Solutions Manual
for

MODERN ORGANIC SYNTHESIS:
An Introduction

Michael H. Nantz
University of Louisville

Hasan Palandoken
Western Kentucky University

George S. Zwiefel
University of California, Davis

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Preface

How does an organic chemist go about synthesizing a desired molecule? The goal of this Solutions Manual is not only to provide you with the "correct" answers to end-of-chapter problems, but also to give you the opportunity to develop a methodical approach to synthesizing a given target molecule using the tools and concepts covered in *Modern Organic Synthesis: An Introduction.*

We assume that the student is well acquainted with the basic concepts of organic chemistry taught at the sophomore level. The introductory chapters provide step-by-step solutions to illustrate how a problem is broken down to smaller problems and solved. Later chapters assume the student is well versed in the concepts covered in the previous chapters; however, the key steps involved in the solutions are highlighted. Throughout the manual, literature references are provided for problems that have been inspired by 'real' world examples.

To assimilate synthetic methodologies and to integrate them into a synthetic design requires actual problem solving and not merely looking at the text. Only by writing the answer do we pay attention to details such as proper choice of reagents, reaction conditions, mechanistic implications, and so forth. Thus, it is important that you refer to the Solutions Manual only after you have made a real effort to solve the problem, or simply to verify that your approach is the same as *or even better* than the one presented in the manual.

We are grateful to the Chemistry 131 students at UC Davis and especially to the teaching assistants of the course for their suggestions and contributions to the development of the problem sets.

Michael Nantz, Hasan Palandoken and George Zweifel
June 2006

ABBREVIATIONS

Ac	acetyl, acetate
acac	acetylacetonate
AIBN	2,2′-azobisisobutyronitrile
anhydr	anhydrous
APA	3-aminopropylamine
aq	aqueous
atm	atmosphere
9-BBN	9-borabicyclo[3.3.1]nonane
Bn	benzyl
Boc	*tert*-butoxycarbonyl
bp	boiling point
BPS	*tert*-butyldiphenylsilyl
n-Bu	*n*-butyl
s-Bu	*sec*-butyl
t-Bu	*tert*-butyl
Bz	benzoyl
cat.	catalytic
CBS	2,5-oxazoborolidine
Cbz	benzyloxycarbonyl
CDI	carbonyldiimidazole
Chx	cyclohexyl
Cp	cyclopentadienyl
CSA	10-camphorsulfonic acid
DABCO	1,4-diazabicyclo[2.2.2]octane
DBN	1,5-diazabicyclo[4.3.0] non-5-ene
DBU	1,8-diazabicyclo[5.4.0] undec-7-ene
DCC	1,3-dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
de	diastereomeric excess
DEAD	diethyl azodicarboxylate
DET	diethyl tartrate
DHP	3,4-dihydro-2*H*-pyran
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutylaluminum hydride
DIPT	diisopropyl tartrate
DMAP	4-dimethylaminopyridine
DMDO	dimethyldioxirane
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane
DMPU	*N*,*N*′-dimethylpropyleneurea
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
DS	diastereofacial selectivity
ee	enantiomeric excess
eq	equivalents
Et	ethyl
EWG	electron-withdrawing group
FG	functional group
h	hour
HMDS	hexamethyldisilazane
HMPA	hexamethylphosphoramide
HQ	hydroquinone
hv	light
IBX	*o*-iodoxybenzoic acid
imid	imidazole
Ipc	isopinocampheyl
KAPA	potassium 3-aminopropylamide
KHMDS	potassium hexamethyldisilazide
L-Selectride	lithium tri-*sec*-butylborohydride
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
LHMDS	lithium hexamethyldisilazide
*m*CPBA	*m*-chloroperoxybenzoic acid
Me	methyl
MEM	2-methoxyethoxymethyl
mol	mole
MOM	methoxymethyl
mp	melting point
Ms	mesyl (methanesulfonyl)
MS	molecular sieves
MVK	methyl vinyl ketone
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NMO	*N*-methylmorpholine *N*-oxide
NMP	*N*-methyl-pyrrolidinone
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
PG	protecting group
Ph	phenyl
Piv	pivaloyl
PMB	4-methoxybenzyl
PPTS	pyridinium *p*-toluenesulfonate
i-Pr	*iso*-propyl
n-Pr	*n*-propyl
psi	pounds per square inch
PT	1-phenyl-1*H*-tetrazol-5-yl
py	pyridine
Ra-Ni	Raney-nickel (usually W-II type)
RCM	ring-closing olefin metathesis
Red-Al	sodium bis (2-methoxyethoxy) aluminum hydride
rt	room temperature
SAE	Sharpless asymmetric expoxidation
SE	synthetic equivalent
SEM	2-(trimethylsilyl)ethoxy-methyl
Sia	disiamyl
TBAF	tetra-*n*-butylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
THP	tetrahydropyranyl
Thx	thexyl (Me_2CHMe_2C-)
TIPS	triisopropylsilyl
TMEDA	*N*,*N*,*N*′,*N*′-tetramethylethylenediamine
TMS	trimethylsilyl
TMSOTf	trimethylsilyl trifluoromethanesulfonate
TPAP	tetra-*n*-propylammonium perruthenate
Tr	trityl (triphenylmethyl)
Ts	tosyl (*p*-toluenesulfonyl)
Δ	heat

CHAPTER 1

Synthetic Design

Overview

Chapter 1 focuses on how to design and execute the synthesis of a variety of target molecules (TM) using the tools and strategies you encountered in *Modern Organic Synthesis: An Introduction.*

Problem 1 (Functional Group Interconversions) introduces how to recognize precursors of key functional groups present in a target molecule. Problem 2 (*Umpolung*) highlights the use of carbonyl group polarity reversal, an important synthetic tool. Problem 3 (Retrosynthetic Analysis) stresses approaches to disassembling a target molecule into simpler fragments and ultimately into starting materials. Problem 4 (Synthesis) provides the opportunity to put into practice these concepts by designing protocols for the syntheses of various target molecules.

Key Concepts

- Retrosynthetic analysis
- Synthetic equivalent (SE)
- Functional group interconversion (FGI)
- Carbonyl group polarity reversal (*Umpolung*)

SOLUTIONS TO CHAPTER 1 PROBLEMS

The more challenging problems are identified by an asterisk (*).

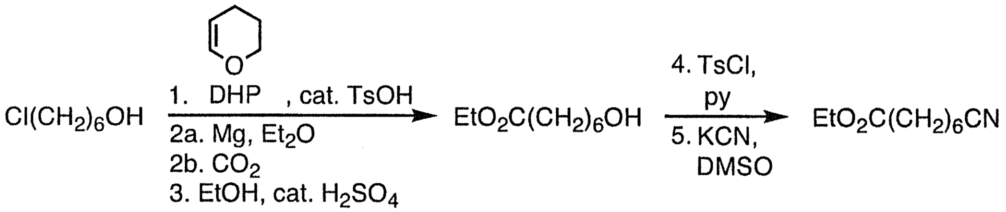
1. **Functional Group Interconversion.** Show how each of the following compounds can be prepared from the given starting material.

a.

$$Cl(CH_2)_6OH \longrightarrow EtO_2C(CH_2)_6CN$$

Solution:

FGIs in this problem:
1. Primary (1^o) alkyl chloride to ethyl ester
2. 1^o alcohol to nitrile



Step 1 The 1° alcohol is protected with dihydropyran (DHP).

Step 2a Reaction of an alkyl chloride with magnesium (Mg) provides the corresponding Grignard reagent (conversion of an electrophilic carbon to a nucleophilic carbon).

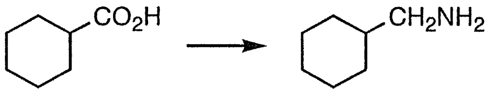
Step 2b Reaction of a Grignard reagent with carbon dioxide affords the carboxylic acid.

Step 3 Fischer esterification (reaction of a carboxylic acid with excess alcohol and a strong acid catalyst).

Step 4 The 1° alcohol is converted to a good leaving group (tosylate) for the ensuing displacement reaction (Step 5).

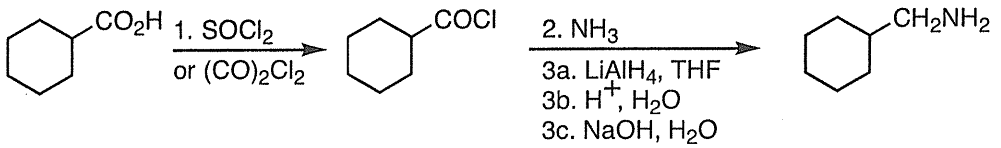
Step 5 S_N2 displacement of the tosylate group with cyanide anion provides the TM.

b.



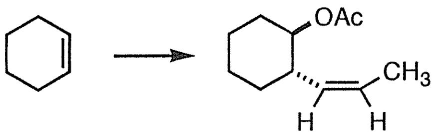
Solution:

FGI in this problem:
Carboxylic acid to 1^o amine



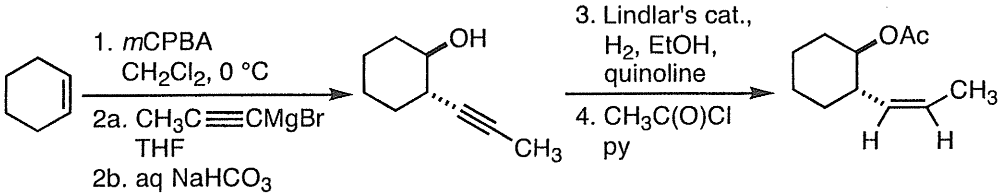
Step 1	Carboxylic acid is converted to an acyl chloride with thionyl chloride ($SOCl_2$) or oxalyl chloride [$(CO)_2Cl_2$].
Step 2	Reaction of the acyl chloride with ammonia (NH_3) affords the amide.
Step 3a	Reduction of the amide with lithium aluminum hydride ($LiAlH_4$) provides the TM.
Steps 3b+c	Workup protocol.

c.



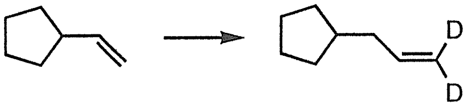
Solution:

FGIs in this problem:
1. Alkene to acetate
2. Alkene to a higher carbon homolog (*Z*)-alkene
(Note: Acetate and propenyl functionalities need to be *trans* to each other.)



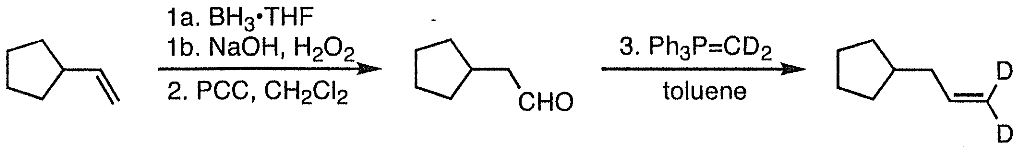
Step 1	Conversion of the alkene to the epoxide.
Step 2a	Epoxide opening proceeds via S_N2 displacement to give the *trans*-adduct.
Step 2b	Workup protocol.
Step 3	Semi-hydrogenation of the triple bond with Lindlar's catalyst gives the (*Z*)-alkene.
Step 4	Conversion of the alcohol to the acetate with acetyl chloride ($CH_3C(O)Cl$ or AcCl) provides the TM.

d.



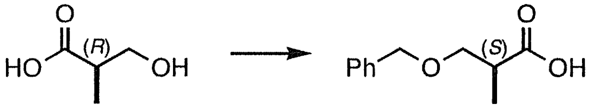
Solution:

FGI in this problem:
One-carbon homologation of a terminal double bond to a terminally deuterated carbon



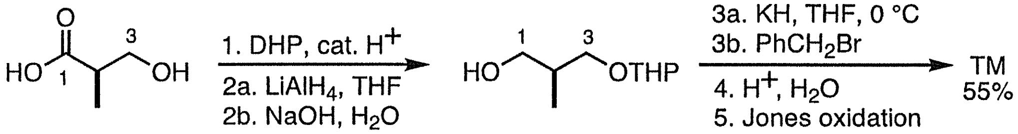
Step 1 Hydroboration-oxidation yields the 1° alcohol.
Step 2 Oxidation with pyridinium chlorochromate (PCC) affords the aldehyde.
Step 3 Wittig reaction provides the TM. (Note: The ylide reagent is prepared by treating Ph_3P with CD_3I to obtain $Ph_3P^+CD_3{\cdot}I^-$ and followed by deprotonation with *n*-BuLi.)

***e.**



Solution:

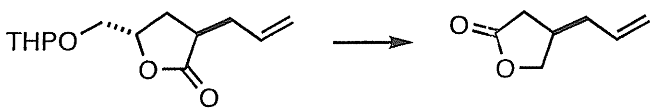
FGIs in this problem:
1. Carboxylic acid to benzyl ether
2. 1° alcohol to carboxylic acid



Step 1 1° alcohol at C(3) is protected as its tetrahydropyranyl (THP) ether.
Step 2a Reduction of the carboxylic acid with lithium aluminum hydride ($LiAlH_4$) affords the alcohol.
Step 2b Workup protocol.
Step 3 Williamson ether synthesis provides the C(1) benzyl ether.
Step 4 THP hydrolysis at C(3).
Step 5 Jones oxidation produces the TM in 55% overall yield.

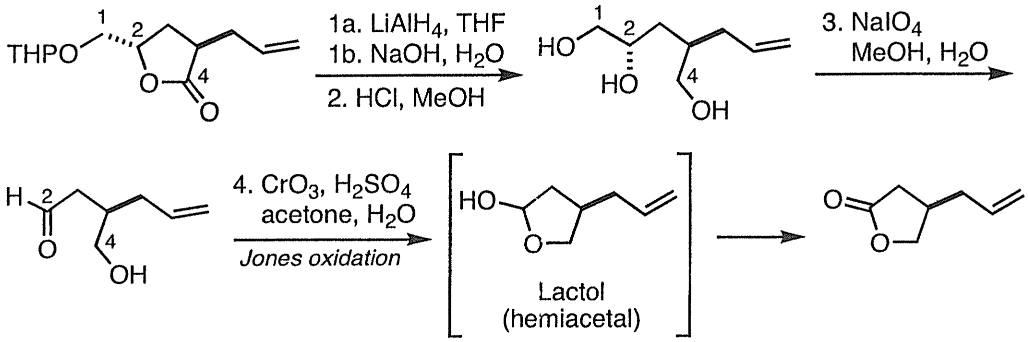
Reference: McGuirk, P. R.; Collum, D. B. *J. Org. Chem.* **1984,** *49*, 843.

***f.**



Solution:

FGIs in this problem:
1. Tetrahydropyran-2-yloxymethyl ($THPOCH_2$–) to carbonyl (C=O)
2. Carbonyl (C=O) to methylene (–CH_2–)

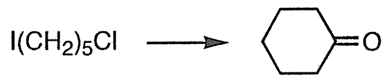


Step 1a Reduction of the lactone with lithium aluminum hydride $LiAlH_4$ provides the diol.
Step 1b Workup protocol.
Step 2 THP hydrolysis affords the triol with C(1), C(2) and C(4) bearing the hydroxyl groups.
Step 3 Oxidative cleavage of the 1,2-diol [C(1)-C(2)] with sodium periodate ($NaIO_4$) gives the aldehyde at C(2).
Step 4 Acidic media of Jones oxidation allows the *in-situ* formation of the lactol (a hemiacetal), which is then oxidized to the lactone (TM).

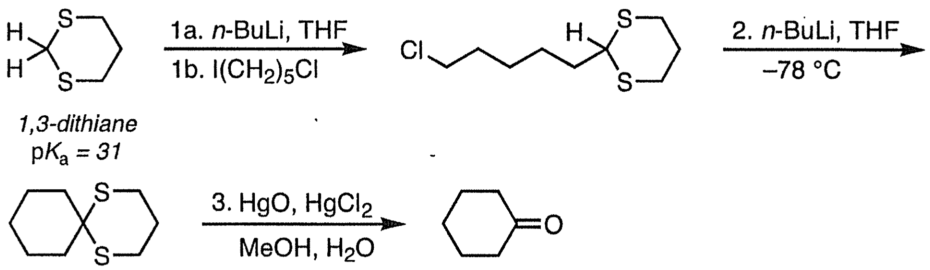
Reference: For a similar synthesis, see Takano, S.; Tamura, N.; Ogasawar, K. *J. Chem. Soc., Chem. Commun.* **1981**, 1155.

2. ***Umpolung.*** Show how each of the following compounds can be prepared from the given starting material using either a formyl or an acyl anion equivalent in the synthetic scheme.

a.

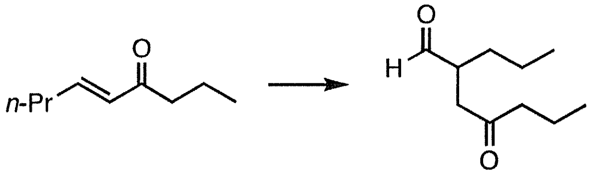


Solution:

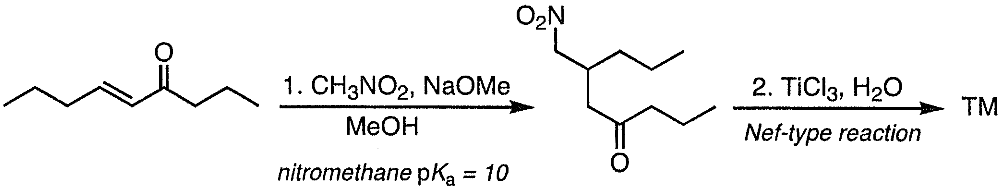


Step 1b Selective S_N2 displacement of the iodide (better leaving group than chloride).
Step 2 Intramolecular displacement of the chloride.

b.

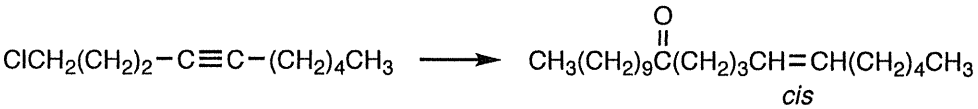


Solution:



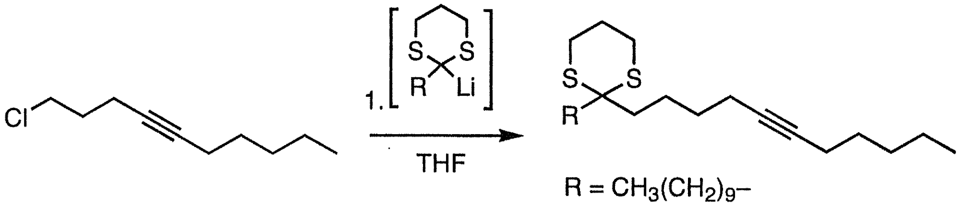
Note that the deprotonation of the strong acid nitromethane (pK_a = 10) is accomplished using the relatively weak base sodium methoxide (NaOMe).

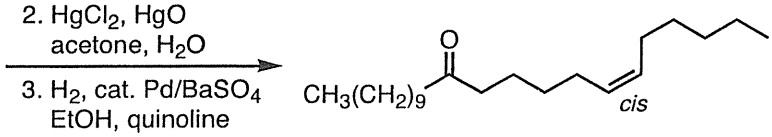
c.



$$ClCH_2(CH_2)_2{-}C{\equiv}C{-}(CH_2)_4CH_3 \longrightarrow \underset{cis}{CH_3(CH_2)_9\overset{O}{\overset{\|}{C}}(CH_2)_3CH{=}CH(CH_2)_4CH_3}$$

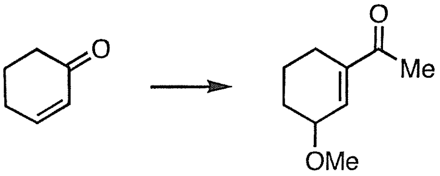
Solution:



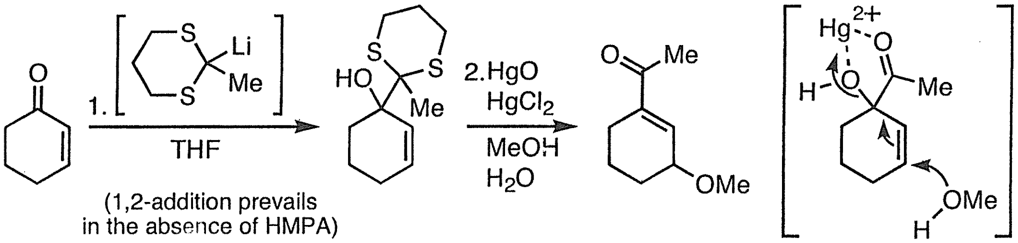


Reference: For an analogous synthesis, see Smith, R. G.; Daves, Jr., G. D.; Daterman, G. E. *J. Org. Chem.* **1975**, *40*, 1593.

***d.**



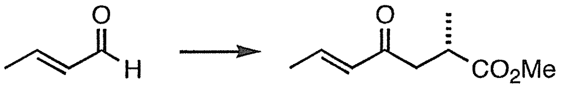
Solution:



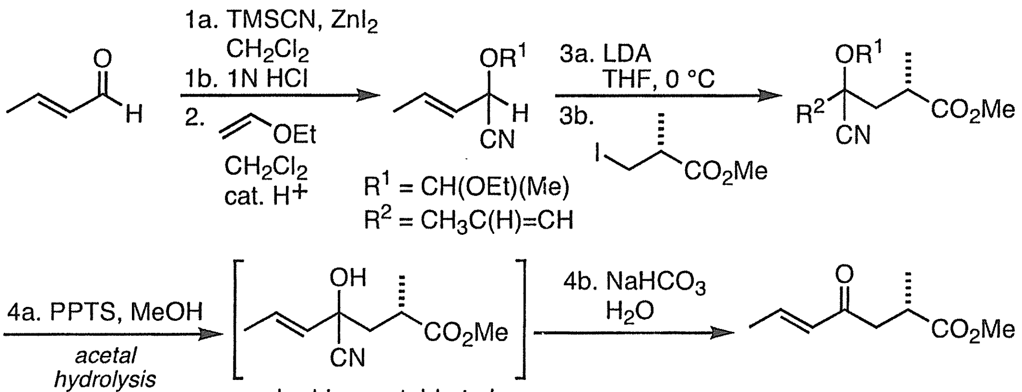
(1,2-addition prevails in the absence of HMPA)

methanolysis of the 3° allylic alcohol

***e.**



Solution:



$R^1 = CH(OEt)(Me)$
$R^2 = CH_3C(H){=}CH$

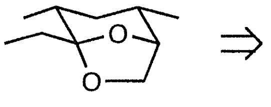
cyanohydrin, unstable to base

Step 3b The resonance-stabilized enolate anion reacts both chemo- and regioselectively: iodide displacement occurs in preference to 1,2-addition; alkylation occurs α to the nitrile moiety.

Reference: For an analogous synthesis, see Kang, S. H.; Lee, H. S. *Tetrahedron Lett.* **1995**, *36*, 6713.

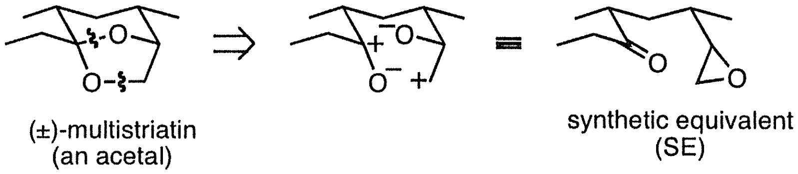
3. **Retrosynthetic Analysis** — *One-Step Disconnections.* For each of the following compounds, suggest a one-step disconnection. Use FGIs as needed. Show charge patterns, the synthons, and the corresponding synthetic equivalents.

a.

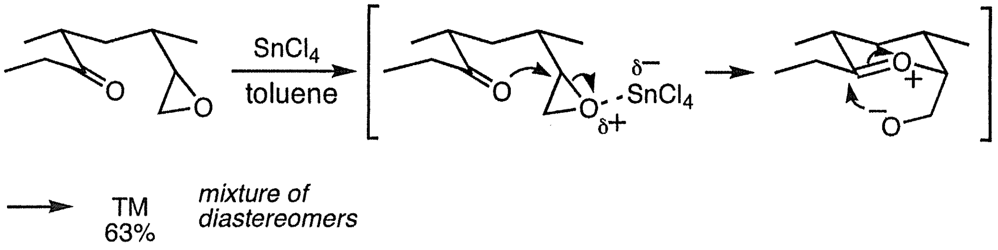


(±)-multistriatin

Retrosynthetic analysis:



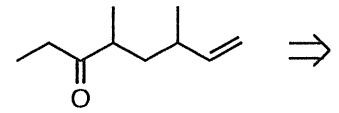
Synthesis:



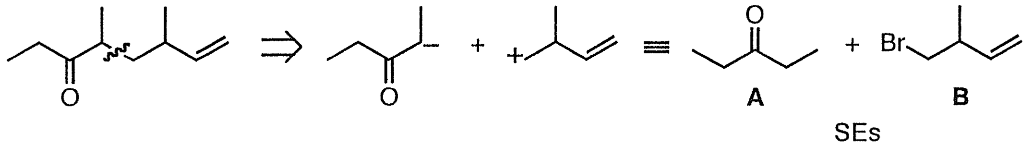
Lewis acid-catalyzed ($SnCl_4$) ring opening of the epoxide is *regioselective*, placing the nucleophile at the more substituted carbon.

Reference: Pearce, G. T.; Gore, W. E.; Silverstein, R. M. *J. Org. Chem.* **1976**, *41*, 2797.

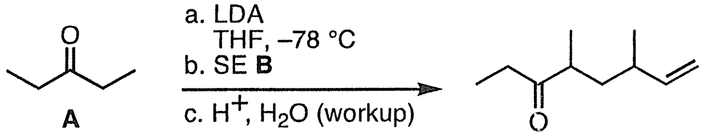
b.



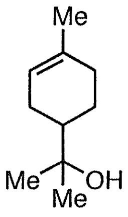
Retrosynthetic analysis:



Synthesis:

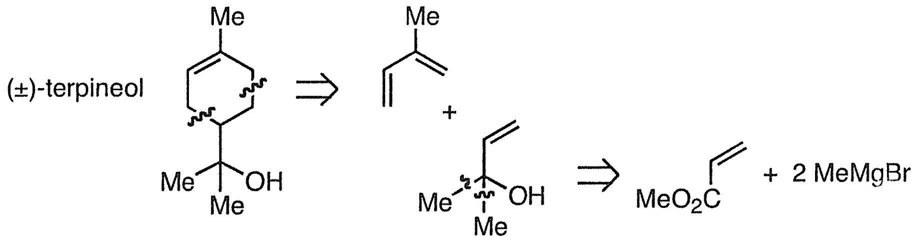


c.



(±)-terpineol

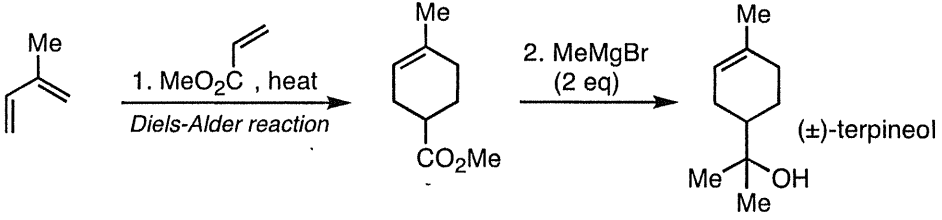
Retrosynthetic analysis:



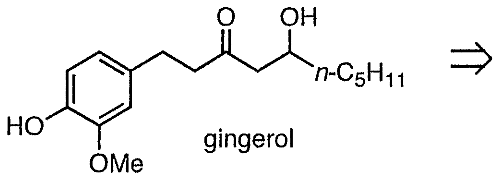
cyclohexene ⇒ Diels-Alder transform

The 3° allylic alcohol is not well suited as a dienophile (bulky, acid-sensitive). A better choice is methyl acrylate (electron-deficient alkene). Addition of MeMgBr to the ester *after* cycloaddition furnishes the 3° alcohol moiety.

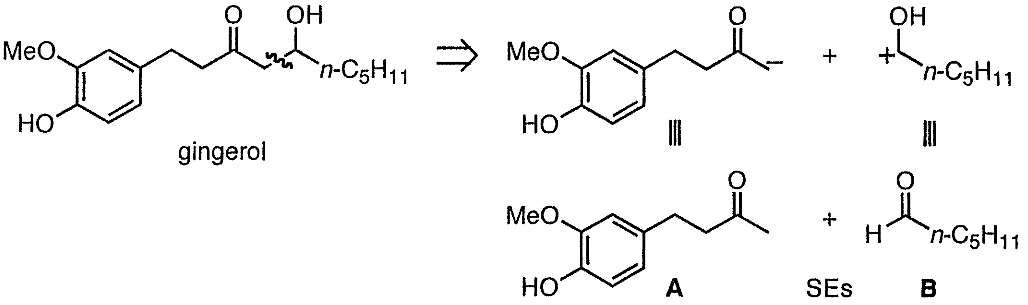
Synthesis:



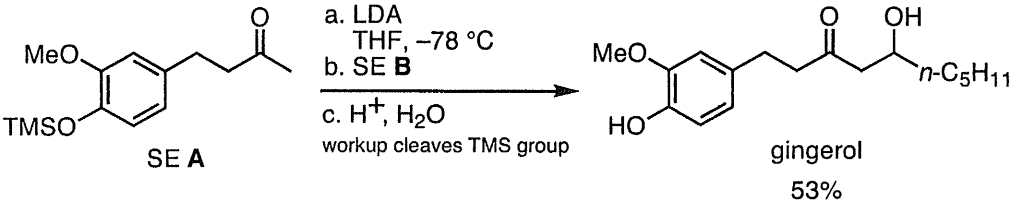
d.



Retrosynthetic analysis:

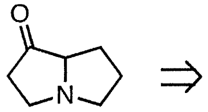


Synthesis:

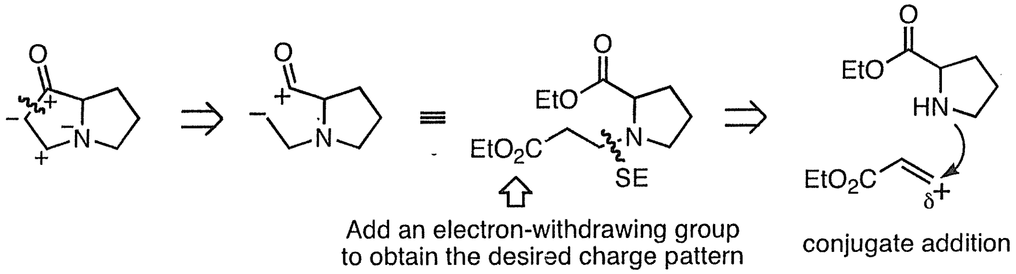


Reference: Denniff, P.; Macleod, I.; Whiting, D. A. *J. Chem. Soc., Perkin Trans. I* **1981**, 82.

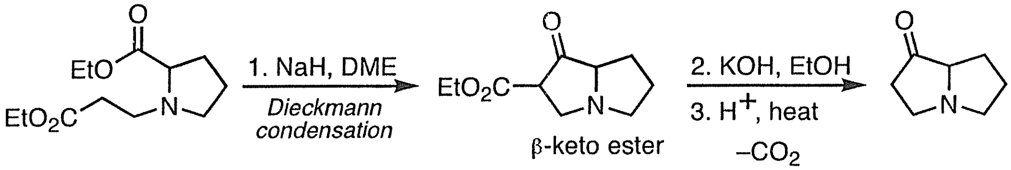
e.



Retrosynthetic analysis:

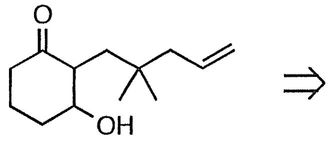


Synthesis:

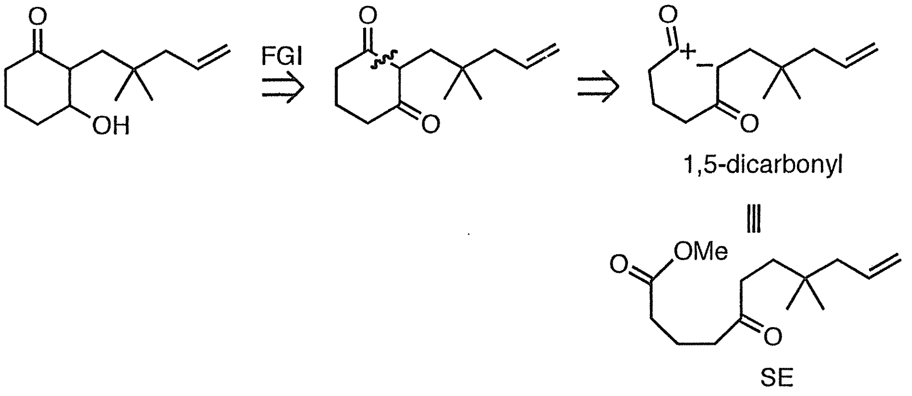


Step 1 Intramolecular condensation of two esters (Dieckmann condensation).
Step 2 Saponification of the ethyl ester provides the β-keto carboxylic acid.
Step 3 Decarboxylation of the carboxylic acid (Note: This requires a β-keto group.)

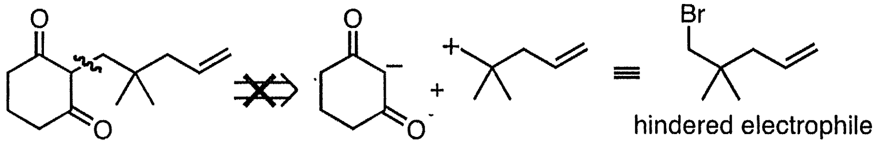
f.



Retrosynthetic analysis:

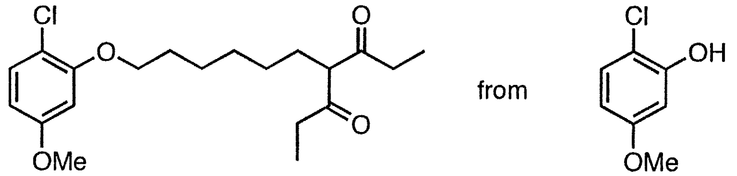


Generally, the alkylation of active methylene compounds proceeds in good yield. However, in this case, as illustrated below, the alkylation requires displacement of a sterically hindered halide. Thus, the alkyation approach (shown below) is not recommended.



4. **Synthesis.** Outline a retrosynthetic scheme for each of the following target molecules using the indicated starting material. Show (1) the *analysis* (including FGI, synthons, and synthetic equivalents) and (2) the *synthesis* of each TM.

a.



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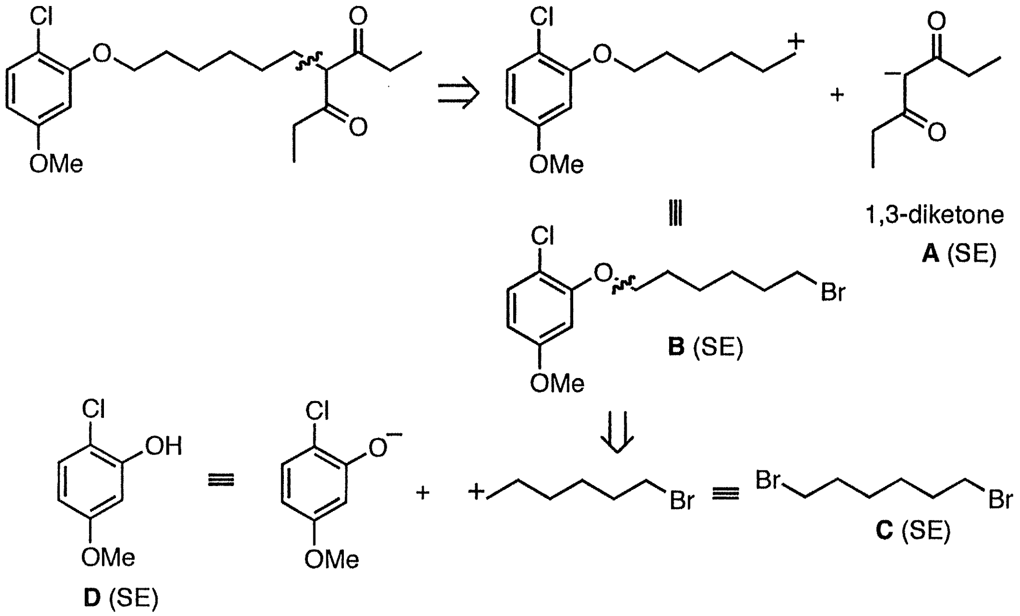
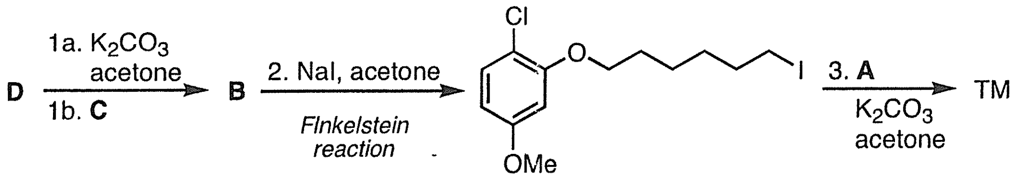


Synthesis:



Step 1 Phenol (pK_a = 10) deprotonation and alkylation gives **B**.
Step 2 Conversion of the alkyl bromide to the corresponding alkyl iodide (Finkelstein reaction).
Step 3 Alkylation of the 1,3-diketone enolate **A** provides the TM.

Reference: For a similar synthesis, see Diana, G. D.; Salvador, U. J.; Zalay, E. S.; Carabateas, P. M.; Williams, G. L.; Collins, J. C. *J. Med. Chem.* **1977**, *20*, 757.

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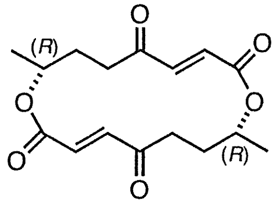
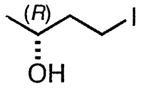
b.

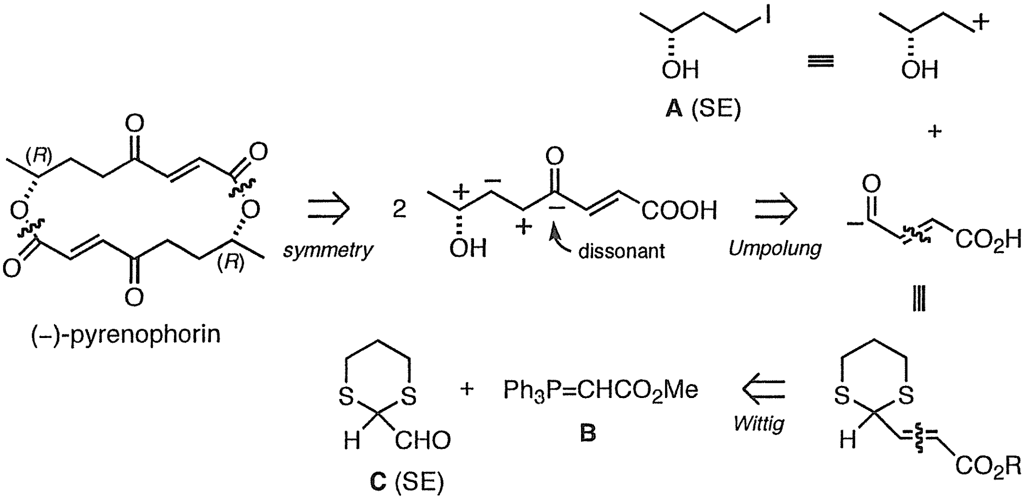


(–)-pyrenophorin
(antifungal compound)

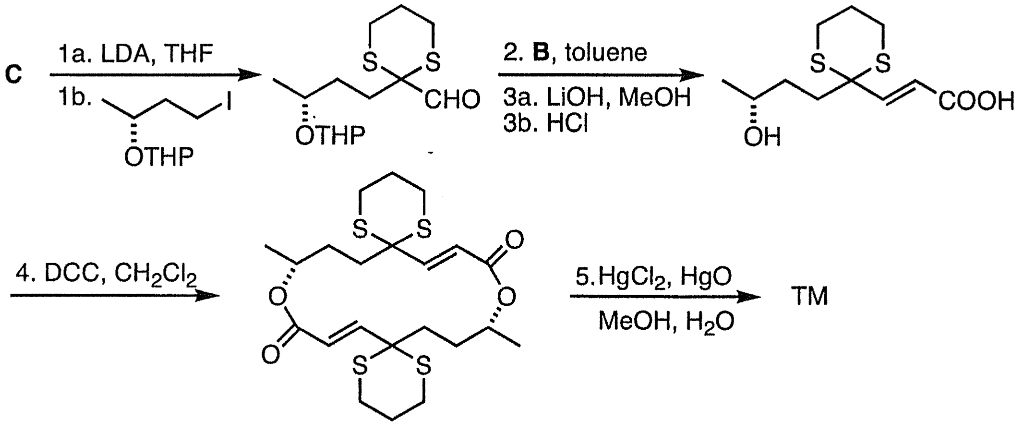
from



Retrosynthetic analysis:



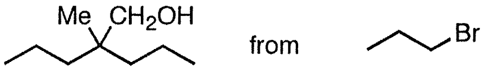
Synthesis:



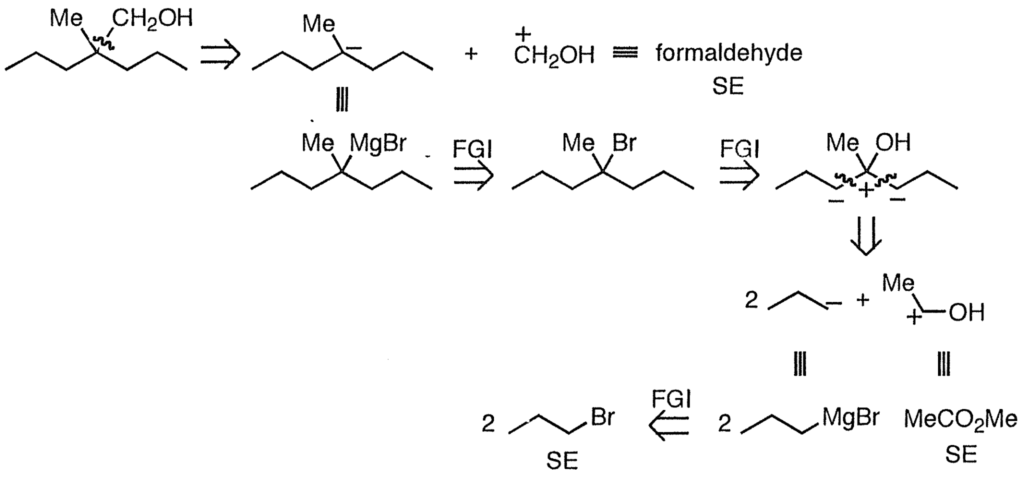
Step 1a	Deprotonation using the non-nucleophilic base LDA avoids 1,2-addition to the aldehyde **C**.
Step 1b	Note that the –OH group of the alkyl iodide substrate **A** must be protected prior to alkylation.
Step 2	Wittig reaction.
Step 3	Ester saponification and acidification, which also cleaves the acid-sensitive THP group.
Step 4	Head-to-tail esterifications of two hydroxy acid substrates give the bis-lactone.
Step 5	Removal of the dithiane provides the TM.

Reference: For an analogous synthesis, see Seebach, D.; Seuring, B.; Kalinowski, H.-O.; Lubosh, W.; Renger, B. *Angew. Chem. Int. Ed.* **1977**, *16*, 264.

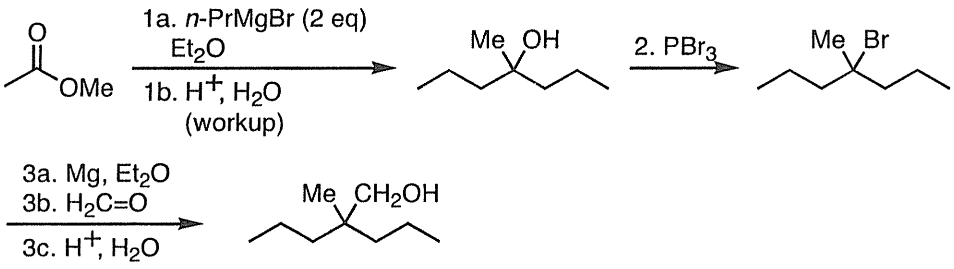
c.



Retrosynthetic analysis:



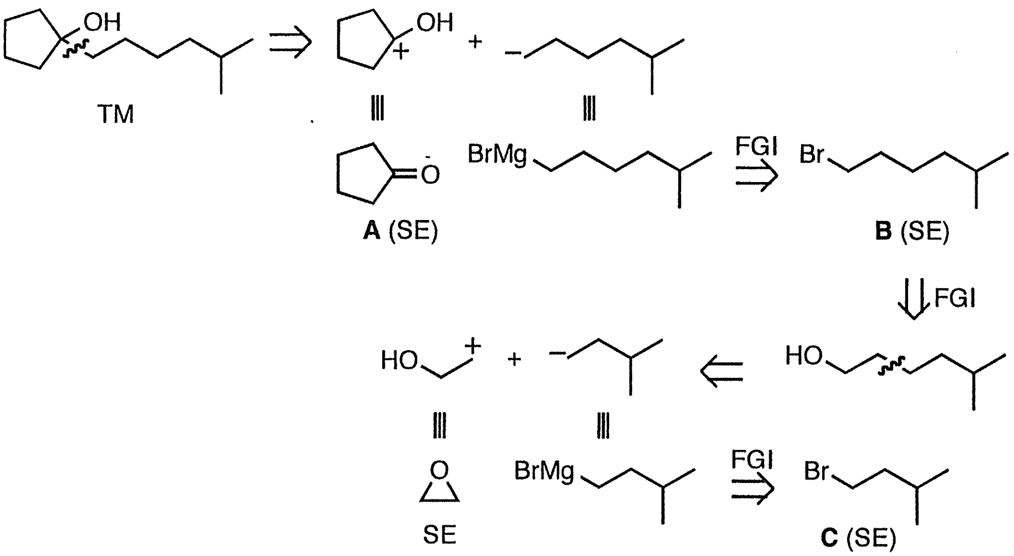
Synthesis:



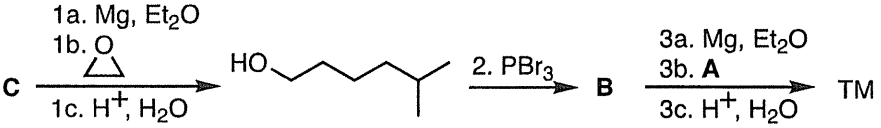
Step 3 The reaction of a *tertiary* Grignard reagent with a hindered ketone may result in reduction and/or enolization of the ketone. However, in the present example, the use of formaldehyde (an excellent electrophile) circumvents these side reactions.

d.

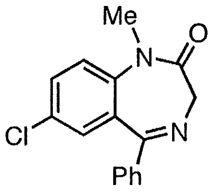
Retrosynthetic analysis:



Synthesis:

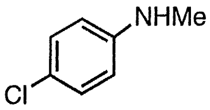


e.

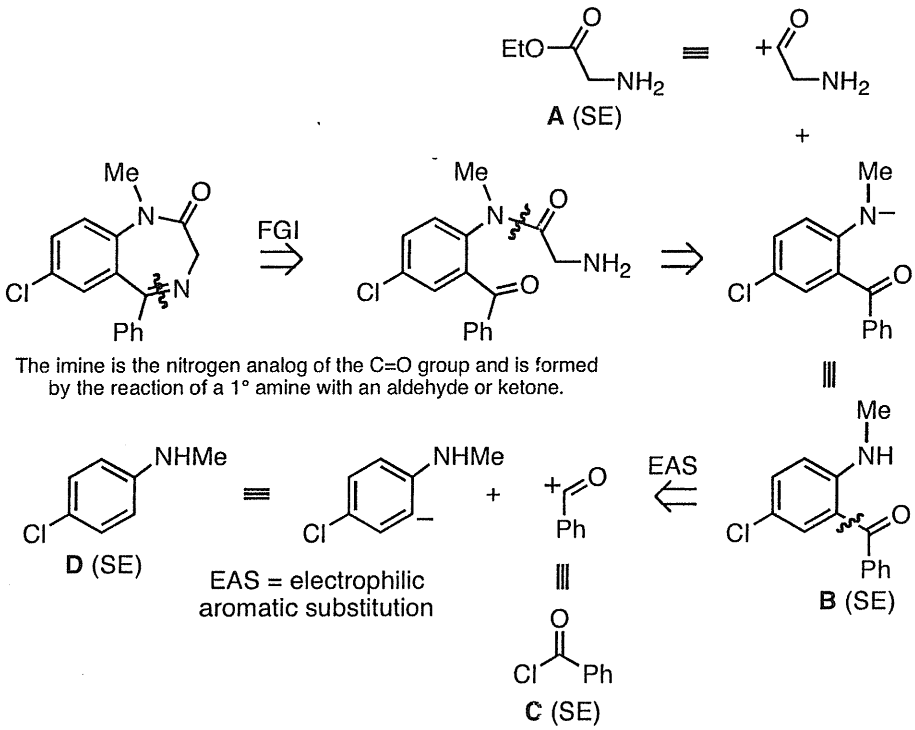


Valium
(tranquilizer)

from



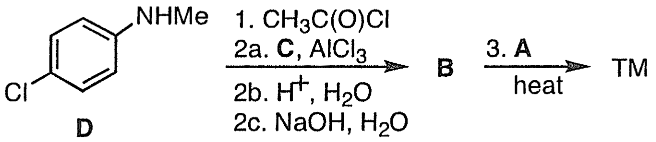
Retrosynthetic analysis:



The imine is the nitrogen analog of the C=O group and is formed by the reaction of a 1° amine with an aldehyde or ketone.

EAS = electrophilic aromatic substitution

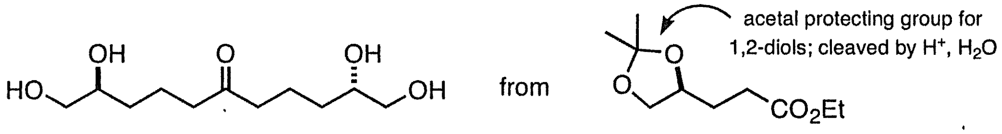
Synthesis:



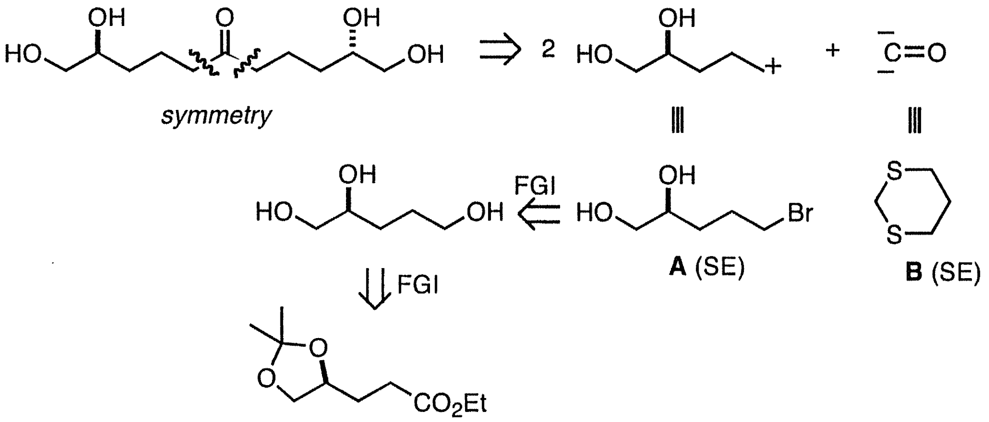
Step 1	Reaction of $CH_3C(O)Cl$ with **D** affords the amide (weak activator compared to an amine), which should circumvent multiple substitutions in Step 2a.
Step 2a	Electrophilic aromatic substitution occurs *ortho* to the amide.
Step 2b	Workup.
Step 2c	Hydrolysis of the amide provides **B.**
Step 3	Reaction of the 2° amine (of the aromatic ring **B**) with the ethyl ester forms the amide while the reaction of the 1° amine (of glycine **A**) with the carbonyl group forms the imine.

Reference: For an analogous synthesis, see Gates, M. *J. Org. Chem.* **1980**, *45*, 1675.

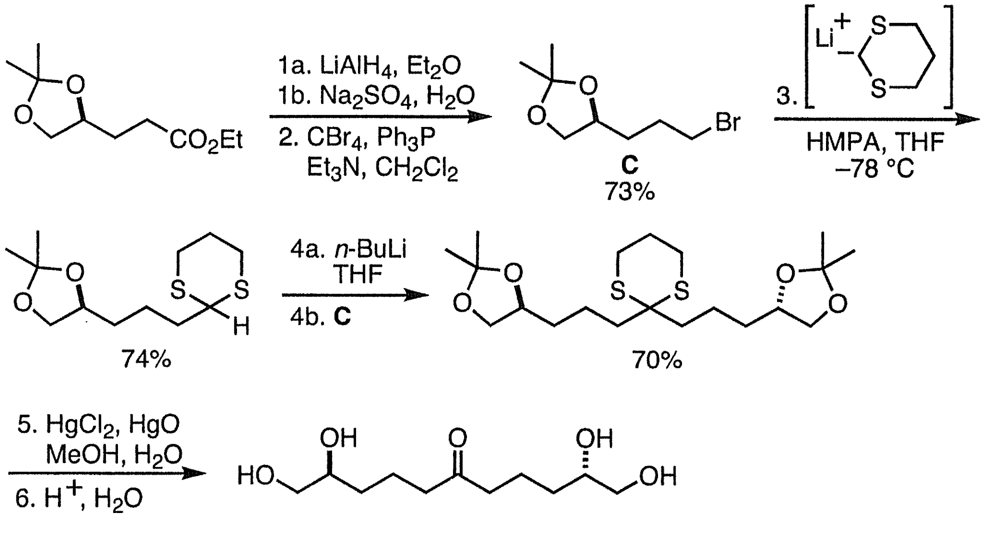
f.



Retrosynthetic analysis:



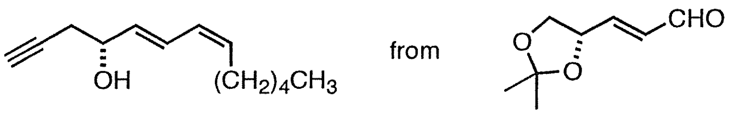
Synthesis:



Step 2 Conversion of the 1° alcohol to the 1° alkyl bromide.

Reference: Sharma, A.; Iyer, P.; Gamre, S.; Chattopadhyay, S. *Synthesis* **2004**, 1037.

g.



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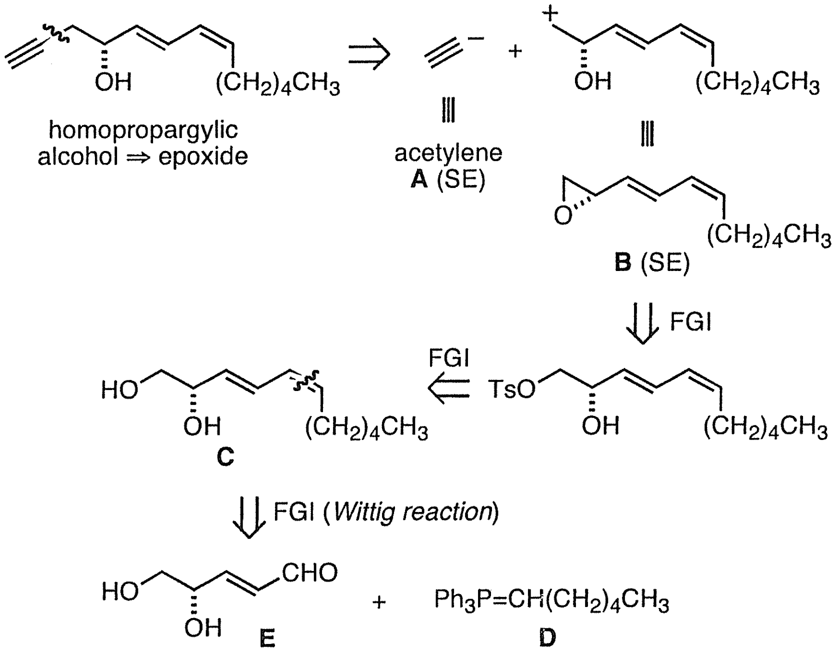
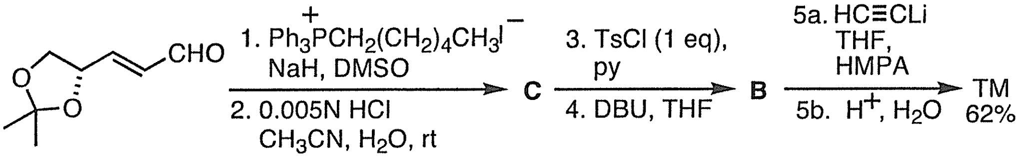


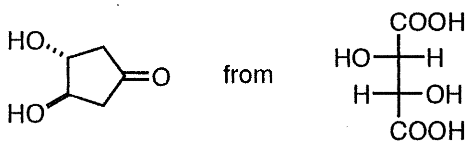
Synthesis:



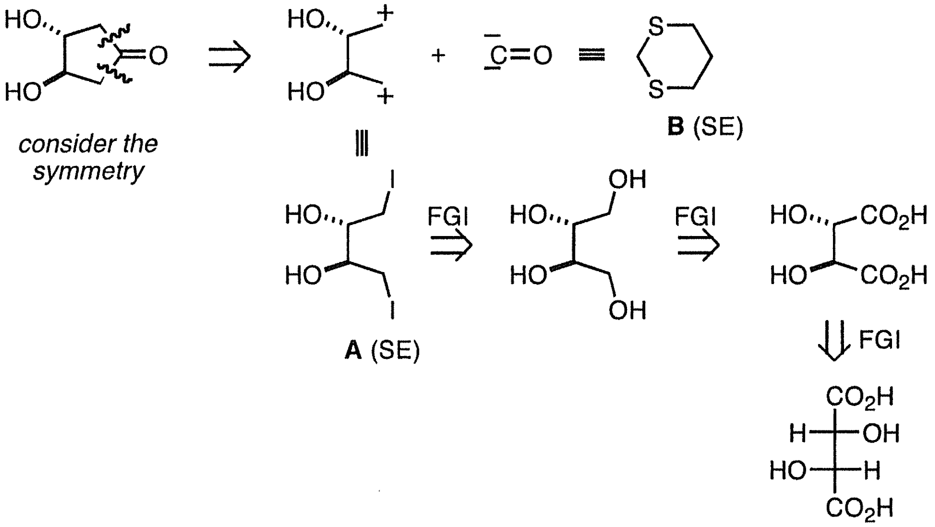
Step 1	The diol **E** must be protected (acetal, in this example) for the Wittig reaction to proceed. The Wittig reagent is prepared from the phosphonium iodide using sodium dimsylate, $NaCH_2S(O)CH_3$.
Step 2	*Mild* acid hydrolysis of the acetonide prevents acid-induced isomerization of the (Z)-alkene.
Step 3	Selective tosylation of the 1° alcohol.
Step 4	DBU (1,8-diazabicyclo[5.4.0]undec-7-ene), a bulky, non-nucleophilic nitrogen base, is used to form the epoxide.
Step 5a	Under basic conditions, the epoxide ring opening proceeds at the less substituted carbon (compare to Problem 3a).
Step 5b	Workup protocol.

Reference: Corey, E. J.; Kang, J. *J. Am. Chem. Soc.* **1981**, *103*, 4618.

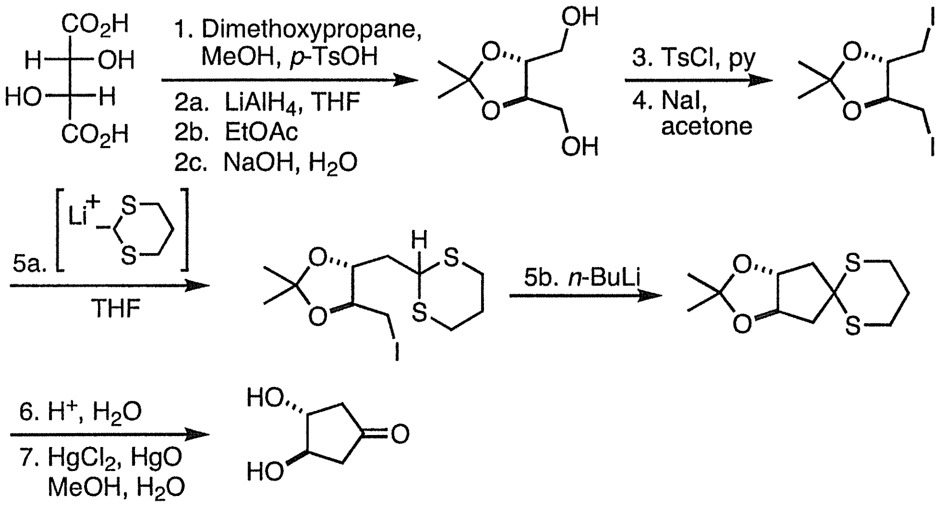
***h.**



Retrosynthetic analysis:



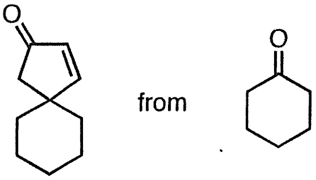
Synthesis:



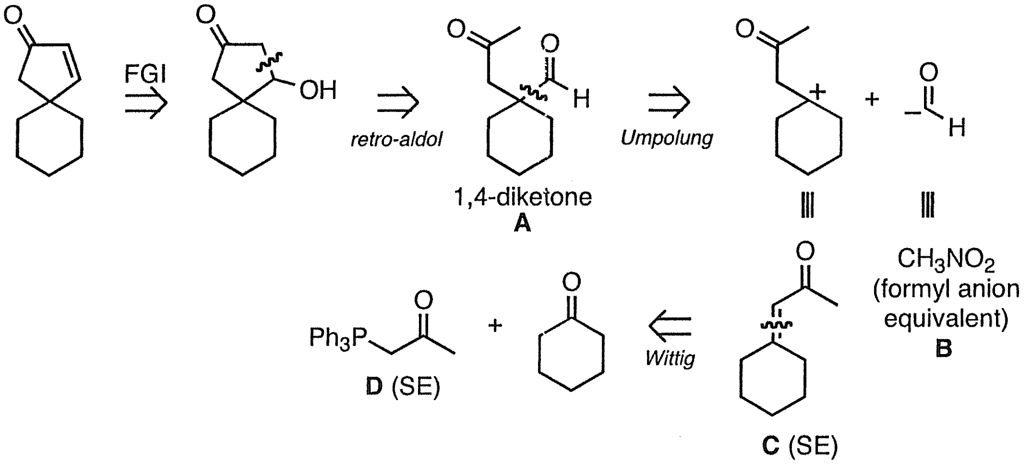
Step 2b+c Workup protocol.

Reference: For an analogous synthesis, see Khanapure, S. P.; Najafi, N.; Manna, S.; Yang, J.-J.; Rokach, J. *J. Org. Chem.* **1995**, *60*, 7548.

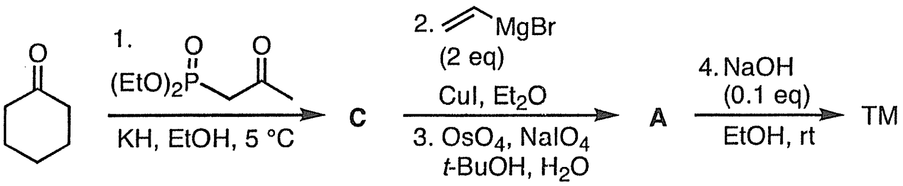
***i.**



Retrosynthetic analysis:



Synthesis:



Step 1 β-keto phosphonates often are used for olefination of ketones (Horner-Wadsworth-Emmons modification of the Wittig reaction).

Steps 2 + 3 The cuprate-mediated 1,4-addition and subsequent Lemieux-Johnson oxidation of a vinyl group are excellent procedures for the introduction of the β-formyl group.

Step 4 Intramolecular aldol condensation provides the TM.

Reference: For the synthetic sequence applied to a similar TM, see Corey, E. J.; Smith, J. G. *J. Am. Chem. Soc.* **1979**, *101*, 1038.

CHAPTER 2

Stereochemical Considerations in Planning Syntheses

Overview

Chapter 2 focuses on conformational analysis as a tool for assessing the relative reactivity and stereochemistry of cyclic compounds.

Problems 1–3 emphasize the three dimensional representation of various cyclic molecules and evaluation of their energies by the A, G, and U parameters. In Problems 4–6, we apply conformational analysis to predict the reactivity of carbocyclic systems toward various reagents and to gather information regarding the preferred stereochemical course of the corresponding reactions. Further examples of applications of conformational analysis in organic synthesis are incorporated in Problems 7–9.

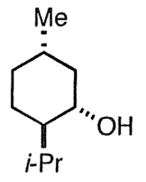
Key Concepts

- Conformational analysis
- Corey and Feiner's A, G, and U energy parameters
- $A^{1,2}$ strain

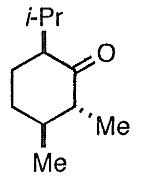
SOLUTIONS TO CHAPTER 2 PROBLEMS

The more challenging problems are identified by an asterisk (*).

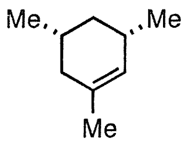
1. Draw the chair or the half-chair conformations (where applicable) for each of the molecules shown below and determine the corresponding E_D and ΔE_D values. Use the A, G, and U values of Table 2.3 and assume 0.7 kcal/mol for Me/H $A^{1,2}$ strain.



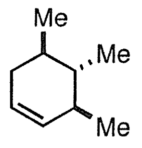
a.



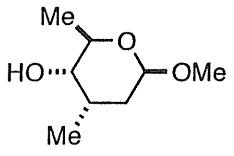
b.



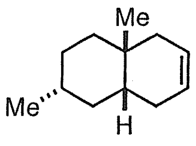
c.



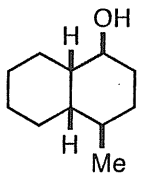
d.



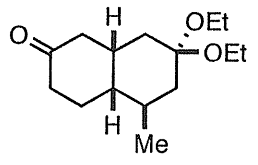
e.



f.



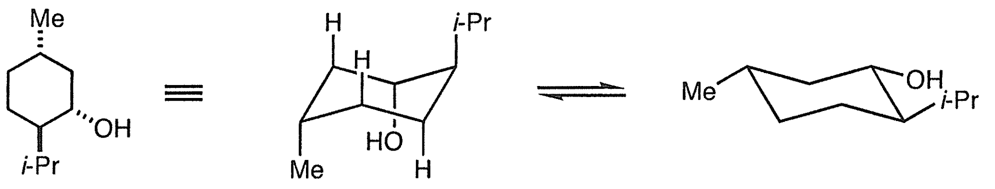
g.



h.

Solution:

a.



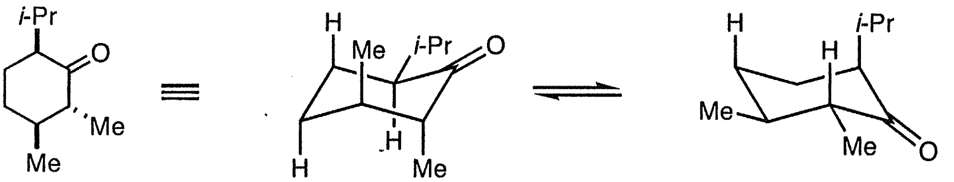
	A	**B**
interactions:	one 1,3-diaxial Me / OH one 1,3-diaxial Me / H one 1,3-diaxial OH / H two 1,3-diaxial i-Pr / H	one 1,2-diequatorial OH / i-Pr

A: E_D $= U_{Me} + U_{OH} + 1/2\ (A_{Me} + A_{OH}) + A_{i\text{-}Pr}$
$= 1.8 + 0.9 + 1/2\ (1.8 + 0.9) + 2.1$
$= 6.15$ kcal/mol

B: E_D $= G_{OH} + G_{i\text{-}Pr}$
$= 0.2 + 0.8$
$= 1.0$ kcal/mol

$\Delta E_D = 6.15 - 1.0 = 5.15$ kcal/mol

b.



A B

interactions:

A: two 1,3-diaxial Me / H
2/3 1,3-diaxial Me / H
(cyclohexanone system)

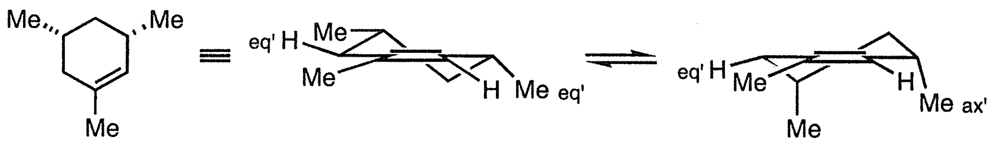
B: two 1,3-diaxial *i*-Pr / H
one 1,2-diequatorial Me / Me

$$\textbf{A: } E_D = A_{Me} + 2/3\,(A_{Me}) = 1.8 + 2/3\,(1.8) = 3.0 \text{ kcal/mol}$$

$$\textbf{B: } E_D = A_{i\text{-Pr}} + G_{Me} + G_{Me} = 2.1 + 0.4 + 0.4 = 2.9 \text{ kcal/mol}$$

$$\Delta E_D = 3.0 - 2.9 = 0.1 \text{ kcal/mol}$$

c.



A B

interactions:

A: two $A^{1,2}$ strain Me / H

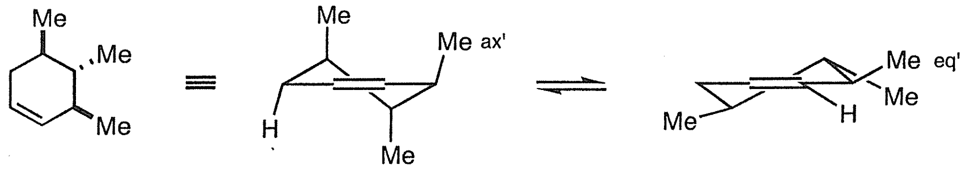
B: one $A^{1,2}$ strain Me / H
one 1,3-diaxial Me / Me

$$\textbf{A: } E_D = 2\,(A^{1,2}\ \text{Me/H}) = 2\,(0.7) = 1.4 \text{ kcal/mol}$$

$$\textbf{B: } E_D = U_{Me} + U_{Me} + A^{1,2}\ \text{Me/H} = 1.8 + 1.8 + 0.7 = 4.3 \text{ kcal/mol}$$

$$\Delta E_D = 4.3 - 1.4 = 2.9 \text{ kcal/mol}$$

d.



A   B

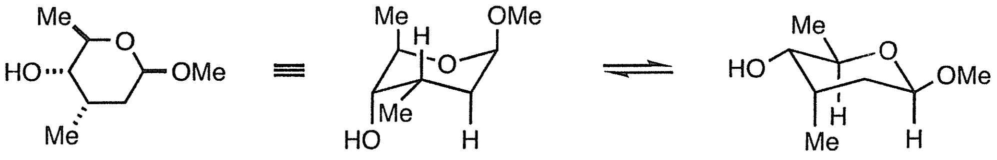
interactions:	one 1,3-diaxial Me / Me one 1,3-diaxial Me / H	one $A^{1,2}$ strain Me/H one 1,2-diequatorial Me / Me

$$\begin{aligned}\textbf{A: } E_D &= U_{Me} + U_{Me} + 1/2\,(A_{Me})\\ &= 1.8 + 1.8 + 0.9\\ &= 4.5 \text{ kcal/mol}\end{aligned}$$

$$\begin{aligned}\textbf{B: } E_D &= 2\,(G_{Me} + G_{Me}) + A^{1,2}\ \text{Me/H}\\ &= 2\,(0.4 + 0.4) + 0.7\\ &= 2.3 \text{ kcal/mol}\end{aligned}$$

$$\Delta E_D = 4.5 - 2.3 = 2.2 \text{ kcal/mol}$$

e.



A   B

interactions:	one 1,3-diaxial Me / OMe one 1,3-diaxial Me / H one 1,3-diaxial OMe / H one 1,3-diaxial OH / H	two 1,3-diaxial Me / H one 1,2-diequatorial Me / OH

$$\begin{aligned}\textbf{A: } E_D &= U_{Me} + U_{OMe} + 1/2\,(A_{Me} + A_{OMe} + A_{OH})\\ &= 1.8 + 0.9 + 1/2\,(1.8 + 0.9 + 0.9)\\ &= 4.5 \text{ kcal/mol}\end{aligned}$$

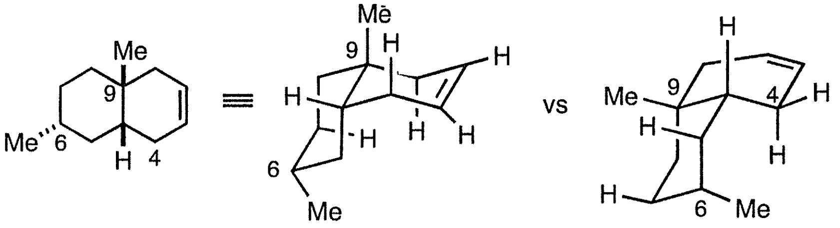
$$\begin{aligned}\textbf{B: } E_D &= A_{Me} + G_{Me} + G_{OH}\\ &= 1.8 + 0.4 + 0.2\\ &= 2.4 \text{ kcal/mol}\end{aligned}$$

$$\Delta E_D = 4.5 - 2.4 = 2.1 \text{ kcal/mol}$$

f.

interactions:

	A	B
	β face: one 1,3-diaxial C(9)-Me / H	**β face:** two 1,3-diaxial C(9)-Me / H
	$\boxed{1/2\ A_{Me}}$	$\boxed{A_{Me}}$



A **B**

interactions:

	A	B
	α face: one 1,3-diaxial C(5)-CH_2 / H one 1,3-diaxial C(7)-CH_2 / H	**α face:** one 1,3-diaxial C(6)-Me / C(4)-CH_2 one 1,3-diaxial C(6)-Me / H one 1,3-diaxial C(4)-CH_2 / H
	$\boxed{A_{RCH_2}}$	$\boxed{U_{Me} + U_{RCH_2} + 1/2\ A_{Me} + 1/2\ A_{RCH_2}}$

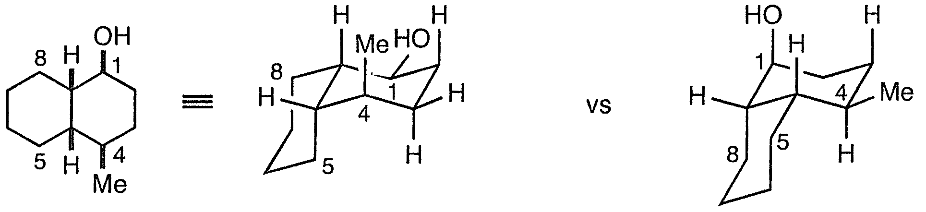
A: $$\begin{aligned} E_D &= 1/2\ (A_{Me}) + A_{RCH_2} \\ &= 0.9 + 1.8 \\ &= 2.7 \text{ kcal/mol} \end{aligned}$$

B: $$\begin{aligned} E_D &= A_{Me} + U_{Me} + U_{RCH2} + 1/2\ (A_{Me} + A_{RCH_2}) \\ &= 1.8 + 1.8 + 1.8 + 1/2\ (1.8 + 1.8) \\ &= 7.2 \text{ kcal/mol} \end{aligned}$$

$$\Delta E_D = 7.2 - 2.7 = 4.5 \text{ kcal/mol}$$

g.

interactions:	**β face:** two 1,3-diaxial C(4)-Me / H one 1,2-diequatorial C(1)-OH / C(8)-CH_2	**β face:** two 1,3-diaxial C(1)-OH / H one 1,2-diequatorial C(4)-Me / C(5)-CH_2
	$\boxed{A_{Me} + G_{OH} + G_{RCH_2}}$	$\boxed{A_{OH} + G_{Me} + G_{RCH_2}}$



A

B

interactions:	**α face:** one 1,3-diaxial C(5)-CH_2 / H one 1,3-diaxial C(1)-CH_2 / H	**α face:** two 1,3-diaxial C(8)-CH_2 / H one 1,3-diaxial C(4)-CH_2 / H
	$\boxed{A_{RCH_2} + 1/2\ A_{RCH_2}}$	$\boxed{A_{RCH_2} + 1/2\ A_{RCH_2}}$

$$\begin{aligned} \textbf{A: } E_D &= A_{Me} + G_{OH} + G_{RCH_2} + A_{RCH_2} + 1/2\,(A_{RCH_2}) \\ &= 1.8 + 0.2 + 0.4 + 1.8 + 1/2\,(1.8) \\ &= 5.1 \text{ kcal/mol} \end{aligned}$$

$$\begin{aligned} \textbf{B: } E_D &= A_{OH} + G_{Me} + G_{RCH_2} + A_{RCH_2} + 1/2\,(A_{RCH_2}) \\ &= 0.9 + 0.4 + 0.4 + 1.8 + 1/2\,(1.8) \\ &= 4.4 \text{ kcal/mol} \end{aligned}$$

$$\Delta E_D = 5.1 - 4.4 = 0.6 \text{ kcal/mol}$$

h.

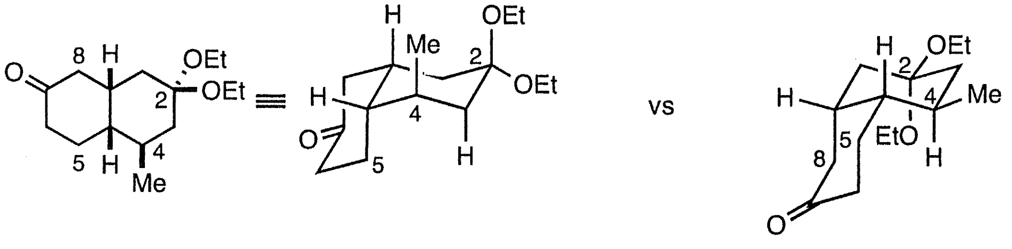
interactions:

β face:
one 1,3-diaxial C(4)-Me / C(2)-OEt
one 1,3-diaxial C(4)-Me / H
one 1,3-diaxial C(2)-OEt / H

$\boxed{U_{Me} + U_{OEt} + 1/2\ A_{Me} + 1/2\ A_{OEt}}$

β face:
one 1,2-diequatorial
C(4)-Me / C(5)-CH$_2$

$\boxed{G_{Me} + G_{RCH_2}}$



A

B

interactions:

α face:
two 1,3-diaxial
C(5)-CH$_2$ / H

$\boxed{A_{RCH_2}}$

α face:
one 1,3-diaxial C(2)-OEt / C(8)-CH$_2$
one 1,3-diaxial C(2)-OEt / H
one 1,3-diaxial C(8)-CH$_2$ / H
one 1,3-diaxial C(4)-CH$_2$ / H

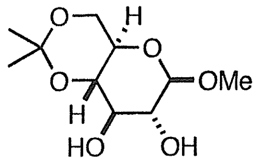
$\boxed{\begin{array}{l} U_{OEt} + U_{RCH_2} + 1/2\ A_{OEt} \\ + 1/2\ A_{RCH_2} + 1/2\ A_{RCH_2} \end{array}}$

$$\begin{aligned} \textbf{A: } E_D &= U_{Me} + U_{OEt} + 1/2\,(A_{Me}) + 1/2\,(A_{OEt}) + A_{RCH_2} \\ &= 1.8 + 0.9 + 1/2\,(1.8) + 1/2\,(0.9) + 1.8 \\ &= 5.85 \text{ kcal/mol} \end{aligned}$$

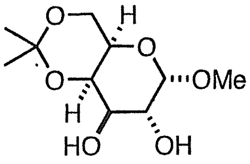
$$\begin{aligned} \textbf{B: } E_D &= G_{Me} + G_{RCH_2} + U_{OEt} + U_{RCH_2} + 1/2\,(A_{OEt}) + 1/2\,(A_{RCH_2}) + 1/2\,(A_{RCH_2}) \\ &= 0.4 + 0.4 + 0.9 + 1.8 + 1/2\,(0.9) + 1/2\,(1.8) + 1/2\,(1.8) \\ &= 4.4 \text{ kcal/mol} \end{aligned}$$

$$\Delta E_D = 5.85 - 5.75 = 0.10 \text{ kcal/mol}$$

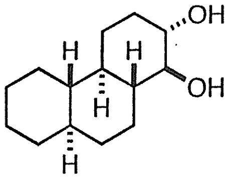
2. Draw the most stable conformation for each of the compounds shown below. You do *not* need to compute the E_D and ΔE_D values.



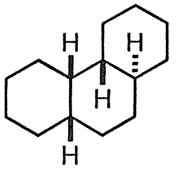
a.



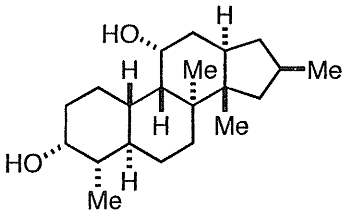
b.



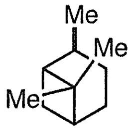
c.



d.



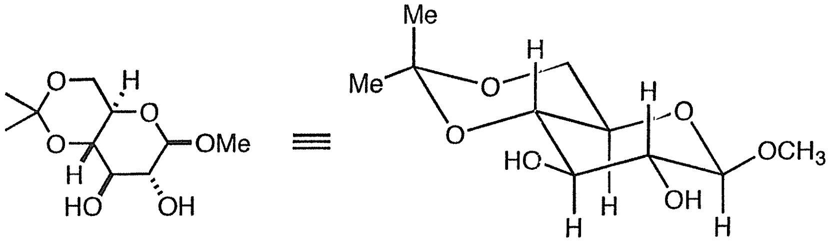
e.



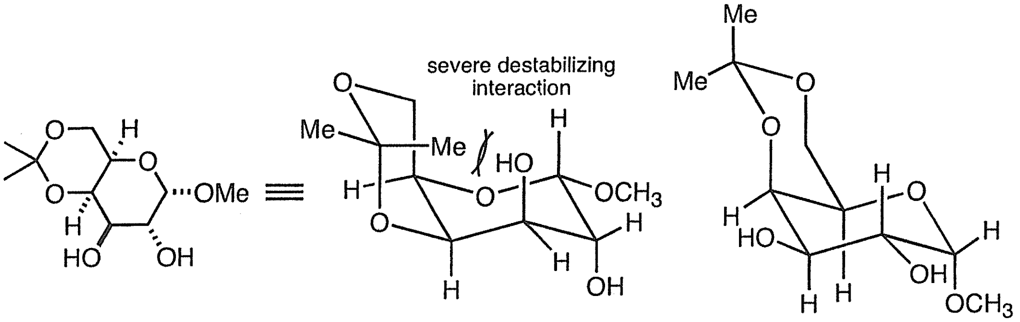
f.

Solution:

a.



b.

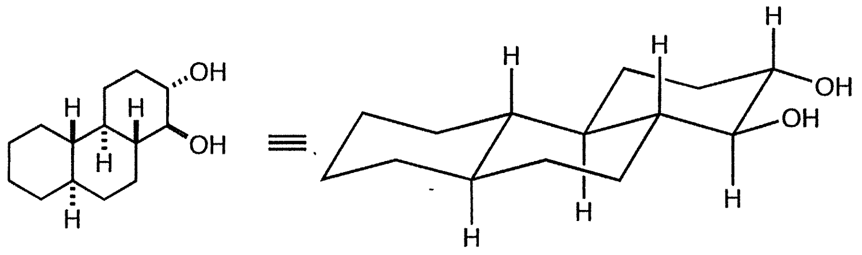


severe destabilizing interaction

A **B**

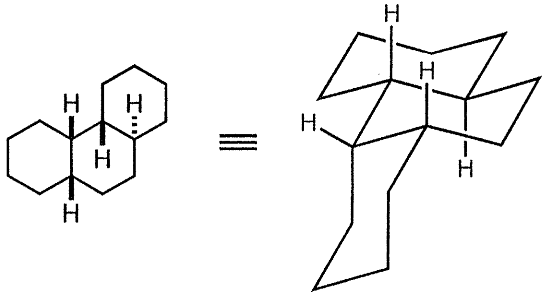
B is the more stable conformer.

c.



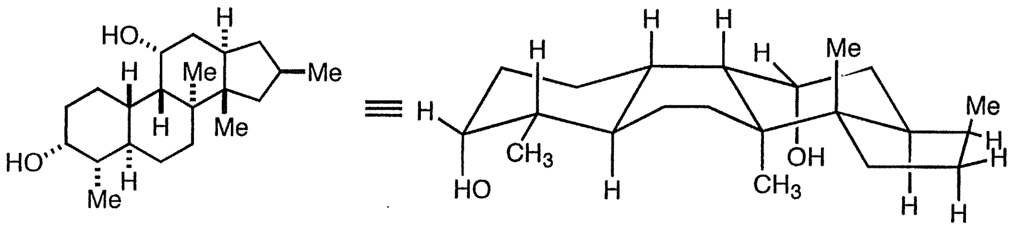
trans-anti-*trans*; each ring is in the chair conformation.

d.



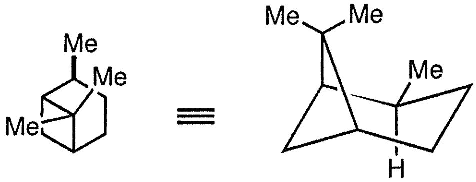
cis-syn-*cis*; each ring is in the chair conformation.

e.

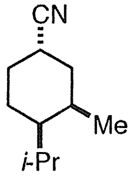


chair-boat-chair-envelope

f.

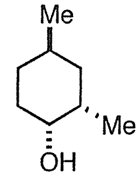


3. For each molecule shown below, calculate the percentage (%) of the more stable conformation at the temperature indicated.



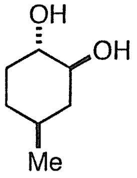
a.

at: 25 °C,
100 °C



b.

50 °C

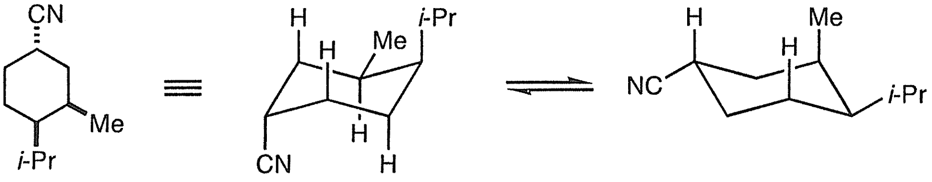


c.

25 °C

Solution:

a.



A **B**

interactions:

A: two 1,3-diaxial CN / H
two 1,3-diaxial i-Pr / H

B: two 1,3-diaxial Me / H

A: $E_D = A_{CN} + A_{i\text{-}Pr}$
$= 0.2 + 2.1$
$= 2.3$ kcal/mol

B: $E_D = A_{Me}$
$= 1.8$ kcal/mol

B has fewer unfavorable interactions (lower E_D), therefore, it is the more stable conformer.

The percentage of conformer **B** at a given temperature can be calculated as shown below:

$$\Delta E_D = 1.8 - 2.3 = -0.5 \text{ kcal/mol}$$

$$\text{Assuming } \Delta E_D \sim \Delta G^o = -RT \ln K_{eq}$$

$$\text{At 25 °C (298 K): } \Delta G^o = -500 \text{ kcal/mol} = -(1.987 \text{ cal/K•mol})(298 \text{ K}) \ln K_{eq}$$

$$\ln K_{eq} = \frac{500}{1.987 \times 298} = 0.844 \quad K_{eq} = 2.33 = \frac{\text{conformer } \mathbf{B}}{\text{conformer } \mathbf{A}}$$

$$\text{conformer } \mathbf{B} + \text{conformer } \mathbf{A} = 1$$

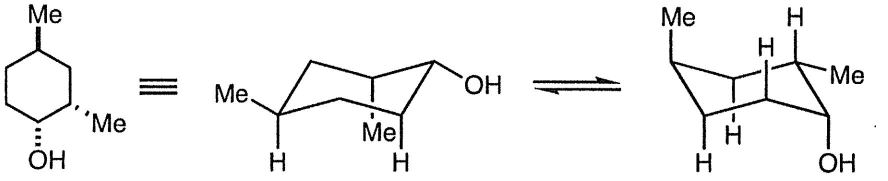
$$\boxed{\%\,\mathbf{B} = \frac{2.33}{(2.33+1)}(100) = 70\% \text{ at } 25\ ^{\circ}\text{C}}$$

At 100 °C (373 K): $\Delta G^{\circ} = -500$ kcal/mol $= -(1.987$ cal/K•mol$)(373$ K$)\ln K_{eq}$

$$\ln K_{eq} = \frac{500}{1.987 \times 373} = 0.675 \qquad K_{eq} = 1.96 = \frac{\text{conformer } \mathbf{B}}{\text{conformer } \mathbf{A}}$$

$$\boxed{\%\,\mathbf{B} = \frac{1.96}{(1.96+1)}(100) = 66\% \text{ at } 100\ ^{\circ}\text{C}}$$

b.



A **B**

interactions: two 1,3-diaxial Me / H

two 1,3-diaxial Me / H
two 1,3-diaxial OH / H

A: $E_D = A_{Me}$
$= 1.8$ kcal/mol

B: $E_D = A_{Me} + A_{OH}$
$= 1.8 + 0.9$
$= 2.7$ kcal/mol

A has fewer unfavorable interactions (lower E_D), therefore, it is the more stable conformer.

The percentage of conformer **A** at 50 °C is calculated in the same manner as in Problem 3a:

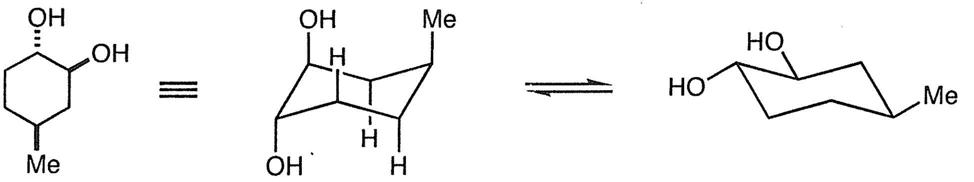
$$\Delta E_D = 1.8 - 2.7 = -0.9 \text{ kcal/mol}$$

At 50 °C (323 K): $\Delta G^{\circ} = -900$ kcal/mol $= -(1.987$ cal/K•mol$)(323$ K$)\ln K_{eq}$

$$\ln K_{eq} = \frac{900}{1.987 \times 323} = 1.40 \qquad K_{eq} = 4.06 = \frac{\text{conformer } \mathbf{B}}{\text{conformer } \mathbf{A}}$$

$$\boxed{\%\,\mathbf{A} = \frac{4.06}{(4.06+1)}(100) = 80\% \text{ at } 50\ ^{\circ}\text{C}}$$

c.



A **B**

	A	B
interactions:	one 1,3-diaxial OH / Me one 1,3-diaxial OH / H one 1,3-diaxial Me / H two 1,3-diaxial OH / H	one 1,2-diequatorial OH / OH

A: $E_D = U_{OH} + U_{Me} + 1/2\,[A_{OH} + A_{Me}] + A_{OH}$
$= 0.9 + 1.8 + 1/2\,[0.9 + 1.8] + 0.9$
$= 4.95$ kcal/mol

B: $E_D = G_{OH} + G_{OH}$
$= 0.2 + 0.2$
$= 0.4$ kcal/mol

B has a considerably lower E_D than **A**, therefore, it is the more stable conformer.

The percentage of conformer **B** at 25 °C is calculated in the same manner as in Problem 3a-b:

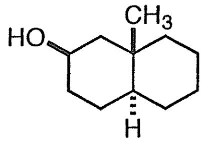
$$\Delta E_D = 0.4 - 4.95 = -4.55 \text{ kcal/mol}$$

At 25 °C (298 K): $\Delta G^o = -4550 \text{ kcal/mol} = -(1.987 \text{ cal/K•mol})(298 \text{ K}) \ln K_{eq}$

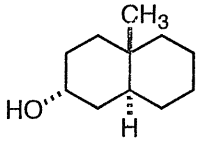
$$\ln K_{eq} = \frac{4550}{1.987 \times 298} = 7.68 \qquad K_{eq} = 2165 = \frac{\text{conformer } \mathbf{B}}{\text{conformer } \mathbf{A}}$$

$$\boxed{\%\,\mathbf{B} = \frac{2165}{(2165 + 1)}(100) = 99.9\% \text{ at } 25\ ^oC}$$

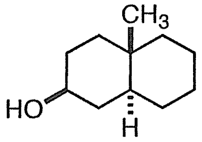
4. Show the conformation of each of the following alcohols and arrange them in order of decreasing ease of esterification with *p*-nitrobenzoyl chloride.



a

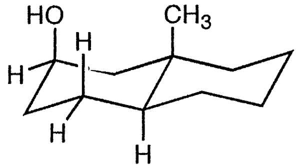


b

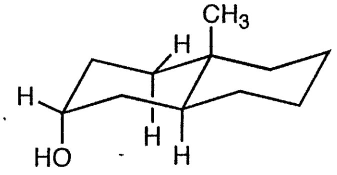


c

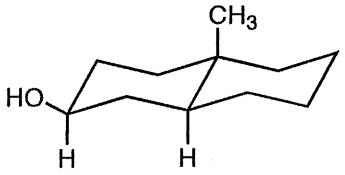
Solution:



a



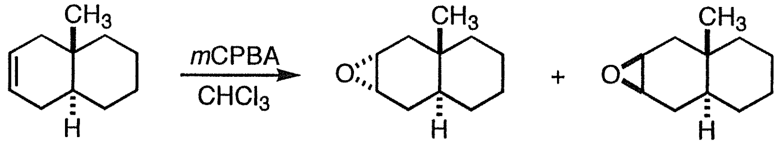
b



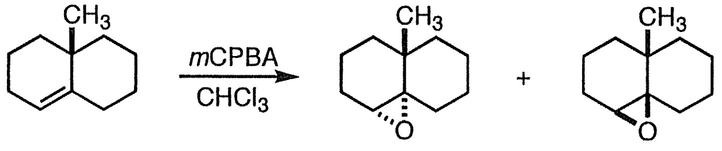
c

The order of reactivity for esterification is **c** > **b** > **a**.

5. Given below are the observed α : β epoxide ratios from epoxidations of the decalins **A** and **B** with *m*-chloroperbenzoic acid (*m*CPBA) in $CHCl_3$. How do you explain the differences in stereoselectivity?

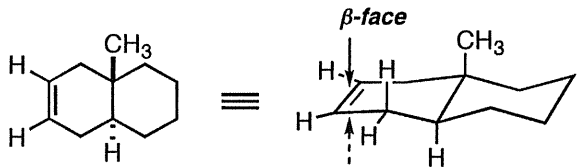


A 95 5

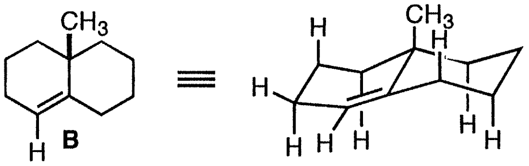


B 60 40

Solution:



The angular CH_3 group shields the β-face of **A**. Hence, the α-face is more accessible for epoxidation, resulting in epoxide ratio of 95 : 5 α to β.

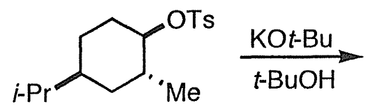


Although the angular CH_3 group also shields the β-face of **B**, the α-face of **B** is less accessible relative to that in **A** due to the axial α-face H's resulting in the epoxide ratio of 60 : 40 α to β.

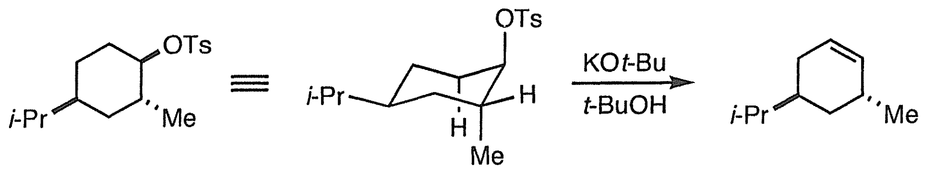
Reference: Marshall, J. A.; Hochstetle, A. R. *J. Org. Chem.* **1966**, *31*, 1020.

6. **Reagents.** Show the major product formed for each of the following reactions.

a.

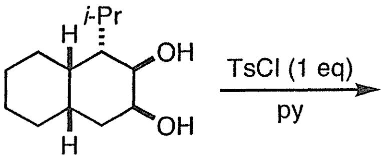


Solution:

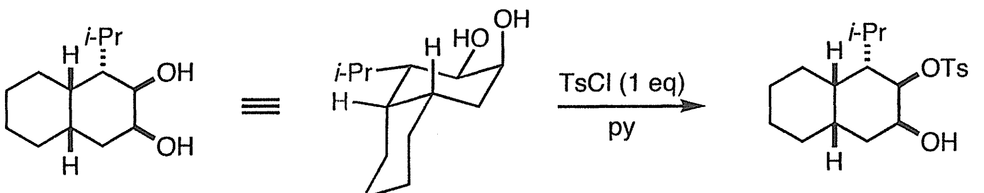


E2 elimination proceeds via *anti*-periplanar arrangement of the OTs and the adjacent H.

b.



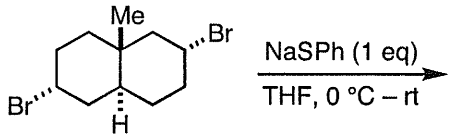
Solution:



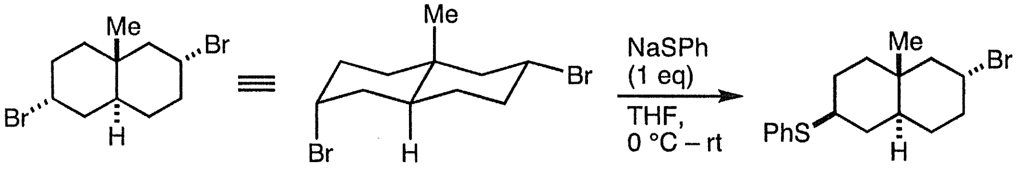
favored conformer

preferential tosylation of the equatorial–OH

c.

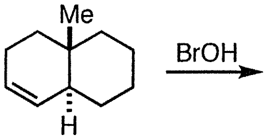


Solution:

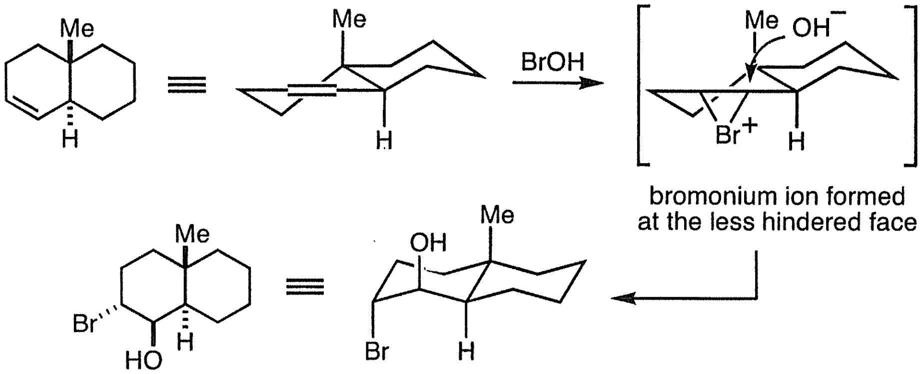


S_N2 displacement of the axial-Br is sterically favored.

d.



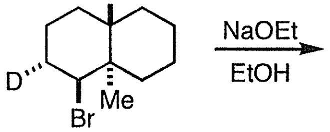
Solution:



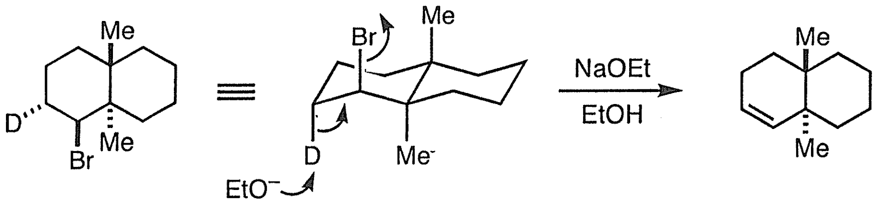
bromonium ion formed at the less hindered face

anti-periplanar and *anti*-parallel opening of bromonium ion

e.



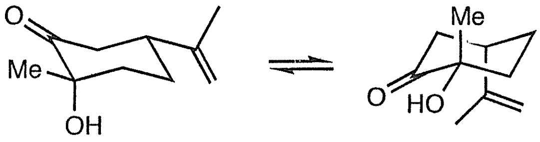
Solution:



E2 elimination proceeds via *anti*-periplanar arrangement of the Br and the adjacent D.

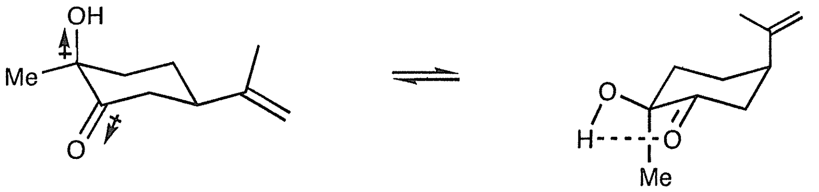
---

*7. Consider the conformational equilibrium of the ketone below. Explain why conformer **A** predominates in DMSO (100% **A**) whereas **B** is the major conformer in isooctane (22% **B**: 78% **A**).



A **B**

Solution:



favored conformer; opposing dipole interaction

sterically disfavored conformer (axial Me and axial isopropenyl groups), but the intramolecular hydrogen-bonding in a non-polar solvent offsets the unfavorable steric and dipole interactions.

Reference: Suga, T.; Shishibori, T. *Chemistry and Industry* **1971**, 733.

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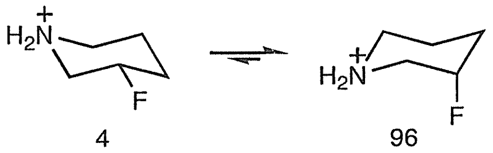
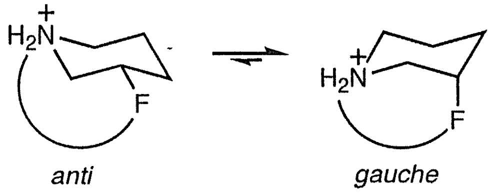
*8. Suggest a reason why the equilibrium below favors the conformation on the right.

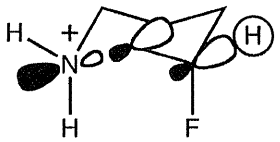


Solution:

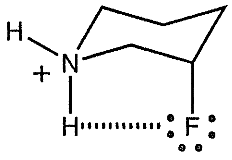
In the compound on the left, the F and $NH_2R_2^+$ groups are *anti* to each other, while in the compound on the right these groups are *gauche* to each other.



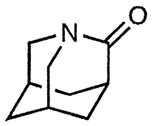
The key orbital interactions that favor the gauche arrangement are shown below.



In addition, there is weak hydrogen bonding between the F lone pairs and one of the H's on N favoring the conformer on the right.



***9.** Why does the adamantyl compound shown below behave more like a ketone than an amide? (*Hint*: Draw the corresponding resonance hybrid.)



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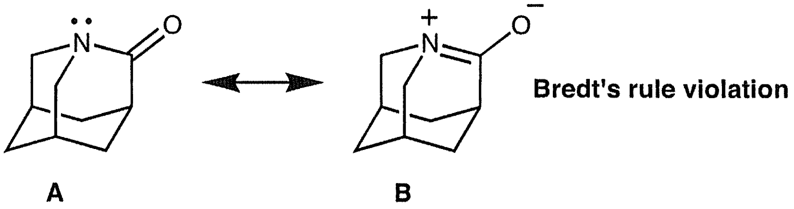


The resonance hybrid **B** with the double bond at a bridgehead violates Bredt's rule. Therefore, without the delocalization of the nitrogen lone pair of electrons, the carbonyl moiety behaves more like a ketone than an amide.

Reference: For a crystallographic and *ab initio* investigation of the amide resonance model, see Quiñonero, D.; Frontera, A.; Capó, M.; Ballester, P.; Suñer, G. A.; Garau, C.; Deyà, P. M. *New J. Chem.* **2001,** *25,* 259.

CHAPTER 3

The Concept of Protecting Functional Groups

Overview

Chapter 3 deals with concepts of protecting functional groups. This important tool allows the chemist to manipulate one functional group selectively in the presence of others in a molecule.

Problems 1 and 2 illustrate the formation and cleavage of various protecting groups. Problems 3 and 4 introduce how to design syntheses of molecules that require the use of protecting groups. Problem 5 provides an example of how a protecting group may influence both the regio- and stereochemical outcome of a reaction sequence.

Key Concepts

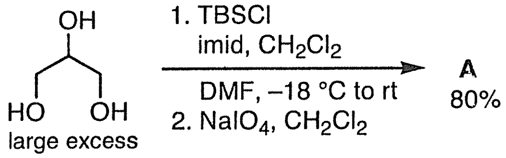
- Protecting and deprotecting a functional group
- Protection of NH groups
  - *N*-benzylamines
  - Carbamates (Boc, Cbz)
- Protection of OH groups of alcohols
  - Alkyl ethers (ROBn, ROBn, ROTr)
  - Silyl ethers (ROTMS, ROTBS, ROBPS)
  - Acetals (ROTHP)
  - Esters
- Protection of diols as acetals
  - 1,2-diols (5-membered cyclic acetals)
  - 1,3-diols (6-membered cyclic acetals)
- Protection of carbonyl groups in aldehydes and ketones
  - *O,O*-acetals
  - *S,S*-acetals
- Deoxygenations

SOLUTIONS TO CHAPTER 3 PROBLEMS

The more challenging problems are identified by an asterisk (*).

1. **Reagents.** Give the structure of the major products (A–G) expected from the following reactions. Assume standard aqueous workup conditions are used for product isolation.

a.



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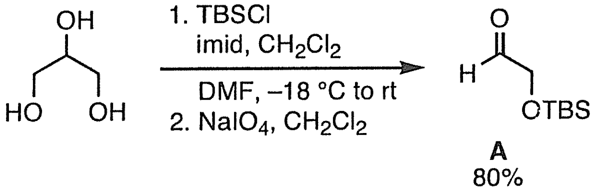
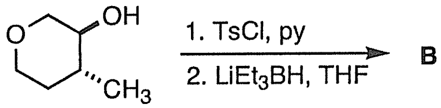


Step 1 To obtain the monosilylation product, a large excess of the starting triol is used.
Step 2 Vicinal diol cleavage.

Reference: Paterson, I.; Delgado, O.; Florence, G. J.; Lyothier, I.; O'Brien, M.; Scott, J. P.; Sereinig, N. *J. Org. Chem.* **2005**, *70*, 150.

b.



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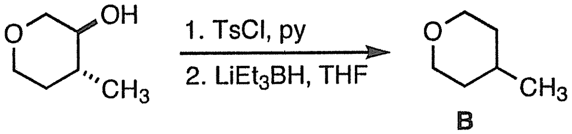
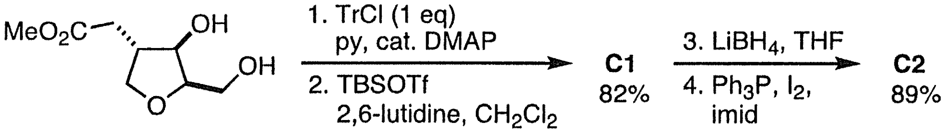


Step 1 Conversion of the 2° alcohol to the corresponding tosylate (a good leaving group).
Step 2 Displacement of the tosylate with a hydride as the nucleophile.
(Note: Steps 1 + 2 represent a common deoxygenation procedure for alcohols.)

c.



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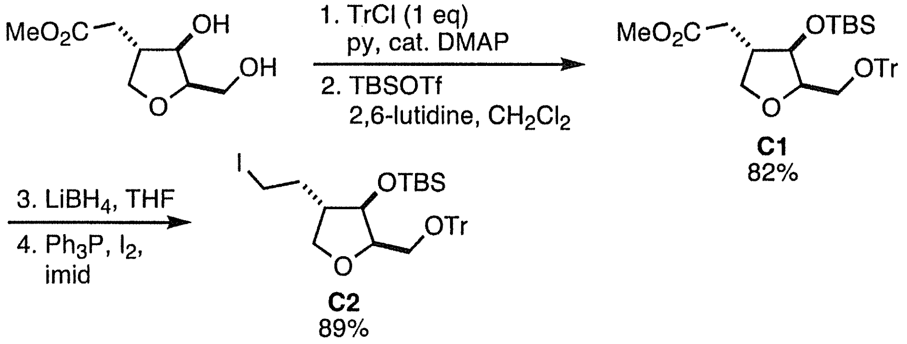
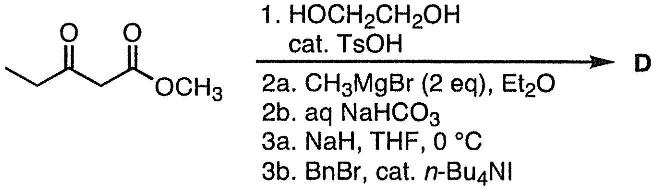


Step 1 Protection of the 1° alcohol in the presence of a 2° alcohol.
Step 2 Protection of the sterically hindered 2° alcohol requires the use of the reactive silylating reagent TBSOTf.
Step 3 The milder reducing agent $LiBH_4$ was used for the reduction of the ester moiety instead of the more powerful $LiAlH_4$, presumably to facilitate the workup in the presence of the acid-labile OTr group.
Step 4 Conversion of the resultant 1° alcohol to the corresponding iodide.

Reference: Gu, Y.; Snider, B. B. *Org. Lett.* **2003**, *5*, 4385.

d.



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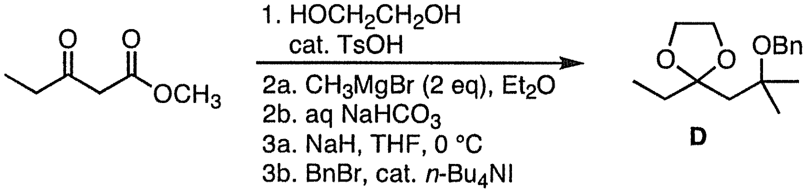
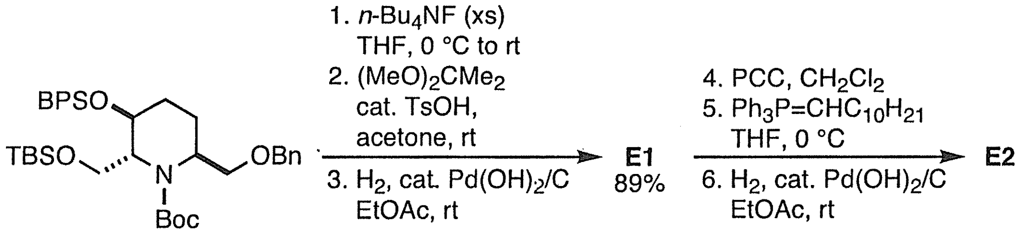


Step 2b Workup protocol.

e.



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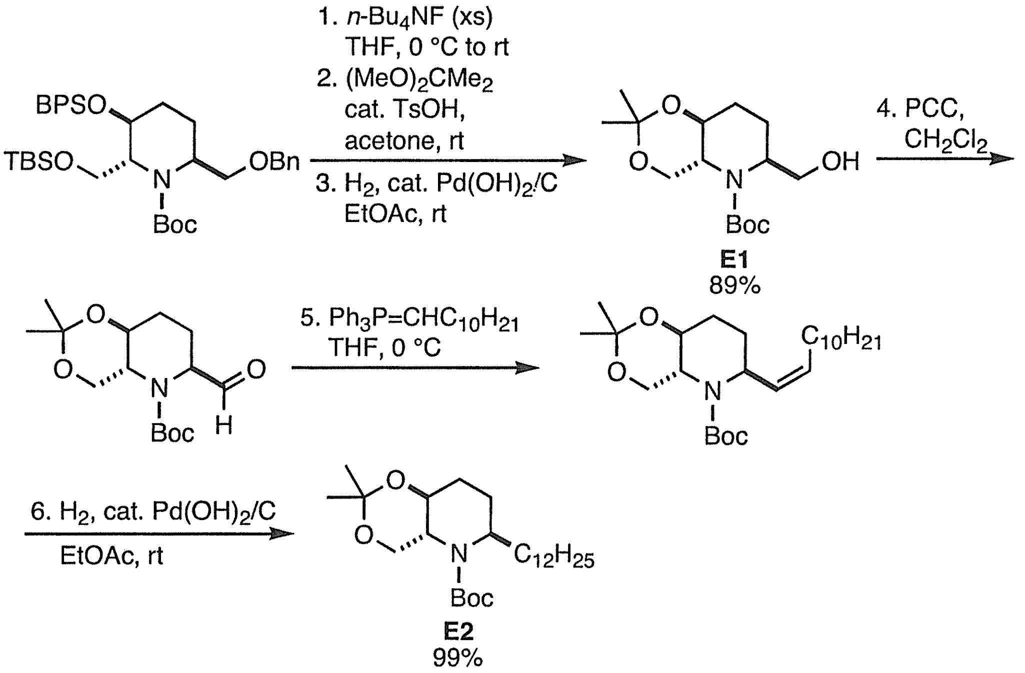
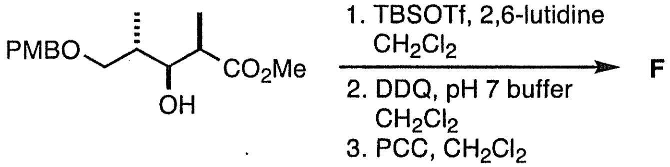


Step 1 Deprotection of the silyl ethers.
Step 2 Acetonide formation.
Step 3 Benzyl ether deprotection.
Step 4 PCC oxidation of the 1° alcohol should furnish the aldehyde; however, the authors (reference below) used the Swern oxidation.
Step 5 Wittig reaction.
Step 6 Alkene hydrogenation.

(Note: Boc, *t*-butoxycarbonyl, protecting group is stable to the reaction conditions in Steps 1–6.)

Reference: Wang, Q.; Sasaki, N. A. *J. Org. Chem.* **2004**, *69*, 4767.

f.



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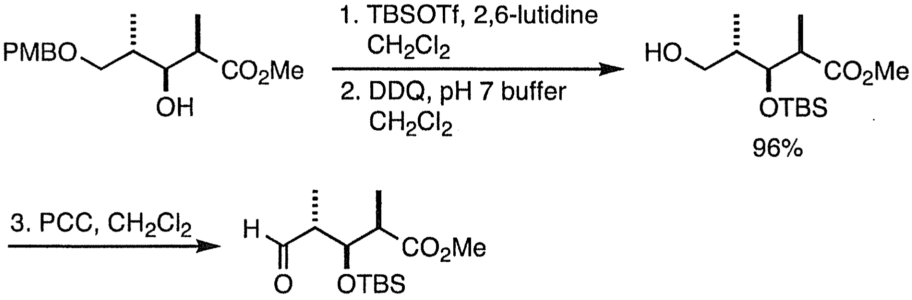


F

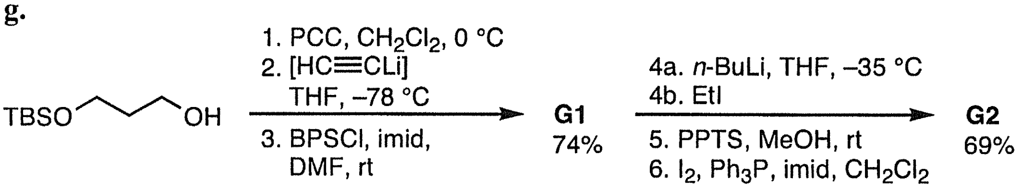
Step 1 Silylation of the 2° alcohol.

Step 2 Removal of *p*-methoxybenzyl (PMB) ether with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) requires H_2O (present in pH 7 buffer).

Step 3 PCC oxidation of the 1° alcohol to the corresponding aldehyde.

Reference: Paterson, I.; Delgado, O.; Florence, G. J.; Lyothier, I.; O'Brien, M.; Scott, J. P.; Sereinig, N. *J. Org. Chem.* **2005**, *70*, 150.

g.



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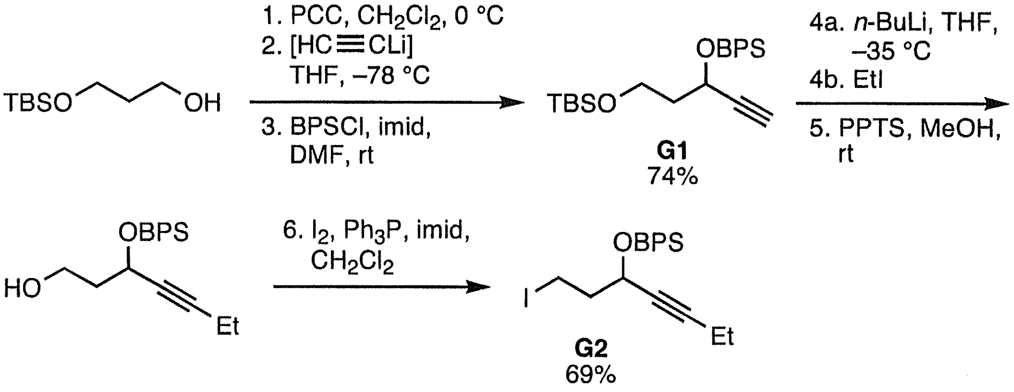
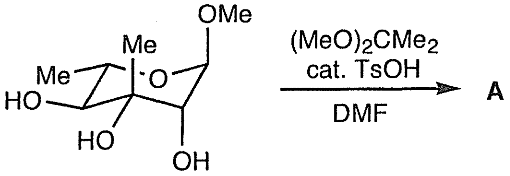


Step 5 Selective cleavage of the sterically less hindered TBS ether.
Step 6 Conversion of the 1° alcohol to the corresponding iodide.

Reference: Nomura, I.; Mukai, C. *J. Org. Chem.* **2004**, *69*, 1803.

2. **Selectivity.** Show the product(s) expected for the following transformations.

a.



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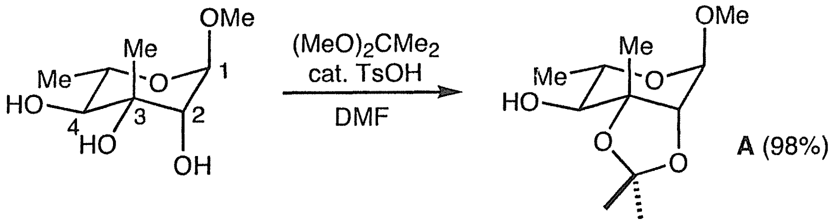
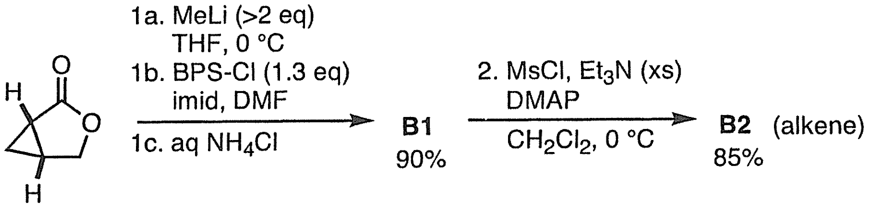


Acetal formation occurs between the *cis* C(2)- and C(3)-OH groups rather than between the *trans* C(3)- and C(4)-OH groups.

Reference: Gyergyói, K.; Tóth, A.; Bajza, I.; Lipták, A. *Synlett* **1998**, 127.

b.



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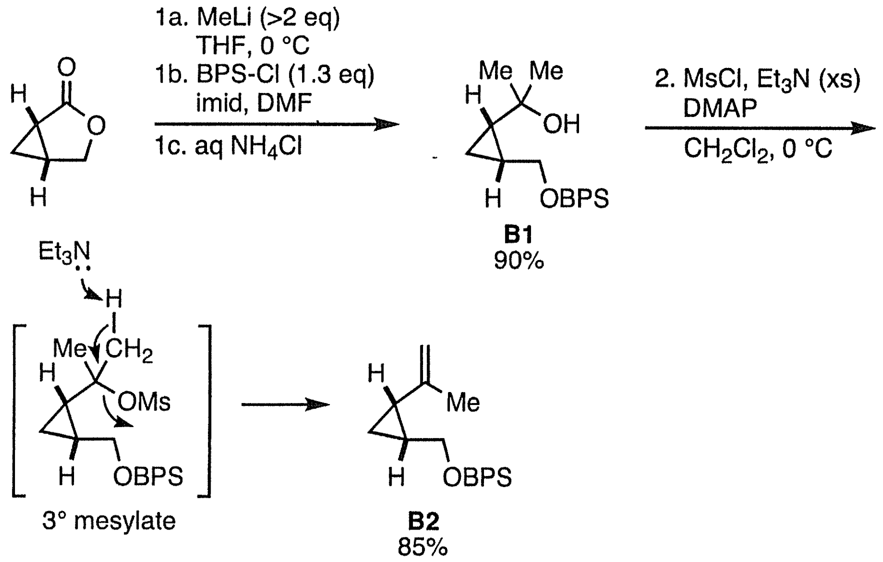


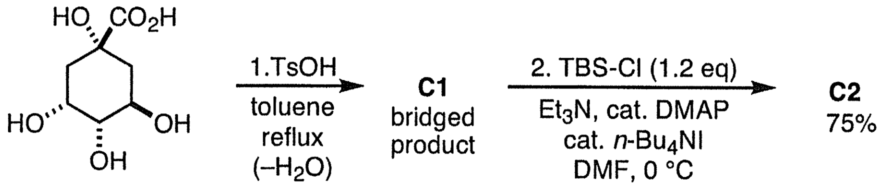
B1
90%

B2
85%

Step 1c Workup protocol.
Step 2 Elimination of the mesylate group.

Reference: Defosseux, M.; Blanchard, N.; Meyer, C.; Cossy, J. *J. Org. Chem.* **2004**, *69*, 4626

c.



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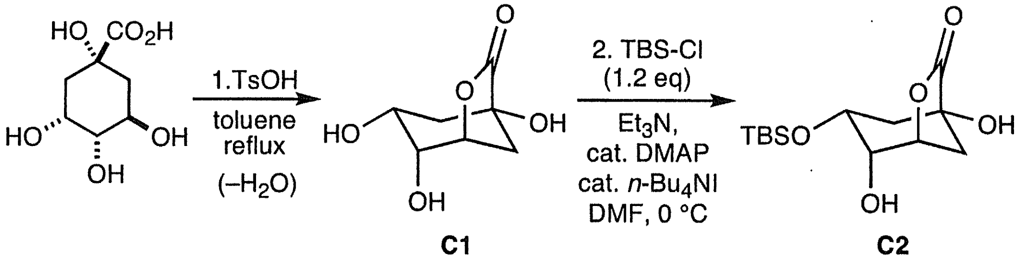


C1

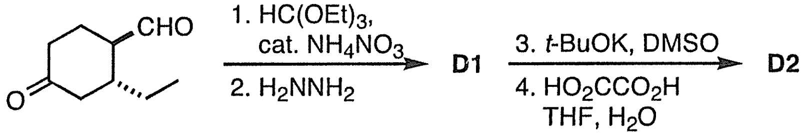
C2
75% overall

Step 1 Lactonization occurs between the carboxylic acid and the –OH that is *cis*.

Step 2 Selective silylation of the 2°-equatorial –OH group (reaction rate: 2°eq > 2°ax > 3°); the ammonium iodide presumably produces the more reactive TBS-I species.

Reference: Sefkow, M.; Kelling, A.; Schilde, U. *Eur. J. Org. Chem.* **2001**, 2735.

d.



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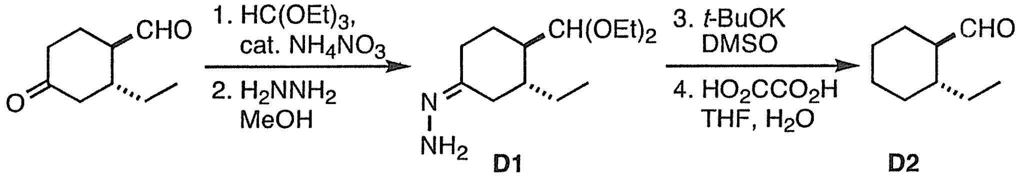
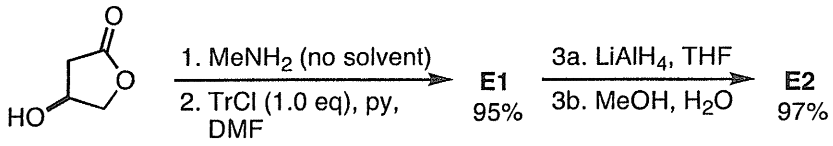


Step 1 Mild conditions for the selective acetalization of the aldehyde.
Step 2 Hydrazone formation.
Step 3 Wolff-Kischner reduction (Huang-Minlong modification).
Step 4 Acetal hydrolysis.

e.



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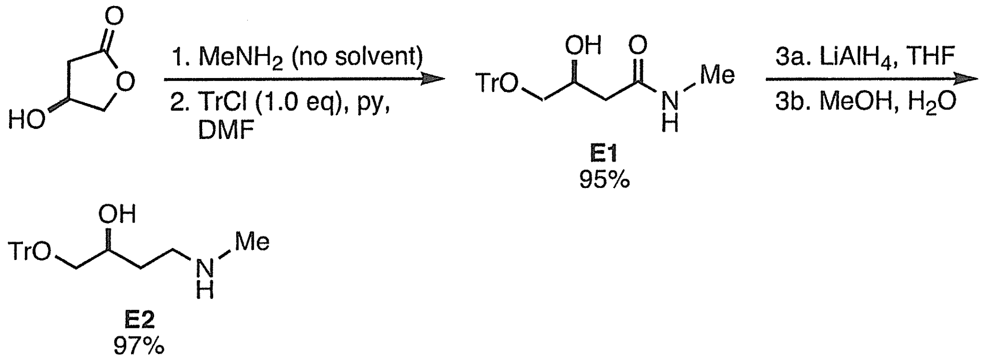
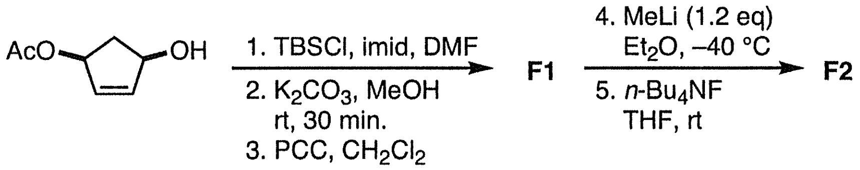


Step 1 Lactone cleavage furnishes the amide.
Step 2 Selective protection of the resultant 1° alcohol.
Step 3b Workup protocol.

Reference: Ella-Menye, J.-R.; Sharma, V.; Wang, G. *J. Org. Chem.* **2005**, *70*, 463.

f.



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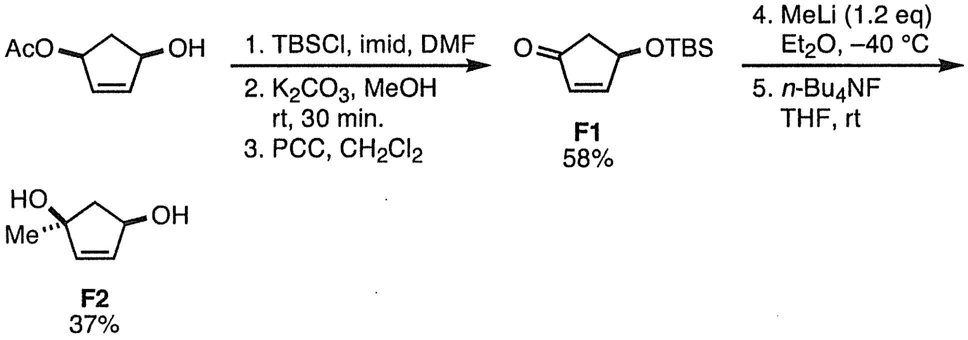
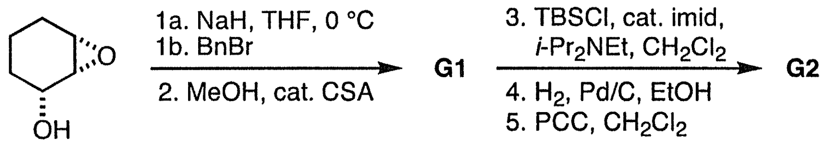


Step 4 1,2-Addition of MeLi occurs from the less hindered face of the 5-membered ring.

Reference: Atanu Roy, A.; Schneller, S. W. *J. Org. Chem.* **2003**, *68*, 9269.

g.



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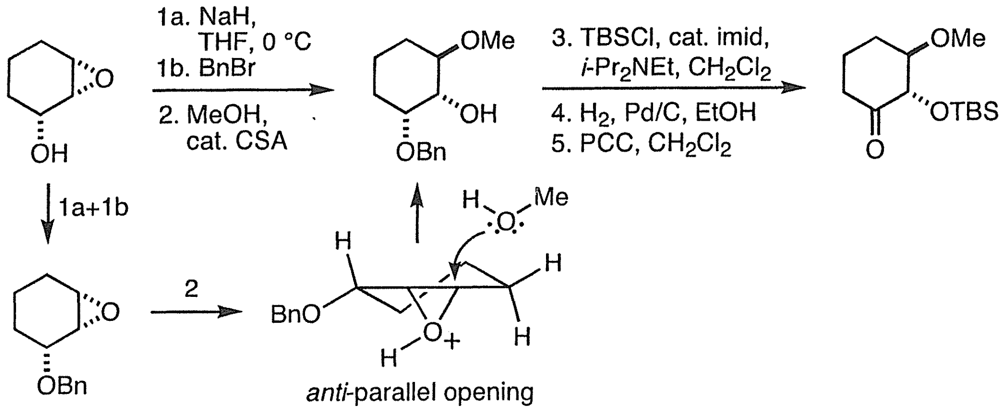
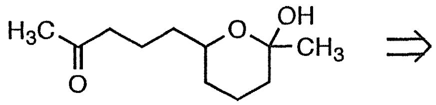
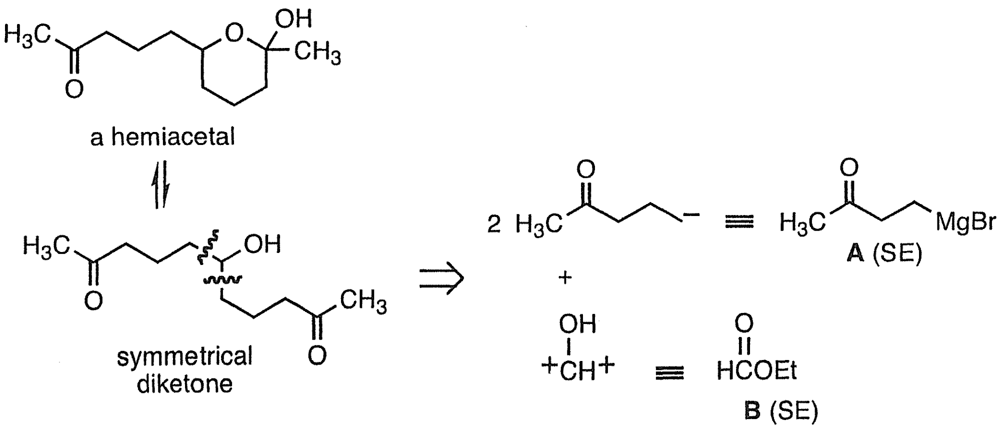


3. **Retrosynthetic analysis.** Outline a retrosynthetic scheme for the following target molecules. Show (1) the *analysis* (including FGI, synthons, synthetic equivalents) and (2) the *synthesis* of each TM. You may only use compounds with five or fewer carbons as starting materials.

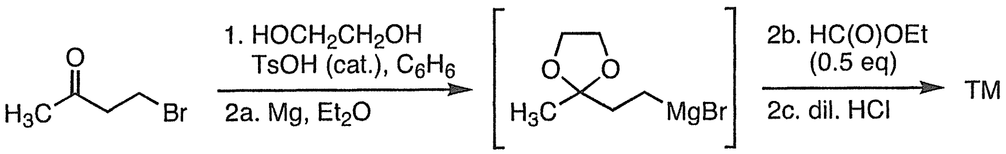
a.



Retrosynthetic analysis:



Synthesis:



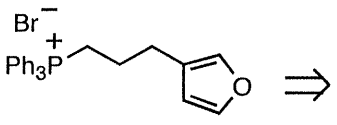
Step 1 Protection of the keto group.

Step 2a Formation of the Grignard reagent (SE **A**).

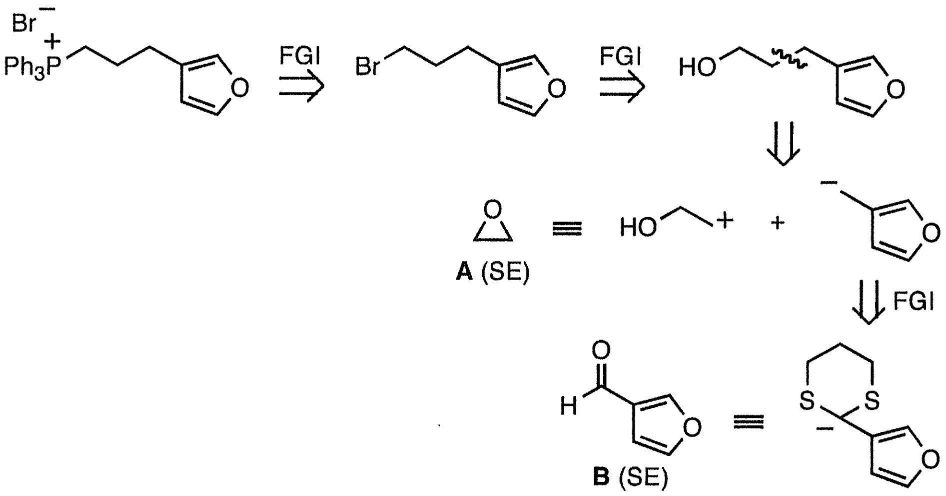
Step 2b Utilization of 0.5 equivalent of ethyl formate HC(O)OEt ensures that the SE **A** and **B** are formed in a 2 : 1 ratio, a prerequisite for the formation of the symmetrical diketone.

Step 2c Dilute HCl deprotects the keto groups and facilitates the formation of the hemiacetal moiety in the TM.

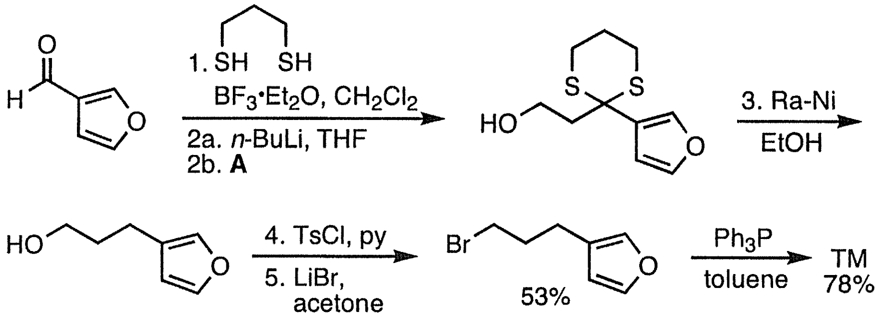
b.



Retrosynthetic analysis:



Synthesis:

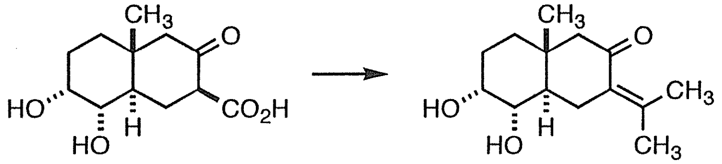


Step 3 THPO–CH_2CH_2–Br was used instead of ethylene oxide as a SE of **A** in the original procedure.

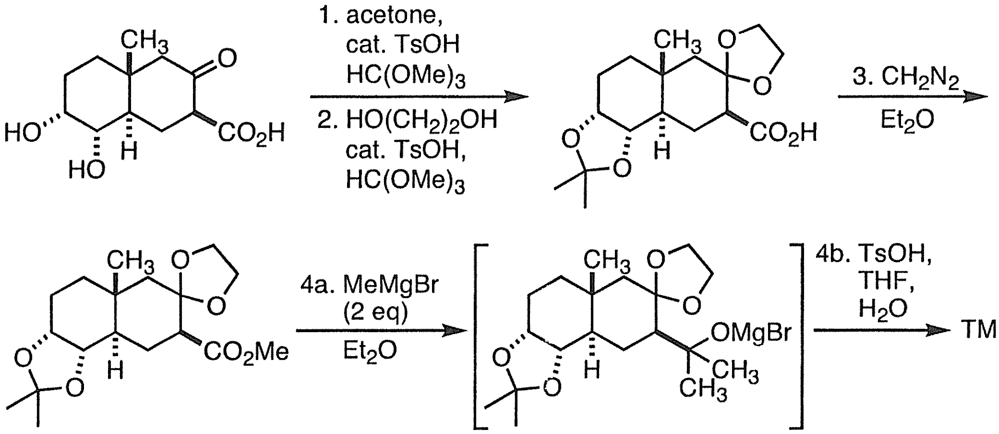
Reference: Magatti, C. V.; Kaminski, J. J.; Rothberg, I. *J. Org. Chem.* **1991**, *56*, 3102.

4. **Synthesis.** Supply the missing reagents required to accomplish each of the following transformations. Be sure to control the relative stereochemistry.

a.



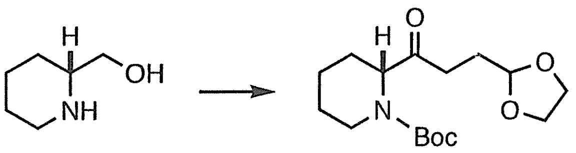
Solution:



Step 3 Fischer esterification (H^+, MeOH) would cleave the acetal protecting groups.

Step 4b Acetal hydrolysis followed by dehydration of the 3° alcohol furnishes the TM.

b.



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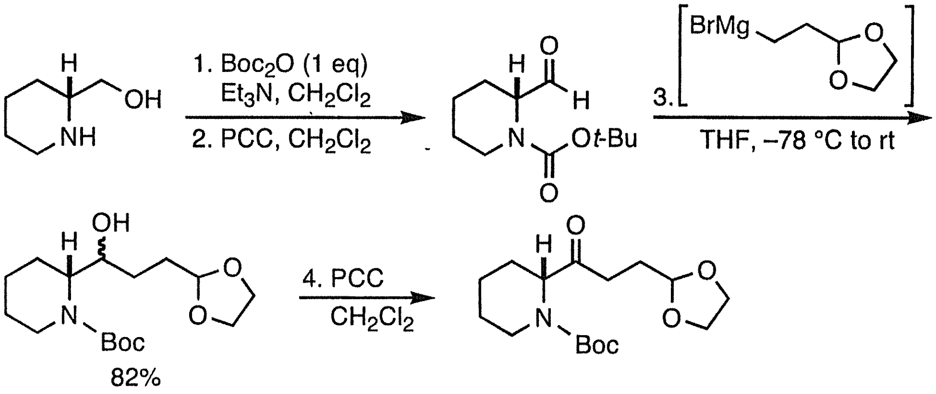
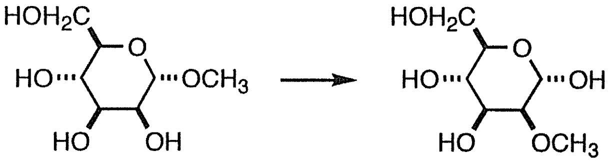


Step 1 *N*-acylation occurs preferentially over *O*-acylation. The amine must be protected to avoid *N*-oxidation in subsequent steps.

Step 4 Dess-Martin oxidation was used in the original procedure.

Reference: Alibs, R.; Ballb, M.; Busqu, F.; de March, P.; Elias, L.; Figueredo, M.; Font, J. *Org. Lett.* **2004**, *6*, 1813.

c.



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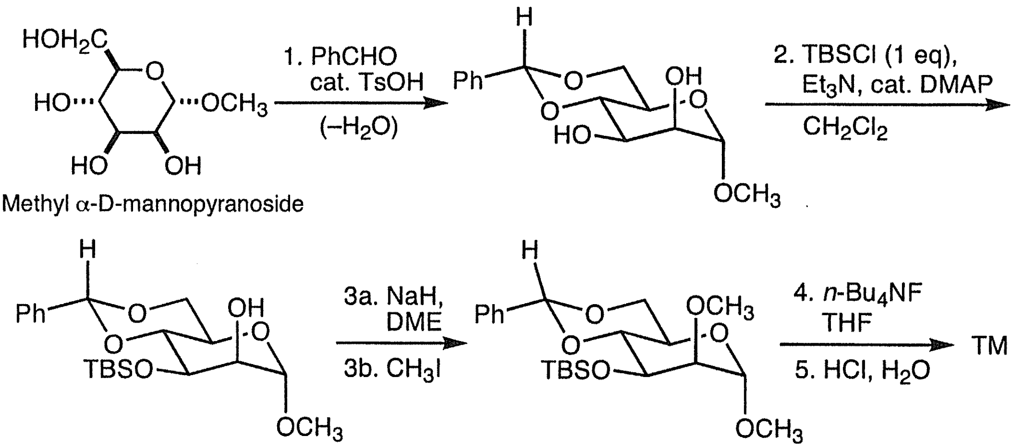
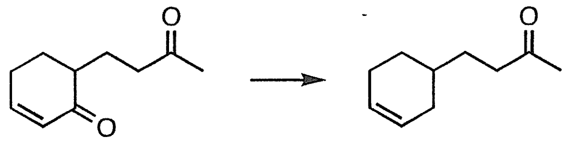


Step 1 Selective formation of a six-membered ring acetal using PhCHO.
Step 2 Selective silylation of the equatorial hydroxyl group.
Step 5 Hydrolysis of *both* the benzylidene acetal and the glycoside.

d.



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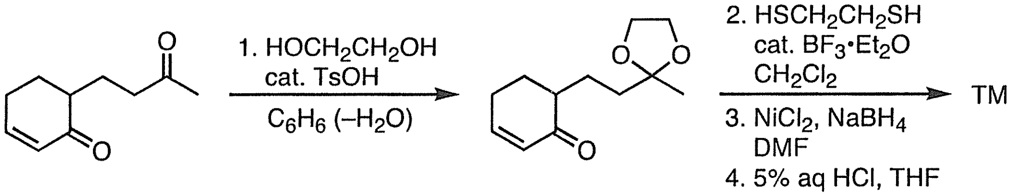
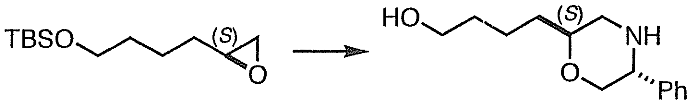


e.



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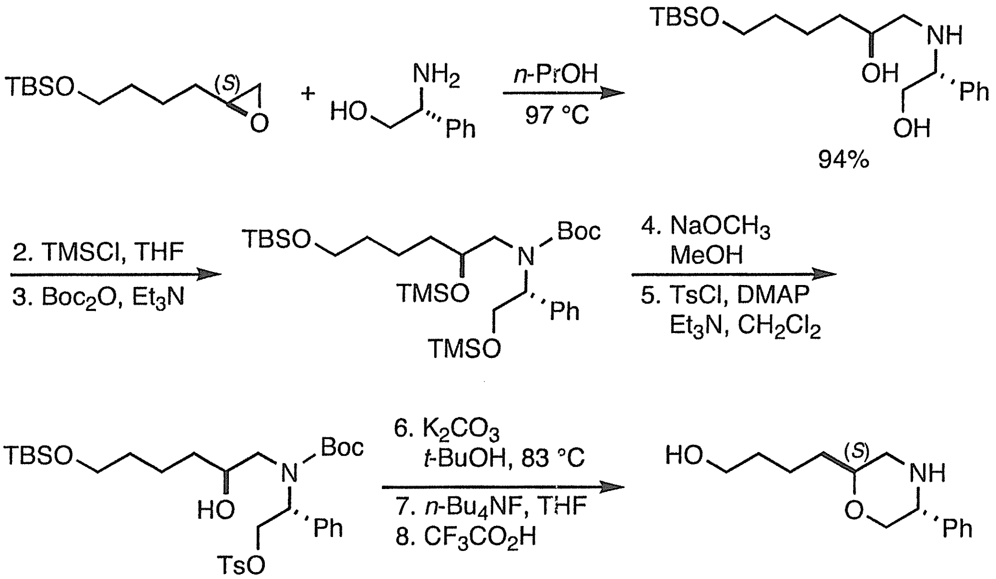
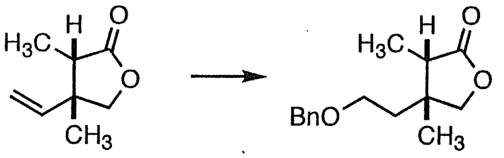


Reference: For a similar synthesis, see Lanman, B. A.; Myers, A. G. *Org. Lett.* **2004**, *6*, 1045.

f.



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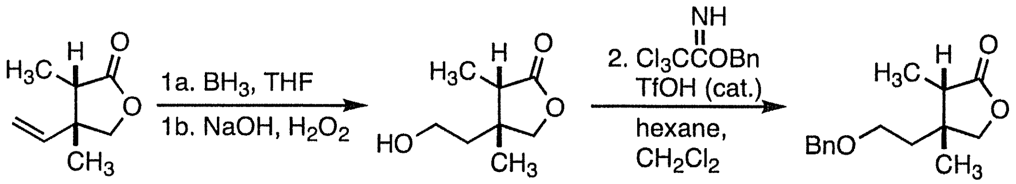
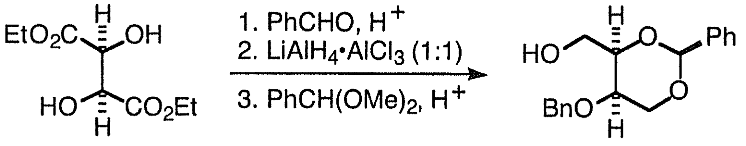
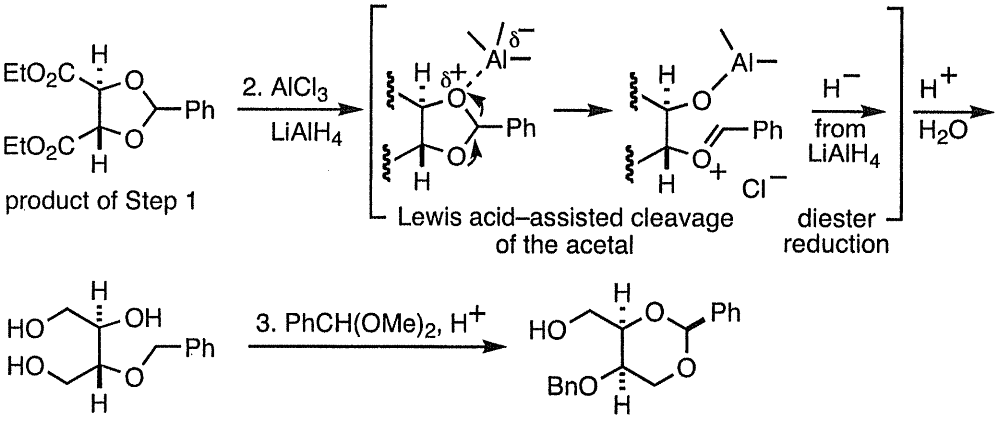


Step 2 The acid-catalyzed benzylation procedure prevents translactonization and/or substrate polymerization.

***5.** Explain the regio- and stereochemical outcome of the following sequence of reactions by showing the structures of the intermediates obtained after each step.



Solution:



Step 2 Reductive cleavage of the acetal and reduction of the ester groups.
Step 3 Selective *trans*-acetalization of the 1,3-diol with benzaldehyde dimethyl acetal.

Reference: Cheol, E. L.; Park, M.; Yun, J. S. *J. Am. Chem. Soc.* **1995**, *117*, 8017.

CHAPTER 4

Functional Group Transformations: Oxidation and Reduction

Overview

Chapter 4 centers on two key transformations in organic synthesis: (1) oxidation of alcohols and of unsaturated hydrocarbons (i.e., alkenes and alkynes) to carbonyl compounds; (2) reduction of various carbonyl compounds to alcohols.

Problem 1 emphasizes reagents for oxidation and reduction. Problems 2–4, stress the selectivity of oxidations and reductions in reaction sequences. Syntheses of Problem 5 TMs require choosing specific reagents to achieve chemo-, stereo-, or enantioselective oxidations or reductions.

Key Concepts

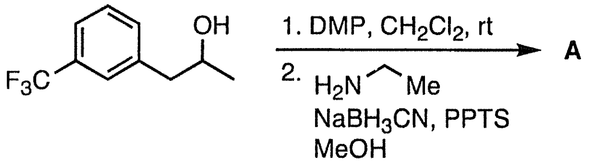
- Alcohol oxidations
    - Jones, Swern, Dess-Martin
- Chemoselective oxidations of allylic or benzylic alcohols
- Oxidation of terminal alkynes
- Allylic oxidation of alkenes
- Reduction of carbonyl compounds
    - Nucleophilic reducing agents
    - Electrophilic reducing agents
- Diastereoselective reduction of cyclic ketones
    - Use of conformational analysis for the prediction of hydride approach (axial vs equatorial)
- Diastereoselective reduction of acyclic ketones
    - Cram's rule
    - Felkin-Anh model
- Mitsunobu reaction (inversion of 2° alcohol stereochemistry)
- Hydroxyl-directed reduction of β-hydroxy ketones
- Enantioselective reductions

SOLUTIONS TO CHAPTER 4 PROBLEMS

The more challenging problems are identified by an asterisk (*).

1. **Reagents.** Give the structure of the major products (**A-H**) expected from the following reactions. Be sure to indicate product stereochemistries. Assume that standard aqueous workup conditions are used for product isolation.

a.



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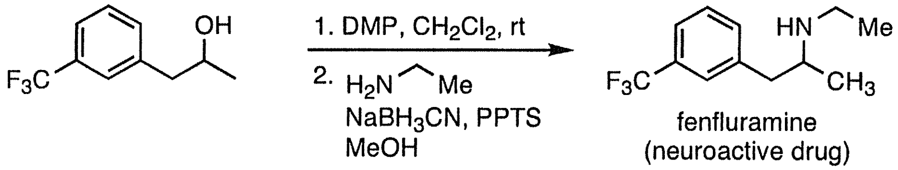
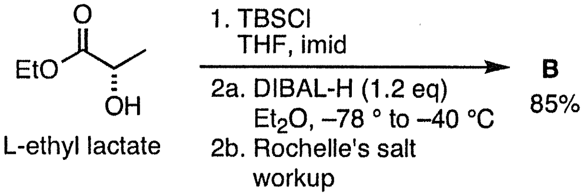


Step 1 Dess-Martin periodinane oxidation.
Step 2 Reductive amination.

b.



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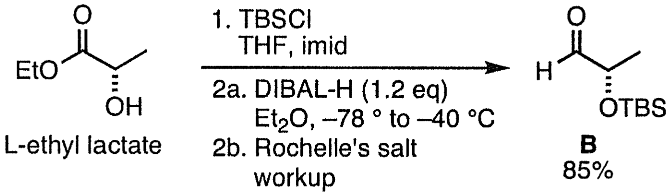
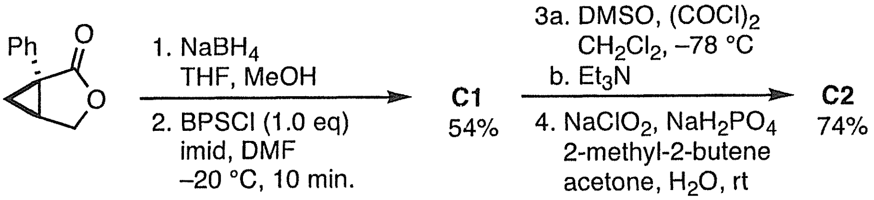


Step 2a Utilization of 1 eq of diisobutylaluminum hydride (DIBAL-H) ensures reduction of the ester group stops to the corresponding aldehyde.

Step 2b Workup protocol (Na-K tartrate).

Reference: Defosseux, M.; Blanchard, N.; Meyer, C.; Cossy, J. *J. Org. Chem.* **2004**, *69*, 4626.

c.



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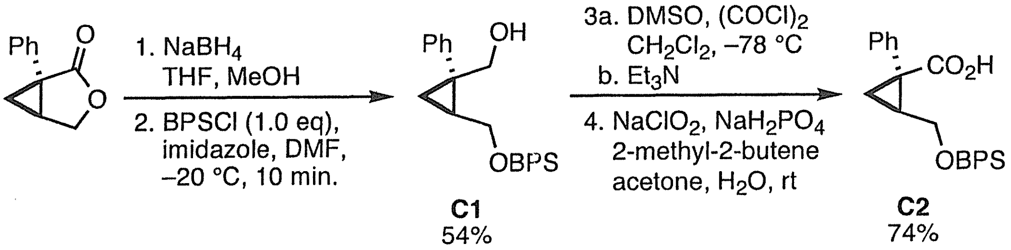


Step 1 Note: Sodium borohydride ($NaBH_4$) can reduce lactones.

Step 2 Selective silylation of the least hindered 1° alcohol.

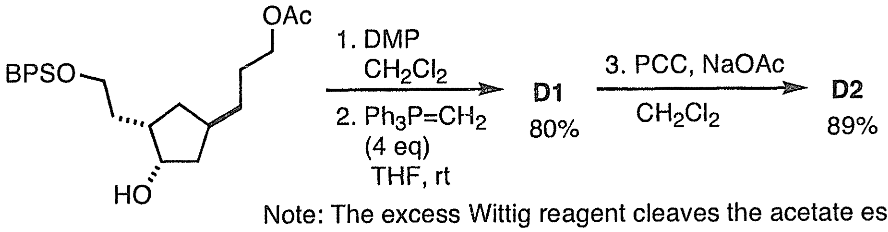
Step 3 Swern oxidation of the 1° alcohol to the aldehyde.

Step 4 Oxidation of the aldehyde to the corresponding carboxylic acid.

(Note: Steps 3 + 4 represent a mild, *stepwise* oxidation of the 1° alcohol to a carboxylic acid.)

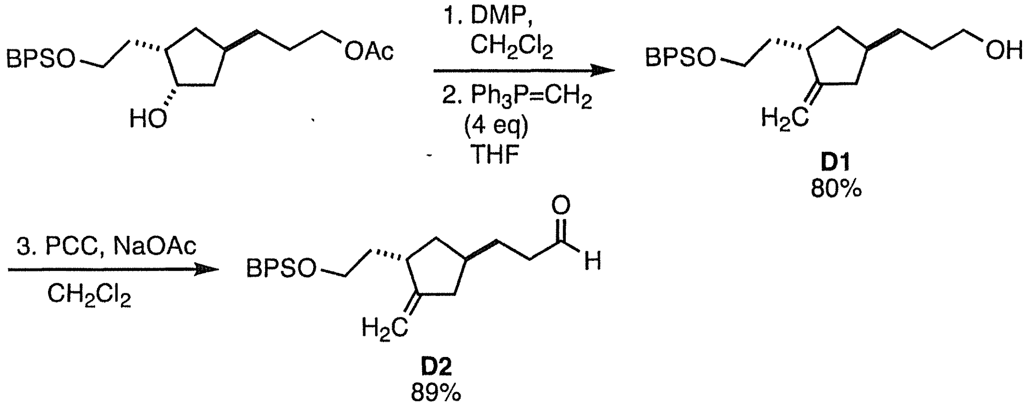
Reference: Yamaguchi, K.; Kazuta, Y.; Abe, H.; Matsuda, A.; Shuto, S. *J. Org. Chem.* **2003**, *68*, 9255.

d.



Note: The excess Wittig reagent cleaves the acetate ester.

Solution:



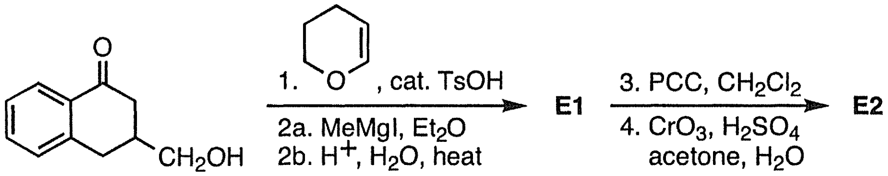
D1 80%

D2 89%

Step 1 Dess-Martin oxidation.

Reference: Jiang, L.; Martinelli, J. R.; Burke, S. D. *J. Org. Chem.* **2003**, *68*, 1150.

e.



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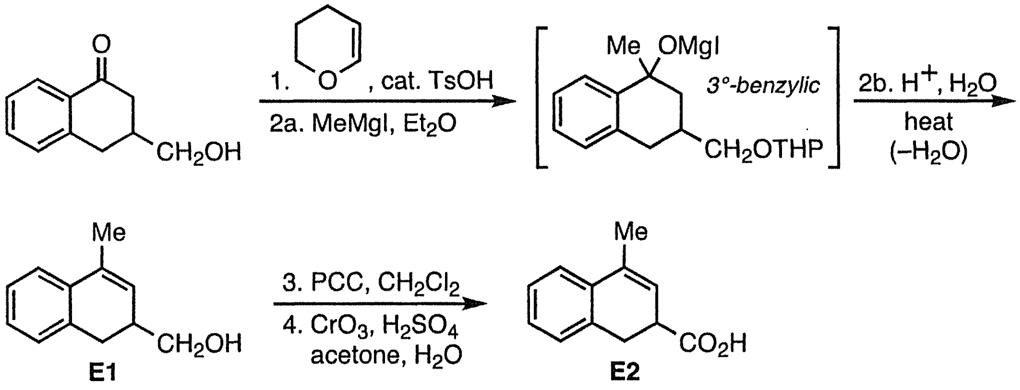
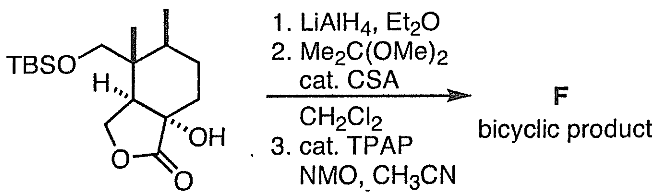


Step 3 PCC oxidation of the 1° alcohol to the aldehyde.

Step 4 Jones oxidation of the aldehyde to the corresponding carboxylic acid.

(Note: Steps 3 + 4 represent another two step oxidation of a 1° alcohol to the corresponding carboxylic acid: see Problem 1c.)

f.



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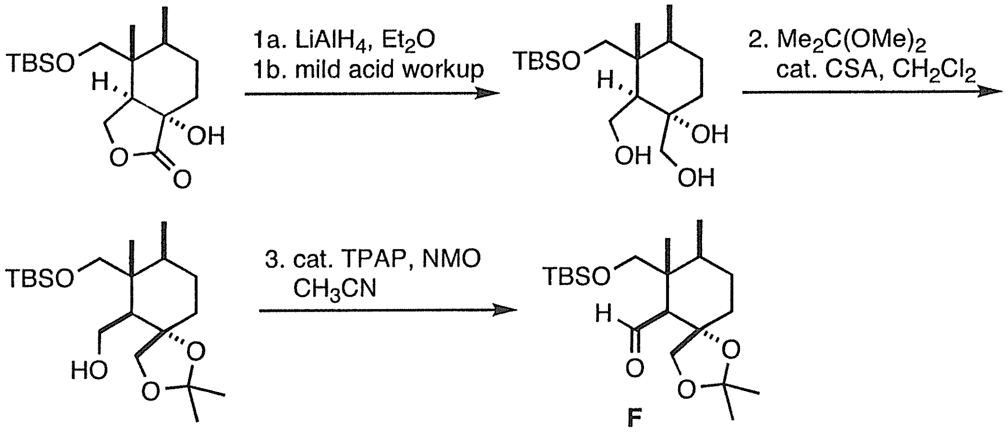
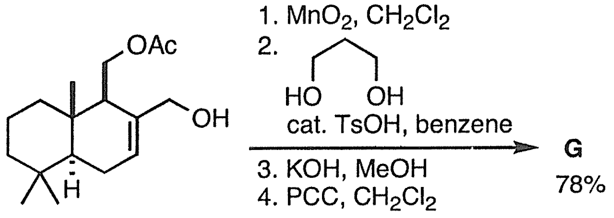


Step 2 Acetonide selectively produces the five-membered ring dioxolane.
Step 3 Oxidation of the 1° alcohol to the corresponding aldehyde.

g.



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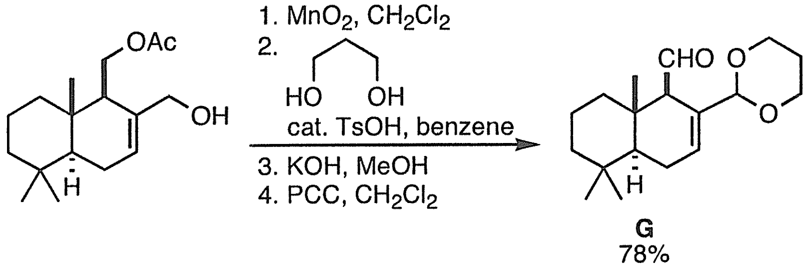
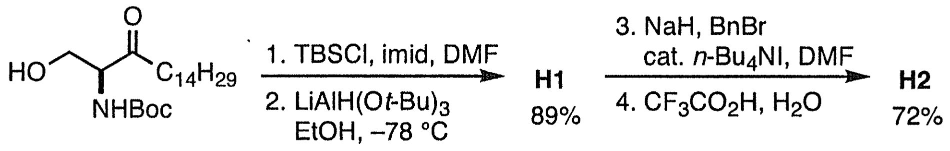


Step 1 Oxidation of the allylic alcohol to the corresponding aldehyde.
Step 2 Protection of the resultant aldehyde as an acetal.

Reference: Tanis, S. P.; Nakanishi, K. *J. Am. Chem. Soc.* **1979**, *101*, 4398.

***h.**



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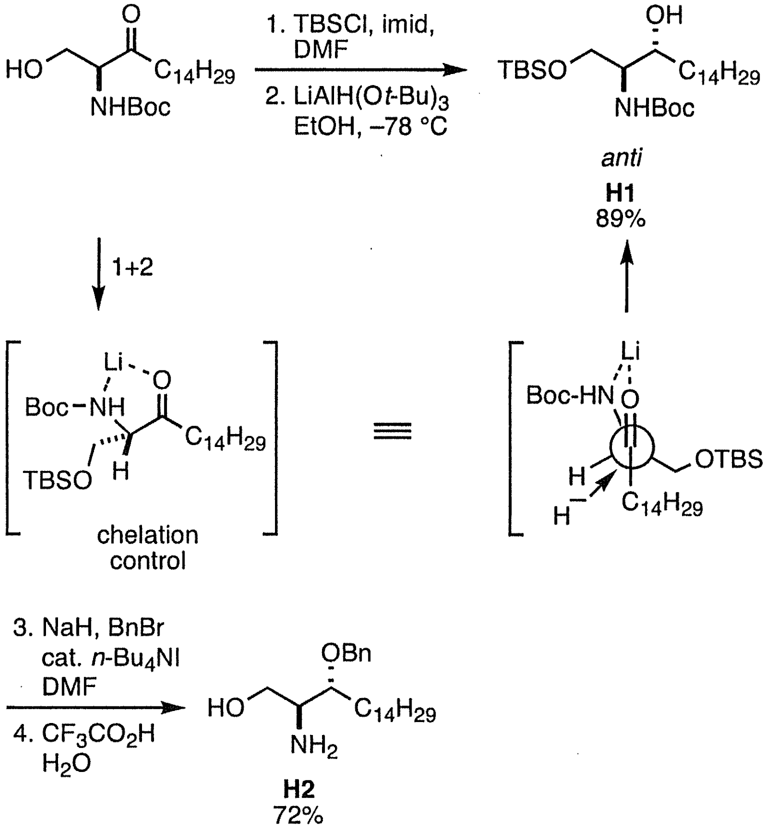


Step 2 Chelation-controlled reduction of the ketone produces the *anti*-alcohol diastereoselectively.

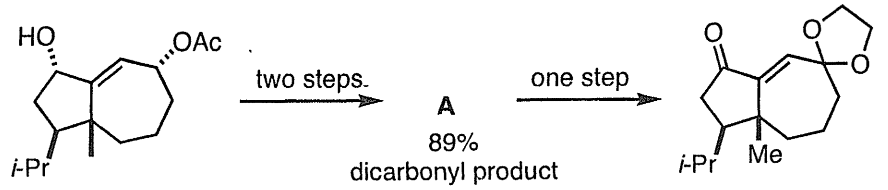
Step 3 The ammonium iodide salt presumably converts the BnBr to the more reactive alkylating agent (BnI).

Step 4 A basic workup is used to obtain the amino-alcohol product.

Reference: So, R. C.; Ndonye, R.; Izmirian, D. P.; Richardson, S. K.; Guerrara, R. L.; Howell, A. R. *J. Org. Chem.* **2004**, *69*, 3233.

2. **Selectivity.** Show the product(s) obtained or the appropriate reagent(s) to be used for the following transformations.

a.



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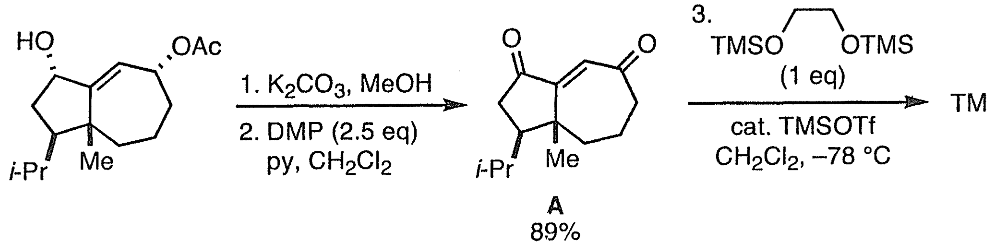
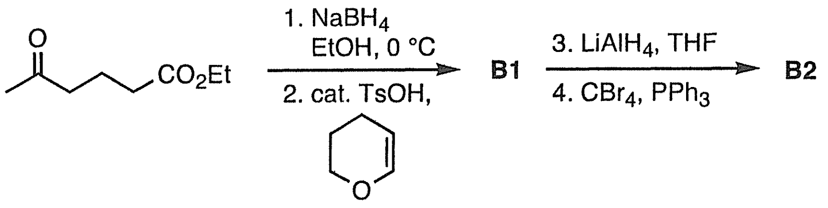


Reference: Shi, B.; Hawryluk, N. A.; Snider, B. B. *J. Org. Chem.* **2003**, *68*, 1030.

b.



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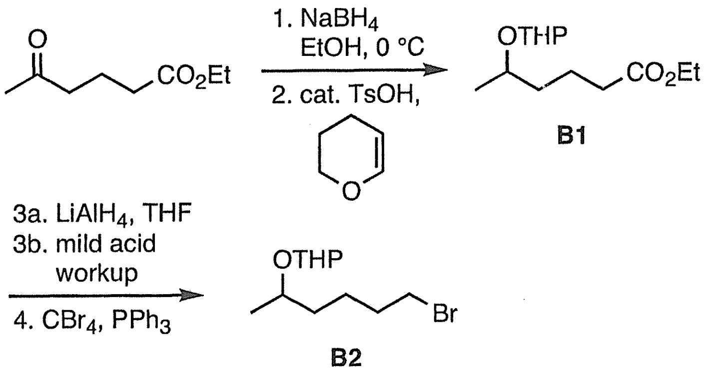
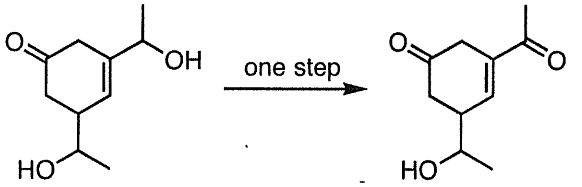


c.



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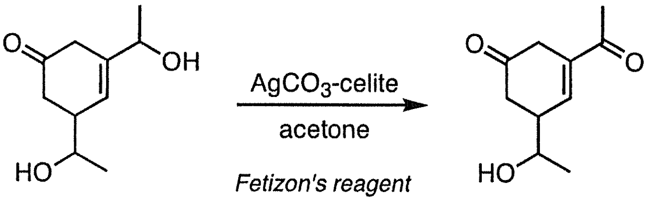
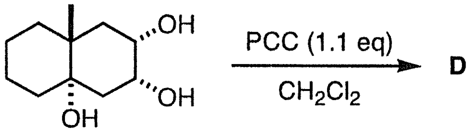


Alternatively, MnO_2 or $Ba[MnO_4]_2$ may be used as selective reagents for the oxidation of allylic or benzylic alcohols.

d.



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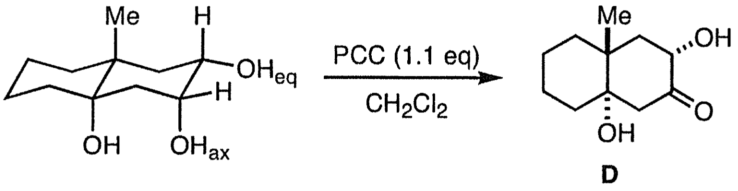
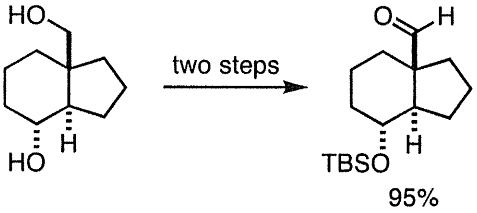


The 2° axial alcohol is oxidized preferentially.

e.



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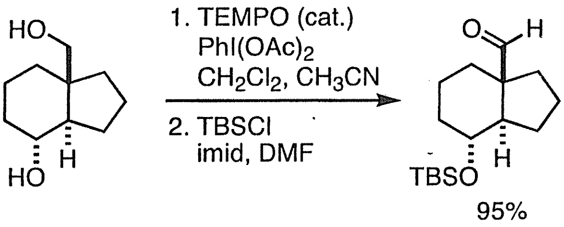
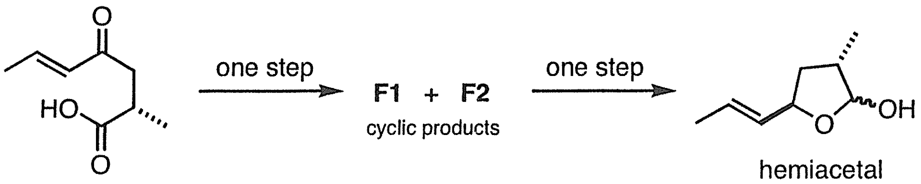


Step 1. Chemoselective oxidation of the primary alcohol; (diacetoxyiodo)benzene (DIB) is the stoichiometric co-oxidant.

Reference: Momán, E.; Nicoletti, D.; Mouriño, A. *J. Org. Chem.* **2004**, *69*, 4615.

***f.**



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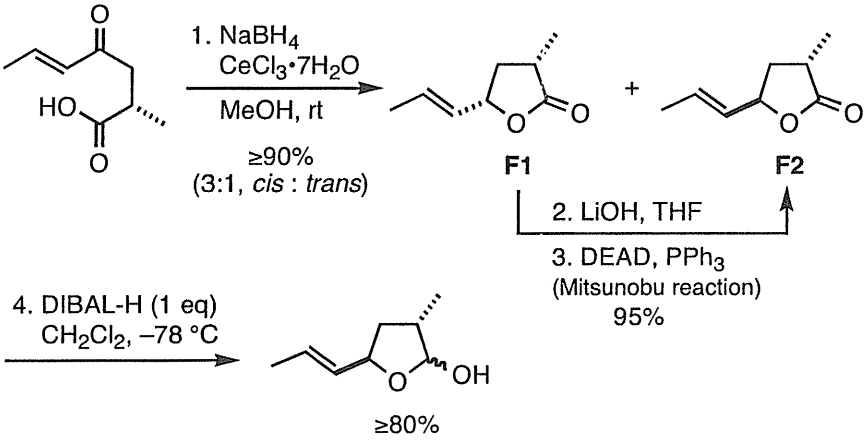
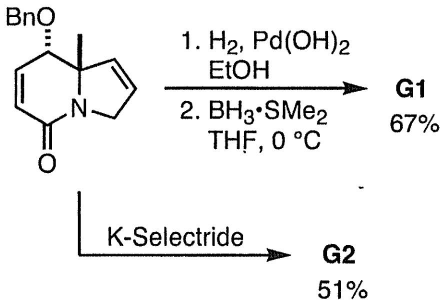


Step1 1,2-reduction of the enone followed by lactonization.
Steps 2 + 3 Intramolecular Mitsunobu reaction.
Step 4 Controlled DIBAL-H reduction (1 eq) to the lactol.

Reference: Kang, S. H.; Lee, H. S. *Tetrahedron Lett.* **1995**, *36*, 6713.

***g.**



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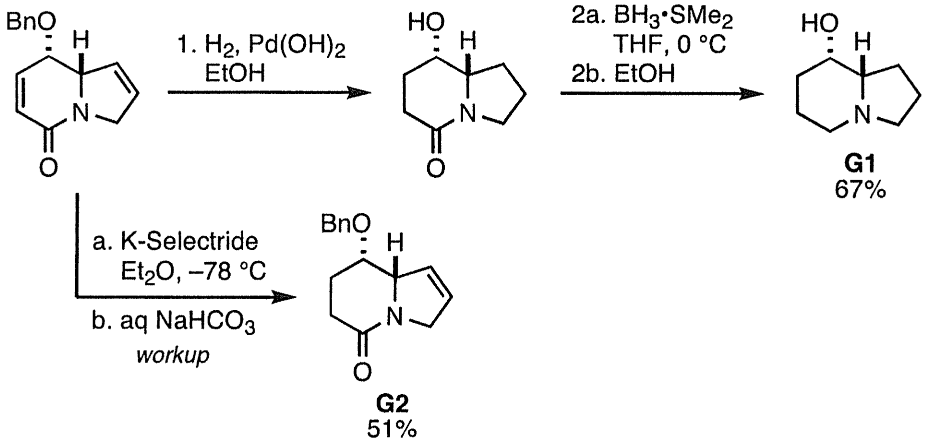
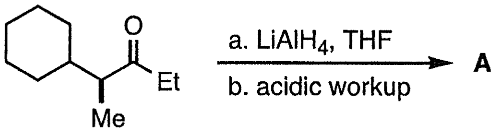


Step 2b Workup protocol where the reaction is quenched with EtOH and the resultant $B(OEt)_3$ is evaporated.

Reference: Lee, H. K.; Chun, J. S.; Chwang, S. P. *J. Org. Chem.* **2003**, *68*, 2471.

3. **Stereochemistry.** Predict the stereochemistry of the major products formed (**A–H**) in the following reactions. Explain your choices.

a.



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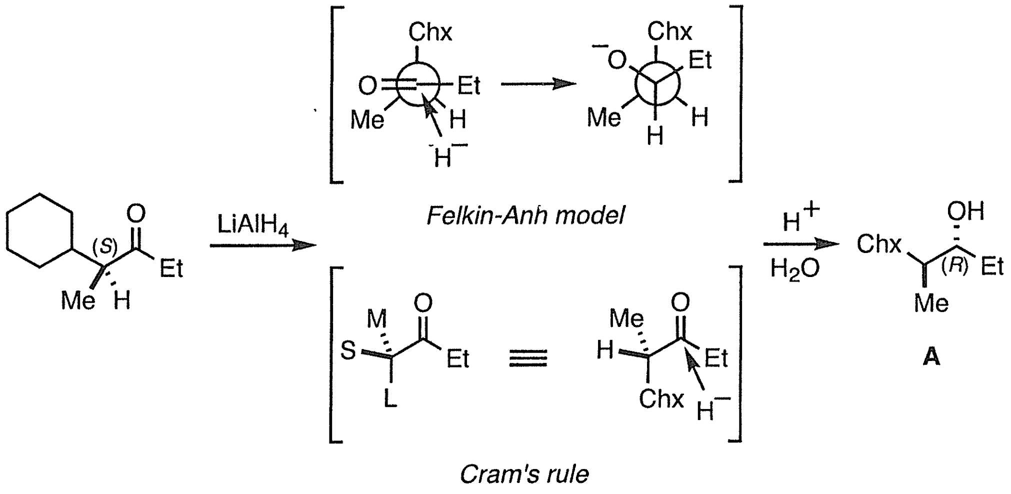
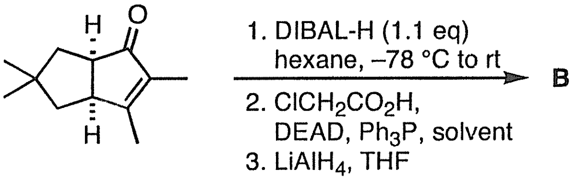


b.



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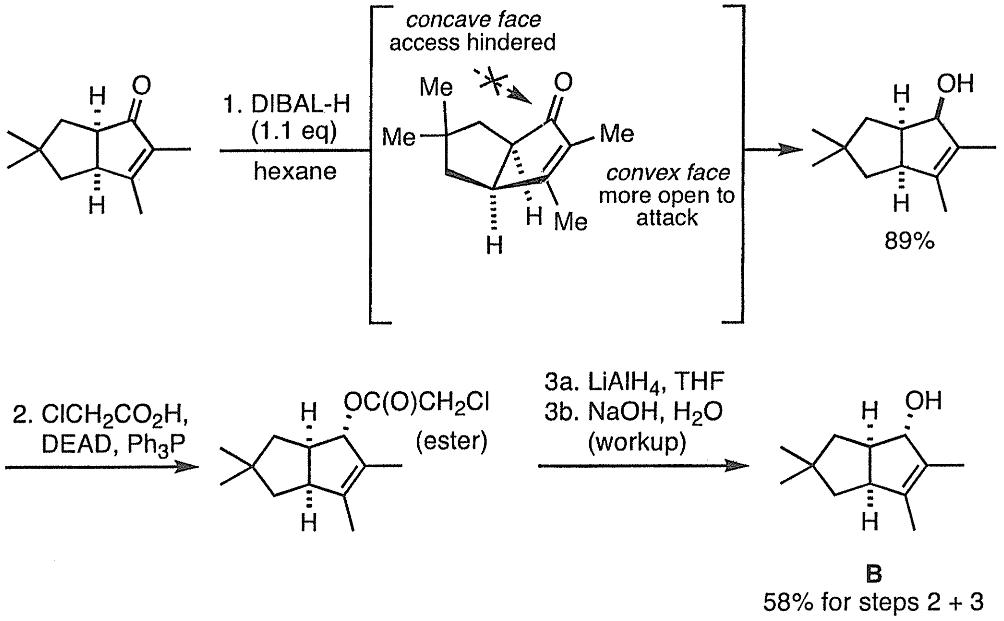
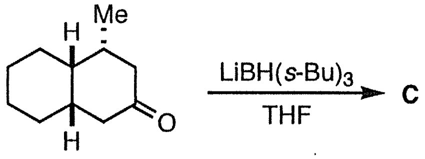


Step 1 1,2-Addition occurs from the least hindered convex face.

Step 2 Several procedures for the Mitsunobu reaction were tried; the best results were achieved using the more acidic $ClCH_2CO_2H$.

Reference: Clive, D. L. J.; Magnuson, S. R.; Manning, H. W.; Mayhew, D. L. *J. Org. Chem.* **1996**, *61*, 2095.

c.



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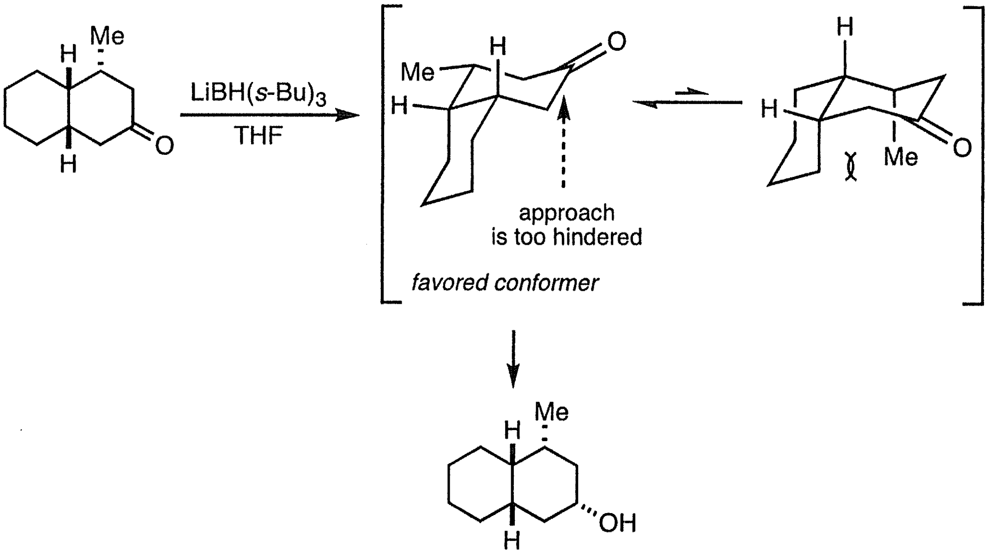
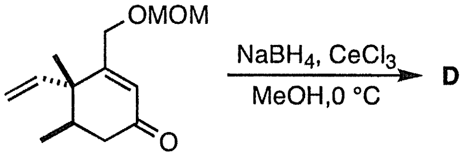


C

The large steric requirement of L-Selectride generally favors reduction of cyclohexanones to form axial alcohols. However, in this *cis*-decalone example, the formation of the axial alcohol is hindered by the adjacent ring.

d.



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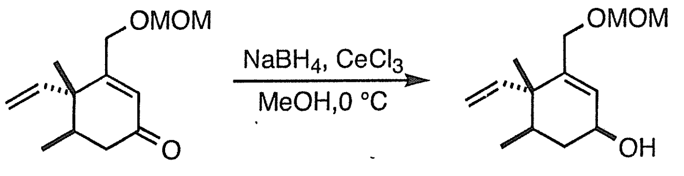
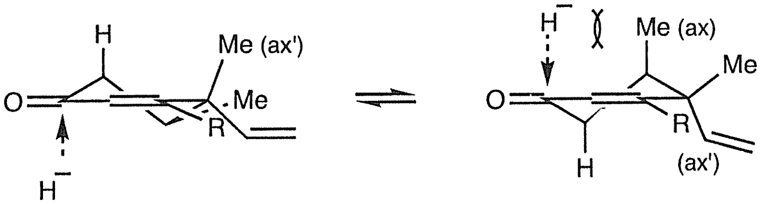


D (≥81%)

consider the axial (antiparallel) addition of hydride (R = CH_2OMOM):



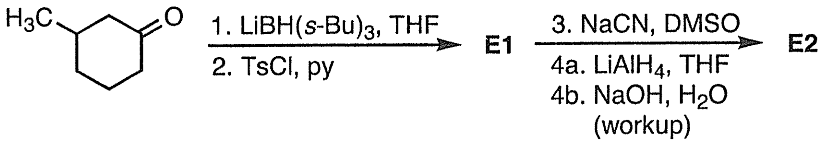
favored approach

disfavored approach

Note: Luche reagent ($NaBH_4$, $CeCl_3$) favors 1,2-additions.

Reference: Mohr, P. J.; Halcomb, R. L. *J. Am. Chem. Soc.* **2003**, *125*, 1712.

e.



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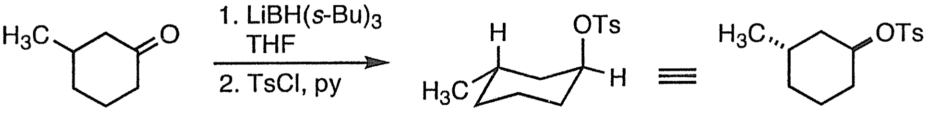
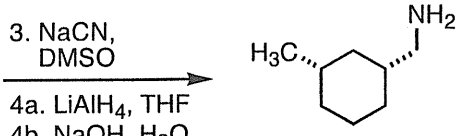


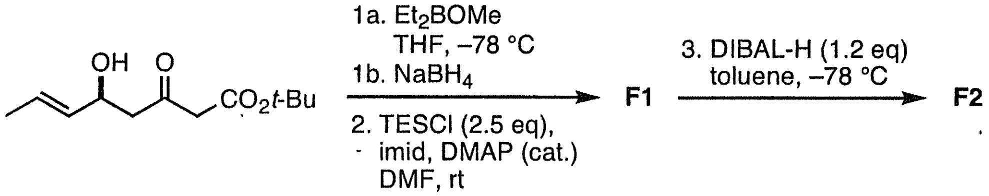
E1



E2 (*cis*)

Step 1 Equatorial delivery of hydride from L-Selectride.
Step 3 Tosylate displacement occurs with an inversion of stereochemistry.
Step 4 The amine (free base) is isolated after a basic workup.

***f.**



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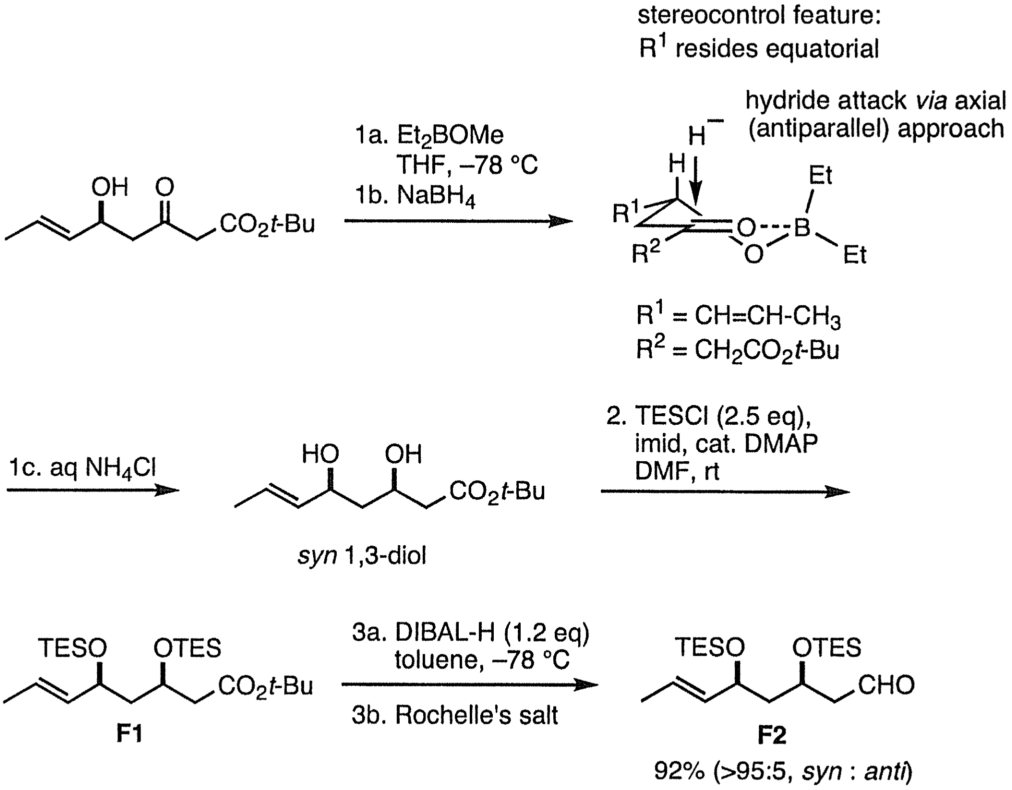
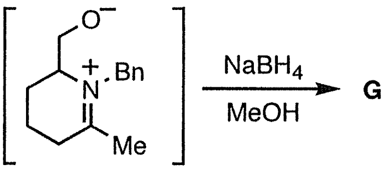


Step 1c Workup protocol.
Step 3b Workup protocol (Na-K tartrate).

Reference: Fettes, A.; Carreira, E. M. *J. Org. Chem.* **2003**, *68*, 9274.

***g.**



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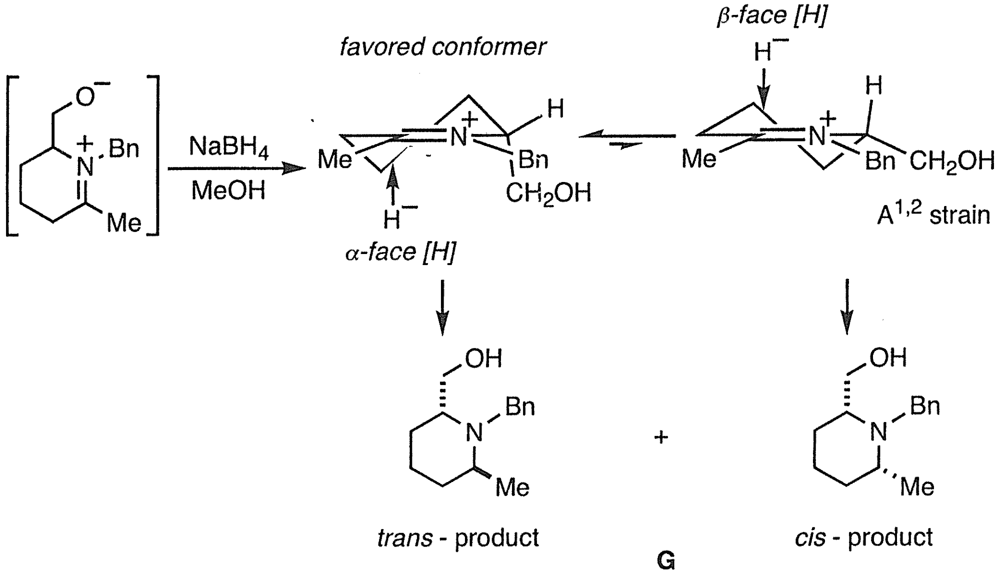
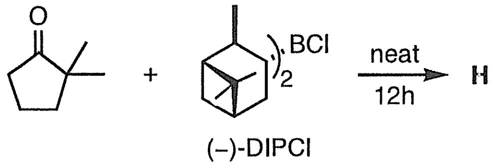


G
93%
92:8 *trans* : *cis*

Reduction of the iminium ion proceeds via perpendicular hydride attack (antiparallel) *via* a chair-like TS minimizing $A^{1,2}$ strain.

Reference: Hofman, S.; De Baecke, G.; Benoit, K.; De Clerq, P. J. *Synthesis* **1998**, 479.

***h.**



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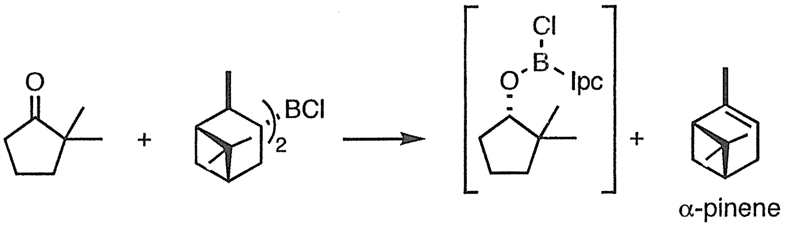
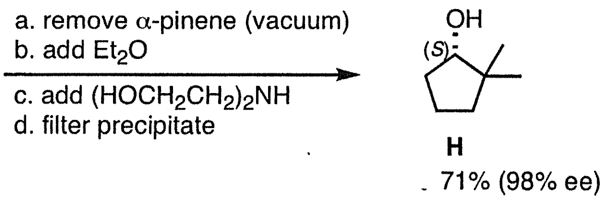
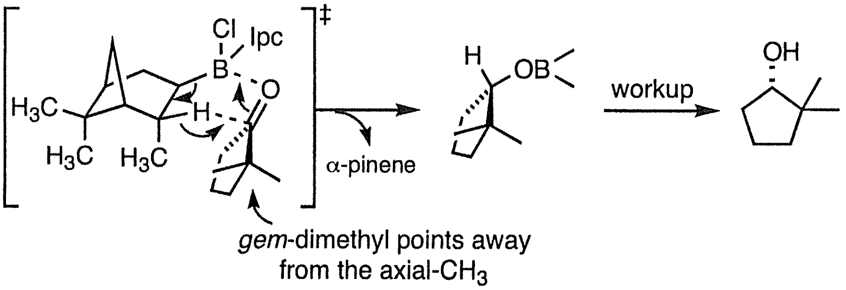


Workup procedure:



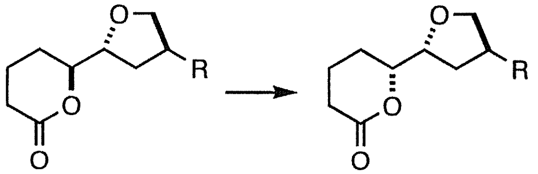
Step a	α-Pinene is the by-product formed in the reduction.
Step c	Diethanolamine is added to sequester boron from the boron intermediates.
Step d	Filtration removes the insoluble diethanolamine•boron complex.

The stereochemical outcome may be explained by considering the following transition state:



Reference: Brown, H. C.; Chandrasekharan, J.; Ramachandran, P. V. *J. Am. Chem. Soc.* **1988,** *110,* 1539.

***i.** Propose a method to accomplish the following stereochemical inversion.



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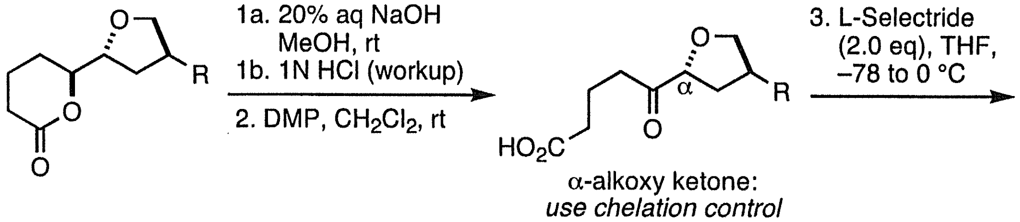
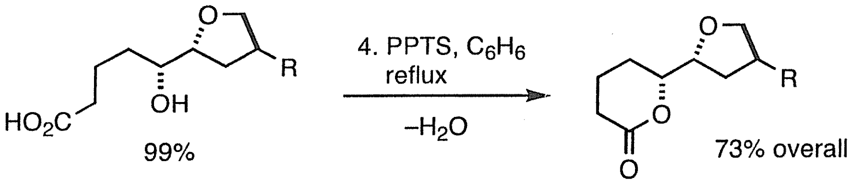


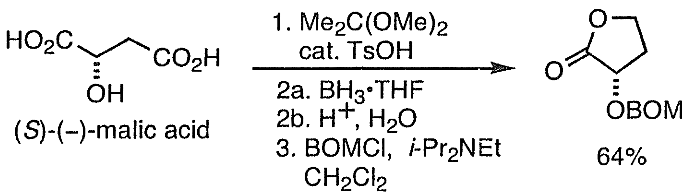


Step 3 2.0 equivalents of L-Selectride are required since the carboxylic acid is deprotonated on addition of the hydride reagent.

Reference: Yoshimitsu, T.; Makino, T.; Nagaoka, H. *J. Org. Chem.* **2004**, *69*, 1993.

4. **Reactivity.** Explain the regioselectivity and stereochemistry observed in the transformations below.

a.



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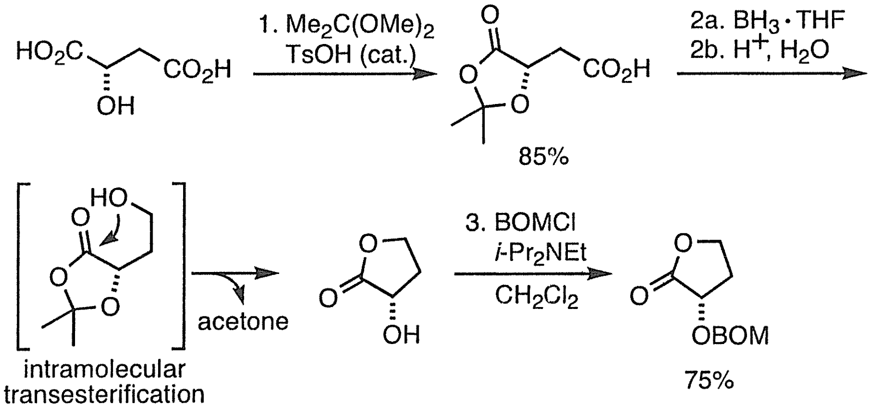
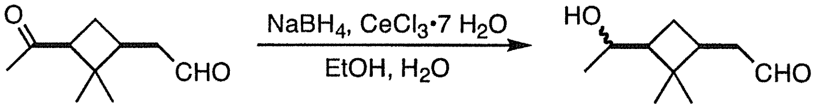


Step 1 Acetonide formation occurs selectively to give the five-membered ring dioxolane.

Step 2 Chemoselective reduction of COOH.

Reference: Collum, D. B.; McDonald, J. H.; Still, W. C. *J. Am. Chem. Soc.* **1980**, *102*, 2118.

b.



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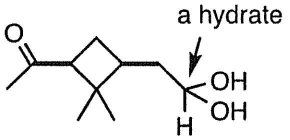
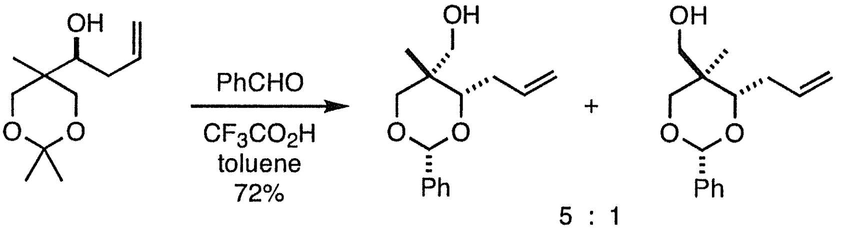


CeCl$_3$ promotes the formation of the hydrate; hence, only the keto group is available for reduction.

Reference: Luche, J. –L.; Gemal, A. L. *J. Am. Chem. Soc.* **1979**, *101*, 5848.

***c.**



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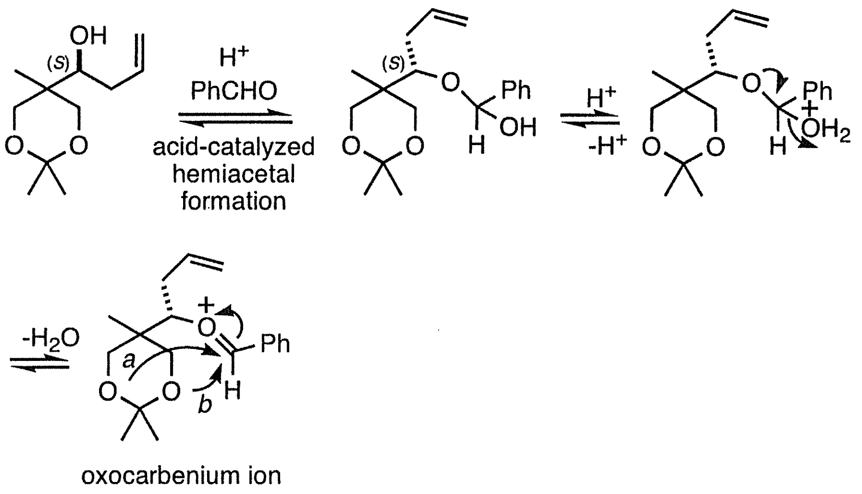
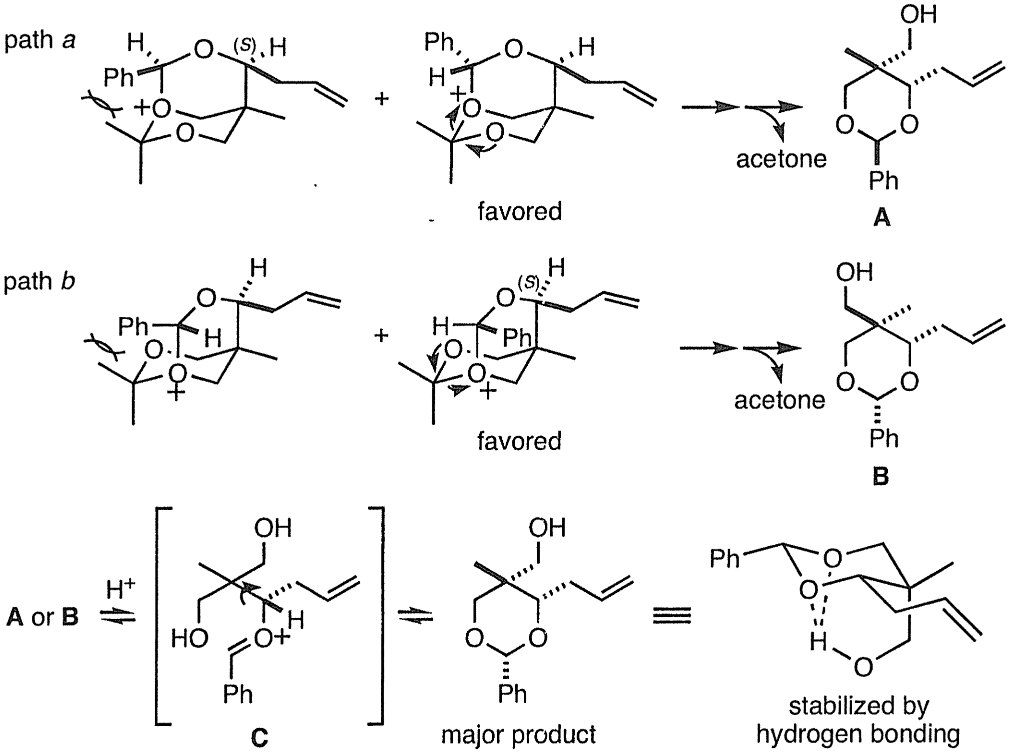
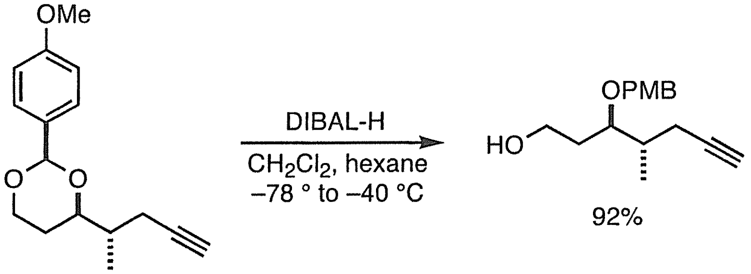


The initially formed oxocarbenium ion intermediate may be intercepted by the acetonide oxygens to form oxonium ion species (depicted below). Acetonide rupture with eventual loss of acetone yields benzylidene acetals (e.g., **A** and **B**), which equilibrate via **C** to afford the axial hydroxymethyl product. Alternatively, in the presence of the water formed, the acetonide may hydrolyze to provide a more direct route to **C**.



Reference: Kang, S. H.; Kang, S. Y.; Kim, C. M.; Choi, H.; Jun, H.-Y.; Lee, B. M.; Park, C. M.; Jeong, J. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 4779.

***d.**



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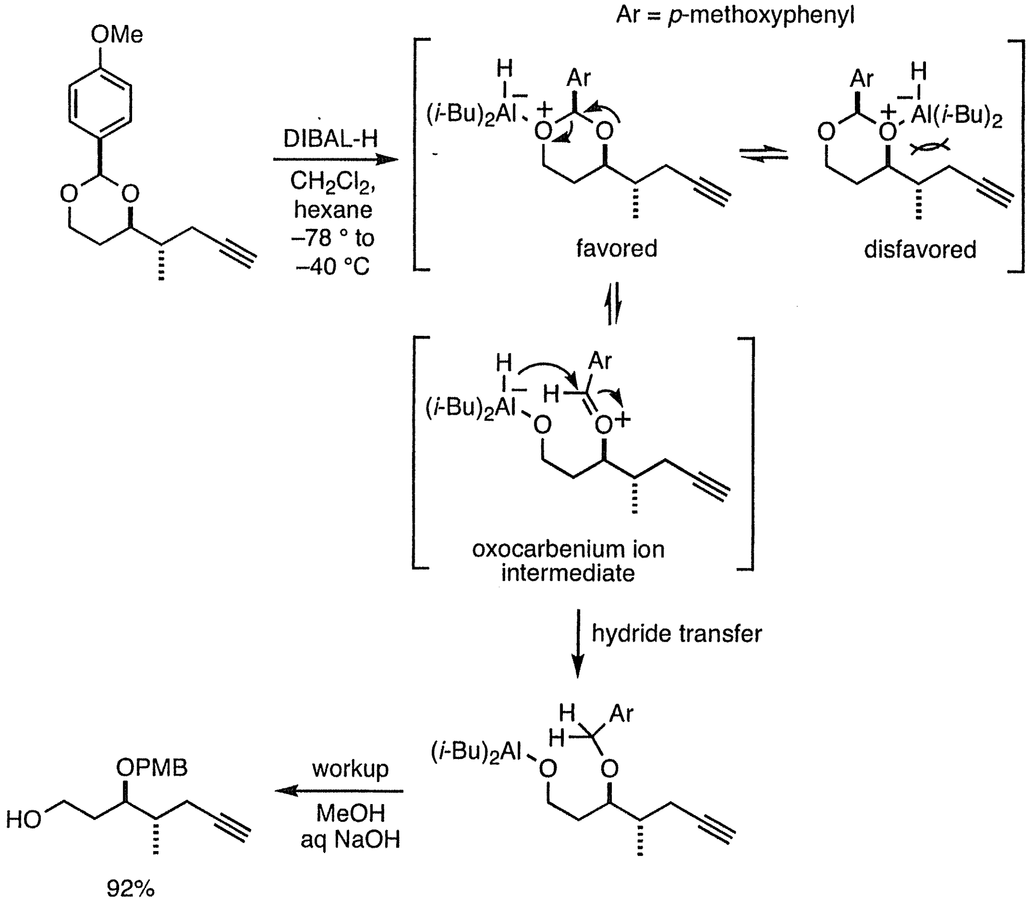
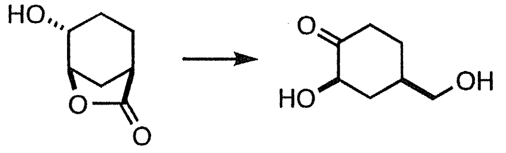


Reference: Holloway, G. A.; Hugel, H. M.; Rizzacasa, M. A. *J. Org. Chem.* **2003**, *68*, 2200.

5. **Synthesis.** Supply the missing reagents required to accomplish each of the following syntheses. Be sure to control the relative stereochemistry.

a.



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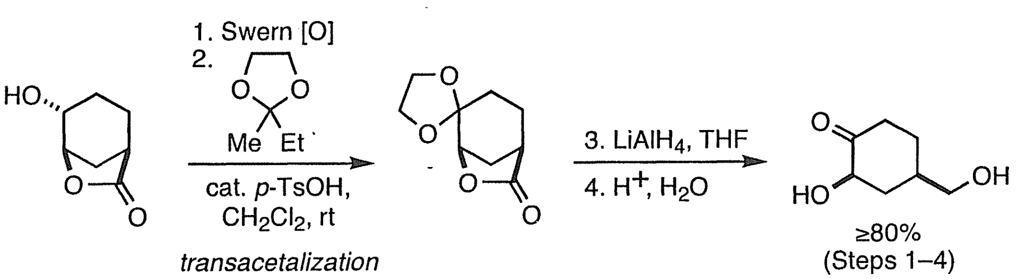
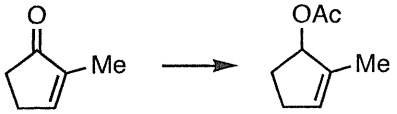


Reference: Su, Z.; Paquette, L. A. *J. Org. Chem.* **1995**, *60*, 764.

b.



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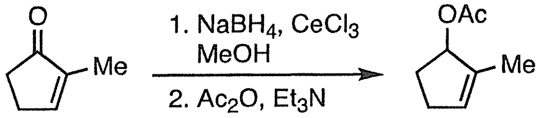
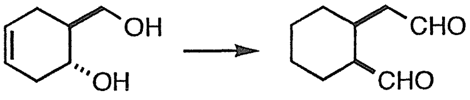


Reference: Curran, D. P.; Rakiewicz, D. M. *J. Am. Chem. Soc.* **1985**, *107*, 1448.

c.



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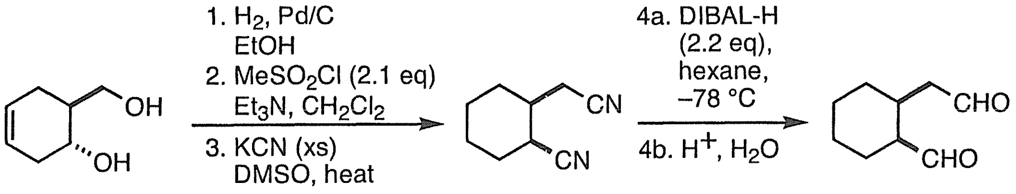
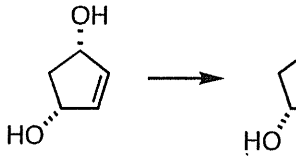


Step 3 Mesylate displacement occurs with inversion of stereochemistry.
Step 4 Acidic workup is required to hydrolize the intermediate imine that is formed on nitrile reduction.

Reference: McDermott, T. S.; Mortlock, A. A.; Heathcock, C. H. *J. Org. Chem.* **1996**, *61*, 700.

d.



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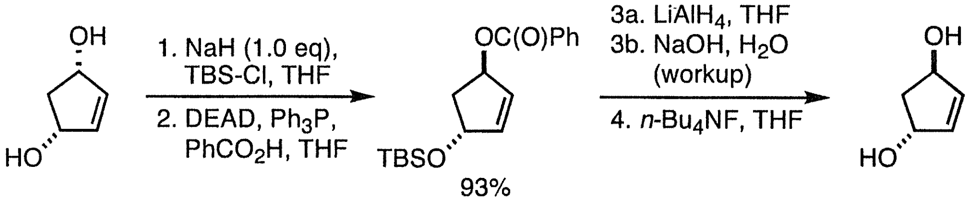
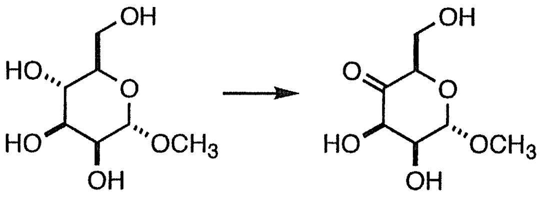


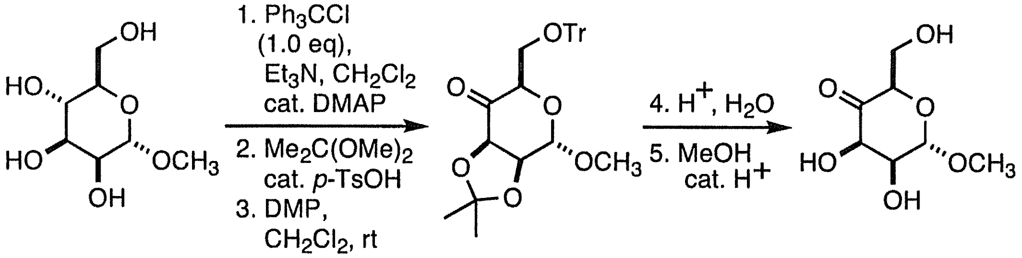
Step 1 NaH treatment results in mono-alkoxide formation, which is critical to minimize formation of a bis-silyl ether. In the original procedure, a 96% yield is reported for the formation of the mono-silyl ether.

Reference: Clive, D. L. J.; Magnuson, S. R.; Manning, H. W.; Mayhew, D. L. *J. Org. Chem.* **1996**, *61*, 2095.

e.

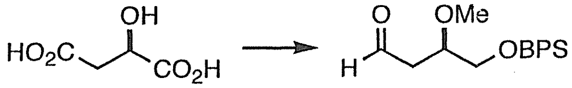


Solution:



Step 2 The *cis* 1,2-diol reacts selectively to form an acetonide.
Step 4 Both acetals (aceonide and glycoside) are hydrolyzed as well as the trityl group. Step 5 is required to selectively re-form the glycoside.

***f.**



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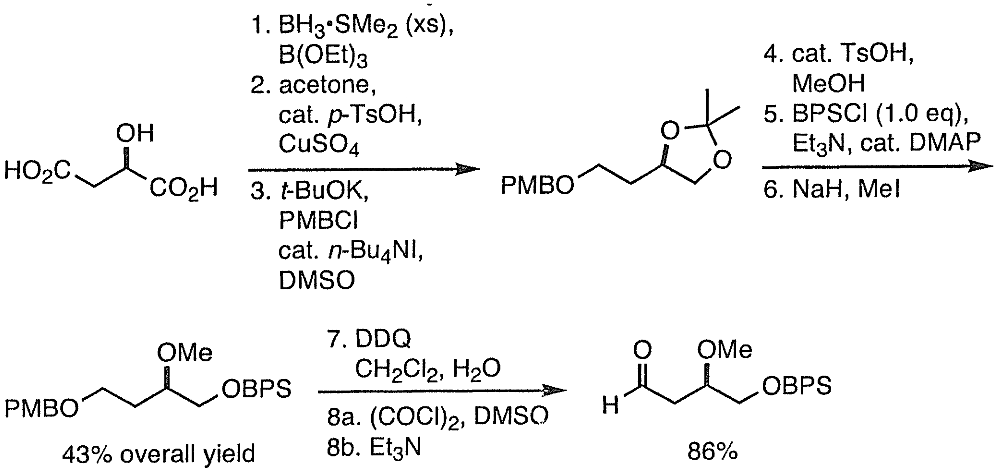
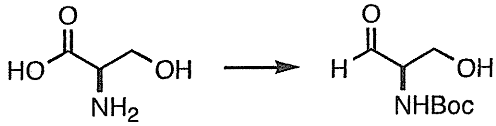


Reference: Pattenden, G.; Plowright, A. T.; Tornos, J. A.; Ye, T. *Tetrahedron Lett.* **1998**, *39*, 6099.

***g.**



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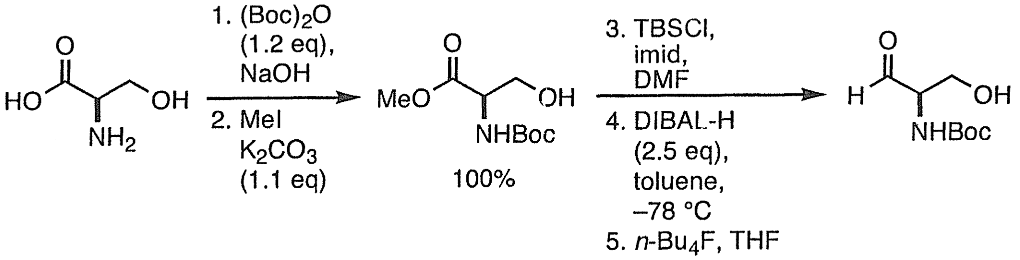
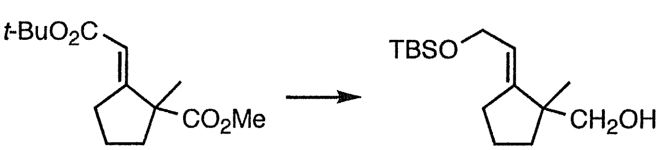


Step 4 A minimum of two equivalents of DIBAL-H is required due to the presence of the active N-H.

Reference: Nicolaou, K. C.; Bunnage, M. E.; Koide, K. *J. Am. Chem. Soc.* **1994**, *116*, 8402.

***h.**



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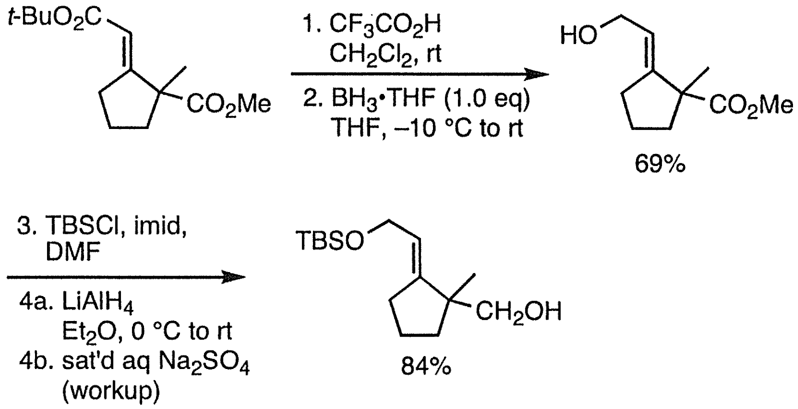
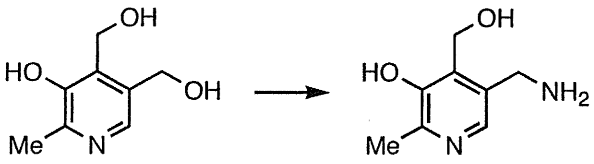


Step 1 Selective cleavage of the *t*-Bu ester (analogous to Boc deprotection).

Step 2 Chemoselective reduction of a carboxylic acid in the presence of an ester.

Reference: Dauben, W. G.; Warshawsky, A. M. *J. Org. Chem.* **1990**, *55*, 3075.

***i.**



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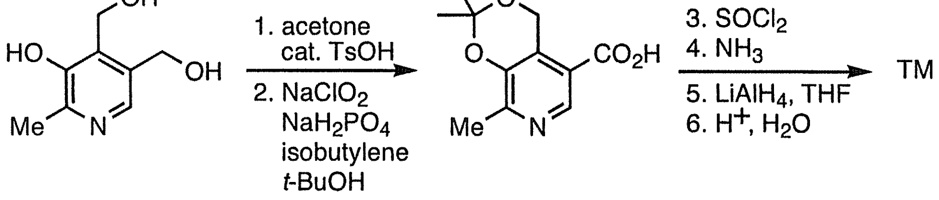

Step 1 Preferential formation of the six-membered acetal rather than the seven-membered acetal.

Step 6 Basic workup after acetal hydrolysis to obtain the amine in its free base form.

CHAPTER 5

Functional Group Transformations: The Chemistry of Carbon-Carbon π-Bonds and Related Reactions

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Overview

Chapter 5 deals with transformations of carbon-carbon π-bonds into a variety of functional groups.

Problem 1 highlights reagents for carbon-carbon π-system transformations. Problems 2-4 and 6 emphasize selectivity in reactions of carbon-carbon π-bonds. The syntheses of TMs in Problems 5 and 7 require the selection of specific reagents to achieve chemo-, stereo-, or enantioselectivity.

Key Concepts

- Hydrogenation of alkenes
- Dissolving metal reductions
  - Birch reduction
- Hydration of alkenes
  - Hydroboration-oxidation of alkenes
  - Oxymercuration-demercuration
- Epoxidation of alkenes
- Epoxidation of allylic alcohols
  - Sharpless asymmetric epoxidation
- Dihydroxylation of alkenes
  - Sharpless asymmetric dihydroxylation
- Halolactonization
- Cleavage of carbon-carbon double bonds
  - Ozonolysis
  - Lemieux-Johnson oxidation
- Semireduction of alkynes
  - Conversion of alkynes to (*E*)-alkenes
  - Conversion of alkynes to (*Z*)-alkenes
- Hydration of alkynes

SOLUTIONS TO CHAPTER 5 PROBLEMS

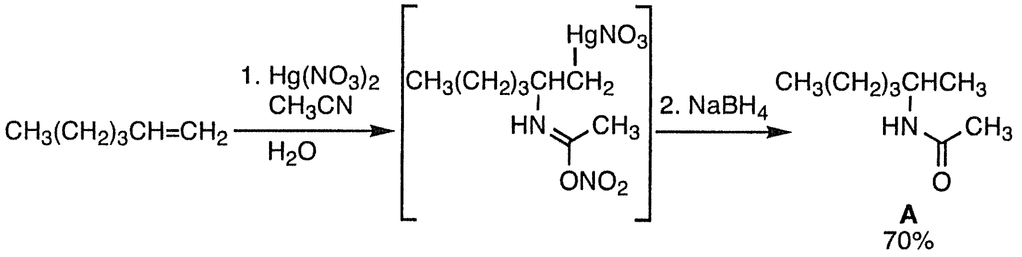
The more challenging problems are identified by an asterisk (*).

1. **Reagents**. Give the structures of the major product(s) expected for each of the following reactions. Be sure to indicate product stereochemistry where applicable.

a.

$$\mathrm{CH_3(CH_2)_3CH{=}CH_2} \xrightarrow[\text{2. NaBH}_4]{\text{1. Hg(NO}_3)_2\ \ \text{CH}_3\text{CN, H}_2\text{O}} \underset{70\%}{\mathbf{A}}$$

Solution:

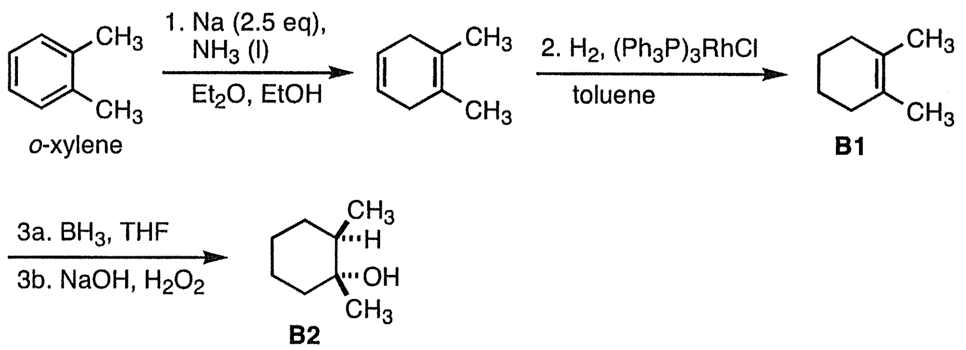


Reference: Brown, H. C.; Kurek, J. T. *J. Am. Chem. Soc.* **1969**, *91*, 5647.

b.

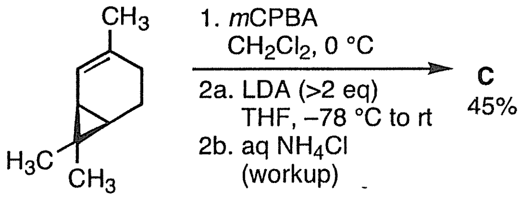
$$o\text{-xylene} \xrightarrow[\text{2. H}_2\text{, cat. (Ph}_3\text{P)}_3\text{RhCl}\ \ \text{toluene}]{\text{1. Na (2.5 eq), NH}_3\text{ (l)}\ \ \text{Et}_2\text{O, EtOH}} \mathbf{B1} \xrightarrow[\text{3b. NaOH, H}_2\text{O}_2]{\text{3a. BH}_3\text{, THF}} \mathbf{B2}$$

Solution:



Step 2 Wilkinson's catalyst allows for the selective hydrogenation of the less substituted double bond.

c.



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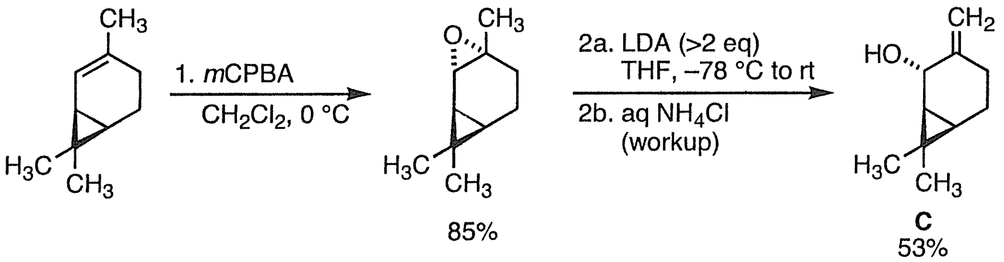
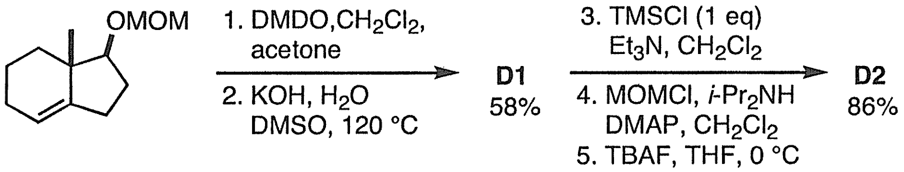


Step 1 Stereoselective epoxidation from the less hindered α-face.
Step 2 Regioselective base-mediated epoxide elimination.

Reference: Malkov, A. V.; Pernazza, D.; Bell, M.; Bella, M.; Massa, A.; Teply, F.; Meghani, P.; Kocovsky, P. *J. Org. Chem.* **2003**, *68*, 4727.

d.



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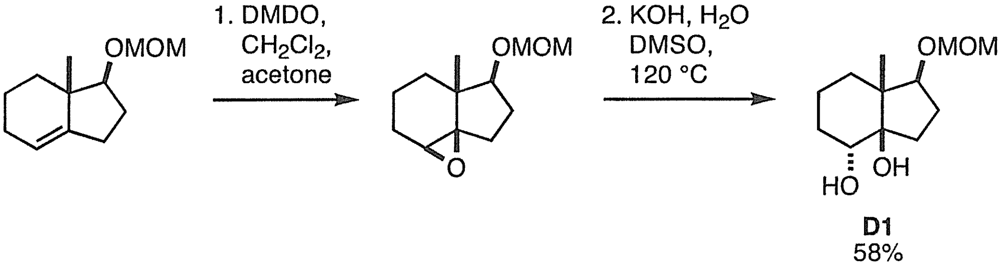
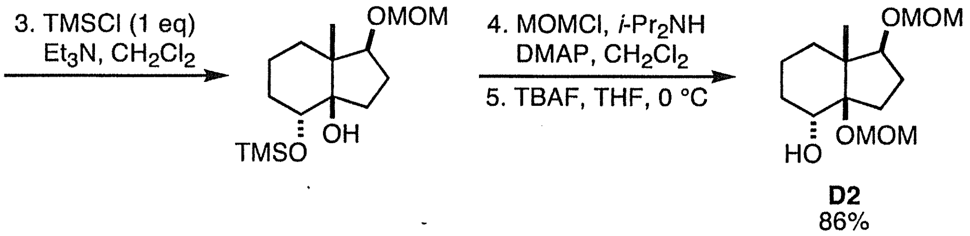
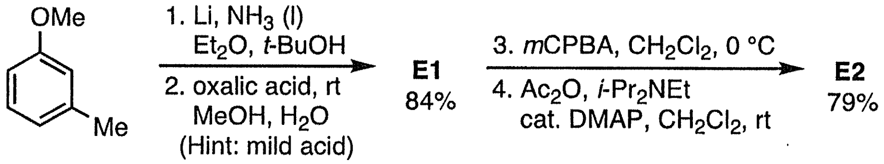


Step 1 Exo (convex) face approach of oxidant gives β-face epoxide.



Reference: Lepage, O.; Deslongchamps, P. *J. Org. Chem.* **2003**, *68*, 2183.

e.



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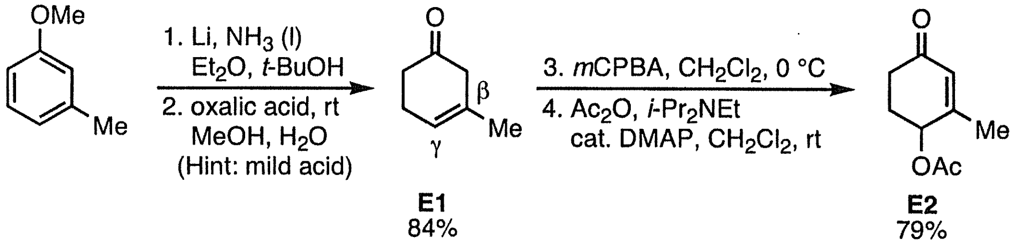
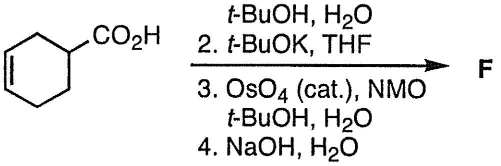


Step 2 Mild acid catalyzes the enol ether hydrolysis without subsequent β, γ to α, β alkene isomerization.
Step 4 Hünig's base promotes β-elimination of the epoxide followed by *O*-acylation.

Reference: Piers, E.; Oballa, R. M. *J. Org. Chem.* **1996**, *61*, 8439.

f.



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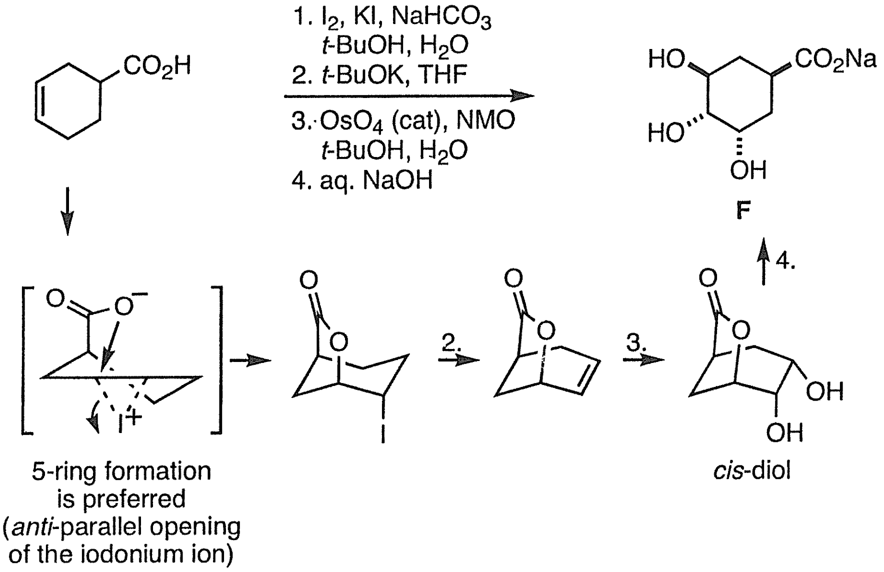
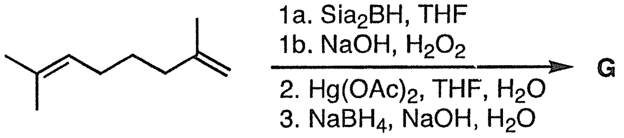


5-ring formation is preferred (*anti*-parallel opening of the iodonium ion)

g.



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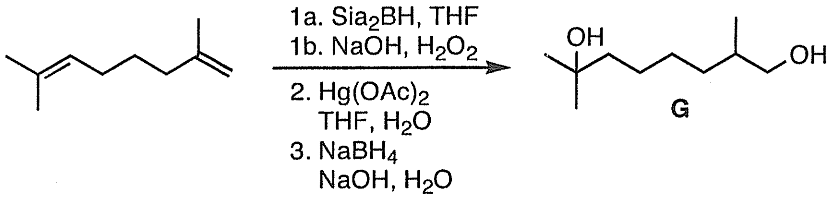
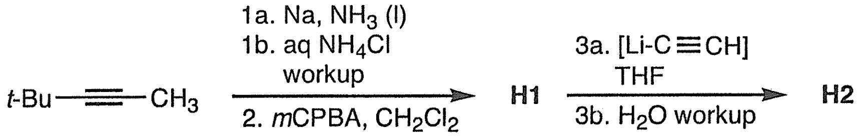


Step 1 Hydroboration-oxidation of sterically less hindered terminal alkene.
Step 2 Oxymercuration-demercuration of the internal alkene yields the diol G.

h.



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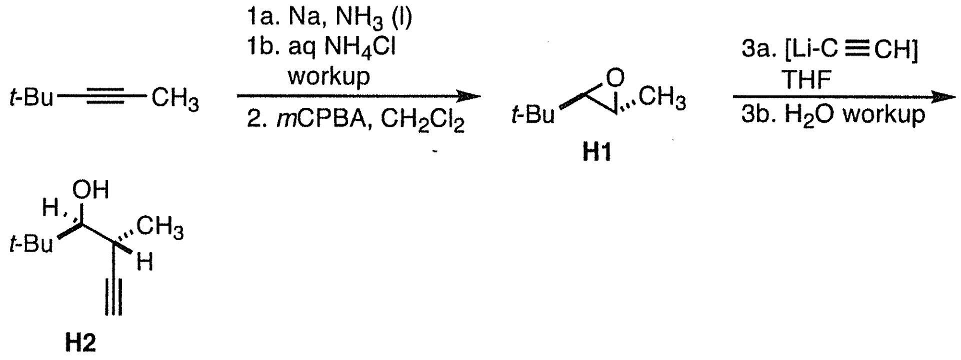
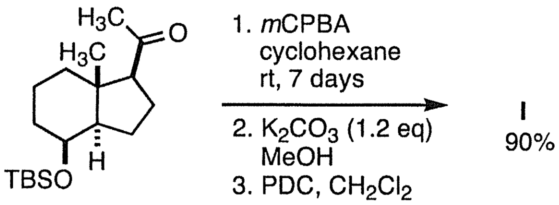


i.



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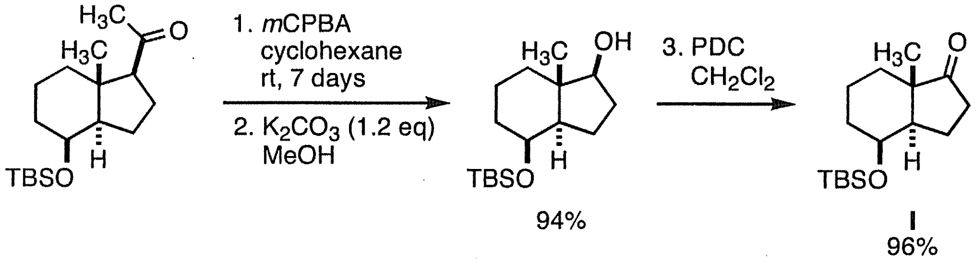
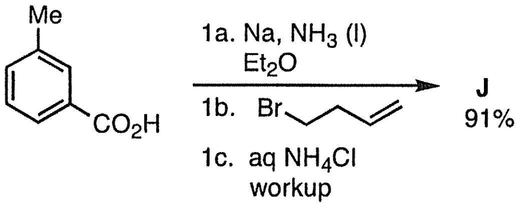


Steps 1-2 Baeyer-Villiger oxidation followed by acetate hydrolysis.

Reference: Momán, E.; Nicoletti, D.; Mouriño, A. *J. Org. Chem.* **2004**, *69*, 4615.

j.



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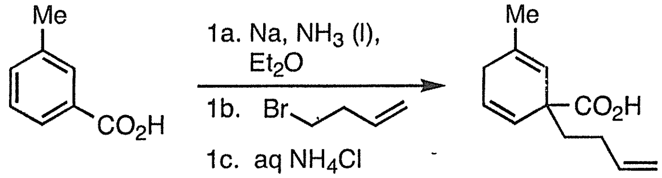
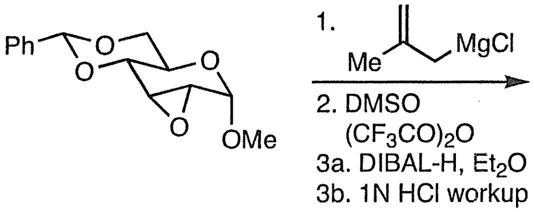


J
91%

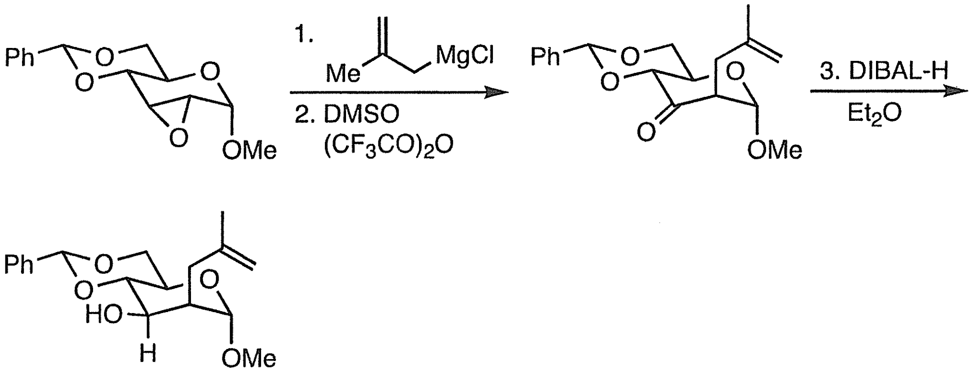
Reference: Chuang, C.–P.; Hart, D. J. *J. Org. Chem.* **1983**, *48*, 1782.

***k.**



K
83%

Solution:



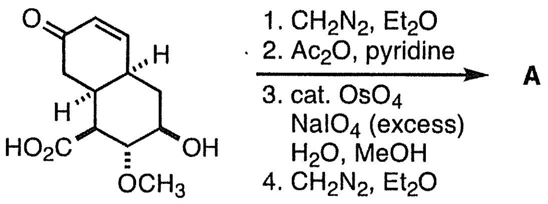
K
83%

Step 1	Diaxial opening of the epoxide.
Step 2	Modified Swern oxidation; see *J. Org. Chem.* **1998**, *63*, 8522.
Step 3	Hydride addition occurs preferentially from the α-face (*anti* to the axial isopropenyl moiety).

Reference: Chen, L.; Wiemer, D. F. *J. Org. Chem.* **2002**, *67*, 7561.

2. **Selectivity.** Show the product(s) obtained or the appropriate reagent(s) to be used for the following transformations.

a.



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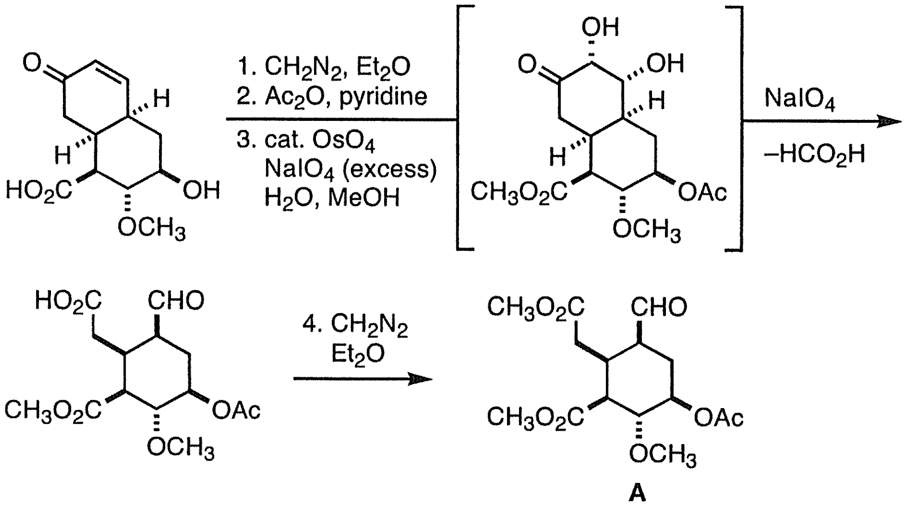
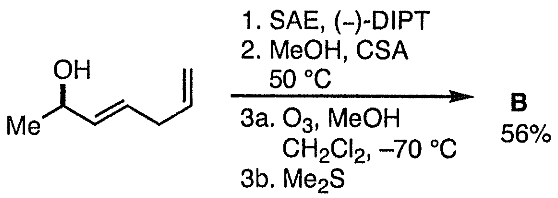


Step 2 Lemieux-Johnson oxidation.

Reference: For an analogous synthesis, see Woodward, R. B.; Bickel, B. H.; Frey, A. J.; Kierstead, R. W. *Tetrahedron* **1958**, *2*, 1.

b.



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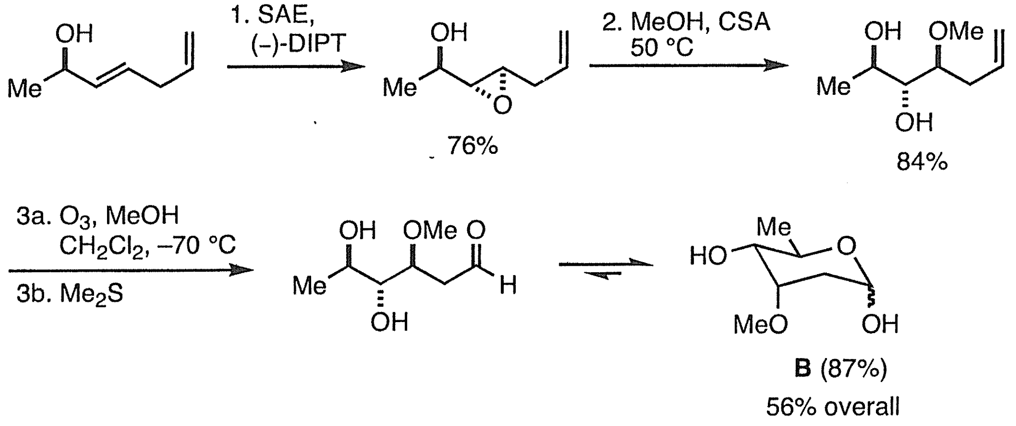
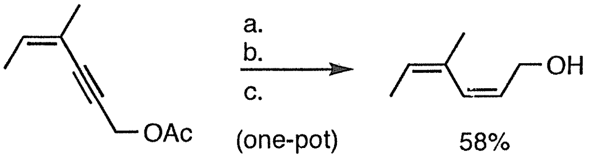


Reference: Roush, W. R.; Brown, R. J. *J. Org. Chem.* **1983**, *48*, 5093.

c.



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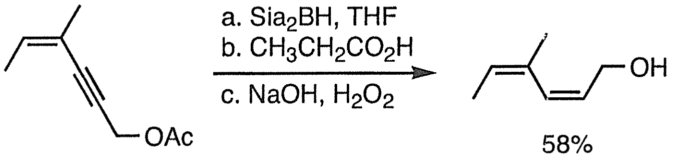
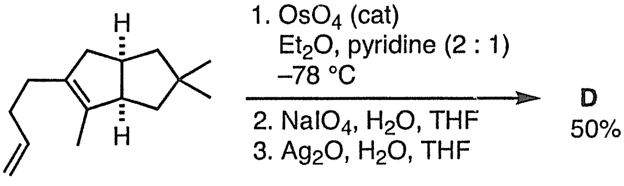


Step b	Protonolysis of the intermediate vinylborane.
Step c	Oxidation of the Sia_2B- moieties as well as saponification of the acetate.

Note: Steps a–c represent a method to prepare *Z*-alkenes without the use of H_2 in the presence of Lindlar's catalyst.

Reference: Corey, E. J.; Herron, D. K. *Tetrahedron Lett.* **1971**, 1641.

d.



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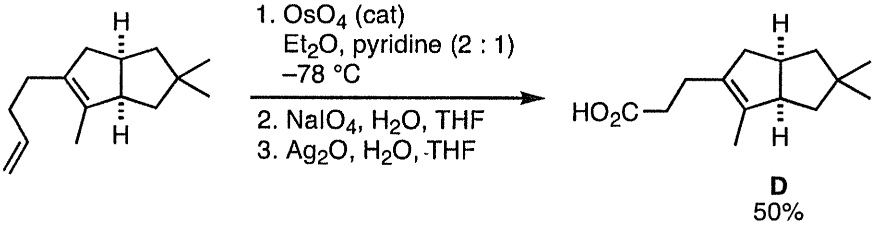
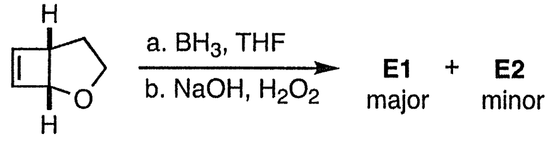


Step 1	Dihydroxylation of the terminal alkene.
Step 2	Oxidative cleavage of the resultant 1,2-diol.
Step 3	Oxidation of the resultant aldehyde to the corresponding carboxylic acid.

Reference: Nozoe, S.; Furukawa, J.; Sankawa, U.; Shibata, S. *Tetrahedron Lett.* **1976**, 195.

e.



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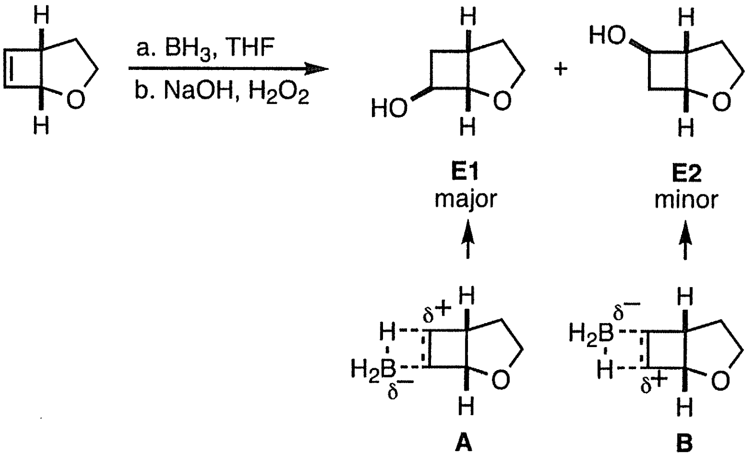
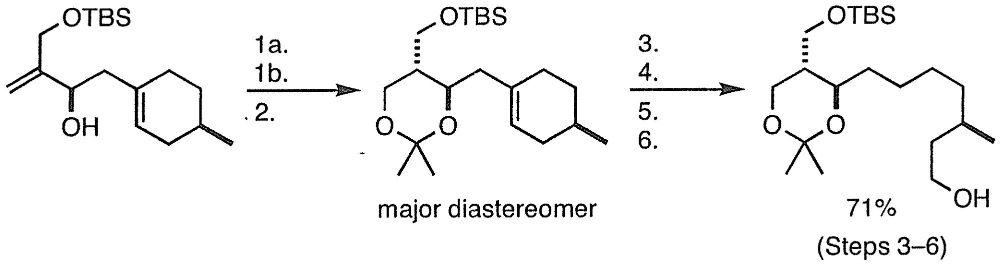


The hydroboration occurs from the less hindered face (i.e., the convex face). Transition state **B** is destabilized by the electron-withdrawing effect of oxygen.

Reference: Paquette, L. A.; Youssef, A. A.; Wise, M. L. *J. Am. Chem. Soc.* **1967**, *89*, 5246.

***f.**



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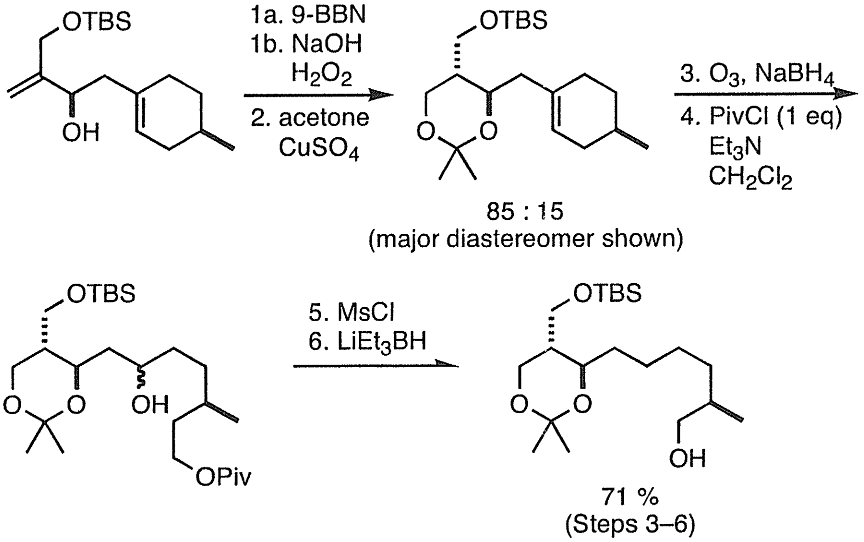

Step 3 Ozonolysis followed by carbonyl reduction.
Step 4 Selective protection of the 1° alcohol.

Reference: Wovkulich, P. M.; Shankaran, K.; Kiegiel, J.; Uskokovic, M. R. *J. Org. Chem.* **1993**, *58*, 832.

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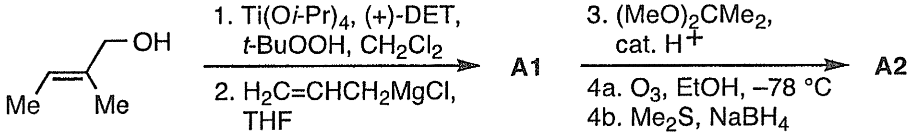
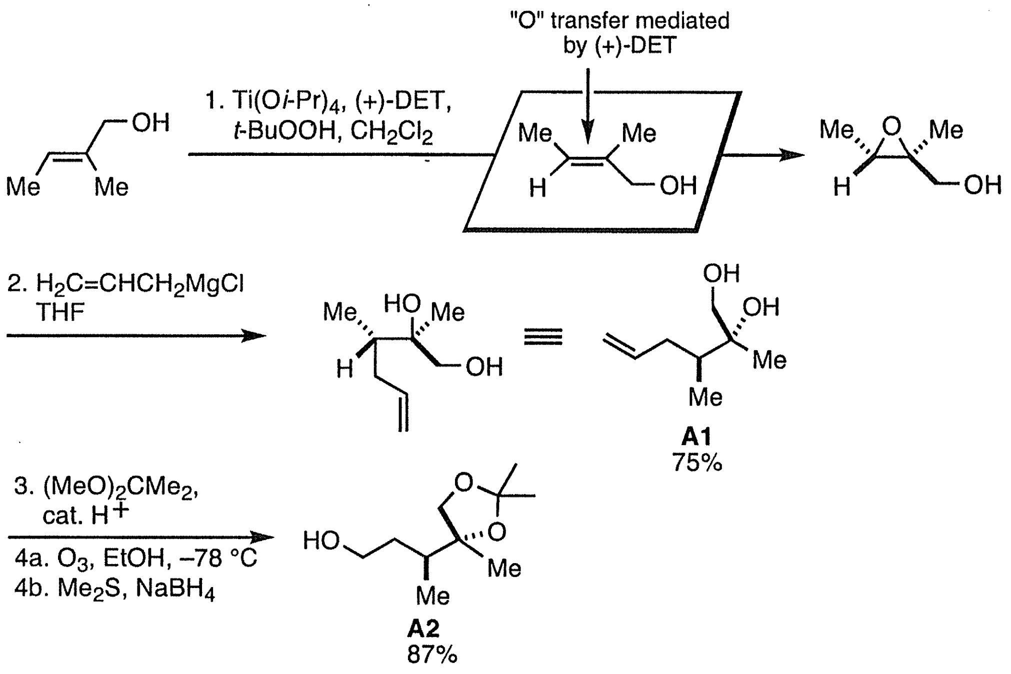
3. **Stereochemistry**. Give the structure and predict the stereochemistry of the major product formed for each of the following reactions. Give an explanation for your choice of stereochemistry.

a.



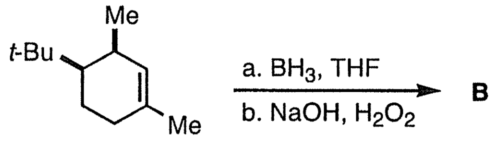
Solution:



Step 1 Sharpless asymmetric epoxidation.
Step 2 *Anti*-periplanar opening of the epoxide at the least substituted carbon.

Reference: Evans, D. A.; Bender, S. L.; Morris, J. *J. Am. Chem. Soc.* **1988**, *110*, 2506.

b.



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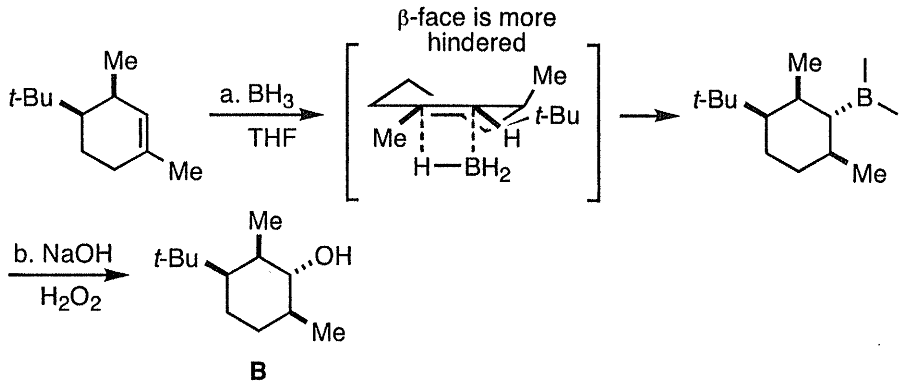
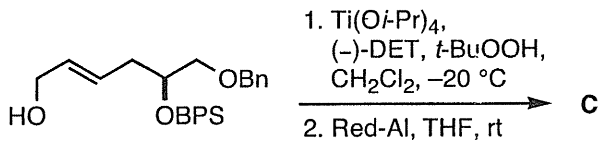


Step a The predominant cyclohexene conformer places (i) the *t*-Bu equatorial and (ii) the allylic-Me pseudoaxial to minimize $A^{1,3}$ strain. *syn*-Addition of the H-B bond at the least, after oxidation, to **B**.

c.



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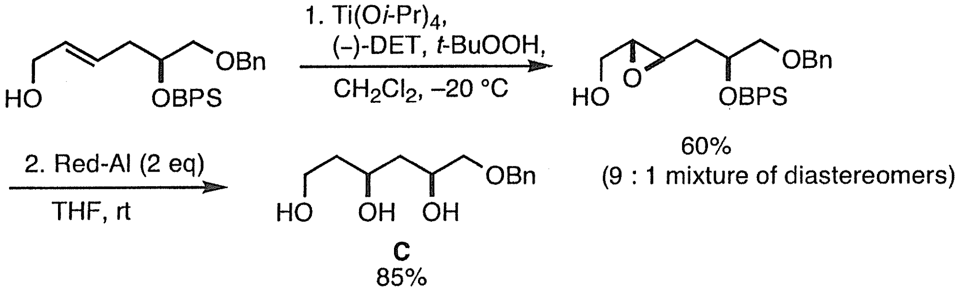
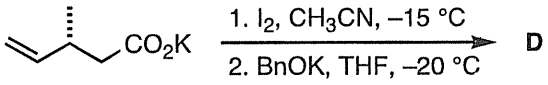


BPS group is cleaved during the Red-Al step.

Reference: Nicolaou, K. C.; Uenishi, D. J.; Li, W. S.; Papahatjis, D. P.; Chakraborty, D. K. *J. Am. Chem. Soc.* **1988**, *110*, 4672.

d.



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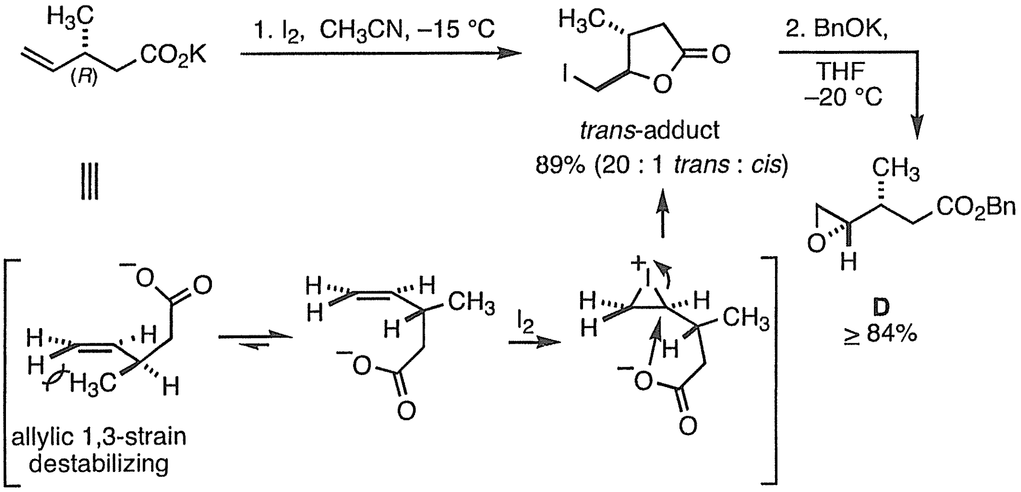
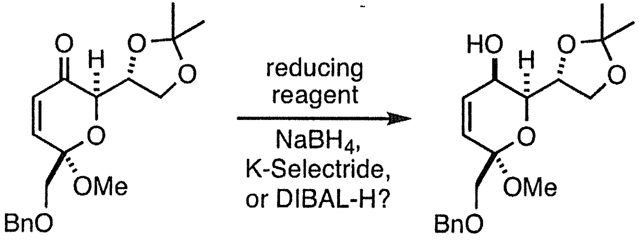
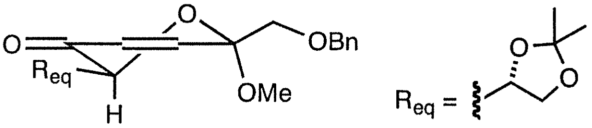


Reference: Collum, D. B.; McDonald, III, J. H.; Still, W. C. *J. Am. Chem. Soc.* **1980**, *102*, 2118.

e. Select the appropriate reducing agent from the list shown below. Explain your choice.



Solution:



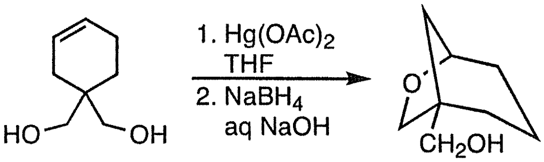
Note that 1,4-reduction is impeded by the adjacent disubsituted carbon center. The sterically hindered reducing agent K-Selectride favors 1,2-addition from the face opposite the R_{eq} substituent.

Reduction with $NaBH_4$ or DIBAL-H furnished a product mixture in which the equatorial allylic alcohol predominated. However, reduction using K-Selectride produced the axial alcohol as the major product (88% yield, 9.8 : 1 mixture of diastereomers).

Reference: Martin, S. F.; Zinke, P. W. *J. Org. Chem.* **1991**, *56*, 6600.

4. **Reactivity**. Explain the regioselectivity and stereochemistry observed in each of the following transformations.

a.



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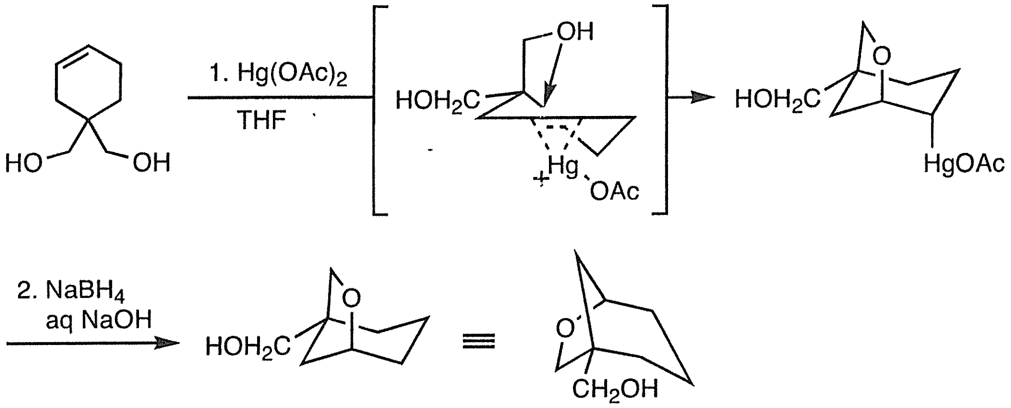
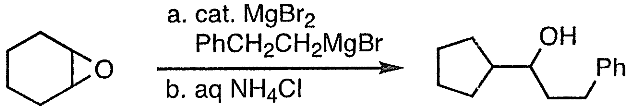


b.



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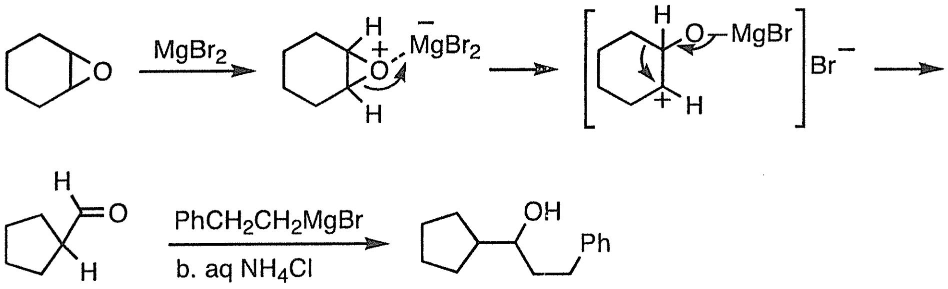
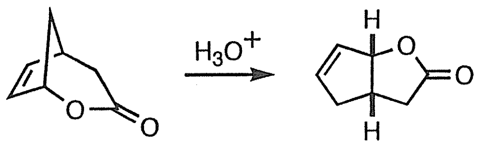
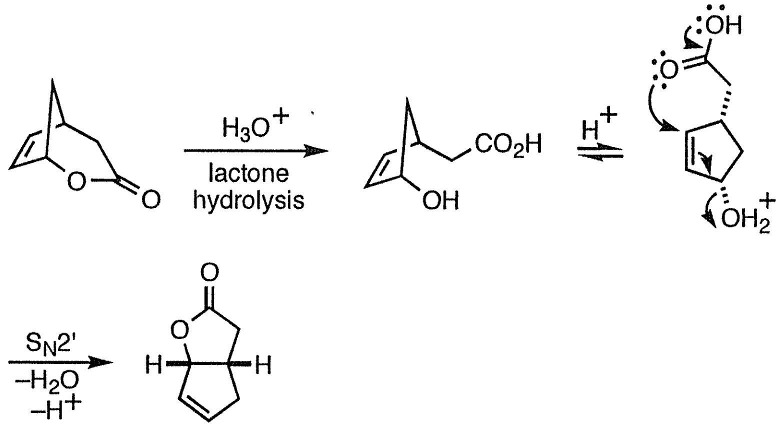


Lewis acid–mediated epoxide rearrangement followed by 1,2-addition.

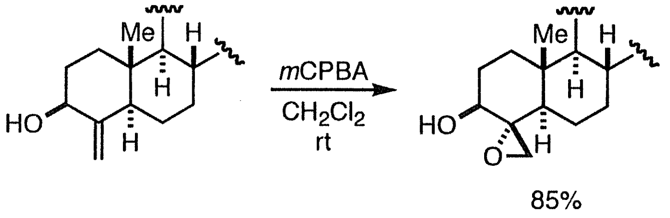
c.



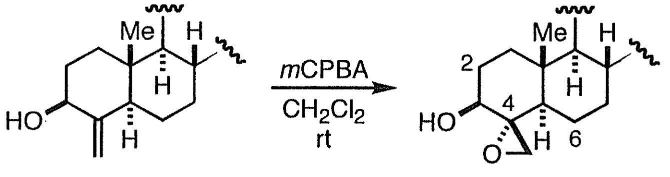
Solution:



d. Why is the β-epoxide not formed on *m*CPBA epoxidation, although the β-epoxide is predicted based on OH-directed epoxidation? Propose a strategy to synthesize the β-epoxide.

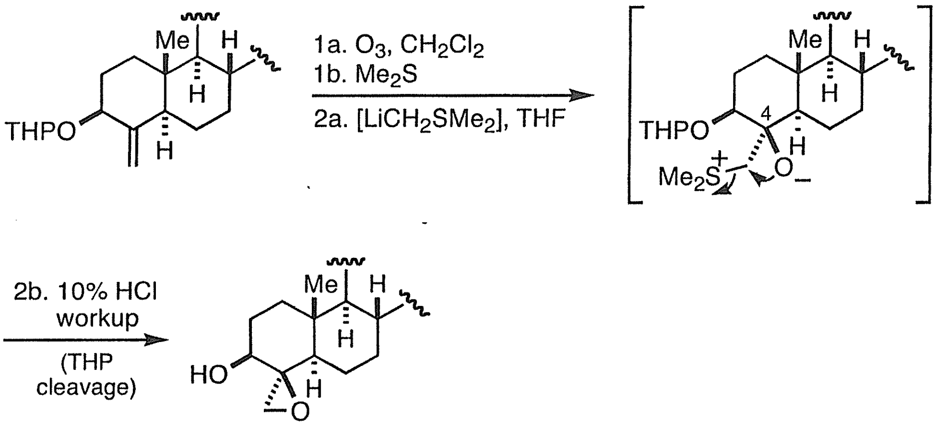


Solution:



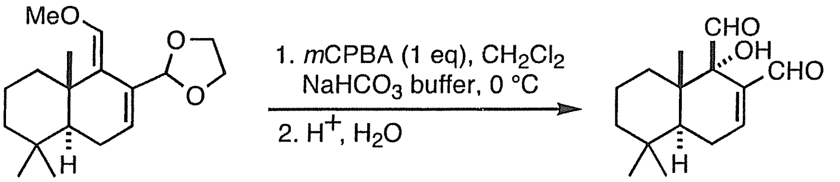
The unfavorable steric interactions of a β-face peracid-hydroxyl group complex with the angular methyl group and with the 2β- and 6β-hydrogens results in the preferential epoxidation from the α-face.

Since an α-face approach to C(4) is favored, presumably attack of the sulfur ylide to a C(4)-carbonyl would yield the β-face alkoxide leading to the β-epoxide after protection of the hydroxyl group.



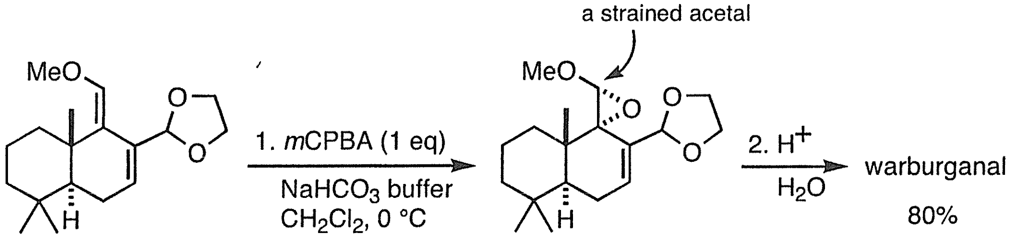
Reference: Ekhato, I. V.; Silverton, J. V.; Robinson, C. H. *J. Org. Chem.* **1988**, *53*, 2180.

e.



80%, warburganal

Solution:

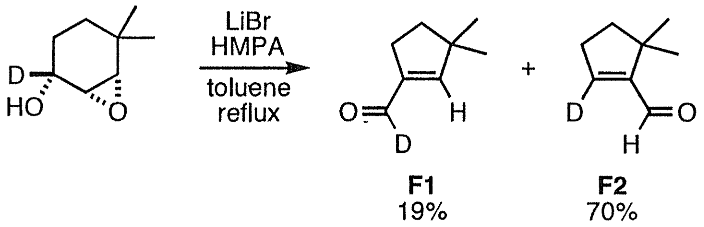


Step 1 Selective epoxidation of the more electron-rich alkene (enol ether) occurs selectively at the α-face to avoid unfavorable interactions with the β-face angular methyl group.

Step 2 Mild acid hydrolysis of the epoxy ether (a strained acetal) and the 1,3-dioxolane acetal.

Reference: Kende, A. S.; Blacklock, T. J. *Tetrahedron Lett.* **1980**, *21*, 3119.

*f. Provide a mechanistic interpretation for the formation of the aldehydes shown below.



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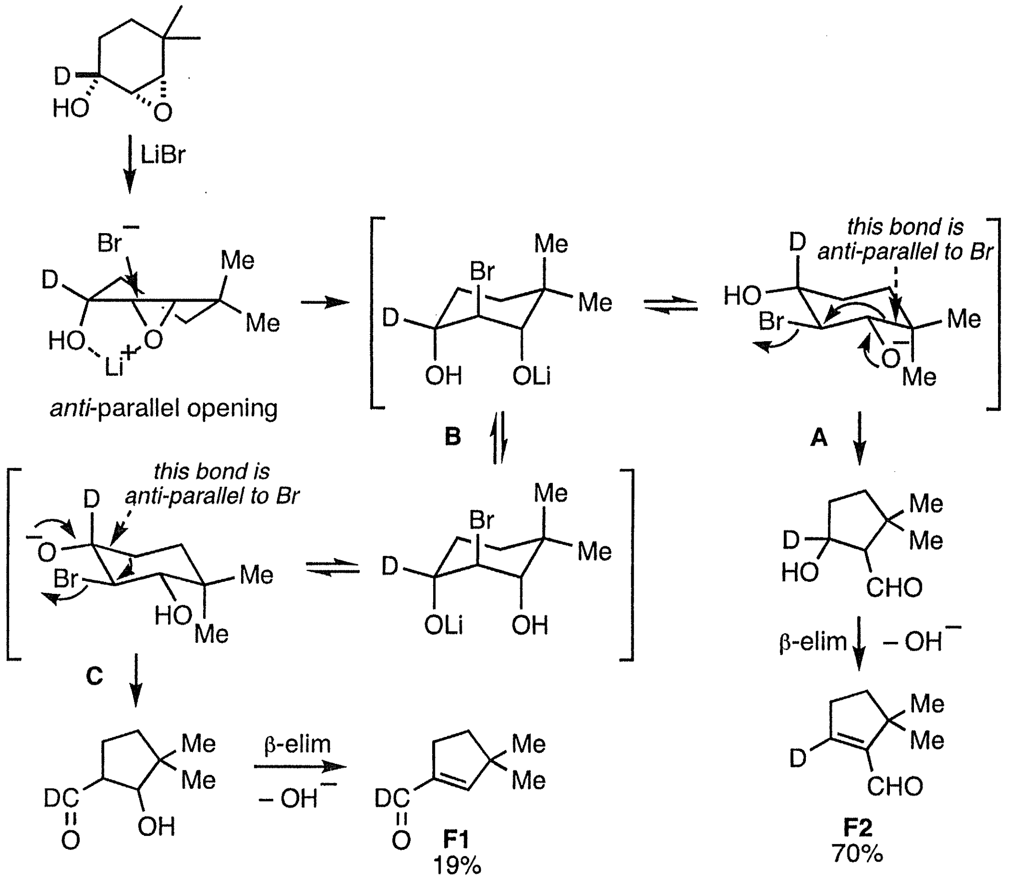
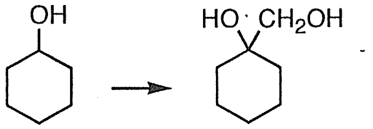


Reaction of the epoxy alcohol with LiBr forms the halohydrin salt that equilibrates to the equatorial-Br conformer, which then undergoes ring contraction via an *anti*-parallel displacement of Br⁻ (Step **A**). Proton transfer (Step **B**), although proceeding at a slower rate, leads to another *anti*-parallel Br⁻ displacement (Step **C**), forming the minor product **F1**.

Reference: Bergman, R.; Magnusson, G. *J. Org. Chem.* **1986**, *51*, 212.

5. **Synthesis.** Supply the reagents required to accomplish each of the following syntheses. Indicate the relative stereochemistry, where applicable, of the products obtained at each step.

a.



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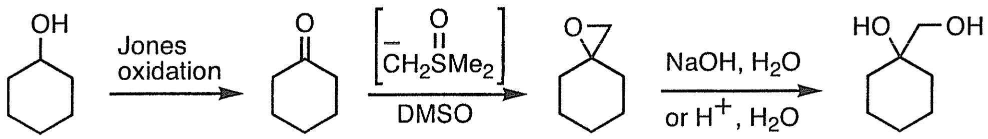
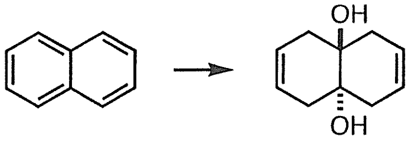


b.



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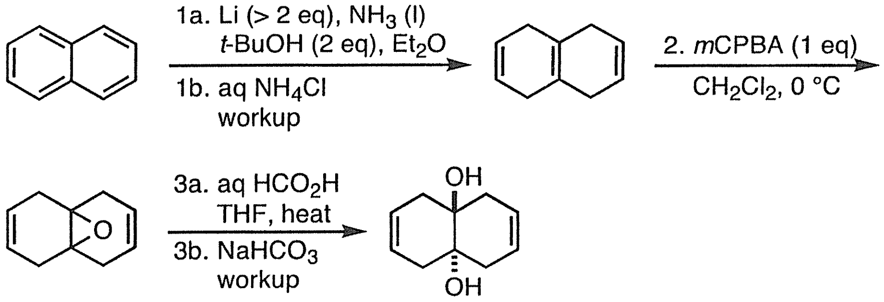
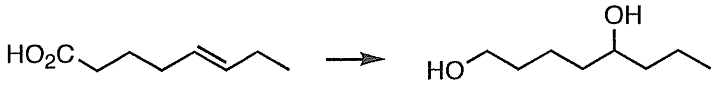


Step 2 Selective epoxidation of the more electron rich double bond.
Step 3a Acid-catalyzed epoxide cleavage.
Step 3b Formate hydrolysis.

c.



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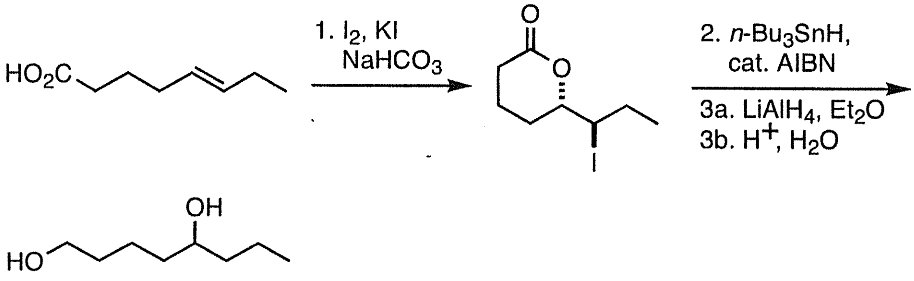
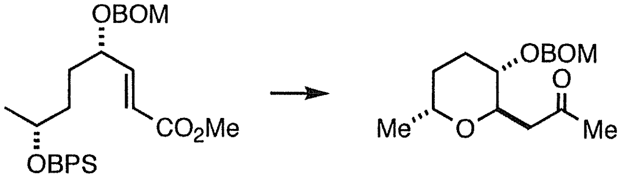


d.



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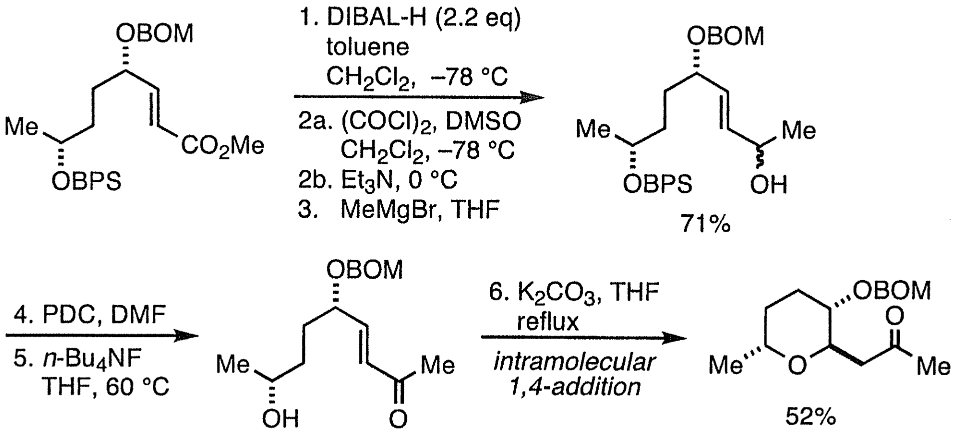
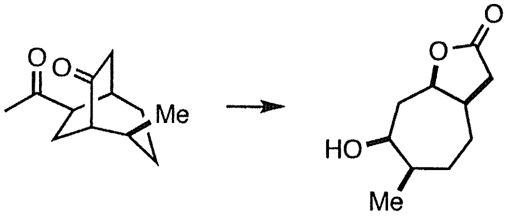


Steps 2–4 R–CH_2OH to R–C(O)Me sequence.

Reference: Machinaga, N.; Kibayashi, C. *Tetrahedron Lett.* **1993**, *34*, 5739.

e.



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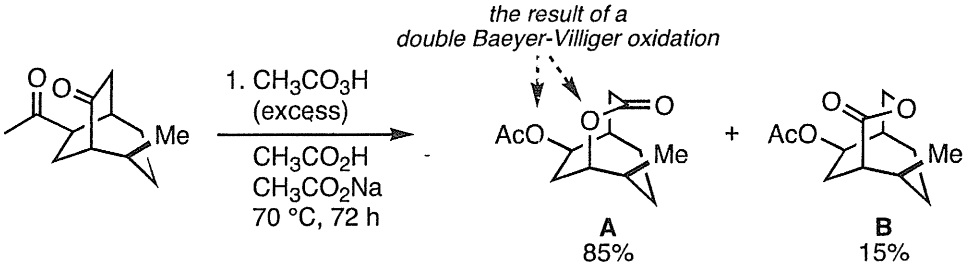
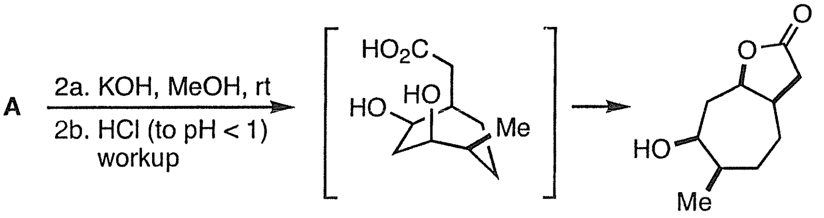
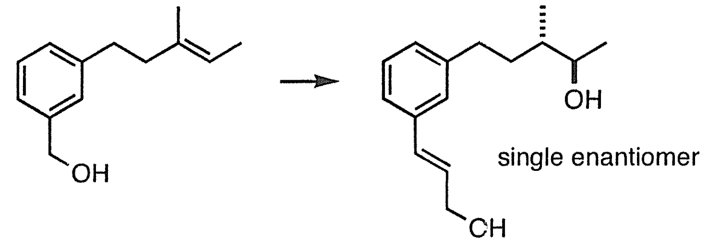




Reference: McWilliams, J. C.; Clardy, J. *J. Am. Chem. Soc.* **1994**, *116*, 8378.

f.



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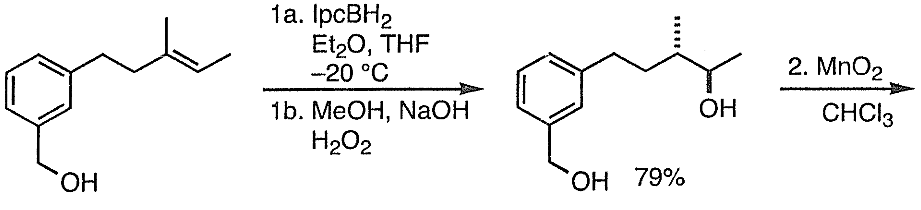
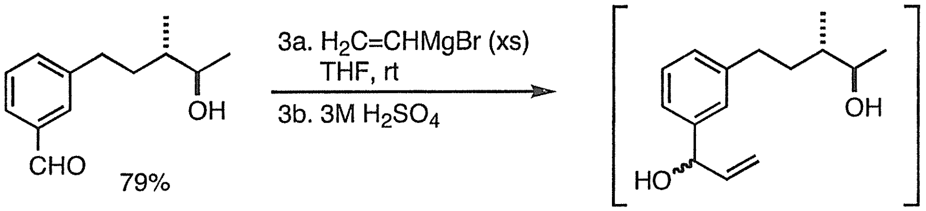
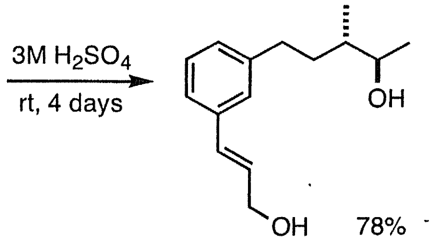


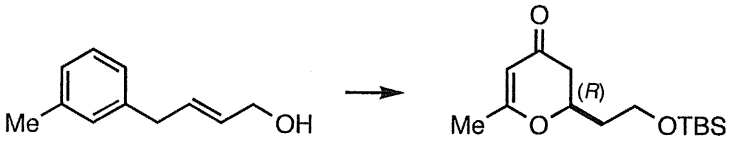




Step 3b Allylic rearrangement via allylic benzylic cation.

Reference: Holoboski, M. A.; Koft, E. *J. Org. Chem.* **1992**, *57*, 965.

***g.**



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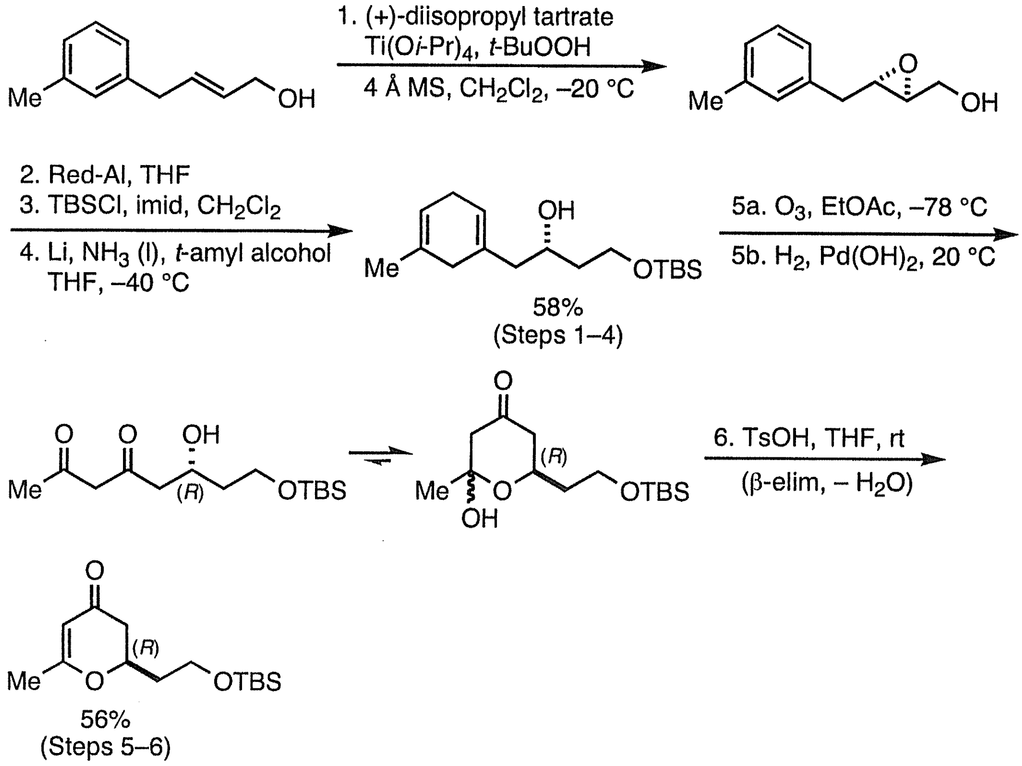
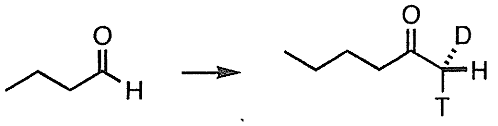


Step 5a–b Ozonolysis followed by reductive workup leads to the β-diketone.

Reference: Wipf, P.; Lim, S. *J. Am. Chem. Soc.* **1995**, *117*, 558.

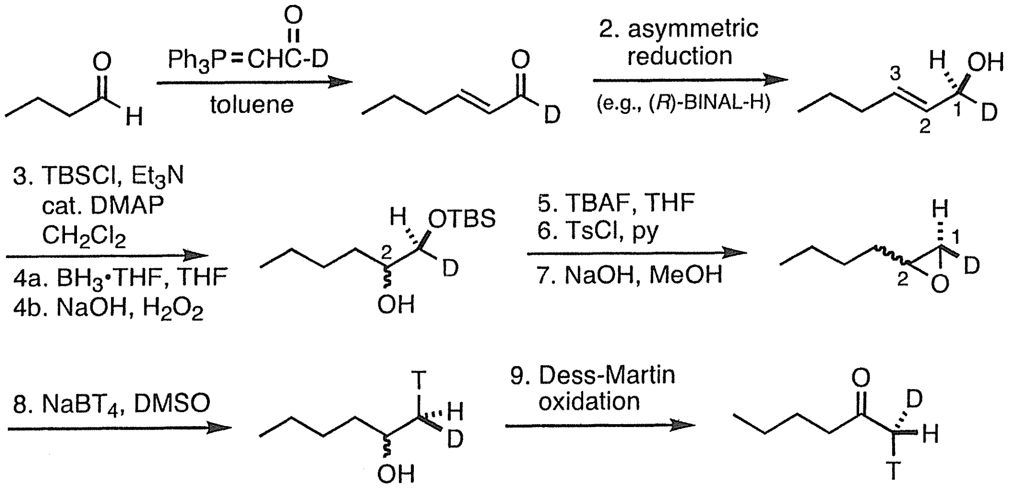
***h.**



chiral methyl group, single enantiomer

Hint: No SAE was employed in the synthesis; however, the sequence did involve an allylic alcohol intermediate

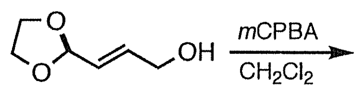
Solution:



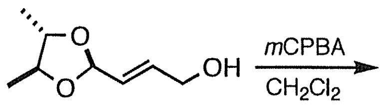
Reference: For an analogous transformation, see Altman, L. J.; Han, C. Y.; Bertolino, A.; Handy, G.; Laungani, D.; Muller, W.; Schwartz, S.; Shanker, D.; de Wolf, W. H.; Yang, F. *J. Am. Chem. Soc.* **1978**, *100*, 3235.

6. Consider the reactions **A**-**F**. Assume that the Sharpless epoxidations proceed with ***complete π-facial selectivity*** regardless of substrate. Select the best answer among the following choices regarding the stereochemical outcome of each of the reactions.

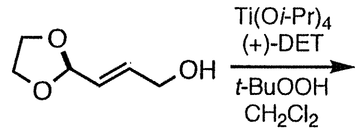
A



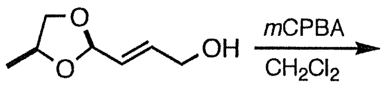
B



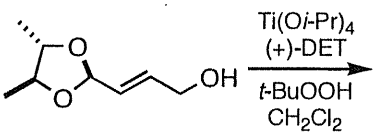
D



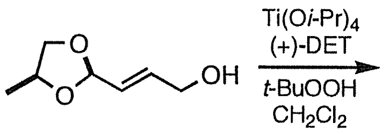
C



E



F



a. Assuming that the stereocenters, if any, in the starting allylic alcohols are racemic, which of the above reactions lead(s) to a mixture of *enantiomers*?

(i) reaction **A** only
(ii) reactions **B** and **E**
(iii) reactions **D** and **F**
(iv) reactions **A** and **B**
(v) reactions **A, B** and **C**

Solution:

Reactions **B, C, E** and **F** lead to mixtures of diastereomers. Reaction **D** affords a single enantiomer since the Sharpless epoxidation proceeds with complete π-facial selectivity.

Only reaction **A** provides a mixture of enantiomers. Therefore, the correct choice is (i).

b. Assuming that the starting allylic alcohols, if chiral, are enantiomerically pure, which of the above reactions lead(s) to a mixture of *diastereomers*?

(i) reactions **E** and **F**
(ii) reaction **B** only
(iii) reactions **B** and **C**
(iv) reaction **E** only
(v) all of them would except reactions **A** and **D**

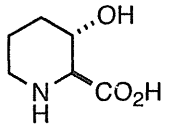
Solution:

Reaction **A** gives a mixture of enantiomers; reactions **D, E** and **F** give a single enantiomer.

Reactions **B** and **C** lead to a mixture of diastereomers. Therefore, the correct choice is (**iii**).

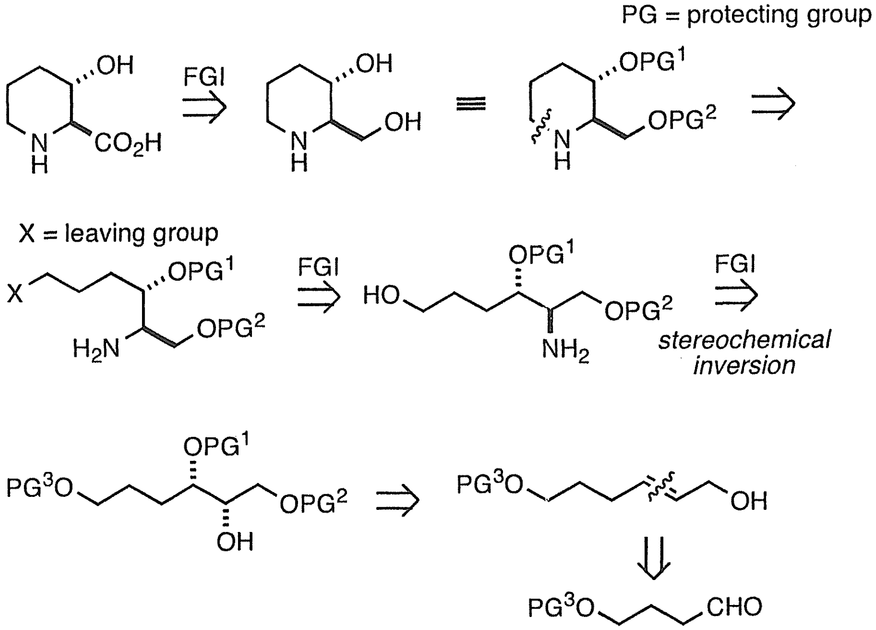
*7. **Retrosynthetic Analysis.** For each of the following syntheses show (1) your retrosynthetic analysis and (2) all reagents and reaction conditions required to transform a commercially available starting material to the target molecule.

a. Propose a synthesis of (+)-*trans*-3-hydroxypipecolic acid using the Sharpless asymmetric dihydroxylation procedure to establish the absolute stereochemistry.

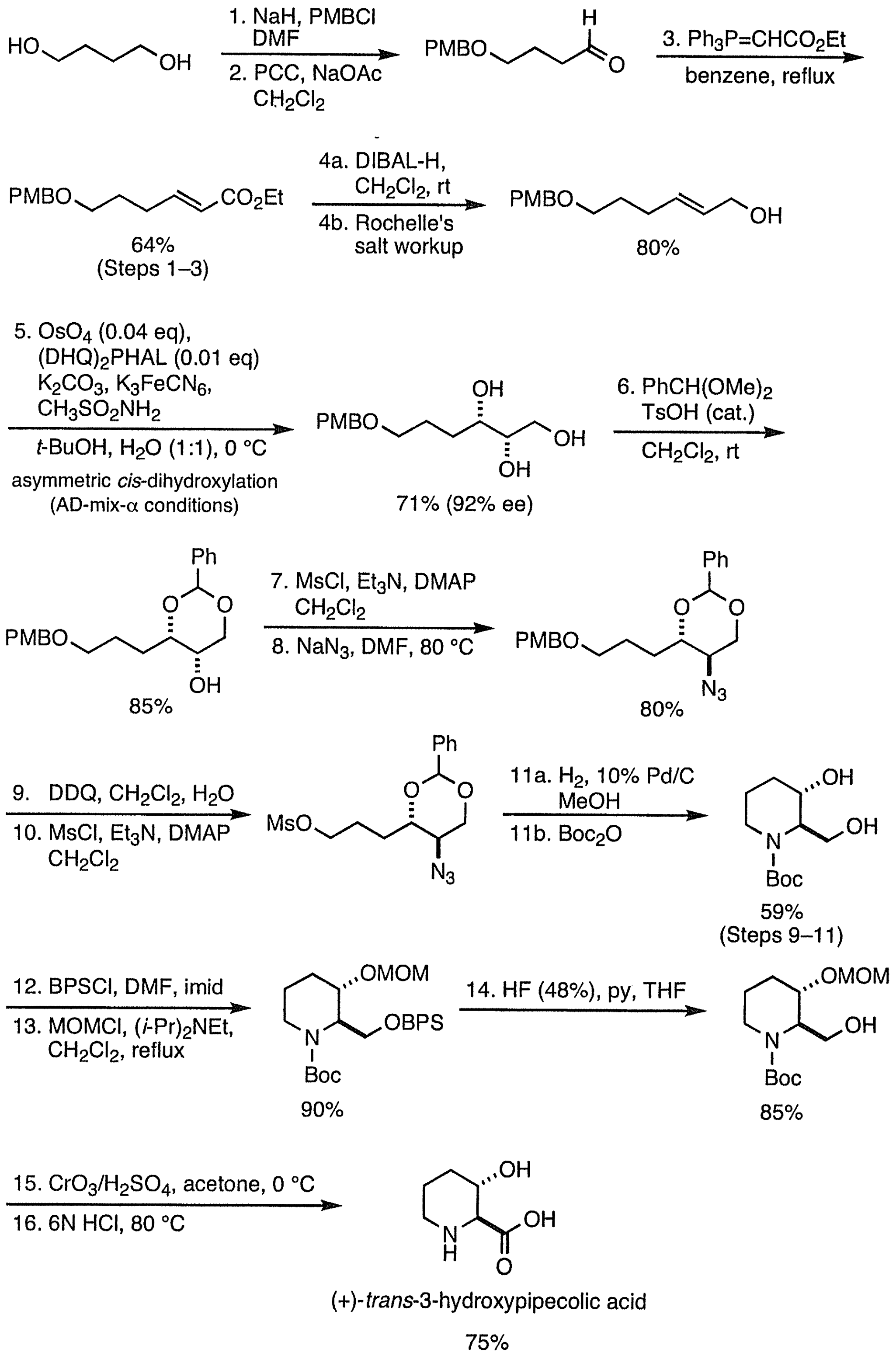


(+)-*trans*-3-hydroxypipecolic acid

Retrosynthetic analysis:



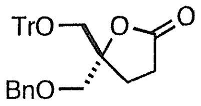
Synthesis:


HO
OH
1. NaH, PMBCl DMF
2. PCC, NaOAc CH_2Cl_2
PMBO
H
O
3. $Ph_3P{=}CHCO_2Et$
benzene, reflux
PMBO
CO_2Et
64%
(Steps 1–3)
4a. DIBAL-H, CH_2Cl_2, rt
4b. Rochelle's salt workup
PMBO
OH
80%
5. OsO_4 (0.04 eq), $(DHQ)_2PHAL$ (0.01 eq) K_2CO_3, K_3FeCN_6, $CH_3SO_2NH_2$
t-BuOH, H_2O (1:1), 0 °C
asymmetric *cis*-dihydroxylation
(AD-mix-α conditions)
PMBO
OH
OH
OH
71% (92% ee)
6. $PhCH(OMe)_2$ TsOH (cat.)
CH_2Cl_2, rt
Ph
O
O
PMBO
OH
85%
7. MsCl, Et_3N, DMAP CH_2Cl_2
8. NaN_3, DMF, 80 °C
Ph
O
O
PMBO
N_3
80%
9. DDQ, CH_2Cl_2, H_2O
10. MsCl, Et_3N, DMAP CH_2Cl_2
Ph
O
O
MsO
N_3
11a. H_2, 10% Pd/C MeOH
11b. Boc_2O
OH
OH
N
Boc
59%
(Steps 9–11)
12. BPSCl, DMF, imid
13. MOMCl, $(i\text{-}Pr)_2NEt$, CH_2Cl_2, reflux
OMOM
OBPS
N
Boc
90%
14. HF (48%), py, THF
OMOM
OH
N
Boc
85%
15. CrO_3/H_2SO_4, acetone, 0 °C
16. 6N HCl, 80 °C
OH
OH
N
H
O
(+)-*trans*-3-hydroxypipecolic acid
75%

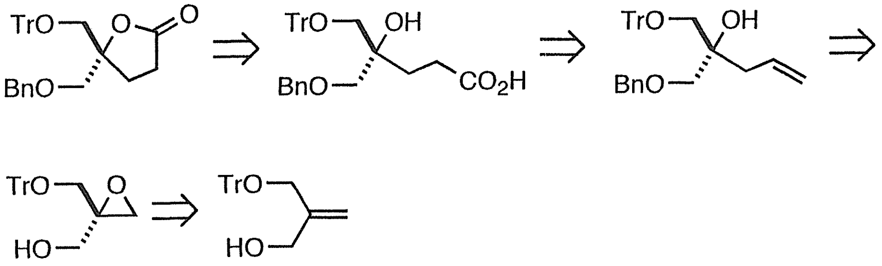
Step 3	Olefination using the stabilized Wittig reagent affords the (*E*)-alkene with good selectivity.
Step 6	Acid-catalyzed *trans*-acetalization using benzaldehyde dimethylacetal favors formation of the six-membered ring acetal.
Step 8	S_N2 displacement of the mesylate establishes the correct nitrogen stereochemistry.
Step 11	Azide reduction to the amine; hydrogenolysis of the benzyl ethers; intramolecular displacement of the mesylate to construct the piperidine ring.
Step 12	Selective protection of the 1° alcohol.
Step 15	Jones oxidation of the 1° alcohol to the corresponding carboxylic acid.
Step 16	Simultaneous removal of MOM ether and Boc protecting groups affords the TM.

References: Kumar, P.; Bodas, M. S. *J. Org. Chem.* **2005**, *70*, 360.
Jourdant, A.; Zhu, J. *Tetrahedron Lett.* **2000**, *41*, 7033.

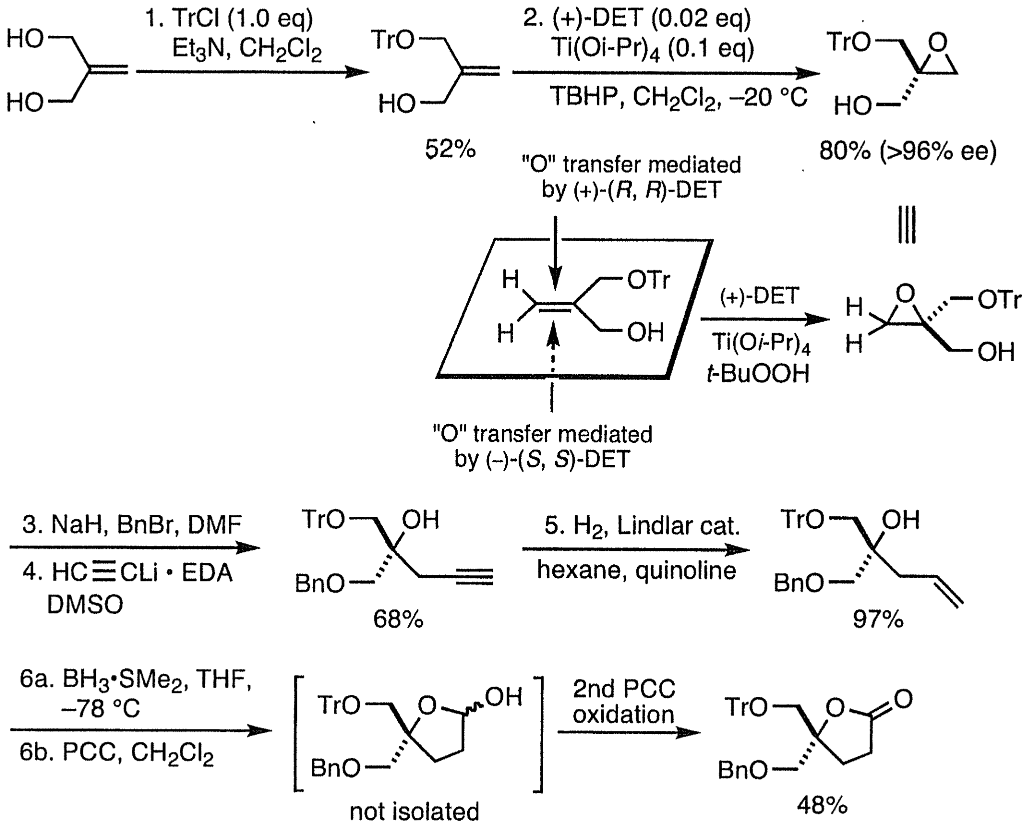
b. Propose a synthesis of the following lactone using the Sharpless asymmetric epoxidation procedure to establish the absolute stereochemistry.



Retrosynthetic analysis:



Synthesis:



Reference: Kang, J.-H.; Siddiqui, M. A.; Sigano, D. M.; Krajewski, K.; Lewin, N. E.; Pu, Y.; Blumberg, P. M.; Lee, J.; Marquez, V. E. *Org. Lett.* **2004**, *6*, 2413.

CHAPTER 6

Formation of Carbon-Carbon Single Bonds Via Enolate Anions

Overview

Chapter 6 focuses on carbon-carbon bond formations via reactions of enolate anions.

Problem 1 stresses the use of appropriate bases for generating enolate anions. Problems 2–4 deal with selectivity issues encountered in enolate anion reactions. The syntheses of TMs in Problems 5 and 6 require the selection of specific reagents to achieve chemo-, stereo-, or enantioselective carbon-carbon bond formations.

Key Concepts

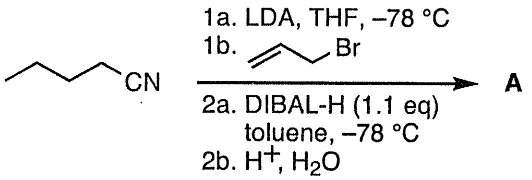
- 1,3-Dicarbonyl compounds
- Claisen condensations
- Dieckmann condensations
- Enolate formation
- Baldwin's rules for ring closure
- Imine and hydrazone anions
- Enamines
- Aldol reactions
    - (*E*)- and (*Z*)-enolate stereochemical control
- Mannich reactions
    - Enone synthesis
- Michael additions
- Robinson annulations

SOLUTIONS TO CHAPTER 6 PROBLEMS

The more challenging problems are identified by an asterisk (*).

1. **Reagents.** Give the structures of the major product(s) expected after each step of the following reactions. Be sure to indicate product stereochemistry where applicable.

a.



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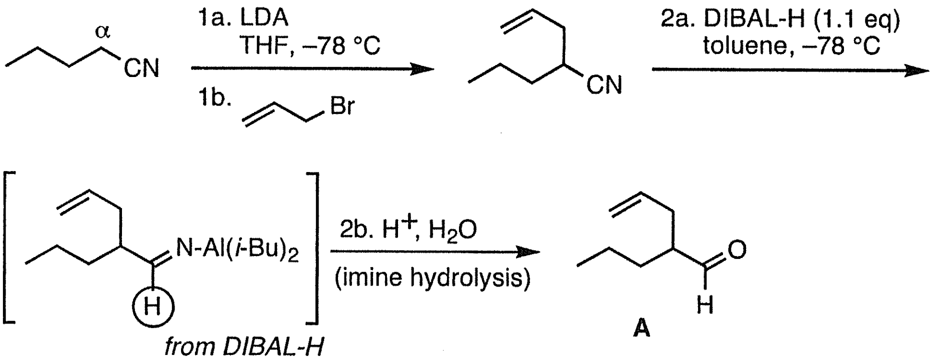
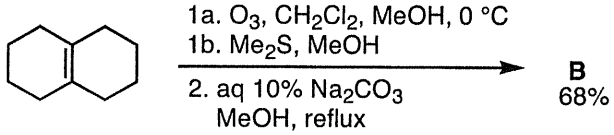


Step 1 Nitrile α-anion formation and alkylation.
Step 2a Controlled reduction of the nitrile with DIBAL-H (1.1 eq).
Step 2b Acid workup gives the imine product which then undergoes hydrolysis to the corresponding aldehyde.

b.



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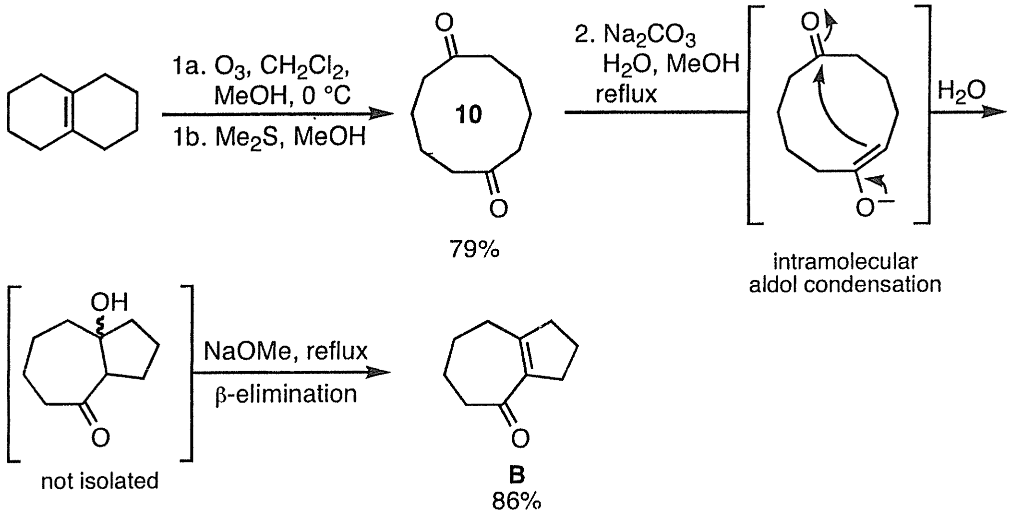
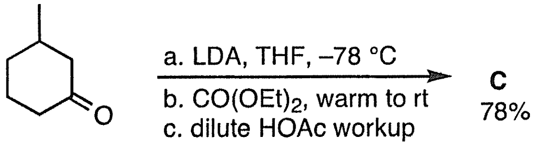


Reference: House, H. O.; Lee, J. H. C.; VanDerveer, D.; Wissinger, J. E. *J. Org. Chem.* **1983**, *48*, 5285.

c.



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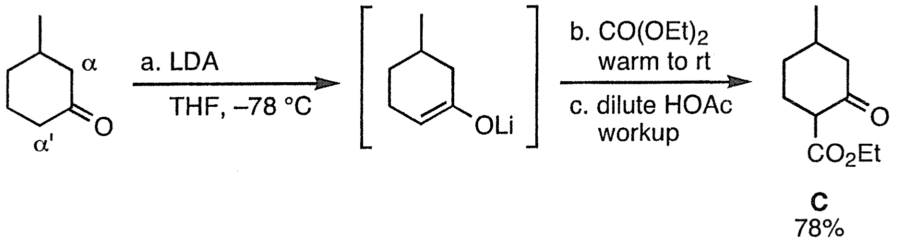
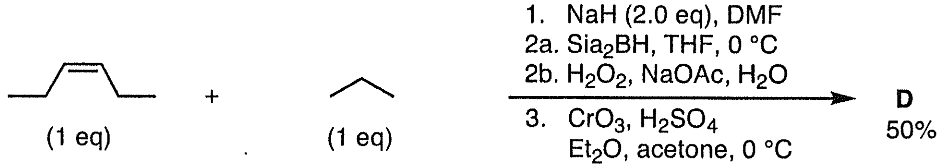


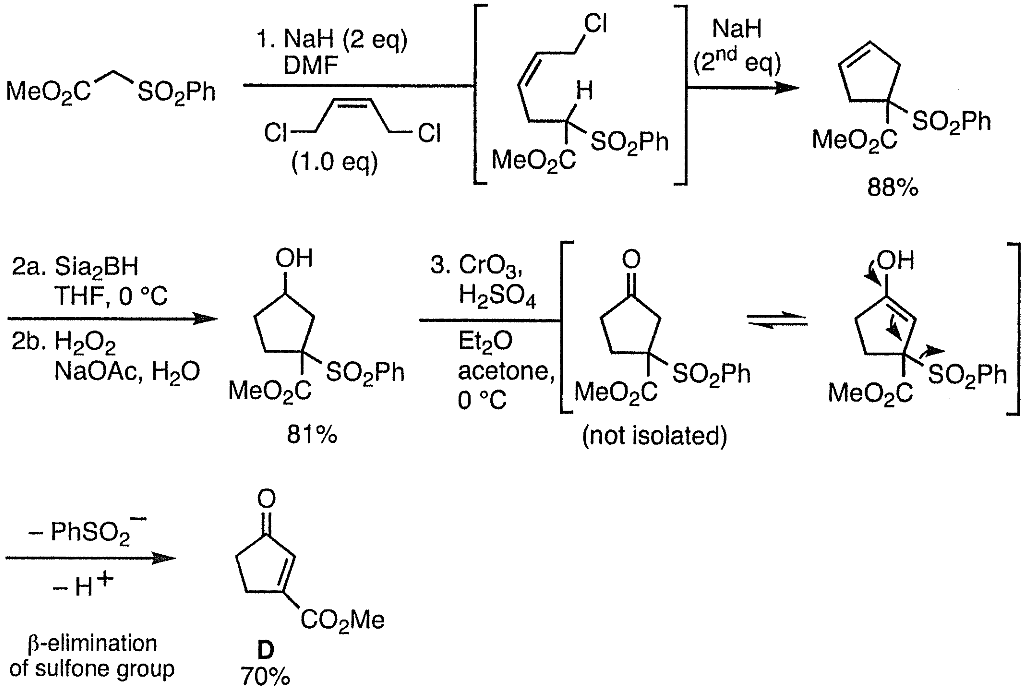
Step a. Regioselective enolate formation, directed toward the sterically less encumbered α'-position.

Reference: Riechers, T.; Krebs, C. H.; Wartchow, R.; Habermehl, G. *Eur. J. Org. Chem.* **1998**, 2641.

d.

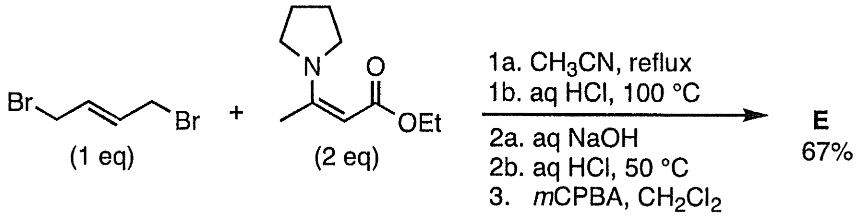


Solution:



Reference: Nantz, M. H.; Radisson, X.; Fuchs, P. L. *Synth. Commun.* **1987**, *17*, 55.

e.



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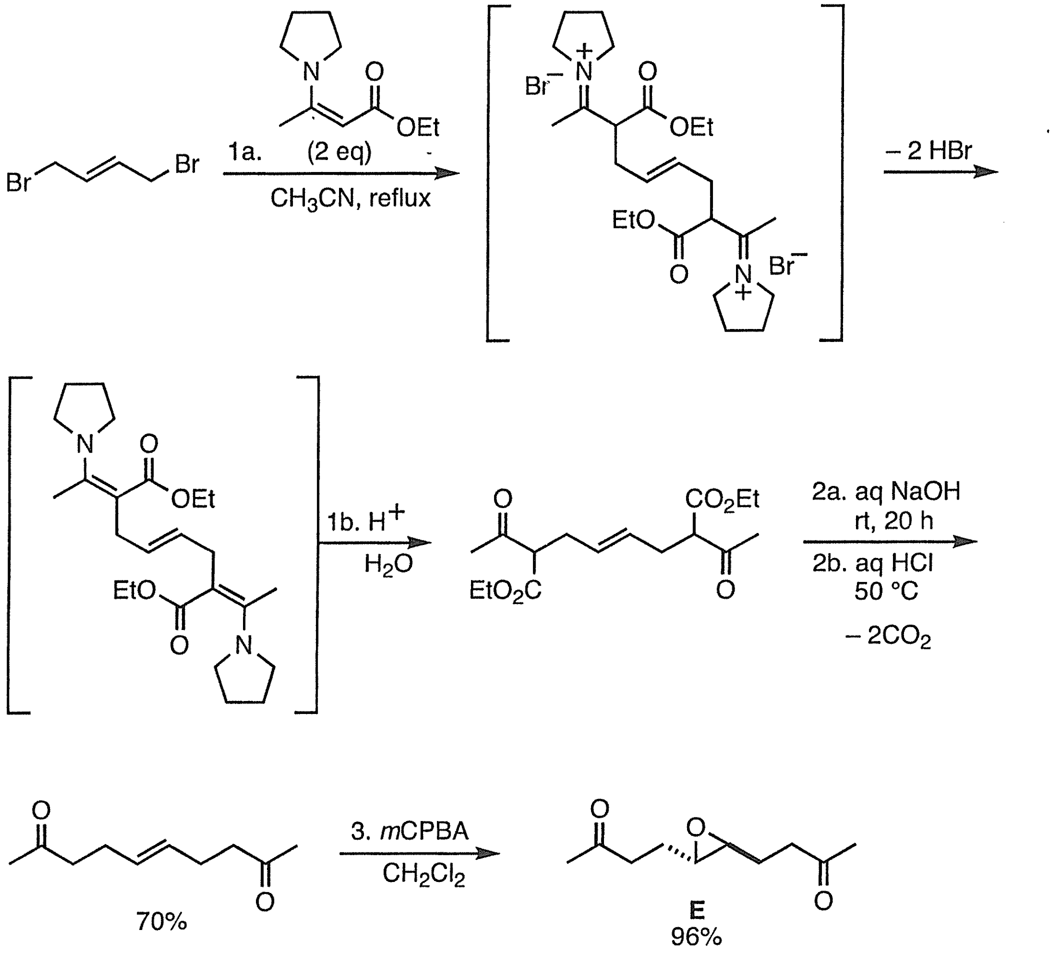
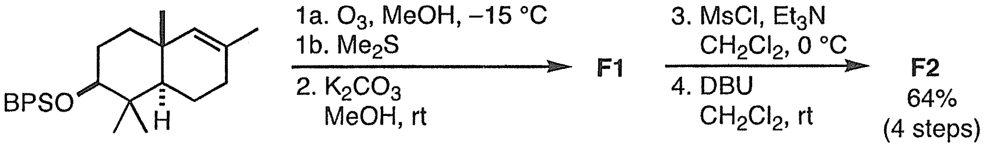


Step 1 Enamine alkylation followed by iminium ion hydrolysis.
Step 2 Ester saponification followed by acidification (–CO$_2$Na to –CO$_2$H) and decarboxylation of the β-keto acids.

Reference: Holland, J. M.; Lewis, M.; Nelson, A. *J. Org. Chem.* **2003**, *68*, 747.

f.



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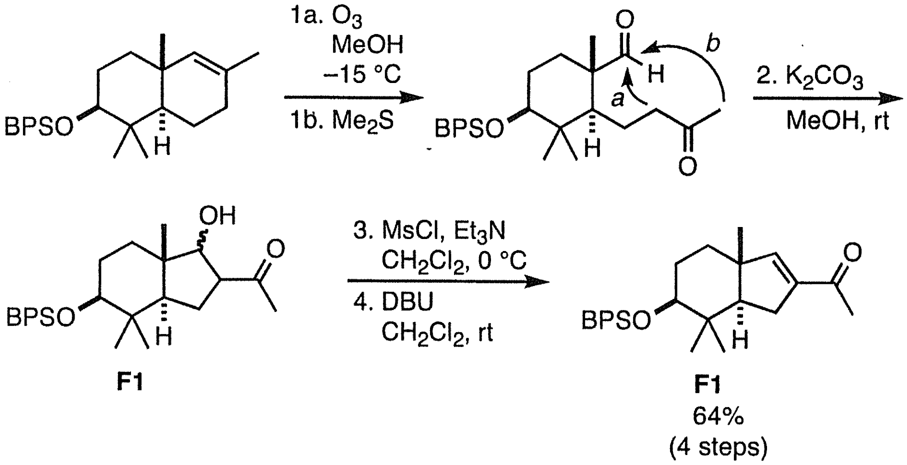
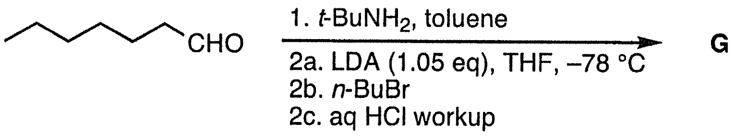


Step 2 Intramolecular aldol condensation; path *a* is favored (five-membered ring formation) over path *b* (seven-membered ring).

Step 4 β-Elimination of OMs^-.

Reference: Falck, J. R.; Manna, S.; Chandrasekhar, S.; Alcaraz, L.; Mioskowski, C. *Tetrahedron Lett.* **1994**, *35*, 2013.

g.



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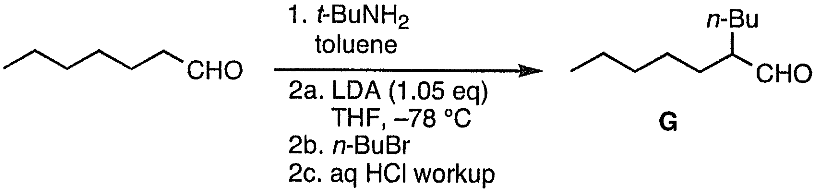
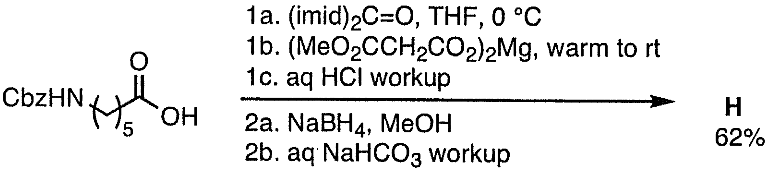


Step 1 Imine formation ensures monoalkylation of the starting aldehyde.

h.



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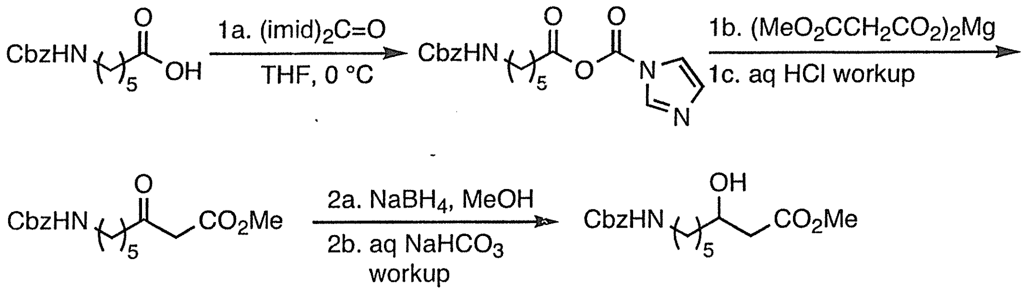
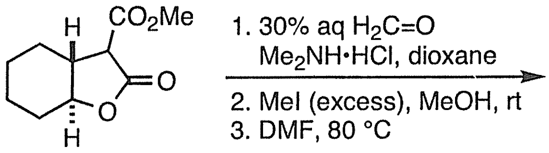


H
62%

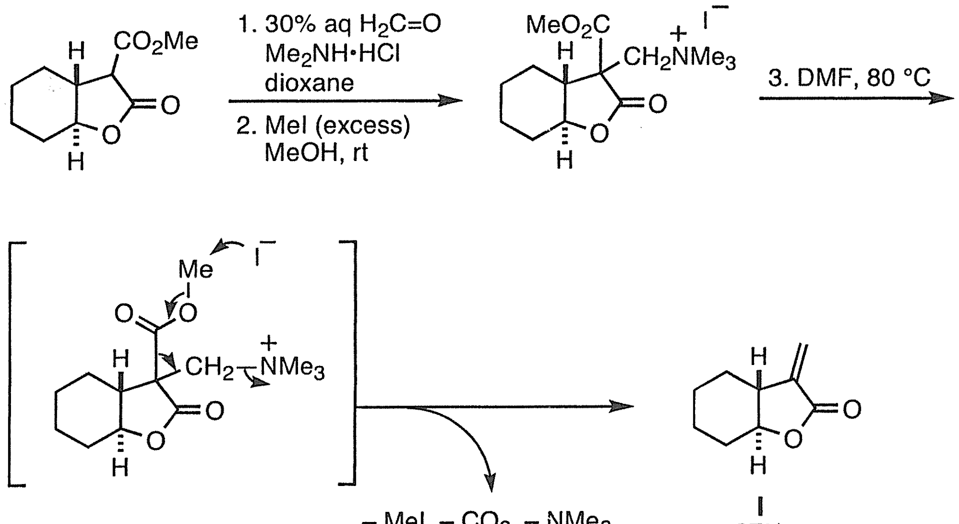
Reference: Durham, T. B.; Miller, M. J. *J. Org. Chem.* **2003**, *68*, 35.

i.



I
67%

Solution:

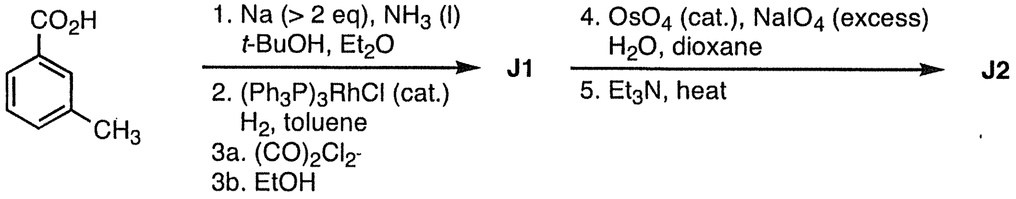


I
67%

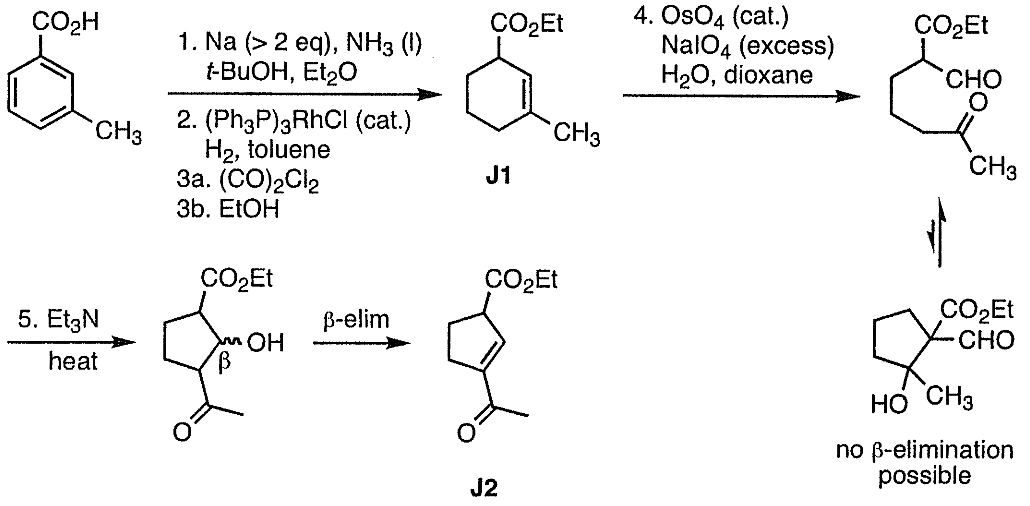
Step 1 Mannich reaction.
Step 3 The reaction proceeds via a nucleophilic decarbalkoxylation.

Reference: Behare, E. S.; Miller, R. B. *J. Chem. Soc. Chem. Commun.* **1970**, 402.

*j.



Solution:



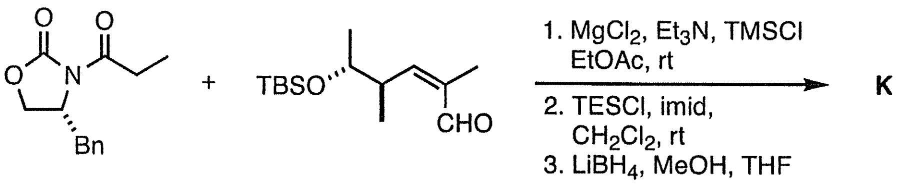
Step 1 Birch reduction.

Step 2 Wilkinson's catalyst $(Ph_3P)_3RhCl$ allows the selective hydrogenation of the less substituted double bond of the 1,4-cyclohexadiene system.

Step 5 Under these thermodynamic conditions, equilibration among the enolate anions leads to ring closure to form the thermodynamically more stable conjugated system.

---

*k.



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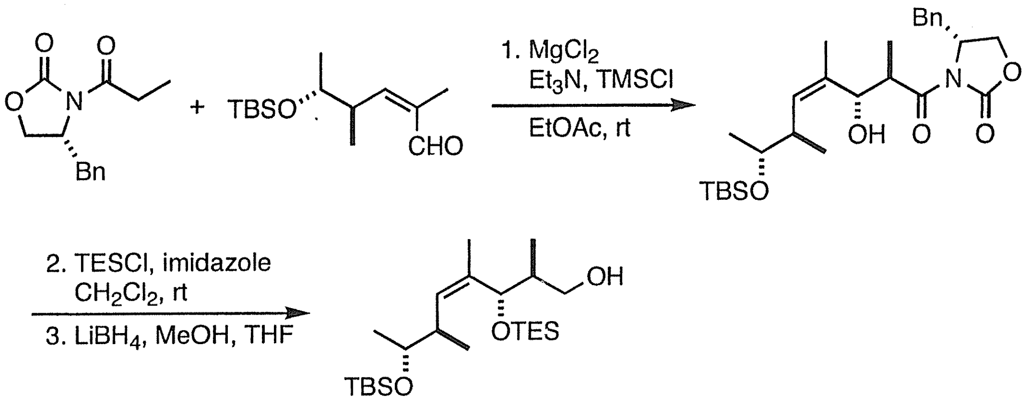
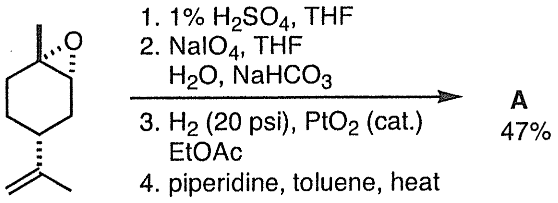


K

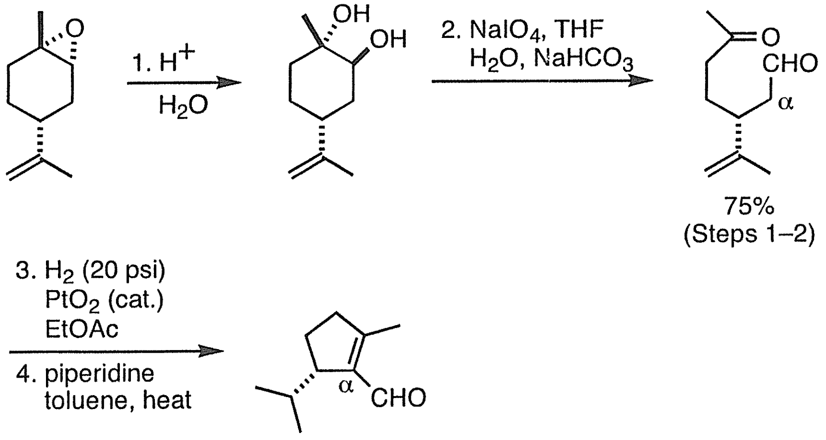
Reference: For an analogous synthesis, see Gaul, C.; Njardarson, J. T.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2003**, *125*, 6042.

2. **Selectivity.** Show the product(s) obtained or appropriate reagent(s) to be used for each step of the following transformations.

a.



Solution:



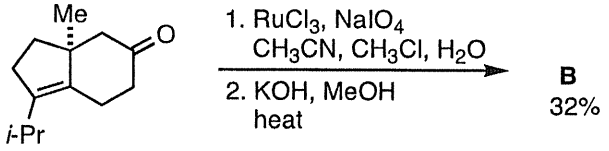
A
63%
(Steps 3–4)

Step 3 Hydrogenation of the terminal double bond.

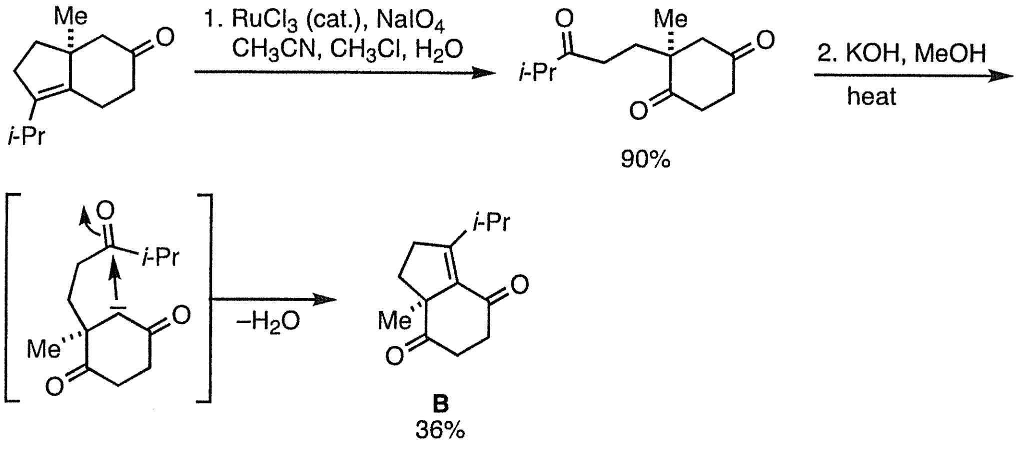
Step 4 Intramolecular aldol condensation favors the five-membered ring over the seven-membered ring (see Baldwin's rules for ring closure).

Reference: Mehta, G. *Pure & Appl. Chem.* **1990**, *62*, 1263.

b.



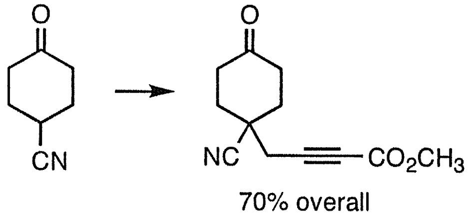
Solution:



Step 4 Intramolecular aldol condensation favors the five-membered ring over the six-membered ring.

Reference: Mehta, G.; Krishnamurthy, N.; Karra, S. R. *J. Am. Chem. Soc.* **1991**, *113*, 5765.

c.



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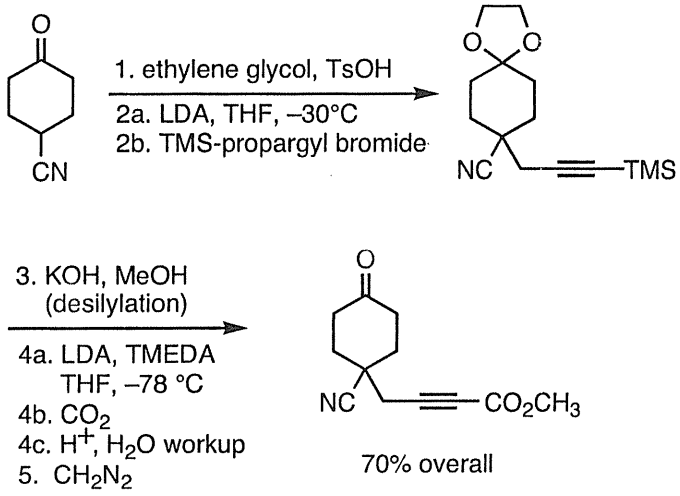
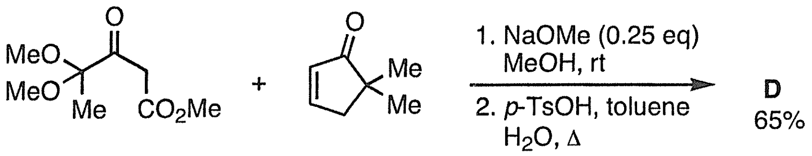


Step 4a Note the use of LDA instead of either *n*-BuLi or MeLi to form the lithium acetylide.

Step 4c Protonation of the lithium carboxylate *and* acetal hydrolysis.

Reference: Trost, B. M.; Shuey, C. D.; DiNinno, F., Jr.; McElvain, S. S. *J. Am. Chem. Soc.* **1979**, *101*, 1284.

d.



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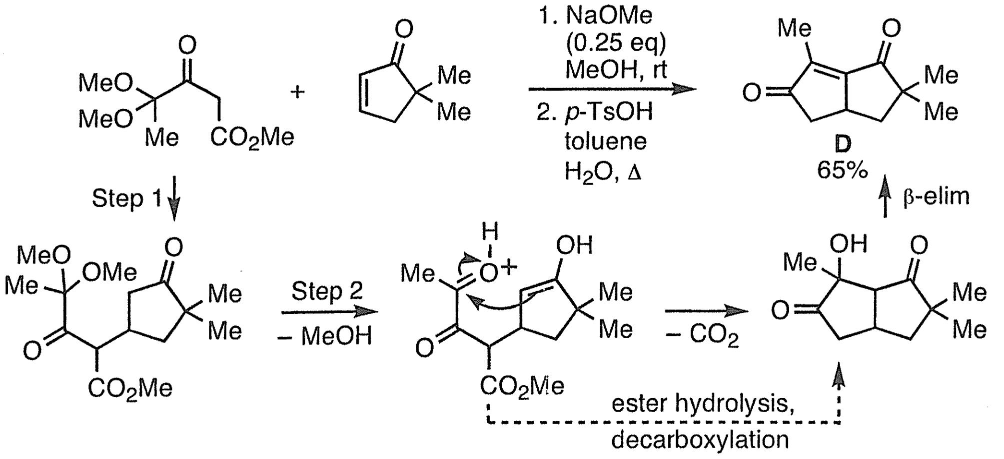
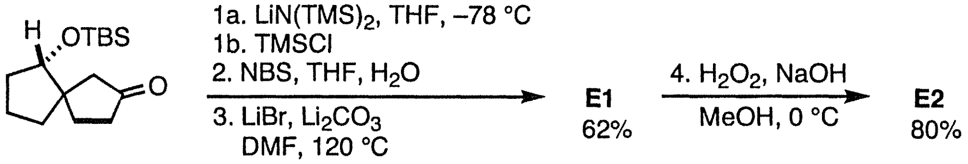


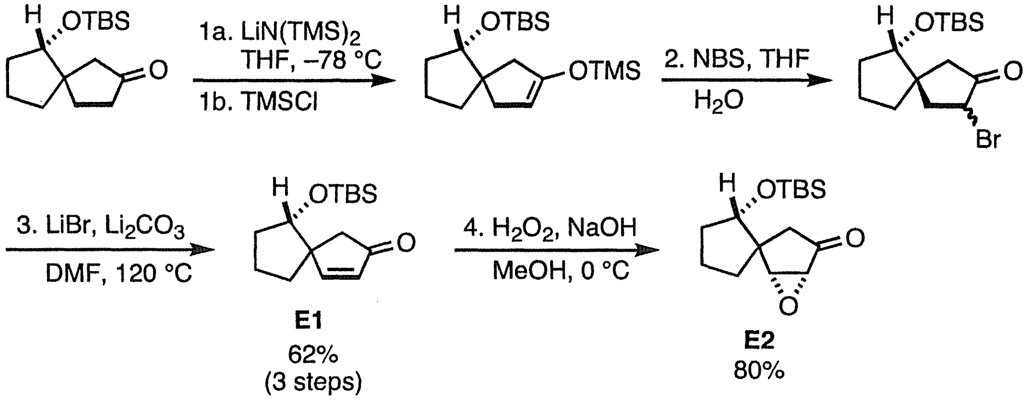
Step 1 Michael addition.
Step 2 Dimethyl acetal hydrolysis; ester hydrolysis followed by decarboxylation; intramolecular acid-catalyzed aldol condensation followed by dehydration.

Reference: Danishefsky, S.; Zamboni, R.; Kahn, M.; Etheredge, S. J. *J. Am. Chem. Soc.* **1980**, *102*, 2097.

***e.**



Solution:

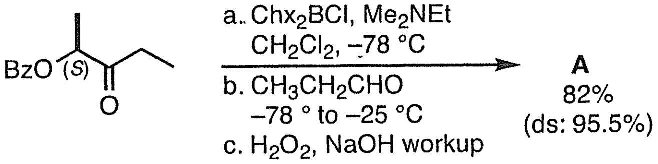


Step 1 Regioselective enolization due to steric shielding of the α-OTBS group followed by *O*-silylation.
Step 2 Bromination of the silyl enol ether to give the α-bromo ketone.
Step 3 Dehydrohalogenation.
Step 4 Conjugate addition of HOO$^-$ from the less shielded α-face of the enone.

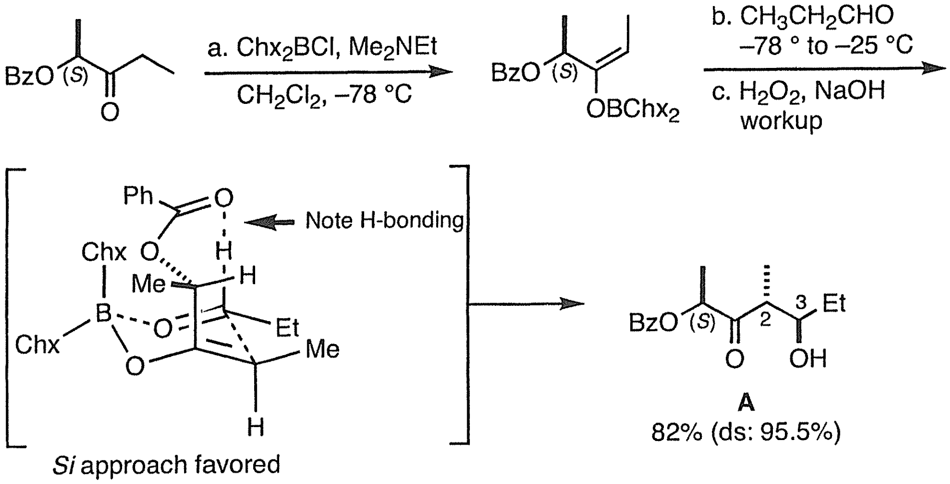
Reference: Hartung, R.; Paquette, L. A. *J. Org. Chem.* **2005**, *70*, 1597.

3. **Stereochemistry**. Give the structure and predict the stereochemistry of the major product formed in each step for each of the following reactions. Give an explanation for your choice.

a.



Solution:

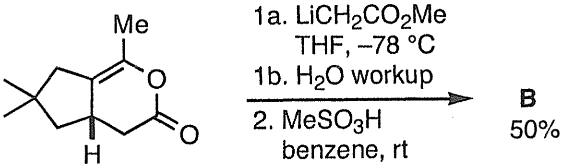


Step a *E*-(*O*)-boron enolate conditions; reaction with RCHO results in a 2,3-*anti* aldol product.

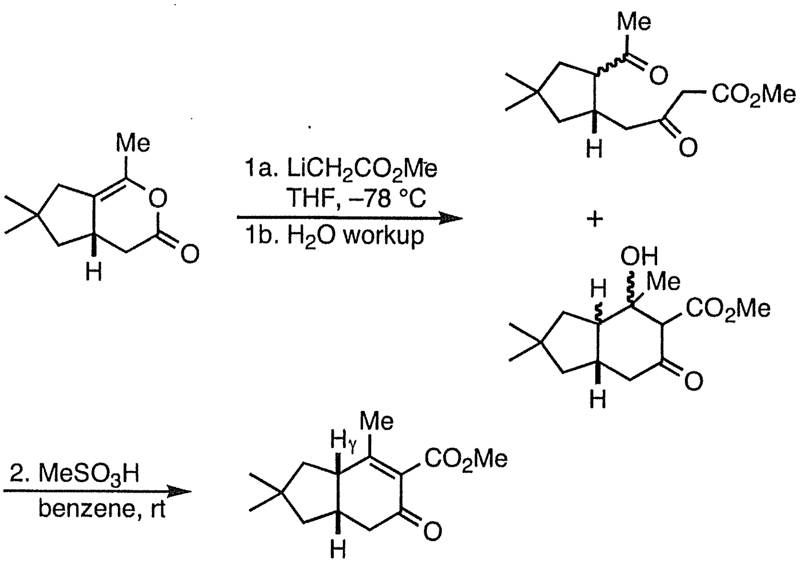
Step b π-Facial selectivity may be determined by the stabilizing effect of the H-bond between the benzoate oxygen with the aldehyde hydrogen (see *Tetrahedron Lett.* **1997**, *38*, 33).

Reference: Paterson, I.; Wallace, D. J.; Cowden, C. J. *Synthesis* **1998**, 639.

b.



Solution:

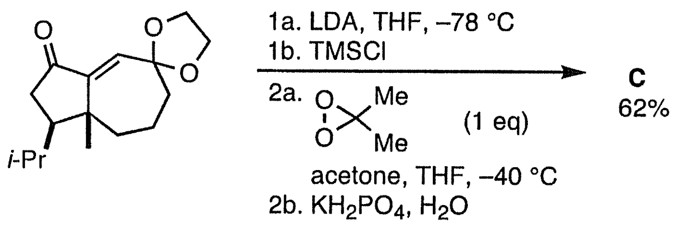


B
50% overall

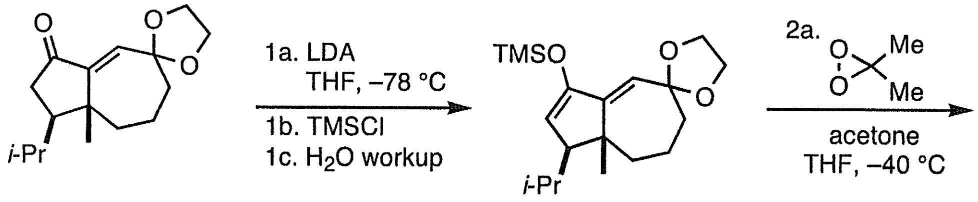
Step 2 Formation of the *cis*-fused 5,6 ring is thermodynamically preferred. The acidic conditions lead to the equilibration (epimerization) of one of the bridgehead positions via enol-keto tautomerization due to the acidity of the γ-hydrogen, activated by the enone and ester groups.

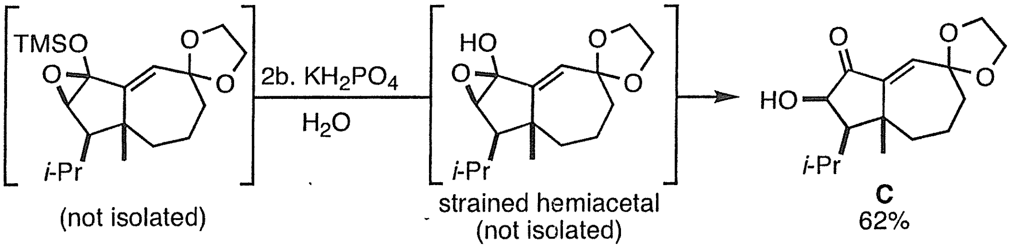
Reference: Thompson, S. K.; Heathcock, C. H. *J. Org. Chem.* **1992**, *57*, 5979.

c.



Solution:





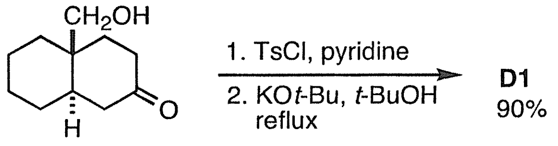
Step 2a Regio- *and* stereoselective epoxidation of the more nucleophilic silyl enol ether (double bond). Although it seems at first counterintuitive, the epoxidation occurs from the β-face (build a molecular model).

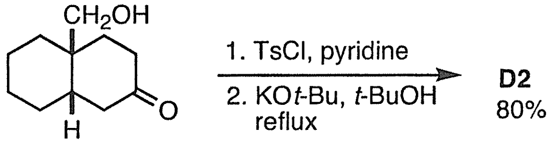
Step 2b Silyl ether hydrolysis followed by hemiacetal equilibration leads to the keto-alcohol. Step 2 is a modified Rubottom reaction (*Org. Synth.* **1985**, *64*, 118).

Note: The acetal functional group survives the reaction conditions in Steps 1–2.

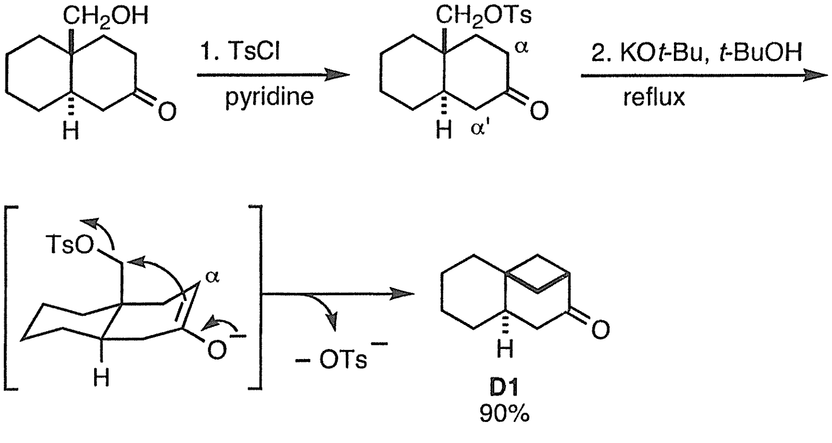
Reference: Shi, B.; Hawryluk, N. A.; Snider, B. B. *J. Org. Chem.* **2003**, *68*, 1030.

d.

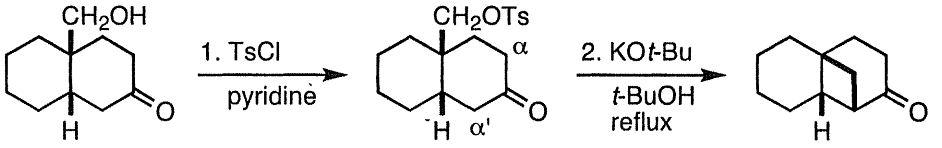




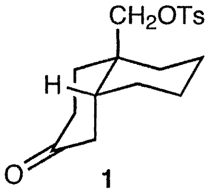
Solution:



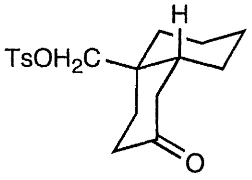
Enolate formation at the less hindered α-position followed by intramolecular tosylate displacement affords **D1**.



D2
80%



1
unreactive conformer

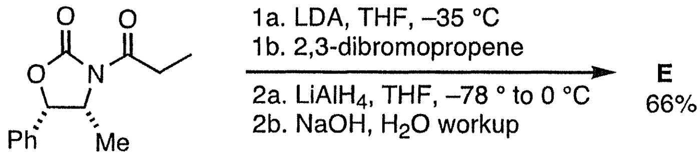


2

Of the two chair conformations for the *cis*-keto tosylate, **1** and **2**, only conformation **2** where the angular TsOCH$_2$– group is axial to the ring bearing the C=O group can undergo intramolecular displacement. The rate of α-enolate vs α'-enolate formation plays a lesser role in determining the regiochemical outcome of the reaction.

Reference: Mukharji, P. C.; Ganguly, A. N. *Tetrahedron* **1969**, *25*, 5267.

***e.**



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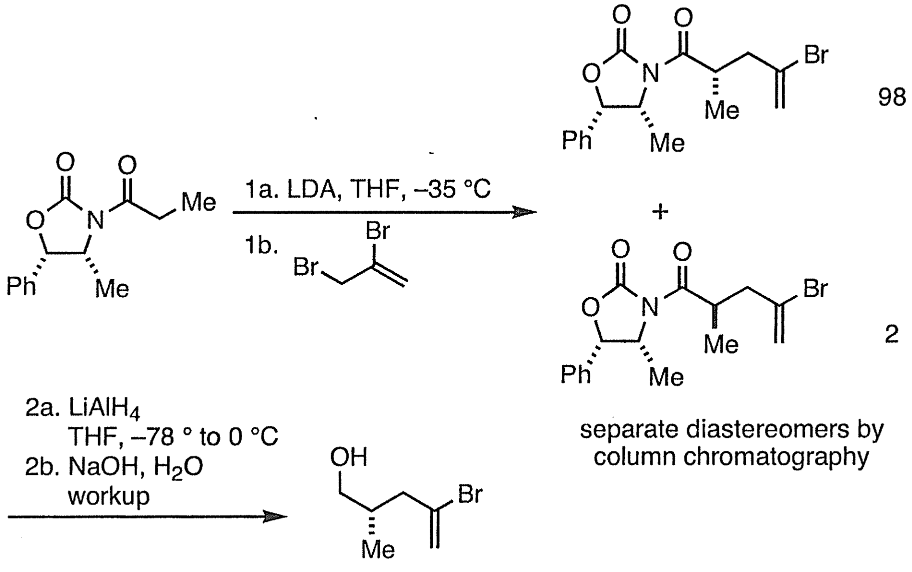
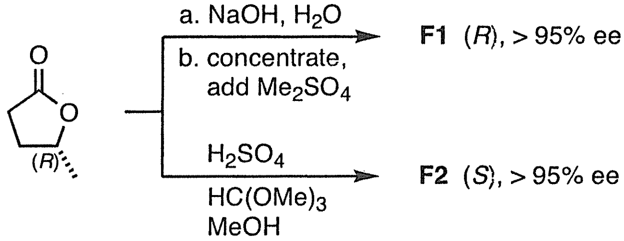


E
66% overall

Reference: Evans, D. A.; Bender, S. L.; Morris, J. *J. Am. Chem. Soc.* **1988**, *110*, 2506.

*f.



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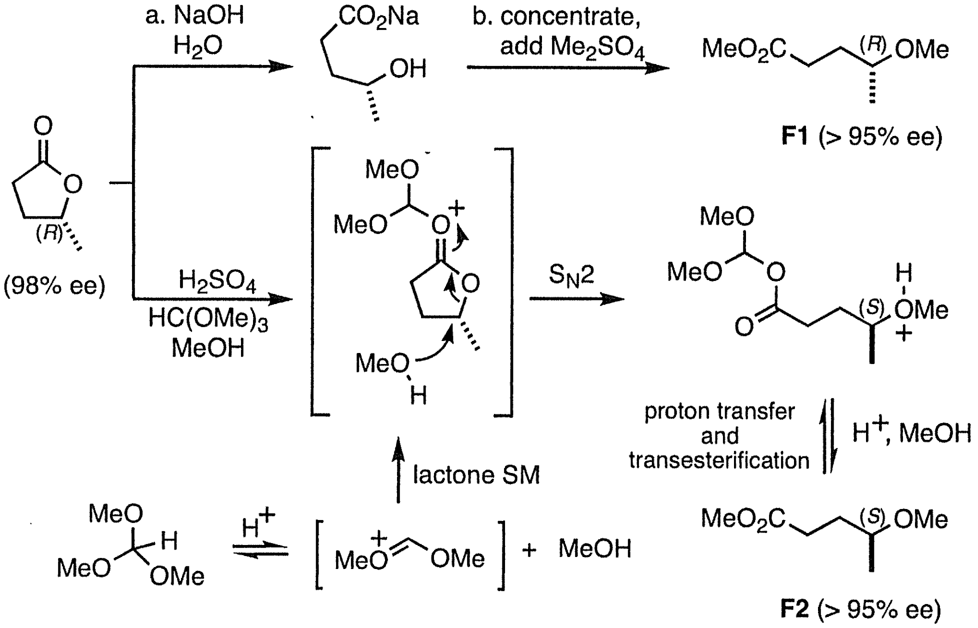


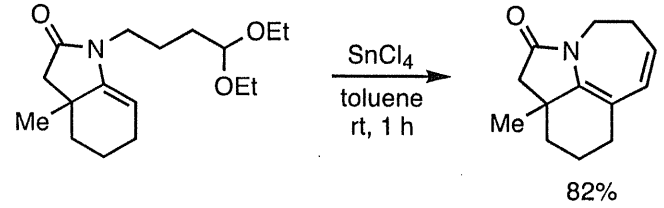
Base–catalyzed reaction (**F1**):
Saponification followed by alkylation with dimethylsulfate; no inversion of the chiral center.

Acid–catalyzed reaction (**F2**):
Trimethylorthoformate forms a stabilized dioxocarbenium ion which activates the lactone towards attack by methanol with S_N2 inversion at the methyl-substituted carbon.

Reference: King, S. A. *J. Org. Chem.* **1994**, *59*, 2253.

4. **Reactivity**. Propose mechanisms for each of the following transformations.

a.



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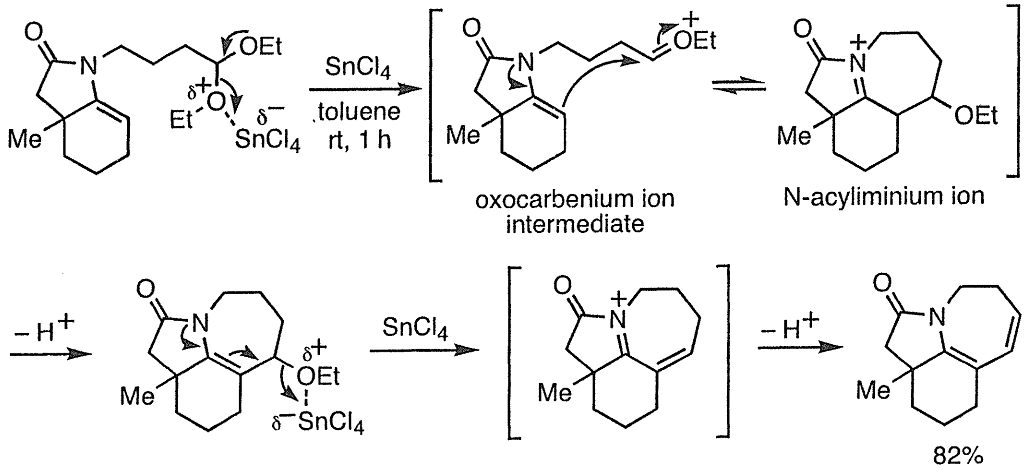
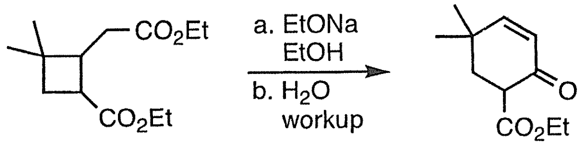


Reference: Padwa, A.; Lee, H. I.; Rashatasakhon, P.; Rose, M. *J. Org. Chem.* **2004**, *69*, 8209.

b.



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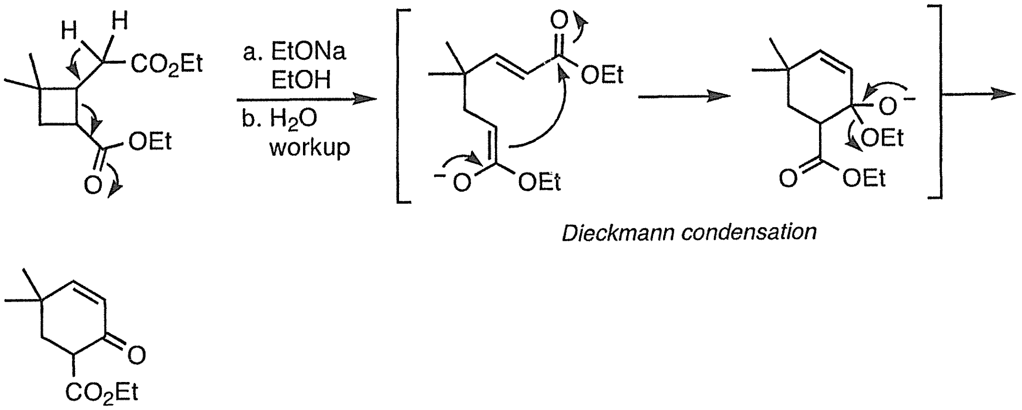
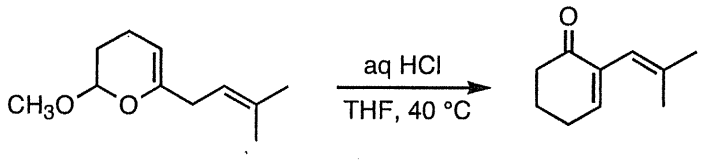


The driving force for the β-elimination of the ester enolate is relief of the cyclobutane ring strain.

c.



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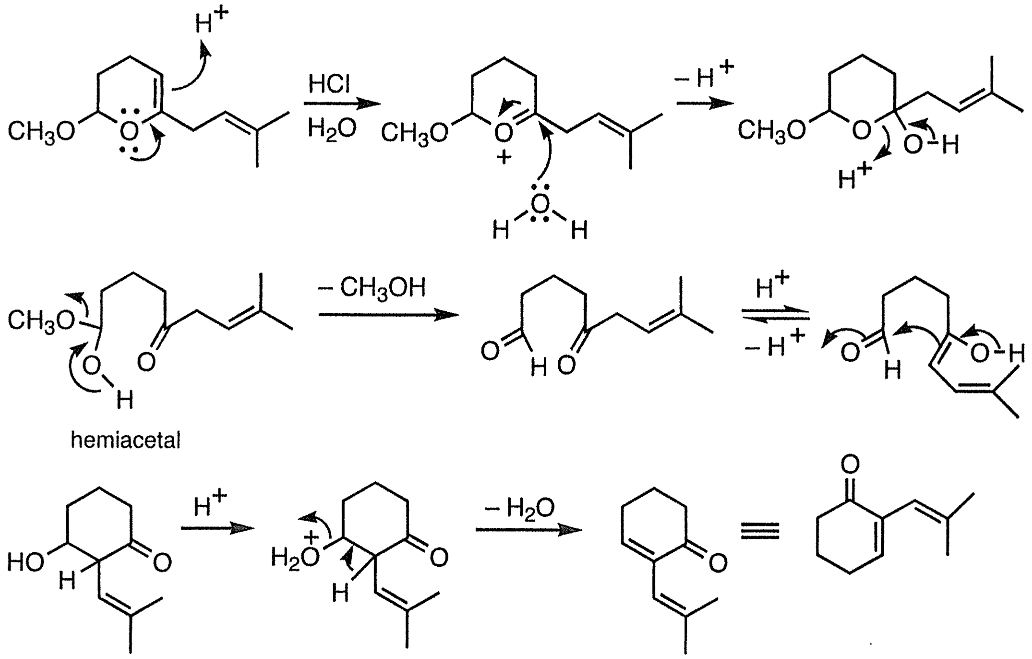
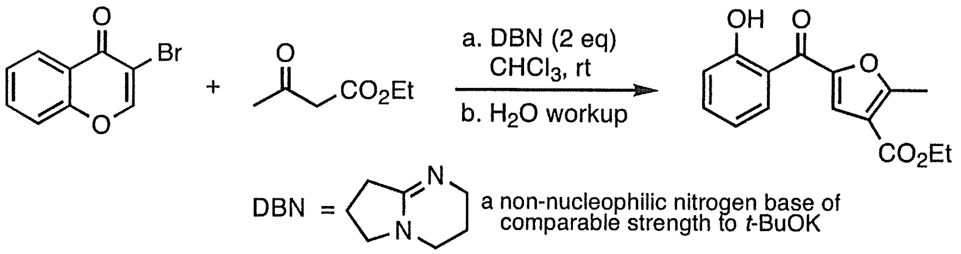


Reference: Boeckman, R. K., Jr.; Bruza, K. J. *Tetrahedron Lett.* **1977**, 4187.

d.



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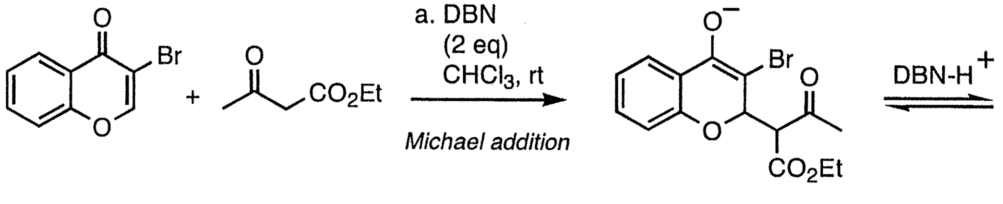
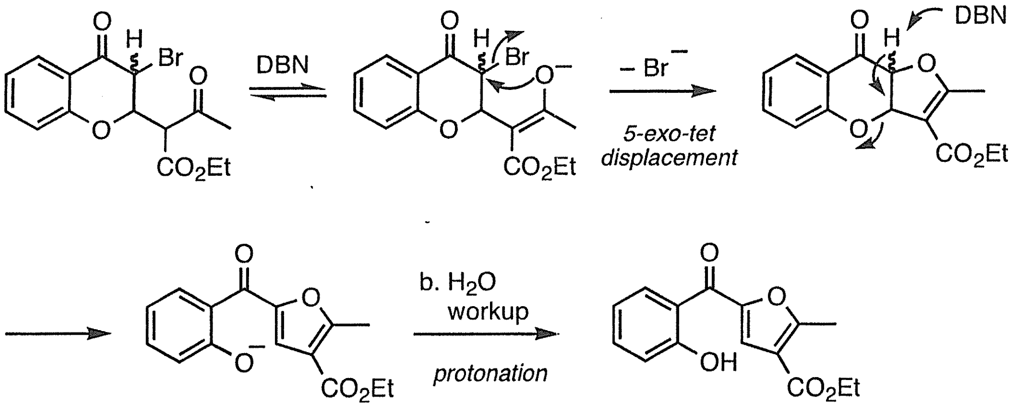
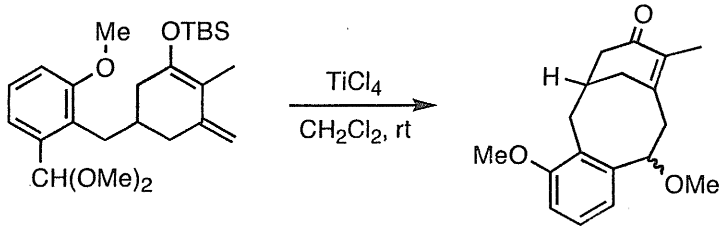




Reference: Gammill, R. B. *J. Org. Chem.* **1979**, *44*, 3988.

***e.**



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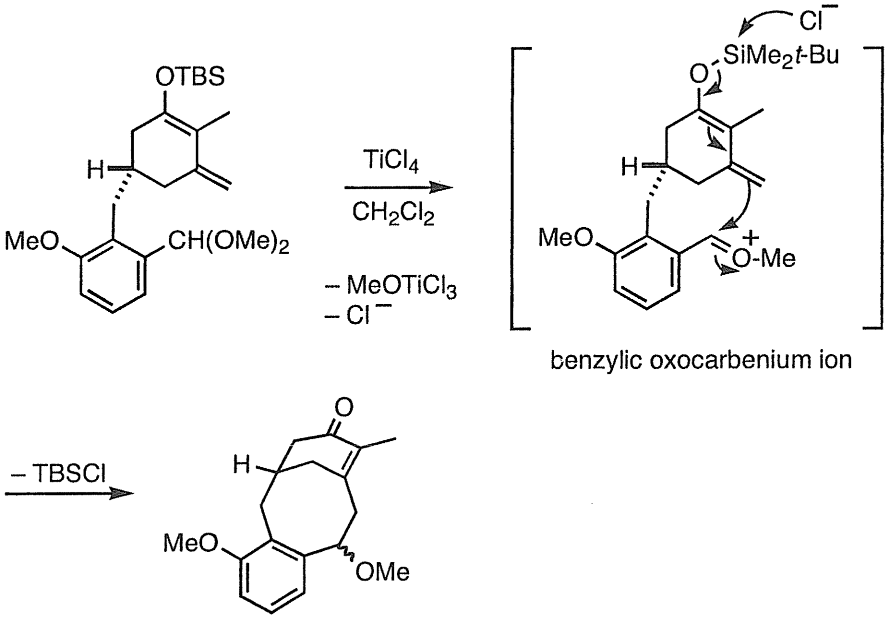
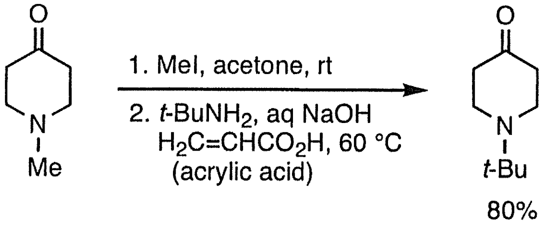


The electron–rich aryl ring assists the Lewis acid–induced formation of the reactive intermediate oxocarbenium ion. Ring closure occurs via Mukaiyama-type trapping of the oxocarbenium ion by the silyl dienol ether.

Reference: Morihira, K.; Seto, M.; Furukawa, T.; Horiguchi, Y.; Kuwajima, I. *Tetrahedron Lett.* **1993**, *34*, 345.

***f.**



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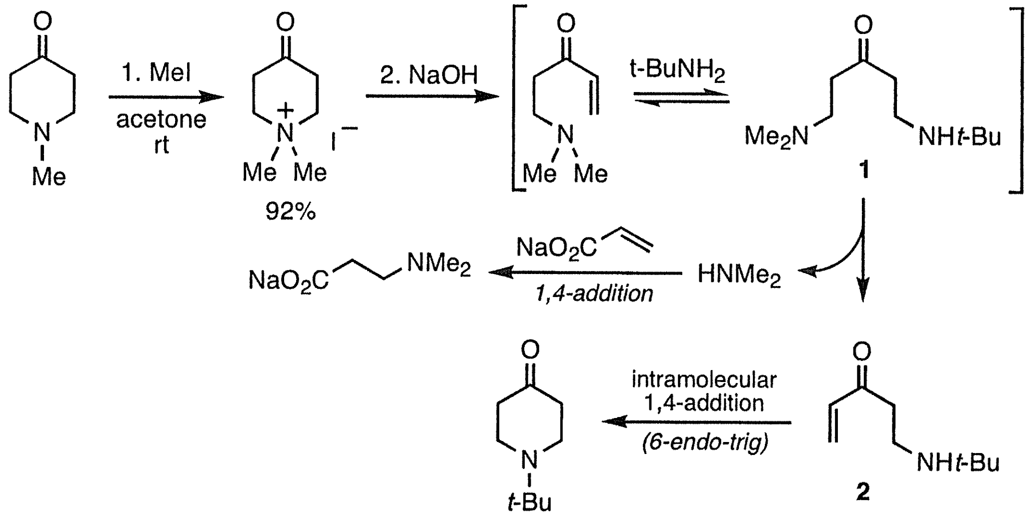
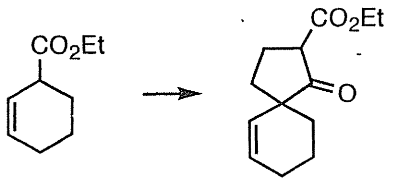


Step 2 Hofmann elimination/Michael addition equilibrations. Acrylic acid functions as an efficient and selective trap for dimethyl amine vs. tert-butylamine, allowing for facile control of the equilibrium between **1** and **2**.

Reference: Amato, J. S.; Chung, J. Y. L.; Cvetovich, R. J.; Gong, X.; McLaughlin, M.; Reamer, R. A. *J. Org. Chem.* **2005**, *70*, 1930.

5. **Synthesis.** Supply the reagents required to accomplish each of the following syntheses. Give the structures of the intermediates obtained after each step and show their relative stereochemistry where applicable.

a.



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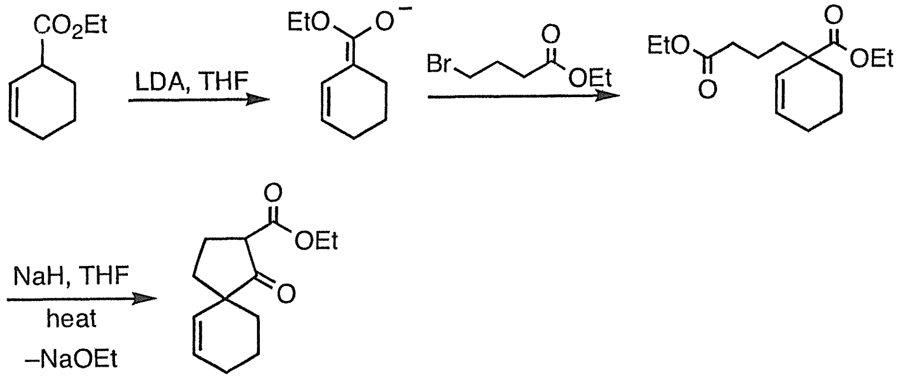
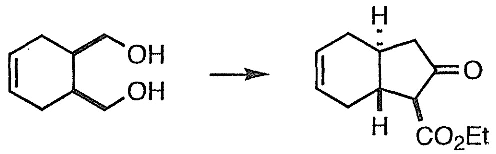


b.



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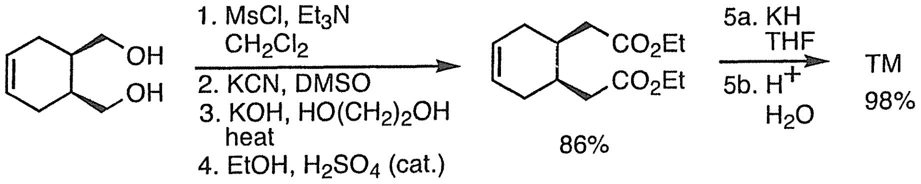
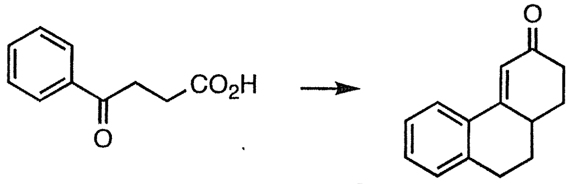


Step 5a Dieckmann condensation.

Reference: McDermott, T. S.; Mortlock, A. A.; Heathcock, C. H. *J. Org. Chem.* **1996**, *61*, 700.

c.



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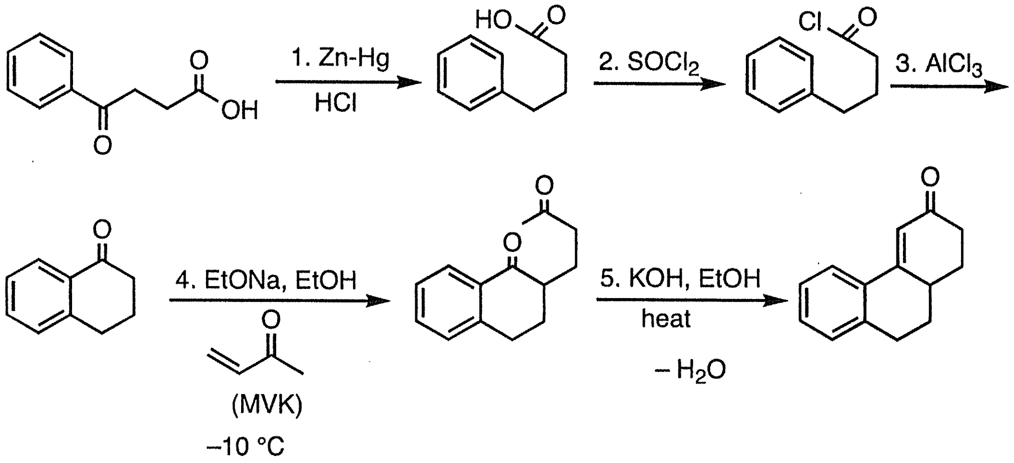
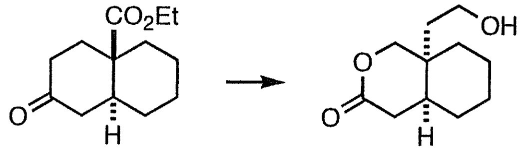


d.



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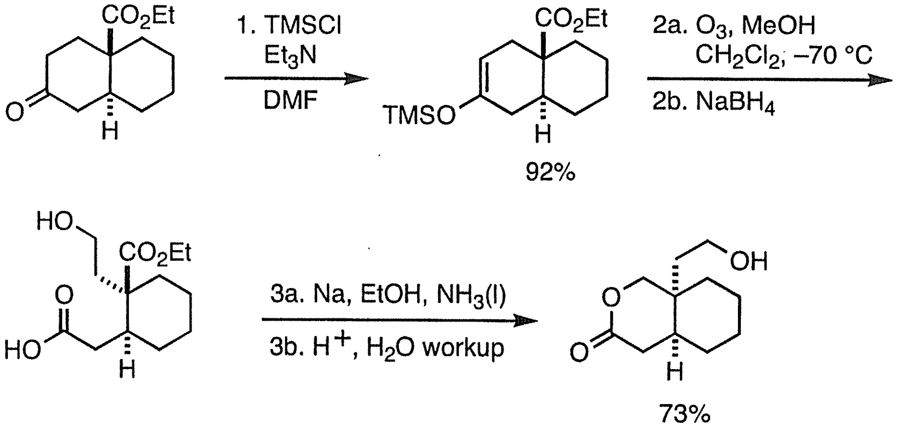

Step 3a Chemoselective reduction of the – CO_2Et group.
Step 3b. Selective lactonization to the six-membered ring lactone.

Reference: Clark, R. D.; Heathcock, C. H. *J. Org. Chem.* **1976**, *41*, 1396.

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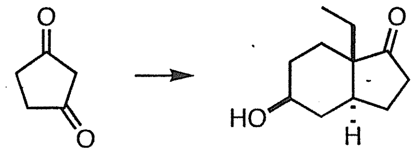
e.



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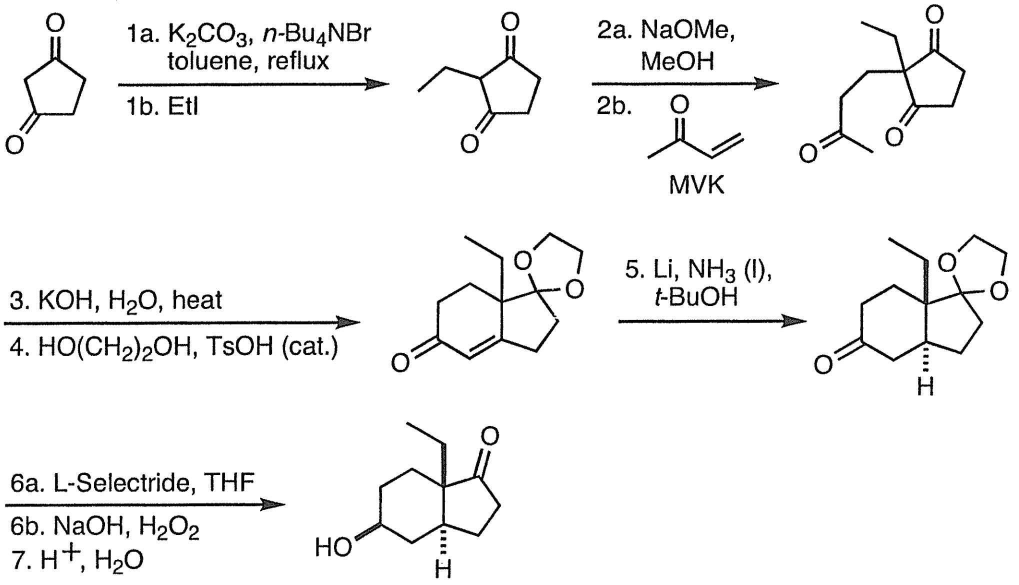

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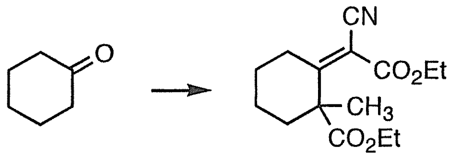
f.



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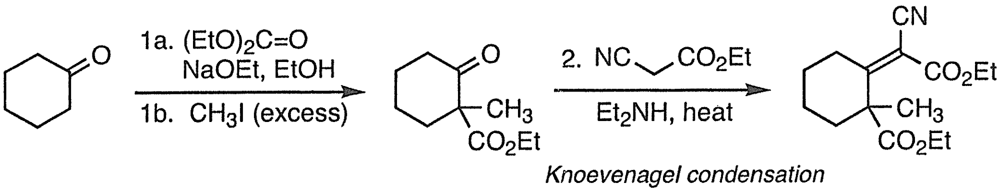
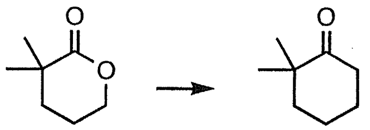


g.



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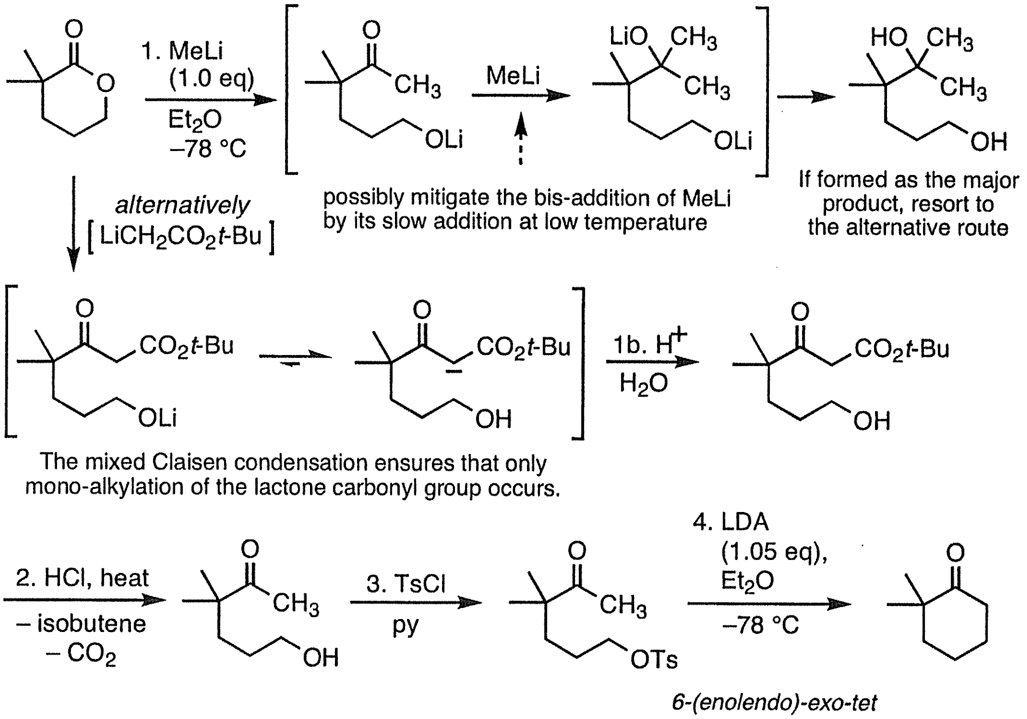


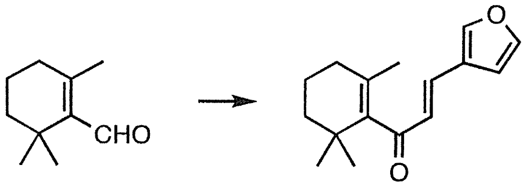
possibly mitigate the bis-addition of MeLi by its slow addition at low temperature

If formed as the major product, resort to the alternative route

The mixed Claisen condensation ensures that only mono-alkylation of the lactone carbonyl group occurs.

6-(enolendo)-exo-tet

h.



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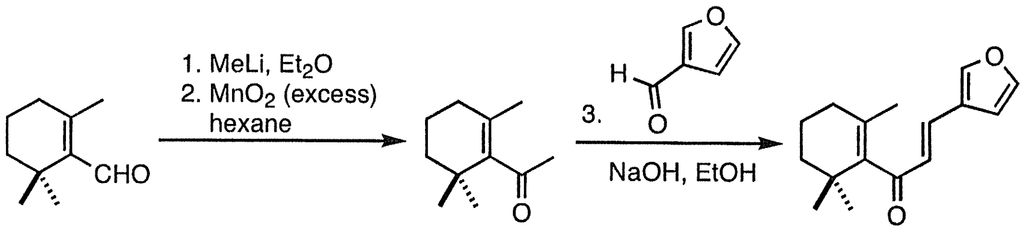
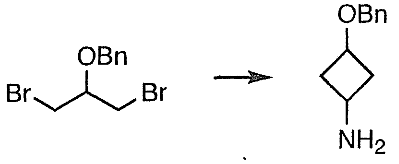


i.



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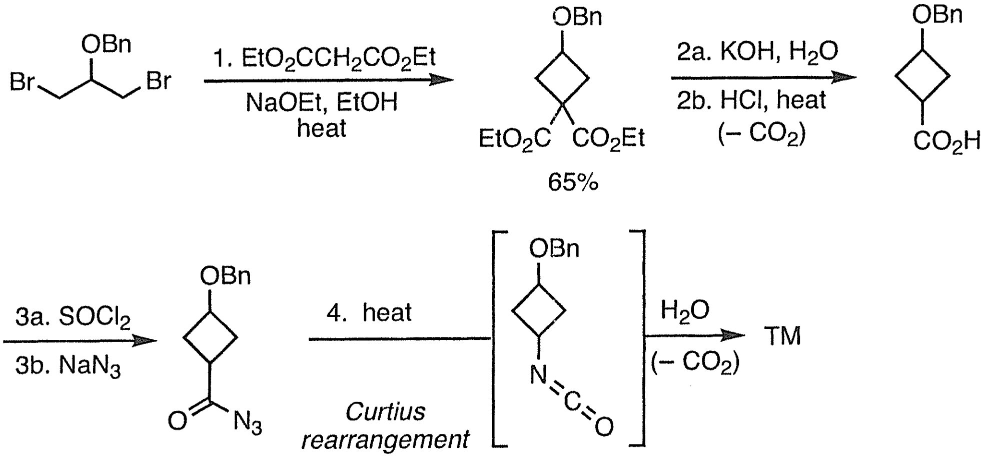
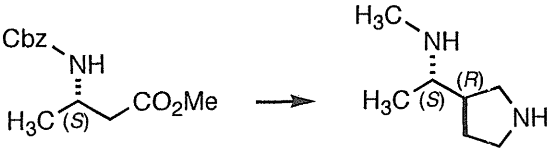


Reference: For analogous synthesis, see Helal, C. J.; Kang, Z.; Lucas, J. C.; Bohall, B. R. *Org. Lett.* **2004**, *6*, 1853.

***j.**



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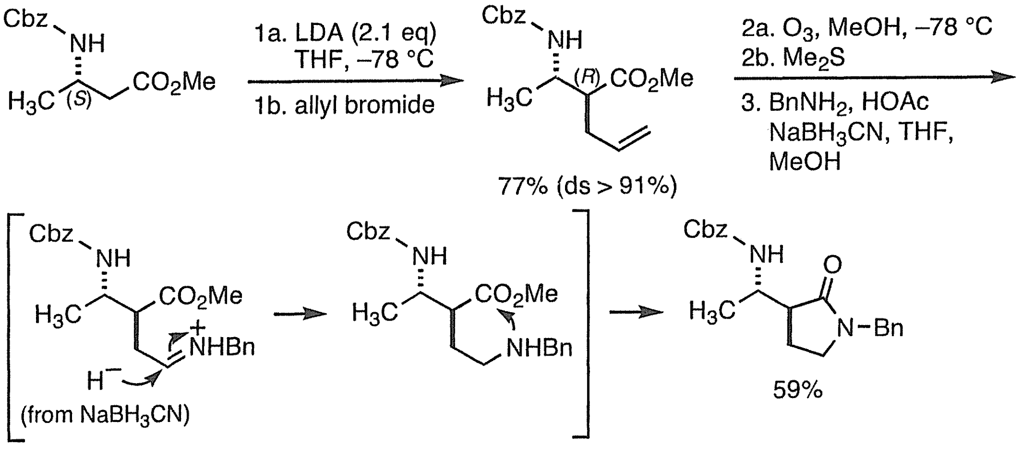
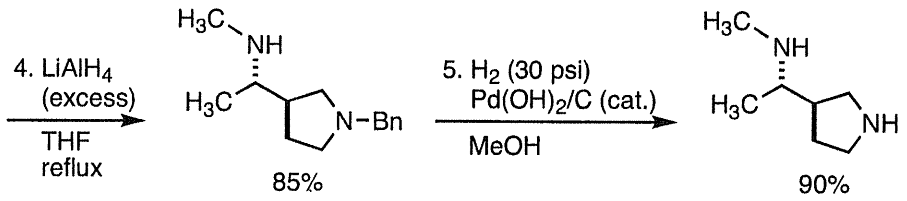




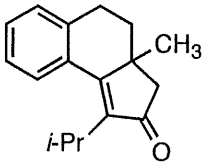
Step 3 Reductive amination of the aldehyde formed in Step 2 followed by intramolecular transamidation.

Step 4 Amide and carbamate reduction.

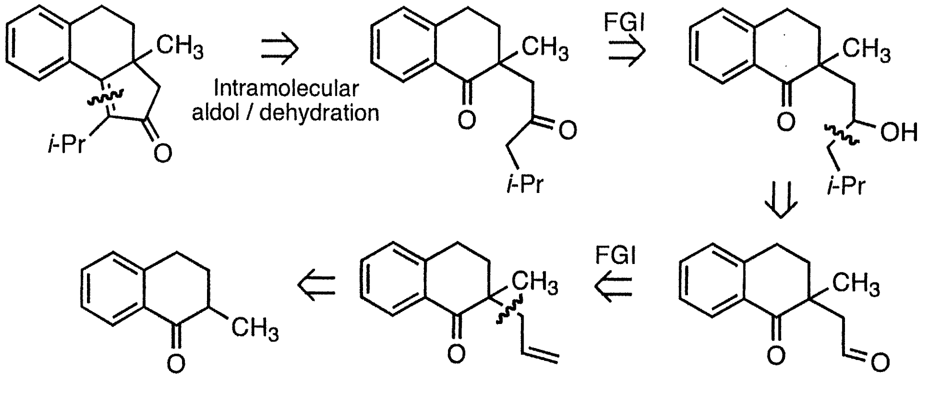
Reference: Fleck, T. J.; McWhorter, W. W., Jr.; DeKam, R. N.; Pearlman, B. A. *J. Org. Chem.* **2003**, *68*, 9612.

6. **Retrosynthetic Analysis.** Outline a synthetic scheme for preparing each of the following target molecules. Show (i) your retrosynthetic analysis, and (ii) all reagents and reaction conditions required to transform a commercially available starting material into the target molecule.

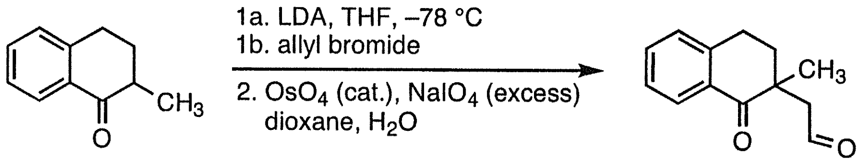
a.

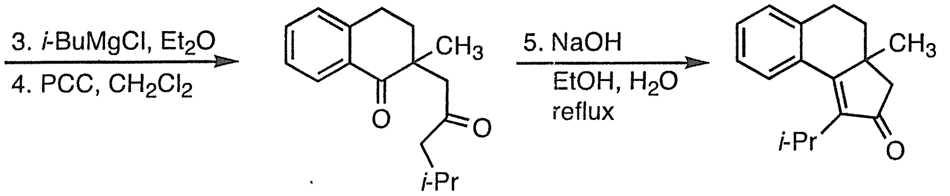


Retrosynthetic analysis:



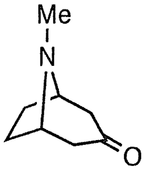
Synthesis:



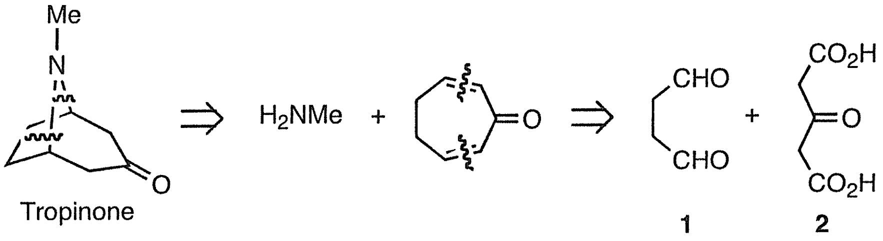


Reference: For analogous synthesis, see Clive, D. L. J.; Wang, J. *J. Org. Chem.* **2004**, *69*, 2773.

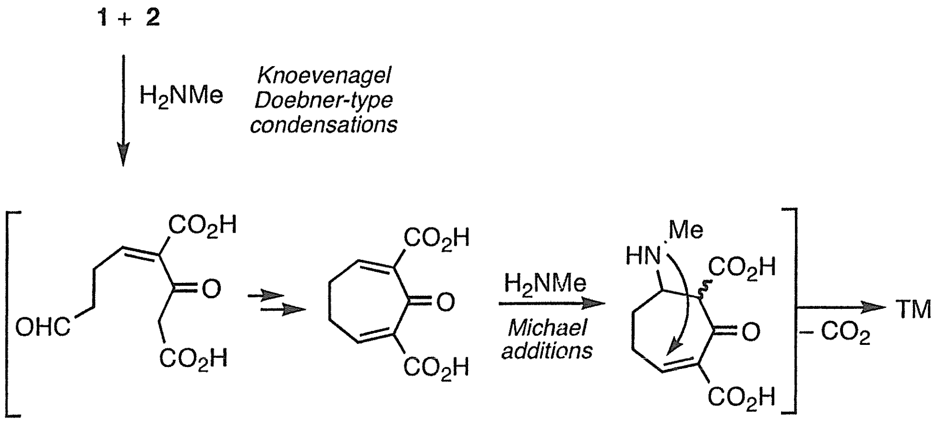
b.



Retrosynthetic analysis:



Synthesis:



Reference: Robinson, R. *J. Chem. Soc.* **1917**, 762.

CHAPTER 7

Formation of Carbon-Carbon Bonds Via Organometallic Reagents

Overview

Chapter 7 deals with the carbon-carbon bond formations via organometallic reagents.

Problem 1 emphasizes the utilization of various organometallic reagents for carbon-carbon bond formations. Problems 2–4 explore the selectivity of reactions involving organometallic reagents. The syntheses of TMs in Problems 5 and 6 require the selection of specific organometallic reagents to achieve chemo-, stereo-, or enantioselective carbon-carbon bond formations.

Key Concepts

- Organolithium reagents
- Organomagnesium (Grignard) reagents
- Organocopper (cuprate) reagents
    - Conjugate (1,4) addition with cuprates
- Preparation of enones
- Organozinc reagents
    - Reformatsky reaction
    - Simmons-Smith reaction
- Organoboron reagents
    - Carbonylations
    - Matteson's boronoc ester homologation
    - Brown's asymmetric crotylboration
- Palladium-catalyzed coupling reactions
    - Heck reaction
    - Negishi reaction
    - Suzuki reaction
    - Stille reaction
    - Trost-Tsuji reaction
    - Sonogashira reaction

SOLUTIONS TO CHAPTER 7 PROBLEMS

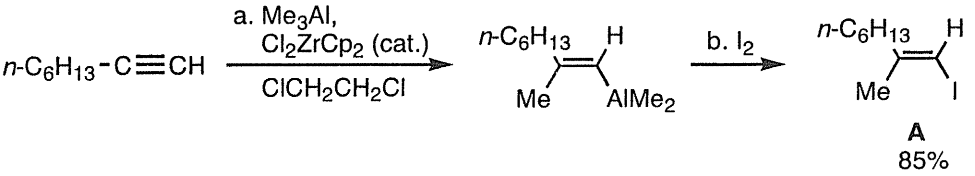
The more challenging problems are identified by an asterisk (*).

1. **Reagents.** Give the structures of the intermediates obtained in each step and the final major product expected for each of the following reaction sequences. Be sure to indicate product stereochemistry where applicable.

a.

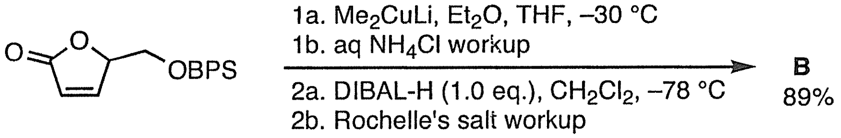
$$n\text{-}C_6H_{13}\text{-}C\equiv CH \xrightarrow[\text{b. } I_2]{\text{a. } Me_3Al,\ Cl_2ZrCp_2 \text{ (cat.)}\ \ ClCH_2CH_2Cl} \underset{85\%}{\mathbf{A}}$$

Solution:



Reference: Negishi, E.; Bagheri, V.; Chatterjee, S.; Luo, F.-T.; Miller, J. R.; Stoll, A. T. *Tetrahedron Lett.* **1983**, *24*, 5181.

b.



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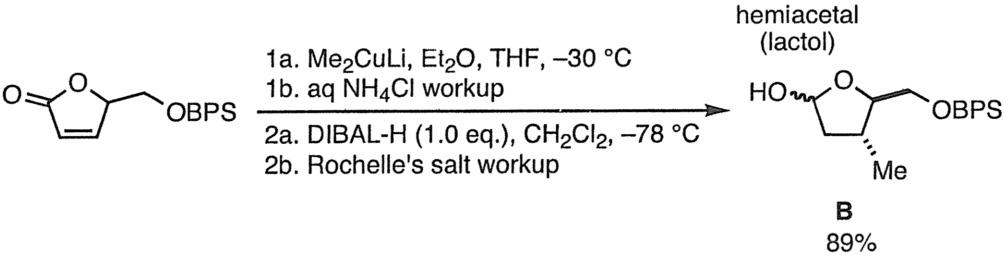
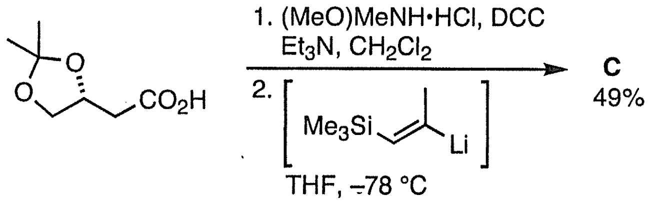


Step 1a Me$_2$CuLi adds in a 1,4-manner.
Step 2a Controlled reduction of the lactone with 1.0 eq. DIBAL-H provides the lactol **B**.

Reference: Paquette, L. A.; Chang, J.; Liu, Z. *J. Org. Chem.* **2004**, *69*, 6441.

c.



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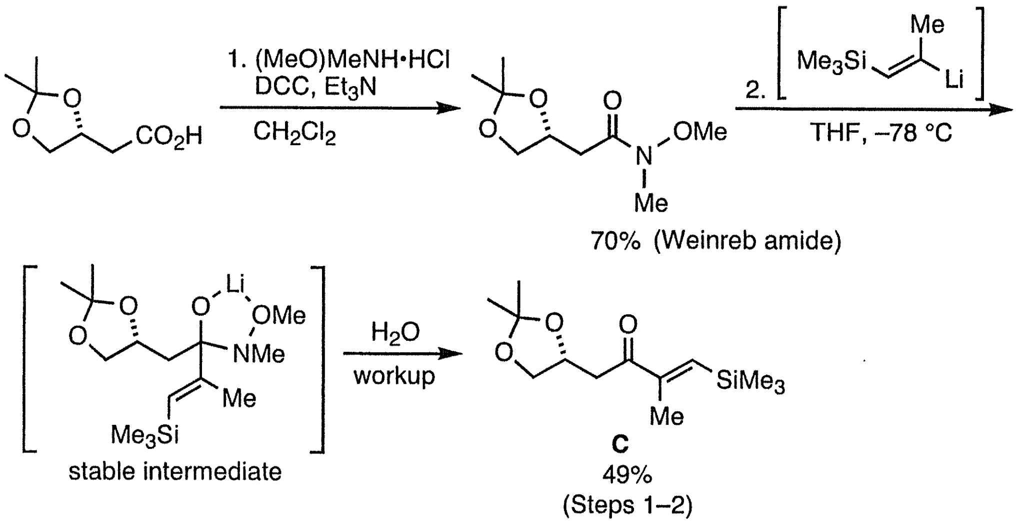
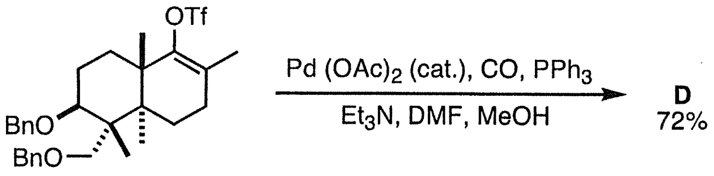


Step 2 The alkyllithium reagent adds only *once* to the Weinreb amide.

Reference: Piscopio, A. D.; Minowa, N.; Chakraborty, T. K.; Koide, K.; Bertinato, P.; Nicolaou, K. C. *J. Chem. Soc., Chem. Commun.* **1993**, 617.

d.



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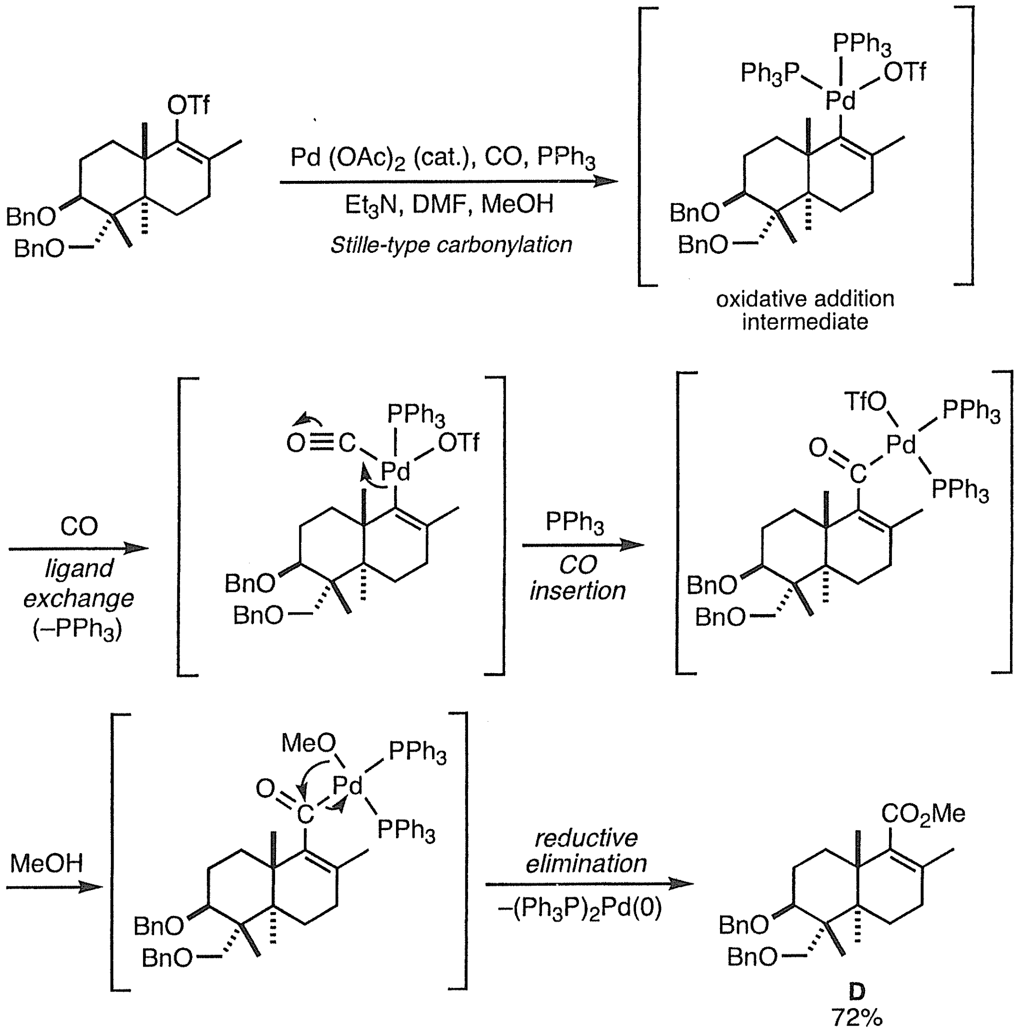
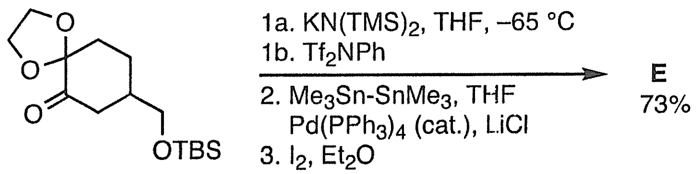


Reference: Nagamitsu, T.; Sunazuka, T.; Obata, R.; Tomoda, H.; Tanaka, H.; Harigaya, Y.; Omura, S.; Smith, III, A. B. *J. Org. Chem.* **1995**, *60*, 8126.

e.



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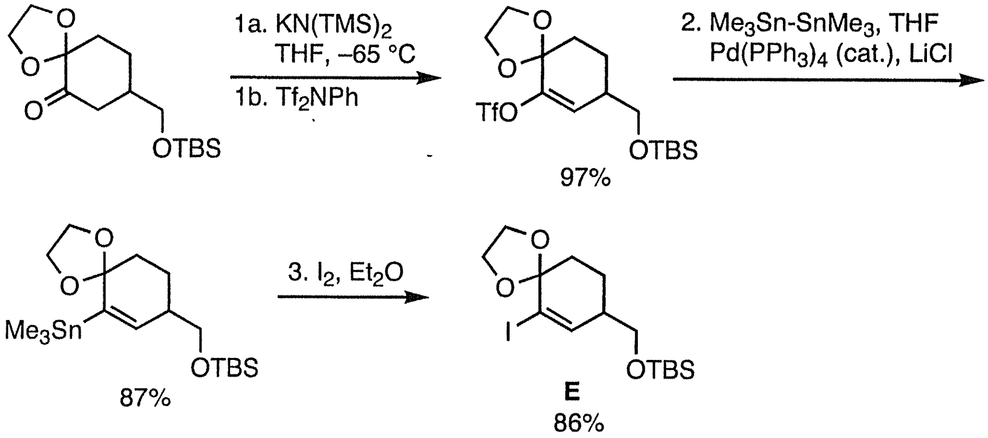
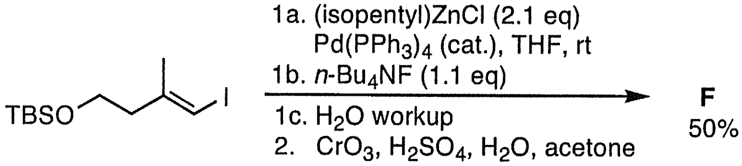


Reference: Su, Z.; Paquette, L. A. *J. Org. Chem.* **1995**, *60*, 764.

f.



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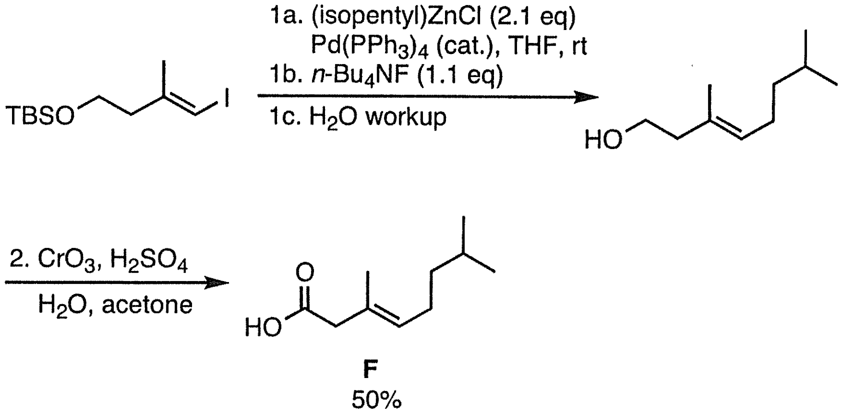
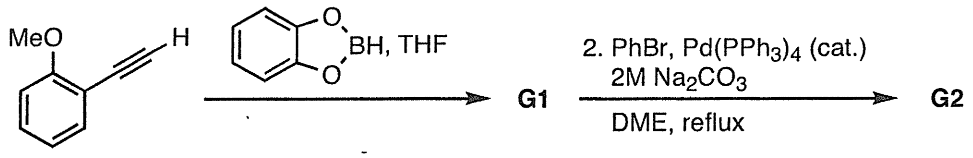


Reference: Rodeschini, V.; Boiteau, J.-G.; Van de Weghe, P.; Tarnus, C.; Eustache, J. *J. Org. Chem.* **2004**, *69*, 357.

g.



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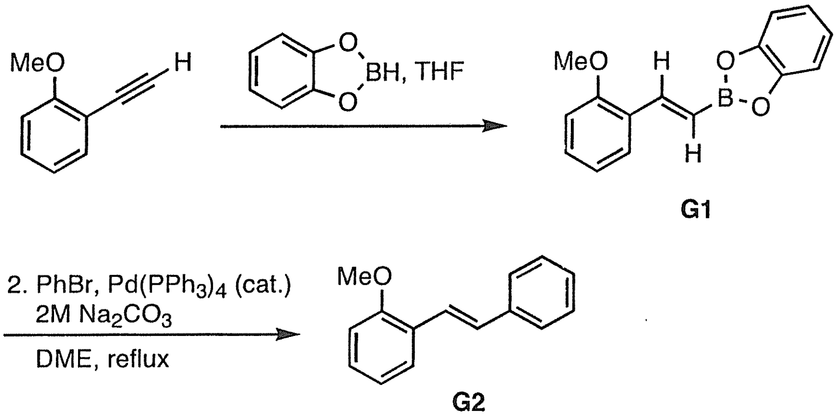
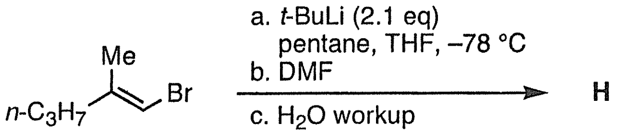


Step 1 Regioselective hydroboration of the terminal alkyne carbon.
Step 2 Suzuki coupling.

h.



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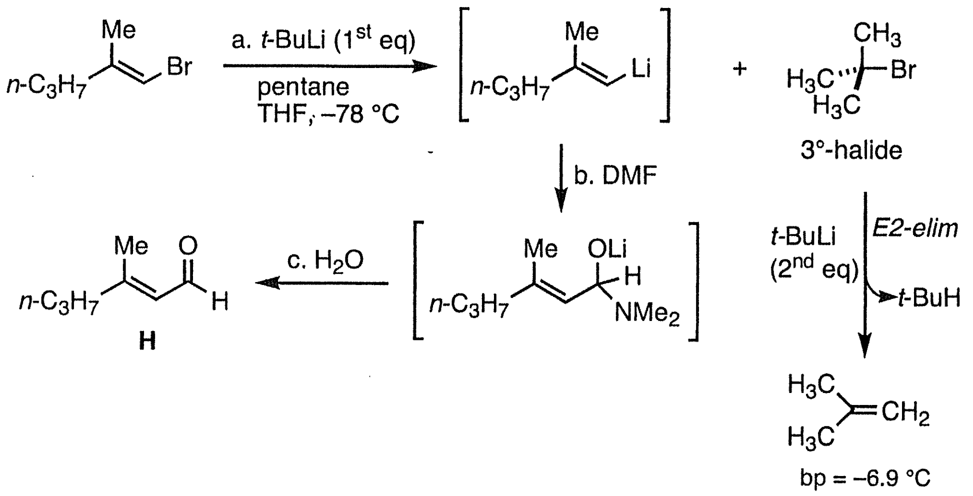
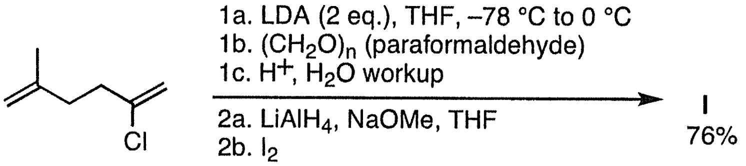


i.



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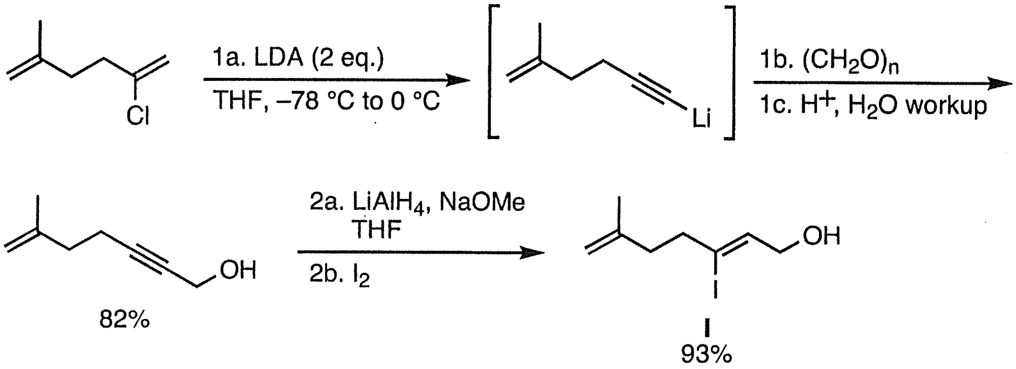
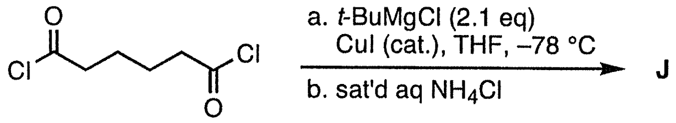


Reference: Zhang, Y.; Wu, G.; Agnel, G.; Negishi, E. *J. Am. Chem. Soc.* **1990**, *112*, 8590.

j.



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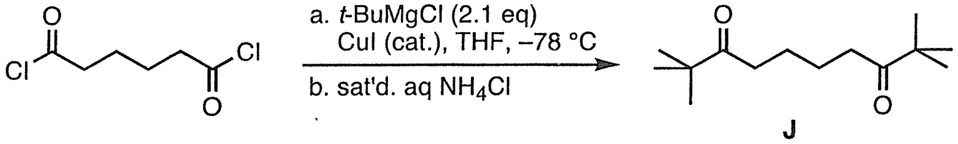
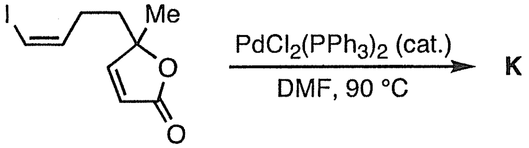


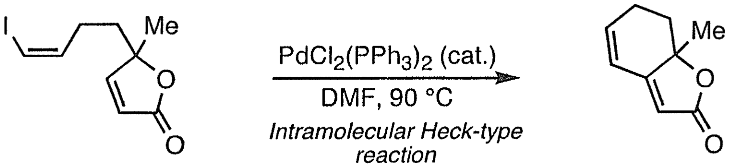
Step a CuI and *t*-BuMgCl generate an *in situ* organocopper reagent which adds only *once* to the acyl chloride functionalities.

Step b Workup protocol.

k.

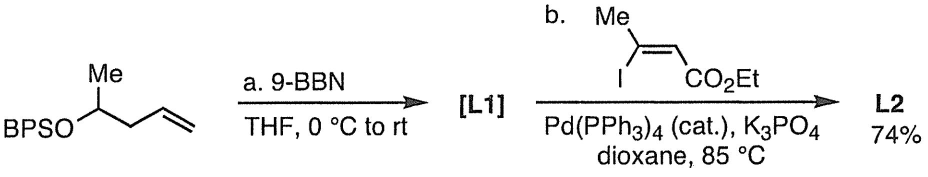


Solution:



Reference: For an analogous synthesis, see Alibés, R.; Ballbé, M.; Busqué, F.; de March, P.; Elias, L.; Figueredo, M.; Font, J. *Org. Lett.* **2004**, *6*, 1813.

l.



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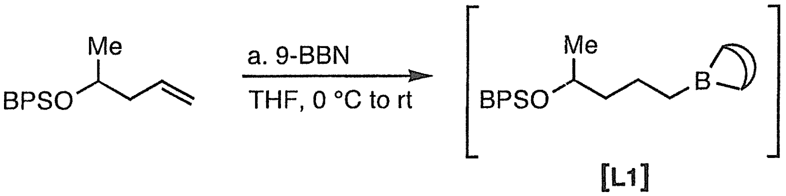
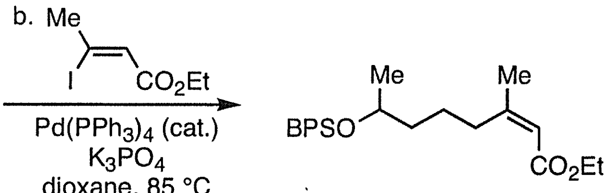
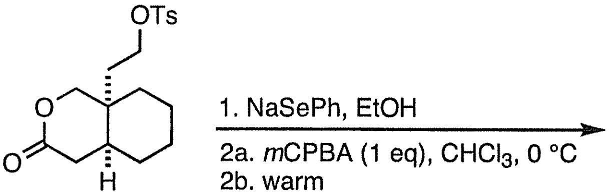




L2
74%

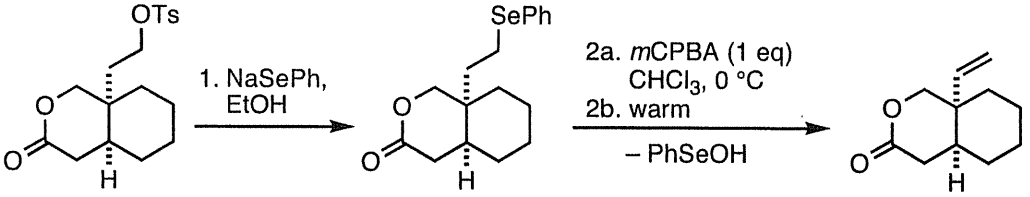
Reference: Taillier, C.; Gille, B.; Bellosta, V.; Cossy, J. *J. Org. Chem.* **2005**, *70*, 2097.

m.



M

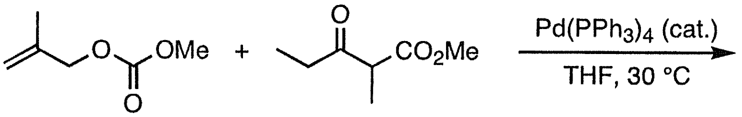
Solution:



M

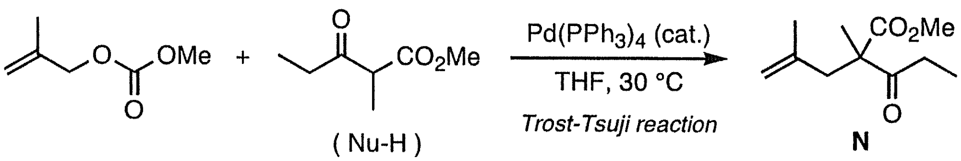
Reference: For a similar synthesis, see Clark, R. D.; Heathcock, C. H. *J. Org. Chem.* **1976**, *41*, 1396.

n.

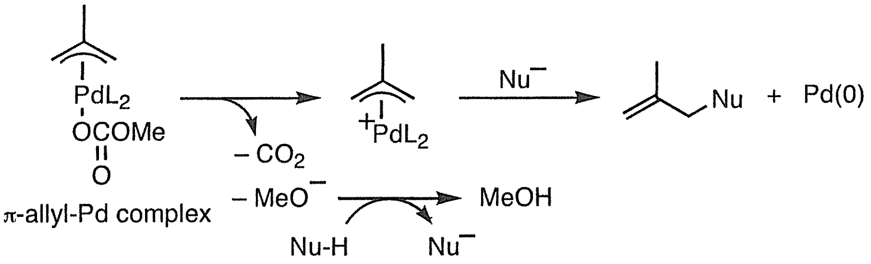


N
92%

Solution:

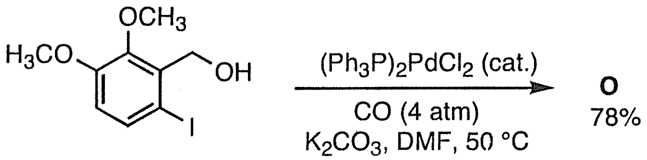


N
92%

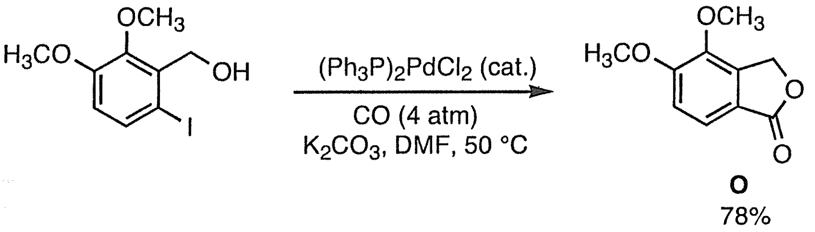


Reference: Tsuji, J. *Tetrahedron* **1986**, *42*, 4361.

***o.**

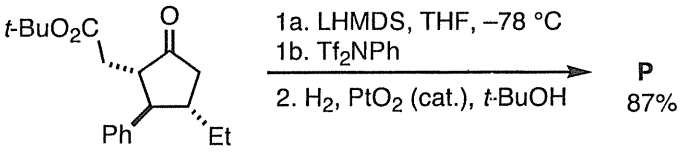


Solution:

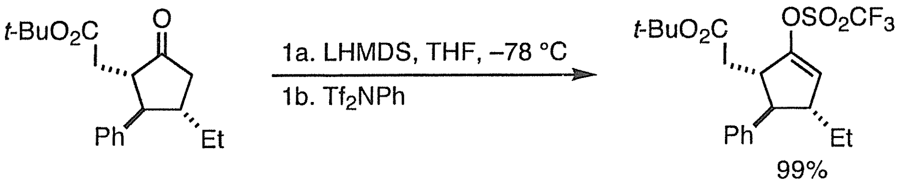


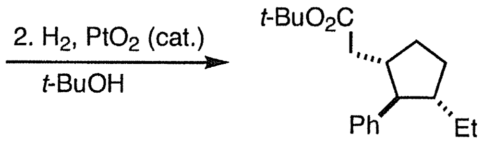
Reference: Cowell, A.; Stille, J. K. *J. Am. Chem.* **1980**, *102*, 4193.

***p.**



Solution:





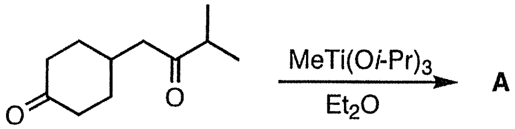
P
88%

Step 2 Reduction of a keto group via hydrogenolysis of the enol triflate (*Tetrahedron Lett.* **1982**, *23*, 117).

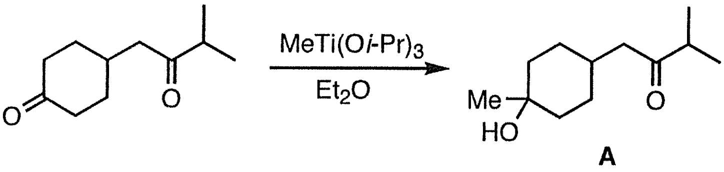
Reference: Burke, S. D.; Piscopio, A. D.; Kort, M. E.; Matulenko, M. A.; Parker, M. H.; Armistead, D. M.; Shankaran, K. *J. Org. Chem.* **1994**, *59*, 332.

2. **Selectivity.** Give the structures of the intermediates obtained after each step, and show the major products obtained for each of the following transformations.

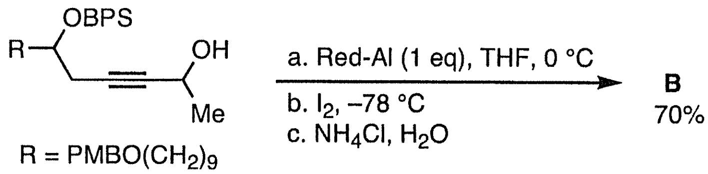
a.



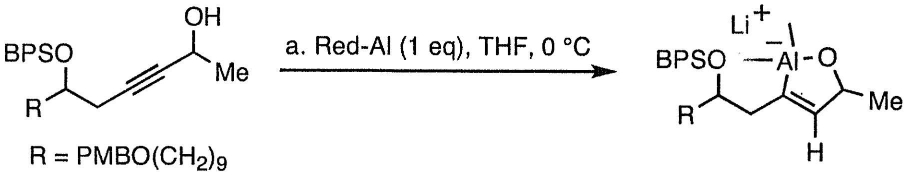
Solution:

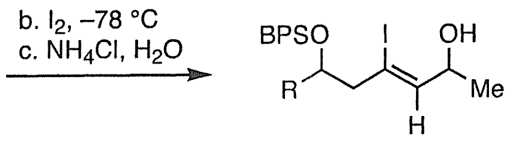


b.



Solution:

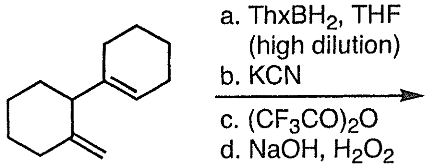




B
70%

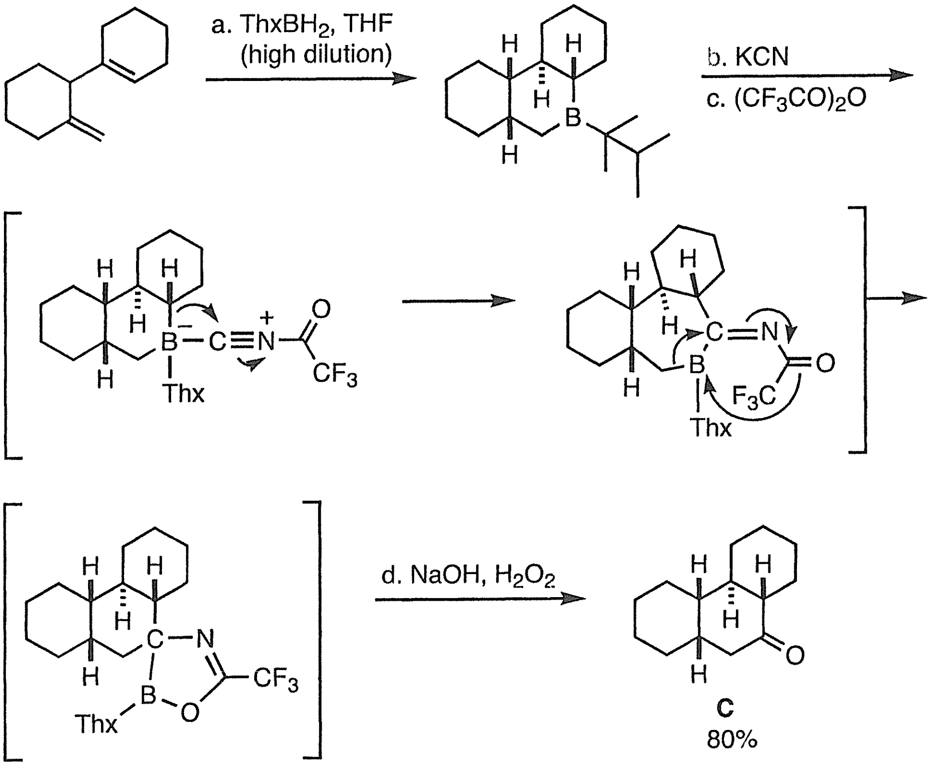
Reference: Hoye, T. R.; Humpal, P. E.; Jiménez, J. I.; Mayer, M. J.; Tan, L.; Ye, Z. *Tetrahedron Lett.* **1994**, *35*, 7517.

c.



C
80%

Solution:

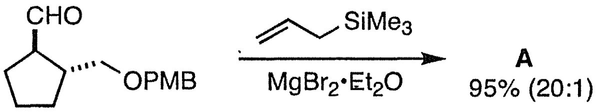


C
80%

Reference: Pelter, A.; Smith, K.; Hutchings, M. G.; Rowe, K. *J. Chem. Soc., Perkin Trans. 1* **1975**, 129.

3. **Stereochemistry**. Predict the stereochemistry of the major product formed for each of the following reactions. Give an explanation for your choice.

a.



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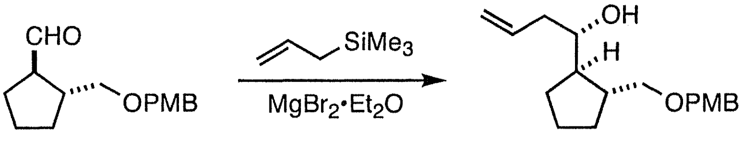
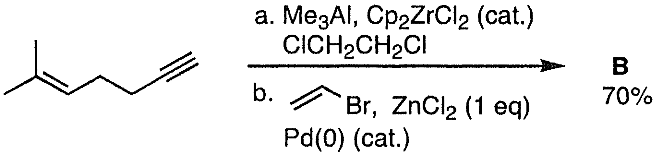


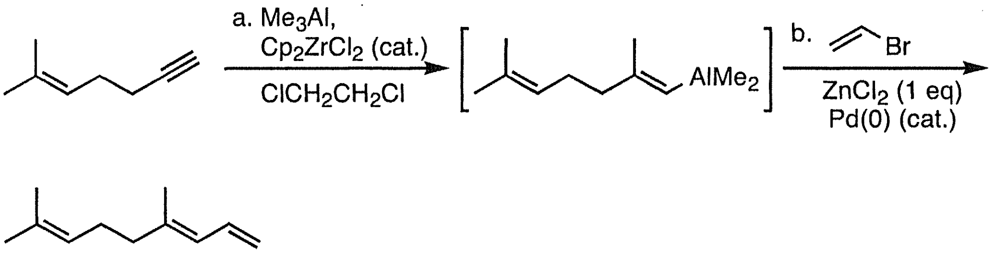
A
95% (20 : 1)

Reference: Nagamitsu, T.; Takano, D.; Fukuda, T.; Otoguro, K.; Kuwajima, I.; Harigaya, Y.; Omura, S. *Org. Lett.* **2004**, *6*, 1865.

b.



Solution:

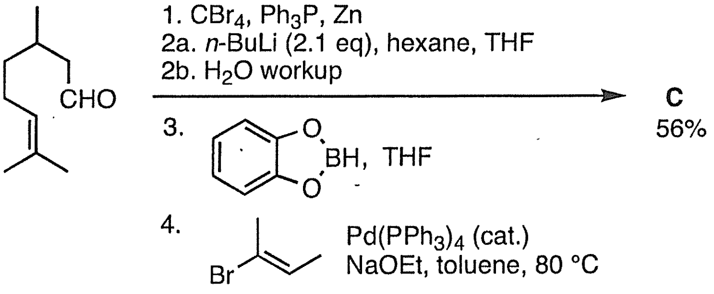


B
70%

Step b Negishi reaction; transmetallation (Al to Zn) followed by cross-coupling of the resultant organozinc species with the vinyl halide. The Pd(0) catalyst was generated by treatment of $(Ph_3P)_2PdCl_2$ with DIBAL-H.

Reference: Negishi, E.; Okukado, N.; King, A. O.; Van Horn, D. E.; Spiegel, B. I. *J. Am. Chem. Soc.* **1978**, *100*, 2254.

c.



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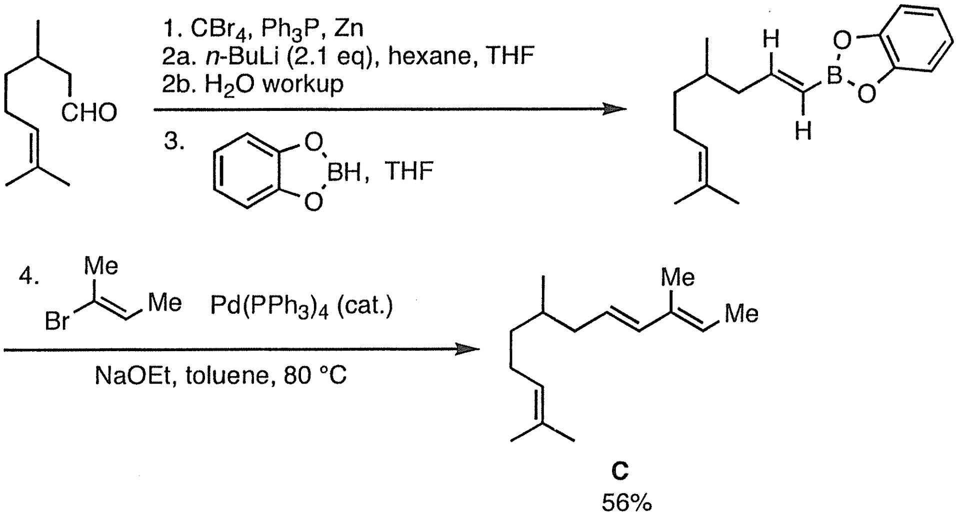
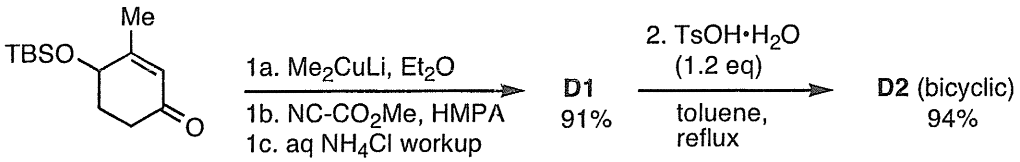


Steps 1–2 Corey-Fuchs reaction: aldehyde to terminal alkyne transformation.
Step 4 Suzuki coupling.

Reference: Vyryan, J. R.; Peterson, E. A.; Stephan, M. L. *Tetrahedron Lett.* **1999**, *40*, 4947.

d.



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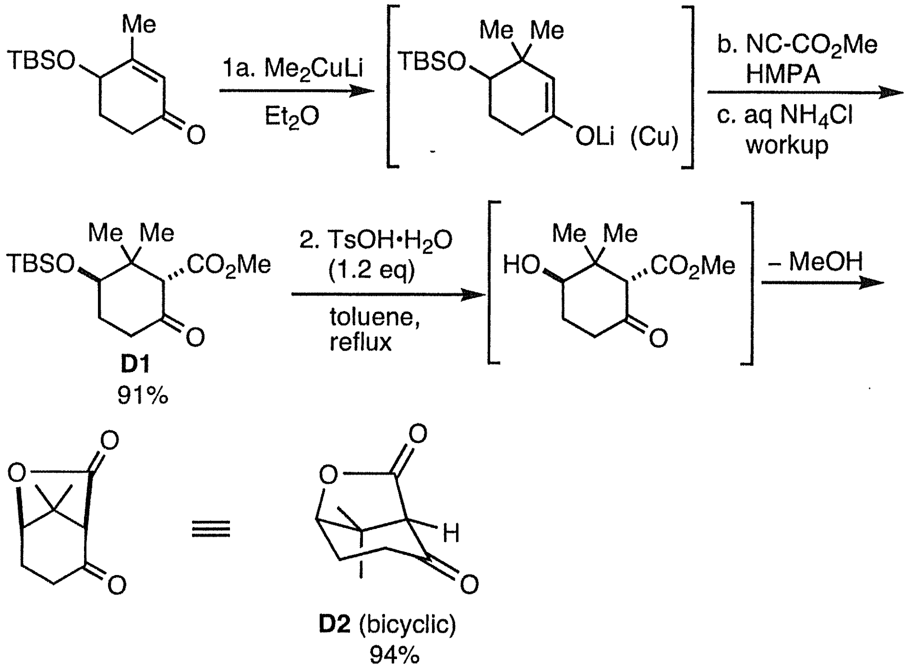
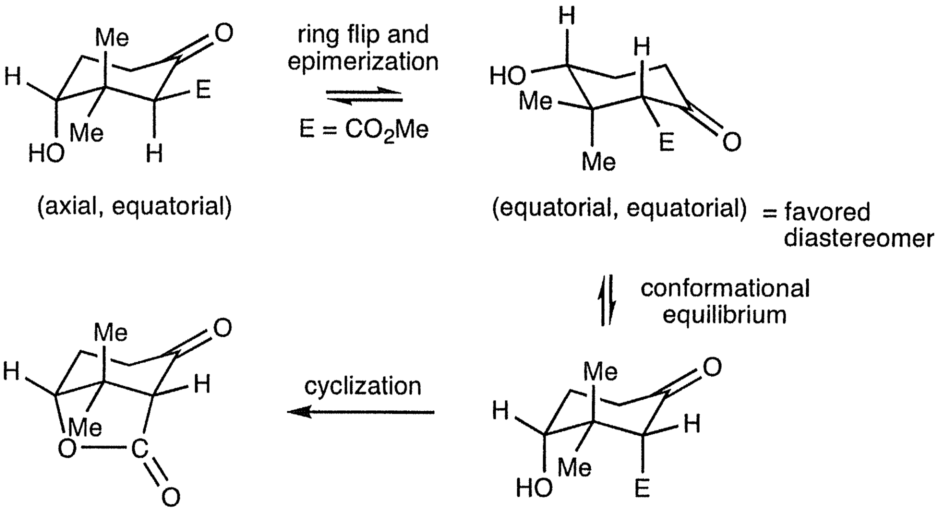
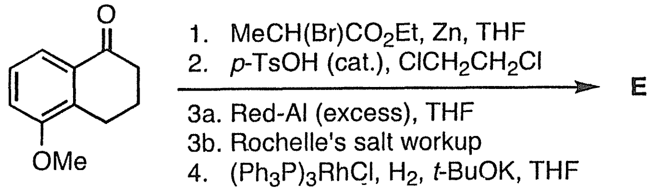


Step 2 Silyl ether hydrolysis and lactonization.



Reference: Galano, J.–M.; Gérard, A.; Honoré, M. *Tetrahedron* **2000**, *56*, 7477.

*e.



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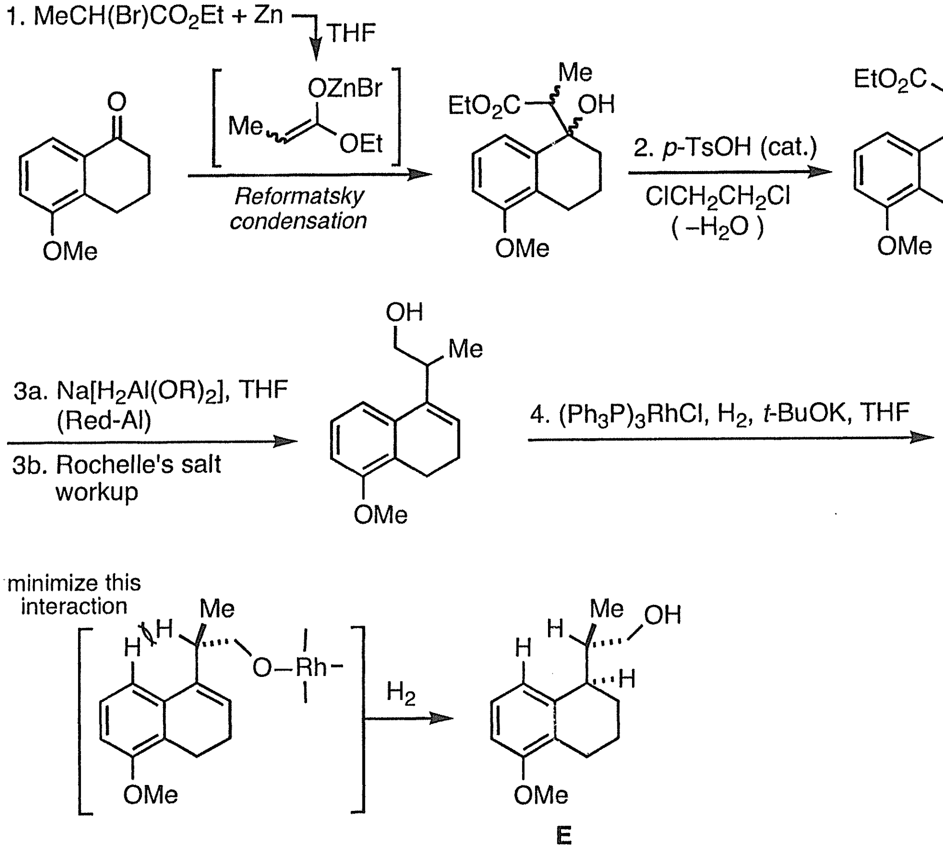
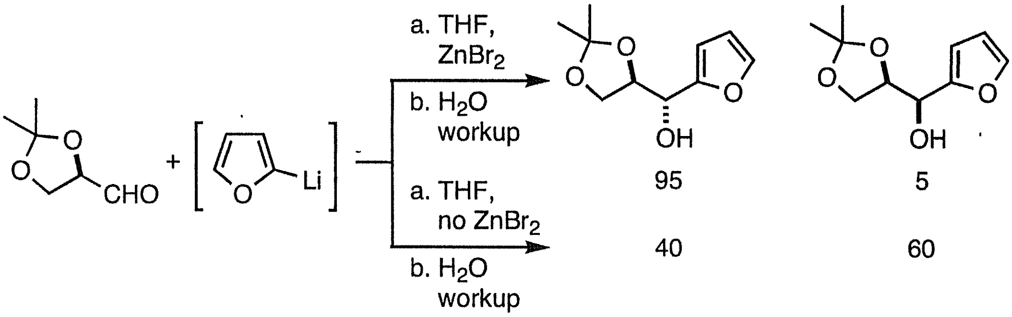


Step 2 Dehydration of a 3°-benzylic alcohol.

Step 4 Conformational bias minimizes interactions with the indicated Ar-H and sets the stage for diastereofacial differentiation in the directed hydrogenation of the double bond. Base-promoted attachment of the alkoxide to rhodium gives the product with high diastereoselectivity.

Reference: McCombie, S. W.; Ortiz, C.; Cox, B.; Ganguly, A. K. *Synlett* **1993**, 541.

***f.** Explain the observed stereoselectivities.



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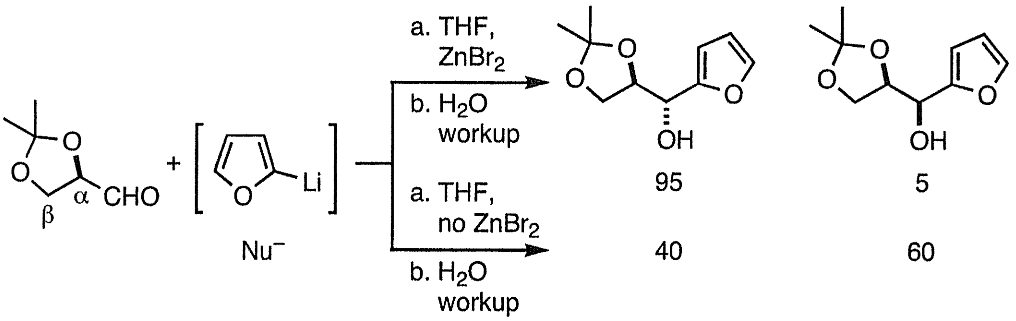
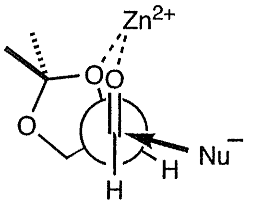
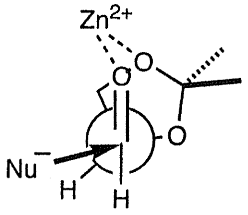


In the presence of Zn^{2+}

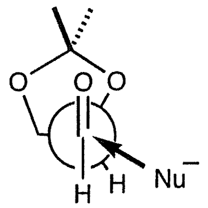


α-chelation leads to the *syn*-product

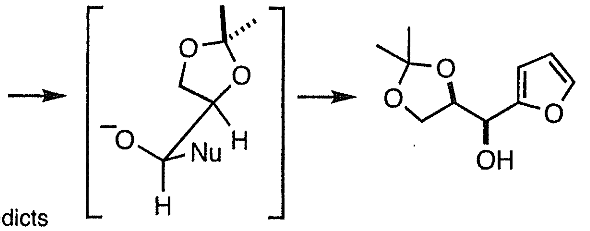


β-chelation leads to the *anti*-product

In the absence of Zn^{2+}



The Felkin-Anh model predicts *syn*-stereoselectivity

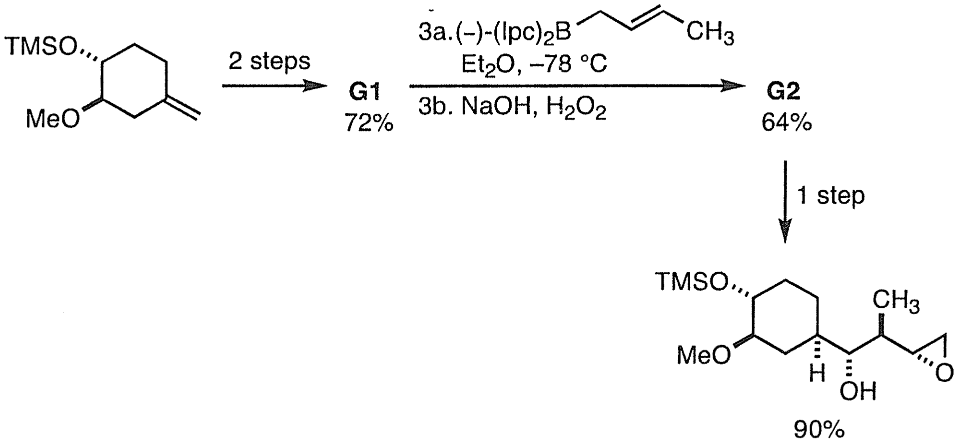


A rationalization of chelation control in carbonyl addition reactions is given in *Acc. Chem. Res.* **1993**, *26*, 462.

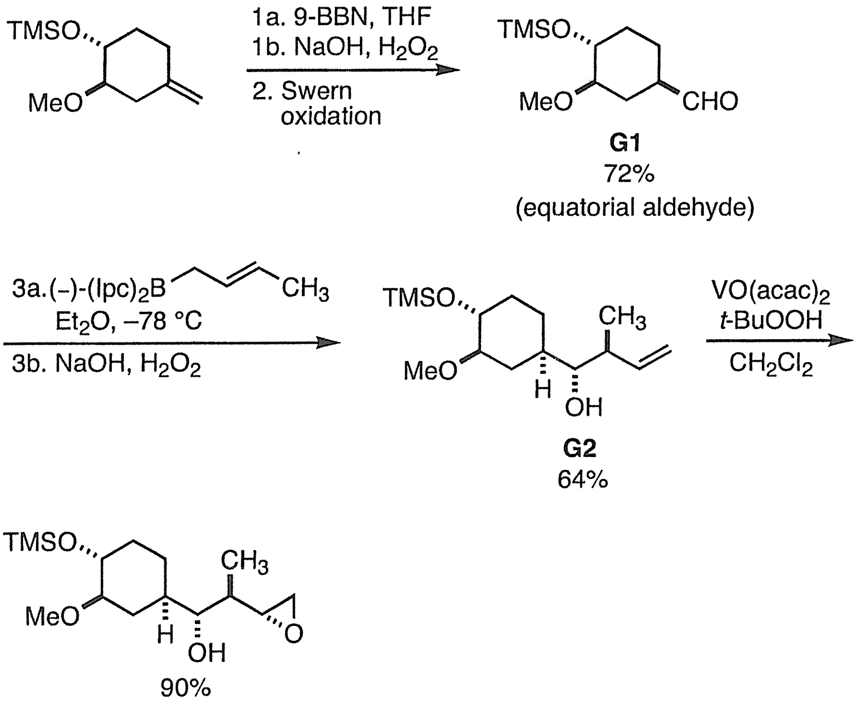
Note: The above interpretation of the Felkin-Anh model differs from that proposed by the authors in that the methylene group of the starting aldehyde is sterically more demanding than the C(2) ether oxygen.

Reference: Mukaiyama, T.; Suzuki, K.; Yamada, T.; Tabusa, F. *Tetrahedron* **1990**, *46*, 265.

***g.** Supply the missing reagents and structures.



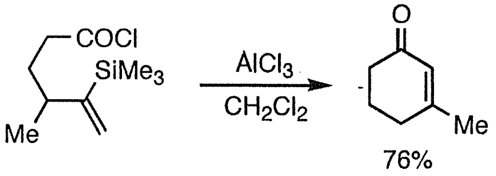
Solution:



Reference: Kouklovsky, C.; Ley, S. V.; Marsden, S. P. *Tetrahedron Lett.* **1994**, *35*, 2091.

4. **Reactivity**. Propose a mechanism for each of the following transformations to explain the observed regioselectivity and stereochemistry.

a.



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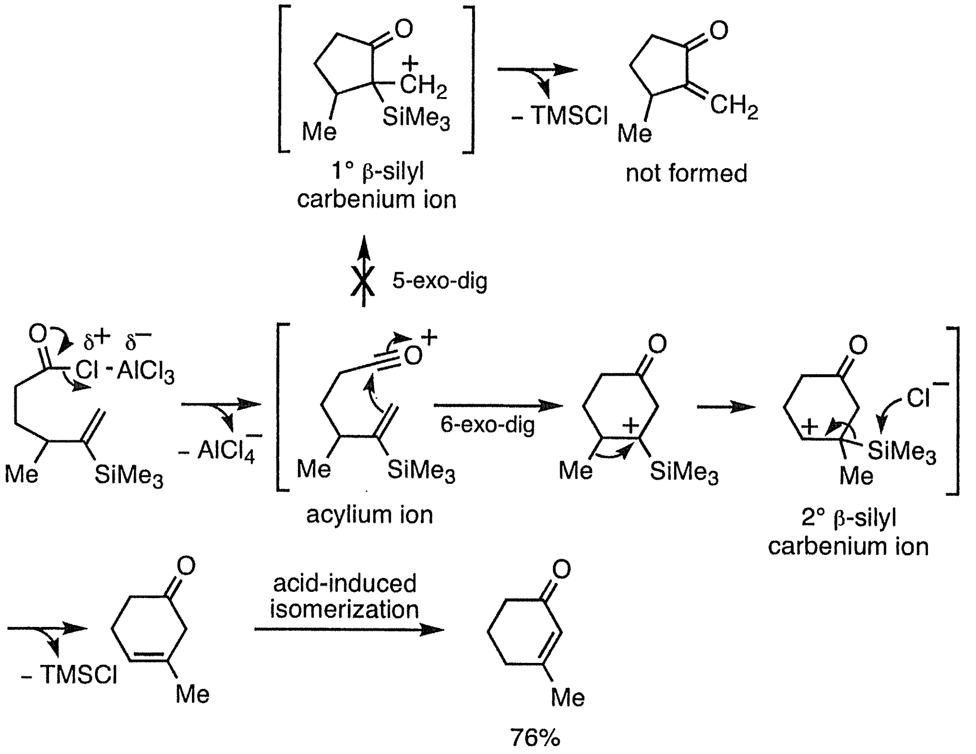
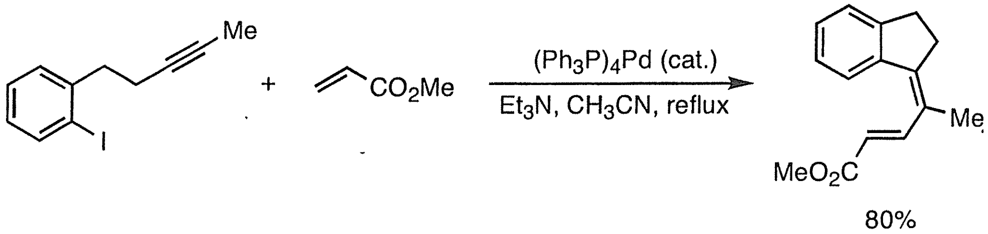


The acylium ion is regioselectively attacked by the double bond to give the 2° carbenium ion, which rearranges to the more stable β-silyl carbenium ion.

Reference: Mikami, H.; Kishi, N.; Nakai, T. *Tetrahedron Lett.* **1983**, *24*, 795.

b.



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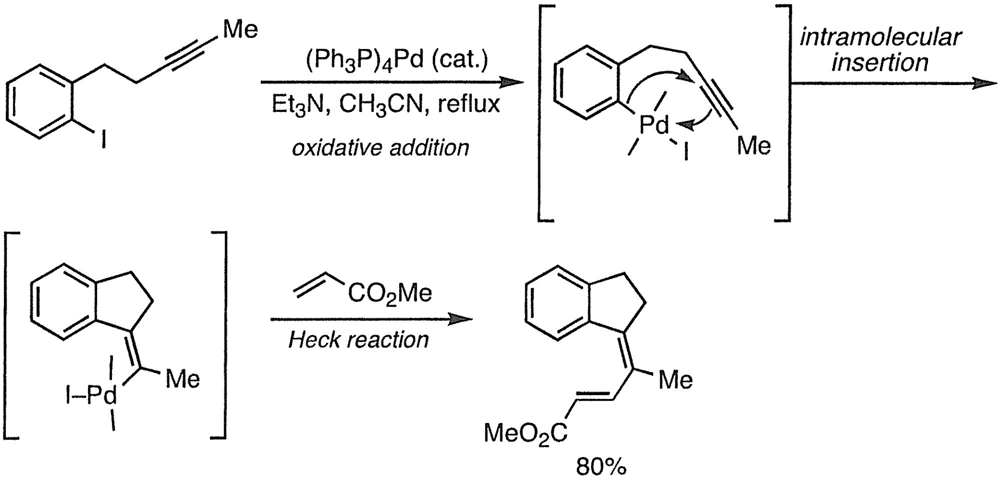
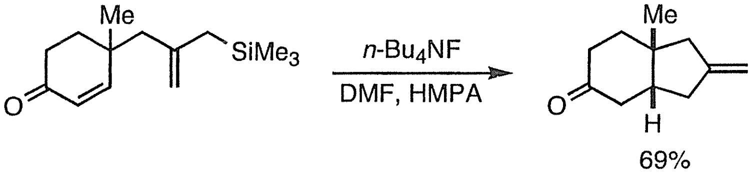
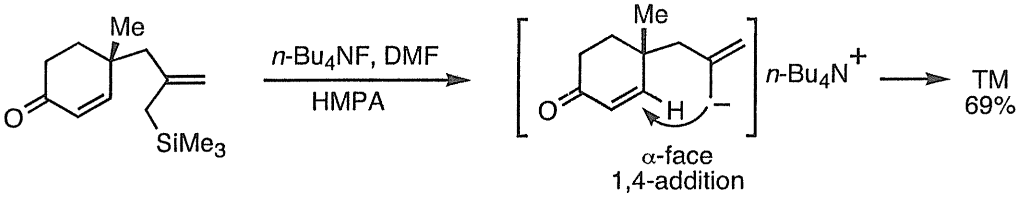


Reference: Zhang, Y.; Negishi, E. *J. Am. Chem. Soc.* **1989**, *111*, 3454.

c.



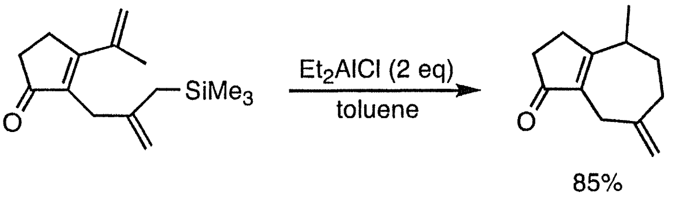
Solution:



The allyl silicon bond is cleaved by fluoride ion under anhydrous conditions to produce an allylic nucleophile which attacks the enone in a 1,4-manner.

Reference: Majetich, G.; Desmond, Jr., R. W.; Soria, J. J. *J. Org. Chem.* **1986,** *51*, 1753.

d.



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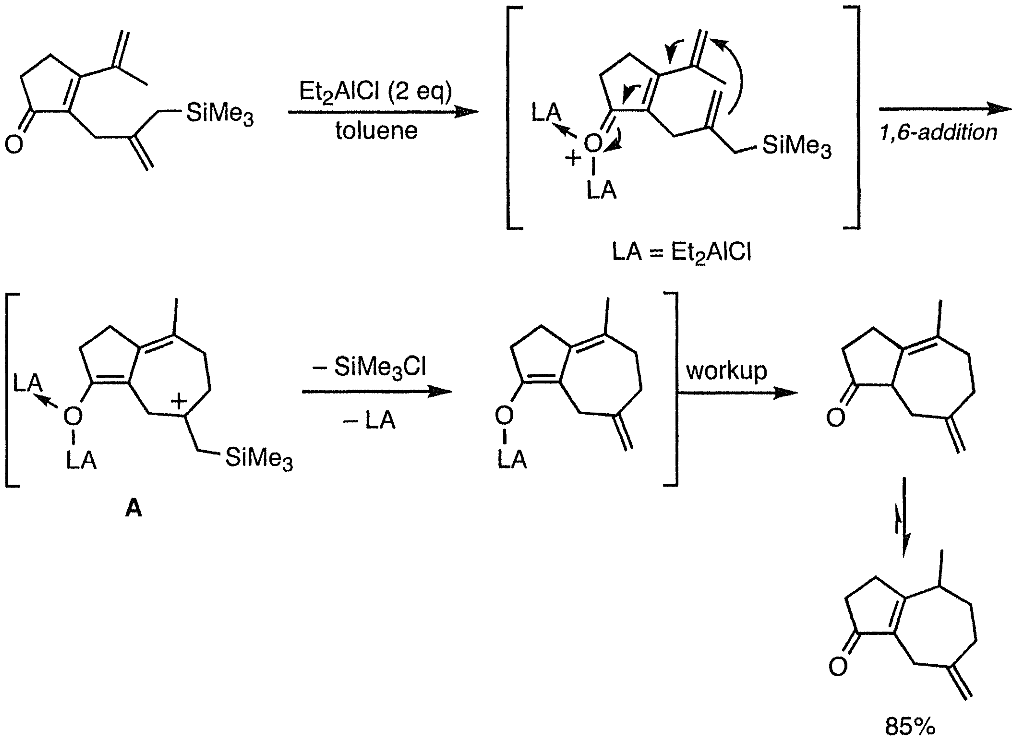
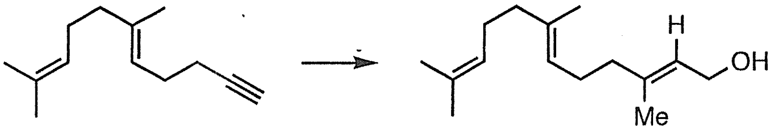


Nucleophilic attack in a 1,6 fashion by the allylsilane double bond at the doubly activated Michael acceptor produces **A** containing the silicon-stabilized carbocation. Loss of the trimethylsilyl group generates the exocyclic methylene moiety.

Reference: Majetich, G.; Song, J.-S.; Leigh, A. J.; Condon, S. M. *J. Org. Chem.* **1993,** *58*, 1030.

5. **Synthesis.** Supply the reagents required to accomplish each of the following syntheses. Show the structures of the intermediates obtained after each step and their relative stereochemistry where applicable.

a.



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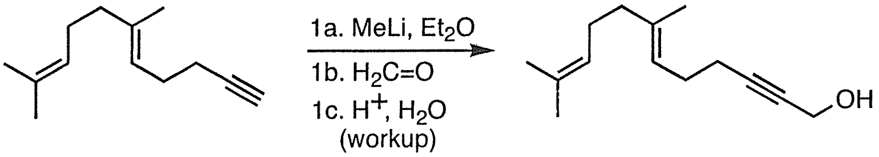
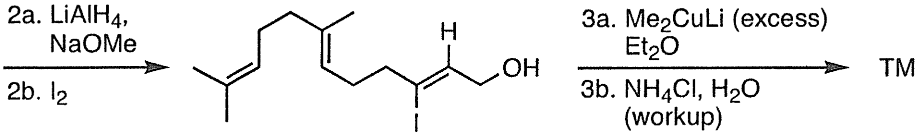
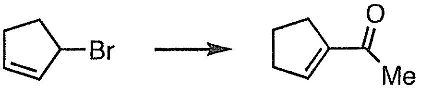




Step 3a A large excess of cuprate reagent is required for this transformation.

b.



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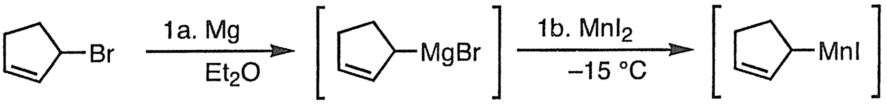
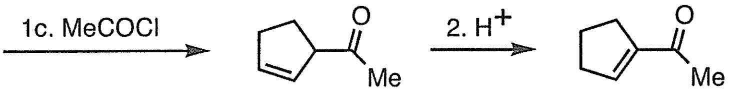
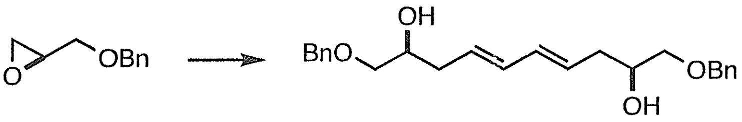




Step 1b Alternatively, CuI can be used to generate an organocopper reagent which would work equally well for a controlled 1,2-addition to an acyl chloride.

c.



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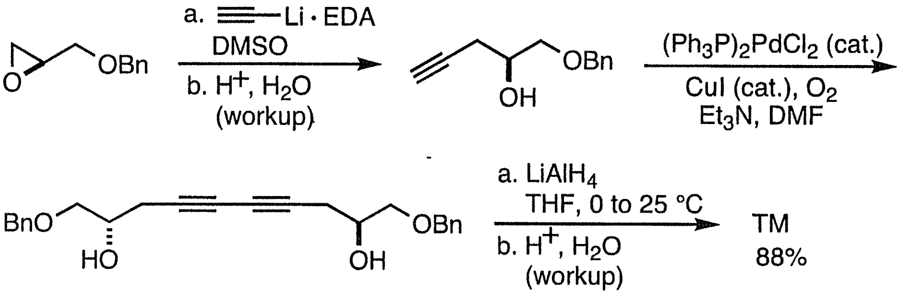
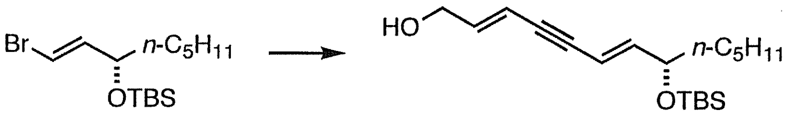


References: (a) Takano, S.; Sugihara, T.; Ogasawara, K. *Synlett* **1990**, 453;
(b) Takano, S.; Murakami, T.; Samizu, K.; Ogasawara, K. *Heterocycles* **1994**, *39*, 67.

d.



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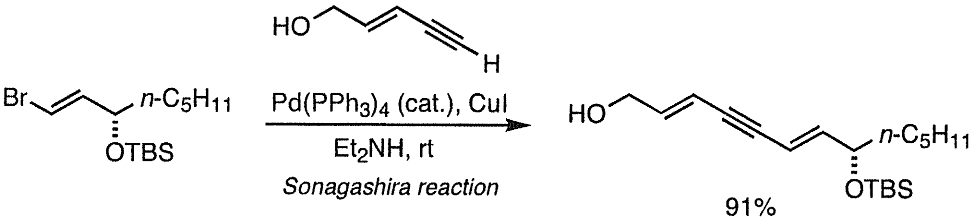
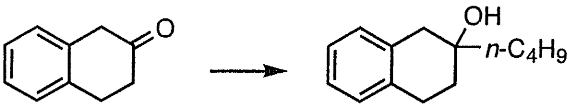


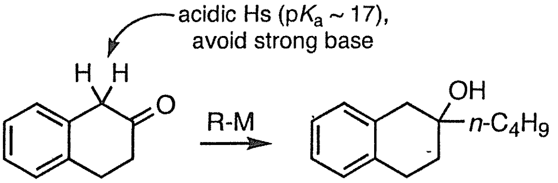
Reference: Nicolaou, K. C.; Webber, S. E. *J. Chem. Soc., Chem. Commun.* **1986**, 1816.

e.



consider the pK_a

Solution:

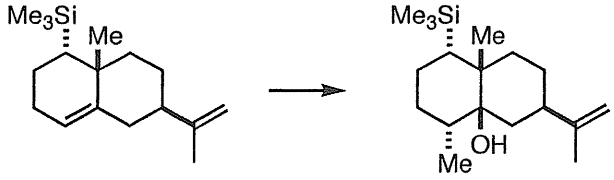


n-C_4H_9-$CeCl_2$ 88% $\Rightarrow$ n-BuLi + $CeCl_3$ $\xrightarrow[-78\ °C]{THF}$ "n-$BuCeCl_2$" + LiCl

n-C_4H_9-MgBr 6%

Reference: Imamoto, T.; Sugiura, Y.; Takiyama, N. *Tetrahedron Lett.* **1984**, *25*, 4233.

f.



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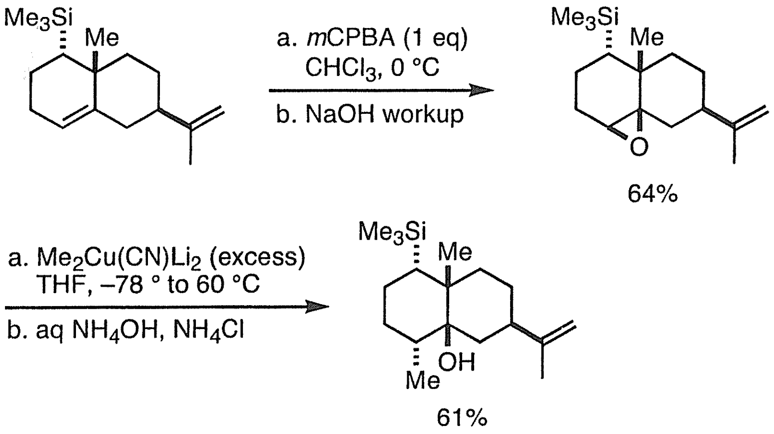
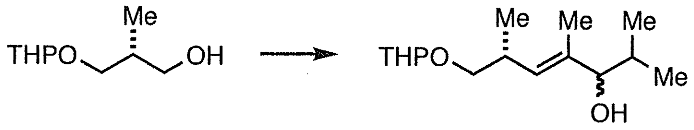


Epoxidation of the more electron rich trisubstituted double bond with mCPBA proceeds stereoselectively. The bulky Me_3Si group blocks the α-face of the trisubstituted double bond.

Reference: Hwu, J. R.; Wetzel, J. M. *J. Org. Chem.* **1992**, *57*, 922.

g.



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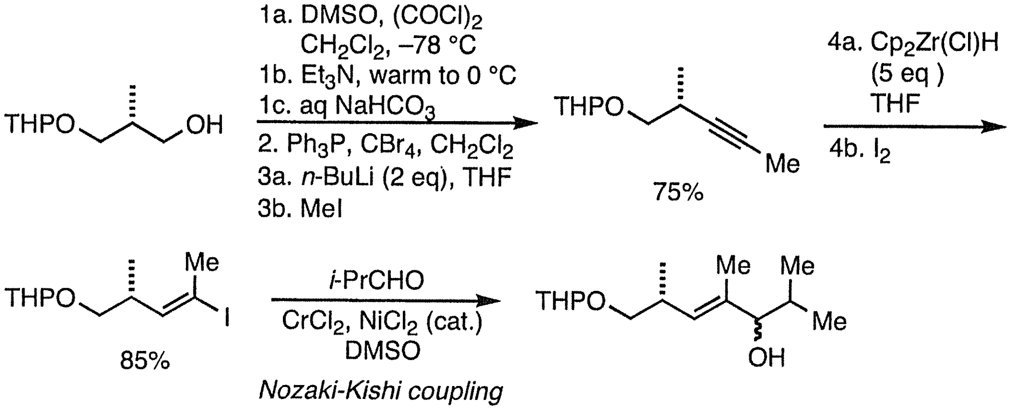
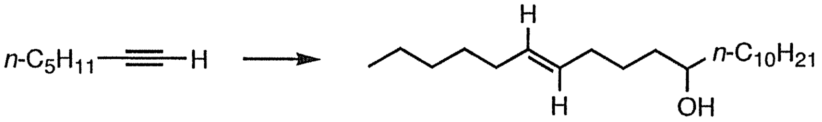


Reference: Anderson, J. C.; Ley, S. V.; Marsden, S. P. *Tetrahedron Lett.* **1994**, *35*, 2087.

h.



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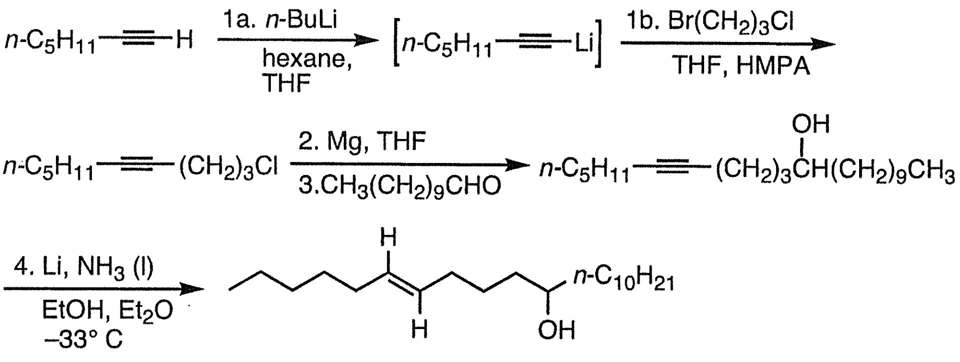
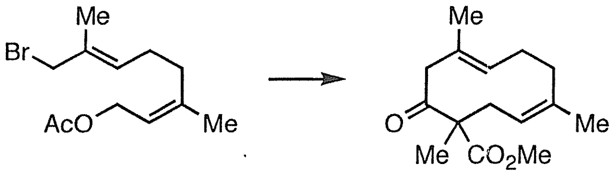


Reference: Henrick, C. A. *Tetrahedron* **1977**, 1845.

i.



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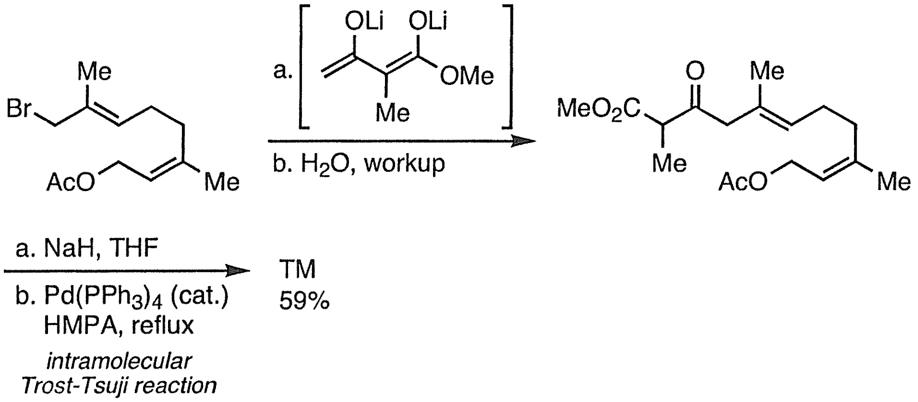
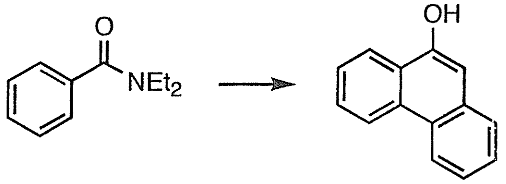


Reference: Kitagawa, Y.; Itoh, A.; Hashimoto, S.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1977**, *99*, 3864.

***j.**



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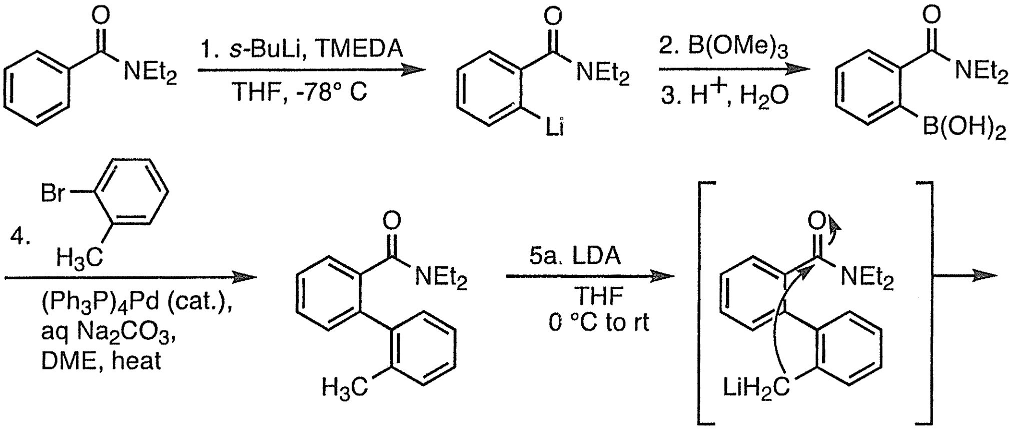
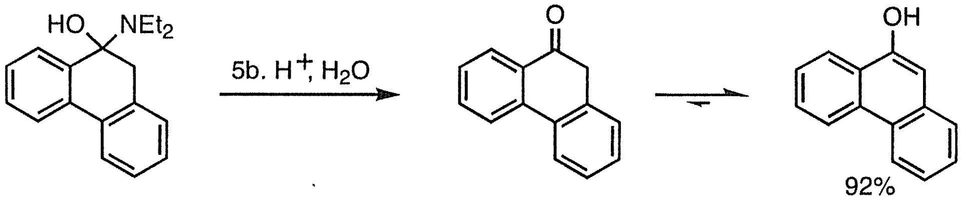


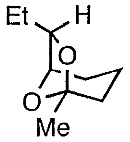


Step 1-2 Regiospecific *ortho*-lithiation followed by boronic acid formation.
Step 4 Suzuki coupling.
Step 5 Benzylic deprotonation followed by intramolecular 1,2-addition and hydrolysis.

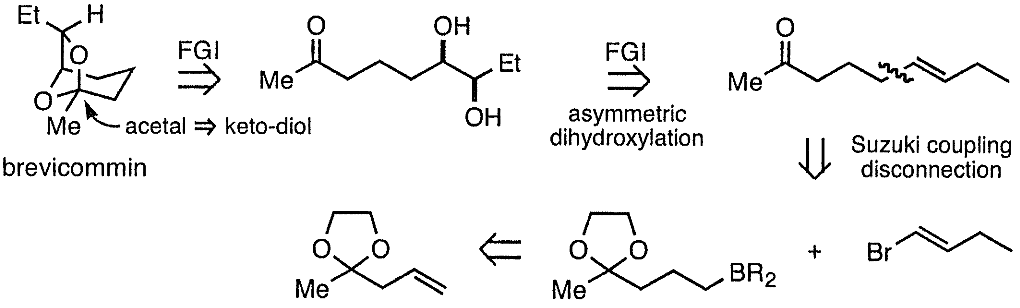
Reference: Fu, J.–M.; Sharp, M. J.; Snieckus, V. *Tetrahedron Lett.* **1988**, *29*, 5459.

6. **Retrosynthetic Analysis.** Propose syntheses of the following compounds using a Suzuki coupling procedure as a key step. Show (1) your retrosynthetic analysis and (2) all reagents and reaction conditions required to transform commercially available starting materials into the target molecules.

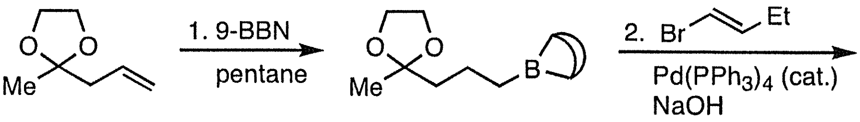
a.

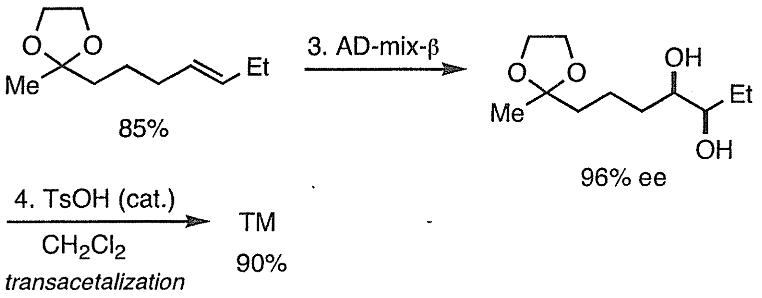


Retrosynthetic analysis:



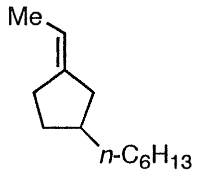
Synthesis:



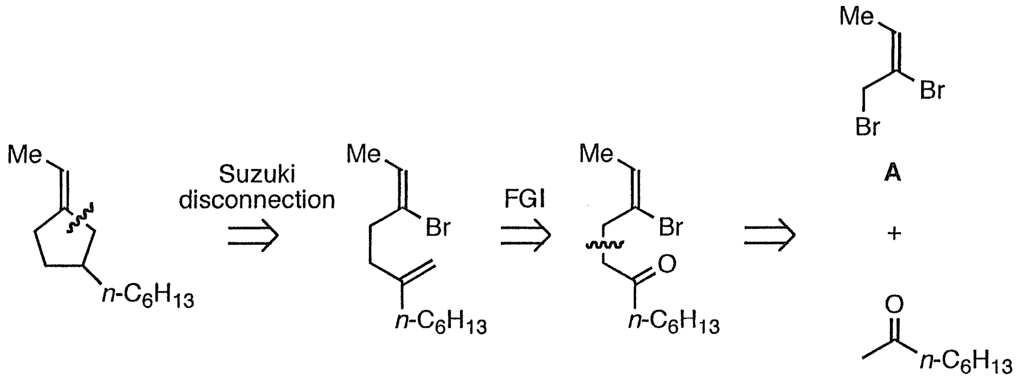


Reference: Soderquist, J. A.; Rane, A. M. *Tetrahedron Lett.* **1993**, *34*, 5031.

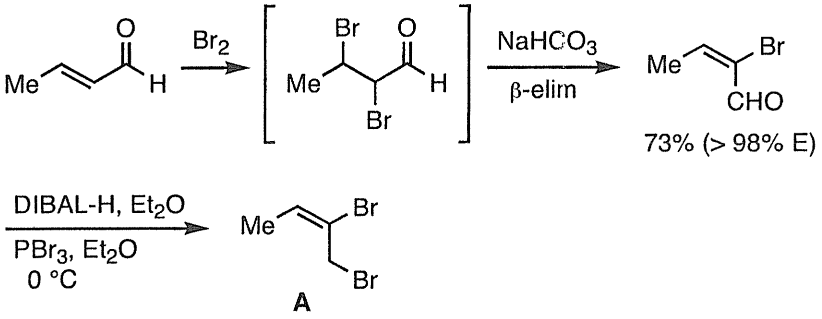
b.

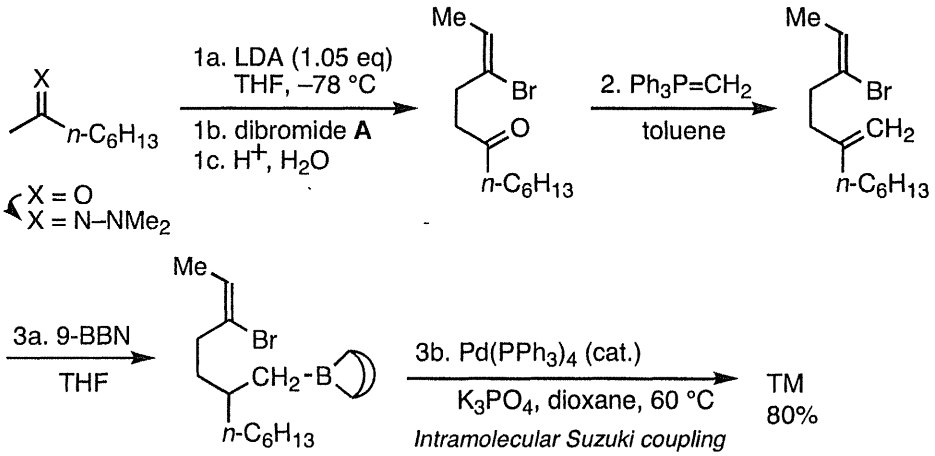


Retrosynthetic analysis:



Synthesis:





Reference: Miyaura, N.; Ishikawa, M.; Suzuki, A. *Tetrahedron Lett.* **1992**, *33*, 2571.

CHAPTER 8

Formation of Carbon-Carbon π-Bonds

Overview

Chapter 8 focuses on the synthetic methods to form carbon-carbon π-bonds.

Problem 1 involves the applications of various reagents for carbon-carbon π-bond formations. Problems 2–4 deal with the selectivity issues associated with carbon-carbon π-bond formation. The syntheses of TMs in Problem 5 require utilization of specific reagents to achieve chemo-, stereo-, or enantioselective carbon-carbon π-bond formation.

Key Concepts

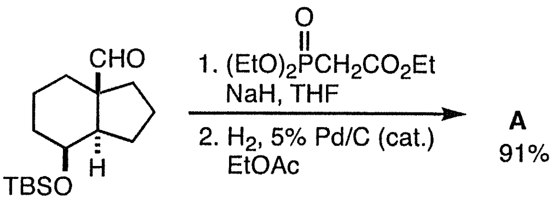
- β-Elimination reactions
- Pyrolytic *syn*-elimination reactions of:
    - Xanthates
    - Selenoxides
    - Sulfoxides
- Preparation of alkenes from alkynes
    - Reduction
    - Hydrometalation
    - Carbometalation
- Preparation of alkenes from aldehydes/ketones
    - Wittig reaction
    - Horner-Wadsworth-Emmons (HWE) reaction
    - Peterson olefination
    - Julia olefination
- Shapiro reaction
- Barton-McCombie deoxygenation
- Claisen rearrangement
- Cope rearrangement
- Preparation of alkynes
    - Corey-Fuchs reaction
    - Gilbert's reagent

SOLUTIONS TO CHAPTER 8 PROBLEMS

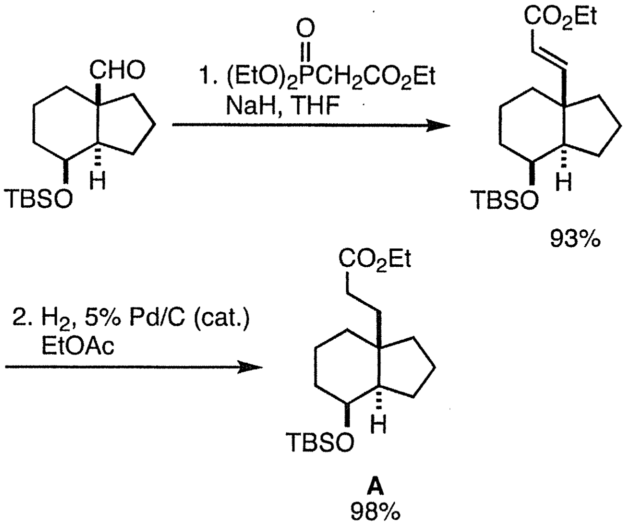
The more challenging problems are identified by an asterisk (*).

1. **Reagents.** Give the structure of the major product expected from each of the following reactions. Be sure to indicate product stereochemistry.

a.



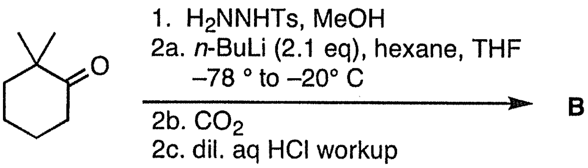
Solution:



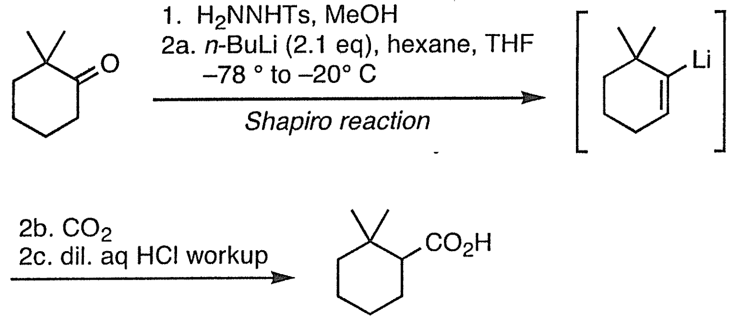
Step 1 Horner-Wadsworth-Emmons (HWE) olefination provides the (*E*)-vinyl ester.

Reference: Momán, E.; Nicoletti, D.; Mouriño, A. *J. Org. Chem.* **2004**, *69*, 4615.

b.



Solution:



B

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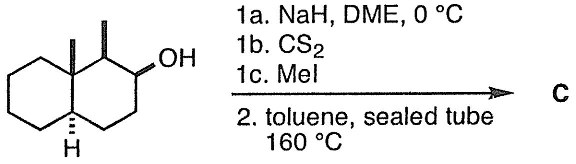
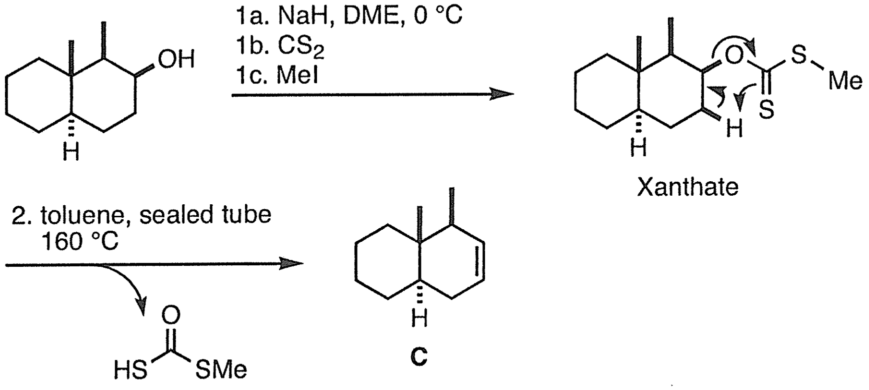
c.



Solution:



Steps 1–2 Xanthate pyrolysis furnishes the alkene C via *syn* elimination.

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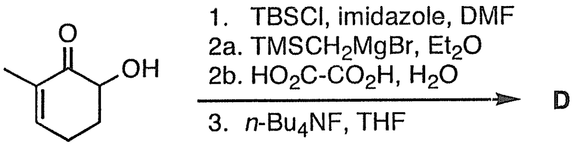
d.



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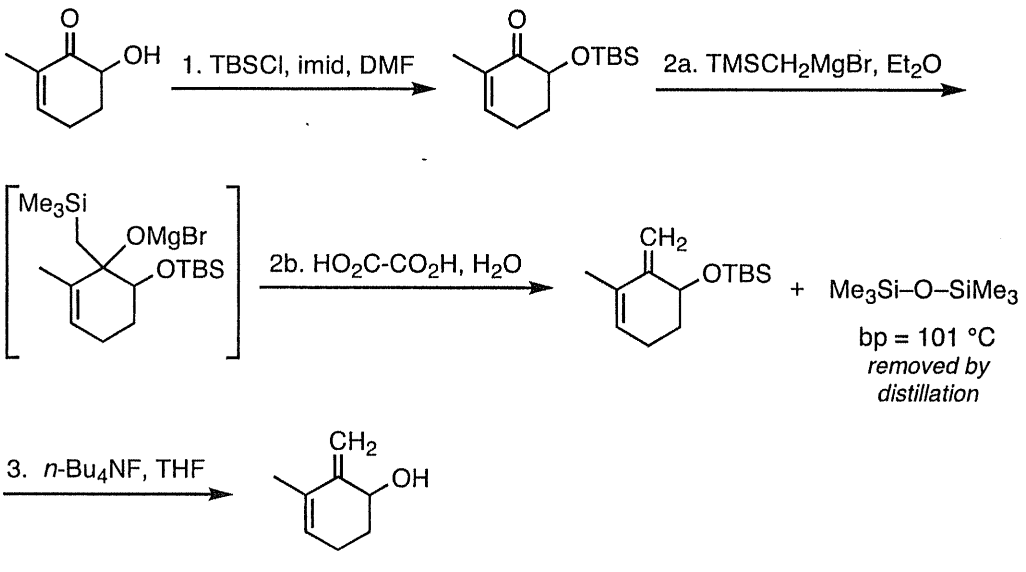
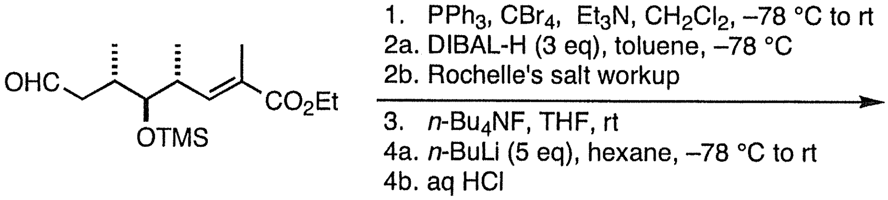


D

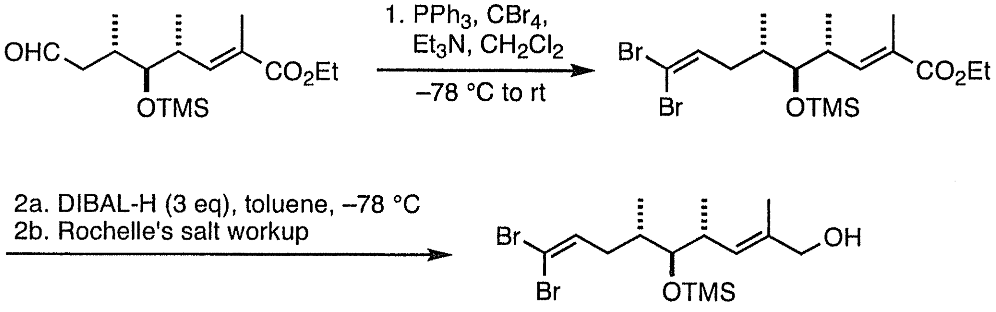
Step 2 Peterson olefination.

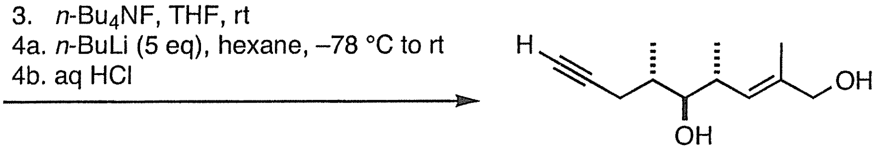
e.



E
71%

Solution:





E
71%

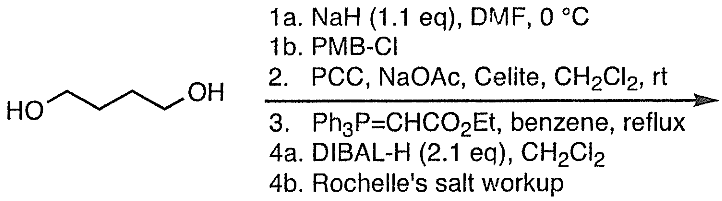
Steps 1 & 4 Corey-Fuchs reaction.

Step 4a At least 4 equivalents of *n*-BuLi are required for the transformation to proceed (2 x –OH deprotonation, 1 x Br elimination, 1 x acetylenic–Br lithium-halogen exchange).

Step 4b Workup protocol.

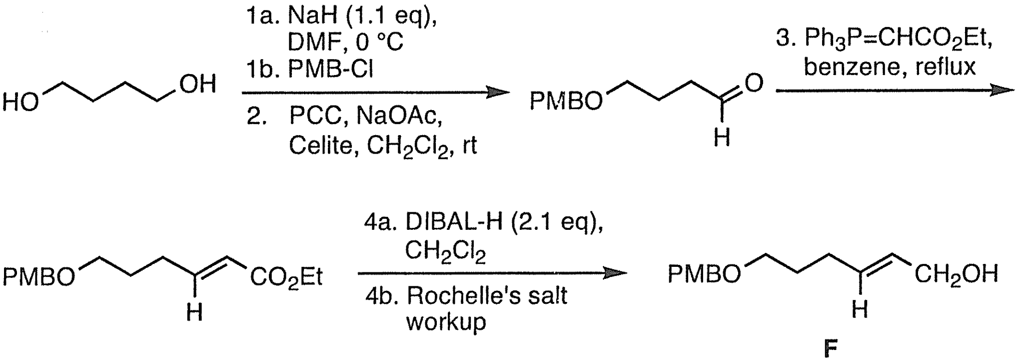
Reference: Quéron, E.; Lett, R. *Tetrahedron Lett.* **2004**, *45*, 4527.

f.



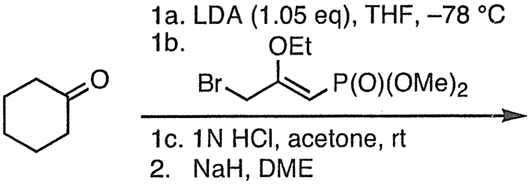
F
52%

Solution:



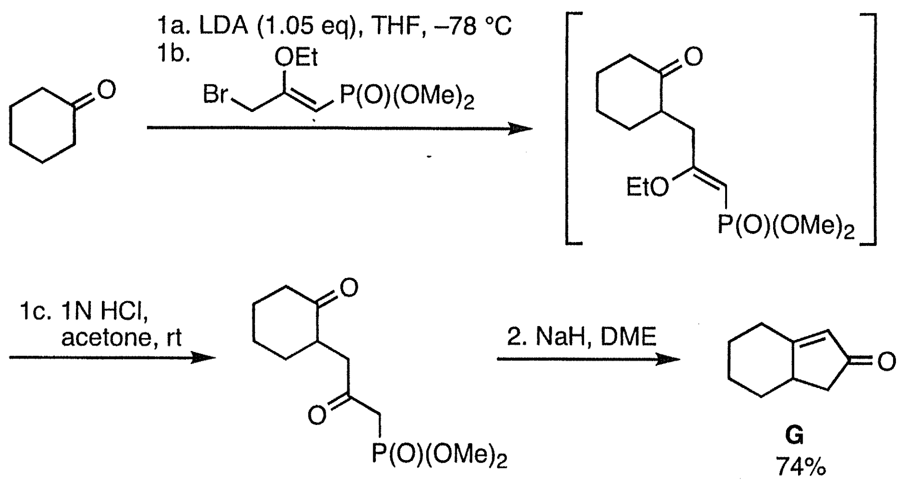
F
52%

g.



G
74%

Solution:

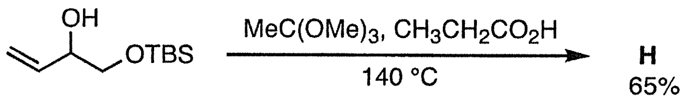


Step 1c Enol ether hydrolysis.

Step 2 Intramolecular Horner-Wadsworth-Emmons (HWE) reaction furnishes the cyclic enone **G**.

Reference: Piers, E.; Abeysekera, B.; Scheffer, J. R. *Tetrahedron Lett.* **1979,** 3279.

h.



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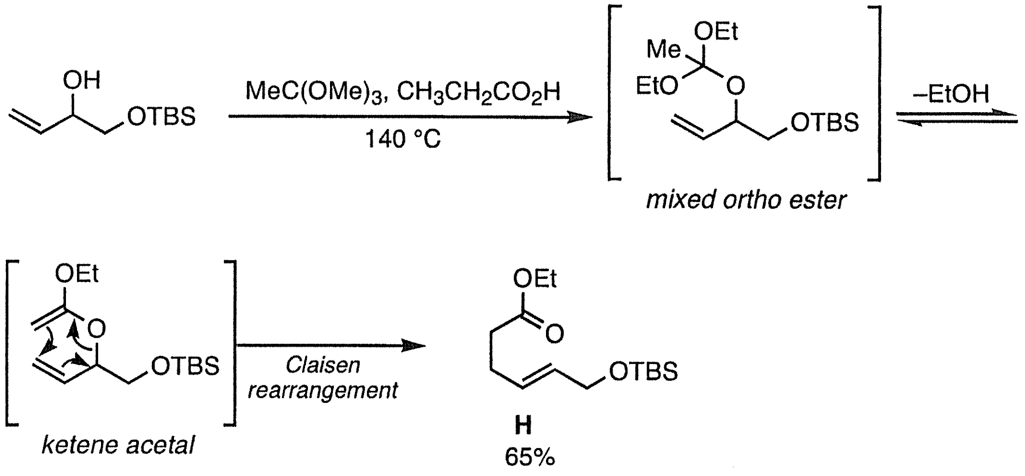
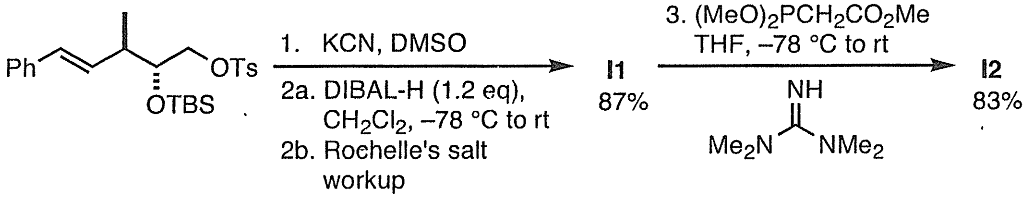


Reference: Wipf, P.; Lim, S. *J. Am. Chem. Soc.* **1995,** 117, 558.

i.



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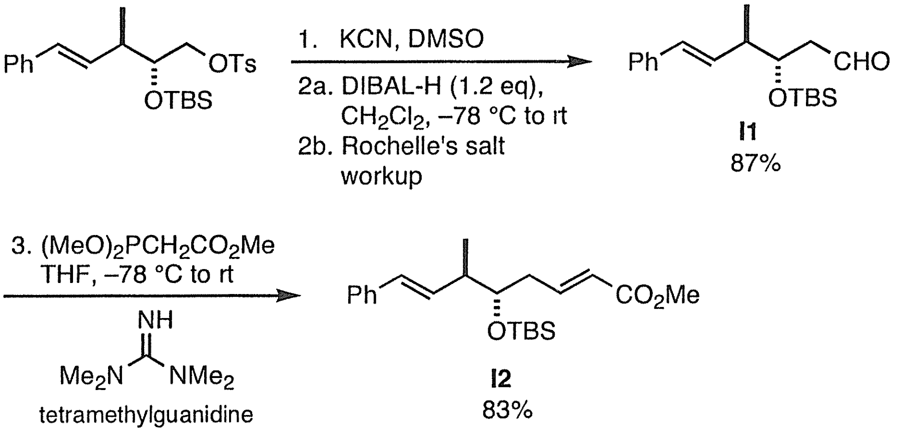
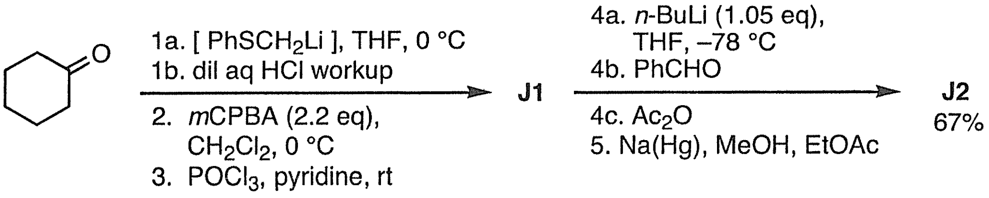


Step 3 HWE-modification of the Wittig reaction; tetramethylguanidine is a mild, non-nucleophilic base (much like DBU) that deprotonates the phosphonate reagent.

Reference: Barrow, R. A.; Hemscheidt, T.; Liang, J.; Paik, S.; Moore, R. E.; Tius, M. A. *J. Am. Chem. Soc.* **1995**, *117*, 2479.

j.



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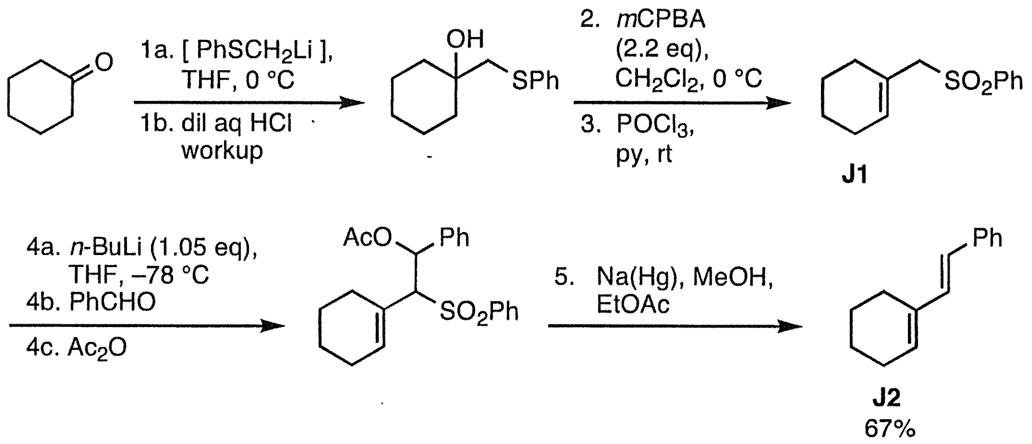
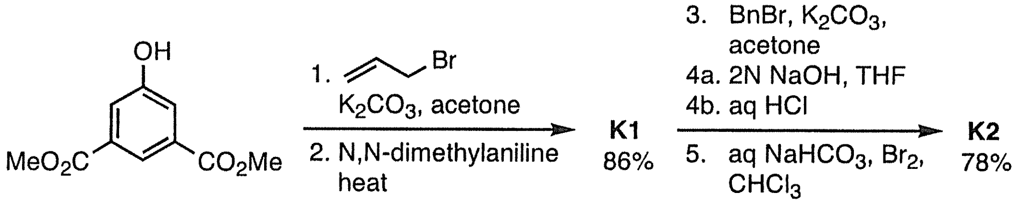


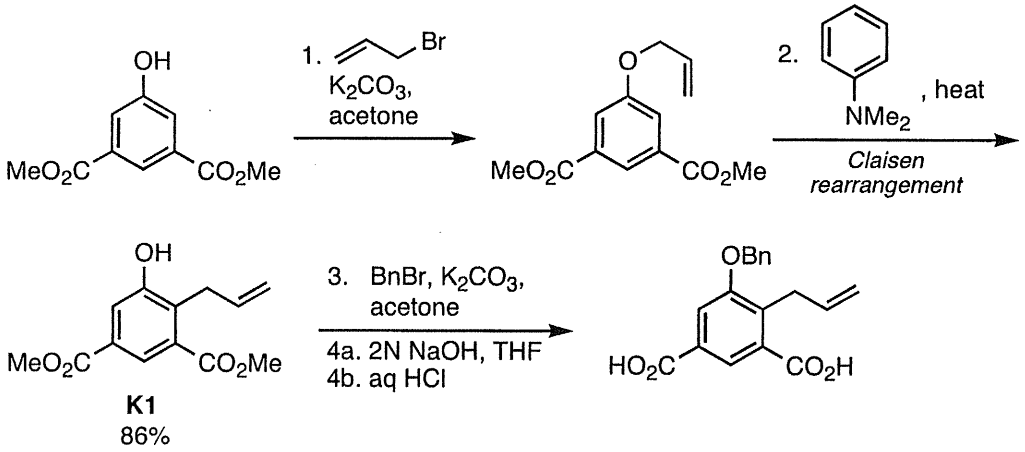
Step 2 Oxidation to the sulfone requires 2 eq *m*CPBA.
Step 3 Alcohol dehydration.
Steps 4–5 Julia olefination provides the (*E*)-olefin exclusively.

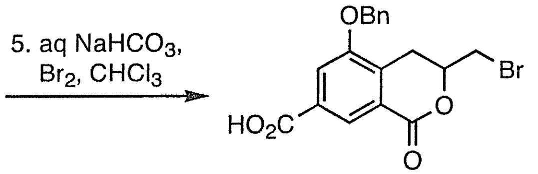
Reference: Kocienski, P. J.; Lythgoe, B.; Ruston, S. *J. Chem. Soc. Perkin Trans. I*, **1978**, 829.

k.



Solution:



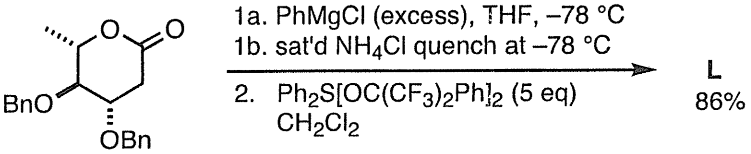


K2
78%

Step 5 Halolactonization.

Reference: Yoshino, T.; Nagata, Y.; Itoh, E.; Hashimoto, M.; Katoh, T.; Terashima, S. *Tetrahedron Lett.* **1996**, *37*, 3475.

I.



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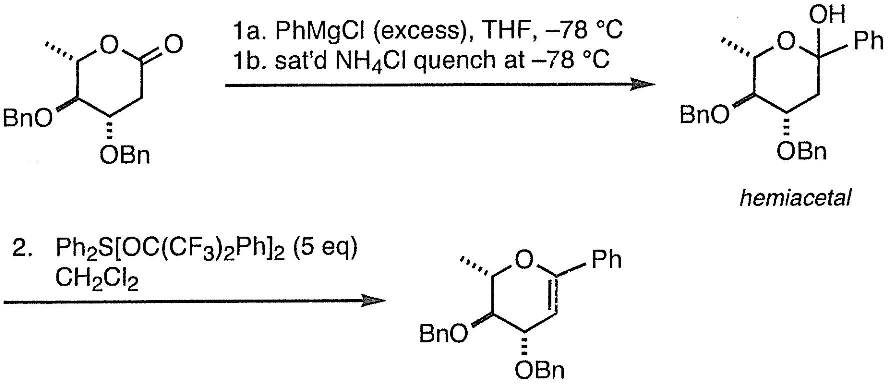


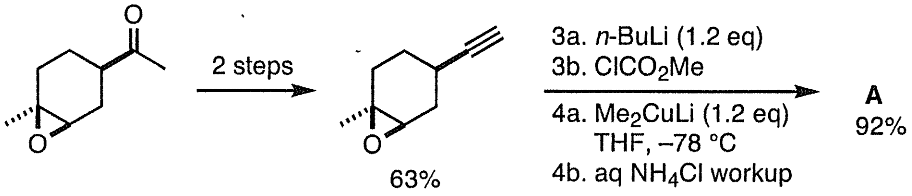
L
86%

Step 2 Alcohol dehydration with Ph$_2$S[OC(CF$_3$)$_2$Ph]$_2$ (Martin sulfurane reagent).

Reference: Boyd, V. A.; Drake, B. E.; Sulikowski, G. A. *J. Org. Chem.* **1993**, *58*, 3191.

2. **Selectivity.** Show the reaction intermediates obtained after each step and the major product obtained as well as provide the reagents and conditions when not given to accomplish the following transformations.

a.



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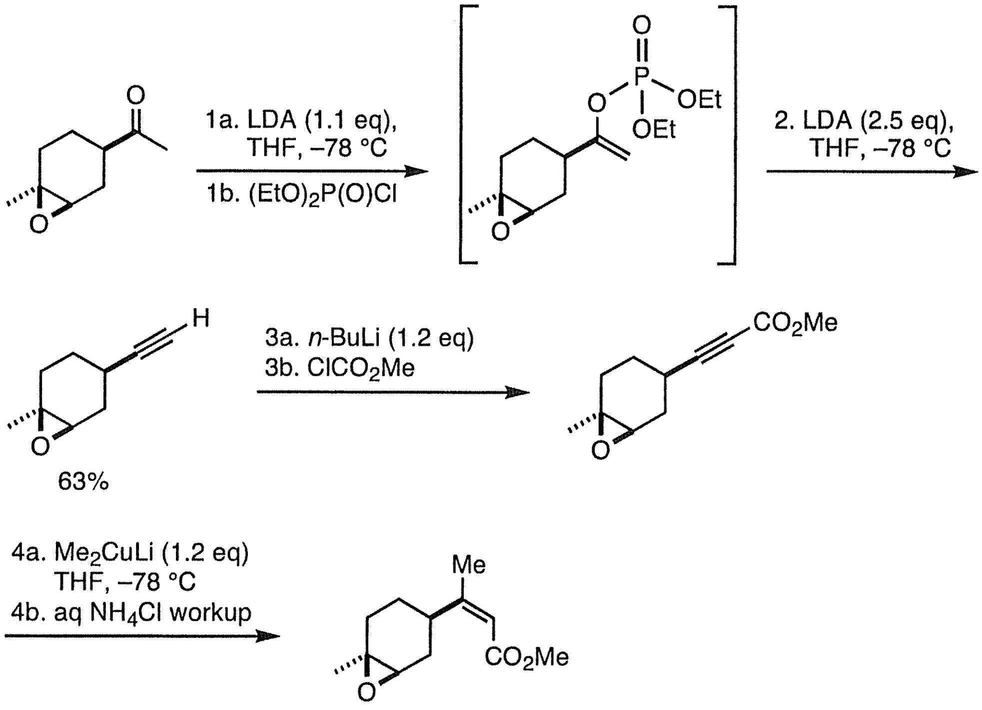


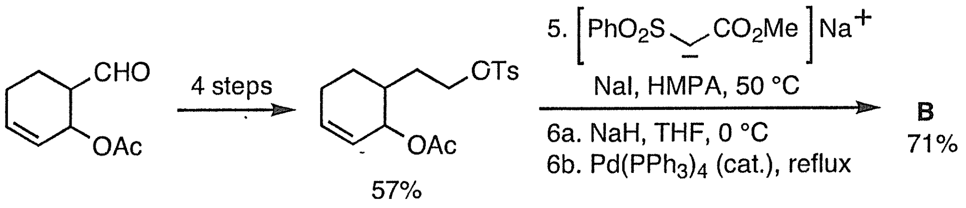
A
92%

Steps 1–2 Conversion of a ketone to a terminal alkyne (compare with Corey-Fuchs reaction where an aldehyde is converted to a terminal alkyne).

Step 4 Me_2CuLi adds to the acetylenic ester in a conjugate manner to provide (*Z*)-olefin.

Reference: Marron, B. E.; Nicolaou, K. C. *Synthesis* **1989**, 537.

b.



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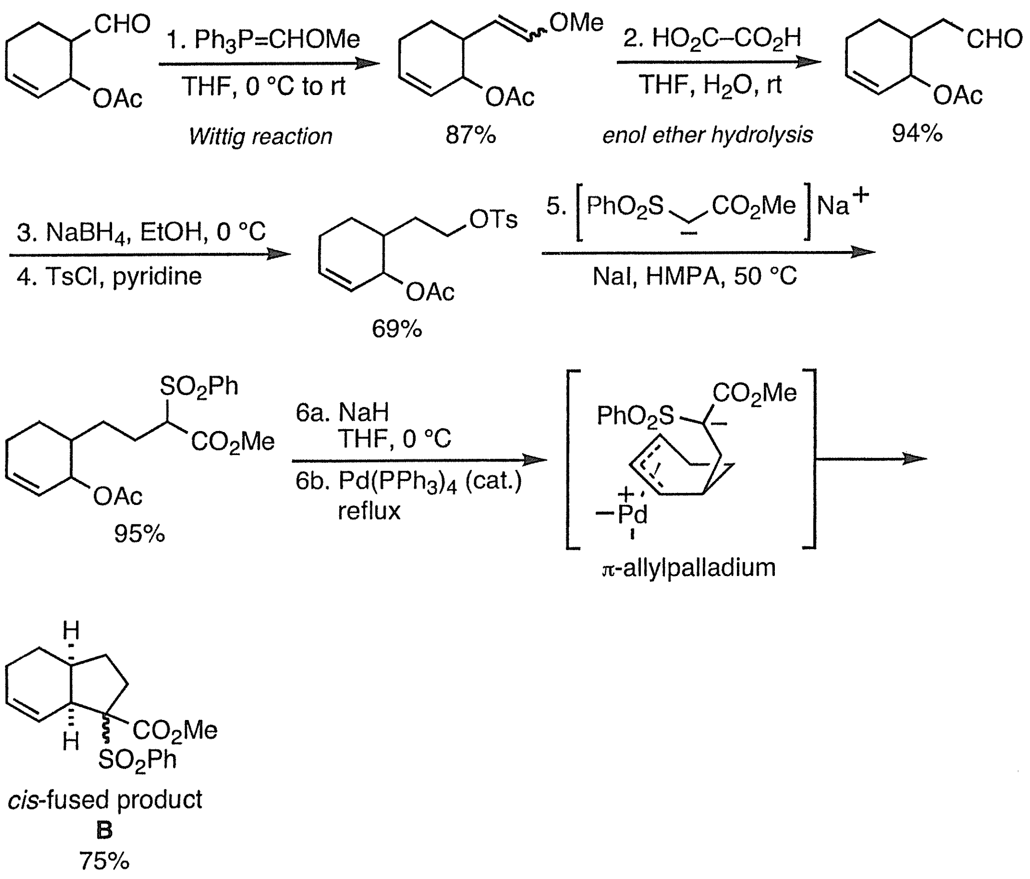
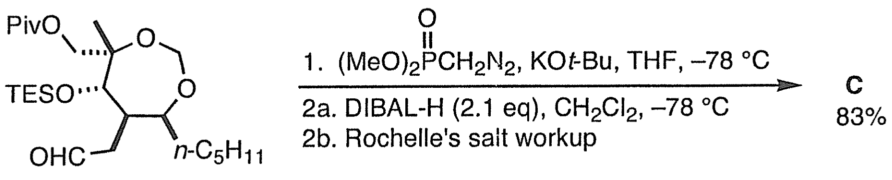


Reference: Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1977**, *99*, 3867.

c.



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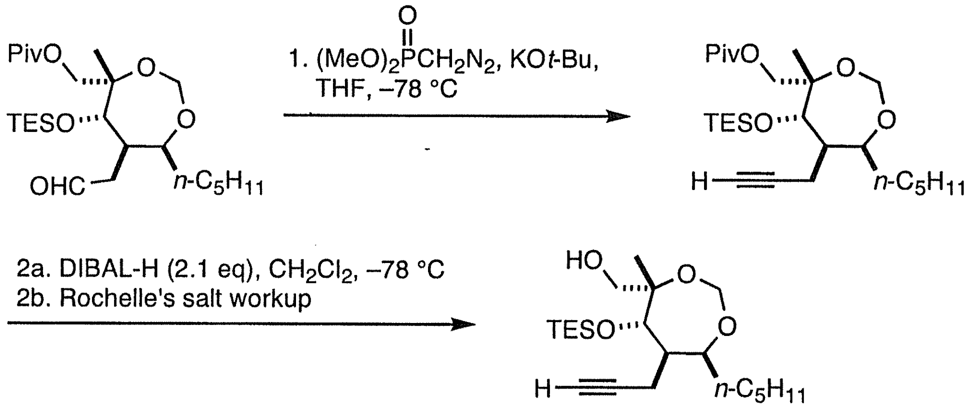
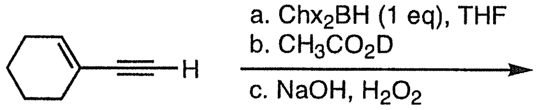


C
83%

Step 1 Conversion of an aldehyde to the corresponding terminal alkyne with Gilbert's reagent.

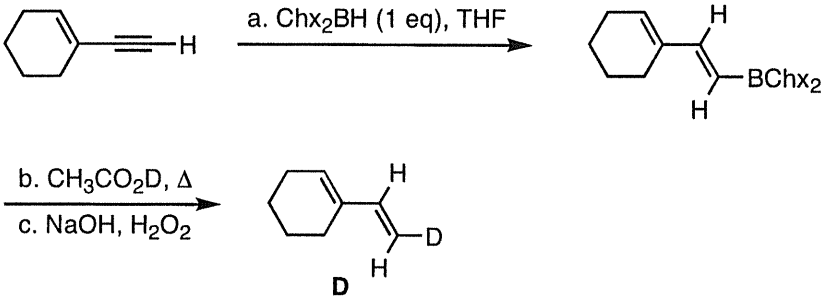
Reference: Powell, N. A.; Roush, W. R. *Org. Lett.* **2001**, *3*, 453.

d.



D
87%

Solution:



D
87%

Steps a–c (hydroboration-protonolysis-oxidation) represent a method for the selective reduction of a terminal alkyne in the presence of an alkene.

Reference: Zweifel, G.; Clark, G. M.; Polston, N. L. *J. Am. Chem. Soc.* **1971**, *93*, 3395.

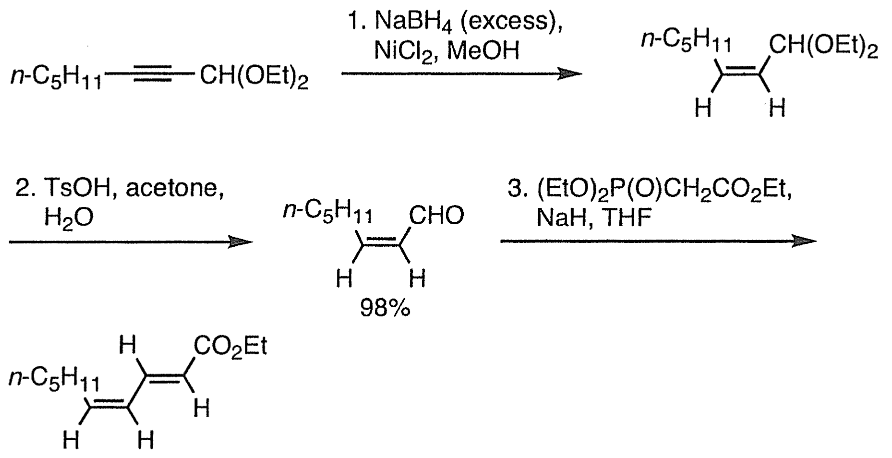
3. **Stereochemistry**. Predict the stereochemistry of the major product formed for each of the following reactions. Give an explanation for your choice.

a.

$$n\text{-}C_5H_{11}-\!\!\equiv\!\!-CH(OEt)_2 \xrightarrow[\text{3. }(EtO)_2P(O)CH_2CO_2Et\text{, NaH, THF}]{\text{1. }NaBH_4\text{ (excess), }NiCl_2\text{, MeOH; 2. TsOH, acetone, }H_2O} \textbf{A}$$

A
46%
(88 : 12 mixture)

Solution:

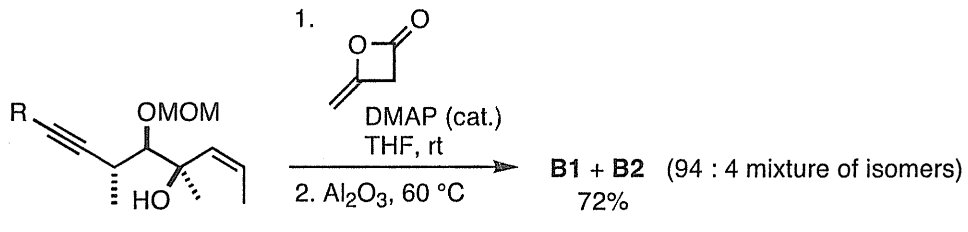


A
46%
(88 : 12 2*E*,4*Z* : 2*E*,4*E* mixture)

Step 3 HWE reaction.

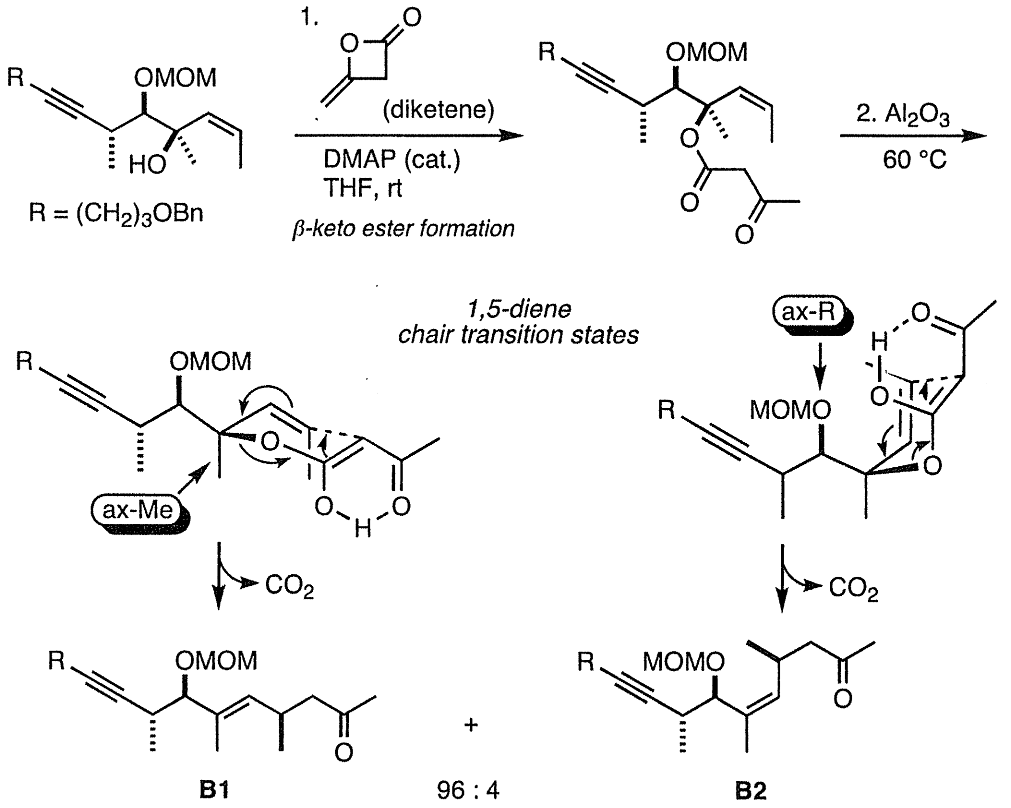
Reference: Byrne, B.; Lawter, L. M. L.; Wengenroth, K. J. *J. Org. Chem.* **1986,** *51*, 2607.

***b.**



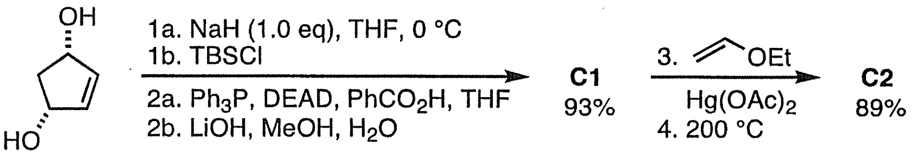
R = $(CH_2)_3OBn$

Solution:

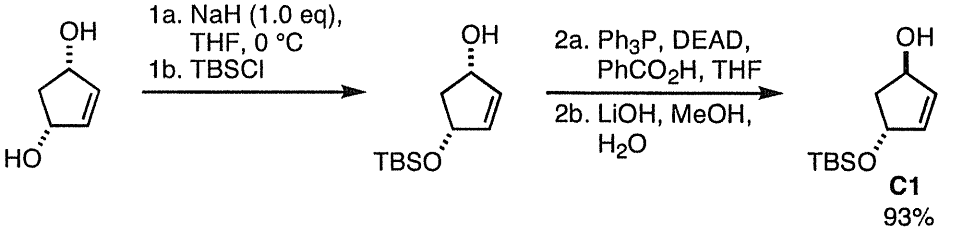


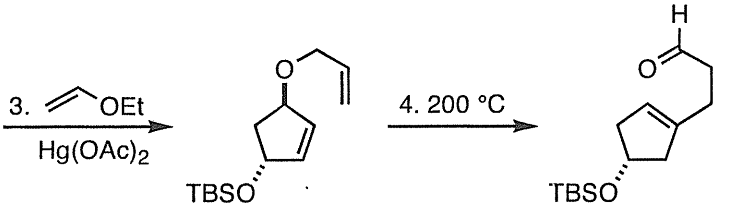
Reference: Defosseux, M.; Blanchard, N.; Meyer, C.; Cossy, J. *J. Org. Chem.* **2004**, *69*, 4626.

c.



Solution:



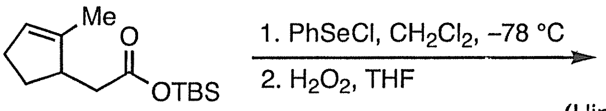


C2
89%

Step 2 Mitsunobu reaction inverts the configuration of a 2° alcohol.
Step 4 Claisen rearrangement.

Reference: Clive, D. L. J.; Magnuson, S. R.; Manning, H. W.; Mayhew, D. L. *J. Org. Chem.* **1996**, *61*, 2095.

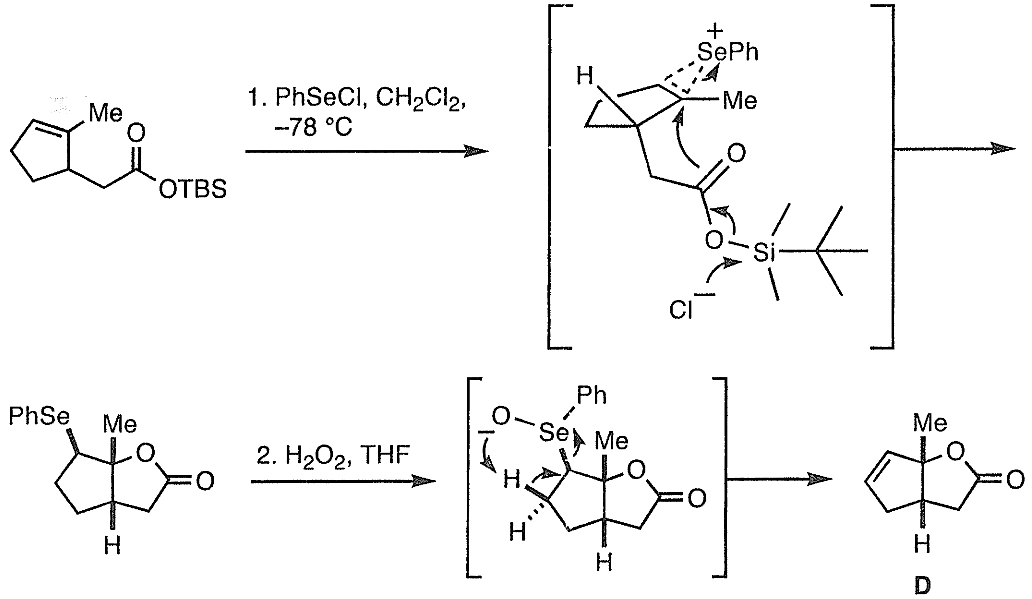
d.



D

(Hint: phenylselenolactonization)

Solution:

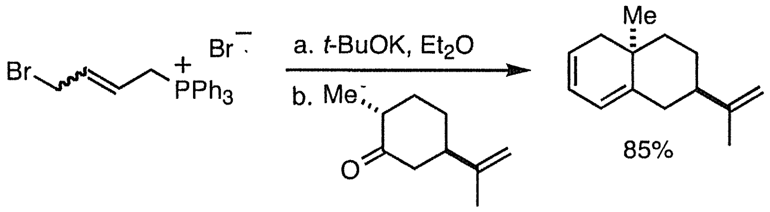


D

Reference: Curran, D. P.; Rakiewicz, D. M. *Tetrahedron* **1985**, *41*, 3943.

4. **Reactivity**. Explain the regioselectivity and stereochemistry observed in each of the following transformations.

a.



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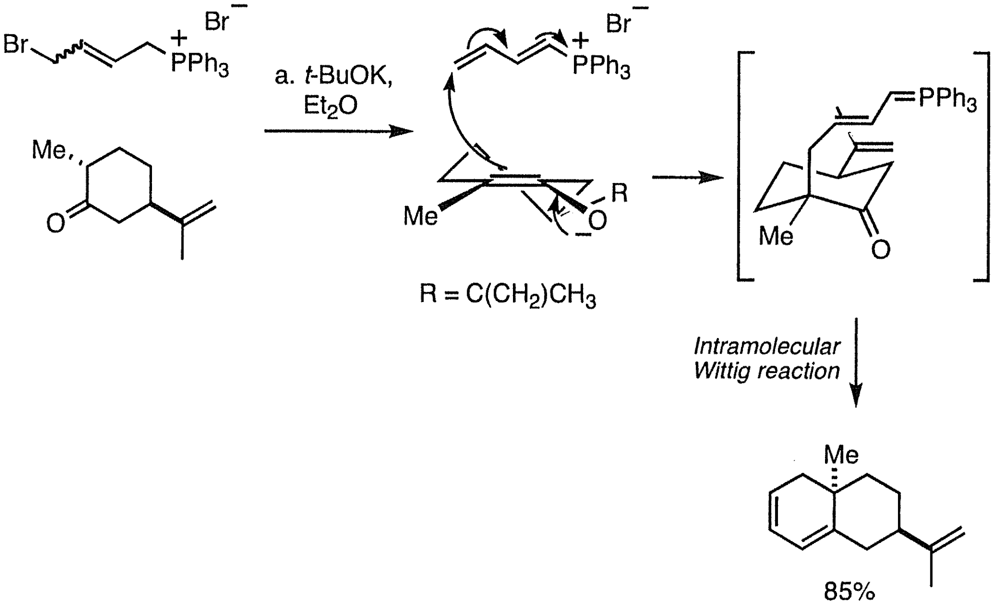
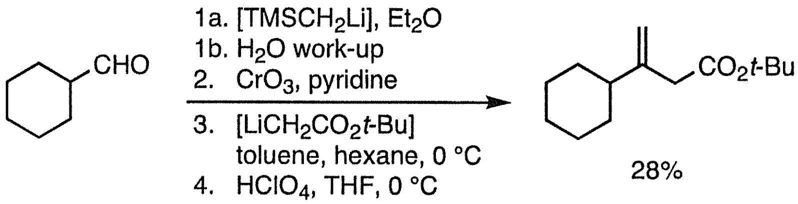


Reference: Büchi, G.; Pawlak, M. *J. Org. Chem.* **1975**, *40*, 100.

b.



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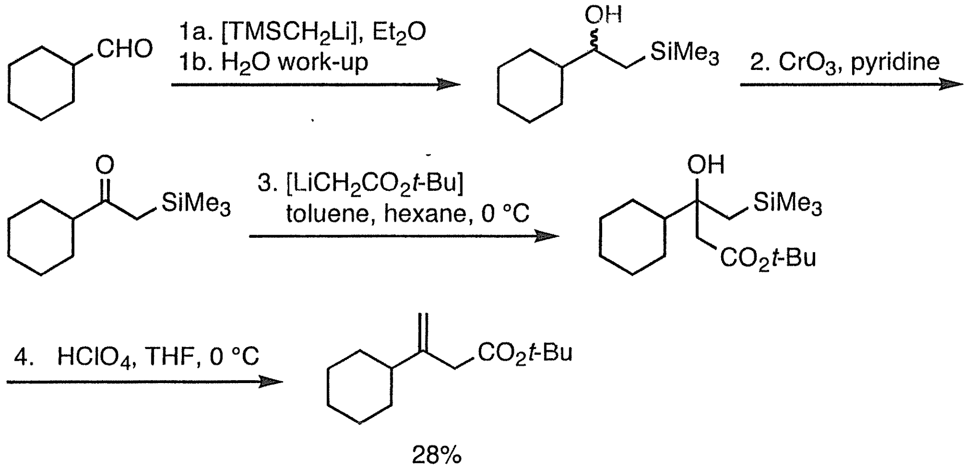
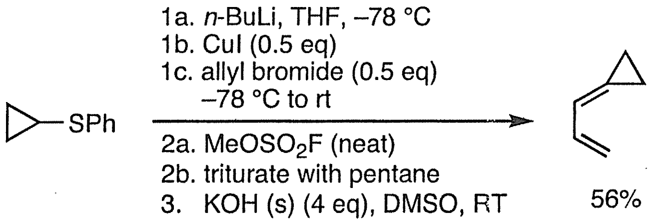


Reference: Ruden, R. A.; Gaffney, B. L. *Synth. Commun.* **1975**, *5*, 15.

***c.**



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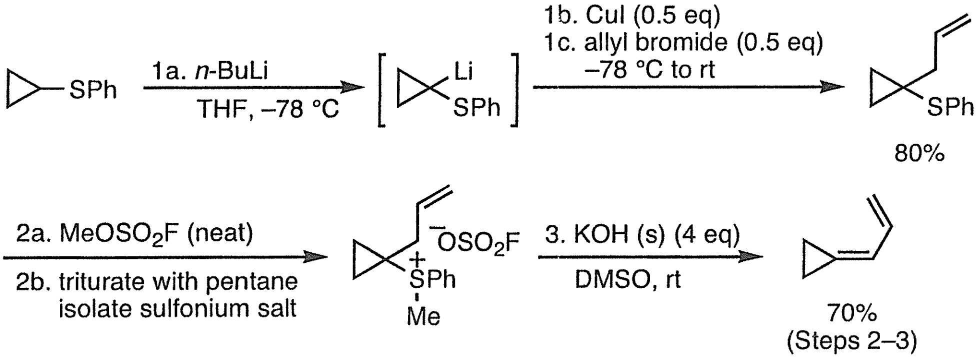


Step 1a The enhanced acidity of cyclopropyl over normal secondary hydrogens permits the facile deprotonation using *n*-BuLi; see *J. Am. Chem. Soc.* **1973**, *95*, 3068.

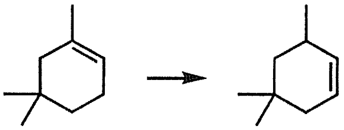
Step 2a Methylation using magic methyl (caution: carcinogen!).

Step 3 Regioselective E2-elimination (no cyclopropene is formed due to ring strain).

Reference: Zutterman, F.; Krief, A. *J. Org. Chem.* **1983**, *48*, 1135.

5. **Synthesis.** Supply the missing reagents required to accomplish each of the following syntheses. Be sure to control the relative stereochemistry.

a.



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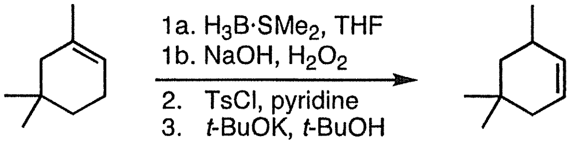
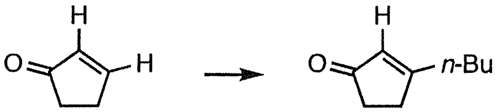


b.



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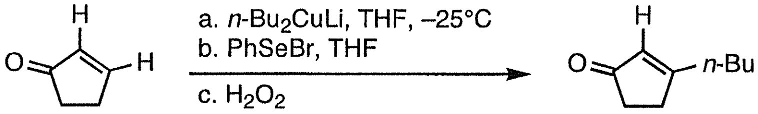
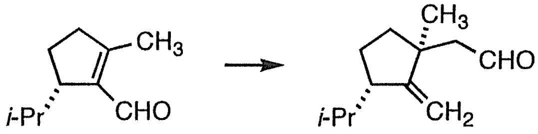


c.



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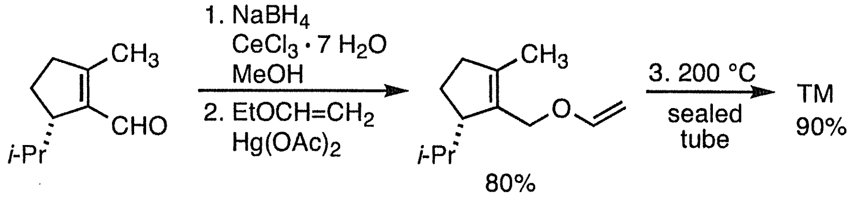
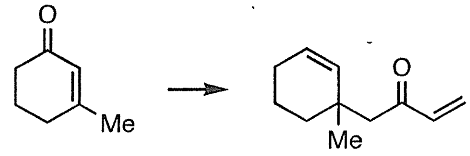
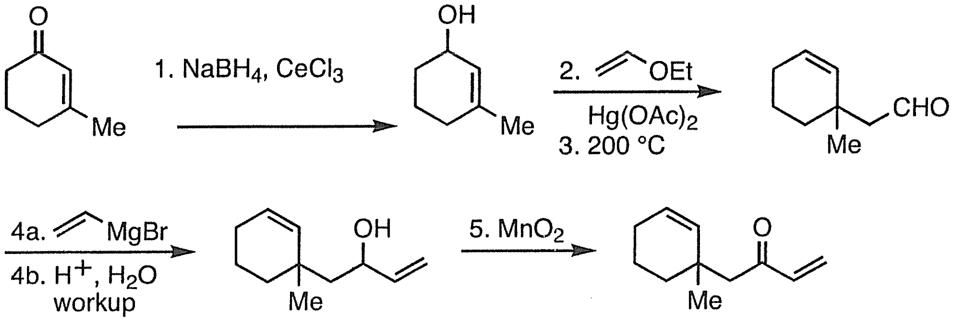


Reference: Mehta, G.; Krishnamurthy, N.; Karra, S. R. *J. Am. Chem. Soc.* **1991**, *113*, 5765.

d.

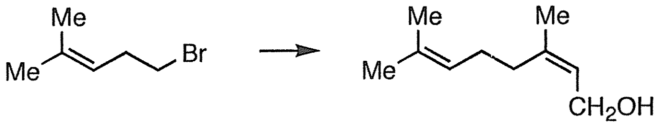


Solution:

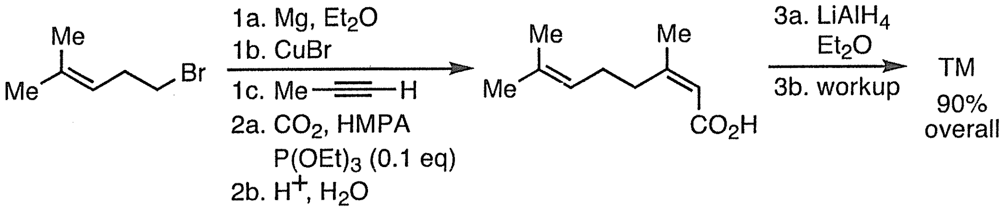


Reference: For an analogous synthesis, see Yamamoto, H.; Sham, H. L. *J. Am. Chem. Soc.* **1979**, *101*, 1609.

e.

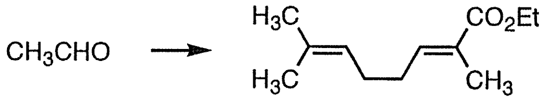


Solution:



Reference: Normant, J. F.; Cahiez, G.; Chuit, C.; Villieras, J. *J. Organomet. Chem.* **1974**, *77*, 281.

f.



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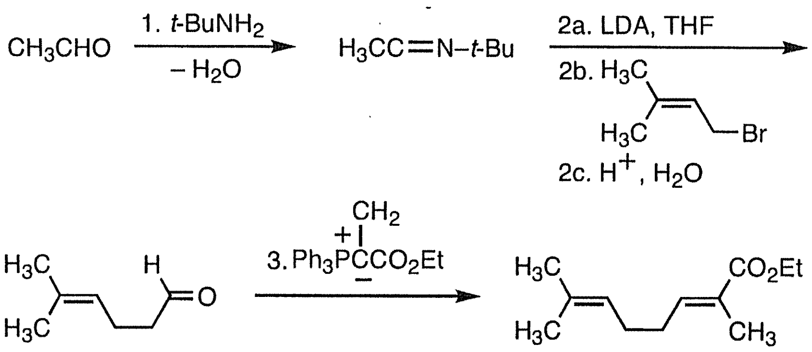
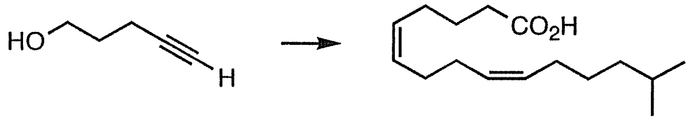


Step 3 The stabilized ylide is generated *in situ* by the treatment of the precursor phosphonium salt with NaH.

g.



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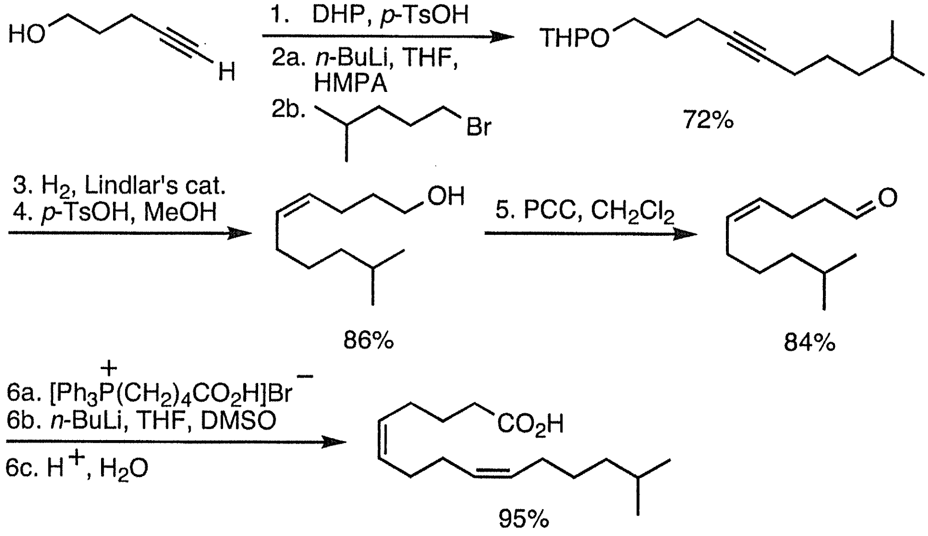
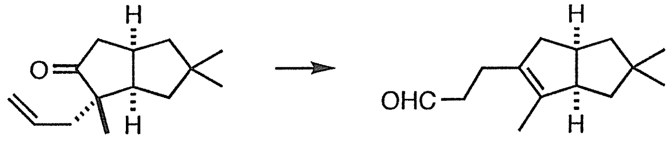
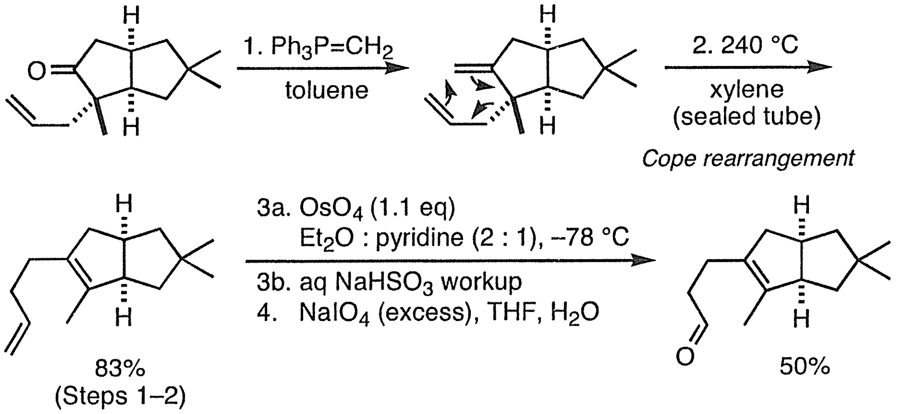


Reference: Reyes, E. D.; Carballeira, N. M. *Synthesis* **1997**, 1195.

h.

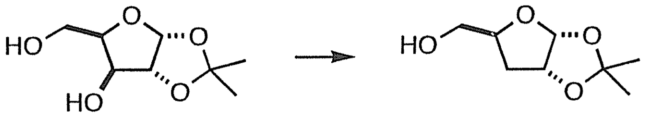


Solution:

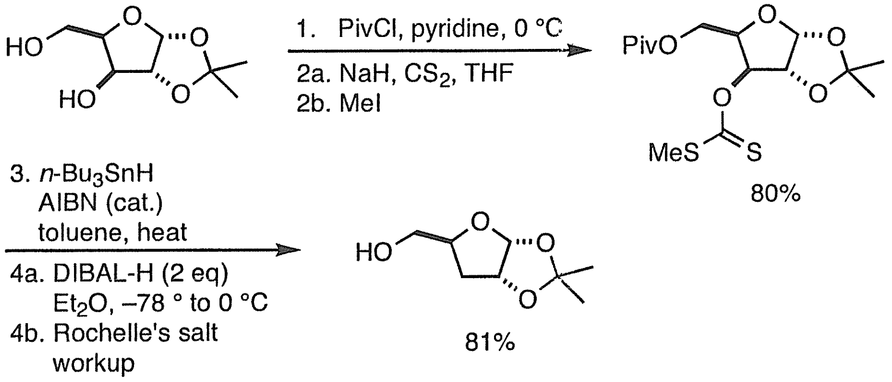


Reference: Nozoe, S. *Tetrahedron Lett.* **1976**, 195.

i.



Solution:



Steps 2–3 Barton-McCombie deoxygenation.

Reference: White, J. D.; Jeffrey, S. C. *J. Org. Chem.* **1996**, *61*, 2600.

CHAPTER 9

Syntheses of Carbocyclic Systems

Overview

Chapter 9 describes various methods for the synthesis of carbocyclic systems. The preparation of such systems can be achieved either by connecting two atoms within a single molecule (*intramolecular* reaction) or joining together two separate molecules (*intermolecular* reaction).

Problem 1 focuses on reagents for the synthesis of carbocyclic systems. Problems 2–4 address selectivity issues associated with carbocyclic systems. The syntheses of TMs in Problems 5 and 6 require the selection of specific reagents to achieve chemo-, stereo-, or enantioselective cyclizations.

Key Concepts

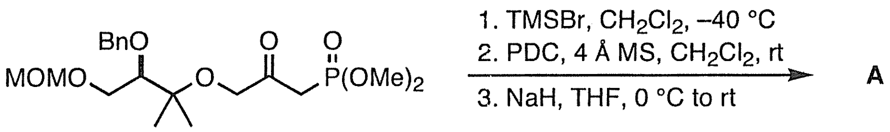
- Intramolecular free radical cyclizations
  - Acyloin condensation
  - Pinacol coupling
  - McMurry reaction
- Cation-π cyclizations
- Pericyclic reactions
  - Diels-Alder reaction
- Ring-closing olefin metathesis (RCM)
  - Grubbs catalyst

SOLUTIONS TO CHAPTER 9 PROBLEMS

The more challenging problems are identified by an asterisk (*).

1. **Reagents.** Give the structure of the major product expected for each of the following reactions. Be sure to indicate product stereochemistry where applicable.

a.



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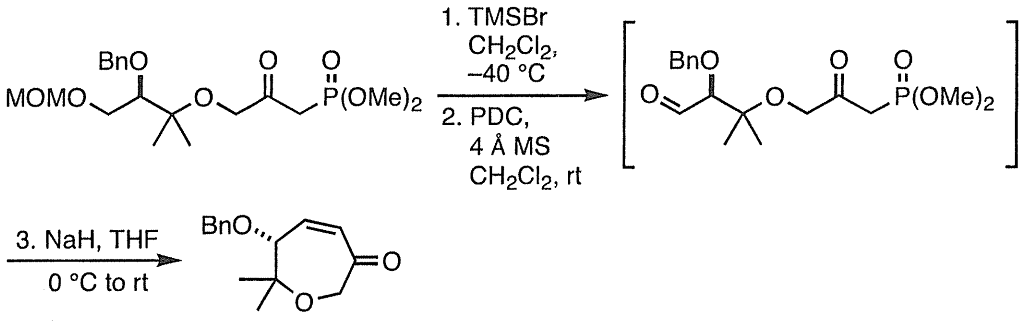
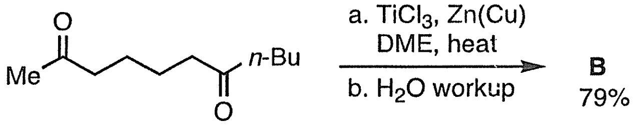


A

Step 1 Lewis acid–mediated MOM deprotection.
Step 3 Intramolecular HWE reaction.

Reference: For an analogous reaction sequence, see Taillier, C.; Gille, B.; Bellosta, V.; Cossy, J. *J. Org. Chem.* **2005**, *70*, 2097.

b.



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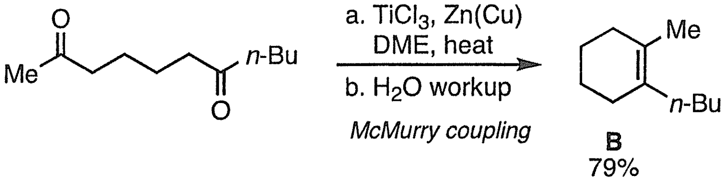
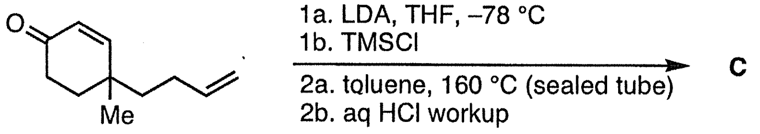


Reference: McMurry, J. E.; Kess, K. L. *J. Org. Chem.* **1977**, *42*, 2655.

c.



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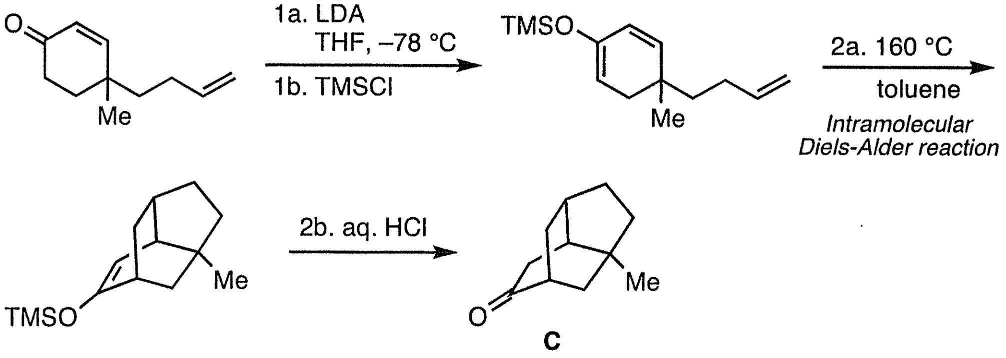
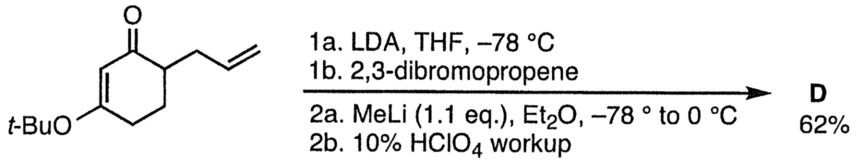
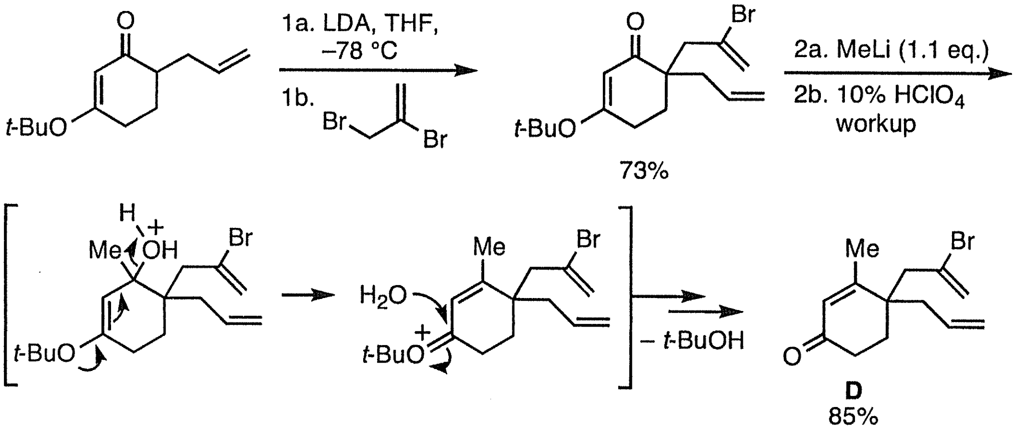


Reference: For an analogous synthesis, see Yamamoto, H.; Sham, H. L. *J. Am. Chem. Soc.* **1979**, *101*, 1609.

d.

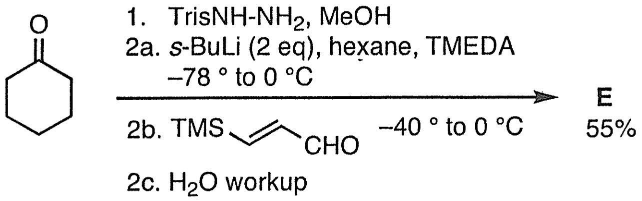


Solution:



Reference: Toyota, M.; Ilangovan, A.; Kashigawi, Y.; Ihara, M. *Org. Lett.* **2004**, *6*, 3629.

e.



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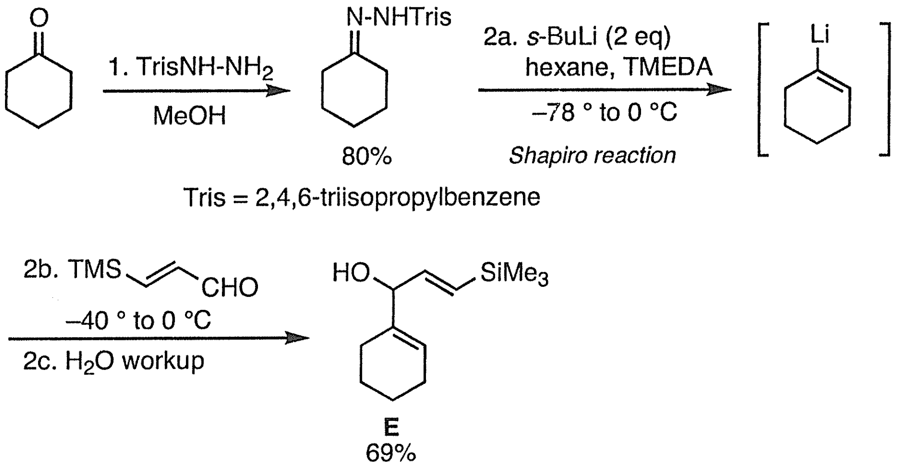
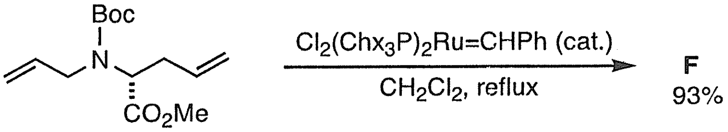


Tris = 2,4,6-triisopropylbenzene

Reference: Jones, T. K.; Denmark, S. E. *Helv. Chim. Acta* **1983**, *66*, 2377.

f.



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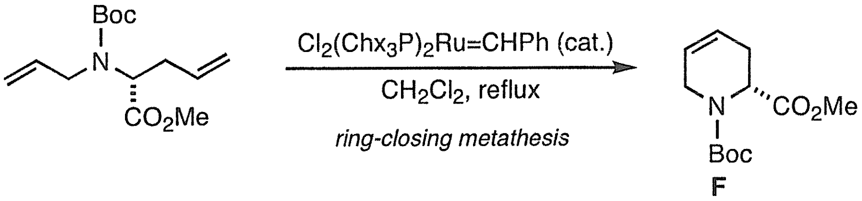
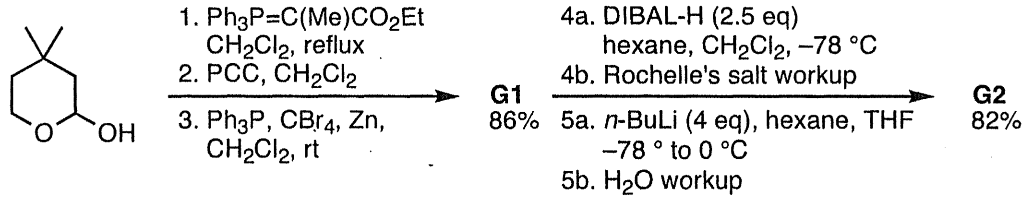
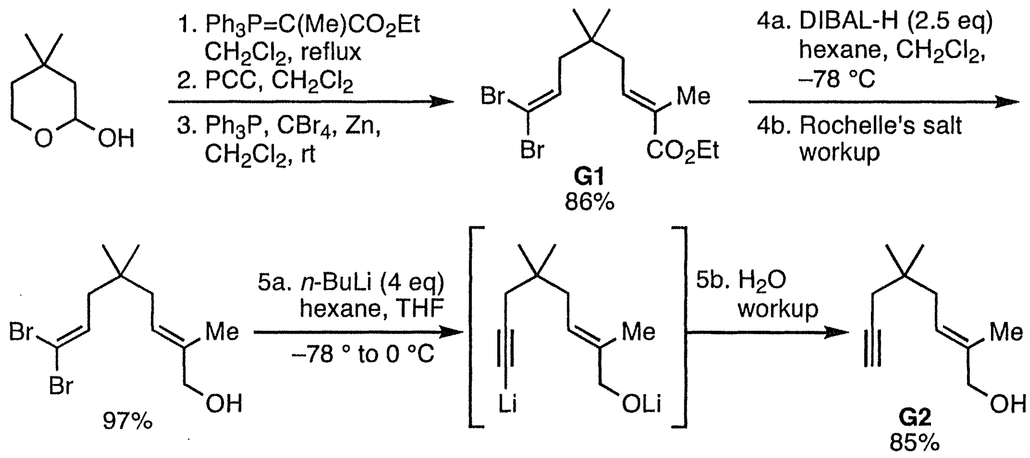


Reference: Rutjes, F. P. J. T.; Schoemaker, H. E. *Tetrahedron Lett.* **1997**, *38*, 677.

g.



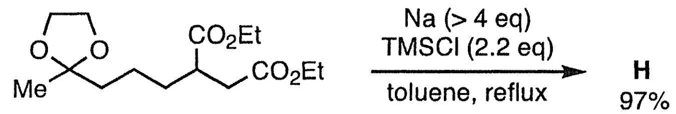
Solution:



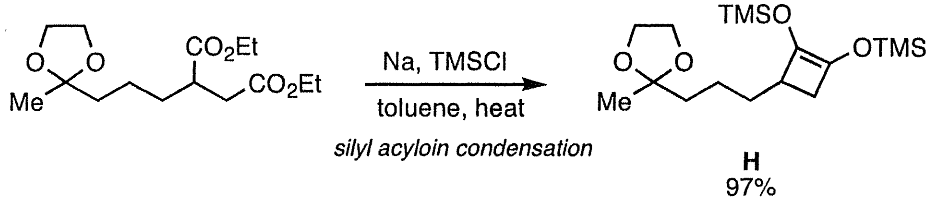
Step 1 Wittig olefination gives the (*E*)-alkene as the major product (93 : 7).
Step 5 Corey-Fuchs alkynylation.

Reference: Oppolzer, W.; Robyr, C. *Tetrahedron* **1994**, *50*, 415.

h.

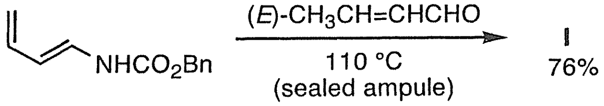


Solution:

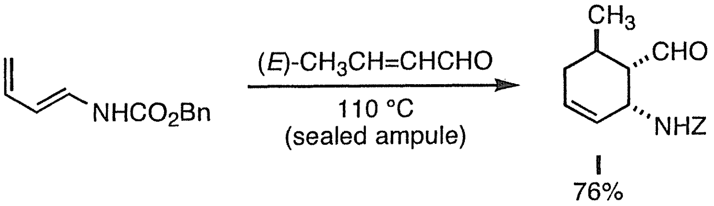


Reference: Blanchard, A. N.; Burnell, D. J. *Tetrahedron Lett.* **2001**, *42*, 4779.

i.

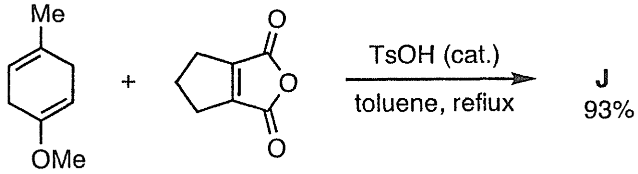


Solution:

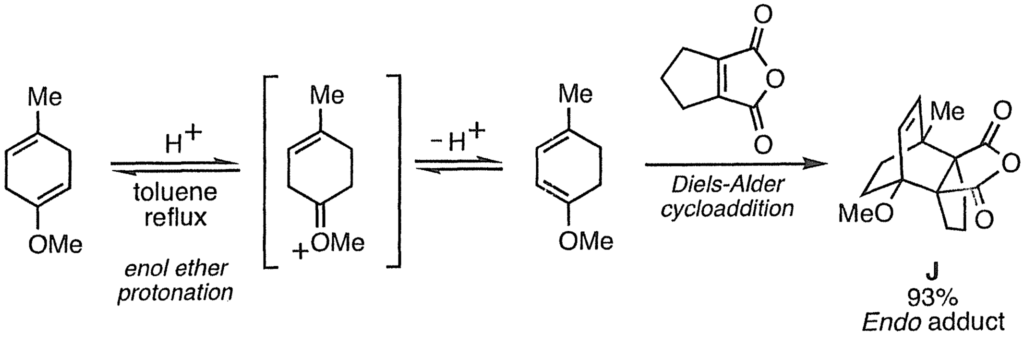


Reference: Overman, L. E.; Jessup, P. J. *J. Am. Chem. Soc.* **1978**, *100*, 5179.

***j.**



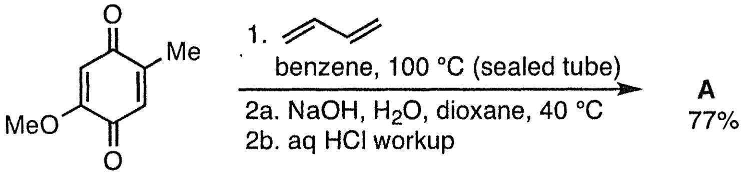
Solution:



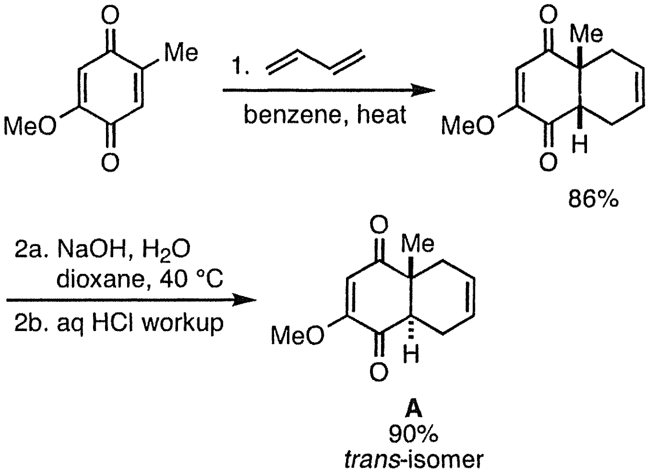
Reference: Kodama, M.; Kurihara, T.; Sasaki, J.; Ito, S. *Can. J. Chem.* **1979**, *57*, 3343.

2. **Selectivity.** Show the product(s) obtained and the appropriate reagent(s) necessary for each of the following transformations.

a.



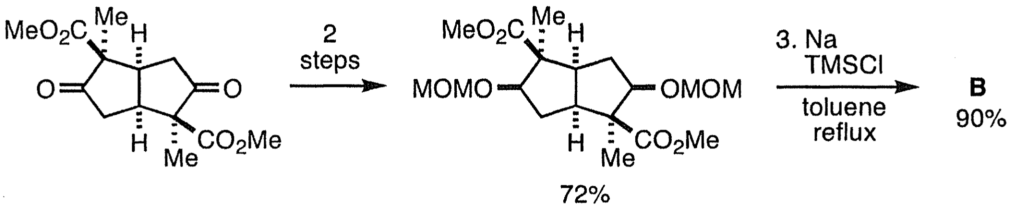
Solution:



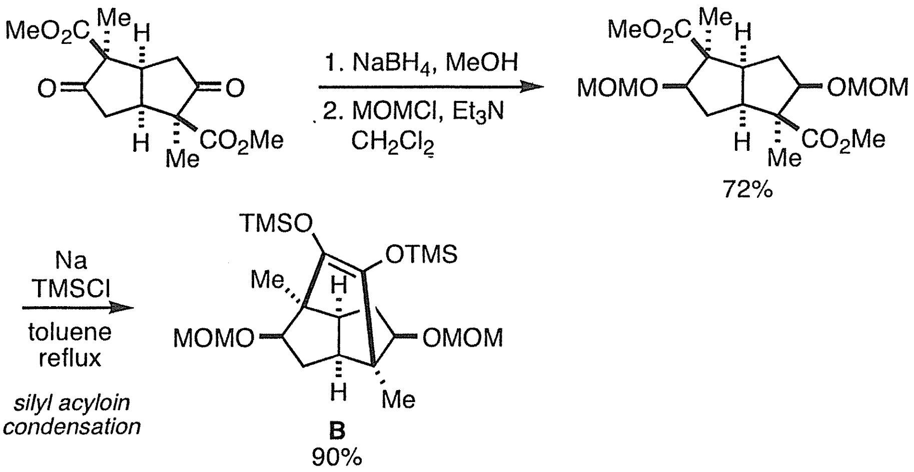
Step 1 The more electron rich, methoxy-substituted double bond is less dienophilic than the methyl-substituted one; hence the cycloaddition occurs selectively at the methyl-substituted double bond.

Reference: Woodward, R. B.; Sondheimer, F.; Taub, D.; Heusler, K.; McLamore, W. M. *J. Am. Chem. Soc.* **1952**, *74*, 4223.

b.

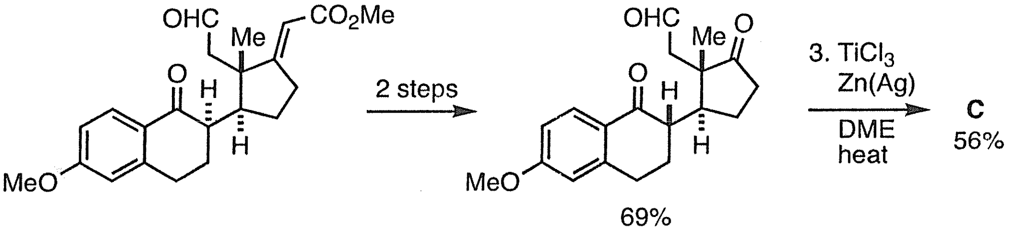


Solution:

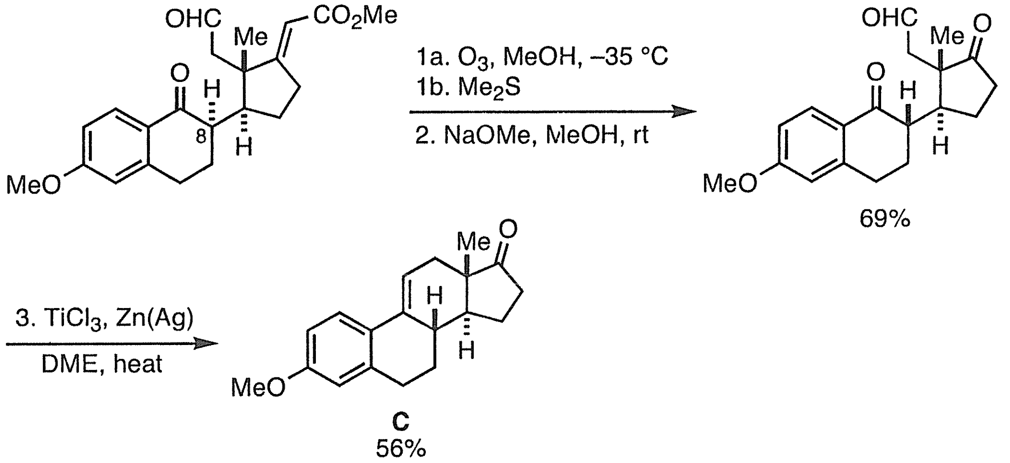


Reference: Sieburth, S. M.; Santos, E. D. *Tetrahedron Lett.* **1994**, *35*, 8127.

c.



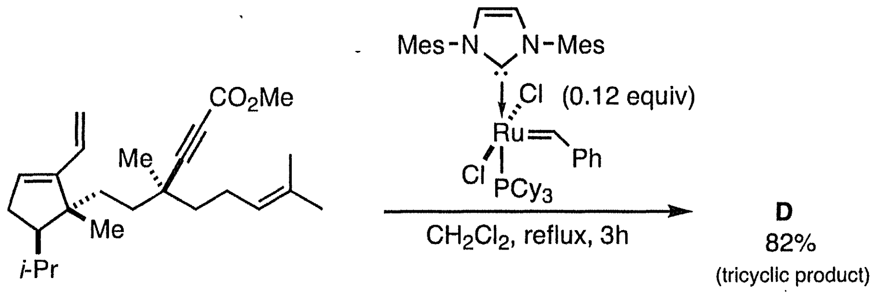
Solution:



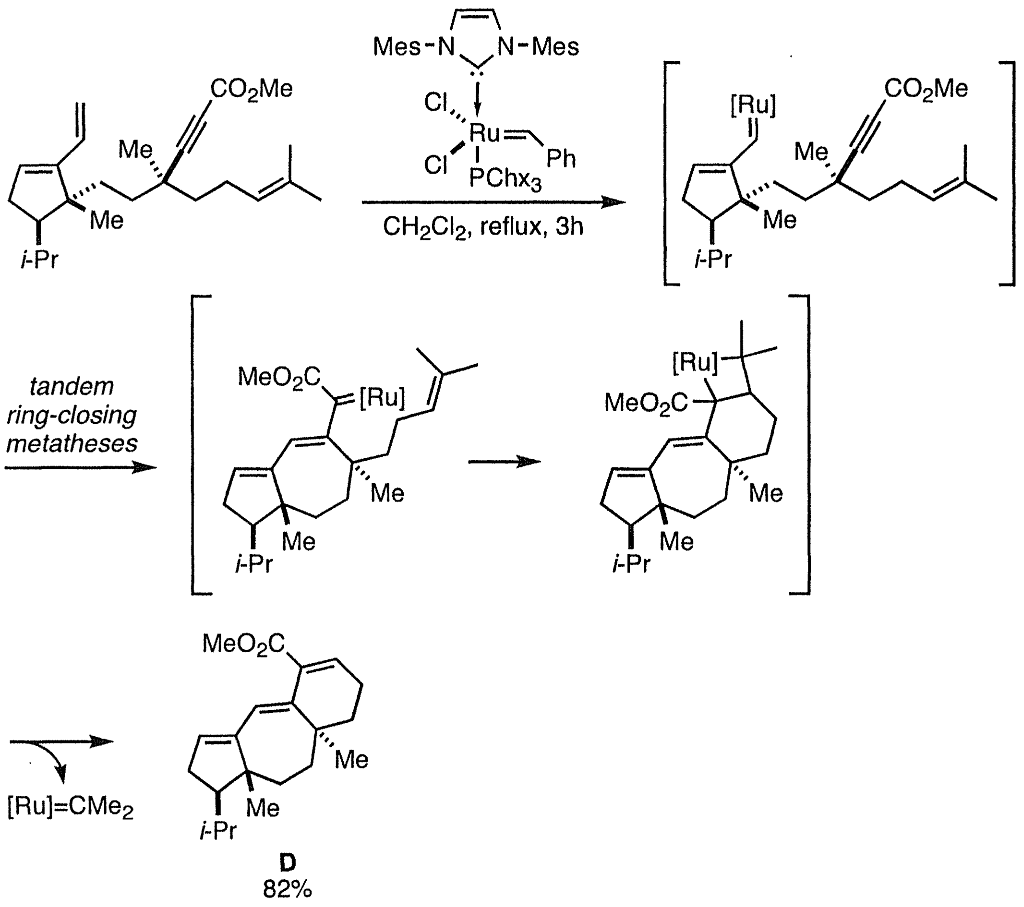
Step 2 Epimerization of C(8) to the more stable C(8)-H_β isomer.
Step 3 Intramolecular McMurry coupling.

Reference: Mikami, K.; Takahashi, K.; Nakai, T. *J. Am. Chem. Soc.* **1990**, *112*, 4035.

***d.**

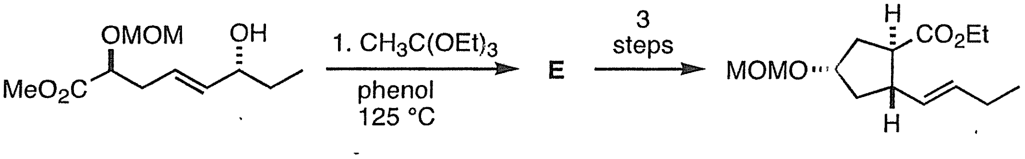


Solution:

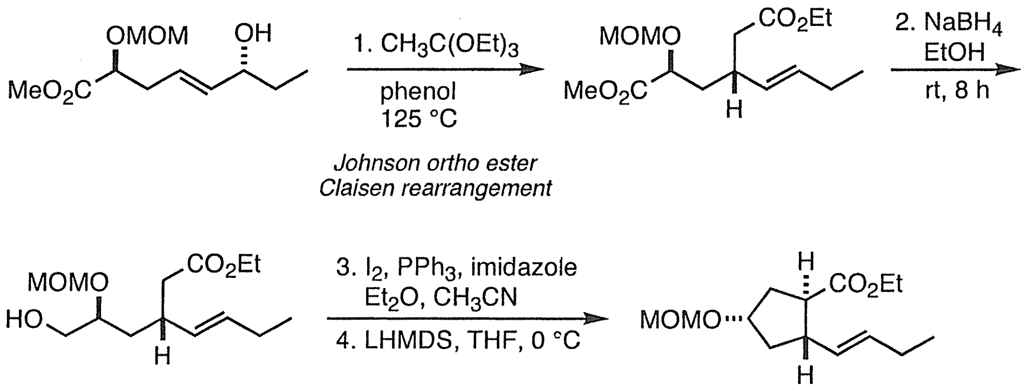


Reference: Boyer, F.–D.; Hanna, I.; Ricard, L. *Org. Lett.* **2004**, *6*, 1817.

***e.**



Solution:

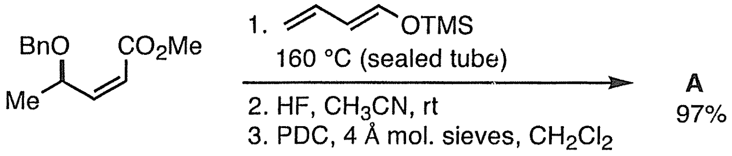


Step 2 Chemoselective reduction of the α-alkoxy ester.
Step 3 Ester enolate alkylation (5-exo-tet cyclization).

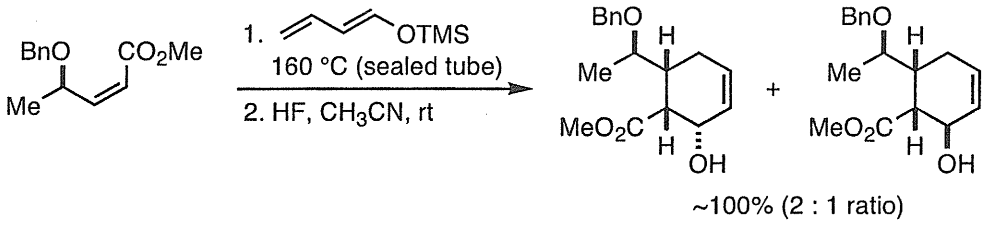
Reference: Kim, D.; Lee, J.; Shim, P. J.; Lim, J. I.; Jo, H.; Kim, S. *J. Org. Chem.* **2002**, *67*, 764.

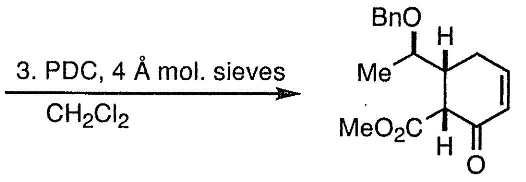
3. **Stereochemistry**. Predict the stereochemistry of the major product formed for each of the following reactions.

a.



Solution:

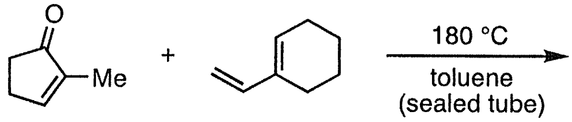




A
97%

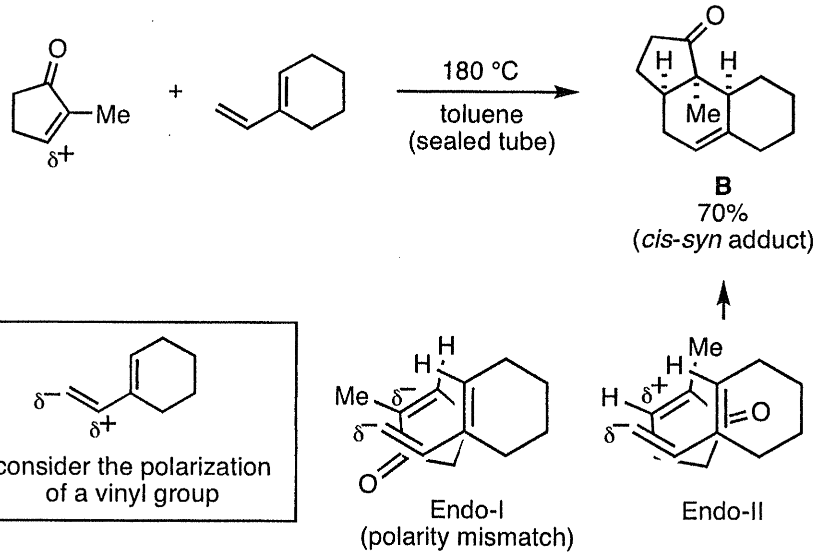
Reference: Kan, T.; Hosokawa, S.; Nara, S.; Oikawa, M.; Ito, S.; Matsuda, F.; Shirahama, H. *J. Org. Chem.* **1994**, *59*, 5532.

b.



B
70%

Solution:



B
70%
(*cis*-*syn* adduct)

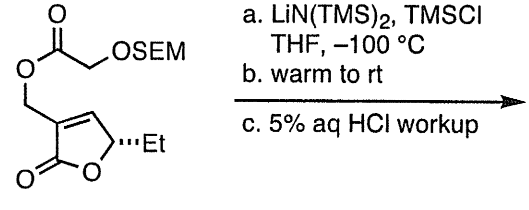
consider the polarization of a vinyl group

Endo-I
(polarity mismatch)

Endo-II

Reference: Ireland, R. E.; Thompson, W. J. *J. Org. Chem.* **1979**, *44*, 3583.

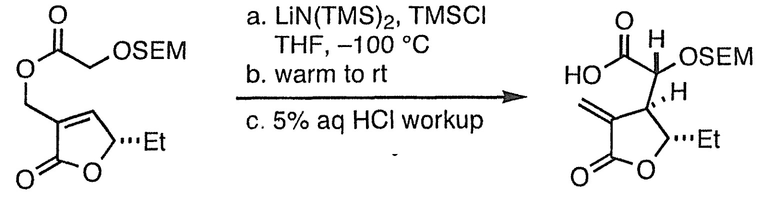
c.



SEM = $CH_2CH_2SiMe_3$

C
71%

Solution:

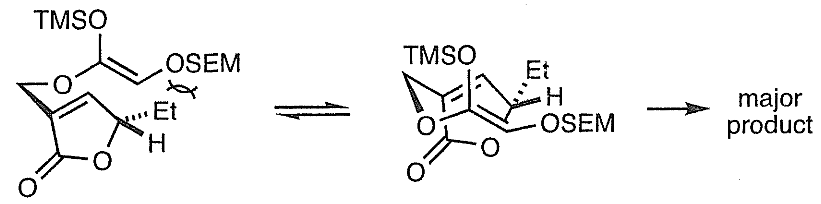


SEM = $CH_2CH_2SiMe_3$

C
71% (> 20 : 1 de)

Step a Silylation of the ester enolate to give a silyl ketene acetal.

Step b [3,3] sigmatropic shift (ester enolate Claisen rearrangement) via a chair transition state on the sterically more accessible β-face of the butenolide (**B** below).

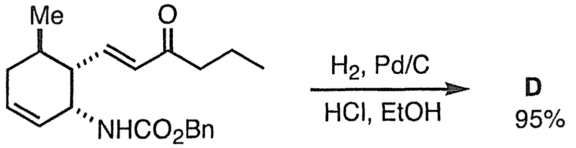


chair TS-**A** (disfavored)

chair TS-**B** (favored)

Reference: Burke, S. D.; Pacofsky, G. J. *Tetrahedron Lett.* **1986**, *27*, 445.

d.



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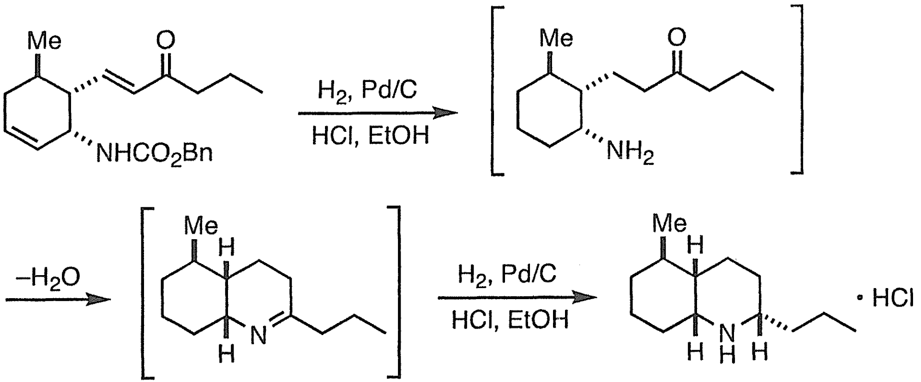
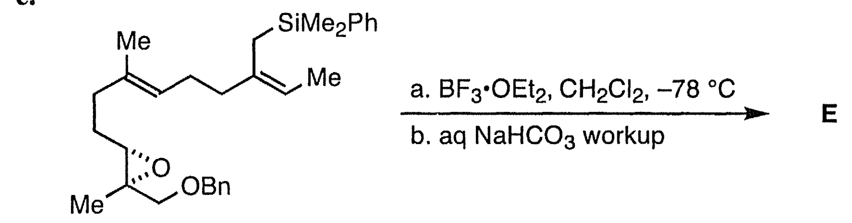


D
95%

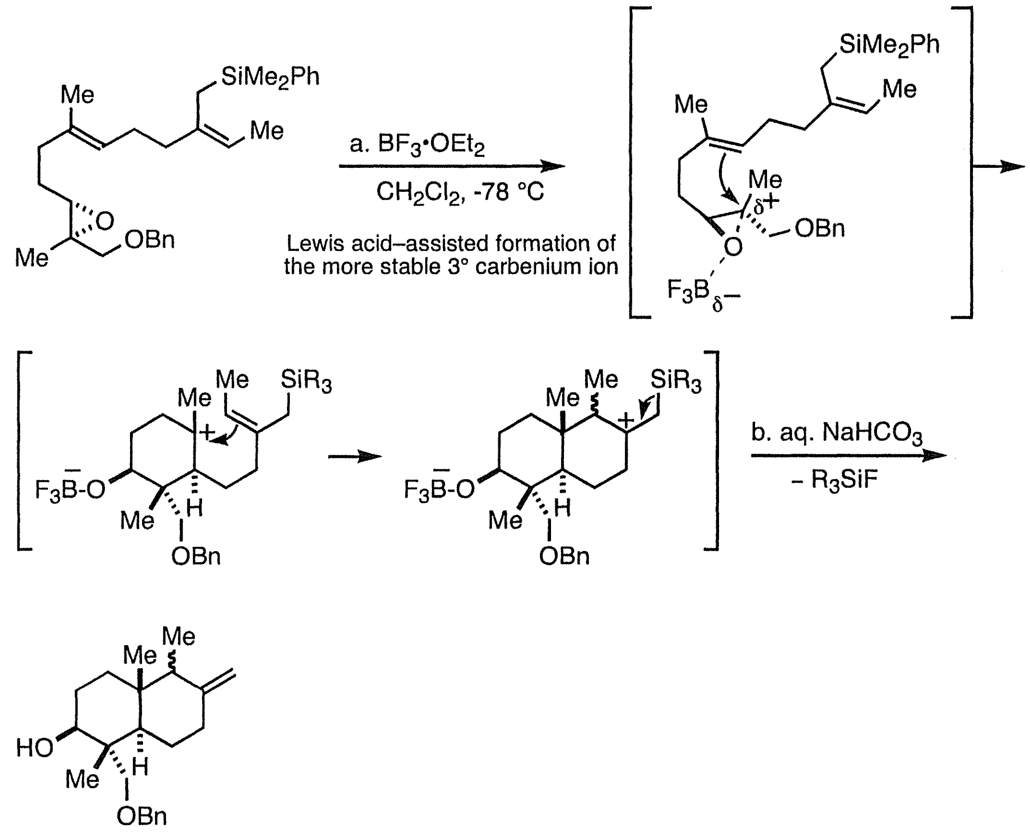
This is one of the finest single-step transformations in the chemical literature. Note that *five* reactions are achieved in *one pot*: hydrogenation of two double bonds, Cbz deprotection, intramolecular imine formation, and convex-face alkene hydrogenation that establishes the *n*-Pr stereocenter.

Reference: Overman, L. E.; Jessup, P. J. *J. Am. Chem. Soc.* **1978**, *100*, 5179.

***e.**



Solution:



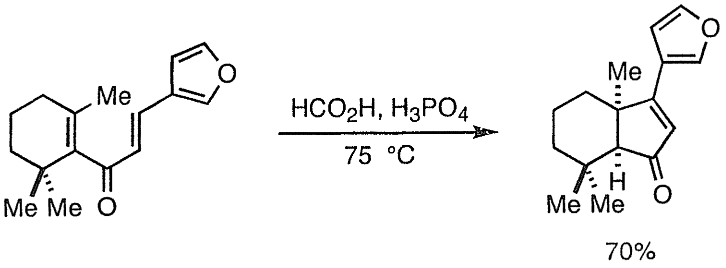
E

It is not obvious which cyclization conformation predominates (e.g., chair-chair vs. chair-boat). 1 : 1 mixture of diastereomers was obtained.

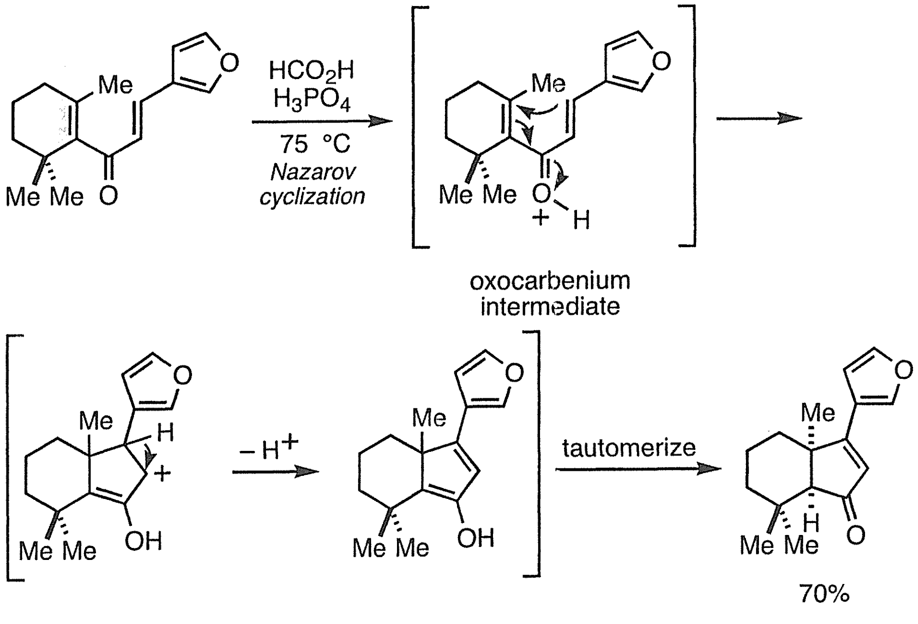
Reference: For an analogous transformation, see Li, W.-D. Z.; Yang, J.-H. *Org. Lett.* **2004**, *6*, 1849.

4. **Reactivity**. Propose a mechanism for each of the following transformations that explains the observed regioselectivity and stereochemistry of the reaction.

a.



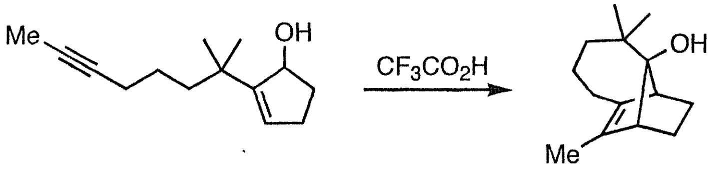
Solution:



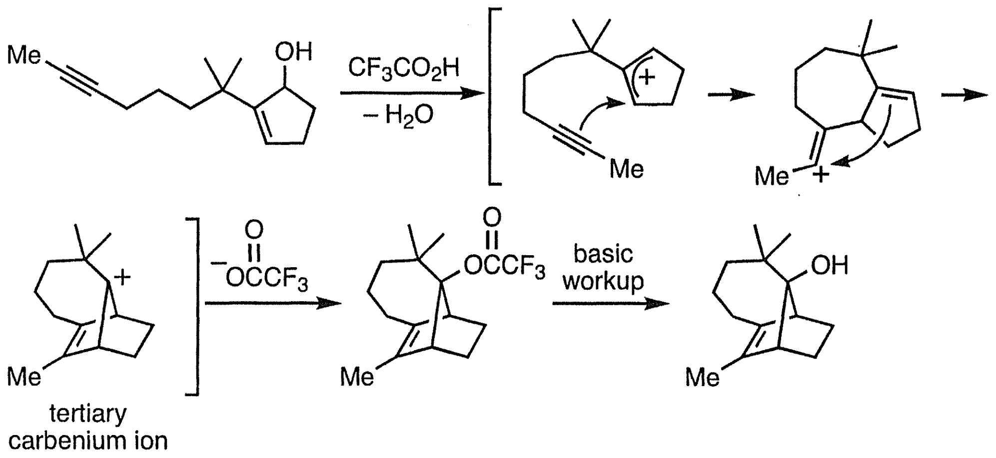
Tautomerization of the enol ether furnishes the more stable *cis*-fused [4.3.0] bicyclic system.

Reference: Mateos, A. F.; Barba, A. L.; Coca, P.; González, R. R.; Hernández, C. T. *Synthesis* **1997**, 1381.

b.



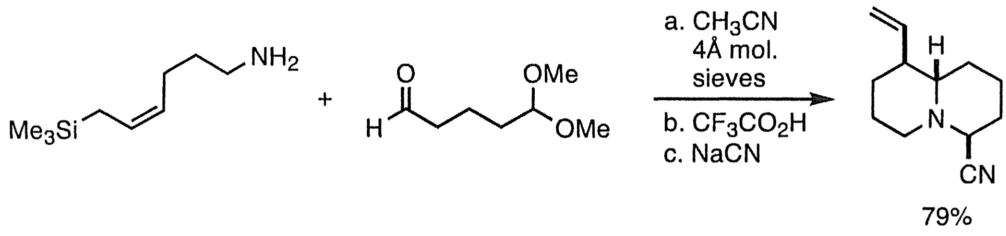
Solution:



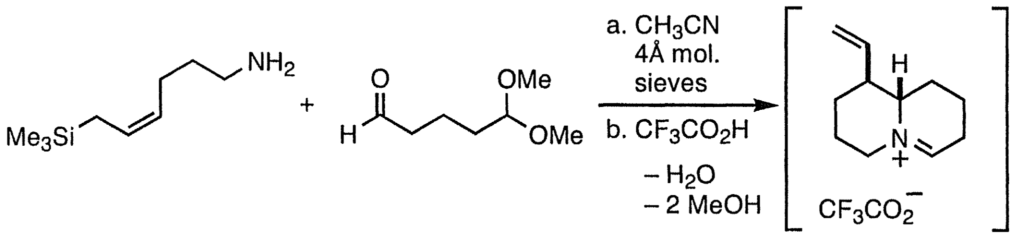
A basic aqueous workup is sufficient to hydrolyze the trifluoroacetyl ester to yield the TM.

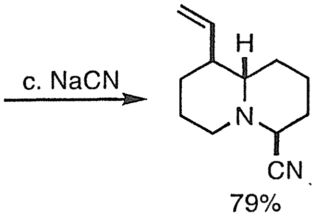
Reference: Volkmann, R. A.; Andrews, G. C.; Johnson, W. S. *J. Am. Chem. Soc.* **1975**, *97*, 4777.

c.



Solution:

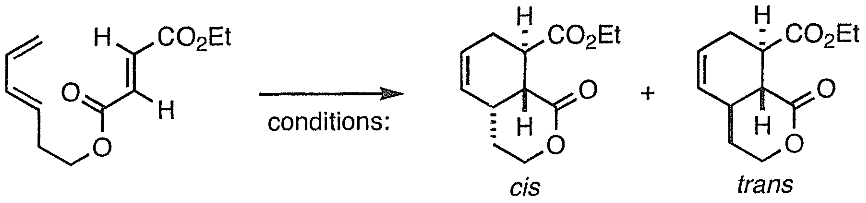




Step a Imine formation.
Step b Two acid-catalyzed cyclizations: allyl silane addition to an iminium ion followed by intramolecular imine alkylation and loss of MeOH.
Step c Exo-face addition of CN^-.

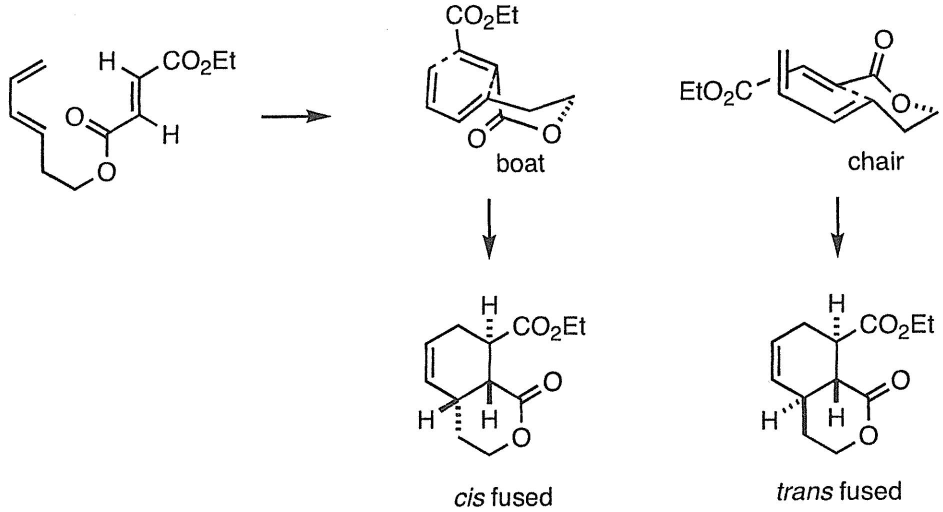
Reference: Amorde, S. M.; Judd, A. S.; Martin, S. F. *Org. Lett.* **2005**, *7*, 2031.

***d.**



conditions	*cis*	*trans*
xylene, heat, 5 h	51%	15%
Et_2AlCl, 0 °C, 20 min	0%	90%

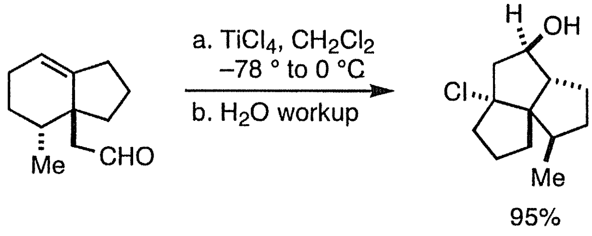
Solution:



A chair conformation (lower in energy than a boat conformation) is required for the formation of the *trans* fused product. Lewis acid-promoted intramolecular Diels-Alder reaction proceeds at 0 °C in the presence of Et_2AlCl leading to the *trans*-fused product. Presumably, there is not sufficient energy to achieve the boat conformation to form the *cis* fused product.

Reference: Chen, C.–Y.; Hart, D. J. *J. Org. Chem.* **1993**, *58*, 3840.

***e.**



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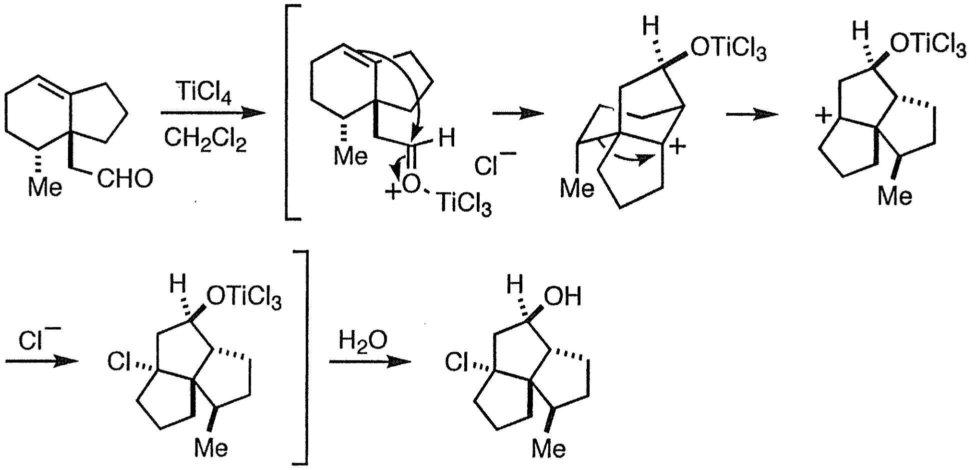
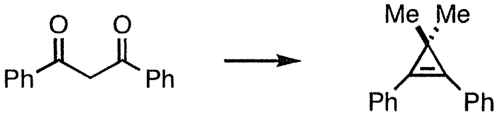


Reference: Willmore, N. D.; Goodman, R.; Lee, H. H.; Kennedy, R. M. *J. Org. Chem.* **1992**, *57*, 1216.

5. **Synthesis**. Supply the missing reagents necessary to accomplish each of the following syntheses. Be sure to control the relative stereochemistry where appropriate.

a.



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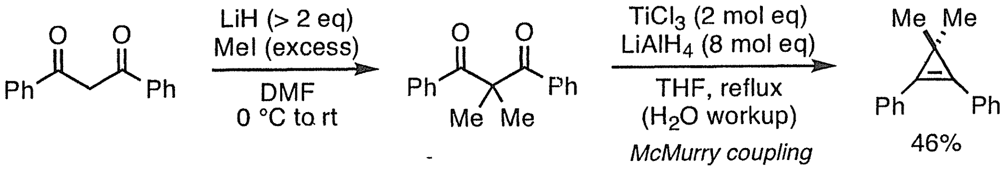
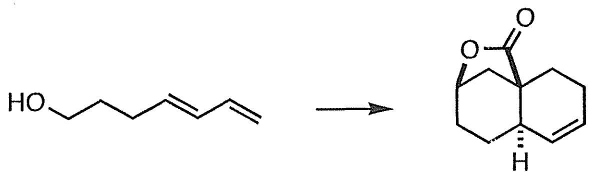


Reference: Baumstark, A. L.; McCloskey, C. J.; Witt, K. E. *J. Org. Chem.* **1978**, *43*, 3609.

b.



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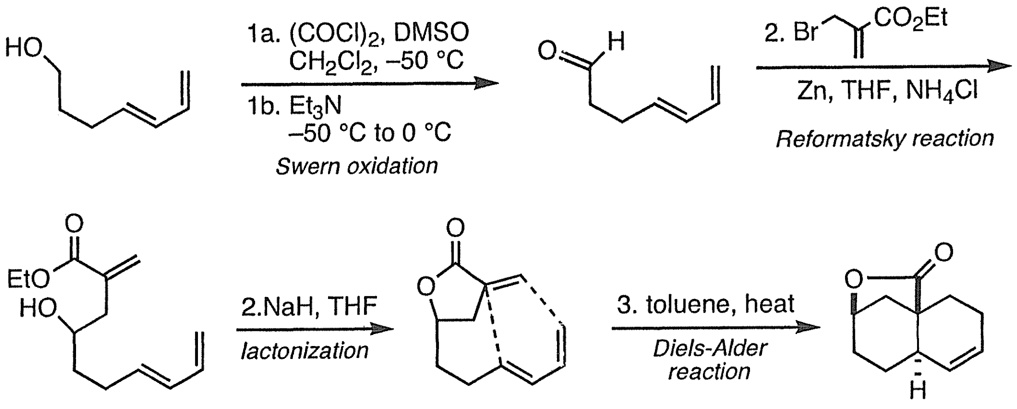
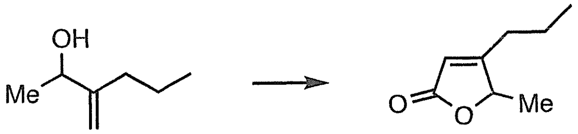


Reference: For the preparation of starting alcohol, see Spino, C.; Crawford, J.; Bishop, J. *J. Org. Chem.* **1995**, *60*, 844.

c.



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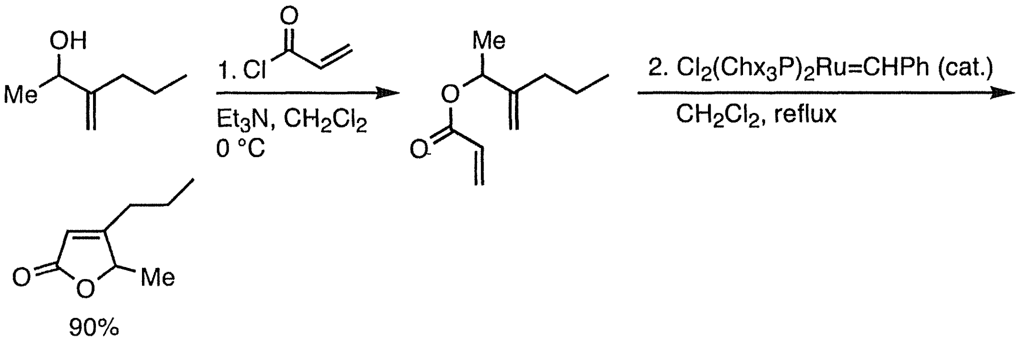
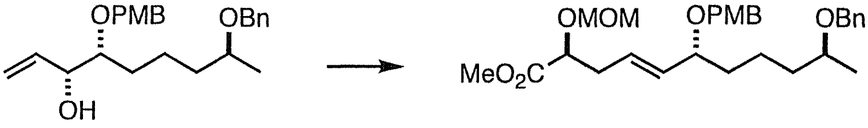


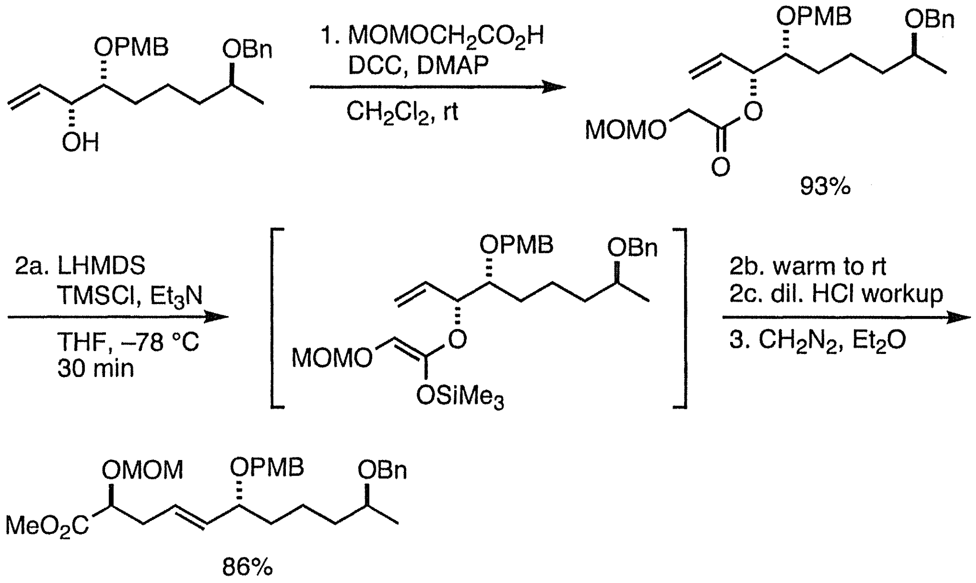
Step 2 Grubbs's first generation ring closing metathesis (RCM) catalyst was employed.

Reference: Bassetti, M.; D'Annibale, A.; Fanfoni, A.; Minissi, F. *Org. Lett.* **2005**, *7*, 1805.

d.



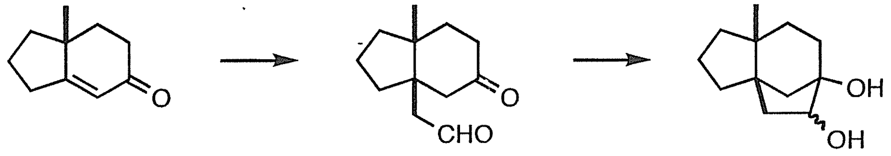
Solution:



Step 2a–c Ireland Claisen rearrangement.

Reference: Kim, D.; Lee, J.; Shim, P. J.; Lim, J. I.; Jo, H.; Kim, S. *J. Org. Chem.* **2002**, *67*, 764.

e.



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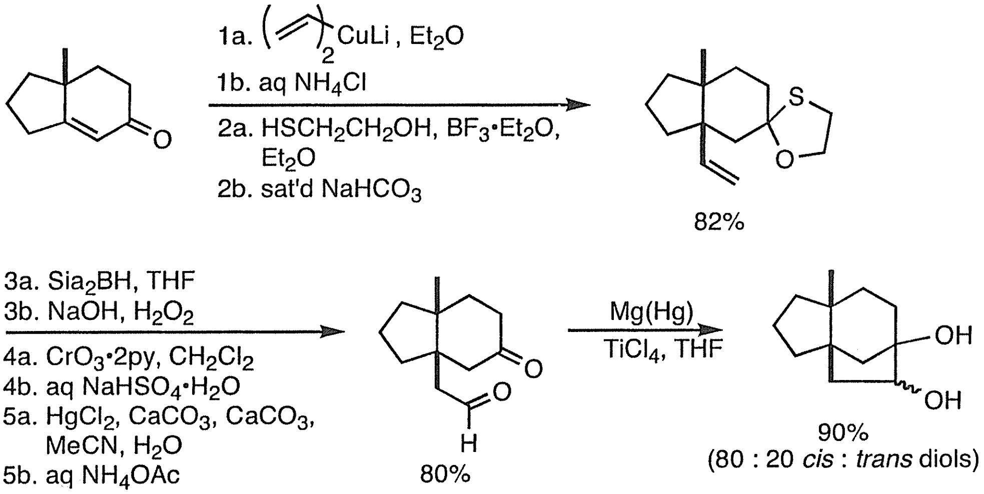
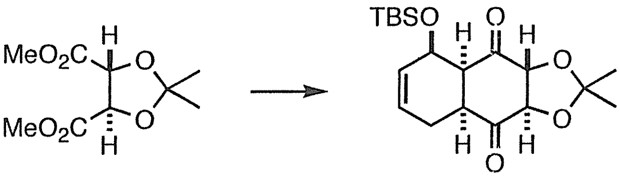
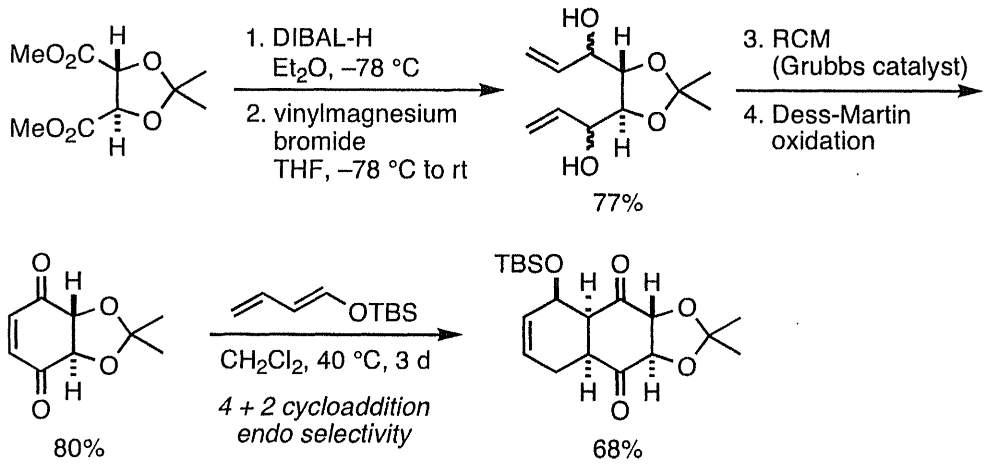


Reference: Corey, E. J.; Danheiser, R. L.; Chandrasekaran, S. *J. Org. Chem.* **1976**, *41*, 260.

f.



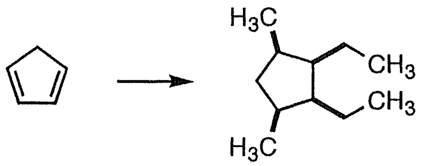
Solution:



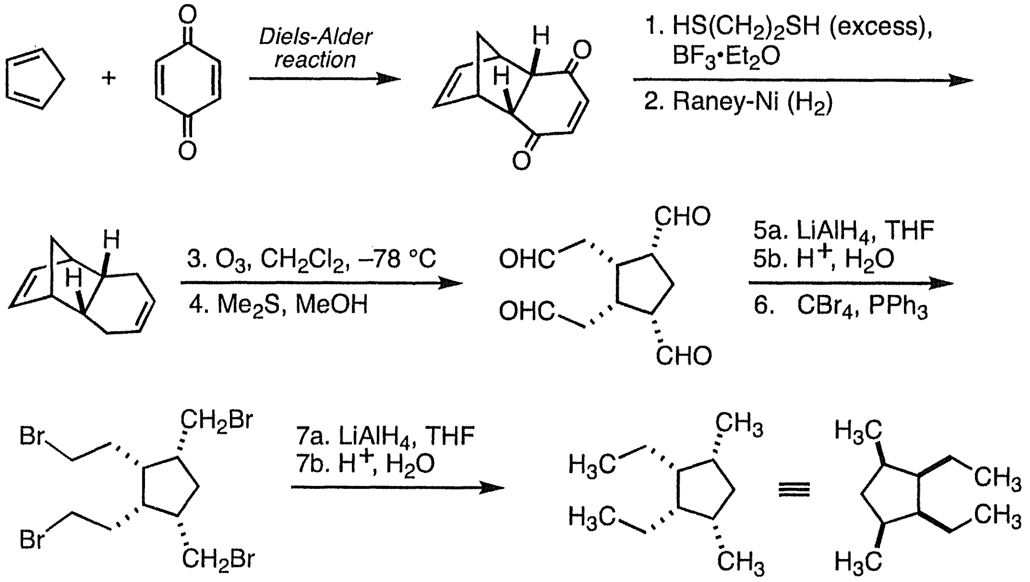
Steps 1–2 See *Tetrahedron* **2000**, *56*, 2195.
Step 4 Swern oxidation resulted in aromatization of the 1,4-quinone.

Reference: Lee, W.-D.; Kim, K.; Sulikowski, G. A. *Org. Lett.* **2005**, *7*, 1687.

g.

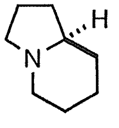


Solution:



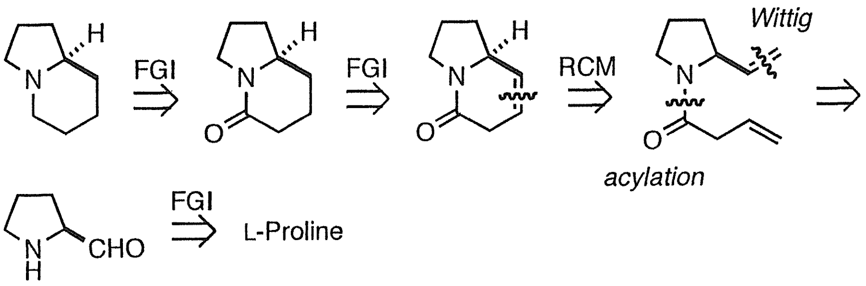
6. Retrosynthetic Analysis.

a. Propose a synthesis of (–)-coniceine using a ring-closing metathesis (RCM) procedure as a key step. Show (1) your retrosynthetic analysis and (2) all reagents and reaction conditions required to transform a commercially available starting material to the target molecule.

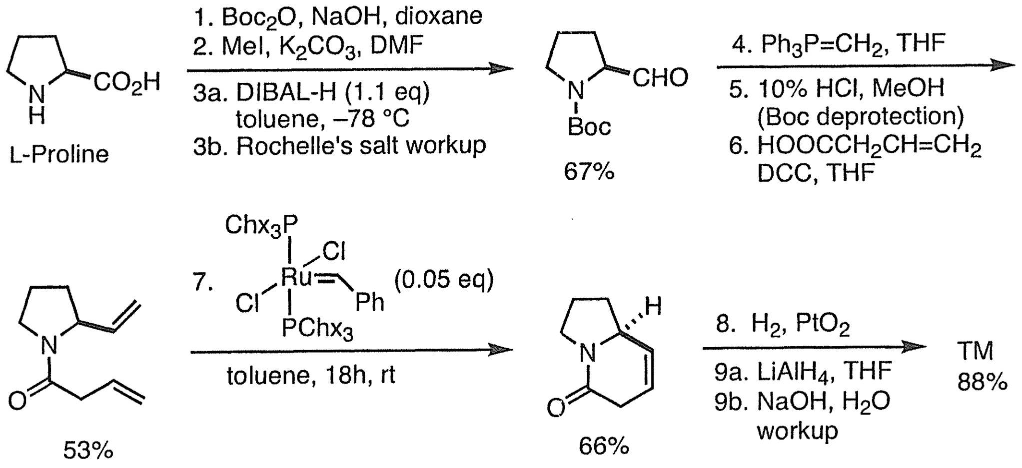


(–)-coniceine

Retrosynthetic analysis:

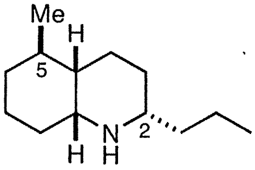


Synthesis:



Reference: Arisawa, M.; Takezawa, E.; Nishida, A.; Mori, M.; Nakagawa, M. *Synlett* **1997**, 1179.

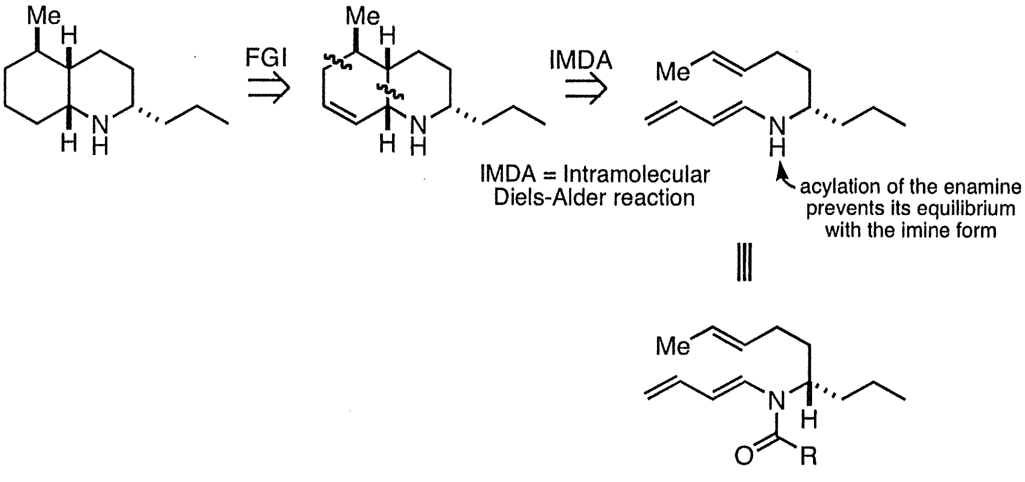
b. Propose syntheses of pumiliotoxin C using (1) an intramolecular Diels-Alder cycloaddition as a key step and (2) via a conjugate addition of a side chain, either the C(5)-methyl or C(2)-*n*-propyl group.



pumiliotoxin C

(1) Intramolecular Diels-Alder cycloaddition approach

Retrosynthetic analysis:

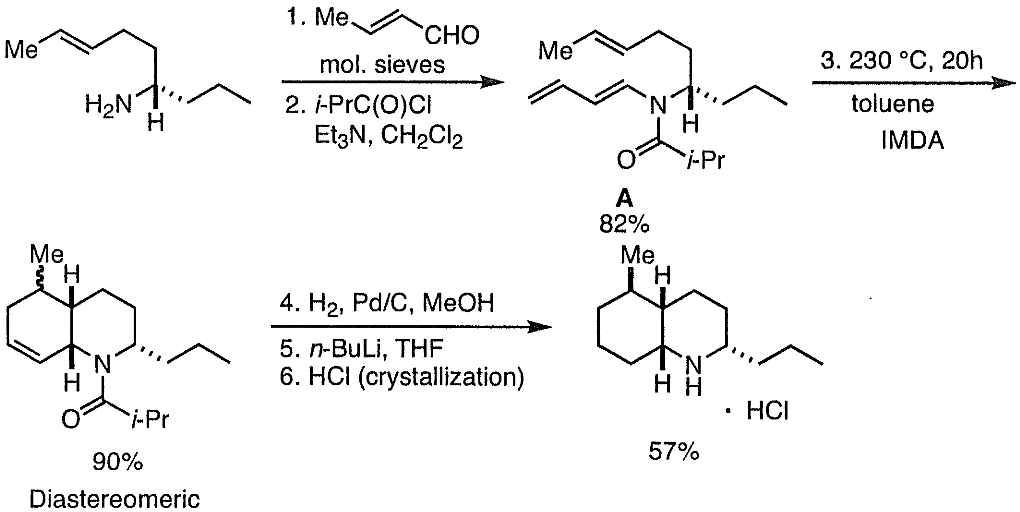


IMDA = Intramolecular Diels-Alder reaction

acylation of the enamine prevents its equilibrium with the imine form

A

Synthesis:



A
82%

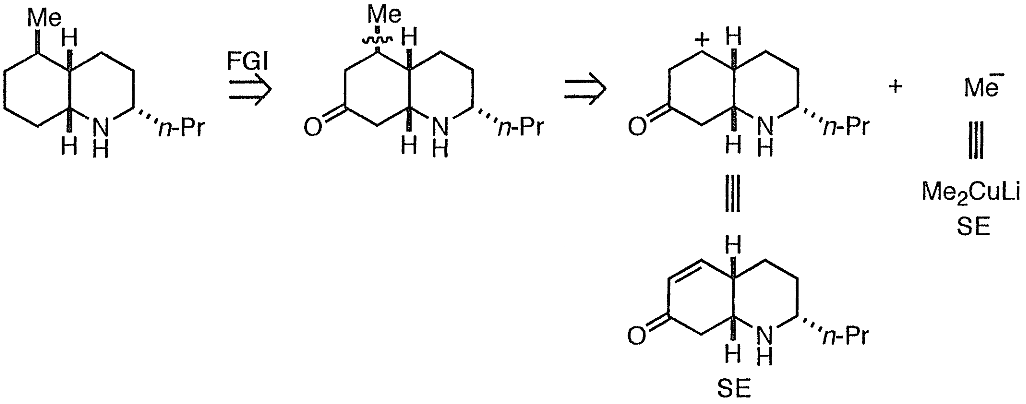
90%
Diastereomeric mixture

57%

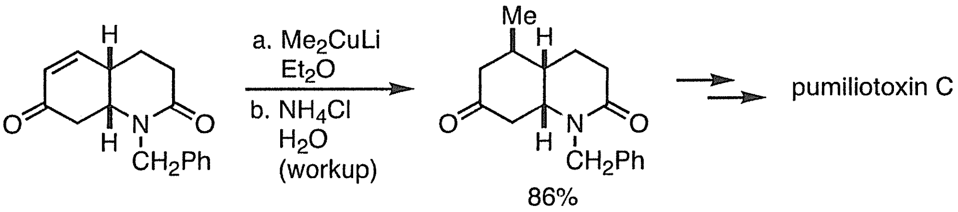
Reference: Oppolzer, W.; Flaskamp, E.; Bieber, L. W. *Helv. Chim. Acta* **2001**, *84*, 141.

(2) Conjugate addition of the C(5)-methyl group

Retrosynthetic analysis:



Synthesis:

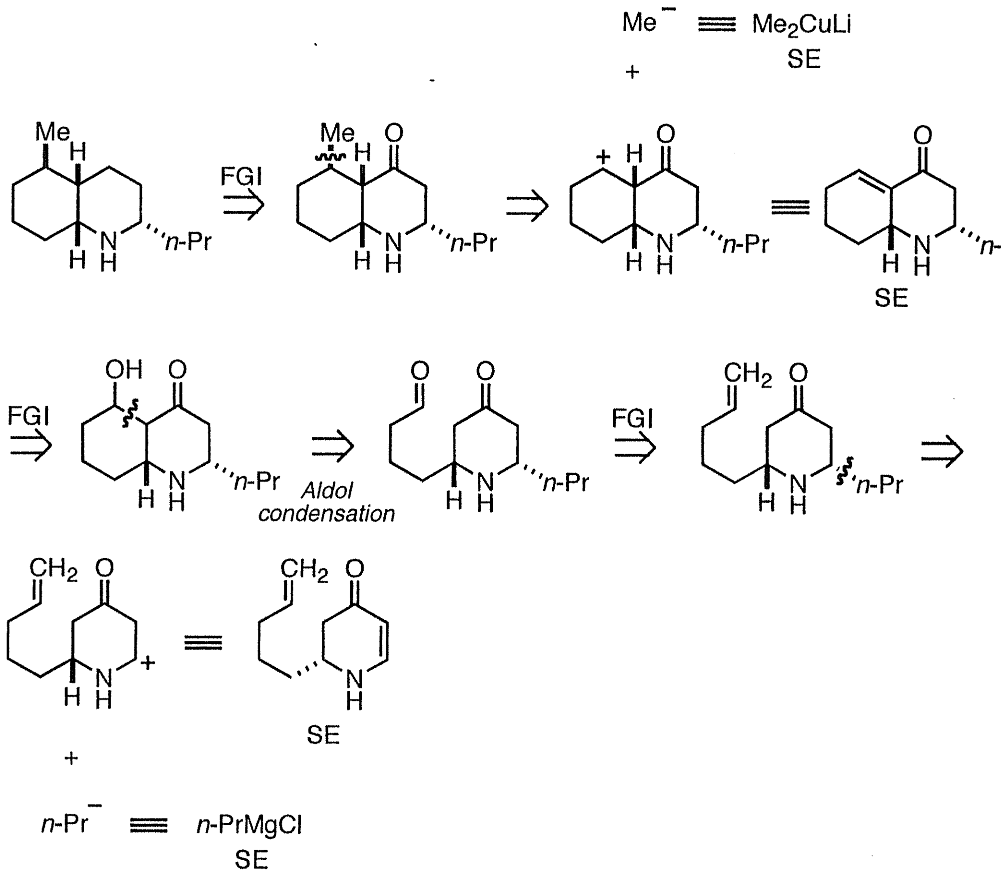


Stereoselective methyl addition occurs from the 'convex' face (the 3°-amide is inert to the cuprate reagent).

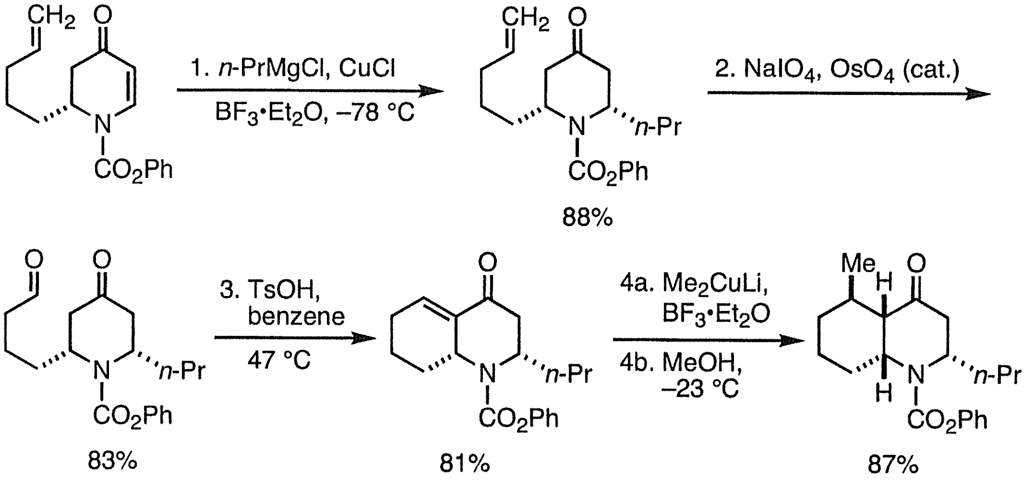
Reference: Ibuka, T.; Inubushi, Y.; Saji, I.; Tanaka, K.; Masaki, N. *Tetrahedron Lett.* **1975**, 323.

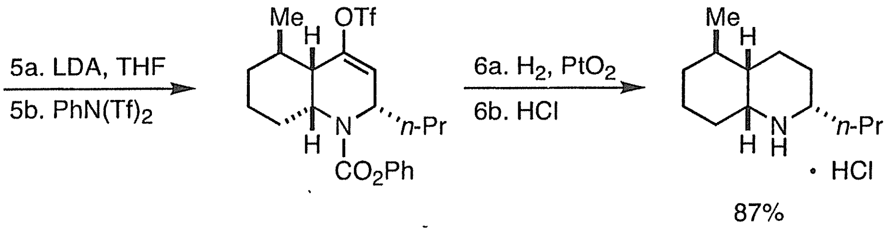
(2) Conjugate addition of the C(2)-*n*-propyl group

Retrosynthetic analysis:



Synthesis:





Step 2 Lemieux-Johnson reaction.
Step 6a Catalytic hydrogenation reduces the vinyl triflate moiety and cleaves the Cbz protecting group.

Reference: Comins, D. L.; Dehghani, A. *J. Chem. Soc., Chem. Commun.* **1993**, 1838.