5] – see also later – alkaloids are formed from amino acids and biogenic amines. The most common precursors of aliphatic alkaloids are L-ornithine and L-lysine. Thus, L-ornithine is the precursor of the pyrrolidine and pyrrolizidine alkaloids. An example of a pyrrolidine alkaloid is the well-known narcotic cocaine (**4**). On the other hand, L-lysine serves as the precursor of the piperidine alkaloids, such as piperine (**5**) from *Piper nigrum* (black pepper) (cf. Section 1.5.1). Here, a piperidine unit, which is formed from L-lysine, is acylated by a phenylpropanoic compound after C_2-chain extension.

Interestingly, the alkaloid coniine (**6**), isolated from hemlock, also contains a piperidine unit, which is formed from acetate via 5-oxooctanoic acid [6].



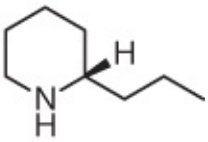
Cocaine

4



Piperine

5



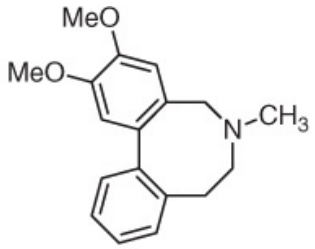
Coniine

6

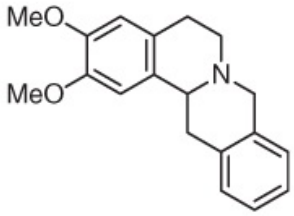
L-Phenylalanine and L-tyrosine are precursors of aromatic alkaloids such as the *Amaryllidaceae* alkaloid buflavine (**7**) (cf. Section 5.2.3), the alkaloid 2,3-dimethoxyberbine (**8**) (cf. Section 5.2.2), and morphine (**1**).

In the formation of aromatic alkaloids such as morphine (**1**) and buflavine (**7**), the so-called phenol oxidation (cf. Section 1.7.6) is a very important transformation, whereby a phenolate is oxidized to give a radical that can undergo C–O or C–C bond formation [7]. Thus, in the biosynthesis of morphine (**1**), the benzyltetrahydroisoquinoline reticulin (**9**) is transformed via the

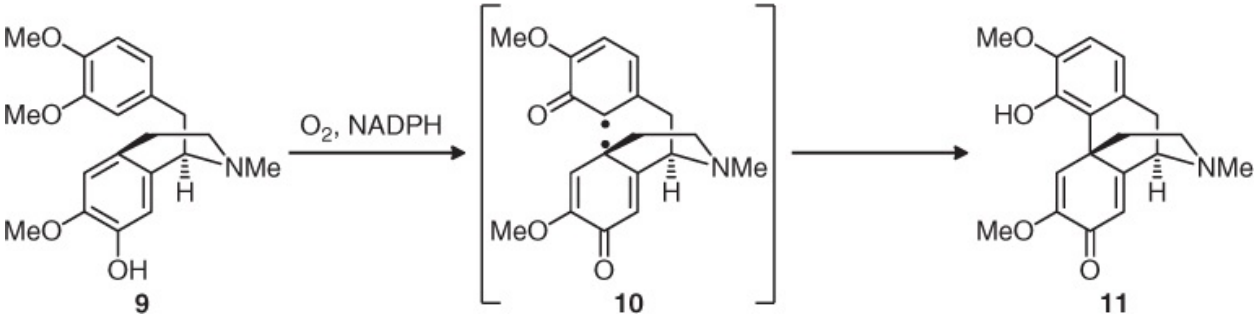
proposed diradical **10** into salutaridine (**11**), which is further converted into **1** via several intermediates [8]. The alkaloid 2,3-dimethoxyberbine (**8**) is also formed from a benzyltetrahydroisoquinoline, but in this case oxidation of the *N*-methyl group takes place to form an iminium ion, which undergoes an electrophilic aromatic substitution.



Buflavine
7

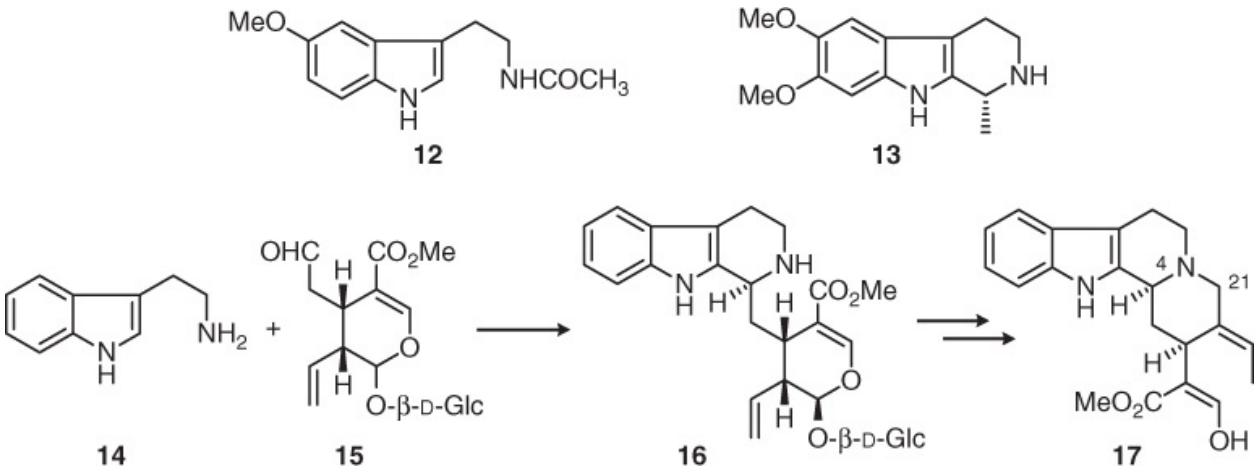


Dimethoxyberbine
8



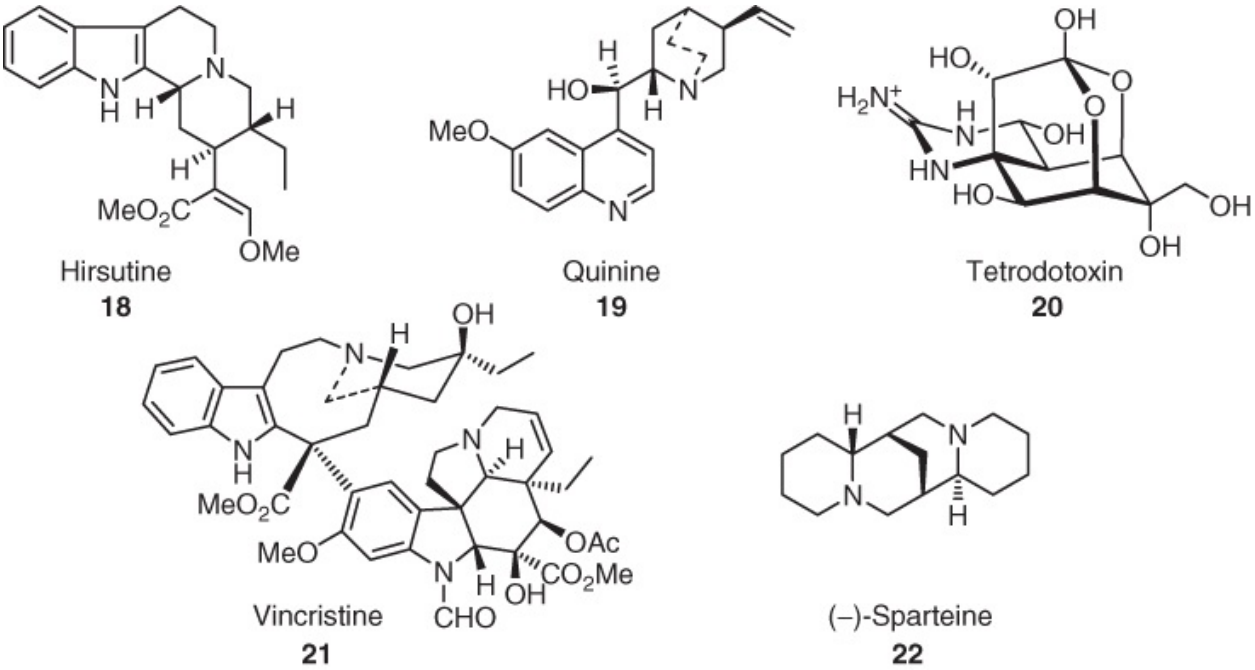
9 **10** **11**

One of the biggest groups of alkaloids is the group of indole alkaloids, which are formed from L-tryptophan and L-tryptamine. Simple compounds belonging to this class of natural products are melatonin (**12**) (cf. Section 3.2.5) and (*R*)-salsolidine (**13**) (cf. Section 3.3.2). However, very complex structures are found in the group of the so-called monoterpenoid indole alkaloids and alkaloids derived from them, such as the cinchona alkaloids and the pyrroloquinoline alkaloids [9]. Several highly bioactive compounds originate from this class. In the biosynthesis of these compounds, L-tryptamine (**14**) is first condensed with the monoterpene secologanin (**15**) to give strictosidine (**16**), which, after cleavage of the glucose moiety, forms indole alkaloids of the corynanthe family such as geissoschizine (**17**).



The alkaloid hirsutine (**18**) (cf. Section 5.2.1) also belongs to the corynanthe family. Further transformations of **17** and its 4,21-didehydro derivative, respectively, lead to indole alkaloids of the aspidosperma and iboga families. Moreover, oxidative cleavage of the indole moiety followed by aldol condensation furnishes cinchona alkaloids such as quinine (**19**), which contains a quinoline moiety as one of the heterocyclic core structures, as well as pyrroloquinoline alkaloids.

Nearly all alkaloids have strong biological activities. They can act as poisons, such as coniine (**6**), which was used by the people of Athens to kill Socrates nearly 2500 years ago [6], and tetrodotoxin (**20**), which is found in the puffer fish [10]. However, at appropriate concentrations, they can also be used as drugs, such as morphine (**1**), a very strong pain reliever, or the dimeric indole alkaloid vincristine (**21**), which is used for the treatment of pediatric leukemia with a success rate of almost 70% [11].



On the other hand, some alkaloids are used as catalysts; for example, sparteine (**22**) is used for some enantioselective addition reactions (cf. Section 1.1.2), and derivatives of quinine (**19**) and quinidine are used for Sharpless bishydroxylations (cf. Section 2.1.1).

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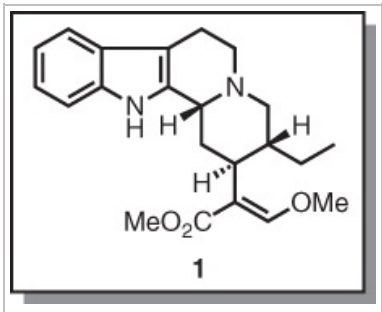
5.2.1 Hirsutine

 1	***Topics:***	• Pictet–Spengler reaction • Enantioselective transfer hydrogenation of an imine • Protection as carbamates (Boc and Cbz) • Reduction of an ethyl ester to an aldehyde • Domino Knoevenagel/hetero-Diels–Alder reaction • Formation of an enamine • Diastereoselective hydrogenation of a cyclic enamine

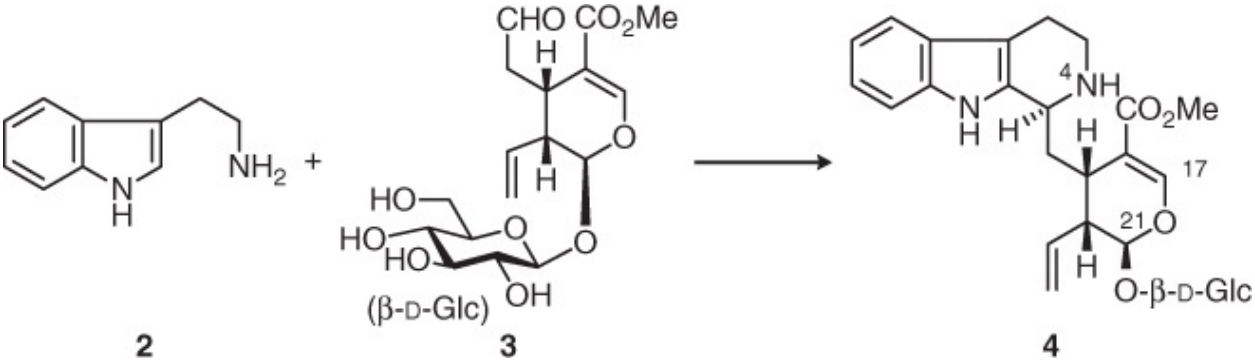
(a) General

Hirsutine (**1**)[1] is an indole alkaloid of the corynanthe subgroup, which has been isolated from the plants *Mitragyna hirsuta* and *Uncaria rhynchophylla* Miq. [1]. The extract of the latter plant is used in the old Chinese folk medicine “Kampo.” Nowadays, hirsutine is of great medicinal interest because it shows a strong inhibition of the influenza A virus of the subtype H3N2 [2, 3]. Its activity, with an ED_{50} value (effective dosage at which 50% of the maximum activity occurs

or at which 50% of the test candidates show a particular reaction) of 0.40–0.57 μg ml^{-1}, is 10–20 times higher than that of the clinically used drug ribavirin. In addition, it shows antihypertensive and antiarrhythmic properties [4].

In 1967, the absolute configuration of hirsutine was established [5], and since then several synthetic methods have been developed. The first enantioselective synthesis of hirsutine (**1**) was published by the Tietze group [6] in 1999, which, incidentally, is an excellent example of a highly efficient domino reaction [7].

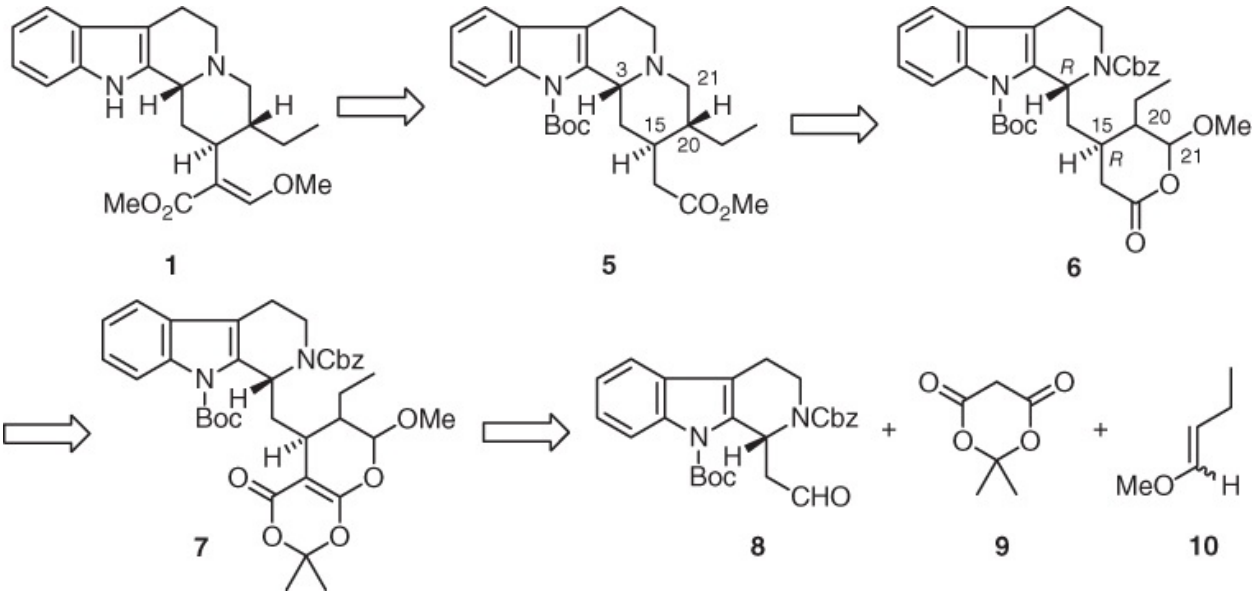
The synthesis of hirsutine partly follows the biosynthesis of the monoterpenoid indole alkaloids, in which – as already mentioned in the introduction to this chapter – the monoterpene secologanin (**3**) [8] undergoes a Pictet–Spengler-type reaction with tryptamine (**2**) to give strictosidine (**4**).



2 **3** **4**

In the next step, the sugar moiety in strictosidine (**4**), used as a protective group by Nature, is removed, and one of the two aldehyde functionalities formed then undergoes a condensation with N-4 to give either the corynanthe (N-4 to C-21) or the vallesiachotamine (N-4 to C-17) indole alkaloids.

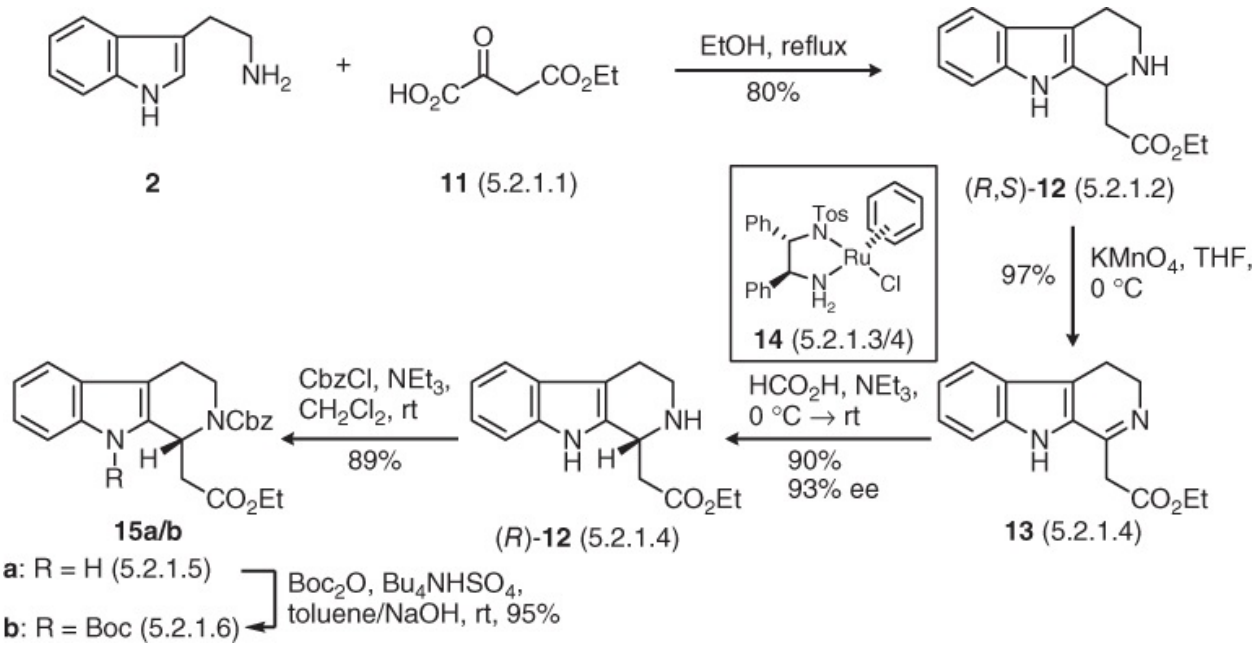
Accordingly, the retrosynthesis of hirsutine (**1**) leads to **5**. The transformation of **5** into **1** can be achieved by an ester condensation with methyl formate followed by a methylation of the formed enol; however, these two steps will not be described here.



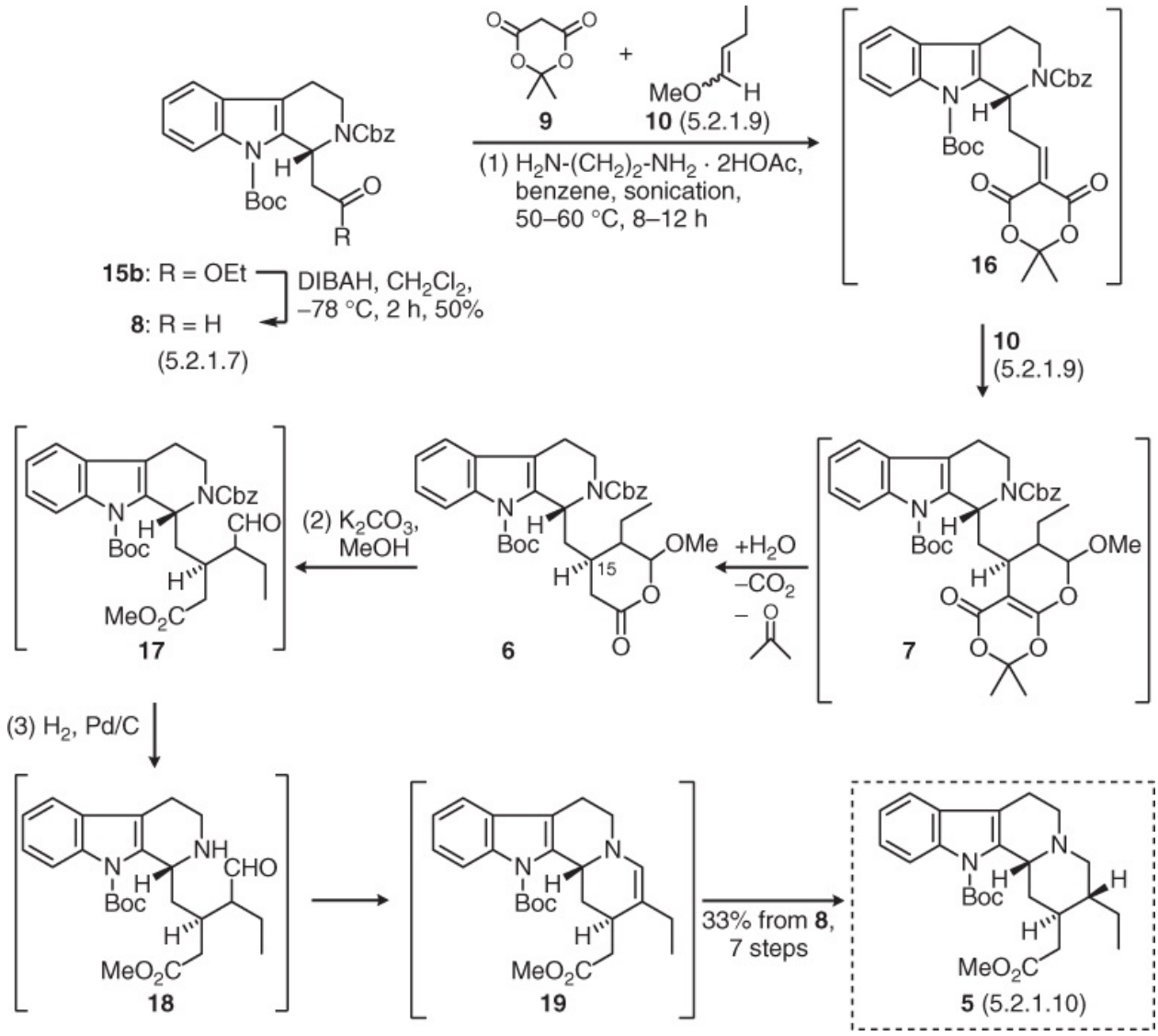
Returning to the retrosynthesis of hirsutine (**1**), the bond between C-21 and N-4 in **5** is obtained as in the biosynthesis by a reductive amination of the aldehyde functionality at C-21, which is protected as an acetal in **6**. Compound **6** can be synthesized by a domino Knoevenagel/hetero-Diels–Alder reaction of the chiral tetrahydro-β-carboline **8** bearing an aldehyde moiety, Meldrum's acid (**9**), and the enol ether **10** via the initially formed cycloadduct **7** which loses acetone and CO_2.

(b) Synthesis of 5

The β-carboline **8** is prepared starting with the so-called Pictet–Spengler reaction of tryptamine (**2**) and carbethoxypyruvic acid (**11**), which can be obtained from diethyl oxalacetate by partial hydrolysis, to give a racemic mixture of **12**. This can be oxidized with $KMnO_4$ to afford the achiral imine **13**.



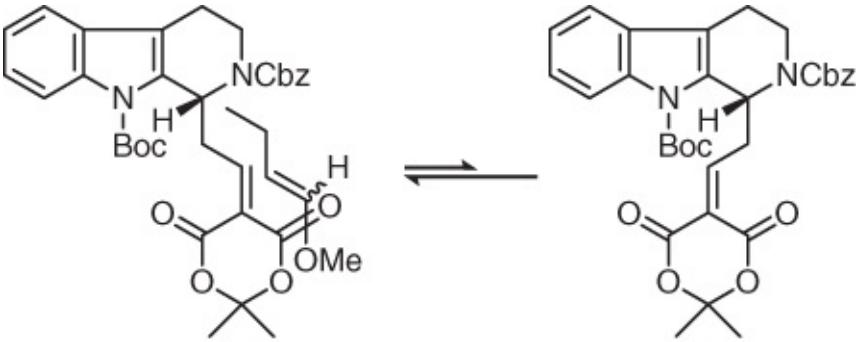
Enantioselective transfer hydrogenation using the chiral Ru catalyst **14** developed by Noyori and coworkers [9] in the presence of formic acid and NEt_3 allows face-selective reduction of the imine **13** to give the almost enantiopure tetrahydro-β-carboline (*R*)-**12**. The catalyst **14** is prepared *in situ* by the reaction of $[RuCl_2(C_6H_6)]_2$, obtained from $RuCl_3 \cdot 3H_2O$ and 1,4-cyclohexadiene, with the mono-toluenesulfonamide of a chiral diamine (cf. **3.3.2.1**). Using the enantiomeric catalyst *ent*-**14**, (*S*)-**12** is also accessible. The subsequent transformations can be performed either using (*R*)-**12**, leading to enantiopure **5**, or with racemic (*R*,*S*)-**12**, which would give racemic **5**. Reaction of (*R*)-**12** with CbzCl in the presence of NEt_3 affords **15a**, which is transformed into **15b** using Boc_2O in the presence of a catalytic amount of DMAP.



Reduction of **15b** with DIBAH (diisobutylaluminum hydride) in CH_2Cl_2 directly affords the aldehyde **8**, which is then used for the domino Knoevenagel/ hetero-Diels–Alder reaction with Meldrum's acid (**9**) and a diastereomeric mixture of the enol ether **10** under sonication in benzene in the presence of a few crystals of ethylenediammonium diacetate (EDDA). After formation of the Knoevenagel adduct **16**, the cycloadduct **7** is obtained, which is unstable under the reaction conditions and loses CO_2 and acetone upon reaction with H_2O formed in the condensation step to give the lactone **6** with an induced 1,3-diastereoselectivity of >24 : 1 with reference to C-15. The other two stereogenic centers are formed unselectively because the enol ether **10** is used as a diastereomeric mixture and the endo/exo selectivity is low. However, this is of no concern because these two stereogenic centers are lost during further transformations. Thus, without isolation, **6** is treated with MeOH and a catalytic amount of K_2CO_3 after removal

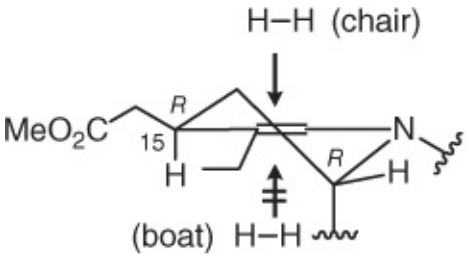
of excess **10**, which is followed by hydrogenation in the presence of Pd/C to afford **5** as a single diastereomer. In this process, the lactone moiety in **6** is attacked by methoxide to give **17** containing a methyl ester and an aldehyde moiety with the elimination of methoxide. The subsequent hydrogenolysis liberates the secondary amino function (**17** → **18**), which attacks the aldehyde function to yield the enamine **19**. The final step is hydrogenation of the enamine **19** under stereoelectronic control to give **5** as a single enantiopure diastereomer.

An unusual feature of the synthesis of **5** that merits discussion is the high 1,3-diastereoselectivity of the hetero-Diels–Alder reaction. It is assumed that the 1-oxa-1,3-butadiene **16** adopts the conformation K-1 rather than K-2 as a result of the steric hindrance caused by the Boc protecting group at the indole nitrogen. Furthermore, the enol ether should attack the (*E*)-1-oxa-1,3-butadiene moiety and not the less reactive (*Z*)-1-oxa-1,3-butadiene, which also exists in the molecule **16**. Finally, the attack should come from above, syn to the hydrogen as the more accessible site of the molecule, to give **6**. Interestingly, employing an aldehyde of type **8** without the Boc protecting group at the indole nitrogen leads to the (*R*,*S*)-diastereomer of **6** as the main product, albeit with lower diastereoselectivity.

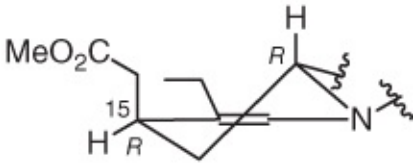


16-K-1 **16**-K-2

The second interesting stereochemical aspect in the formation of **5** is the high selectivity in the formation of the stereogenic center C-20. One can assume that the enamine **19** is the intermediate, which may exist in the conformations K-1 and K-2. However, K-1 should be preferred because of a favorable pseudo-equatorial orientation of the acetate moiety at C-15. Assuming that the attack of the hydrogen should come from the β-face due to a favorable chair-like transition state, the stereoselective formation of **5** can be easily explained.



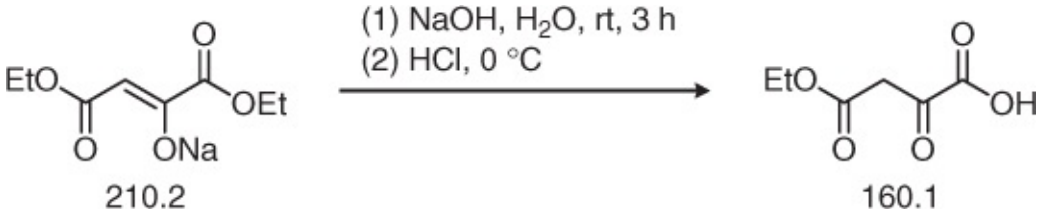
19-K-1



19-K-2

(c) Experimental Procedures for the Synthesis of 5

5.2.1.1 * **Carbethoxypyruvic acid** [10]



210.2 160.1

An aqueous NaOH solution (6 M, 33.4 ml) is added dropwise to a stirred solution of the sodium salt of diethyl oxalacetate (42.0 g, 200 mmol) in H_2O (400 ml) at room temperature. The resulting mixture is vigorously stirred for 3 h, and then HCl (6 M, 70 ml) is added at 0 °C.

The acidic solution is extracted with Et_2O (8 × 140 ml) and EtOAc (3 × 140 ml), and the combined organic fractions are dried over $MgSO_4$, and filtered. Removal of the solvent *in vacuo* affords the acid as an orange suspension, consisting of the crystalline enolic form and the oily ketonic form; 28.0 g (88%).

UV (CH_3CN): λ_{max} (nm) (log ϵ) = 257.0 (0.353), 211.5 (0.126), 194.0 (0.196).

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 2986, 1729, 1415, 1217, 1026, 853, 787.

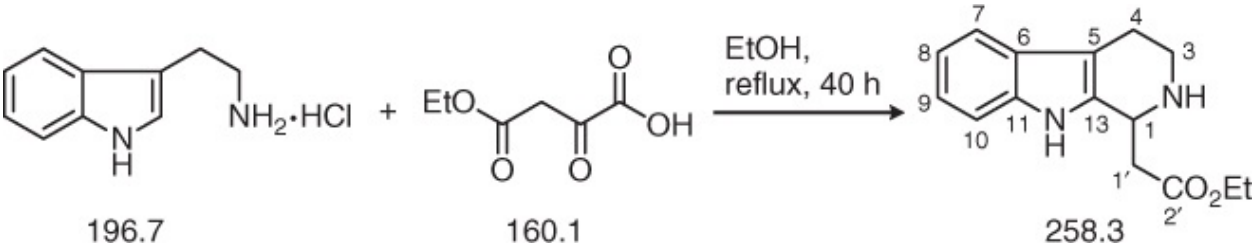
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 5.93 (s, enolic form, 0.6H, CH), 4.25 (q, ketonic form, *J* = 7.0 Hz, 2H, CH_2), 4.09 (q, enolic form, *J* = 7.0 Hz, 1.5H, CH_2), 1.29 (t, ketonic form, *J* = 7.0 Hz, 3.0H, CH_3), 1.22 (t, enolic form, *J* = 7.0 Hz, 2.4H, CH_3).

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 172.4 ($\underline{C}(O)CO_2H$), 170.7 ($\underline{C}(O)OCH_2CH_3$), 170.0 ($CO_2H$), 96.9 (CH), 61.9, 61.7 (CH_2), 47.7

($O\underline{C}H_2CH_3$), 14.4, 14.3 ($OCH_2\underline{C}H_3$).

MS (DCI-NH_3): *m*/*z* (%) = 178 (29) $[M+NH_4]^+$, 195 (11) $[M+NH_3+NH_4]^+$.

5.2.1.2	*	**1-Carbethoxymethyl-1,2,3,4-tetrahydro-β-carboline** [10]



A solution of the acid **5.2.1.1** (28.4 g, 178 mmol) in EtOH (85 ml) is added over 30 min to a stirred solution of tryptamine hydrochloride (25.0 g, 127 mmol) in EtOH (400 ml) under reflux. The mixture is refluxed for an additional 40 h and is then kept overnight at 0–5 °C to allow crystallization of the hydrochloride of the formed β-carboline.

The precipitate is filtered off and added to a saturated $NaHCO_3$ solution, and the suspension is stirred until the solid has dissolved. The liberated free amine is extracted with EtOAc. The organic layer is washed with brine (2 × 20 ml), dried over Na_2SO_4, and filtered, and the solvent is removed *in vacuo* to afford the β-carboline as a light-brown oil; 36.7 g (80%), R_f = 0.55 (MeOH/EtOAc, 1 : 3, +1% (v/v) NEt_3).

UV (CH_3CN): λ_{max} (nm) (log ϵ) = 289.0 (0.314), 280.5 (0.390), 226.5 (1.659), 195.0 (1.183).

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3400, 2930, 1722, 1451, 1373, 1157, 1112, 1023, 742.

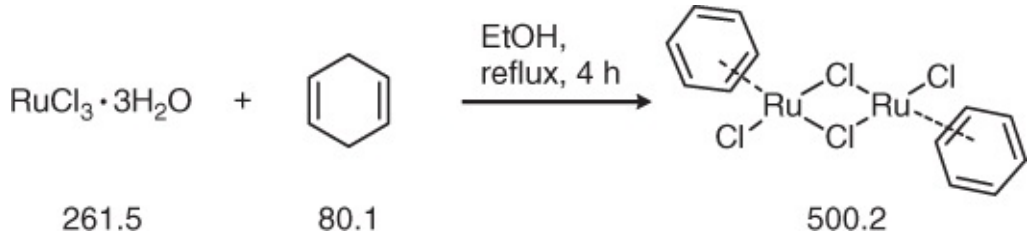
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.64 (s_{br}, 1H, N–H indole), 7.48 (d, *J* = 10.0 Hz, 1H, 7-H), 7.28 (d, *J* = 10.0 Hz, 1H, 10-H), 7.10 (2 × ddd, *J* = 7.0, 7.0, 1.0 Hz, 2H, 8-H, 9-H), 4.44 (t, *J* = 7.0 Hz, 1H, 1-H), 4.20 (q, *J* = 7.0 Hz, 2H, $C\underline{H}_2CH_3$), 3.21 (dt, *J* = 13.0, 5.5 Hz, 1H, 3-H_b), 3.07 (dt, *J* = 13.0, 5.5 Hz, 1H, 3-H_a), 2.79 (d, *J* = 7.0 Hz, 2H, 1′-H_2), 2.72 (m, 2H, 4-H_2), 1.90 (s_{br}, 1H, NH), 1.28 (t, *J* = 7.0 Hz, 3H, $CH_2C\underline{H}_3$).

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 173.0 (C-2′), 135.4 (C-11), 134.9

(C-13), 127.0 (C-6), 121.6 (C-8), 119.1 (C-9), 118.0 (C-7), 110.8 (C-10), 108.9 (C-5), 61,0 ($\underline{C}H_2CH_3$), 48.7 (C-1), 41.8 (C-3), 40.6 (C-1′), 22.5 (C-4), 14.1 ($CH_2\underline{C}H_3$).

MS (DCI-NH_3): *m*/*z* (%) = 259 (100) $[M+H]^+$, 517 (20) $[2M+H]^+$.

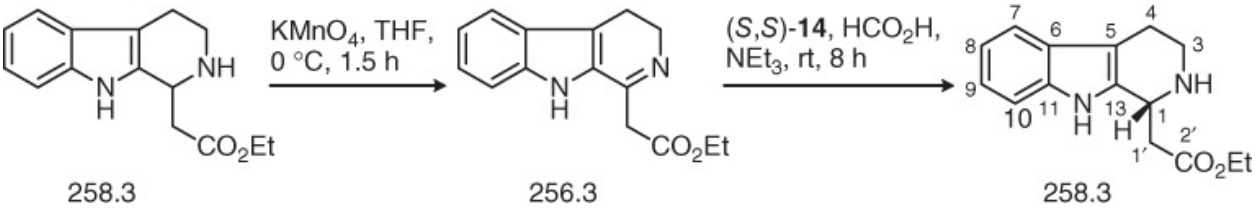
5.2.1.3	**	**Dichloro(η^6-benzene)ruthenium(II) dimer** [11]



A mixture of ruthenium trichloride monohydrate (300 mg, 41% Ru), EtOH (4 ml), and 1,4-cyclohexadiene (3 ml) is refluxed for 4 h. Afterward, the suspension is filtered under argon. The residue is washed with anhydrous MeOH and dried *in vacuo* to give $[RuCl_2(C_6H_6)]_2$ as an orange powder; 300 mg (98%).

MS (DCI): *m*/*z* (%) = 285 $[M+NH_3+NH_4]^+$.

5.2.1.4	***	**(1*R*)-1-Carbethoxymethyl-1,2,3,4-tetrahydro-β-carboline** [11]



Powdered $KMnO_4$ (1.00 g) is added in small portions over a period of 0.5 h to a vigorously stirred solution of the β-carboline **5.2.1.2** (260 mg, 1.00 µmol) in anhydrous THF (20 ml) at 0 °C. The reaction mixture is kept at 0 °C and stirred for 1.5 h (TLC (thin-layer chromatography) control). The precipitate is then filtered off and washed with THF (2 × 10 ml). The combined filtrates and washings are concentrated to leave the crude imine as a pale-yellow solid; 250 mg (97%).

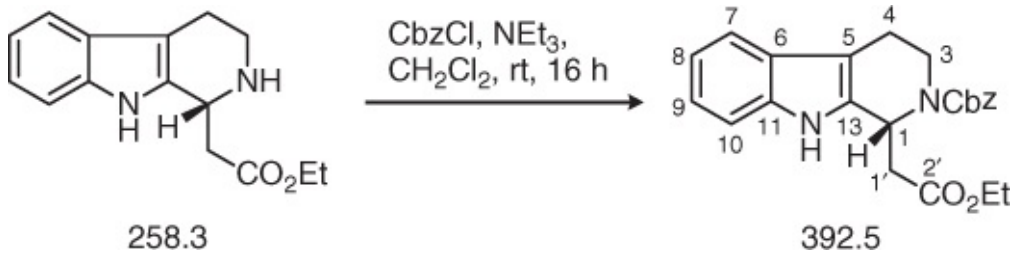
The catalyst for the enantioselective hydrogenation is prepared *in situ* by stirring $[RuCl_2(C_6H_6)]_2$ (**5.2.1.3**, 6.0 mg, 24 µmol) and the diamine **3.3.2.1** (7.3 mg, 20

μmol) in CH_3CN (2.0 ml) for 5 min.

Formic acid/NEt_3 (5 : 2, 2.0 ml) and the preformed catalyst are added to a solution of the imine (120 mg, 500 μmol) in CH_3CN (5.0 ml) at 0 °C, and the mixture is stirred at room temperature for 8 h. Direct purification of the crude product by flash chromatography eluting with EtOAc/EtOH/NEt_3 (100 : 10 : 1) gives the (1*R*)-β-carboline as brown oil; 230 mg (90%, 93% ee), $[\alpha]^{20}_D$ = +61.9 (*c* = 0.5, $CHCl_3$).

The spectra are identical to those of the racemic compound.

5.2.1.5	*	**1-Carbethoxymethyl-2-benzyloxycarbonyl-1,2,3,4-tetrahydro-β-carboline**[2]



A solution of benzyl chloroformate (4.78 ml, 33.6 mmol) in CH_2Cl_2 (17 ml) is added to a stirred solution of the β-carboline **5.2.1.4** (7.28 g, 28.0 mmol), NEt_3 (11.6 ml, 84 mmol), and a catalytic amount of DMAP in anhydrous CH_2Cl_2 (28 ml) at 0 °C; stirring is continued at room temperature for 12 h.

The organic layer is then washed with H_2O (45 ml), HCl (2 M, 45 ml), further H_2O (45 ml), saturated Na_2CO_3 solution (45 ml), and brine (45 ml). The organic layer is dried over Na_2SO_4 and filtered, and the solvent is removed *in vacuo*. The brown oily residue is used for the next reaction without further purification; 9.80 g (89%), R_f = 0.69 (EtOAc).

UV (CH_3CN): λ_{max} (nm) (log ϵ) = 289.0 (0.176), 278.5 (0.235), 273.0 (0.237), 224.0 (1.107).

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3395, 2981, 1699, 1424, 1361, 1266, 1218, 1100, 1020, 742, 699.

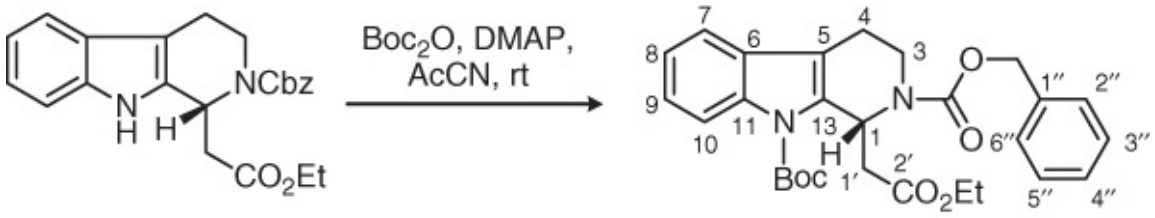
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.91, 8.75 (2 × s_{br}, 1H, indole NH), 7.47 (dd, *J* = 7.1, 7.1 Hz, 1H, 10-H), 7.42–7.32 (m, 6H, 7-H, Ph–H), 7.16

(ddd, *J* = 7.1, 7.1, 1.0 Hz, 1H, 9-H), 7.08 (dd, *J* = 7.1, 7.1 Hz, 1H, 8-H), 5.67 (ddd, *J* = 25.0, 8.0, 4.0 Hz, 1H, 3-H_b), 5.19 (s, 2H, Ph–CH_2), 4.51 (ddd, *J* = 39.0, 13.0, 5.0 Hz, 1H, 1-H), 4.20 (m, 2H, CH_2), 3.14 (m_c, 1H, 3-H_a), 2.99–2.67 (m, 4H, 4-H_2, 1′-H_2), 1.26 (td, *J* = 7.0, 3.5 Hz, 3H, CH_3).

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 172.9 (C-2′), 155.0 (C-1″), 136.5 (C-13), 135.6 (C-11), 133.0, 128.5, 128.0, 127.8 (Ph–C), 126.3 (C-6), 121.9 (C-8), 119.3 (C-9), 118.0 (C-7), 111.1 (C-10), 108.1 (C-5), 61.2 (CH_2), 47.5 (C-1), 39.3 (C-3), 39.1 (C-2″), 39.0 (C-1′), 21.1 (C-4), 14.1 (CH_3).

MS (DCI-NH_3): *m*/*z* (%) = 393 (70) $[M+H]^+$, 410 (62) $[M+NH_4]^+$.

5.2.1.6	*	**1-Carbethoxymethyl-2-benzyloxycarbonyl-12-*tert*-butyloxycarbonyl-**
		1,2,3,4-tetrahydro-β-carboline[2)]



392.5 492.6

A solution of 2,2-dimethylpropionic acid anhydride (6.81 g, 31.2 mmol) in CH_3CN (80 ml) and DMAP (826 mg, 6.76 mmol) is added to a stirred solution of the β-carboline **5.2.1.5** (9.62 g, 24.5 mmol) in CH_3CN (80 ml) at room temperature; stirring is continued for 12 h.

The reaction is then quenched with aqueous HCl (0.4 M, 160 ml). After separation of the organic layer, the aqueous layer is extracted with CH_2Cl_2 (2 × 160 ml). The combined organic layers are washed with a saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4, and filtered, and the solvent is removed *in vacuo* to afford the protected β-carboline as a light-brown oil, which is used for the next reaction without further purification; 11.2 g (95%), R_f = 0.41 (EtOAc/*n*-pentane, 1 : 4).

UV (CH_3CN): λ_{max} (nm) (log ϵ) = 293.0 (0.093), 265.5 (0.336), 228.5

(0.557).

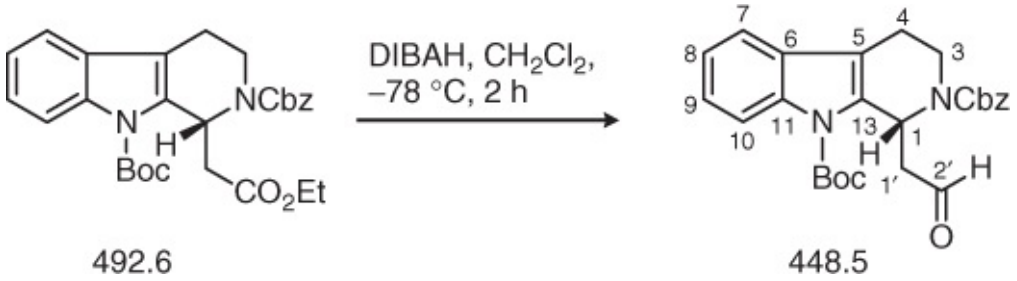
IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 2980, 1732, 1457, 1424, 1323, 1141, 1116, 1036, 855, 749, 699.

^{1}H NMR (300 MHz, $CDCl_3$) (ratio of rotamers: 3 : 2): δ (ppm) = 8.18 (d, *J* = 7.0 Hz, 1H, 10-H), 7.44–7.18 (m, 8H, 7-H, 8-H, 9-H, Ph–H), 6.37, 6.27 (2 × dd, *J* = 10.2, 3.5 Hz, 1H, 1-H), 5.18, 5.14 (2 × s, 2H, Ph–CH_2), 4.52, 4.40 (m, dd, *J* = 14.4, 6.0 Hz, 1H, 3-H_b), 4.15–3.99 (m, 2H, CH_2), 3.32 (m_c, 1H, 3-H_a), 3.10–2.60 (m, 4H, 4-H_2, 1′-H_2), 1.73, 1.60 (2 × s, 9H, $C(CH_3)_3$), 1.16 (m, 3H, CH_3).

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 170.2, 169.9 (C-2′), 155.5 (N-2-CO), 149.8 (N-12-CO), 136.7 (Ph–C), 136.7 (C-13), 136.3 (C-11), 133.5 (C-11), 128.6 (C-6), 128.4 (2 × Ph–C), 128.2, 128.0, 124.7 (3 × Ph–C), 124.6 (C-8), 122.9 (C-7), 118.1, 118.0 (C-9), 115.9 (C-10), 115.4 (C-5), 84.8 ($\underline{C}(CH_3)_3$), 67.8, 67.3 (Ph–$\underline{C}H_2$), 60.7 ($\underline{C}H_2$), 49.9 (C-1), 39.1, 39.0 (C-1′), 36.8, 36.4 (C-3), 28.2, 28.1 ($C(\underline{C}H_3)_3$), 21.3, 20.6 (C-4), 14.1 (CH_3).

MS (DCI-NH_3): *m*/*z* (%) = 510 (74) $[M+NH_4]^+$, 493 (38) $[M+H]^+$.

5.2.1.7	**	**1-(2-Formylmethyl)-2-benzyloxycarbonyl-12-*tert*-butyloxycarbonyl-**
		1,2,3,4-tetrahydro-β-carboline[2)]



492.6 448.5

A solution of DIBAH (1 M in *n*-hexane, 22.7 ml, 22.7 mmol), precooled to −78 °C, is added to a stirred solution of the ethyl ester **5.2.1.6** (11.2 g, 22.7 mmol) in anhydrous CH_2Cl_2 (230 ml) at −78 °C via a transfer cannula. Stirring is continued at the same temperature for 2 h, and then the reaction is carefully quenched by the dropwise addition of a 9 : 1 mixture of MeOH and 2 M aqueous HCl (68 ml).

The reaction mixture is quickly warmed to room temperature and washed with a saturated NH_4Cl solution (250 ml). After separation of the organic layer, the aqueous layer is extracted with CH_2Cl_2 (2 × 300 ml). The combined organic layers are washed with saturated $NaHCO_3$ solution (300 ml), dried over Na_2SO_4, and filtered, and the solvent is removed *in vacuo*. The residue is purified by flash chromatography on silica gel (EtOAc/*n*-pentane, 1 : 4) to give the aldehyde as a colorless foam; 5.07 g (50%), (1*R*): $[\alpha]^{20}_D = -88.8$ (*c* = 0.16, CH_2Cl_2), R_f = 0.32 (EtOAc/*n*-pentane, 1 : 2).

UV (CH_3CN): λ_{max} (nm) (log ϵ) = 293.0 (0.102), 264.5 (0.361), 228.5 (0.621).

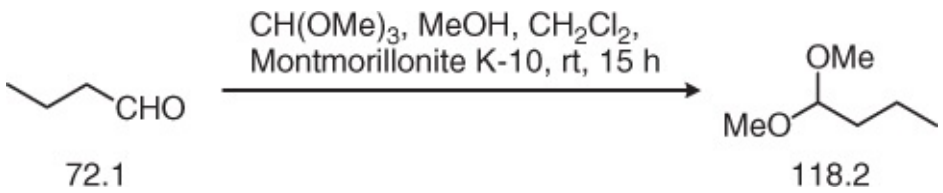
IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 2979, 1725, 1456, 1423, 1369, 1235, 1143, 1117, 1016, 853, 751, 699.

^{1}H NMR (300 MHz, $CDCl_3$) (ratio of rotamers: 1 : 1): δ (ppm) = 9.90, 9.77 (2 × d, *J* = 4.0 Hz, 1H, CHO), 8.07 (d, *J* = 7.5 Hz, 1H, 10-H), 7.38–7.17 (m, 8H, 7-H, 8-H, 9-H, Ph–H), 6.53, 6.38 (2 × d, *J* = 8.9 Hz, 1H, 1-H), 5.16 (dd, *J* = 15.0 Hz, 2H, Ph–CH_2), 4.51, 4.37 (2 × dd, *J* = 13.8, 5.0 Hz, 1H, 3-H_b), 3.30–2.50 (m, 5H, 3-H_a, 4-H_2, 1′-H_2), 1.69, 1.58 (2 × s, 9H, $C(CH_3)_3$).

^{13}C NMR (76 MHz, $CDCl_3$): *δ* (ppm) = 200.9, 200.1 (C-2′), 155.5 (N-2-CO), 149.9 (N-12-CO), 136.2 (Ph–C), 135.6 (C-11), 133.5 (C-13), 128.5 (C-6), 128.4 (2 × Ph–C), 128.3, 128.0, 127.7 (3 × Ph–C), 124.6, 124.5 (C-8), 122.9 (C-7), 118.0, 117.9 (C-9), 115.8 (C-10), 116.0, 115.4 (C-5), 84.6 ($\underline{C}(CH_3)_3$), 67.8, 67.5 (Ph–CH_2), 48.2 (C-1), 47.7 (C-1′), 36.8, 36.4 (C-3), 28.1 ($C(\underline{C}H_3)_3$), 20.4, 21.0 (C-4).

MS (DCI-NH_3): *m*/*z* (%) = 466 (100) $[M+NH_4]^+$, 914 (3) $[2M+NH_4]^+$.

5.2.1.8	**	**1,1-Dimethoxybutane** [10]



72.1 118.2

A suspension of trimethyl orthoformate (16.0 ml), methanol (16.0 ml), and

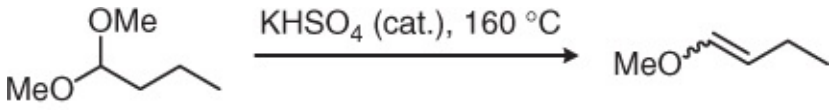
Montmorillonite K-10 clay (10.0 g) is stirred for 10 min at room temperature under an argon atmosphere. The mixture is then diluted with CH_2Cl_2 (50.0 ml), cooled to 0 °C, and treated with butanal (8.00 ml, 6.42 g, 89.0 mmol, note). The resulting suspension is stirred for 15 h at room temperature and then filtered through Celite®. The filter cake is washed with CH_2Cl_2 (150 ml), and the combined filtrates are washed with saturated $NaHCO_3$ solution (100 ml), water (100 ml), and brine (100 ml). The organic layer is dried over $MgSO_4$, and the solvent is removed *in vacuo* (not below 400 mbar at 30 °C). The residue is distilled over a 10-cm Vigreux column at ambient pressure to afford the acetal as a colorless liquid (bp 113 °C); 7.64 g (73%), n^{20}_D = 1.3882.

IR (NaCl): $\tilde{\nu}$ (cm^{-1}) = 2960, 2940, 2880, 2830, 1190, 1135, 1125.

^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) = 4.33 (t, *J* = 5.0 Hz, 1H, CH), 3.28 (s, 6H, OCH_3), 1.70–0.80 (m, 7H, CH_2, CH_3).

Note: Distilled, bp 75–76 °C.

5.2.1.9	**	**(*E*/*Z*)-1-Methoxy-1-butene** [10]



118.2 86.1

A distillation apparatus consisting of a 25-ml, two-necked, round-bottomed flask and a 10-cm Vigreux column with a cooler is charged with $KHSO_4$ (15.0 mg, 110 µmol) and 1,1-dimethoxybutane **5.2.1.8** (7.00 g, 59.2 mmol). The stirred mixture is heated to 160 °C (bath temperature) while the enol ether and MeOH formed are continuously distilled off into a flask containing 10 ml of 1% K_2CO_3 solution. The temperature of the column should not be higher than 50–55 °C. The distillate is washed with 1% K_2CO_3 solution (3 × 10 ml) to remove MeOH. After distillation of the crude product over the 10-cm Vigreux column, the enol ether is obtained as a 1.8 : 1 mixture of the *Z*- and *E*-isomers (bp 70–72 °C); 2.04 g (40%).

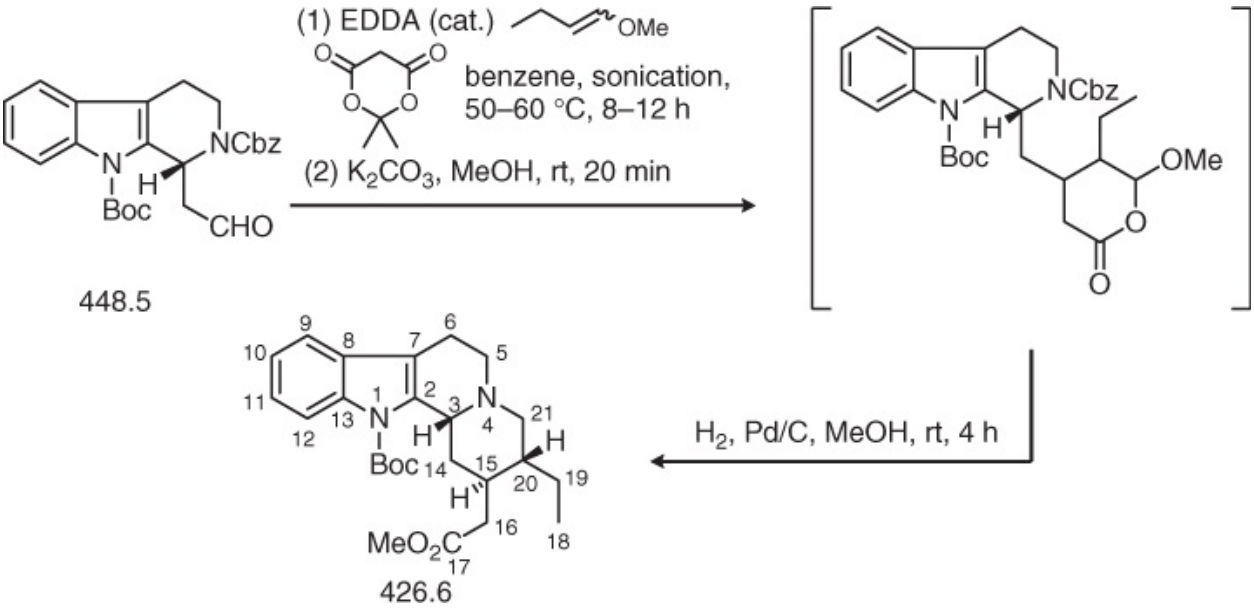
^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) = 6.28 (dt, *J* = 12.5, 1.0 Hz, 1H, 1-H (*E*-isomer)), 5.82 (*J* = 6.5, 1.5 Hz, 1H, 1-H (*Z*-isomer)), 4.76 (dt, *J* = 12.5,

7.0 Hz, 1H, 2-H (*E*-isomer)), 4.32 (dt, *J* = 6.5, 6.0 Hz, 1H, 2-H (*Z*-isomer)), 3.60 (s, 3H, OCH_3 (*Z*-isomer)), 3.50 (s, 3H, OCH_3 (*E*-isomer)), 2.06 (dqd, *J* = 7.5, 6.5, 1.5 Hz, 2H, 3-H_2 (*Z*-isomer)), 1.94 (dqd, *J* = 7.0, 7.0, 1.0 Hz, 2H, 3-H_2 (*E*-isomer)), 0.97 (t, *J* = 7.0 Hz, 3H, CH_3 (*E*-isomer)), 0.94 (t, *J* = 7.5 Hz, 3H, CH_3 (*Z*-isomer)).

^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) = 146.4 (C-1 (*E*-isomer)), 145.5 (C-1 (*Z*-isomer)), 108.8 (C-2 (*Z*-isomer)), 104.9 (C-2 (*E*-isomer)), 59.4 (OCH_3 (*Z*-isomer)), 55.8 (OCH_3 (*E*-isomer)), 21.0 (C-3 (*E*-isomer)), 17.3 (C-3 (*Z*-isomer)), 15.4 (CH_3 (*E*-isomer)), 14.5 (CH_3 (*Z*-isomer)).

MS (EI, 70 eV): *m*/*z* (%) = 86 (32) $[M]^+$, 71 (100) $[M-CH_3]^+$.

5.2.1.10	***	**(3*RS*,15*RS*,20*RS*)-15-(Methoxycarbonylmethyl)-20-ethyl-1-(*tert*-**
		butyloxycarbonyl)-3,4,5,6,14,15,20,21-octahydro-indolo[2,3*a*]
		quinolizine [10]



A few crystals of EDDA are added to a solution of the aldehyde **5.2.1.7** (50 mg, 0.11 mmol), the *E*/*Z* mixture of the enol ether **5.2.1.9** (28.4 mg, 0.33 mmol), and Meldrum's acid (19.0 mg, 0.13 mmol) in benzene (0.5 ml; Caution: carcinogenic!). The reaction vessel is sealed under an argon atmosphere, and the red solution obtained is sonicated at 50–60 °C for 8–12 h (TLC monitoring).

After complete conversion, the solution is subjected to column filtration through silica gel (gradient: petroleum ether to petroleum ether/EtOAc, 2 : 1). The solvents are evaporated and the crude product is dissolved in MeOH (5 ml). K_2CO_3 (10 mg) and Pd/C (50 mg) are added, and the resulting mixture is stirred at room temperature for 30 min. The suspension is then stirred vigorously under a hydrogen atmosphere for 4 h, and thereafter is filtered through silica gel (MeOH/EtOAc/NEt_3, 1 : 3 : 0.05). The solvent is removed *in vacuo* to give the desired product as yellow foam; 15.6 mg (33%), R_f = 0.29 (petroleum ether/EtOAc, 3 : 1), (+)-enantiomer: $[\alpha]^{20}_D$ = +93.0 (*c* = 0.3, CH_2Cl_2).

UV (CH_3CN): λ_{max} (nm) (log ϵ) = 293 (3.452), 268 (4.066), 229 (4.304).

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.92 (dd, *J* = 8.0, 1.5 Hz, 1H, 12-H), 7.39 (dd, *J* = 8.0, 1.5 Hz, 1H, 9-H), 7.24, 7.20 (2 × ddd, *J* = 8.0, 8.0, 1.5 Hz, 2H, 10-H, 11-H), 4.03 (s_{br}, 1H, 3-H), 3.71 (s, 3H, OCH_3), 3.00–2.52 (m, 8H, 5-H_2, 6-H_2, 21-H_2, 16-H_2), 2.10 (m_c, 1H, 15-H), 1.95 (ddd, *J* = 13.0, 3.5, 3.0 Hz, 1H, 14-H_{eq}), 1.88 (ddd, *J* = 13.0, 9.0, 5.0 Hz, 1H, 14-H_{ax}), 1.66 (s, 9H, *t*-butyl-H), 1.58–1.49 (m, 2H, C$\underline{H}_2$$CH_3$), 0.91 (t, *J* = 7.5 Hz, 3H, CH_3).

^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) = 173.6, 150.5 (2 × CO), 136.6, 133.2, 129.4, 123.6, 122.5, 117.9, 117.0, 115.1 (8 × Ar–C), 83.6 ($\underline{C}(CH_3)_3$), 56.0 (C-3), 54.0 (C-5), 51.4 (OCH_3), 50.9 (C-21), 40.5 (C-20), 37.5 (C-16), 33.5 (C-15), 31.6 (C-14), 28.1 (C($\underline{C}H_3)_3$), 25.8 (C-19), 21.4 (C-6), 12.2 (CH_3).

MS (70 eV, EI): *m*/*z* (%) = 426 (20) $[M]^+$, 369 (100) $[M-t\text{-butyl}]^+$, 325 (20) $[M-Boc]^+$, 57 (15) $[t\text{-butyl}]^+$.

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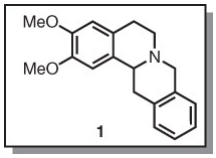
5.2.2 *rac*-2,3-Dimethoxyberbine



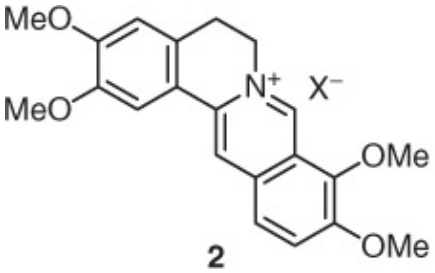
Topics:

- Baeyer–Villiger oxidation of a cycloalkanone to a lactone
- Aminolysis of a lactone

		• Domino process: Bischler–Napieralski isoquinoline synthesis/transformation CH_2OH → CH_2Cl/cycloalkylation • Reduction of iminium salts: $R_2C=^{+}NR'_2$ → $HR_2C–NR'_2$

(a) General

The target molecule **1** is a protoberberine alkaloid with interesting physiological and pharmacological properties, including cytostatic activity [1, 2]. In Nature, the 1-benzylisoquinoline-based protoberberine alkaloids mainly occurs in two structural varieties, namely as protoberberinium salts (e.g., **2**, palmatine) and tetrahydroprotoberberine (e.g., **3**, tetrahydropalmatine). They usually bear hydroxy, methoxy, or methylenedioxy groups on the terminal aromatic rings (A/D). The unsubstituted tetracyclic system **4** has been named *berbine* [3].



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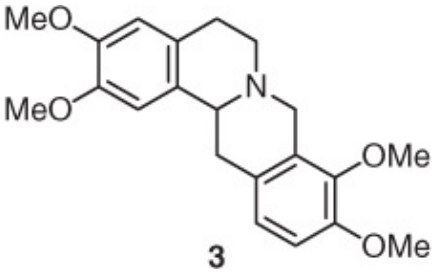
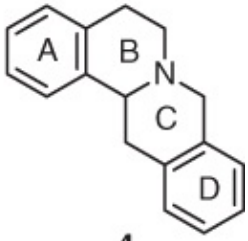
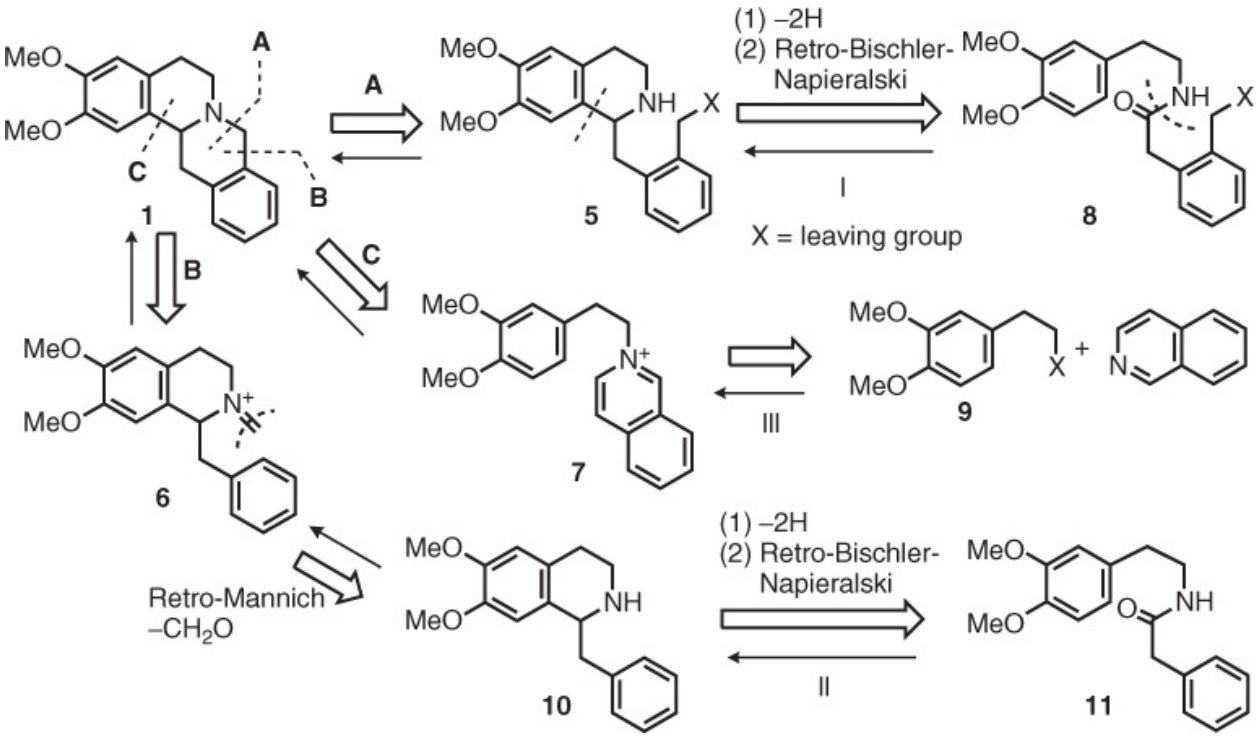


3



4

Retrosynthesis of **1** can be conducted in two ways:

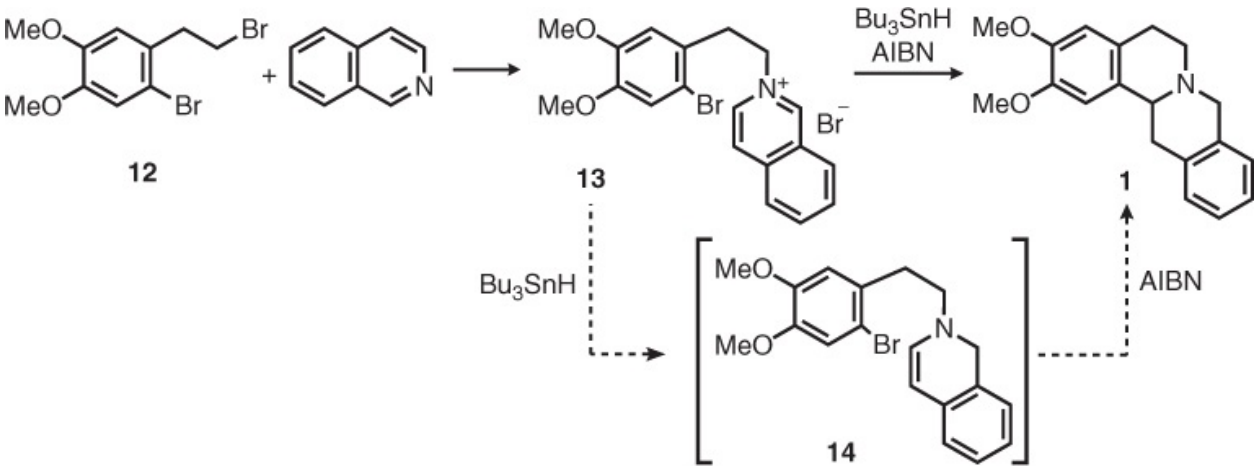


Disconnections A and B lead to the 1-benzylisoquinoline derivatives **5** and **10**, respectively, the latter via **6**, which might be accessible by Bischler–Napieralski reactions of the amides **8** and **11**, respectively. A different approach could be followed according to disconnection path C, leading to the isoquinolinium salts **7**, which should be accessible by alkylation of isoquinoline with the halide **9**. A problem could arise from the need for regioselective cyclization of **7** at C-3 (**7** → **1**) because, in general, the more reactive position of isoquinolinium salts is C-1.

Approach **I** allows the most straightforward access to **1**, and is presented in detail in Section (b) [4].

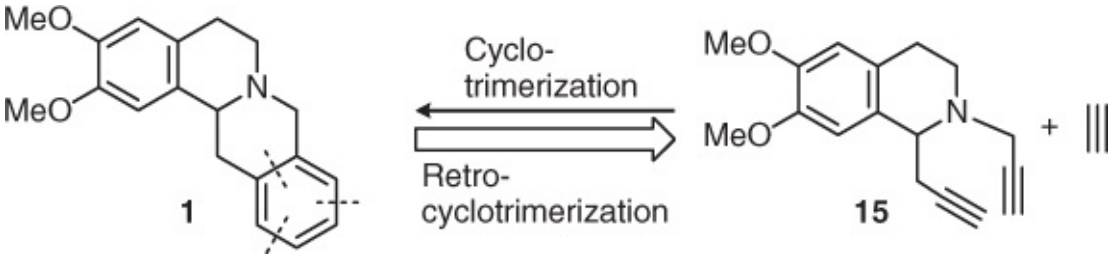
Approach **II** is the basis of a reported synthesis of **1** [5] by intramolecular aminoalkylation of the 1-benzyltetrahydroisoquinoline **10** with formaldehyde (**11** → **10** → **6** → **1**) [6].

The aforementioned problem associated with approach **III** is elegantly solved by a radical cyclization strategy [2], which starts from the ortho-brominated (β-arylethyl)halide **12** and thus involves the corresponding isoquinolinium salt **13**:



Reaction of **13** with *n*-Bu_3SnH/AIBN (2,2′-azobisisobutyronitrile) (3 : 1) induces a domino process to give **1**, which comprises initial reduction of the more reactive C1–N double bond in **13** followed by formation of an aryl radical at the bromoaryl position and subsequent cyclization by addition to the C-3/C-4 double bond of the intermediate 1,2-dihydroisoquinoline **14**.

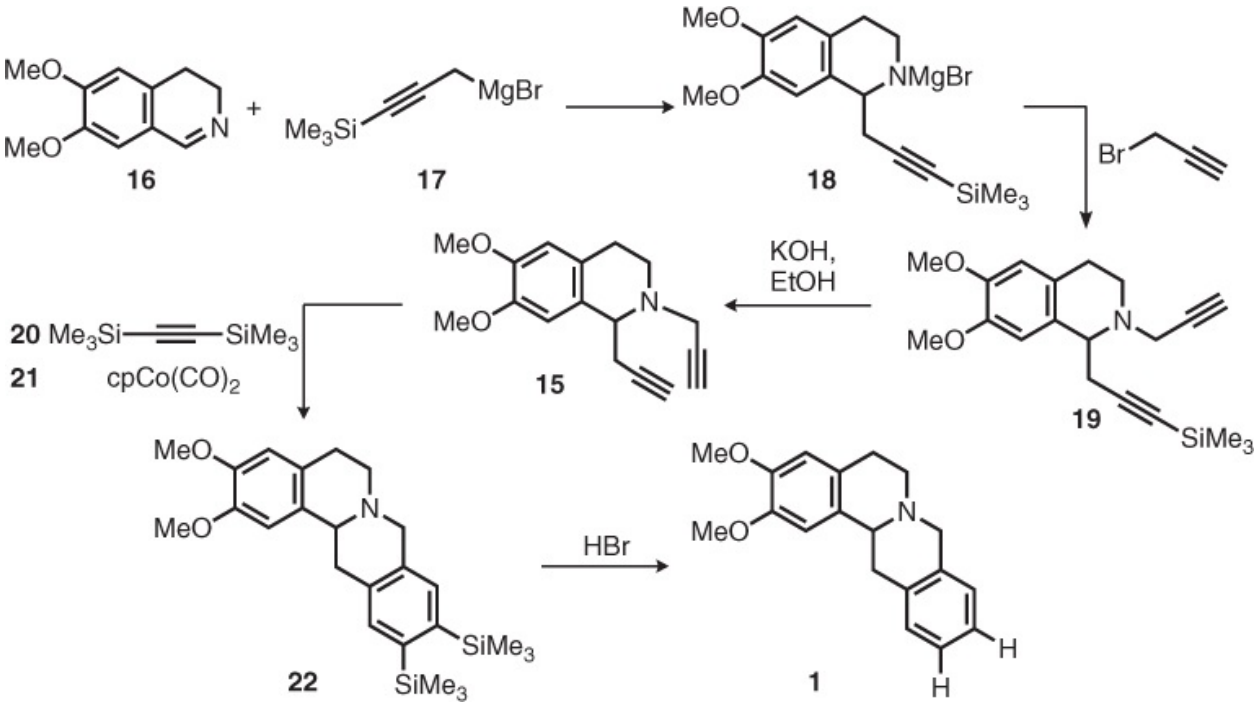
A concept completely different from approaches I–III is based on a cycloaddition of the diyne **15** with acetylene to give the tetrahydroisoquinoline moiety in **1** in one step.



The cyclooligomerization of alkynes [7] is preferentially mediated by Co(I) complexes, and its potency is demonstrated by a further synthesis of **1** [8].

The required diyne **15** is obtained from 3,4-dihydro-6,7-dimethoxyisoquinoline (**16**) by the addition of the TMS-protected propargylic Grignard compound **17** at C-1 of **16** and subsequent N-propargylation of the intermediately formed Mg amide **18** to afford **19**. After removal of the TMS group (KOH in EtOH), the diyne **15** is subjected to a co-cyclooligomerization with bis(trimethylsilyl)acetylene (**20**) catalyzed by the commercially available η^5-cyclopentadienyl-Co(I)-dicarbonyl (**21**), leading to the cycloadduct **22**. The use of the bis-TMS-acetylene (**20**) is superior to that of acetylene itself, since the bulky TMS substituents prevent the otherwise inevitable acetylene autotrimerization. The synthesis is completed by protodesilylation of **22** with

HBr to give the HBr salt of **1**.

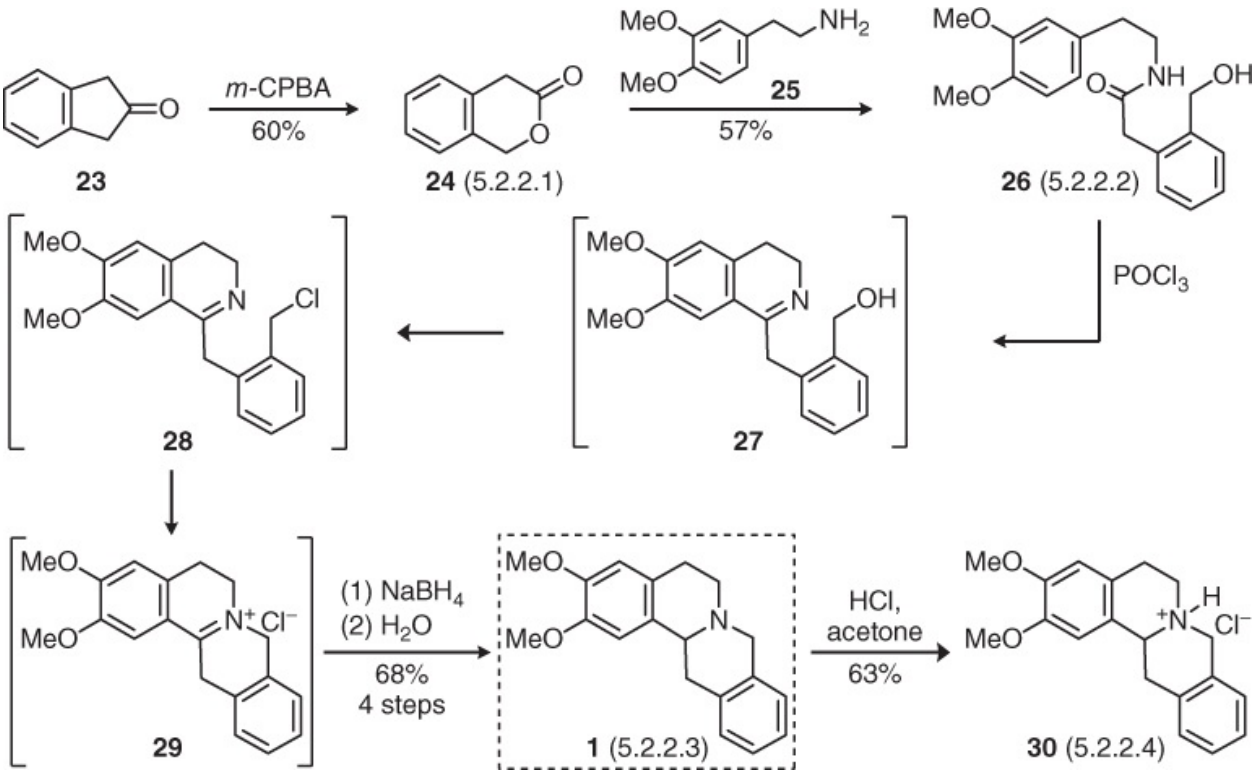


(b) Synthesis of 1

The starting material for the synthesis of **1** according to approach **I** is 2-indanone (**23**), which is first subjected to a Baeyer–Villiger oxidation [9] with *m*-chloroperbenzoic acid. This oxidative O-sextet rearrangement effects ring-expansion of the cyclopentanone derivative **23** to the lactone **24**, which is ring-opened by reaction with homoveratrylamine (**25**) to afford the amide **26**. On treatment with $POCl_3$, the amide **26** undergoes a twofold ring closure, which is followed by reduction with $NaBH_4$ to give the tetracyclic alkaloid **1**. This is transformed into the hydrochloride salt **30**.

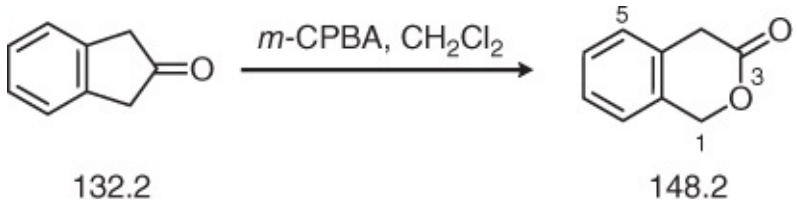
The sequence **26** → **1** can be reasonably understood in terms of (i) a domino process consisting of Bischler–Napieralski cyclization (**26** → **27**, cf. Section 3.3.2), transformation of the benzylic alcohol into the corresponding chloride (**26** → **28**), and ring closure by an intramolecular N-alkylation (cycloalkylation **28** → **29**) and (ii) hydride reduction of the iminium moiety in **29** to give the tertiary amine functionality of **1** ($R_2C{=}NR'_2{}^+$ → $HR_2C{-}NR'_2$).

Thus, the target molecule **1** is obtained by a three-step sequence in an overall yield of 21% based on 2-indanone **23**.



(c) Experimental Procedures for the Synthesis of 1

5.2.2.1	**	**3-Isochromanone** [4]



An ice-cold solution of 2-indanone (5.00 g, 37.8 mmol) in anhydrous CH_2Cl_2 (10 ml) is added to an ice-cold solution of *m*-chloroperbenzoic acid (7.82 g, 45.5 mmol) in anhydrous CH_2Cl_2 (50 ml) over 20 min, and the reaction mixture is kept at 0 °C for 10 days.

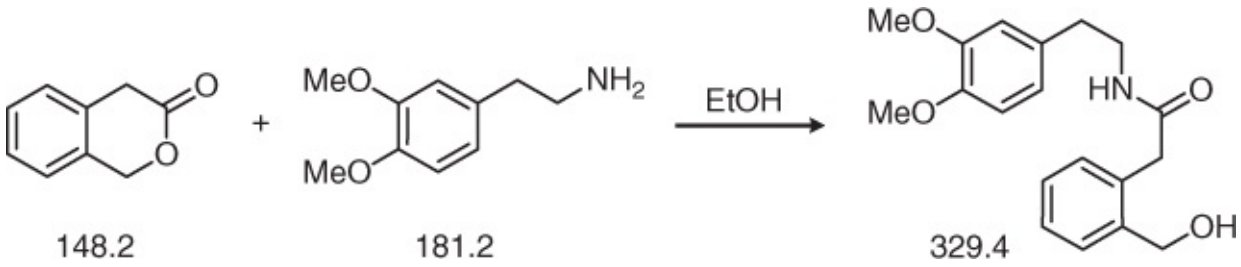
The precipitated *m*-chloroperbenzoic acid is filtered off and washed with CH_2Cl_2. The combined organic layers are washed with 1% sodium hydrogencarbonate solution (100 ml) and H_2O (100 ml). The organic layer is dried over Na_2SO_4, and filtered, and the solvent is removed *in vacuo*. The residue is crystallized from MeOH to give a white solid: 3.23 g (58%), mp 81 °C; R_f (SiO_2; EtOAc/toluene, 95 : 5) = 0.76.

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 1746, 1486, 1458, 1406, 1392, 1299, 1252, 1224, 743.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.34–7.18 (m, 4H, 5-H, 6-H, 7-H, 8-H), 5.28 (s, 2H, 4-H_2), 3.68 (s, 2H, 1-H_2).

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 169.7 (C-3), 128.7, 127.3, 127.0, 124.8, 70.0 (C-4) 36.0 (C-1).

5.2.2.2	*	***N*-[2-(3,4-Dimethoxyphenyl)ethyl]-2-(hydroxymethyl)**
		phenylacetamide [4]



A solution of 3-isochromanone **5.2.2.1** (2.20 g, 14.9 mmol) and 2-(3,4-dimethoxyphenyl)ethylamine (3.20 ml, 19.3 mmol) in EtOH (50 ml) is refluxed for 20 h.

The solvent is removed *in vacuo*, and the residue is purified by column chromatography on silica gel (toluene/EtOAc, 95 : 5) to give a light-yellow solid: 2.80 g (57%), mp 98–99 °C; R_f (SiO_2; EtOAc/toluene, 95 : 5) = 0.30.

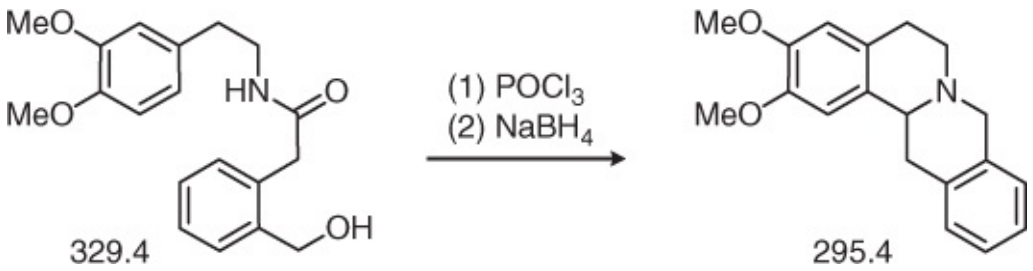
IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3294, 3078, 1640, 1558, 1466, 1252, 1236, 1138, 757.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.34–7.15 (m, 4H, Ph), 6.73–6.55 (m, 3H, Ph), 6.33 (m_c, 1H, NH), 4.59 (s, 2H, C$\underline{H}_2$OH), 3.83 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.55 (s, 2H, $CH_2C(O)$), 3.41 (q, *J* = 6 Hz, 2H, $CH_2C\underline{H}_2NH$), 2.67 (t, *J* = 6 Hz, 2H, C$\underline{H}_2CH_2NH$).

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 171.5 (C(O)), 148.9, 147.6, 139.4, 134.0, 131.1, 130.3, 130.2, 128.4, 127.7, 120.6, 111.8, 111.2 (12 × Ar), 63.6 (CH_2OH), 55.9, 55.8 (2 × OCH_3), 40.9, 34.8 (3 × CH_2).

HRMS: calcd. for $C_{19}H_{24}NO_4$ ($[M+H]^+$): 330.1705, observed 330.1700.

5.2.2.3 ** *rac*-2,3-Dimethoxyberbine [4]



A solution of phosphoryl chloride (4.16 ml, 44.6 mmol) in anhydrous toluene (15 ml) is added at room temperature over 15 min to a stirred solution of amide **5.2.2.2** (978 mg, 2.97 mmol) in anhydrous toluene (15 ml) under a nitrogen atmosphere, and the mixture is heated under reflux for 1.5 h. The reaction mixture is then cooled to about 50 °C, and excess phosphoryl chloride and toluene are evaporated *in vacuo*. The residue obtained is dissolved in MeOH (20 ml) and, after cooling the solution to 0 °C, sodium borohydride (3.20 g, 84.4 mmol) is added in small portions over a period of 1 h. The solution is kept overnight at 0 °C.

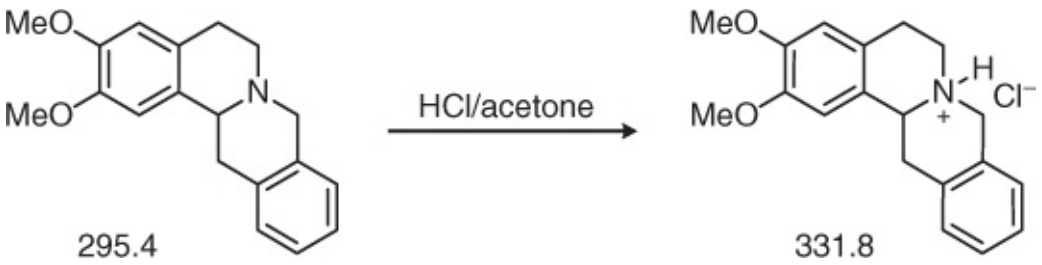
Excess sodium borohydride is then decomposed by the addition of ice-cooled water (20 ml), and the mixture is extracted with chloroform (3 × 20 ml). The combined organic layers are washed with H_2O (20 ml) and brine (20 ml), dried over Na_2SO_4, and filtered. After removal of the solvent, a yellowish gum is obtained, which is purified by column chromatography on neutral alumina (toluene/EtOAc, 4 : 1) to give a yellow solid; 600 mg (68%), mp 193–194 °C, R_f (SiO_2; EtOAc/toluene, 1 : 1) = 0.83; R_f (neutral alumina; EtOAc/toluene, 1 : 1) = 0.50.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.21–7.06 (m, 4H, Ar), 6.74 (s, 1H, Ar), 6.60 (s, 1H, Ar), 4.03 (d, *J* = 15 Hz, 1H, NCH), 3.92–3.81 (m, 6H, 2 × OCH_3), 3.74 (d, *J* = 15 Hz, 1H, NCH), 3.62 (dd, *J* = 10, 5 Hz, 1H, CH), 3.33 (dd, *J* = 15, 6 Hz, 1H, $NC\underline{H}_BCH_2$), 3.20–3.06 (m, 2H, CH_A), 2.96–2.84 (m, 1H, $NC\underline{H}_ACH_2$), 2.72–2.54 (m, 2H, CH_2).

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 147.4, 134.3, 128.6, 126.2, 126.1, 125.8, 111.3, 108.4, 59.5, 58.5, 56.0, 55.8, 51.4, 36.7, 29.0.

ESI MS: *m*/*z* (%) = 296 (100) $[M+H]^+$.

5.2.2.4 * *rac*-2,3-Dimethoxyberbine hydrochloride [4]



A 2 M solution of HCl in acetone (2 ml) is added to a stirred solution of dimethoxyberbine **5.2.2.3** (600 mg, 2.03 mmol) in acetone (20 ml). The precipitate formed is collected by filtration and crystallized from MeOH to afford the desired product as a yellow solid: 425 mg (63%), mp 205–206 °C.

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3424, 3071, 3003, 2937, 2909, 2836, 2689, 2497, 1613, 1591, 1525, 1455, 1411, 1364, 1342, 1277, 1264, 1252, 1237, 1216, 1185, 1157, 1129, 1109, 1081, 1053, 1036, 1019, 993, 962, 889, 858, 832, 793, 773, 739, 722, 550, 528, 472, 436.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.35–7.22 (m, 4H, Ph_D), 7.06 (s, 1H, Ph_A), 6.82 (s, 1H, Ph_A), 4.82–4.69 (m, 1H), 4.66–4.52 (m, 2H), 4.00–3.88 (m, 1H), 3.84–3.70 (m, 6H, OCH_3), 3.45–3.06 (m, 4H), 2.94–2.81 (m, 1H).

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 147.4, 128.6, 126.2, 126.1, 125.8, 111.3, 108.4, 59.5, 58.5, 56.0, 55.8, 51.4, 36.7, 29.0.

HRMS: calcd. for $C_{21}H_{23}N$ 295.1572; found 296.1645 ($[M+H]^+$).

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3. Meise, W. and Zymalkowski, F. (1971) *Arch. Pharm.*, **304**, 175–181; W. Meise, F. Zymalkowski, *Arch. Pharm.* (1971) **304**, 182–188.

4. Chatterjee, A. and Ghosh, S. (1981) *Synthesis*, 818–820.

5. Smith, Kline & French English Patent 1004077; *Chem. Abstr.* **63** (1965), 18054d); this synthesis, however, could not be verified according to Ref. [3].

6. For other syntheses of tetrahydroprotoberberines, see: Pakrashi, S.C., Mukhopadhyay, R., Ghosh Dastidar, P.P., and Bhattacharya, A. (1985) *J. Indian Chem. Soc.*, **62**, 1003.

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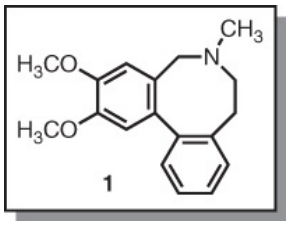
9. Smith, M.B. (2013) *March's Advanced Organic Chemistry*, 7th edn, John Wiley & Sons, Inc., New York, p. 1368.

5.2.3 Buflavine



Topics:

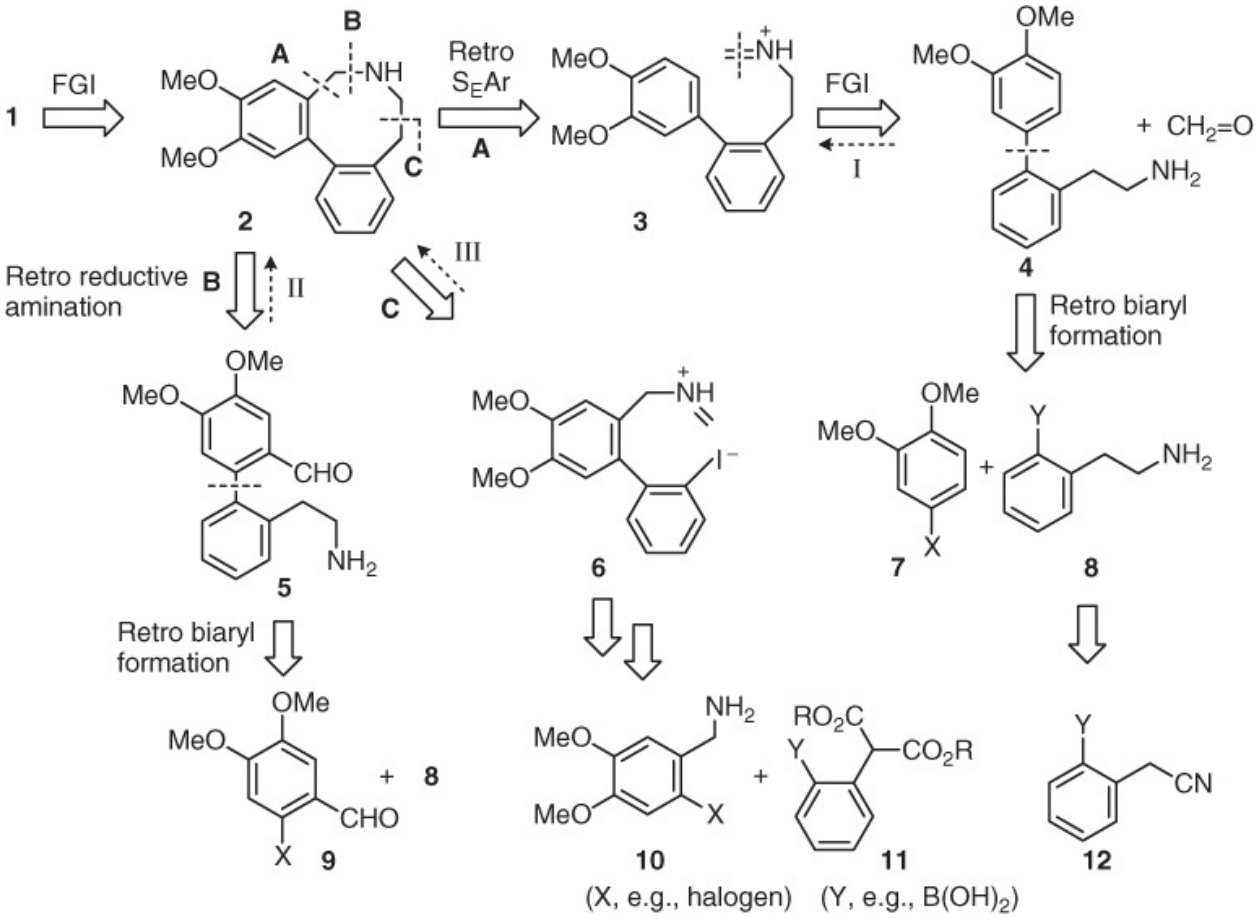
- Synthesis of an *Amaryllidaceae* alkaloid
- Suzuki–Miyaura cross-coupling reaction
- Reduction R–CN → R–CH_2–NH_2
- *Domino process:* Pictet–Spengler synthesis/Eschweiler–Clarke reaction

(a) General

Buflavine (**1**) belongs to the group of *Amaryllidaceae* alkaloids and possesses the very rare 5,6,7,8-tetrahydrodibenz[*c*,*e*]azocine skeleton, which is composed of a biaryl unit integrated at its *o*,*o*′-positions in an eight-membered N-heterocyclic ring system. Compounds of this type have been shown to exhibit potential α-renolytic and anti-serotonin activities [1].

For the retrosynthesis of buflavine (**1**), after N-demethylation to give the

secondary amine **2**, three reasonable disconnections (a/b/c) can be envisaged. Two of them (a and c) involve iminium ion formation (**2** → **3**, **2** → **6**) as a favorable retroanalytical operation, while the third (b) involves the retro-process of a reductive amination (**2** → **5**):



The retroanalytical pathways **A** and **B** straightforwardly lead to the substrates **7**, **8**, **12** and **5**, **9**, **8**, respectively. Accordingly, two relatively simple approaches **I**/**II** for the synthesis of **1** can be envisaged.

In I, after biaryl coupling of **7** and **12** and reduction of the coupling product to give the primary amine **4**, the eight-membered ring of **2** should result from a Pictet–Spengler-like cyclization of the iminium ion **3**, which is formed *in situ* by reaction of **4** with formaldehyde.

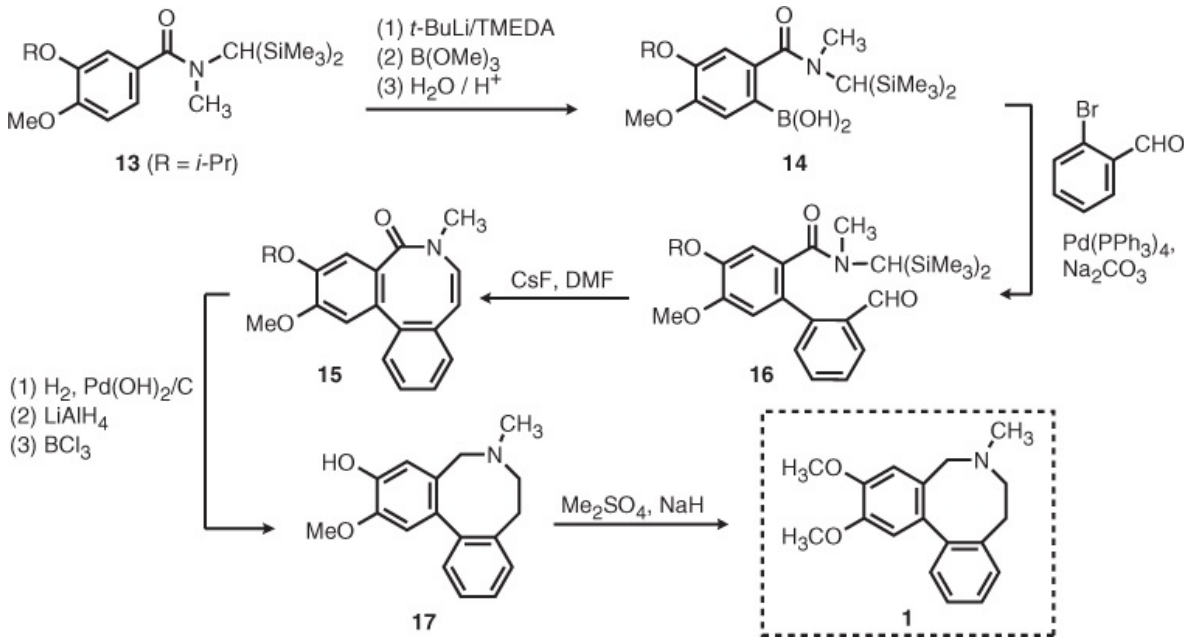
In II, after biaryl coupling of the (protected) aldehyde **9** with **12** and reduction/deprotection to give the amino aldehyde **5**, intramolecular reductive amination should provide the dibenzazocine system **2**.

Retrosynthetic pathway **C** leads to the synthon **6** with the functionalities of an iminium cation and a benzyl anion. Suitable substrates might be **10** and **11**.

However, route **III** to the target molecule will be more complex than routes **I** and **II** and will therefore not be discussed in detail here.

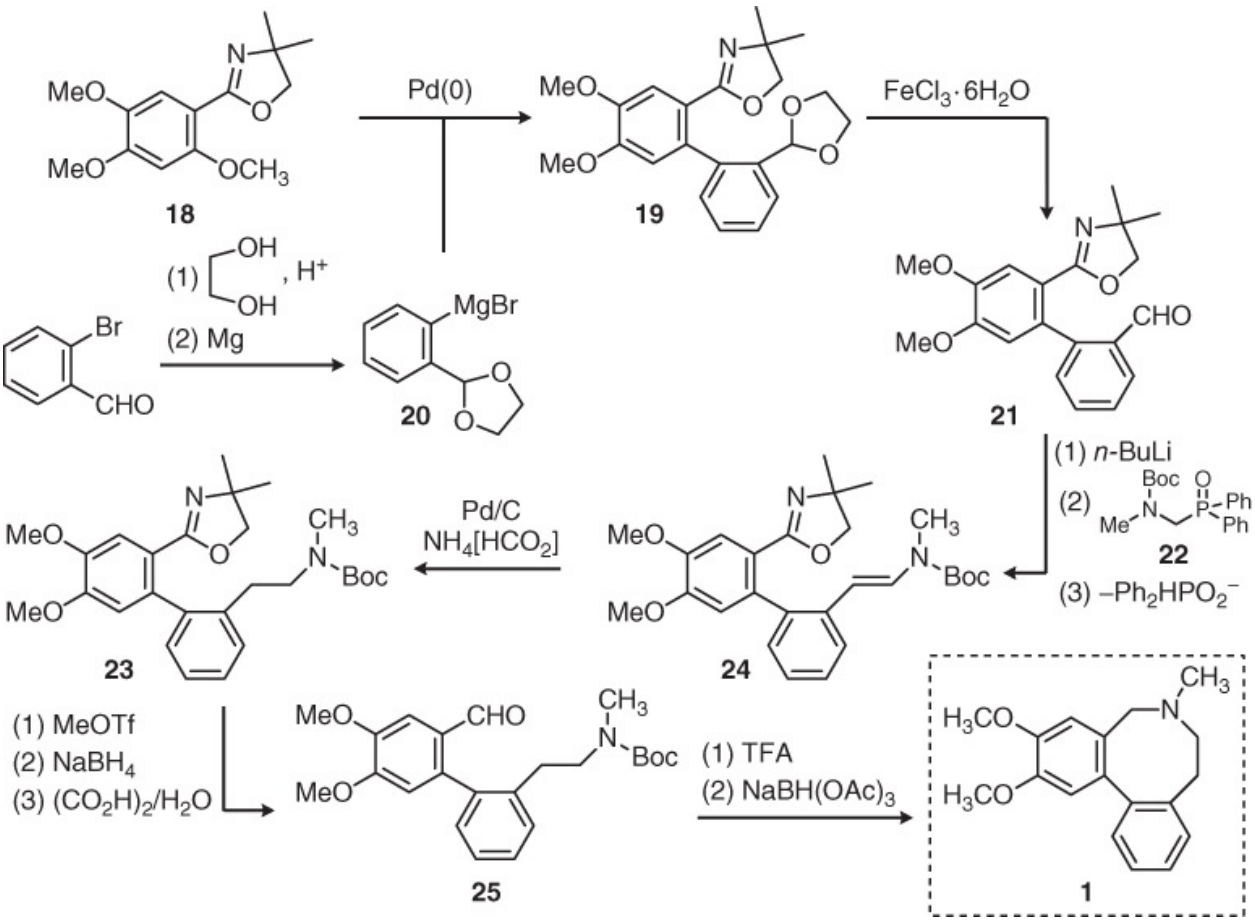
Nevertheless, all three approaches, **I–III**, have been used in actual syntheses of **1**.

1. The *N*-methyl-*N*′-bis(trimethylsilyl)methyl amide **13** is regioselectively metallated in the ortho position with respect to the amide function (cf. Section 3.2.3) and then the aryllithium is treated with trimethyl borate to give the boronic acid **14** after acid hydrolysis. Suzuki–Miyaura cross-coupling of **14** with 2-bromobenzaldehyde gives the highly functionalized biaryl **16**, which is subjected to an intramolecular Peterson olefination (cf. Section 1.1.5) under high dilution conditions to give the cyclization product **15**. Catalytic hydrogenation, $LiAlH_4$ reduction of the amide moiety (C=O → CH_2), and selective cleavage of the isopropyl ether lead to 8-*O*-demethylbuflavine (**17**, another *Amaryllidaceae* alkaloid), which is methylated to yield buflavine (**1**) [2]. This synthesis covers the essentials of approach **III**.



2. Oxazoline **18** (derived from 2,4,5-trimethoxybenzoic acid) undergoes a Pd(0)-catalyzed unsymmetrical biaryl coupling according to Meyers' protocol [3] with the Grignard compound **20** (derived from 2-bromobenzaldehyde), leading to the biaryl **19**. Cleavage of the dioxolane moiety using $FeCl_3 \cdot 6H_2O$ leads to the aldehyde **21**, which is subjected to a PO-activated olefination with the Boc-protected phosphine oxide **22** to yield

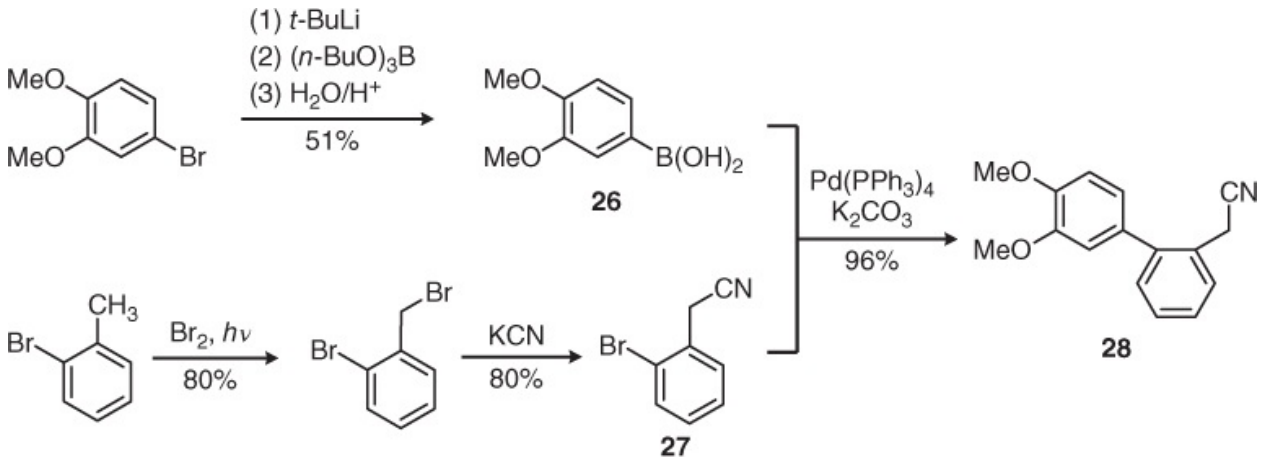
the enecarbamate **24**. Subsequent hydrogenation of **24** affords the oxazoline **23**, which is reductively cleaved by $NaBH_4$ after N-alkylation [4] to yield the aldehyde **25**. After Boc-deprotection (TFA, trifluoroacetic acid), intermolecular reductive amination of the corresponding secondary amine with $Na[HB(OAc)_3]$ results in the formation of the azocine **1** [5] according to approach **II**:



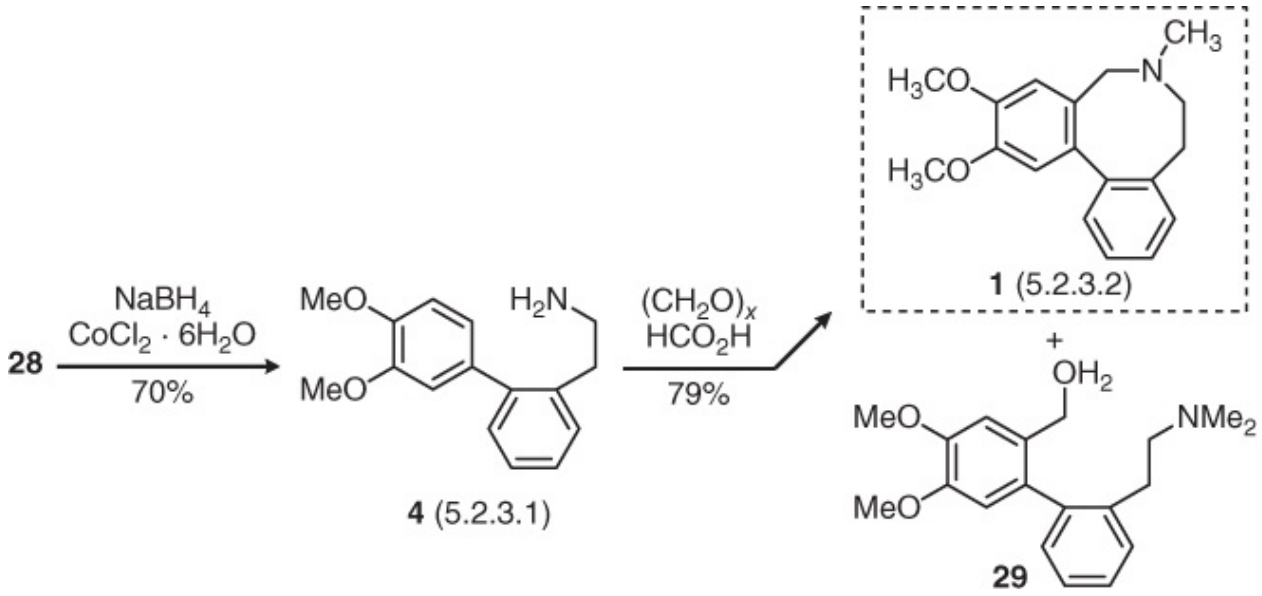
Realization of the retrosynthesis-based approach **I** leads to a short and efficient synthesis of **1** [1], which is presented in Section (b).

(b) Synthesis of 1

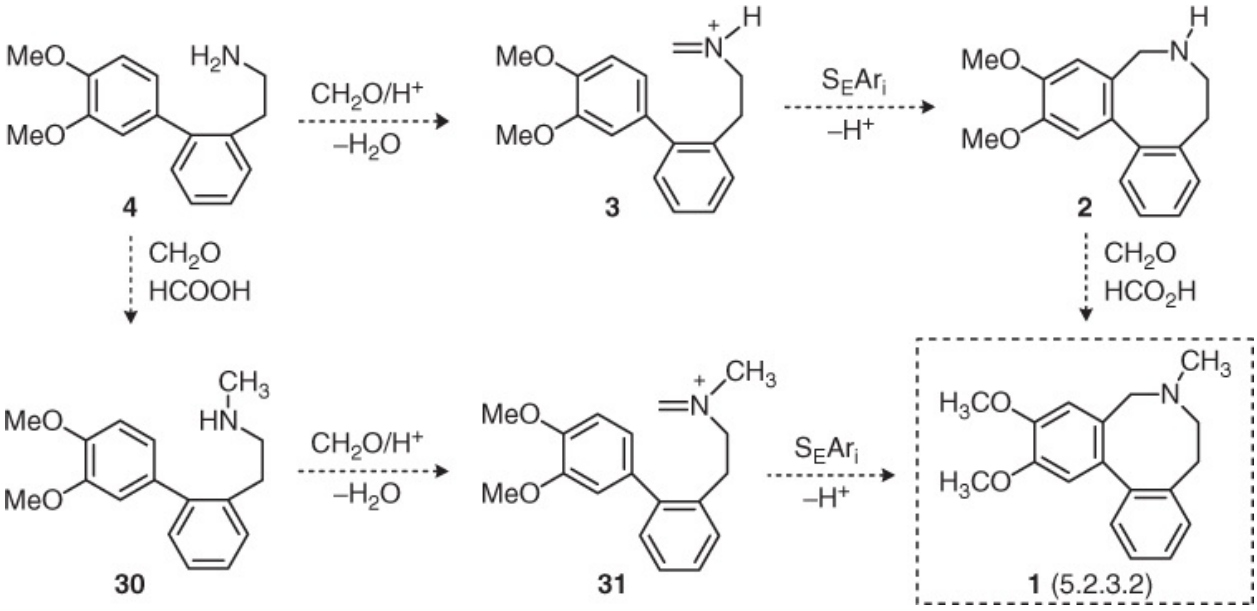
Substrates for the key intermediate **28** are the readily accessible arylboronic acid **26** and arylacetonitrile **27**, which are connected (cf. Section 1.6.2) by a Suzuki–Miyaura cross-coupling reaction in the presence of $Pd(PPh_3)_4$ and K_2CO_3 in almost quantitative yield to give the biaryl **28** [1].



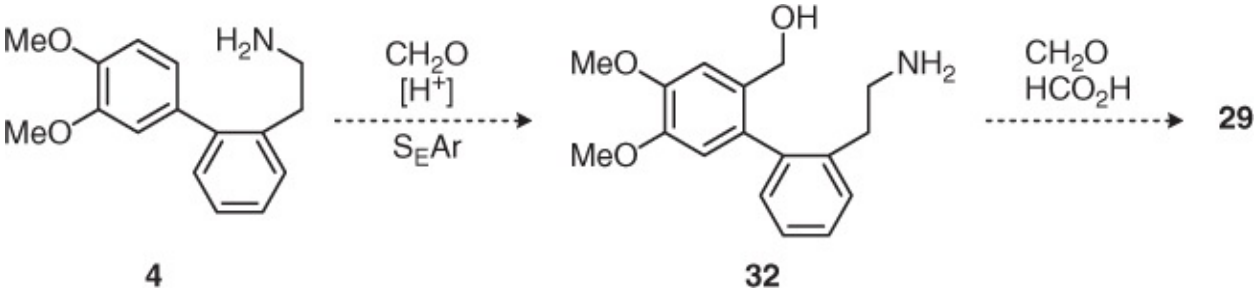
In the concluding steps, the arylacetonitrile **28** is transformed into the β-arylethylamine **4** by $CoCl_2$-assisted reduction with $NaBH_4$. The amine **4** is then treated with a fivefold excess of paraformaldehyde in formic acid to give the target molecule **1** in 55% yield. In addition, according to Ref. [1], 5% of a side product **29** can be isolated by preparative TLC. This product is not described in the experimental part.



Apparently, in the key step (**4** → **1**), the eight-membered ring is closed in a manner similar to the formation of 1,2,3,4-tetrahydroisoquinolines according to a Pictet–Spengler synthesis [6] by iminium ion formation followed by an intramolecular S_EAr reaction with ring closure and N-methylation according to the Eschweiler–Clarke reaction [7]. For this domino process [8], two alternative routes (either **4** → **3** → **2** → **1** or **4** → **30** → **31** → **1**) are possible:



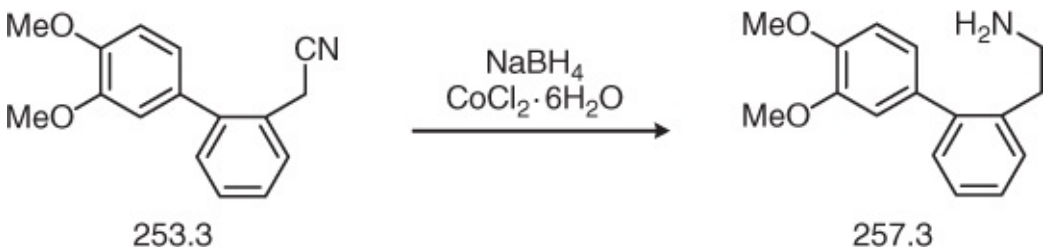
The side product **29** is presumably derived from **4** by a hydroxymethylation (S_EAr) of the donor-activated A ring in **4** with (protonated) formaldehyde (**4** → **32**). This is then followed by an Eschweiler–Clarke N,N-dimethylation (**32** → **29**) of the primary amine function in **32**.



Since the substrates **26** and **27** are commercially available, the target molecule **1** is prepared in a three-step sequence with an overall yield of 53%.

(c) Experimental Procedures for the Synthesis of 1

5.2.3.1	*	**2-(2-Aminoethyl)-3,4-dimethoxybiphenyl** [1]



Cobalt chloride hexahydrate (3.76 g, 15.8 mmol) is added to a stirred solution of

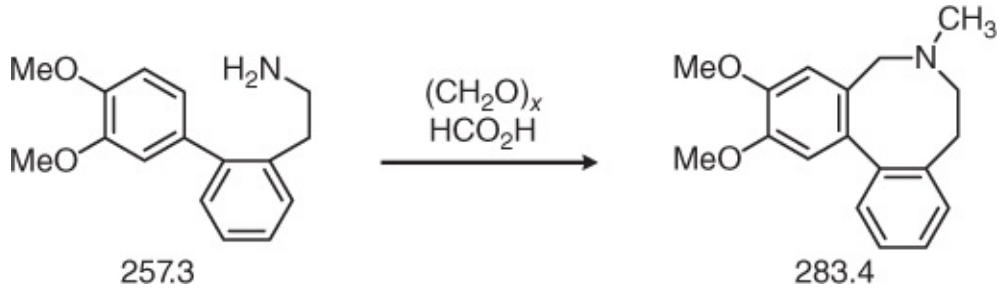
the nitrile **1.6.2.3** (2.00 g, 7.90 mmol) in methanol/benzene (4 : 1, 100 ml). The mixture is then cooled to 0 °C, and sodium borohydride (2.99 g, 79.0 mmol) is added. The resulting dark solution is allowed to warm to room temperature and stirred for 3.5 h, after which HCl (3 M, 100 ml) is added and stirring is continued for additional 1.5 h.

The mixture is then concentrated *in vacuo* and basified with concentrated ammonia, and the resulting slurry is extracted with Et_2O (3 × 100 ml). The ethereal layers are combined, washed with water and brine, dried over $MgSO_4$, and filtered, and the solvent is removed *in vacuo* to give the desired product as yellow oil; 1.42 g (70%).

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.32–7.20 (m, 4H, Ar–H), 6.95–6.80 (m, 4H, Ar–H), 3.92 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 2.78 (m, 4H, Ar–CH_2–CH_2), 1.21 (s_{br}, 2H, NH_2).

^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) = 148.6, 148.0, 142.2, 137.4, 134.6, 130.4, 129.6, 127.3, 126.1, 121.4, 112.8, 111.0 (12 × Ar–C), 56.0 (2 × OCH_3), 43.4 ($CH_2\underline{C}H_2NH_2$), 37.6 ($\underline{C}H_2CH_2NH_2$).

5.2.3.2	*	**2,3-Dimethoxy-6-methyl-5,6,7,8-tetrahydrodibenzo[*c*,*e*]azocine**
		(buflavine) [1]



A mixture of the β-arylethylamine **5.2.3.1** (800 mg, 3.11 mmol), paraformaldehyde (516 mg, 15.5 mmol, 90–92%), and formic acid (20 ml) is stirred at room temperature for 24 h. Additional paraformaldehyde (516 mg, 15.5 mmol) is then added, and the solution is heated to reflux for 24 h.

The mixture is then concentrated *in vacuo*, made alkaline with aqueous Na_2CO_3 (2 M, 100 ml), and extracted with $CHCl_3$ (3 × 80 ml). The combined organic phases are washed with water (3 × 100 ml), dried over $MgSO_4$, and filtered. The

solvent is removed *in vacuo*, and the viscous oil is purified by column chromatography on silica gel using MeOH/CH_2Cl_2 (1 : 9) to afford the product as yellow oil; 700 mg (79%).

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3050, 2930, 2840, 2785, 1605, 1515, 1440, 1210, 1145, 1020, 860, 750.

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.36–7.27 (m, 3H, Ar), 7.25–7.22 (m, 1H, Ar), 6.90 (s, 1H, Ar), 6.80 (s, 1H, Ar), 3.95 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 3.52 (d, *J* = 13.6 Hz, 1H), 3.26 (m, 1H), 3.06 (d, *J* = 13.6 Hz, 1H), 2.75–2.67 (m, 1H), 2.55–2.49 (m, 2H) (3 × CH_2), 2.49 (s, 3H, CH_3).

^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) = 148.5, 147.6, 141.4, 140.1, 133.0, 130.1, 129.5, 129.1, 127.9, 126.1, 113.7, 112.3 (12 × Ar–C), 58.8, 58.4 (2 × OCH_3), 56.0, 56.0 ($CH_2\underline{C}H_2N(CH_3)\underline{C}H_2$), 45.9 ($N\underline{C}H_3$), 32.7 ($\underline{C}H_2CH_2NH_2$).

References

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2. Patil, P.A. and Snieckus, V. (1998) *Tetrahedron Lett.*, **39**, 1325–1326.

3. Hutchings, R.H. and Meyers, A.I. (1996) *J. Org. Chem.*, **61**, 1004–1013.

4. For comparison, see: Tietze, L.F. and Eicher, T. (1991) *Reaktionen und Synthesen im Organisch-Chemischen Praktikum und Forschungslaboratorium*, 2nd edn, Georg Thieme Verlag, Stuttgart, p. 384.

5. Hoarau, C., Couture, A., Deniau, E., and Grandclaudon, P. (2002) *J. Org. Chem.*, **67**, 5846–5849.

6. Eicher, T., Hauptmann, S., and Speicher, A. (2012) *The Chemistry of Heterocycles*, 3rd edn, Wiley-VCH Verlag GmbH, Weinheim, p. 681.

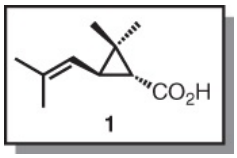
7. *Organikum* (2001) 21st edn, Wiley-VCH Verlag GmbH, Weinheim, p. 578 (Leuckart–Wallach reaction).

8. (a) Tietze, L.F. (1996) *Chem. Rev.*, **96**, 115–136;(b) Tietze, L.F., Brasche, G.,

and Gericke, K. (2006) *Domino Reactions in Organic Synthesis*, Wiley-VCH Verlag GmbH, Weinheim.

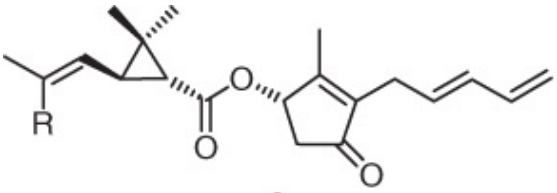
5.3 Domino Reactions in the Synthesis of Isoprenoids

5.3.1 (±)-*trans*-Chrysanthemic acid

 1	***Topics:***	• Synthesis of a cyclic monoterpene carboxylic acid • Allylic halides from allylic alcohols and HX with allyl inversion • Esterification/ester hydrolysis • Sulfinates by reduction of sulfochlorides • Sulfones by rearrangement of sulfinic esters • *Domino process*: Michael addition/cyclopropane formation by 1,3-elimination

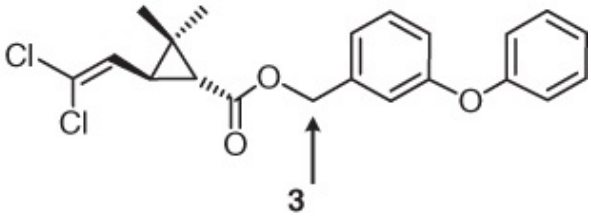
(a) General

Chrysanthemic acid (**1**) is a *gem*-dimethyl-substituted cyclopropane carboxylic acid, in which a β-dimethylvinyl moiety is attached trans to the CO_2H group. It belongs to the monoterpene natural product family and occurs in pyrethrums (e.g., *Chrysanthemum cinerariaefolium* Vis.) as an ester of a hydroxycyclopentenone (pyrethrolones). These esters (pyrethrins), such as Pyrethrin I/II (**2**), are important insecticides. They are only slightly toxic for warm-blooded animals but possess effective and rapid activity (knock-down effect) against insects.



2

Pyrethrin I: R = CH_3
Pyrethrin II: R = CO_2CH_3



3

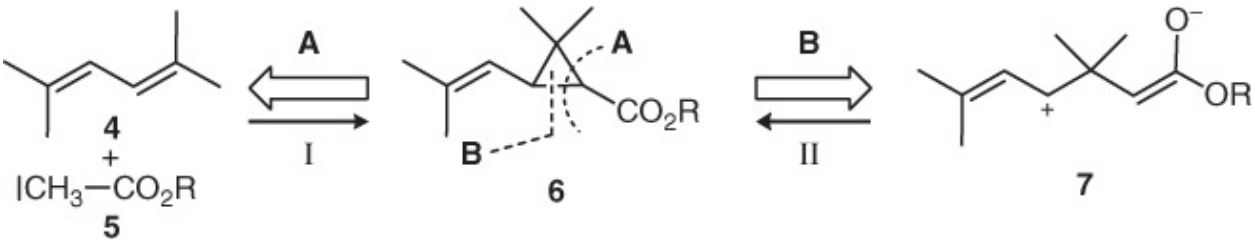
Permethrin

By structural modifications of chrysanthemic acid (**1**) and of the alcohol component, the insecticidal activity can be improved. Thus, the ester **3** of (β-dichlorovinyl) dimethyl cyclopropane carboxylic acid with (3-phenoxy)benzyl alcohol finds wide application in plant protection under the name Permethrin [1]. In comparison to other established insecticides, Permethrin (**3**) shows low toxicity in warm-blooded animals and reasonable stability under light and in air and it is easily metabolized. For its application, only relatively small amounts of the substance are required. However, recently some disadvantages have emerged, such as its potential as an allergen or its toxicity for bees and fishes [2]. The introduction of a cyano group at the benzyl position (↑) of the alcohol component and the replacement of chlorine by bromine in the dihalovinyl group further increase the activity of the insecticide **3** [3].

Retrosynthesis of the cyclopropane-containing target molecule conventionally entails the following considerations:

- [2 + 1]-Cycloreversion of the three-membered ring leading to olefinic substrates and carbenes (and their precursors);
- Opening of a cyclopropane C–C bond leading to cyclizable 1,3-functionalized open-chain compounds.

Accordingly, chrysanthemic acid (**1**) and its ester **6**, respectively, offer two principal disconnection modes, **A** (leading to synthons **4** and **5**) and **B** (leading to synthon **7**):



4 + $ICH_3—CO_2R$ **5**

I

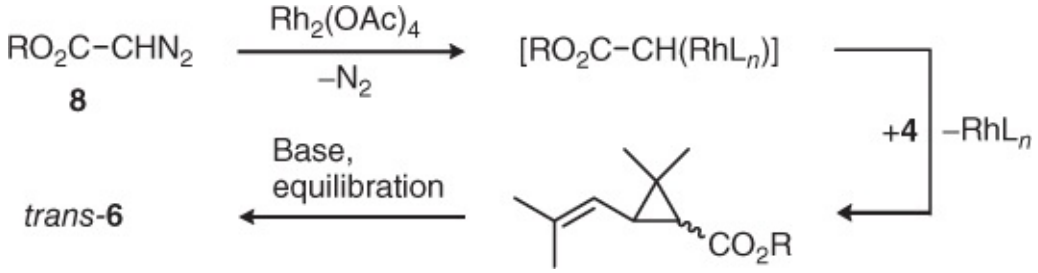
6

II

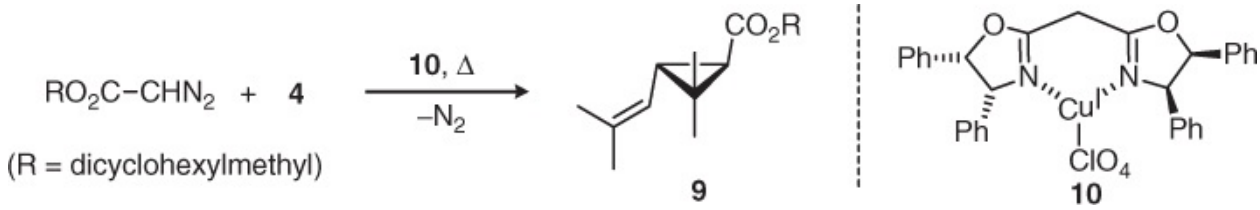
7

Retrosynthesis according to **A** directly discloses a pattern of synthesis for **6** (strategy I), which is realized by the [2 + 1]-cycloaddition of carbalkoxy carbene

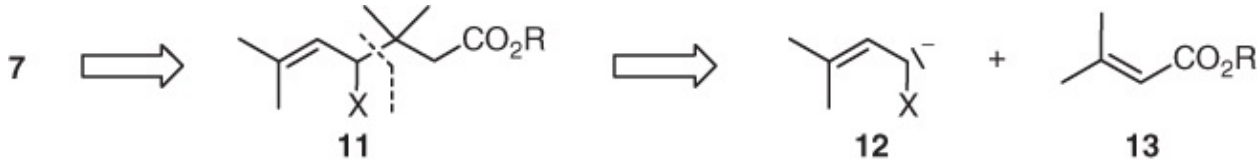
5 – generated by Cu-or Rh-catalyzed thermolysis of diazoacetic ester **8** – to the easily accessible 2,5-dimethylhexa-2,4-diene (**4**) [4]. Mono-cyclopropanation and subsequent base-induced equilibration leads to the *trans*-ester **6** with >95% stereoselectivity [5]. Using the (dimeric) $Rh_2(OAc)_4$ as catalyst, cyclopropanation with diazoacetate is likely to proceed via a rhodium(II) carbene complex (after elimination of N_2) and its addition to one of the double bonds of diene **4** [6]:



The asymmetric synthesis of *trans*-chrysanthemate **6** is achieved by the use of chiral ester components in the diazoacetate and/or catalysis by chiral Cu catalysts based on amino acids (Aratani catalysts, >90% ee) [7, 8]. Particularly effective is the chiral Cu(I) catalyst **10**, which facilitates the generation of the chrysanthemate **9** in a trans/cis ratio of 95 : 5 with 94% ee [9, 10].

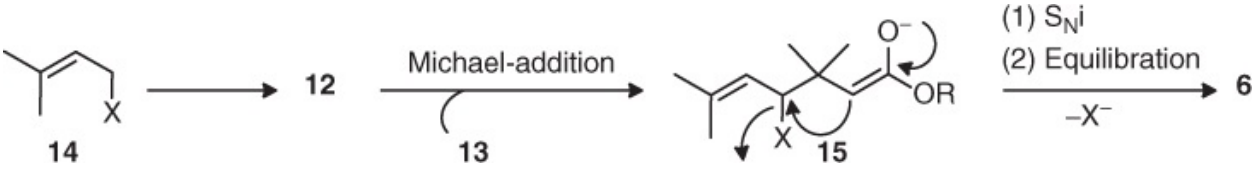


Retrosynthesis according to **B** leads to synthon **7**, which might be represented by a building block **11**, a ring-open ester bearing a suitable functionality **X** in the γ-position and retrosynthetically deduced from the anionic synthon **12,** and β,β-dimethyl acrylate **13** (acting as a Michael acceptor):



In the γ-functionalized system **11**, it is necessary that the functionality **X** not only increases the CH-acidity of the C–H bonds in the α-position but also serves as a good leaving group. This prerequisite is fulfilled, for example, by the group SO_2R. Thus, a key intermediate for strategy II is compound **14**, which is suitably predisposed for a sequence of base-induced deprotonation to give **12**, Michael addition of **12** to **13** to give **15**, cyclopropane ring closure of the ester enolate **15**

by intramolecular nucleophilic substitution (S_Ni, 1,3-elimination), and finally equilibration in favor of the thermodynamically more stable trans product **6**. For reasons of efficiency, it is desirable to conduct the series of base-induced reactions (leading from **14** to **6**) as a domino process [11]. Indeed, a synthesis of **1** following this strategy has been documented in the literature (see Section (b)).

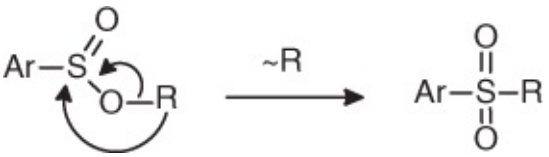


It should be noted that, because of the unsymmetrical cyclopropane structure of the target molecule **1**, further possibilities of syntheses according to **A** and **B** can be deduced following the [2 + 1]-cycloaddition or 1,3-elimination protocols [12]. A third principle for the formation of cyclopropane carboxylic acids is the ring contraction of α-halogeno cyclobutanones by the Favorskii reaction, which has been successfully applied to the synthesis of β,β-dihalovinyl analogs of chrysanthemic acid [13].

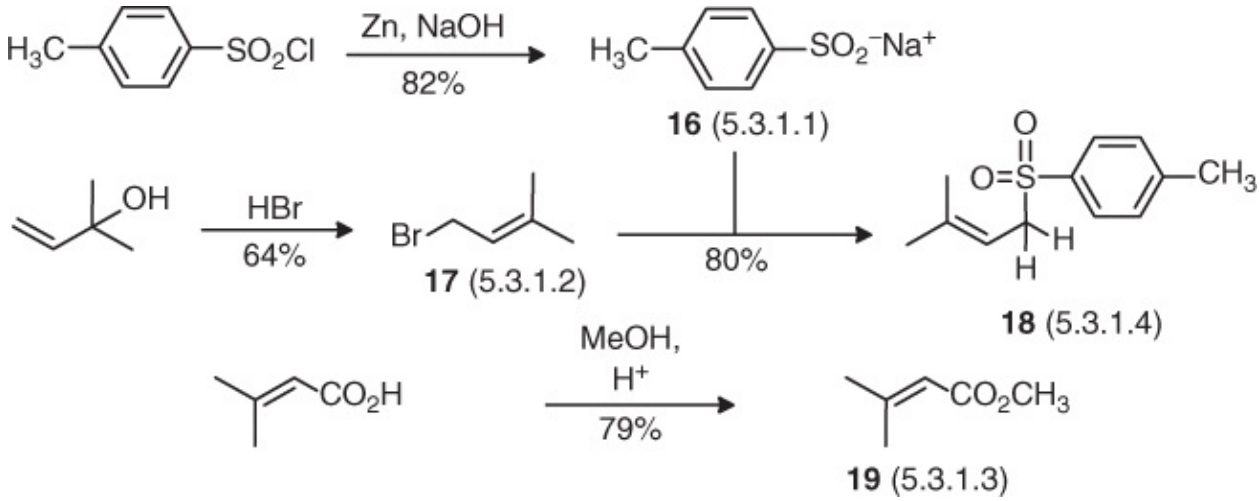
(b) Synthesis of 1

For reasons of handling and practicability, a synthesis of **1** based on strategy II is chosen, which was specifically designed for laboratory use and which employs easily accessible substrates [14].

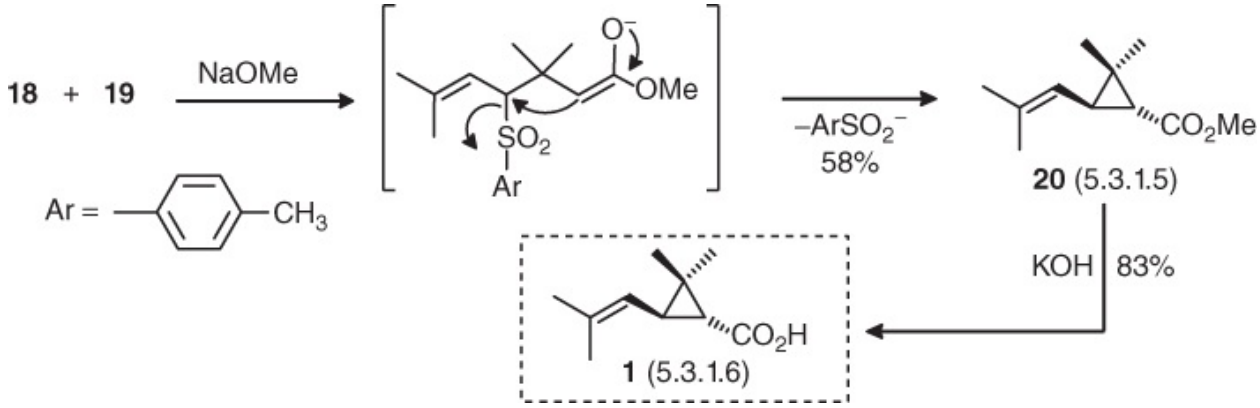
The key intermediate is (*p*-tolyl)-3,3-dimethylsulfone **18**, which is obtained from sodium *p*-toluenesulfinate (**16**) and 3,3-dimethylallyl bromide (**17**). Initial Oalkylation of the sulfinate anion leads to an allyl sulfinate, which rearranges under the reaction conditions to give the allyl sulfone. For this rearrangement, the mechanism of an electrophilic 1,2-O,S migration is discussed, since it is restricted to sulfinates with ester residues representing resonance-stabilized carbenium ions such as benzyl or allyl [15]:



Sodium *p*-toluenesulfinate **16** is obtained by the reduction of *p*-toluenesulfonyl chloride with Zn in aqueous NaOH, and the allyl bromide **17** is derived from dimethyl vinyl carbinol and 48% HBr by way of an S_N' reaction with allyl inversion [16].



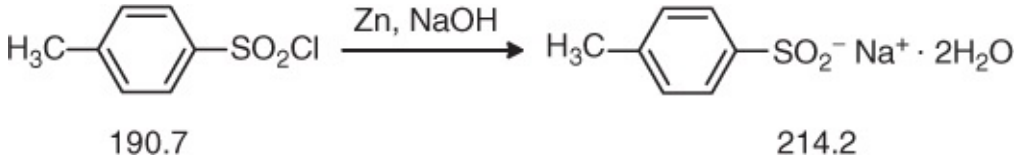
Methyl 3-methyl-2-butenoate (**19**) is obtained by esterification of 3-methyl-2-butenoic acid (senecic acid) with methanol according to the Fischer method. The α,β-unsaturated ester **19** is reacted with the sulfone **18** in the presence of sodium methoxide to furnish racemic methyl chrysanthemate (**20**), which comprises >95% of the desired trans diastereomer (according to ^{1}H NMR, see **5.3.1.5**). The final step of the synthesis is saponification of the ester **20** by KOH in methanol to give (±)-*trans*-chrysanthemic acid **1**.



By this doubly convergent approach, the target molecule **1** is obtained in six steps with an overall yield of 32% (based on **16**).

(c) Experimental Procedures for the Synthesis of 1

5.3.1.1	*	**Sodium *p*-toluenesulfinate** [16]



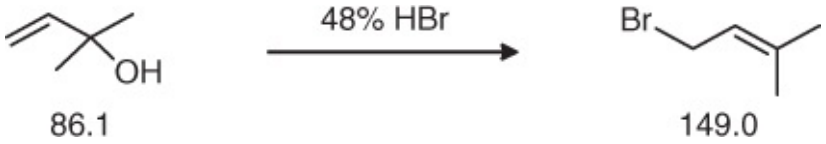
Powdered *p*-toluenesulfonyl chloride (50.0 g, 0.26 mol) is added in portions over 10 min to a stirred suspension of zinc dust (45.0 g, 0.69 mol) in water (500 ml) maintained at 70–75 °C. The temperature rises slightly. After stirring for 10 min, a solution of sodium hydroxide (12.0 g, 0.30 mol) in water (25 ml) is added dropwise over 3 min at 70–75 °C. The reaction mixture becomes lighter in color and reaches pH ≈ 7. Sodium carbonate (20.0 g, 0.20 mol) is then added to reach pH 9–10.

The hot suspension is rapidly filtered through a large Büchner funnel, and the solid is triturated twice with hot H_2O (250 ml). The combined filtrates are concentrated to a volume of 130 ml in an open flask. On cooling, sodium *p*-toluenesulfinate hydrate crystallizes in large needles. It is collected by filtration and dried to constant weight. A second crop can be obtained by reducing the volume of the mother liquor to approximately one-third. The total yield is 46.0 g (82%). The salt does not have a sharp melting point, but starts to decompose at approximately 340 °C.

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 1010, 970.

^{1}H NMR (300 MHz, [D_6]DMSO): δ (ppm) = 7.39 (d, *J* = 7.7 Hz, 2H, Ar), 7.13 (d, *J* = 7.7 Hz, 2H, Ar), 2.29 (s, 3H, CH_3).

5.3.1.2	*	**1-Bromo-3-methyl-2-butene** [17]



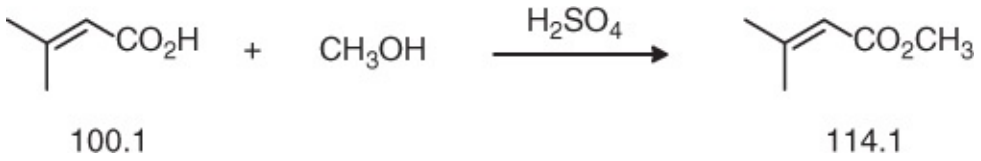
2-Methyl-3-buten-2-ol (86.1 g, 1.00 mol) in 48% hydrobromic acid (400 ml) is vigorously stirred at room temperature for 15 min.

The aqueous phase is separated from the oil formed and extracted with benzene (250 ml) (Caution: carcinogenic!). The combined organic phases are rapidly washed with an ice-cold diluted $NaHCO_3$ solution (100 ml), dried over $MgSO_4$, and filtered. The solution is fractionally distilled at 150 mbar to give 1-bromo-3-methyl-2-butene as a slightly yellow oil. The yield is 95.0 g (64%), bp_{150} 82–83 °C.

IR (film): $\tilde{\nu}$ (cm^{-1}) = 1670.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 5.49 (t, *J* = 8.2 Hz, 1H, =C–H), 4.03 (d, *J* = 8.2 Hz, 2H, =C–CH_2), 1.80, 1.75 (s, 2 × 3H, 2 × CH_3).

5.3.1.3 * Methyl 3-methyl-2-butenoate [15]



100.1 114.1

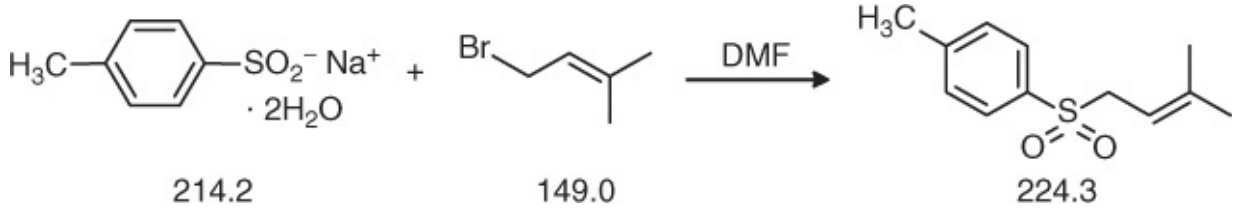
Concentrated sulfuric acid (5.0 ml by pipette) is carefully added to a solution of 3-methyl-2-butenoic acid (3,3-dimethylacrylic acid; senecic acid) (18.0 g, 0.18 mol) in anhydrous MeOH (100 ml), and the mixture is heated under reflux for 2 h.

The solution is then cooled, poured into iced water (100 ml), and extracted with Et_2O (3 × 75 ml). The combined organic extracts are washed with brine (100 ml), dried over $MgSO_4$, and filtered. The solution is distilled at atmospheric pressure to give Et_2O, a small forerun, and then the ester as colorless oil with a fruit-like odor. The yield is 16.2 g (79%), bp_{760} 133–134 °C, n^{20}_D = 1.4375.

IR (film): $\tilde{\nu}$ (cm^{-1}) = 1720, 1660.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 5.68 (s, 1H, vinyl-H), 3.68 (s, 3H, OCH_3), 2.17 (s, 3H, =C–CH_3 cis to CO_2Me), 1.89 (s, 3H, =C–CH_3 trans to CO_2Me).

5.3.1.4 * (3-Methyl-2-butenyl)-(*p*-tolyl) sulfone [15]



214.2 149.0 224.3

1-Bromo-3-methyl-2-butene **5.3.1.2** (16.0 g, 0.10 mol) is added dropwise to a stirred suspension of sodium *p*-toluenesulfinate hydrate **5.3.1.1** (27.0 g, 0.13 mol) in DMF (100 ml) over a period of 15 min at room temperature. The temperature rises by approximately 8 °C and a clear solution forms in about 10

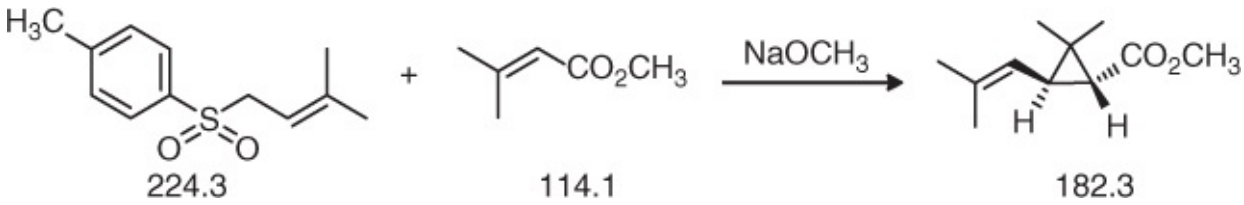
min. After the addition, the temperature is held at 85 °C for 1.5 h.

The colorless solution is cooled to room temperature and poured into H_2O (500 ml), forming a flocculent precipitate. If an oil forms, the mixture is stirred for 14 h. The solid is collected by filtration, washed with H_2O, and recrystallized from isopropanol (20 ml) to give colorless prisms; 18.6 g (80%), mp 80–81 °C.

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 1665.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.75 (d, *J* = 8.4 Hz, 2H, Ar), 7.34 (d, *J* = 8.4 Hz, 2H, Ar), 5.16 (t, *J* = 8.0 Hz, 1H, vinyl-H), 3.75 (d, *J* = 8.0 Hz, 2H, allyl-CH_2), 2.44 (s, 3H, *p*-tolyl-CH_3), 1.68, 1.33 (2 × s, 2 × 3H, =C–$(CH_3)_2$).

5.3.1.5 ** Methyl (±)-*trans*-chrysanthemate [15]



Sodium methoxide (10.0 g, 185 mmol) is added in one portion to a stirred solution of ester **5.3.1.3** (9.00 g, 79.0 mmol) and dimethylallyl sulfone **5.3.1.4** (15.0 g, 67.0 mmol) in anhydrous DMF (75 ml) under nitrogen atmosphere. The suspension turns brown, and is stirred at room temperature for 72 h.

The mixture is then poured into a mixture of concentrated HCl (25 ml), H_2O (50 ml), and ice (50 g). An orange oil separates. The resulting mixture is extracted with *n*-pentane (5 × 50 ml). A small amount of brown oil that forms between the layers is separated with the aqueous layer and discarded. The combined organic extracts are washed with saturated $NaHCO_3$ solution and brine (each 100 ml), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue is fractionally distilled *in vacuo* to give a colorless oil with a refreshing odor; 7.40 g (58%), bp_1 49–50 °C, n^{20}_D = 1.4645.

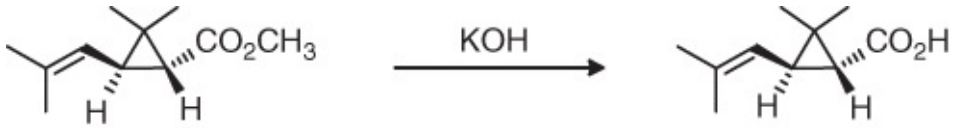
IR (film): $\tilde{\nu}$ (cm^{-1}) = 1730, 1650.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 4.84 (d, *J* = 7.9 Hz, 1H, vinyl-H;

note), 3.60 (s, 3H, $CO_2C\underline{H}_3$), 1.98–2.02 (m, 1H, allyl-H), 1.66, 1.65 (2 × s, 2 × 3H, $=C(CH_3)_2$), 1.33 (d, *J* = 5.4 Hz, 1H, $C\underline{H}–CO_2CH_3$), 1.21, 1.08 (2 × s, 2 × 3H, $C(CH_3)_2$).

Note: The peak at δ = 4.84 is assigned to the vinyl proton of the *trans*-ester. The signal of the vinyl proton of the *cis*-isomer (approximately 5%) appears at δ = 5.40 ppm. A long reaction time favors the formation of the trans form.

5.3.1.6	*	**(±)-*trans*-Chrysanthemic acid** [15]



182.3 168.2

A mixture of the ester **5.3.1.5** (5.00 g, 27.4 mmol) and potassium hydroxide (5.00 g, 90.0 mmol) in 95% EtOH (75 ml) is heated under reflux for 2 h.

The solvent is then evaporated *in vacuo*, and the dark oily residue is dissolved in H_2O (100 ml). The solution is extracted with Et_2O (50 ml), and the reddish aqueous phase is acidified to pH 1–2 with concentrated HCl and extracted with Et_2O (3 × 40 ml). The chrysanthemic acid separates from the acidic solution as dark oily drops, which dissolve in the Et_2O. The combined organic phases are dried over $MgSO_4$, filtered, and concentrated. The residue is vacuum-distilled in a microdistillation apparatus. The product distils at a bath temperature of 105–120 °C. The yield is 3.80 g (83%), $bp_{0.4}$ 83–85 °C, n^{20}_D = 1.4782; the product solidifies on standing at 4 °C for 14 h; mp 45–47 °C.

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 1685.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 11.7 (s, 1H, CO_2H), 4.90 (d, *J* = 7.8 Hz, 1H, vinyl-H; note), 2.07–2.12 (m, 1H, allyl-H), 1.72, 1.71 (2 × s, 2 × 3H, $=C(CH_3)_2$), 1.39 (d, *J* = 5.4 Hz, 1H, $C\underline{H}CO_2H$), 1.30, 1.15 (s, 3H, $C(CH_3)_2$).

Note: An additional peak appears at δ = 5.35 ppm, which is assigned to the cis form of the acid formed as a byproduct (<5%).

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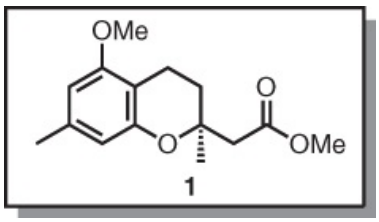
17. (a) British Patent 735,428, 31.8.1955; *Chem. Abstr*., **50** (1956), 88706a;(b) prenyl bromide has alternatively been prepared by surface-mediated hydrobromination of isoprene: De Mattos, M.C.S. and Sanseverino, A.M. (2003) *Synth. Commun.*, **33**, 2181–2186.

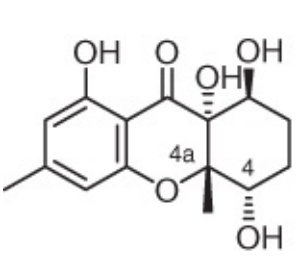
5.4 Domino Reactions for the Synthesis of Chromans and Dioxins

5.4.1 Methyl [(*S*)-5-methoxy-2,7-dimethyl-2-chroman-2-yl]acetate

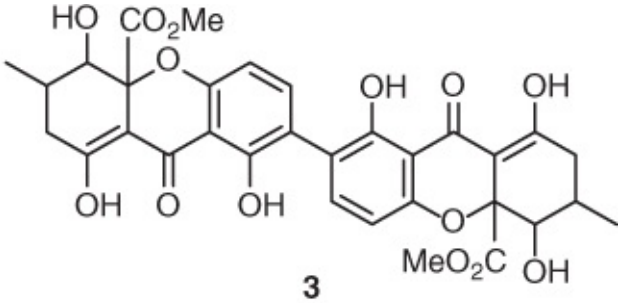
 1	***Topics:***	• Lombardo reaction • Ether cleavage • Domino Wacker/carbonylation/methoxylation reaction

(a) General

Chroman **1** [1] was used as an intermediate in the total synthesis of diversonol (**2**) using a domino Wacker/carbonylation/methoxylation reaction [2]. Diversonol (**2**) is a fungal metabolite, and was isolated from different fungi such as *Penicillium diversum* [3a] and *Microdiplodia* sp. [3b]. Its absolute configuration was determined using circular dichroism (CD) spectroscopy combined with time-dependent density functional theory electronic circular dichroism (TDDFT ECD) calculations [3b], and three more total syntheses of this compound have been published so far [4].

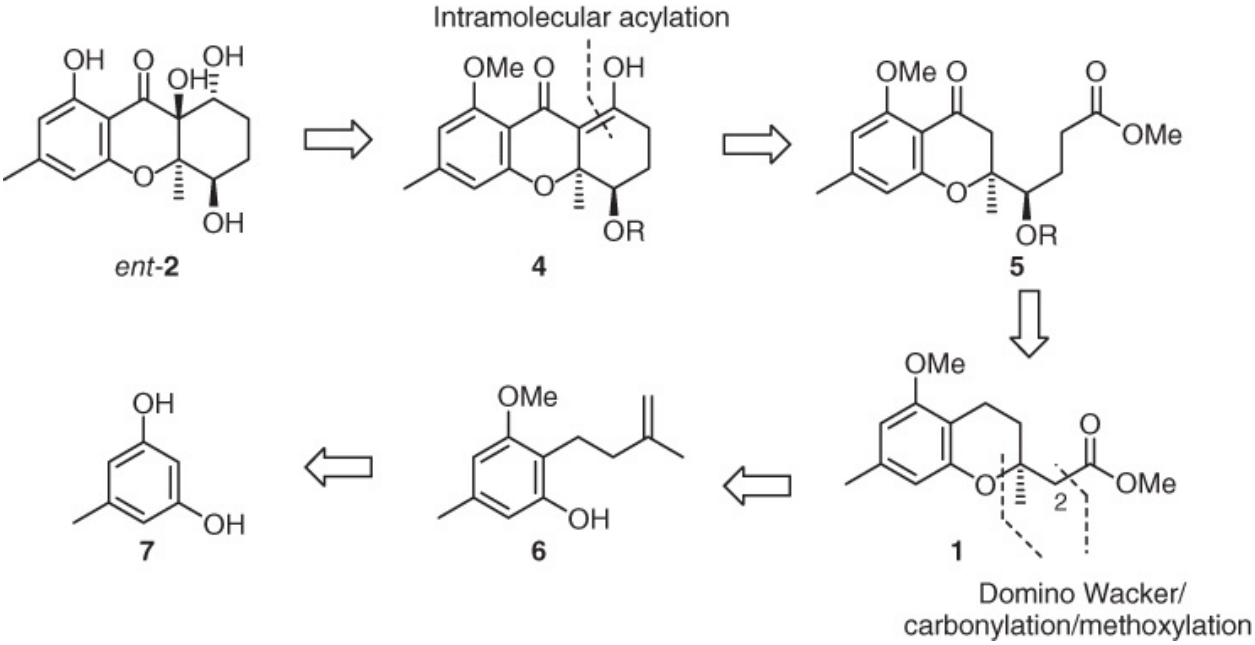


2
Diversonol



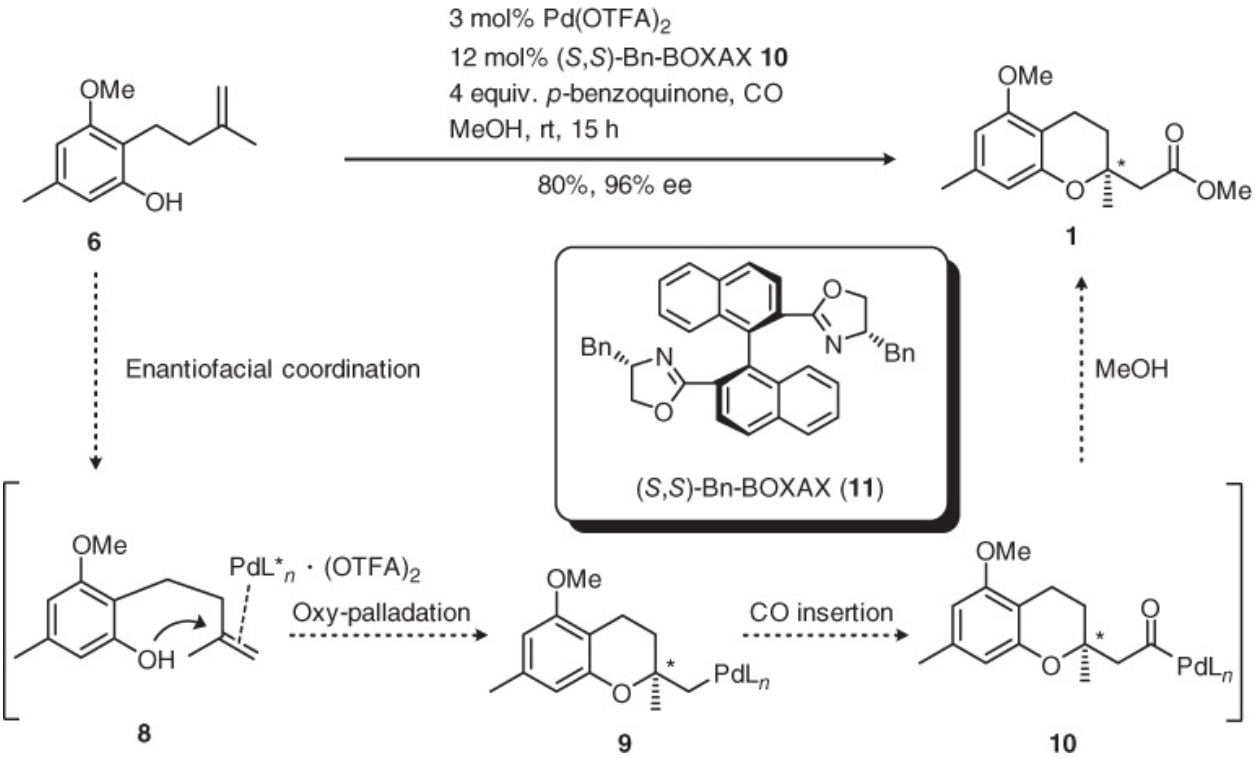
3
Secalonic acids

Diversonol (**2**) with its hexahydroxanthenone skeleton has close resemblance to a multitude of natural products from fungi as the biologically highly active secalonic acids (**3**) with antibacterial, cytostatic, and anti-HIV (human immunodeficiency virus) properties [5].



The retrosynthetic analysis of *ent*-**2** leads to the chroman **1** via the tetrahydroxanthenone **4** and the chromanone **5**, which would be accessible from **1** by hydroxylation at C-2, chain elongation, hydrogenation, and benzylic oxidation. On the other hand, **1** could be obtained from phenol **6** containing an alkenyl side chain by an enantioselective domino Wacker/carbonylation/methoxylation reaction in the presence of a chiral BOXAX ligand [6] (cf. Section 2.6.1). Finally, **6** is easily accessible from orcinol (**7**) (cf. Section 2.6.1).

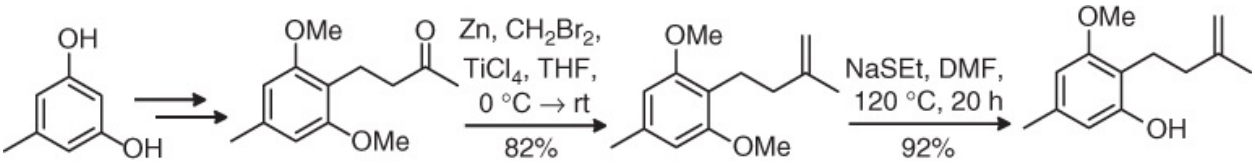
For the intramolecular enantioselective Wacker oxidation [7], carbonylation, and methoxylation of alkene **6** containing a phenolic hydroxyl group in the presence of the chiral BOXAX ligand **11** (**2.6.1.10**), the following mechanism can be assumed (see also Section 2.5).



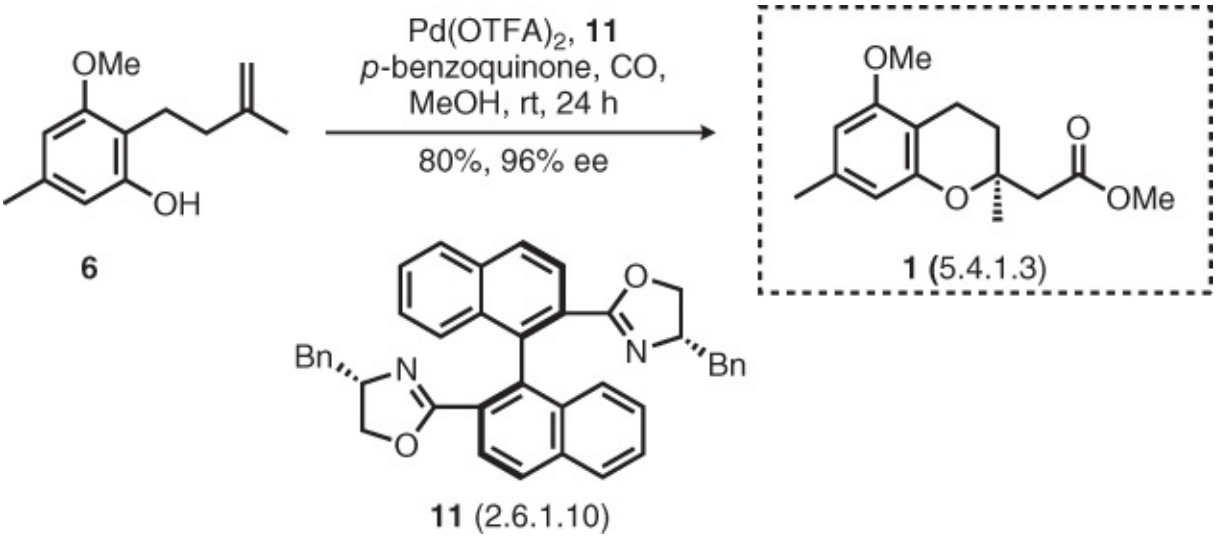
First, an enantioselective coordination of the *in situ* formed chiral Pd(II) complex with the alkene unit takes place to give **8**; then the phenolic hydroxyl group reacts with the double bond in a facial selective nucleophilic addition (Umpolung). The formed chroman **9** with a σ-Pd bond is rather stable, since it cannot undergo a β-hydride elimination. Thus, it can insert CO to give an acyl-Pd species **10**, which then reacts with methanol used as solvent to form the final chromanyl acetate **1** containing one stereogenic center.

(b) Synthesis of 1

For the synthesis of **1**, commercially available orcinol (**7**) is transformed into the ketone **12** (**2.6.1.4**), which by a Lombardo reaction [8] (cf. Section 1.1.5) using dibromomethane, zinc, and titaniumtetrachloride leads to the alkene **13** (**5.4.1.1**). The final step in the preparation of the substrate **6** (**5.4.1.2**) for the domino reaction is the selective cleavage of one of the methyl ether moieties in **13** using sodium ethylthiolate. The selectivity in this nucleophlic substitution is caused by the intermediate formation of a phenolate anion which prohibits a second attack of the thiolate as a result of electrostatic repulsion.

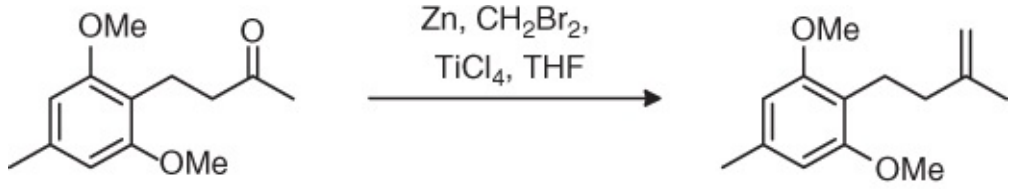


For the three-component enantioselective domino Wacker/carbonylation/methoxylation reaction of **6**, the Bn-BOXAX ligand **11** (**2.6.1.10**) [6] is used. The reaction is performed with catalytic amounts of palladium(II) trifluoroacetate [$Pd(OTFA)_2$] under carbon monoxide atmosphere and methanol as solvent to give **1** (**5.4.1.3**) in 80% yield and 96% ee. In this process, *p*-benzoquinone is used to oxidize the formed Pd^0 into Pd^{II} needed for the Wacker oxidation.



(c) Experimental Procedures for the Synthesis of 1

5.4.1.1	***	**1,3-Dimethoxy-5-methyl-2-(3-methyl-but-3-enyl)-benzene** [1]



222.3 220.3

A slurry of zinc powder (13.2 g, 202 mmol) and CH_2Br_2 (5.36 ml, 11.7 g, 67.5 mmol) in THF (220 ml) is treated dropwise with $TiCl_4$ (5.46 ml, 9.35 g, 49.5 mmol) at 0 °C, and the resulting mixture is stirred at 0 °C for 15 min. Subsequently, a solution of ketone **12** (**2.6.1.4**) (10.0 g, 45.0 mmol) in THF (50 ml) is added dropwise at 0 °C, and stirring is continued at room temperature for further 45 min.

The solids are removed by filtration over Celite® (washing with Et_2O), and the filtrate is washed with 1 M aqueous HCl solution (500 ml) and brine (500 ml). The organic layer is dried over Na_2SO_4 and filtered, and the solvent is removed *in vacuo*. Column chromatography of the residue on silica gel (*n*-pentane/Et_2O 97 : 3) yields alkene **5.4.1.1** as a colorless oil; 8.13 g (82%), R_f = 0.47 (*n*-pentane/Et_2O 97 : 3).

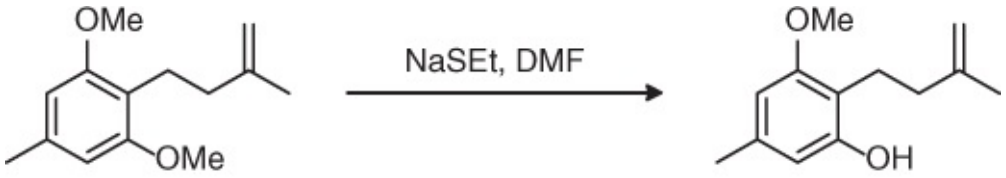
IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3072, 2937, 2835, 1588, 1464, 1314, 1241, 1123, 970, 884, 813.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 6.36 (s, 2H, 2 × Ar–H), 4.70 (d, *J* = 1.0 Hz, 2H, 2 × 4′-H), 3.79 (s, 6H, 2 × OCH_3), 2.70–2.79 (m, 2H, 1′-H_2), 2.33 (s, 3H, Ar–CH_3), 2.09–2.19 (m, 2H, 2′-H_2), 1.79 (s, 3H, 3′-CH_3).

^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) = 158.2 (C-2, C-6), 147.0 (C-3′), 136.7 (C-4), 115.9 (C-1), 109.1 (C-4′), 104.6 (C-3, C-5), 55.5 (OCH_3), 37.2 (C-2′), 22.4 (3′-CH_3), 21.8 (Ar–CH_3), 21.2 (C-1′).

MS (70 eV, EI): *m*/*z* (%): 220.3 (13) $[M]^+$, 165.2 (100) $[M-C_4H_7]^+$.

5.4.1.2	**	**3-Methoxy-5-methyl-2-(3-methyl-but-3-enyl)-phenol** [1]



220.3 206.3

A solution of **5.4.1.1** (5.00 g, 22.7 mmol) in DMF (35.0 ml) is treated with NaSEt (4.23 g, technical grade (90% (w/w)), 45.4 mmol) and stirred at 120 °C for 20 h.

After cooling to room temperature, the mixture is poured into water (200 ml) and extracted with Et_2O (3 × 100 ml). The combined organic layers are washed with water (2 × 100 ml) and brine (100 ml), dried over Na_2SO_4, and filtered, and the solvent is removed *in vacuo*. Column chromatography on silica gel (*n*-pentane/Et_2O 97 : 3 → 93 : 7) yields phenol **5.4.1.2** as a pale-yellow oil which solidifies upon storage at −30 °C; 4.31 g (92%), R_f = 0.34 (*n*-pentane/Et_2O 95 : 5).

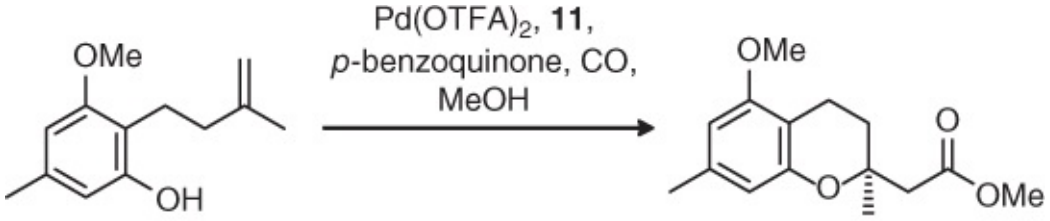
IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3442, 3072, 2937, 1619, 1593, 1464, 1163, 1097, 886, 816.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 6.34 (s, 1H, Ar–H), 6.29 (s, 1H, Ar–H), 4.93 (s, 1H, OH), 4.78 (m_c, 2H, 4′-H_2), 3.82 (s, 3H, OCH_3), 2.73–2.82 (m, 2H, 1′-H_2), 2.29 (s, 3H, Ar–CH_3), 2.17–2.27 (m, 2H, 2′-H_2), 1.82 (s, 3H, 3′-CH_3).

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 158.4, 154.0 (C-1, C-3), 146.8 (C-3′), 136.9 (C-5), 113.6 (C-2), 109.6 (C-4′), 109.0, 104.3 (C-4, C-6), 55.6 (OCH_3), 37.0 (C-2′), 22.7 (3′-CH_3), 21.7 (C-1′), 21.5 (Ar–CH_3).

MS (70 eV, EI): *m*/*z* (%): 206.1 (28) $[M]^+$, 151.1 (100) $[M-C_4H_7]^+$.

5.4.1.3	***	**Methyl (*S*)-2-(5-methoxy-2,7-dimethylchroman-2-yl)acetate** [1]



206.3 264.3

A solution of $Pd(OTFA)_2$ (49.0 mg, 148 µmol, 3 mol%) and (*S*,*S*)-Bn-BOXAX **11** (**2.6.1.10**) (338 mg, 590 µmol, 12 mol%) in MeOH (5.0 ml) is stirred at room temperature for 15 min. After addition of a solution of phenol **5.4.1.2** (1.00 g, 4.92 mmol) in MeOH (10 ml) and *p*-benzoquinone (2.12 g, 19.7 mmol), carbon monoxide is passed through the resulting mixture for 5 min before being stirred under a CO atmosphere (balloon; Caution: CO!) at room temperature for further 24 h.

The slurry is poured into aqueous 1 N HCl (100 ml) and extracted with Et_2O (3 × 50 ml). The combined extracts are washed with aqueous 1 N NaOH (3 × 50 ml), dried over Na_2SO_4, and filtered, and the solvent is removed *in vacuo*. Column chromatography on silica gel (*n*-pentane/Et_2O 9 : 1) yields chroman **5.4.1.3** as a yellowish oil (1.04 g, 80% yield, 96% ee). HPLC (high-performance liquid chromatography) (column: Daicel Chiralcel OD): wavelength: 272 nm, flow: 0.8 ml min^{-1}, eluent: *n*-hexane/isopropanol 98 : 2, t_R = 19.7 min ((−)-**1**), 28.9 min ((+)-**1**); R_f = 0.28 (*n*-pentane/Et_2O 9 : 1); $[\alpha]^{20}_D$ = −7.0 (*c* = 0.5 in $CHCl_3$).

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 2949, 2856, 1738, 1619, 1586, 1354, 1227, 1108, 1023, 814.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.42 (s, 3H, 2-CH_3), 1.85 (dt, *J* = 13.8, 6.8 Hz, 1H, 3-H_a), 1.99 (dt, *J* = 13.8, 6.8 Hz, 1H, 3-H_b), 2.26 (s, 3H, Ar–CH_3), 2.55–2.66 (m, 4H, 2′-H_2, 4-H_2), 3.68 (s, 3H, CO_2CH_3) 3.79 (s, 3H, Ar–OCH_3), 6.24 (s, 1H, Ar–H), 6.29 (s, 1H, Ar–H).

^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) = 170.9 (C-1′),157.5, 153.5 (C-5, C-8a), 137.1 (C-7), 106.8 (C-4a), 110.4, 102.9 (C-6, C-8), 74.2 (C-2), 55.3 (Ar–OCH_3), 51.5 (CO_2CH_3), 43.5 (C-2′), 30.3 (C-3), 24.6 (2-CH_3), 21.5 (Ar–CH_3), 16.4 (C-4).

ESI-HRMS: *m*/*z* calcd. for $[C_{15}H_{20}O_4 + H]^+$: 265.1434, found: 265.1435.

References

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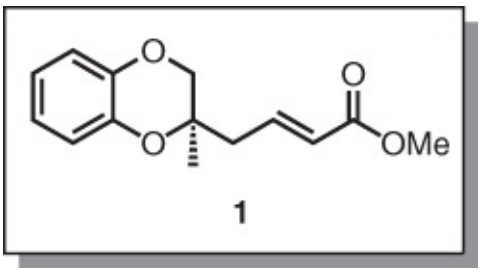
5.4.2 (*rac*)-(*E*)-5-(2-Methyl-2,3-dihydrobenzo[*b*][1,4]dioxin-2-yl)pent-3-ene-2-one



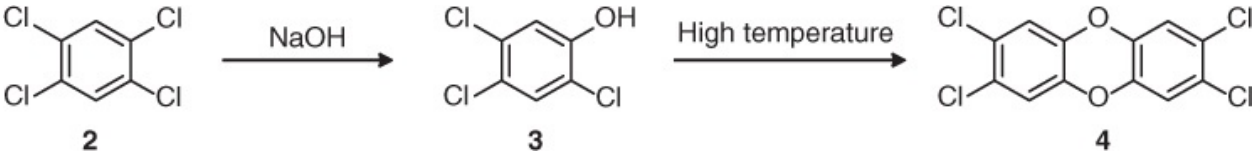
1

Topics:

- Dioxin synthesis
- Palladium catalysis
- Monoalkylation
- Finkelstein reaction
- Domino Wacker/Heck reaction

(a) General

Heterocycles containing two oxygens in a six-membered ring in a 1,4-orientation are well known in the form of 2,3,7,8-tetrachlorodibenzo-1,4-dioxin (**4**, TCDD, LD_{50} = 45 µg kg^{-1} in rats). This highly toxic material was released in an industrial accident in Seveso in 1976 by overheating a batch of 1,2,4,5-tetrachlorobenzene with sodium hydroxide to obtain 2,4,5-trichlorophenol (**3**), which can be used in the synthesis of the herbicide 2,4,5-T (2,4,5-trichlorophenoxyacetic acid) and the disinfectant hexachlorophene [1]. However, at higher temperature, in the presence of NaOH substrate, **3** is transformed to some extent into TCDD (**4**).



2 3 4

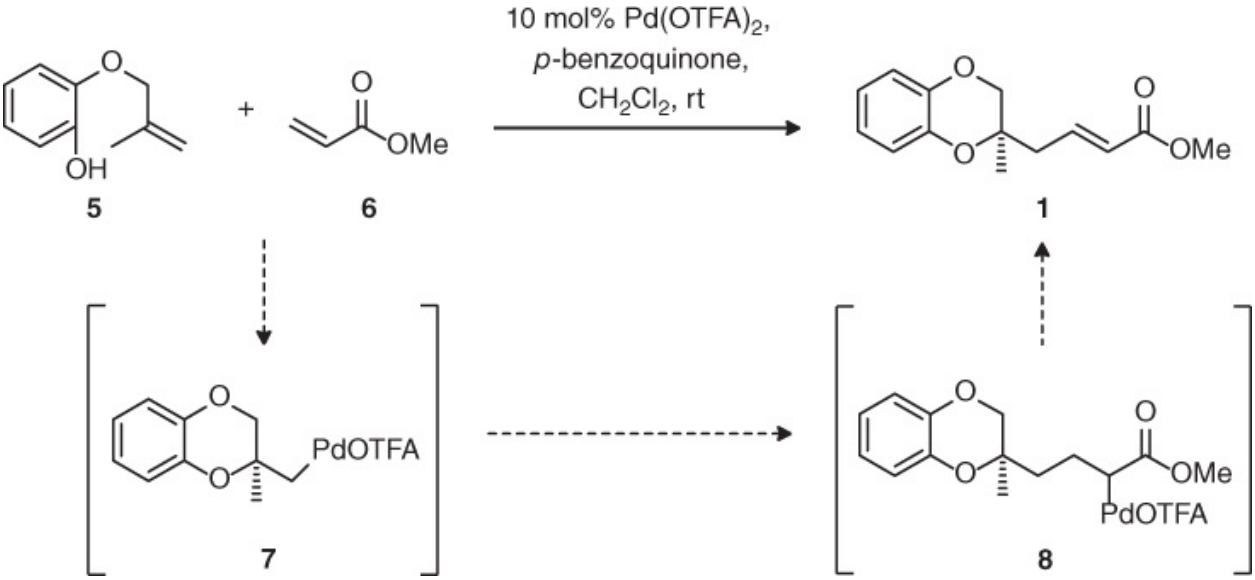
A multitude of studies followed, and nowadays there are very strict standardized industrial safety regulations to avoid the formation of this dangerous teratogenic compound, which additionally is very difficult to degrade biologically [2]. On the contrary, 1,4-dioxanes have no pronounced toxicity, and the parent

compound 1,4-dioxane is used as solvent. Moreover 1,4-dioxane can easily be employed for further transformations such as chlorination to give 2,3-and 2,5-dichlorodioxanes, or the ring opening with HBr to give di-(2-bromoethyl) ether, or with acetic anhydride in the presence of $FeCl_3$ to provide the corresponding diacetate [3].

The synthesis of 1,4-dioxane can be performed by an acid-catalyzed cyclodehydration of ethylene glycol or by an acid-catalyzed dimerization of oxirane. In general, 1,4-dioxanes are accessible by the following procedures:

1. reaction of alkali hydroxide with di-(2-haloethyl) ethers,
2. acid-catalyzed reaction of di-(2-hydroxyethyl) ethers,
3. reaction of 2-hydroxyethyl 2-haloethyl ethers under basic conditions in a nucleophilic Williamson ether synthesis,
4. acid-catalyzed reaction of 1,2-glycols with an oxirane, or
5. Wacker oxidation of allyl phenoxy ethers.

For the synthesis of the substituted 2,4-dihydrobenzodioxin **1**, a domino Wacker/Heck reaction is used [4].



In the reaction of **5** and methyl acrylate **6** in the presence of Pd(II) trifluoroacetate, first a Wacker oxidation takes place to give a σ-Pd complex **7** as intermediate, which is rather stable because a β-hydride elimination cannot take place. However, it can react with acrylate **6** present in the solution to give an adduct **8**, which now can undergo a β-hydride elimination to yield the desired compound **1**. Benzoquinone is necessary to reoxidize Pd^0 formed in the reaction

to give Pd(II) to restart the catalytic cycle.

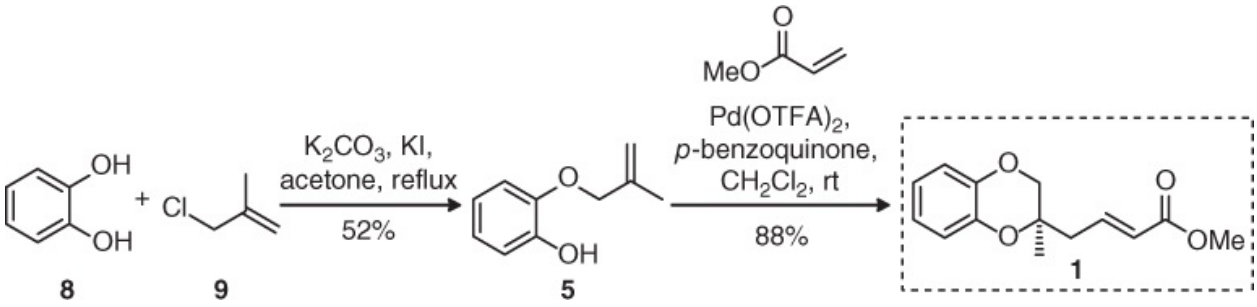
A similar process was employed for the enantioselective synthesis of vitamin E [5].

Moreover, also the combination of a Wacker oxidation and a carbonylation together with a methoxylation has been used for the synthesis of heterocycles and natural products such as diversonol [6].

The Wacker oxidation is discussed in Sections 2.6.1 and 5.4.1, and the Heck reaction in Section 1.6.1.

(b) Synthesis of 1

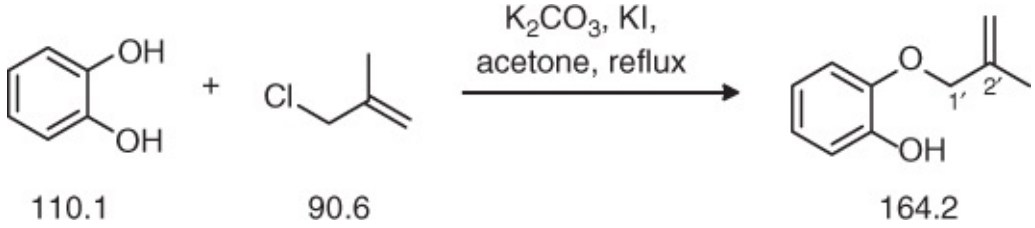
The racemic synthesis of **1** starts with the mono-O-alkylation of 1,2-dihydroxybenzene (catechol) (**8**) to give the phenol **5** using potassium carbonate as base and 3-chloro-2-methylpropene (**9**), which is *in situ* converted through a Finkelstein reaction into the corresponding iodide that undergoes the S_N1-type reaction with the deprotonated form of 1,2-dihydroxybenzene (**8**). Using 10 mol% of $Pd(OTFA)_2$ as catalyst and *p*-benzoquinone as reoxidant, the phenol **5** (**5.4.2.1**) and methyl acrylate (**6**) undergo a domino Wacker/Heck reaction to yield 88% of the racemic dioxin **1** (**5.4.2.2**).



Using the described procedure, the dioxin **1** is available in two steps starting from catechol **8** in an overall yield of 46%.

(c) Experimental Procedures for the Synthesis of 1

5.4.2.1	*	**2-(2-Methylallyloxy)phenol** [4, 7]



Under an argon atmosphere, a suspension of anhydrous K_2CO_3 (6.92 g, 50.1 mmol) and KI (8.30 g, 50.1 mmol) in acetone (80 ml) is treated with pyrocatechol (5.01 g, 45.5 mmol) and stirred at room temperature until the end of gas release (approximately 30 min). Afterward, 3-chloro-2-methylpropene (5.34 ml, 4.94 g, 54.6 mmol) is added, and the resulting mixture stirred under reflux for 4 h.

The mixture is cooled to room temperature and poured into water (200 ml). The solution is neutralized with aqueous 1 N HCl, and the aqueous phase is extracted with Et_2O (3 × 100 ml). The combined organic layers are dried over $MgSO_4$ and filtered, and the solvent is removed *in vacuo*. Purification of the crude product by column chromatography (SiO_2, *n*-pentane/ethyl acetate 50 : 1 → 10 : 1) affords the title compound as a colorless liquid; 3.90 g (52%).

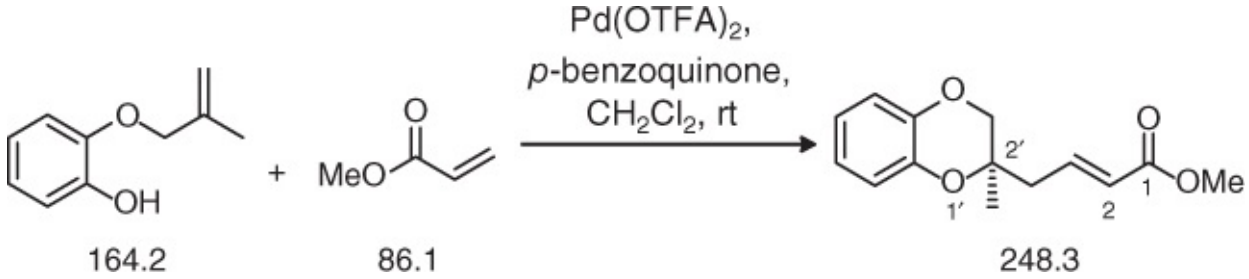
IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3536, 2919, 1597, 1501, 1454, 1373, 1259, 1219.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 6.79–6.99 (m, 4H, Ar–H), 5.70 (s, 1H, OH), 5.10 (m_c, 1H, 3′-H_a), 5.03 (m_c, 1H, 3′-H_b), 4.51 (s, 2H, 1′-H_2), 1.85 (s, 3H, 2′-CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 145.6, 145.8 (C-1, C-2), 140.4 (C-2′), 120.0, 121.6 (C-4, C-5), 112.1, 114.6, (C-3, C-6), 113.3 (C-3′), 72.6 (C-1′), 19.4 (2′-CH_3).

MS: (EI, 70 eV): *m*/*z* (%) = 164 (57) $[M]^+$, 109 (30) $[M-C_4H_7]^+$, 55 (100) $[C_4H_7]^+$.

5.4.2.2	******	**(*rac*)-(*E*)-Methyl 4-(2-methyl-2,3-dihydrobenzo[*b*][1,4]dioxin-2-yl)but-2-enoate** [4]



A mixture of $Pd(OTFA)_2$ (10.1 mg, 30.3 µmol) and *p*-benzoquinone (131 mg,

1.21 mmol) in CH_2Cl_2 (0.20 ml) is stirred for 10 min at room temperature under an argon atmosphere. Then, a solution of 2-(2-methylallyloxy)phenol **5.4.2.1** (49.8 mg, 303 µmol) and methyl acrylate (55.0 µl, 52.2 mg, 607 µmol) in CH_2Cl_2 (0.20 ml) is added via a syringe to the suspension and the mixture is stirred for 12 h at room temperature.

The reaction is quenched by the addition of 1 N HCl (10 ml), and the aqueous phase is extracted with Et_2O (3 × 10 ml). The combined organic phases are washed with aqueous 1 N NaOH (3 × 10 ml), dried over $MgSO_4$, and filtered, and the solvent is removed *in vacuo*. The residue is purified by column chromatography (SiO_2, *n*-pentane/ethyl acetate 6 : 1) to afford the dioxin as a colorless oil; 66.1 mg (88%).

UV (CH_3CN): λ_{max} (nm) (log ϵ) = 201.1 (4.720), 277.5 (3.472).

IR (film): $\tilde{\nu}$ (cm^{-1}) = 2981, 1724, 1659, 1594, 1494, 1436, 1264.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.00 (ddd, *J* = 15.6, 8.2, 7.2 Hz, 1H, 3-H), 6.79–6.92 (m, 4H, 4 × Ar–H), 5.92 (dt, *J* = 15.7, 1.4 Hz, 1H, 2-H), 3.96 (d, *J* = 11.3 Hz, 1H, 3′-H_a), 3.85 (d, *J* = 11.3 Hz, 1H, 3′-H_b), 3.74 (s, 3H, OCH_3), 2.60 (ddd, *J* = 14.2, 7.2, 1.6 Hz, 1H, 4-H_a), 2.48 (ddd, *J* = 14.4, 8.3, 1.3 Hz, 1H, 4-H_b), 1.32 (s, 3H, 2′-CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 166.4 (C-2), 142.6 (C-3), 142.0, 142.1 (C-4′a, C-8′a), 124.8 (C-2), 121.1, 122.0 (C-6′, C-7′), 117.0, 117.6 (C-5′, C-8′), 73.6 (C-3′), 70.3 (C-2′), 51.5 (OCH_3), 38.5 (C-4), 21.2 (2′-CH_3).

MS (EI, 70 eV): *m*/*z* (%) = 248 (24) $[M]^+$, 149 (100) $[M-C_5H_7O_2]^+$.

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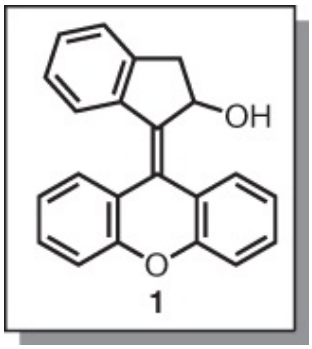
5.5 Domino Reactions in the Synthesis of Chiroptical Switches

5.5.1 1-(9*H*-Xanthen-9-ylidene)-2,3-dihydro-1*H*-inden-2-ol



1

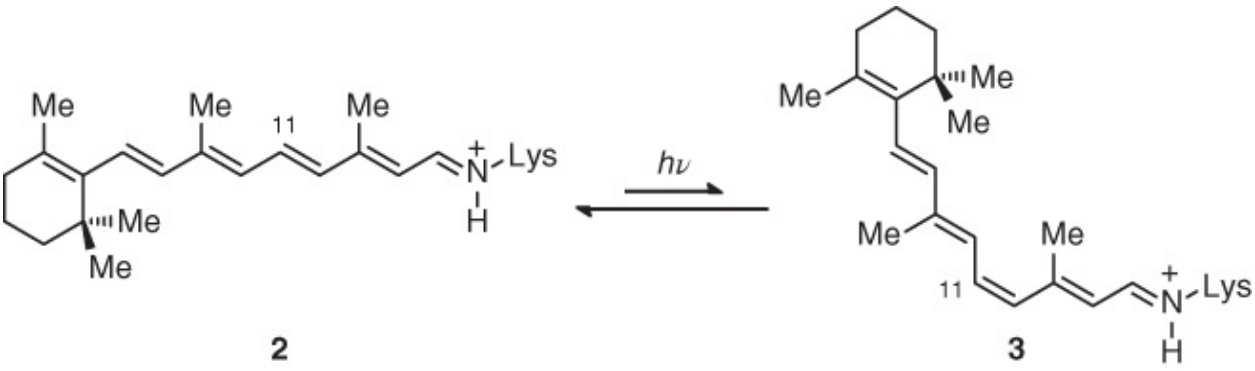
Topics:

- Molecular switches
- Palladium catalysis
- CH activation
- Diazotization and Sandmeyer reaction
- Sonogashira reaction
- Wittig reaction

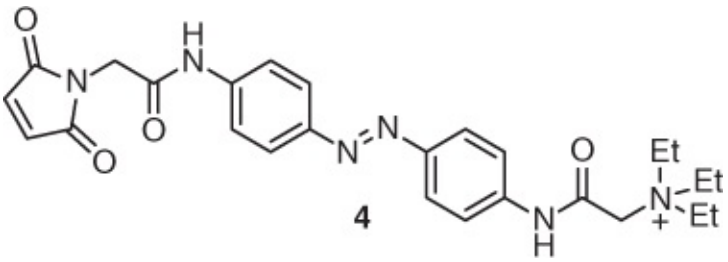
		• Microwave irradiation • Domino carbopalladation/CH-activation process

(a) General

The field of material science in chemistry has developed over the last decades with high pace. Blooming research areas are molecular machines, logic elements, and molecular switches [1]. The latter can be used for data storage with the advantage of miniaturization. A prerequisite for molecular switches is their bistability of two distinct states, which can be interconverted by different external stimuli such as light or electron transport [2]. Rotaxanes and certain transition-metal complexes featuring ambidentate ligands can be triggered electrochemically by oxidation or reduction, but the main work has been done on switches where light is used as a trigger to induce rapid switching between states [3, 4]. A very well known example of switching by light is the isomerization of all-trans retinal (**2)** to give 11-*cis*-retinal **3** in rhodopsin during the visual process [5].



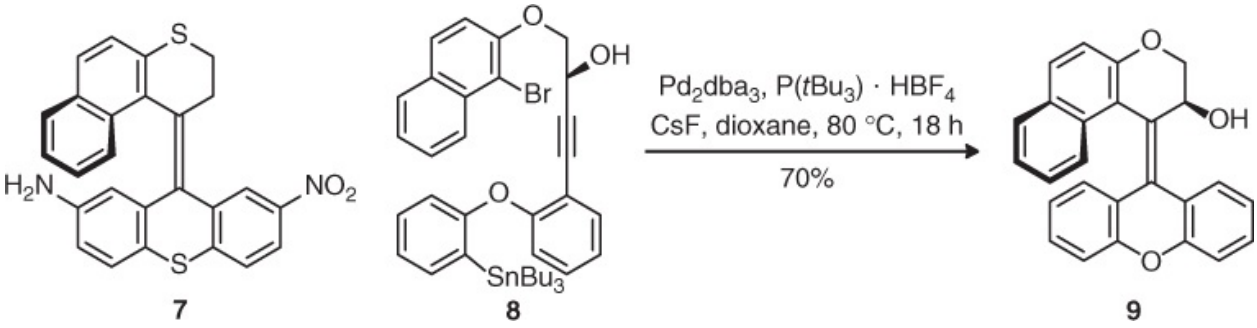
Other well-investigated optical switches are azo compounds, which also can undergo a light-induced *E*/*Z*-isomerization. An interesting example is the azobenzene **4**, which acts as a selective K^+-channel blocker in the *E*-configuration whereby, after irradiation with light (λ = 390 nm) with formation of the *Z*-configuration, the channel is activated again [6].



Another important group of compounds with light-induced switching properties are diarylethenes such as **5**/**6**, which are rather stable in the closed form **6** [7].

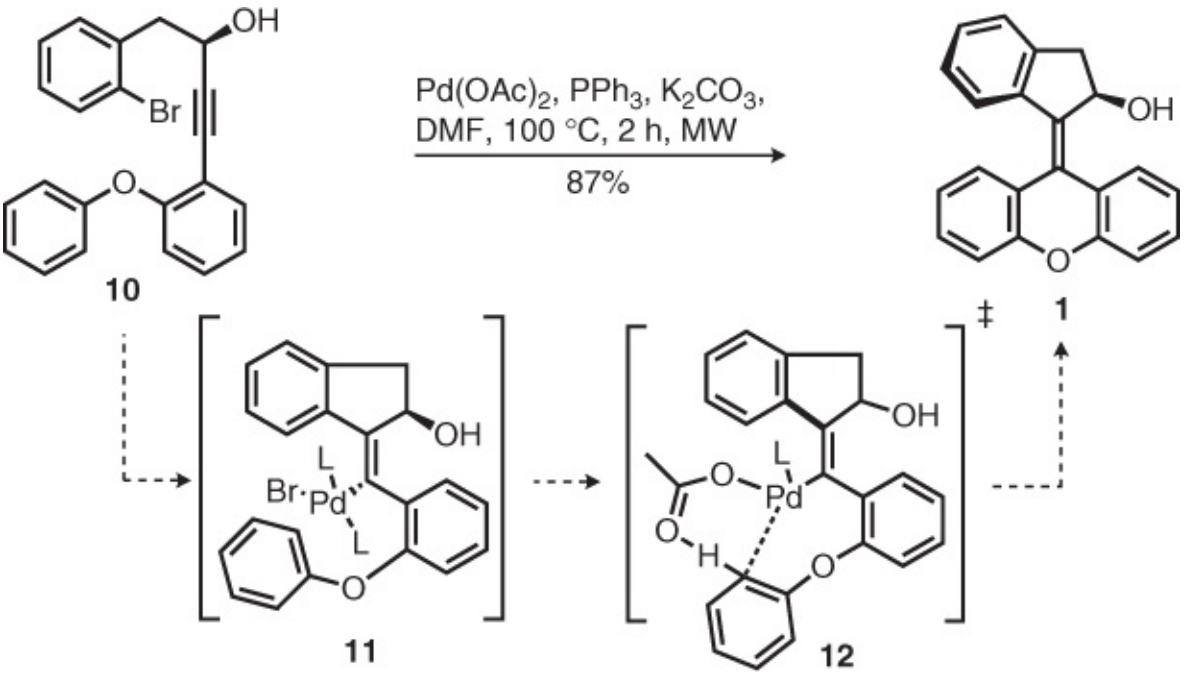
5 *Open*-form (uncolored) ⇌ **6** *Closed*-form (colored)

Recently, special interest has been shown on chiroptical switches such as **7** [8] containing a helical tetra-substituted alkene moiety because their stable states can be accessed using circularly polarized light. Moreover, through an additional thermal isomerization following a photoinduced *P*/*M*-isomerization, unidirectional motors have been realized. Such compounds with a helical alkene unit can easily be obtained in enantio-and diastereopure form by a diastereoselective domino carbopalladation/Stille reaction as in the case of **8** to give **9** [9]. In this process, two six-membered rings and the tetra-substituted double bond are formed as a single diastereomer. The helical alkene **9** shows excellent switching properties from the P to the M configuration and backwards using different wavelength, and it is rather stable.



7 **8** **9**

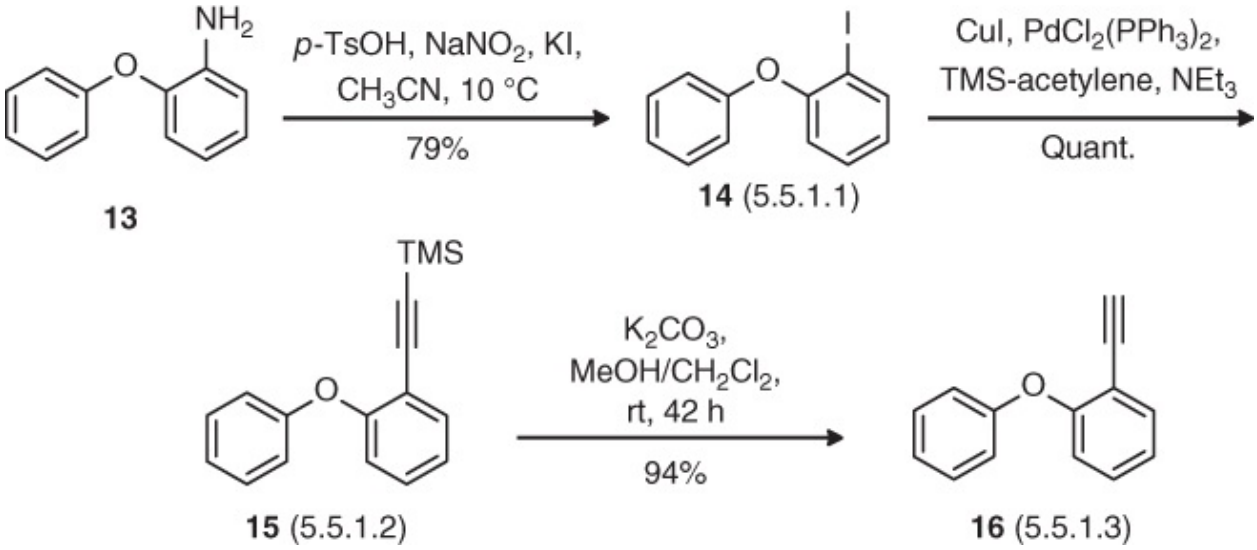
However, the use of stannanes is neither environmentally friendly nor appropriate for a large-scale synthesis. A cyclization using CH activation without introducing additional functional groups would be more appropriate [10]. Thus, tetra-substituted alkenes of type **1** have been synthesized through a domino carbopalladation/CH activation of **10** with high yield [11]. The following mechanism can be proposed:



After the oxidative addition of **10** using a Pd(0) source, a carbopalladation takes place to give **11**, which is followed by a CH activation probably via **12** to provide the desired product **1** in 87% yield. Furthermore, a threefold two-component domino Sonogashira/carbopalladation/C–H-activation process has also been developed to give tetra-substituted alkenes [12].

(b) Synthesis of 1

The racemic synthesis starts with the *in situ* formation of the diazonium salt of **13** followed by the subsequent displacement by iodide (S_NAr process) to afford the iodide **14** (**5.5.1.1**) in 79% yield. The following Sonogashira reaction of the iodide **14** (**5.5.1.1)** and TMS-acetylene using 10 mol% CuI and 1.8 mol% $PdCl_2(PPh)_3$ as the Pd source yields alkyne **15** (**5.5.1.2**) in quantitative yield. Subsequent TMS deprotection at room temperature with potassium carbonate affords the alkyne **16** (**5.2.1.3**) in 94% yield.



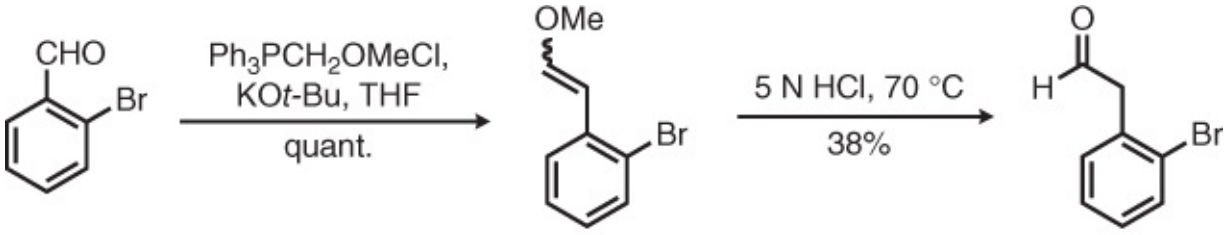
13

14 (5.5.1.1)

15 (5.5.1.2)

16 (5.5.1.3)

The second required building block is the aldehyde **19** (**5.5.1.5**). It can be synthesized from 2-bromobenzaldehyde **17** through a Wittig reaction to give enol ether **18** (**5.5.1.4**), which is hydrolyzed with HCl.

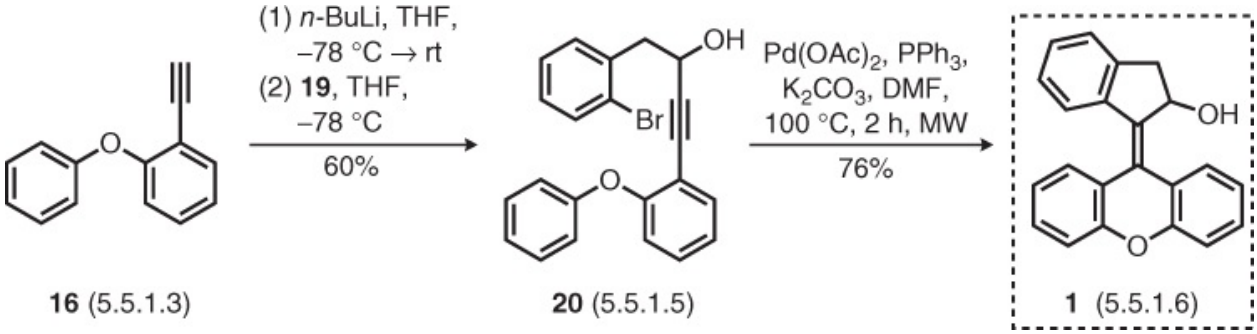


17

18 (5.5.1.4)

19

The precursor of the domino reaction **20** (**5.5.1.6**) is obtained by addition of the lithiated alkyne **16** (**5.5.1.3**) to aldehyde **19** to give **20** (**5.5.1.5**) in 60% yield, and the domino carbopalladation/CH activation to give the racemic tetra-substituted alkene **1** (**5.5.1.6**) in 76% yield is performed using 20 mol% $Pd(OAc)_2$ and potassium carbonate in DMF at 100 °C under microwave irradiation.



16 (5.5.1.3)

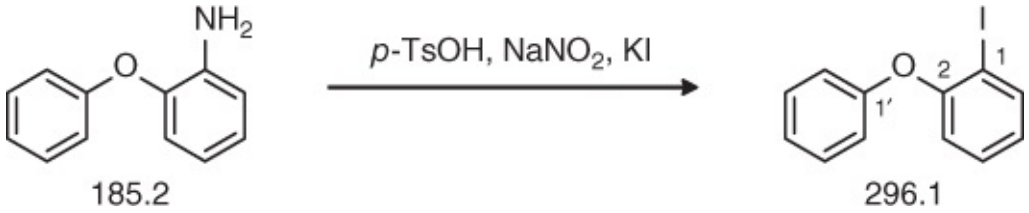
20 (5.5.1.5)

1 (5.5.1.6)

Using the described procedure, the tetra-substituted alkene **1** is available in seven steps starting from 2-phenoxyaniline **13** with an overall yield of 13%.

(c) Experimental Procedures for the Synthesis of 1

5.5.1.1	**	**1-Iodo-2-phenoxybenzene** [11]



2-Phenoxyaniline (1.13 g, 6.12 mmol) is added at room temperature to a stirred solution of *p*-TsOH·H_2O (3.51 g, 18.4 mmol) in MeCN (60 ml), and the resulting suspension is cooled to 10 °C. Afterward, a solution of $NaNO_2$ (840 mg, 12.2 mmol) and KI (2.54 g, 15.3 mmol) in water (7.50 ml) is added dropwise. After additional stirring for 10 min at 10 °C, the solution is allowed to reach room temperature and stirred for another 2 h.

The reaction is quenched with H_2O (120 ml), saturated aqueous $NaHCO_3$ solution (80 ml), and saturated aqueous $Na_2S_2O_3$ solution (30 ml). The aqueous phase is extracted with *t*-BuOMe (3 × 150 ml), the combined organic extracts are dried over $MgSO_4$ and filtered, and the solvent is removed *in vacuo*. Flash column chromatography (SiO_2, petroleum ether) affords the product as a colorless oil; 1.44 g, (79%), R_f = 0.34 (petroleum ether).

UV (CH_3CN): λ_{max} (nm) (log ϵ) = 270 (3.309), 277 (3.303).

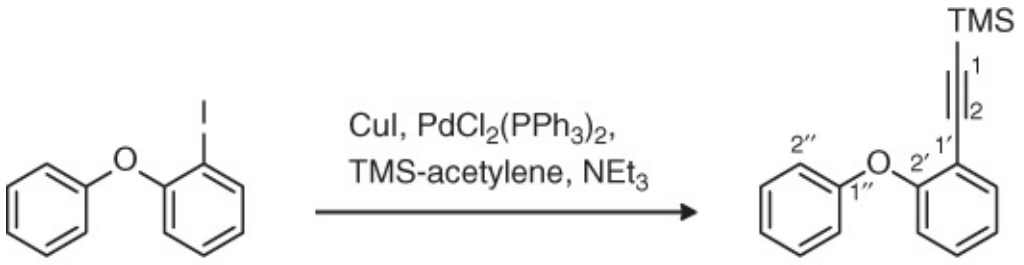
IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3061, 1573, 1488, 1464, 1436, 1235, 1162, 1020, 874, 748.

^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 7.85 (dd, *J* = 1.5, 7.8 Hz, 1H, 6-H), 7.29 (m, 3H, 4-H, 3′-H, 5′-H), 7.11 (t, *J* = 7.4 Hz, 1H, 4′-H), 6.97 (m, 2H, 2′-H, 6′-H), 6.78 (m, 2H, 3-H, 5-H).

^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) = 156.9 (C-2), 156.5 (C-1′), 139.9 (C-6), 129.8 (C-3′, C-5′), 129.6 (C-4), 125.3 (C-5), 123.5 (C-4′), 119.4 (C-3), 118.4 (C-2′, C-6′), 88.9 (C-1).

MS (EI, 70 eV): *m*/*z* (%) = 296.0 (100) $[M]^+$, 169.1 (61) $[M-I]^+$.

5.5.1.2	**	**Trimethyl[(2-phenoxyphenyl)ethynyl]silane** [11]



296.1 266.4

TMS-acetylene (3.54 g, 34.2 mmol), CuI (188 mg, 2.85 mmol, 10 mol%), and $PdCl_2(PPh_3)_2$ (371 mg, 529 µmol, 1.8 mol%) are added at room temperature to a stirred and thoroughly degassed solution of 1-iodo-2-phenoxybenzene **5.5.1.1** (8.43 g, 28.5 mmol) in NEt_3 (220 ml). The reaction mixture is stirred for 40 h at room temperature.

The reaction is quenched by addition of *t*-BuOMe (500 ml). The organic layer is washed with aqueous 2 N HCl (300 ml) and a saturated aqueous $NaHCO_3$ solution (400 ml). The aqueous layer is extracted with *t*-BuOMe (3 × 500 ml), the combined organic layers are dried over $MgSO_4$ and filtered, and the solvent is removed *in vacuo*. Flash column chromatography (SiO_2, petroleum ether) affords the product as a colorless oil; 6.88 g (quant.), R_f = 0.29 (petroleum ether).

UV (CH_3CN): λ_{max} (nm) (log ϵ) = 208 (4.364), 236 (4.202), 247 (4.270), 259 (4.297), 291 (3.508), 301 (3.406).

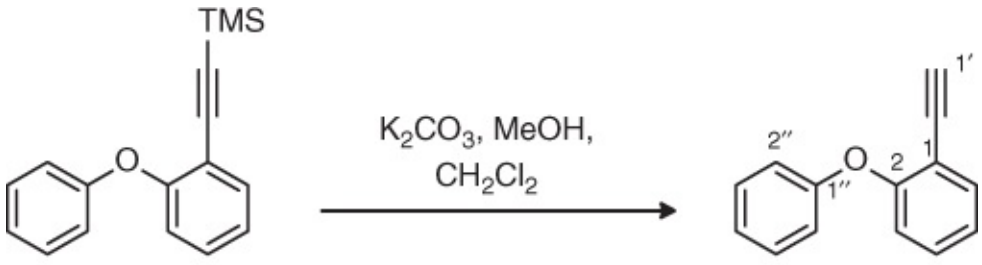
IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2159, 1590, 1480, 1442, 1241, 1208, 1103, 837, 745.

^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 0.11 (s, 9H, 3 × $Si(CH_3)_3$), 6.95 (m, 3H, 3′-H, 2″-H, 6′-H), 7.06 (m, 2H, 5′-H, 4″-H), 7.28 (m, 3H, 4′-H, 3″-H, 5″-H), 7.49 (dd, *J* = 1.7, 7.7 Hz, 1H, 6′-H).

^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) = 0.24 (3 × $Si(\underline{C}H_3)_3$), 99.9 (C-1), 100.3 (C-2), 116.1 (C-1′), 117.9 (C-2″, C-6″), 119.9 (C-3′), 122.7 (C-4″), 123.6 (C-5′), 129.5 (C-3″, C-5″), 129.9 (C-4′), 134.1 (C-6′), 157.5 (C-2′, C-1″).

MS (DCI-NH_3): *m/z* (%) = 259 (100) $[M+H]^+$, 517 (20) $[2M+H]^+$.

5.5.1.3	*	**1-Ethynyl-2-phenoxybenzene** [11]



266.4 194.2

K_2CO_3 (18.2 g, 131 mmol) is added to a stirred solution of trimethyl[(2-phenoxyphenyl)ethynyl]silane **5.5.1.2** (7.79 g, 29.6 mmol) in MeOH/CH_2Cl_2 (1 : 1, 600 ml), and stirring is continued for 42 h at room temperature.

The reaction is quenched by the removal of the solvent *in vacuo*, and the residue is dissolved in CH_2Cl_2 (200 ml). The organic layer is washed with saturated aqueous $NaHCO_3$ solution (300 ml), and the aqueous layer is extracted with CH_2Cl_2 (4 × 300 ml). The combined organic layers are dried over $MgSO_4$ and filtered, and the solvent is removed *in vacuo* to afford the alkyne as a pale brown solid; 5.33 g (94%), R_f = 0.17 (petroleum ether).

UV (CH_3CN): λ_{max} (nm) (log ϵ) = 204 (4.471), 232 (4.174), 271 (3.244), 278 (3.303), 288 (3.372), 297 (3.297).

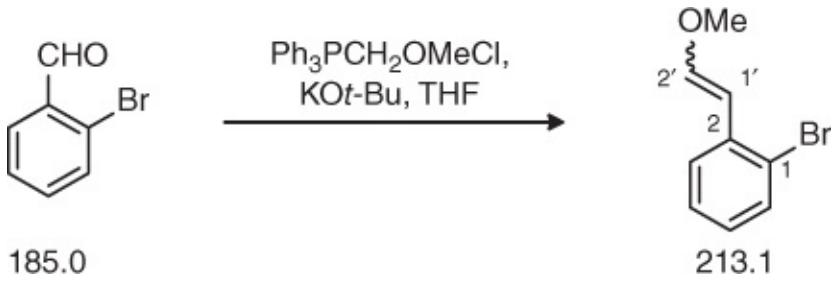
IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3283, 3054, 1477, 1236.

^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 7.54 (dd, *J* = 1.7, 7.6 Hz, 1H, 6-H), 7.30 (m, 3H, 4-H, 3″-H, 5″-H), 7.09 (m, 2H, 5-H, 4″-H), 7.02 (m, 2H, 2″-H, 6″-H), 6.86 (dd, *J* = 1.1, 8.3 Hz, 1H, 3-H), 3.21 (s, 1H, 1′-H).

^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) = 158.4 (C-2), 156.9 (C-1″), 134.3 (C-6), 130.2 (C-4), 129.7 (C-3″, C-5″), 123.5 (C-4″), 123.2 (C-5), 118.9 (C-2″, C-6″), 118.5 (C-3), 114.3 (C-1), 81.7 (C-1′), 79.3 (C-2′).

MS (EI, 70 eV): *m*/*z* (%) = 194.1 (100) $[M]^+$.

5.5.1.4	*	**1-Bromo-2-(2-methoxyvinyl)benzene** [11]



185.0 213.1

A suspension of Ph_3PCH_2OMeCl (32.4 g, 94.6 mmol) in THF (270 ml) is cooled to 0 °C and treated with KO*t*-Bu (12.1 g, 108 mmol). The reaction mixture is warmed to room temperature within 15 min and subsequently cooled to 0 °C, and 2-bromobenzaldehyde (10.0 g, 54.0 mmol) is added. The reaction mixture is warmed to room temperature and stirred for 2 h.

The reaction is quenched by the addition of a saturated aqueous NH_4Cl solution (200 ml), the aqueous layer is extracted with EtOAc (3 × 200 ml), the combined organic layers are dried over Na_2SO_4 and filtered, and the solvent is removed *in vacuo*. Purification of the residue by flash column chromatography (SiO_2, petroleum ether/MTBE 20 : 1) affords the enol ether as light-yellow liquid as a mixture of *E*- and *Z*-isomers (*E*/*Z* = 5 : 4); 11.7 g (quantitative), R_f = 0.29 (petroleum ether).

E-Isomer:

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.51 (dd, *J* = 8.0, 1.2 Hz, 1H, 3-H), 7.15–7.34 (m, 2H, 4-H, 5-H), 6.96–7.03 (m, 1H, 6-H), 6.97 (d, *J* = 12.6 Hz, 1H, 2′-H), 6.07 (d, *J* = 12.6 Hz, 1H, 1′-H), 3.71 (s, 3H, OCH_3).

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 149.1 (C-2′), 136.2 (C-2), 132.9 (C-4), 127.4 (C-6), 127.1 (C-3), 125.6 (C-5), 122.9 (C-1), 103.9 (C-1′), 56.5 (OCH_3).

MS (ESI, MeOH): *m*/*z* (%) = 237.0 (100) $[M+Na]^+$.

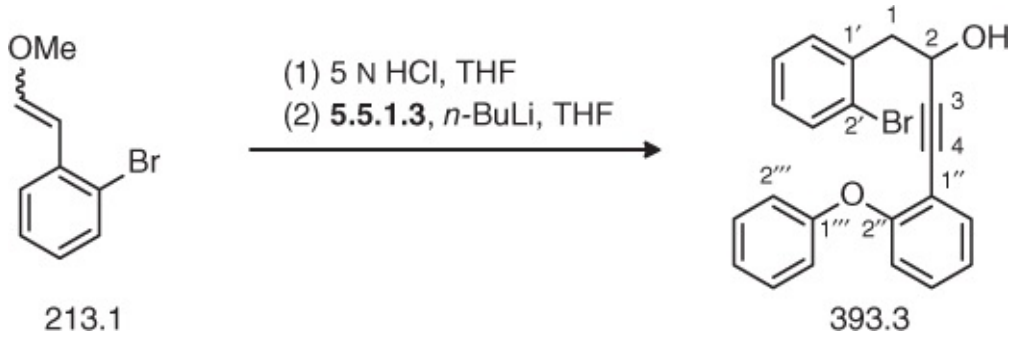
Z-Isomer:

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.02 (dd, *J* = 7.8, 1.7 Hz, 1H, 6-H), 7.15–7.34 (m, 3H, 3-H, 4-H, 5-H), 6.23 (d, *J* = 6.3 Hz, 1H, 2′-H), 5.59 (d, *J* = 6.3 Hz, 1H, 1′-H), 3.76 (s, 3H, OCH_3).

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 150.4 (C-2′), 134.9 (C-2), 132.5 (C-4), 130.3 (C-6), 127.0 (C-3), 126.9 (C-3), 122.6 (C-1), 104.3 (C-1′), 60.8 (OCH_3),

MS (ESI, MeOH): *m*/*z* (%) = 237.0 (100) $[M+Na]^+$.

5.5.1.5	**	**1-(2-Bromophenyl)-4-(2-phenoxyphenyl)but-3-yn-2-ol** [11]



213.1 393.3

A solution of enol ether **5.5.1.4** (500 mg, 2.35 mmol) and 5 N HCl (0.5 ml) in THF (2.0 ml) is heated at 70 °C for about 1–2 h (under TLC control).

The reaction is quenched by the addition of ice and a saturated aqueous $NaHCO_3$ solution (10 ml), and the aqueous layer is extracted with EtOAc (100 ml). The combined organic extracts are dried over Na_2SO_4 and filtered, and the solvent is removed *in vacuo*. Flash column chromatography (SiO_2, petroleum ether/MTBE 20 : 1) affords the aldehyde **5.5.1.5** as colorless oil; 177 mg (38%), R_f = 0.23 (petroleum ether/*t*-BuOMe 20 : 1), R_f (byproduct) = 0.35 (petroleum ether/*t*-BuOMe 20 : 1). (Caution: The aldehyde is not very stable and should be used immediately after its formation.)

A solution of alkyne **5.5.1.3** (310 mg, 1.63 mmol) in THF (6.5 ml) is lithiated by dropwise addition of *n*-BuLi (0.64 ml, 2.5 M in *n*-hexane, 3.26 mmol) at −78 °C. The reaction mixture is stirred for 15 min at −78 °C, warmed to room temperature within 30 min, and then slowly added to a solution of the aldehyde **5.5.1.5** (162 mg, 814 µmol) in anhydrous THF (3.0 ml) at −78 °C. The reaction mixture is stirred for 12 h at −78 °C and warmed to room temperature within 1 h.

The reaction is quenched by the addition of a saturated aqueous NH_4Cl solution (15 ml), the aqueous layer is extracted with *t*-BuOMe (3 × 50 ml), the combined organic extracts are dried over Na_2SO_4 and filtered, and the solvent is removed *in vacuo*. Flash column chromatography (SiO_2, petroleum ether/*t*-BuOMe 5 : 1)

affords the alcohol as a yellow oil; 192 mg (60%), R_f = 0.33 (*t*-BuOMe/petroleum ether 1 : 5).

UV (CH_3CN): λ_{max} (nm) (log ϵ) = 195 (4.831), 242 (4.160), 253 (4.126), 279 (3.481), 289 (3.503).

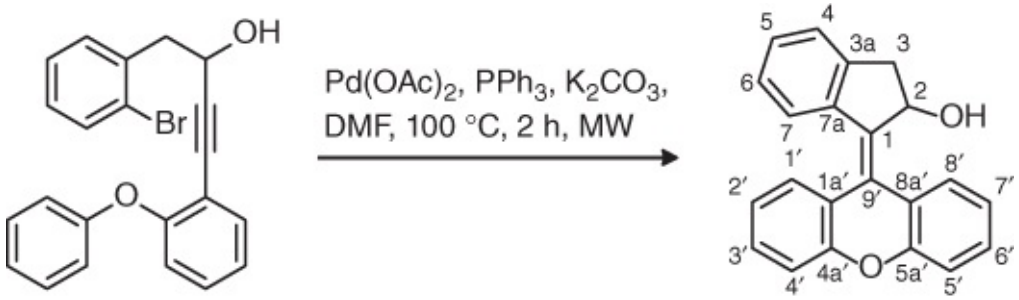
IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 1588, 1567, 1483, 1440, 1250, 1220, 1160, 1024, 870, 746, 689.

^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 7.50 (dd, *J* = 7.9, 1.2 Hz, 1H, 3′-H), 7.42 (dd, *J* = 7.7, 1.7 Hz, 1H, 6″-H), 7.34–7.25 (m, 4H, 4″-H, 3‴-H, 5‴-H, 6′-H), 7.12 (td, *J* = 7.5, 1.2 Hz, 1H, 5′-H), 7.09–7.02 (m, 3H, 4‴-H, 5″-H, 4′-H), 6.96 (dt, *J* = 9.1, 1.8 Hz, 2H, 2‴-H, 6‴-H), 6.94–6.90 (m, 1H, 3″-H), 4.77 (dd, *J* = 11.9, 6.8 Hz, 1H, 2-H), 3.14 (dd, *J* = 13.5, 7.1 Hz, 1H, 1-H_b), 3.06 (dd, *J* = 13.5, 6.7 Hz, 1H, 1-H_a), 1.84 (d, *J* = 5.4 Hz, 1H, OH).

^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) = 157.2 (C-2″, C-1‴), 136.1 (C-1′), 133.7 (C-6″), 132.6 (C-3′), 132.2 (C-6′), 129.8 (C-4″), 129.6 (C-3‴, C-5‴), 128.4 (C-4′), 127.1 (C-5′), 124.8 (C-2′), 123.4 (C-5″), 123.0 (C-4‴), 119.3 (C-3″), 118.2 (C-2‴, C-6‴), 114.9 (C-1″), 94.3 (C-3), 81.5 (C-4), 62.3 (C-2), 44.0 (C-1).

MS (ESI, MeOH): *m*/*z* (%) = 417.1 (20) $[M+Na]^+$, 809.1 (100) $[2M+Na]^+$.

5.5.1.6	**	**1-(9*H*-Xanthen-9-ylidene)-2,3-dihydro-1*H*-inden-2-ol** [11]



393.3 312.4

A solution of propargylic alcohol **5.5.1.5** (30.0 mg, 76.3 µmol), PPh_3 (20.0 mg, 76.3 µmol), and K_2CO_3 (117 mg, 854 µmol) in DMF (2.8 ml) is thoroughly degassed before $Pd(OAc)_2$ (3.80 mg, 15.0 µmol) is added. Then it is heated to 100 °C for 2 h under microwave irradiation.

The reaction mixture is cooled to room temperature and quenched by the addition of a saturated aqueous NH_4Cl solution (10 ml). The aqueous layer is extracted with *t*-BuOMe (3 × 100 ml), the combined organic extracts are dried over $MgSO_4$ and filtered, and the solvent is removed *in vacuo*. Purification of the residue by flash column chromatography (SiO_2, petroleum ether/*t*-BuOMe 5 : 1) affords the product as a yellow solid; (18.1 mg, 76%), R_f = 0.24 (petroleum ether/*t*-BuOMe 5 : 1).

UV (CH_3CN): λ_{max} (nm) (log ϵ) = 195 (4.61), 283 (3.92), 359 (3.87).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 1706, 1594, 1477, 1444, 1241, 751, 733.

^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 8.10 (dd, *J* = 7.8, 1.5 Hz, 1H, 8′-H), 7.80 (dd, *J* = 7.7, 1.4 Hz, 1H, 1′-H), 7.68 (d, *J* = 8.1 Hz, 1H, 7-H), 7.36 (ddd, *J* = 8.2, 7.3, 1.6 Hz, 1H, 3′-H), 7.31–7.27 (m, 2H, 4′-H, 6′-H), 7.27–7.20 (m, 3H, 7′-H, 5′-H, 4-H), 7.19 (td, *J* = 7.4, 0.9 Hz, 1H, 5-H), 7.15 (ddd, *J* = 7.6, 5.9, 1.2 Hz, 1H, 2′-H), 6.99 (t, *J* = 7.7 Hz, 1H, 6-H), 5.41 (d, *J* = 6.0 Hz, 1H, 2-H), 3.30 (dd, *J* = 17.1, 6.2 Hz, 1H, 3-H_a), 2.99 (d, *J* = 17.1 Hz, 1H, 3-H_b), 2.01 (s, 1H, OH).

^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) = 154.2 (C-4a′), 153.3 (C-5a′), 144.5 (C-3a), 140.3 (C-1), 137.9 (C-7a), 129.3 (C-3′), 129.1 (C-1′), 128.6 (C-5), 128.1 (C-6′), 126.5 (C-9′), 126.4 (C-8a′), 126.3 (C-6), 126.1 (C-8′), 125.6 (C-4), 124.6 (C-1a′), 124.1 (C-7), 123.6 (C-7′), 122.4 (C-2′), 117.0 (C-4′), 116.4 (C-5′), 72.6 (C-2), 40.7 (C-3).

MS (EI, 70 eV): *m*/*z* (%) = 312.1 (18) $[M]^+$, 295.1 (18) $[M-OH]^+$, 181.1 (100) $[M-C_9H_8O]^+$.

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[1] The name hirsutine was also used for a sesquiterpene of the triquinane type. Nowadays, these compounds are named as hirsutane and hirsutene.

[2] L.F. Tietze and K. Klapa, unpublished results

Index of Reactions

In this index, reactions and methods are covered, which are performed in the foregoing syntheses in experimental detail. Reaction types, methods and principles only mentioned in the text are not listed here.

b

[2+1]-

[2+2]-

[4+2]- see: Diels– Alder reaction

1,3-dipolar

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cationic

Cyclopropanation

Cyclotetramerization, of a pyrrole

d

Dakin– West reaction

Dealkylation (demethylation, debenzylation)

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of a β-ketoacid

of a malonic acid

of a pyrrole carboxylic acid

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- of a ketone
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Hantzsch synthesis (pyridine)

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Hetero-Diels-Alder reaction

High-pressure reaction

Hilbert-Johnson nucleosidation

Hydrogenation

- catalytic

Hydrolysis

- of an acetal
- of a carboxamide
- of a carboxylic ester

i

Imidazole synthesis

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- Cbz (= Z)
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Pyridine synthesis

Pyrimidine synthesis

Pyrimidinone synthesis

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- of C=O to CH^2
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4-Benzyl-3,5-bis(ethoxycarbonyl)-2,6-dimethylpyridine

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6-Benzyl-10,11-dimethoxy-5,6,6a,7,8,12b-hexahydrobenzo[*a*]-phenanthridine, *trans*

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1-Bromo-2-(dibromomethyl)naphthalene

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1-Bromo-2-naphthalenecarbaldehyde

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(2-Bromophenyl)acetonitrile

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1-(2-Bromophenyl)-4-(2-phenoxyphenyl) but-3-yn-2-ol

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1-Carbethoxymethyl-1,2,3,4-tetrahydro- β-carboline, (1*R*)

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1-Carbethoxymethyl-2-benzyloxy- carbonyl-12-*tert*-butyloxycarbonyl-1,2,3,4-tetrahydro-β-carboline

Carbethoxypyruvic acid

(4-Chlorobenzylidene)-(4-methoxy- phenyl)-imine

1-Chloro-2-methyl-3-buten-2-ol

4-(5-Chloromethylimidazol-1-ylmethyl)- benzonitrile HCl salt

4-(4-Chlorophenyl)-3,4-dihydro-5-methoxycarbonyl-6-methylpyrimidin-2(1*H*)-one

3-(3-Chlorophenyl)-5,6-dimethyl-4*H*- pyrrolo[2,3-*d*]pyrimidine-4-imine

4-(3-Chlorophenyl)-5,6-dimethyl-7*H*- pyrrolo[2,3-*d*]pyrimidine

N-(3-Chlorophenyl)-2-(2-hydroxyethyl- amino)acetamide

4-(4-Chlorophenyl)-5-methoxycarbonyl- 6-methylpyrimidin-2(1*H*)-one

4-(4-Chlorophenyl)-1-(4-methoxyphenyl)- 3-phenoxy-azetidin-2-one, *cis*-

4-{5-[4-(3-Chlorophenyl)-3-oxopiperazin- 1-ylmethyl]imidazol-1-ylmethyl} benzonitrile

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Chrysanthemic acid, (±)-*trans*-

Cicloxilic acid

N-Cyanoacetyl-*N*,*N*′-dimethylurea

4-Cyanobenzylamine

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Cyclohexyl 2-benzoylaminoacetate

Cyclohexyl 2-benzoylamino-2-bromoacetate

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Cyclopentyl-2,3,4,6-tetraacetyl-β-D- glucopyranoside I

Cyclopentyl-2,3,4,6-tetraacetyl-β-D- glucopyranoside II

Cyclopentyl-2,3,4,6-tetraacetyl-β-D- glucopyranoside III

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Dess-Martin-Periodinane (DMP)

Diaminocyclohexane, (*R*,*R*) mono-(+)-tartrate salt

Dibenzopyridino[18]crown-6

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(2,3-Dibenzoyl-6-*O*-(dimethoxytrityl)-β-D- glucopyranosyl)-uracil 4-*O*- ((2-cyanoethyl)-*N*,*N*-diisopropylamino-phosphoramidite)

(2′,3′-Dibenzoyl-6′-*O*-(dimethoxytrityl)-β-D- glucopyranosyl)-uracil 4′-*O*-(succinylacid-CPG-amid)-ester

(2,3-Dibenzoyl-6-*O*-(dimethoxytrityl)-β-D- glucopyranosyl)-uracil 4-*O*-

(succinylacid)-ester

(2,3-Dibenzoyl-6-*O*-(dimethoxytrityl)-β-D- glucopyranosyl)-uracil 4-*O*-(succinylacid-4-nitrophenyl-ester)- ester

1,2-Di-(4,4′dipyridyliumtetrafluoro-borate)-ethane

(2,3-Dibenzoyl-β-D-glucopyranosyl)-uracil

Dibenzyl *N*-benzyloxycarbonyl-L-aspartate

Dibenzyl (2*S*,3*S*)-2-O-(2,6-diisopropoxy- benzoyl) tartate

Dibenzyl tartrate; (*S*,*S*)

2,5-Dibromo-1,4-benzoquinone

1,6-Dibromopentacyclo-[6.4.0$^{3.6}$.0$^{4.12}$.0$^{5..9}$] dodeca-2,7-dione

2,5-Dibromotricyclo[6.2.2.0$^{2.7}$] dodeca-4,9-dien-3,6-dione

4,4′-Di-(*tert*-butyl)-1,1′-biphenyl (DBBP)

Dichloro(η^{6}-benzene)ruthenium(II)-dimer

1,5-Dichloro-3-oxapentane

2-[(2,6-Dichlorophenyl)hydroxymethyl]- acrylic acid ethyl ester

Diethyl cyclopent-3-ene-1,1-dicarboxylate

Diethyl 2,4-diacetyl-3-phenylpentanedioate

N,*N*-Diethyl-2,4-dimethoxybenzamide

Diethyl 2,6-dimethyl-1,4-dihydropyridine-3, 5-dicarboxylate

N, *N*-Diethyl-2-methylsulfanyl-4,6-dimethoxybenzamide

N,*N*-Diethylnerylamine

11,11-Difluoro-1,6-methano[10]annulene

11,11-Difluorotricyclo[4.4.1.0$^{1.6}$] undeca-2,8-diene

2,3-Dihydro-4,6-dimethoxy-benzo[*b*] thiophen-3-one

7,7a-Dihydro-7a-methyl-1,5(6*H*)- indanedione, (+)-(7a*S*)

10,11-Dihydroxy-5,6,6a,7,8,12b-hexahydrobenzo[*a*]phenanthridine hydrobromide, *trans*

1,3-Dihydroxy-5-pentylbenzene

1,3-Dihydroxy-5-pentylbenzene

2,6-Diisopropoxybenzoic acid

2-*O*-(2,6-Diisopropoxybenzoyl)tartaric acid, (2*S*,3*S*)

Dimedone

4,6-Dimethoxybenzo[*b*]thiophene

2,3-Dimethoxyberbine, *rac*-

2,3-Dimethoxyberbine hydrochloride, *rac*-

3,3-Dimethoxy-5,7-bis(methoxycarbonyl)- 7-methylbicyclo[2.2.2]oct-5-en-2-one, (1*R**, 4*S**, 7*S**)-

1,1-Dimethoxybutane

6,7-Dimethoxy-3,4-dihydro-1*H*-naphthalen-2-one

10,11-Dimethoxy-5,6,6a,7,8,12b-hexahydrobenzo[*a*]phenanthridine hydrochloride, *trans*

3-(4,5-Dimethoxy-2-methoxycarbonyl- methylphenyl)acrylic acid methyl ester, (*E*)

3-(4,5-Dimethoxy-2-methoxycarbonyl- methylphenyl)propionic acid methyl ester

2,6-Dimethoxy-4-methylbenzaldehyde

1,3-Dimethoxy-5-methylbenzene

6,7-Dimethoxy-1-methyl-3,4-dihydro- isoquinoline

1,3-Dimethoxy-5-methyl-2-(3-methyl- but-3-enyl)-benzene

4-(2,6-Dimethoxy-4-methylphenyl)- butan-2-one

4-(2,6-Dimethoxy-4-methylphenyl)but-3- en-2-one

2,3-Dimethoxy-6-methyl-5,6,7,8-tetra- hydrodibenzo[*c*,*e*]azocine

6,7-Dimethoxy-1-methyl-1,2,3,4-tetra- hydroisoquinoline, (*R*)

3,4-Dimethoxyphenylboronic acid

N-[2-(3,4-Dimethoxyphenyl)-ethyl]-2- (hydroxymethyl)-phenylacetamide

6,7-Dimethoxy-β-tetralone

3,3-Dimethylacryloyl chloride

6-Dimethylamino-1,2-dimethyl- quinolinium iodide

6-Dimethylamino-2-methylquinoline

Dimethyl 1,8-bishomocubane- 4,6-dicarboxylate

5,5-Dimethylcyclohexane-1,3-dione

3,3-Dimethylcyclohexenone

Dimethyl *N*-[2-(ethoxycarbonyl)-4-oxo-8-propyl-4*H*-1-benzopyran-7-yl]-2-amino-2-butene-1,4-dioate, (*Z*)

Dimethyl heptalene-1,2-dicarboxylate

2,3-Dimethyl-hex-5-en-3-ol, (*S*)

3,7-Dimethylocta-2(*Z*)-6-dien-1-ol

2-(3,7-Dimethyloct-6-enylidene)-malonic acid dimethyl ester, (3*R*)

3,7-Dimethyl-1-octyn-6-en-3-ol

2,5-Dimethyl-1-phenylpyrrole

2,5-Dimethyl-1-phenylpyrrole-3-carbaldehyde

4,5-Dimethyl-4-(1′-phenyl-2′-trifluoro-acetamido-1′-ethoxy)-1-hexene, (4*S*,1′S)

3,4-Dimethylpyrrole

3,4-Dimethylpyrrole-2-carboxylic acid

3,4-Dimethylpyrrole-2-carboxylic acid ethyl ester

6,10-Dimethylundeca-3,5,9-trien-2-one

1,3-Dimethylxanthine

1,8-Dioxacyclotetradec-11-yne-2,7-dione

Di(pent-3-yn-1-yl) adipate

1,2-Diphenyl-1,2-ethanediol, (*R*,*R*)-(+)-

(*R*)-1,2-Diphenylethanol

(*R*)-(1,2-Diphenylethoxy)trimethylsilane

(*R*)-1,2-Diphenylethyl 3,5-dinitrobenzoate

2,4-Diphenylfuran

2-(Diphenylhydroxymethyl)pyrrolidine, (*S*)

Di-*tert*-butyl 3-ethoxycarbonyl-indolizine-1,2-dicarboxylate

3,5-Di-*tert*-butyl-2-hydroxybenzaldehyde

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EGF-R-Pyrrolo[2,3-*d*]pyrimidine

Epirizole

2,3-Epoxypropyl-1-(1′-naphthyl) ether

3-Ethoxycarbonylindolizine-1,2-dicarboxylic acid

3-Ethoxycarbonylindolizine-1,2-dicarboxylic anhydride

N-(Ethoxycarbonylmethyl)pyridinium bromide

6-Ethoxycarbonylnaphtho[2,3-*a*]indolizine-7,12-quinone

Ethyl 5-(3-amino-4-methylphenyl) hexanoate

Ethyl 7-amino-4-oxo-8-propyl-4*H*-1-benzopyran-2-carboxylate

Ethyl 3-(benzo[*d*][1,3]dioxol-5-yl)acrylate, (*E*)

Ethyl 3-(benzo[*d*][1,3]dioxol-5-yl)- 2-bromo-3-(prop-2-ynyloxy)propanoate

Ethyl 2-(benzo[*d*][1,3]dioxol-5-yl)-4-methylenetetrahydrofuran-3-carboxylate

Ethyl 8-chloro-4-methylnaphthalene- 2-carboxylate

Ethyl diazoacetate

Ethyl 3,3-dimethyl-4-pentenoate

Ethyl 2-hydroxycyclopentane-1-carboxylate, (+)-(1*R*,2*S*)

Ethyl 2-hydroxy-1-methylcyclopentane- 1-carboxylate, (+)-(1*R*,2*S*)

Ethyl (1*S*,2*R*,6*R*)-2-hydroxy-4-oxo-2,6-diphenylcyclohexane-1-carboxylate

Ethyl 2-hydroxy-4-phenylbutanoate, (*R*)

Ethyl 2-hydroxy-4-phenylbutanoate, (*S*)

Ethyl (*S*)-2-hydroxy-4-phenylbutanoate

Ethyl isocyanoacetate

Ethyl (*S*)-2-methanesulfonyloxy-4-phenylbutanoate

2-Ethyl 8-methyl 6,9-dihydro-4,6-dioxo- 10-propyl-4*H*-pyrano[3,2-*g*]quinoline-2,8-dicarboxylate

Ethyl 5-(4-methyl-3-nitrophenyl)- 4-hexenoate

Ethyl 1-methyl-2-oxocyclopentane-1-carboxylate, (–)-(1*R*)

Ethyl 2-oxo cyclopentane-1-carboxylate

Ethyl 2-phenylcyclopropane-1-carboxylate

Ethyl 2-(3-phthalimidopropyl)- acetoacetate

Ethyl 4,6,6,6-tetrachloro-3,3-dimethyl- hexanoate

1-Ethynyl-2-phenoxybenzene

f

2-Formamidino-5-methyl-2,4-dihydro- 3*H*-pyrazol-3-one

(2-Formamidophenyl)-(2-thiazolyl) ketone

(2-Formylamino)-3-methyl-1-butanol, (*2S*)

(2-Formylamino)-3-methyl-1-tetrahydropyranyloxybutane, (*2S*)

N-Formylglycine ethyl ester

1-(2-Formylmethyl)-2-benzyloxy- carbonyl-12-*tert*-butyloxycarbonyl-1,2,3,4-tetrahydro-β-carboline

h

Homoproline, (*S*)

1-Hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide (IBX)

2-{[2′-(4″-Hydroxy-1″-buten-2″-yl)-5′- methyl]-cyclohex-1′-yl}-acetic acid methyl ester, (1′*R*,2′*R*,5′*R*)

2-Hydroxy-3,9-dimethyl-6,7,8,9-tetra-hydro-5*H*-benzo[*a*]cyclohepten-5-one

1-Hydroxy-1,3-diphenyl-3-propanone, (*S*)

5-(2-Hydroxyisopropyl)-8-methyl-2-methylene-bicyclo[4.4.0]-decane,

(1*R*,5*R*,6*R*,8*R*)

4-(5-Hydroxymethylimidazol-1-yl- methyl)-benzonitrile

4-(5-Hydroxymethyl-2-mercapto- imidazol-1-ylmethyl)benzonitrile

2-Hydroxymethyl-1-phenylcyclohexan- 1-ol, *cis*-

N-(2-Hydroxy-1-methyl-2-phenylethyl)- *N*-methyl-3-phenylacrylamide, (*E*)-[(1*S*,2*R*)]

5-(3-Hydroxy-4-methylphenyl)hexanoic acid

2-Hydroxy-2-phenylcyclohexane carboxylic acid, *cis*

2-Hydroxy-4-oxo-4-phenylbutanoic acid, (*S*)

2-Hydroxy-4-phenylbutanoic acid, (*S*)

2-Hydroxy-3,5,5,9-tetramethyl-6,7,8,9-tetrahydro-5*H*-benzo[*a*]cycloheptene

i

IBX

Indigo

2-Iodobenzoic acid

2-{[2′-(4″-Iodo-1″-buten-2″-yl)-5″- methyl]-cyclohex-1′-yl}-acetic acid methyl ester, (1′*R*,2′*R*,5′*R*)

2-(Iodo-4,5-dimethoxyphenyl)acetic acid

(2-Iodo-4,5-dimethoxyphenyl)acetic acid methyl ester

1-Iodo-2-phenoxybenzene

Ionone, β-

Ionylidenethanol, β-

(Ionylidenethyl)triphenylphosphonium bromide, β-

3-Isochromanone

2-Isocyano-3-methyl-1-tetrahydro- pyranyloxybutane, (*2S*)

Isoprene chlorohydrin

[(2′-Isopropenyl-5′-methyl)-cyclohex-1′-yl]- acetic acid methyl ester,

(1′*R*,2′*R*,5′*R*)

2-[(2′-Isopropenyl-5′-methyl)-cyclohex-1′- yl]-malonic acid dimethyl ester, (1′*R*,2′*R*,5′*R*)

1-Isopropylamino-3-(1′-naphthyloxy)-2-propanol

2-Isopropylhex-4-yn-1-ol, (*S*)

4-Isopropyl-3-(2-isopropyl-hex-4-ynoyl)- oxazolidin-2-one, (*S*,*S*)

4-Isopropyl-3-isovaleroyl-oxazolidin-2-one, (*S*)

Isopropyloxazolidin-2-one, (4*S*)

Isopulegol

j

Jörgensen's catalyst

m

Mandelic acid amide, (*S*)

Manual solid-phase β-peptide synthesis

Manual solid-phase synthesis of glucopyranosyl-DNA

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Menthol, (–)-

3-Mesyloxy-2-cyclohexenone

6,14-Methano-2,4,6-trimethyl-6,7,8,14-tetrahydro-4*H*-5,9-dioxa-2,4-diazadibenzo-[*a*,*d*]cyclodecene-1,3-dione, (6*R*,14*S*)-(±)-

Methionine, L

1-Methoxy-1-butene, (*E*/*Z*)

15-(Methoxycarbonyl-methyl)-20-ethyl-1- (*tert*-butyloxycarbonyl)-3,4,5,6,14, 15,20,21-octahydro-indolo-[2,3-a]-quinolizine, (3*RS*,15*RS*,20*RS*)

2-Methoxy-3,9-dimethyl-6,7,8,9-tetra-hydro-5*H*-benzo[*a*]cyclohepten-5-one

(*S*)-5-Methoxy-2,7-dimethyl-2-vinylchroman

N-[2-(5-Methoxy-1*H*-indol-3-yl)ethyl]- acetamide

4-Methoxy-2-(5-methoxy-3-methyl-1*H*- pyrazol-1-yl)-6-methylpyrimidine

3-Methoxy-5-methyl-2-(3-methylbut-3-enyl)-phenol

(*E*)-3-Methoxy-5-methyl-2-(3-methylpent- 3-en-1-yl)phenol and (Z)-3-Methoxy-5-methyl-2-(3-methylpent-3-en-1-yl)phenol

2-(6-Methoxy-2-naphthyl)propionic acid, (*R*,*S*)

(*S*)-2-(6-Methoxy-2-naphthyl)propionic acid, (*S*)-; by enzymatic resolution;

2-(6-Methoxy-2-naphthyl)propionic acid, (*S*)-; by resolution with cinchonidine

N-(3-Methoxyphenyl)acetamide

1-(4-Methoxyphenyl)-4,5,6,7-tetrahydro- 6,6-dimethylindazol-4-one

5-Methoxy-3-(2-phthalimidoethyl)- indole-2-carboxylic acid ethyl ester

6-Methoxy-2-propionylnaphthalene

2-Methoxy-3,5,5,9-tetramethyl-6,7,8,9-tetrahydro-5*H*-benzo[*a*]cycloheptene

5-Methoxytryptamine

2-[(3-Methyl-2-acetoxybutyryl)-amino]- 3-methyl-1-tetrahydro-pyranyloxybutane, (2*S*)

2-(2-Methylallyloxy)-phenol

Methyl (2*S*)-2-amino-3-phenylpropionate hydrochloride

3-(4-Methylbenzoylamino)-1-phenyl-4,5-dihydropyrazole

3-Methyl-3-butenyl-methanesulfonate

2-(3-Methyl-3-butenyloxy)-benzaldehyde

5-[2-(3-Methyl-3-butenyloxy)- benzylidene]-1,3-dimethyl-pyrimidine-2,4,6-trione

(3-Methyl-2-butenyl)-(*p*-tolyl) sulfone

Methyl (±)-*trans*-chrysanthemate

4-Methylcyclohex-3-ene-1-carboxylic acid methyl ester

2-Methylcyclopentane-1,3-dione

2-Methylcyclopentane-1,3-dione

2-(5-Methyl-2,4-dihydro-3*H*-pyrazol-3- on-2-yl)-6-methylpyrimidin-4(3*H*)-one

Methyl 2,6-diisopropoxybenzoate

(*R*,*R*)-Methyl 4-(1,2-diphenylethoxy)-4-methylhept- 6-enonate

(6-Methyl-3,5-dioxo-8-phenyl-7-oxa-2,4-diazabicyclo[4.2.0]oct-2-yl)-acetic acid

Methylenecyclododecane

3-(3,4-Methylenedioxyphenyl)acrolein

4-(3,4-Methylenedioxyphenyl)-1,3-butadiene-1-carboxylic acid

4-(3,4-Methylenedioxyphenyl)-1,3-butadiene carboxypiperidide

4-Methylheptan-3-one, (*S*)

6-Methylhept-5-en-2-one

Methyl 2-hydroxy-4-oxo-6-pentylcyclohex- 2-ene-1-carboxylate

Methyl ionylidene acetate, β-

Methyl (S)-2-(5-methoxy-2,7-dimethylchroman-2-yl) acetate

Methyl 2-(6-methoxy-2-naphthyl)- propionate, (*R*,*S*)-

Methyl 3-methyl-2-butenoate

Methyl (*R*)-4-methylcyclohex-3-enecarboxylate

(*rac*)-(*E*)-Methyl 4-(2-methyl-2,3-dihydro- benzo[b][1,4] dioxin-2-yl)but-2-enoate

Methyl 4-(3,4-methylenedioxyphenyl)-1,3-butadiene-1-carboxylate

8-Methyl-2-methylene-bicyclo[4.4.0]- decane-5-carboxylic acid methyl ester, (1*R*,5*R*,6*R*,8*R*)

2-Methyl-2-(3-oxobutyl)-cyclopentane-1,3-dione

Methyl (*S*)-5-oxo-3,5-diphenylpentanoate

Methyl 3-oxo-5-phenylpentanoate

1*N*-Methyl-3-phenylpropane-1,2-diamine, (2*S*)

3-Methyl-2-(trifluoroacetyl-amino)-4-pentenoic acid, (*2R, 3S*)

1-Morpholino-1-cyclohexene

n

Naproxen, (*S*)

Naproxen, *rac*-

Nerol

Neryl acetate

Neryl chloride

2-Nitrobutan-3-ol

1-(4-Nitrophenyl)-2-nitroethanol, Na salt

(2-Nitrophenyl)-(2-thiazolyl) ketone

(2-Nitrophenyl)-(2-thiazolyl)methanol

3-Nonen-2-one

o

2,3,7,8,12,13,17,18-Octamethylporphyrin

Octanal, n-

Olivetol

(3-Oxocyclohexyl)phenyl(trimethylsilyloxy)acetonitrile

5-Oxo-3,5-diphenylpentanoic acid, (*S*)

p

1,2,3,4,6-Penta-*O*-acetyl-α/β-D- glucopyranose

Phenylalanine methyl ester hydrochlorideL-

1-Phenylbutanol, (*S*)-(-)-

1-Phenylcyclohex-1-ene

2-Phenylcyclopropane-1-carboxylic acid, *trans*

2-Phenylcyclopropyl-1-amine, (±)-*trans*

1-Phenylethanol, (*R*)-(+)-

[1-(1-Phenylethyl)-2,5-dihydro-1*H*- pyrrol-2-yl]-acetic acid *tert*-butyl ester

[1-(1-Phenylethyl)-pyrrolidin-2-yl]-acetic acid *tert*-butyl ester

2-(Phenylethynyl)aniline

3-Phenylglutaric acid

3-Phenylglutaric anhydride

3-Phenylheptanoic acid, (*S*)

3-Phenyl-heptanoic acid ((1*S*,*2R*)-2-hydroxy-1-methyl-2-phenylethyl)methyl amide, (*S*)

2-Phenylindole

7-Phenyl-1,6-naphthyridine

Phenyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D- glucopyranoside

Phenyl(trimethylsilyloxy)acetonitrile

Piperine

Piperonal diethyl acetal

Propranolol, *rac*

Propranolol, (*S*)

2-(2-Propynyloxy)tetrahydropyran

Pseudoionone

Pyrrolidin-2-yl-acetic acid *tert*-butyl ester

Pyrvinium iodide

r

Rotaxane

Ruthenium catalyst, (*S*, *S*)

Ruthenium Phenylindenylidene Complex

s

Salsolidine, (*R*)

SAMP-hydrazone of 4-methylheptan-3-one, (*S*)

SAMP-hydrazone of diethylketone

Senecyl chloride

Sodium *p*-toluenesulfinate

Solid-phase synthesis of glucopyranosyl-DNA

t

Terpineol, *rac*-α-

Terpineol, (*R*)-(+)-α-

2,3,4,6-Tetra-*O*-acetyl-α/β-D- glucopyranose

2,3,4,6-Tetra-*O*-acetyl-α-D- glucopyranosyl bromide

2,3,4,6-Tetra-*O*-acteyl-α-D- glucopyranosyl trichloroacetimidate

2-Tetrahydro-1-methyl-3,3-diphenyl- 1*H*,3*H*-pyrrolo[1,2-*c*][1,3,2] oxaza-borolidine, (*S*)

1,4,5,8-Tetrahydronaphthalene

Theophylline

Thymine-1-acetic acid

(*O*-Toluenesulfonyl)glycidol, (*S*)

2-{[2′-(4″-*p*-Toluene-sulfonyloxy-1″- buten-2″-yl)-5′-methyl]-cyclohex-1′-yl}-acetic acid methyl ester, (1′*R*,2′*R*,5′*R*)

N-Tosyl-1,2-diphenylethylenediamine, (1*S*,2*S*)

Tranylcypromine

1,1,1-Triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one (DMP)

1,1,3-Triethyl-3-(3,4-methylenedioxy- phenyl)propane

(*N*-Trifluoroacetyl)glycine crotyl ester

2,2,2-Trifluoro-*N*-(2-phenyl-2-trimethyl- silanyloxyethyl)acetamide, (*S*)

4-(2,6,6-Trimethylcyclohex-1-en-1-yl)- but-3-en-2-one

3,3,6-Trimethylhepta-1,5-dien-4-one

Trimethyl[(2-phenoxyphenyl)ethynyl] silane

Trimethylphenylammonium perbromide

1-Trimethylsilyl-3-methyl-2-butene

1,3,7-Trimethylxanthine

2,2,3-Triphenyloxirane, (*R*)

2,2,3-Triphenyloxirane, (*rac*)

2,4,6-Triphenylpyrylium tetrafluoroborate

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Veticadinol

Vitamin A acetate, all-*trans*-

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1-(9*H*-Xanthen-9-ylidene)-2,3-dihydro- 1*H*-inden-2-ol

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