Problems to accompany

Organic Chemistry, 2nd edition

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Uncorrected draft of 31 Dec 2012

Note:
5 Problems to add to Ch 12
9 Problems to add to Ch 24
3 Spectra to add to Ch 13

Chapter	No. of problems		
2	10	23	8
3	10	24	1
4	8	25	13
5	9	26	12
6	10	27	12
7	9	28	10
8	11	29	10
9	8	30	10
10	12	31	14
11	11	32	12
12	5	33	12
13	10	34	12
14	12	35	13
15	11	36	20
16	8	37	12
17	10	38	13
18	14	39	14
19	8	40	10
20	8	41	12
21	10	42	14
22	12	**Total**	**440**

Problems for Chapter 2

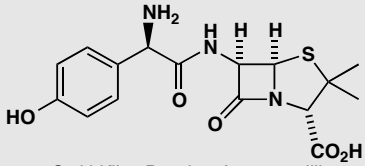
2

PROBLEM 1

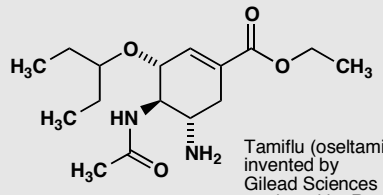
Draw good diagrams of saturated hydrocarbons with seven carbon atoms having (a) linear, (b) branched, and (c) cyclic structures. Draw molecules based on each framework having both ketone and carboxylic acid functional groups in the same molecule.

PROBLEM 2

Draw for yourself the structures of amoxicillin and Tamiflu on page 10 of the textbook. Identify on your diagrams the functional groups present in each molecule and the ring sizes. Study the carbon framework: is there a single carbon chain or more than one? Are they linear, branched, or cyclic?



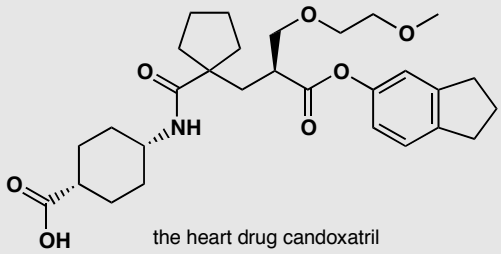
SmithKline Beecham's amoxycillin
β-lactam antibiotic
for treatment of bacterial infections



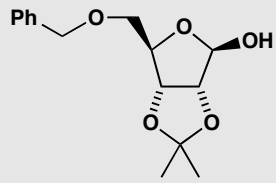
Tamiflu (oseltamivir)
invented by
Gilead Sciences
marketed by Roche

PROBLEM 3

Identify the functional groups in these two molecules



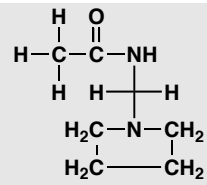
the heart drug candoxatril

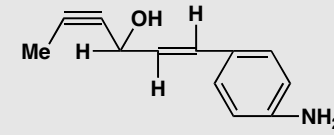


a derivative
of the sugar ribose

PROBLEM 4

What is wrong with these structures? Suggest better ways to represent these molecules





PROBLEM 5

Draw structures for the compounds named systematically here. In each case suggest alternative names that might convey the structure more clearly if you were speaking to someone rather than writing.

(a) 1,4-di-(1,1-dimethylethyl)benzene

(b) 1-(prop-2-enyloxy)prop-2-ene

(c) cyclohexa-1,3,5-triene

PROBLEM 6

Translate these very poor structural descriptions into something more realistic. Try to get the angles about right and, whatever you do, don't include any square planar carbon atoms or any other bond angles of 90°.

(a) $C_6H_5CH(OH)(CH_2)_4COC_2H_5$

(b) $O(CH_2CH_2)_2O$

(c) $(CH_3O)_2CH{=}CHCH(OCH_3)_2$

PROBLEM 7

Identify the oxidation level of all the carbon atoms of the compounds in problem 6.

PROBLEM 8

Draw full structures for these compounds, displaying the hydrocarbon framework clearly and showing all the bonds in the functional groups. Name the functional groups.

(a) $AcO(CH_2)_3NO_2$

(b) MeO_2CCH_2OCOEt

(c) $CH_2{=}CHCONH(CH_2)_2CN$

PROBLEM 9

Draw structures for the folllowing molecules, and then show them again using at least one 'organic element' symbol in each.

(a) ethyl acetate

(b) chloromethyl methyl ether

(c) pentanenitrile

(d) *N*-acetyl *p*-aminophenol

(e) 2,4,6,-tri-(1,1-dimethylethyl)phenylamine

PROBLEM 10

Suggest at least six different structures that would fit the formula C_4H_7NO. Make good realistic diagrams of each one and say which functional groups are present.

Problems for Chapter 3

3

PROBLEM 1

Assuming that the molecular ion is the base peak (100% abundance) what peaks would appear in the mass spectrum of each of these molecules:

(a) C_2H_5BrO

(b) C_{60}

(c) C_6H_4BrCl

In cases (a) and (c) suggest a possible structure of the molecule. What is (b)?

PROBLEM 2

Ethyl benzoate $PhCO_2Et$ has these peaks in its ^{13}C NMR spectrum: 17.3, 61.1, 100-150 (four peaks) and 166.8 ppm. Which peak belongs to which carbon atom? You are advised to make a good drawing of the molecule before you answer.

PROBLEM 3

Methoxatin was mentioned on page 44 of the textbook where we said 'it proved exceptionally difficult to solve the structure by NMR.' Why is it so difficult? Could anything be gained from the ^{13}C or ^{1}H NMR? What information could be gained from the mass spectrum and the infra red?

PROBLEM 4

The solvent formerly used in some correcting fluids is a single compound $C_2H_3Cl_3$, having ^{13}C NMR peaks at 45.1 and 95.0 ppm. What is its structure? How would you confirm it spectroscopically? A commercial paint thinner gives two spots on chromatography and has ^{13}C NMR peaks at 7.0, 27.5, 35.2, 45.3, 95.6, and 206.3 ppm. Suggest what compounds might be used in this thinner.

PROBLEM 5

The 'normal' O–H stretch in the infrared (i.e. without hydrogen bonding) comes at about 3600 cm^{-1}. What is the reduced mass (μ) for O–H? What happens to

the reduced mass when you double the mass of each atom in turn, i.e. what is μ for O–D and what is μ for S–H? In fact, both O–D and S–H stretches come at about 2,500 cm^{-1}. Why?

PROBLEM 6

Three compounds, each having the formula C_3H_5NO, have the IR data summarized here. What are their structures? Without ^{13}C NMR data it might be easier to draw some or all possible structures before trying to decide which is which. In what ways would ^{13}C NMR data help?

(a) One sharp band above 3000 cm^{-1} and one strong band at about 1700 cm^{-1}

(b) Two sharp bands above 3000 cm^{-1} and two bands between 1600 and 1700 cm^{-1}

(c) One strong broad band above 3000 cm^{-1} and a band at about 2200 cm^{-1}

PROBLEM 7

Four compounds having the formula $C_4H_6O_2$ have the IR and NMR data given below. How many DBEs (double bond equivalents—see p. 75 in the textbook) are there in $C_4H_6O_2$? What are the structures of the four compounds? You might again find it useful to draw a few structures to start with.

(a) IR: 1745 cm^{-1}; ^{13}C NMR 214, 82, 58, and 41 ppm

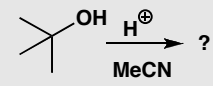
(b) IR: 3300 cm^{-1} (broad); ^{13}C NMR 62 and 79 ppm.

(c) IR: 1770 cm^{-1}; ^{13}C NMR 178, 86, 40, and 27 ppm.

(d) IR: 1720 and 1650 cm^{-1} (strong); ^{13}C NMR 165, 133, 131, and 54 ppm.

PROBLEM 8

You have dissolved *tert*-butanol in MeCN with an acid catalyst, left the solution overnight, and found crystals in the morning with the following characteristics. What are the crystals?

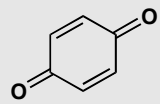


IR: 3435 and 1686 cm^{-1}; ^{13}C NMR: 169, 50, 29, and 25 ppm; ^{1}H NMR: 8.0, 1.8, and 1.4 ppm; Mass spectrum (%): 115 (7), 100 (10), 64 (5), 60 (21), 59 (17), 58 (100), and 56 (7). Don't try to assign all the peaks in the mass spectrum.

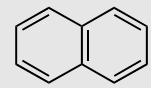
PROBLEM 9

How many signals would you expect in the ^{13}C NMR spectrum of these compounds?

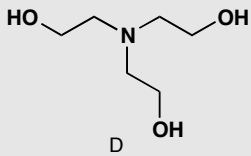
A



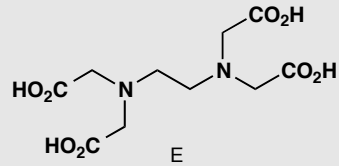
B



C



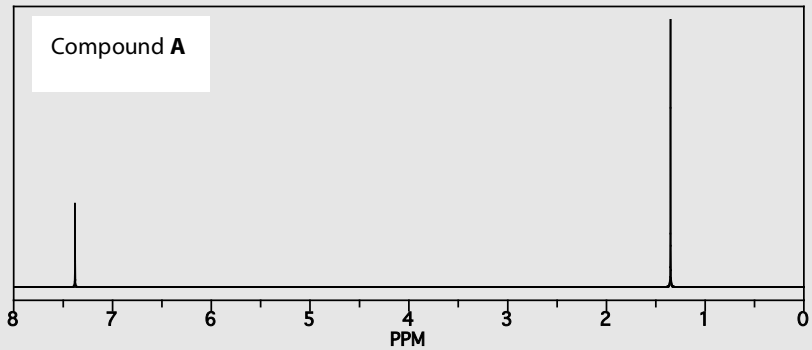
D



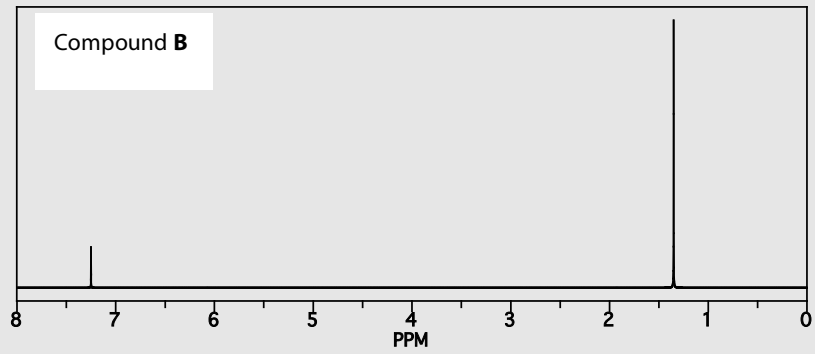
E

PROBLEM 10

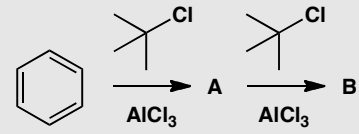
When benzene is treated with *tert*-butyl chloride and aluminium trichloride, a crystalline product **A** is formed that contains only C and H. Mass spectrometry tells us the molecular mass is 190. The ^{1}H NMR spectrum looks like this:



If crystals of **A** is treated again with more *tert*-butyl chloride and aluminium chloride, a new oily compound **B** may be isolated, this time with a molecular mass of 246. Its ^{1}H NMR spectrum is similar to that of **A**, but not quite the same:



What are the two compounds? How many signals do you expect in the ^{13}C NMR spectrum of each compound?



Problems for Chapter 4

4

PROBLEM 1

Textbooks sometimes describe the structure of sodium chloride like this 'an electron is transferred from the valence shell of a sodium atom to the valence shell of a chlorine atom.' Why would this not be a sensible way to make sodium chloride?

PROBLEM 2

The H–C–H bond angle in methane is 109.5°. The H–O–H bond angle of water is close to this number but the H–S–H bond angle of H_2S is near 90°. What does this tell us about the bonding in water and H_2S? Draw an diagram of the molecular orbitals in H_2S.

PROBLEM 3

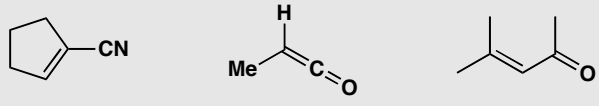
Though the helium molecule He_2 does not exist (p. 91 of the textbook explains why), the cation He_2^+ does exist. Why?

PROBLEM 4

Construct an MO diagram for LiH and suggest what type of bond it might have.

PROBLEM 5

What is the hybridization and shape of each carbon atom in these molecules?



PROBLEM 6

Draw detailed structures for these molecules and predict their shapes. We

have deliberately made non-committal drawings to avoid giving away the answer to the question. Don't use these sorts of drawings in your answer.

CO_2, $CH_2{=}NCH_3$, CHF_3, $CH_2{=}C{=}CH_2$, $(CH_2)_2O$

PROBLEM 7

Draw the shapes, showing estimated bond angles, of the following molecules:

(a) hydrogen peroxide, H_2O_2

(b) methyl isocyanate CH_3NCO

(c) hydrazine, NH_2NH_2

(d) diimide, N_2H_2

(e) the azide anion, N_3^-

PROBLEM 8

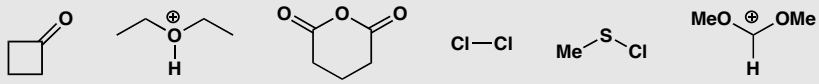
Where would you expect to find the lone pairs in (a) water, (b) acetone ($Me_2C{=}O$), and (c) nitrogen (N_2)?

Problems for Chapter 5

5

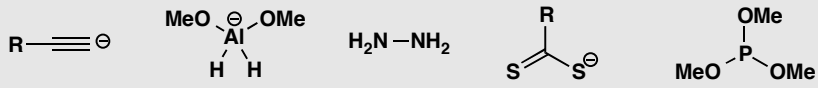
PROBLEM 1

Each of these molecules is electrophilic. Identify the electrophilic atom and draw a mechanism for a reaction with a generalised nucleophile Nu^-, giving the structure of the product in each case.



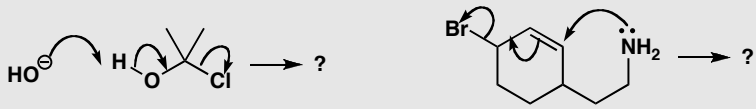
PROBLEM 2

Each of these molecules is nucleophilic. Identify the nucleophilic atom and draw a mechanism for a reaction with a generalised nucleophile E^+, giving the structure of the product in each case.



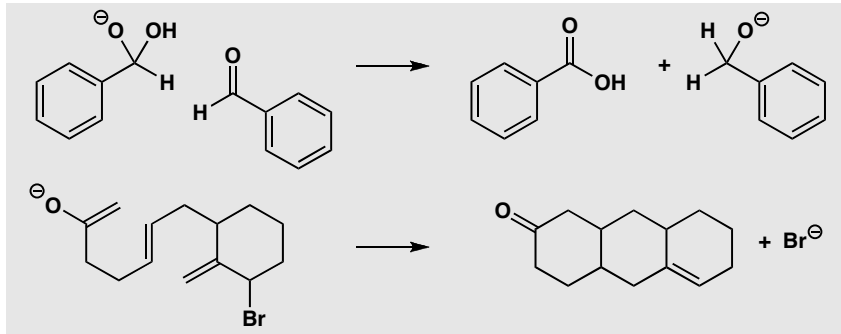
PROBLEM 3

Complete these mechanisms by drawing the structure of the product(s).



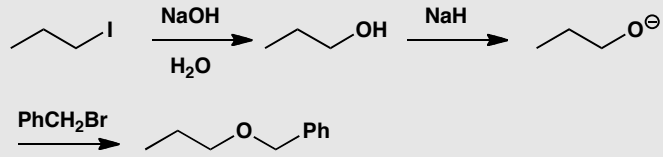
PROBLEM 4

Put in the curly arrows on these starting materials to show how the product is formed. The compounds are drawn in a convenient arrangement to help you.



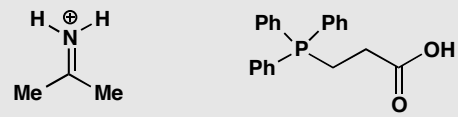
PROBLEM 5

Draw mechanisms for the reactions in the following sequence.



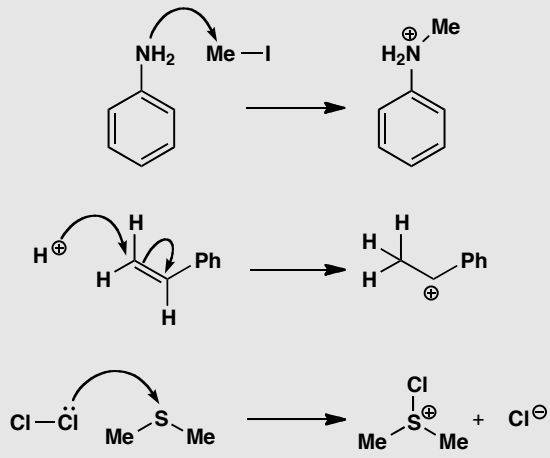
PROBLEM 6

Each of these electrophiles could react with a nucleophile at one of (at least) two atoms. Identify these atoms and draw a mechanism and products for each reaction.



PROBLEM 7

These three reactions all give the products shown, but not by the mechanisms drawn! For each mechanism, explain what is wrong, and draw a better one.



PROBLEM 8

In your corrected mechanisms for problem 8, explain in each casewhich orbital is the HOMO of the nucleophile and which orbital is the LUMO of the electrophile.

PROBLEM 9

Draw a mechanism for the following reaction. (This is harder, but if you draw out the structures of the reactants first, and consider that one is an acid and one is a base, you will make a good start.)

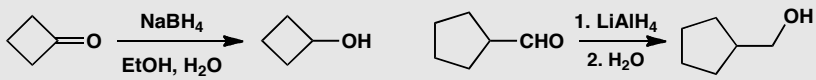
$$PhCHBrCHBrCO_2H + NaHCO_3 \longrightarrow PhCH{=}CHBr + NaHCO_3$$

Problems for Chapter 6

6

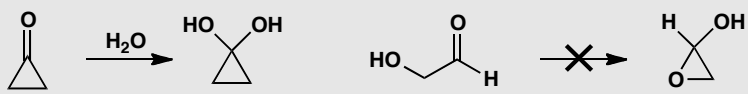
PROBLEM 1

Draw mechanisms for these reactions:



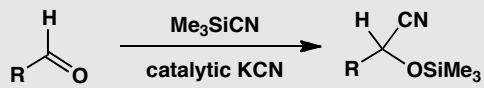
PROBLEM 2

Cyclopropanone exists as the hydrate in water but 2-hydroxyethanal does not exist as the hemiacetal. Explain.



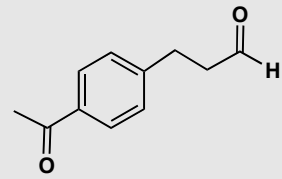
PROBLEM 3

One way to make cyanohydrins is illustrated here. Suggest a detailed mechanism for the process.



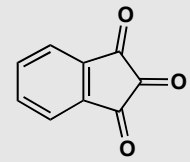
PROBLEM 4

There are three possible products from the reduction of this compound with sodium borohydride. What are their structures? How would you distinguish them spectroscopically, assuming you can isolate pure compounds?



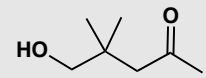
PROBLEM 5

The triketone shown here is called 'ninhydrin' and is used for the detection of amino acids. It exists in aqueous solution as a hydrate. Which ketone is hydrated and why?



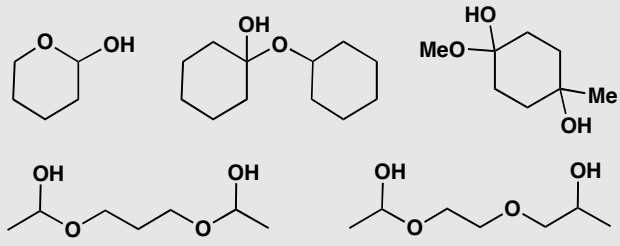
PROBLEM 6

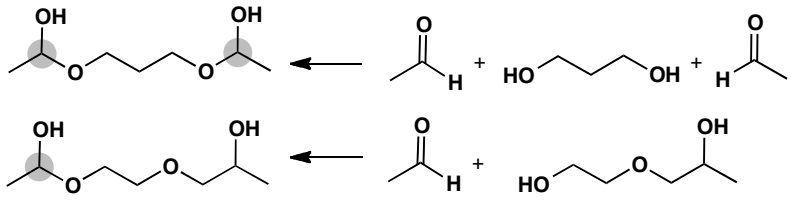
This hydroxyketone shows no peaks in its infrared spectrum between 1600 and 1800 cm^{-1}, but it does show a broad absorption at 3000–3400 cm^{-1}. In the ^{13}C NMR spectrum there are no peaks above 150 ppm but there is a peak at 110 ppm. Suggest an explanation.



PROBLEM 7

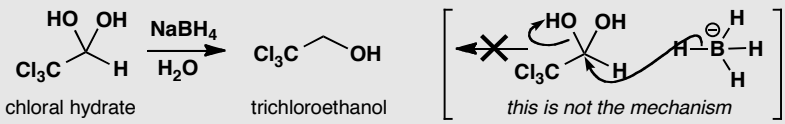
Each of these compounds is a hemiacetal and therefore formed from an alcohol and a carbonyl compound. In each case give the structures of the original materials.





PROBLEM 8

Trichloroethanol my be prepared by the direct reduction of chloral hydrate in water with sodium borohydride. Suggest a mechanism for this reaction. Take note that sodium borohydride does not displace hydroxide from carbon atoms!



PROBLEM 9

It has not been possible to prepare the adducts from simple aldehydes and HCl. What would be the structure of such compounds, if they could be made, and what would be the mechanism of their formation? Why can't these compounds be made?

PROBLEM 10

What would be the products of these reactions? In each case give a mechanism to justify your prediction.

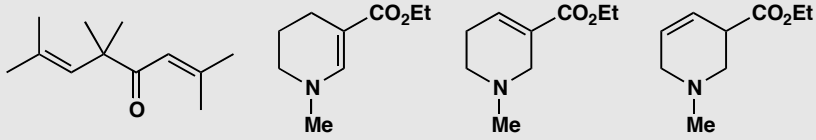

O
EtMgBr
Et2O
?
O
O
O
NaBH4
?

Problems for Chapter 7

7

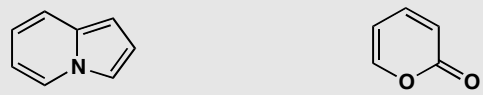
PROBLEM 1

Are these molecules conjugated? Explain your answer in any reasonable way.



PROBLEM 2

How extensive is the conjugated system(s) in these compounds?

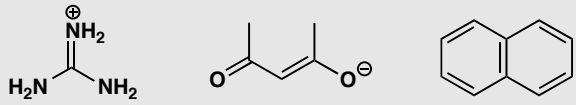


PROBLEM 3

Draw diagrams to represent the conjugation in these molecules. Draw two types of diagram:

(a) Show curly arrows linking at least two different wats of representing the molecule

(b) Indicate with dotted lines and partial charges (where necessary) the partial double bond (and charge) distribution.



PROBLEM 4

Draw curly arrows linking alternative structures to show the delocalisation in

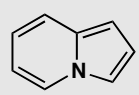
(a) diazomethane CH_2N_2

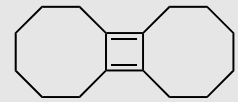
(b) nitrous oxide, N_2O

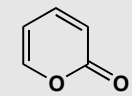
(c) dinitrogen tetroxide, N_2O_4

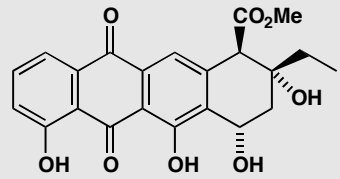
PROBLEM 5

Which (parts) of these compounds are aromatic? Justify your answer with some electron counting. You may treat rings separately or together as you wish. You may notice that two of them are compounds we met in problem 2 of this chapter.

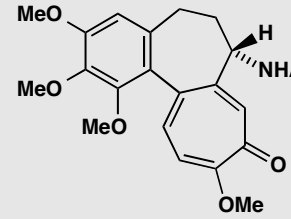




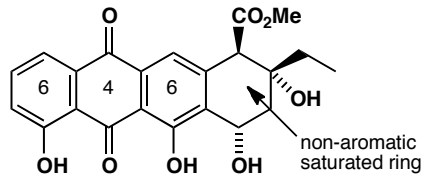




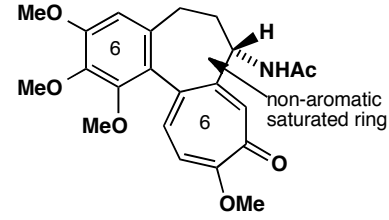
aklavinone: a tetracycline antibiotic



colchicine: a compound from the Autumn crocus used to treat gout



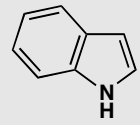
non-aromatic saturated ring



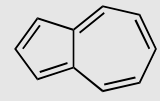
non-aromatic saturated ring

PROBLEM 6

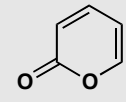
The following compounds are considered to be aromatic. Account for this by identifying the appropriate number of delocalised electrons.



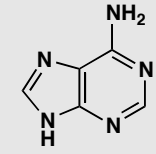
indole



azulene



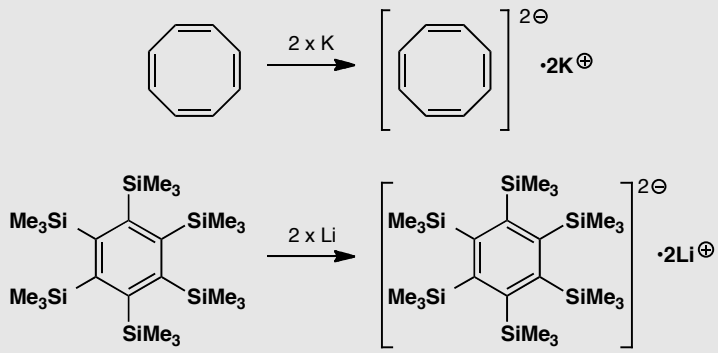
α-pyrone



adenine

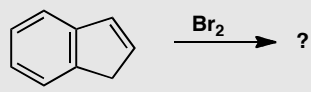
PROBLEM 7

Cyclooctatetraene (see p. 158 of the textbook) reacts readily with potassium metal to form a salt, K_2[cyclooctatetraene]. What shape do you expect the ring to have in this compound? A similar reaction of hexa(trimethylsilyl)benzene with lithium also gives a salt. What shape do you expect this ring to have?



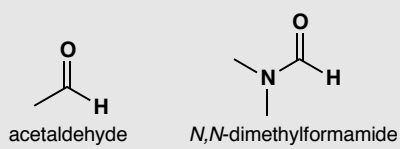
PROBLEM 8

How would you expect the hydrocarbon below to react with bromine, Br_2?



PROBLEM 9

In aqueous solution, acetaldehyde (ethanal) is about 50% hydrated. Draw the structure of the hydrate of acetaldehyde. Under the same conditions, the hydrate of *N,N*-dimethylformamide is undetectable. Why the difference?

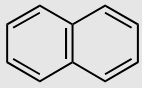


Problems for Chapter 8

8

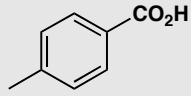
PROBLEM 1

How would you separate a mixture of these three compounds?



naphthalene

pyridine



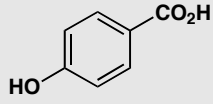
para-toluic acid

PROBLEM 2

In the separation of benzoic acid from toluene on p. 164 of the textbook we suggested using KOH solution. How concentrated a solution would be necessary to ensure that the pH was above the pK_a of benzoic acid (4.2)? How would you estimate how much KOH solution to use?

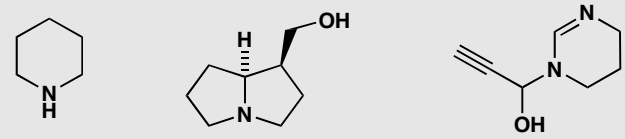
PROBLEM 3

What species would be present in a solution of this hydroxy-acid in (a) water at pH 7, (b) aqueous alkali at pH 12, and (c) in concentrated mineral acid?



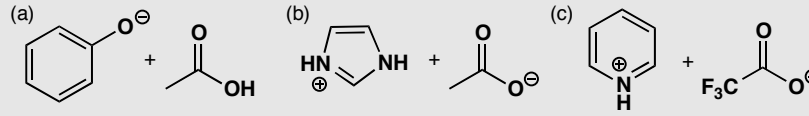
PROBLEM 4

What would you expect to be the site of (a) protonation and (b) deprotonation if these compounds were treated with the appropriate acid or base? In each case suggest a suitable acid or base and give the structure of the products.



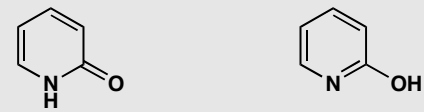
PROBLEM 5

Suggest what species would be formed by each of these combinations of reagents. You are advised to use estimated pK_a values to help you and to beware of those cases where nothing happens.



PROBLEM 6

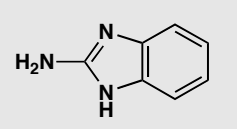
What is the relationship between these two molecules? Discuss the structure of the anion that would be formed by the deprotonation of each compound.

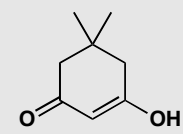


PROBLEM 7

The carbon NMR spectrum of these compounds can be run in D_2O under the conditions shown. Why are these conditions necessary? What spectrum would you expect to observe?

^{13}C NMR spectrum run in DCl/D_2O

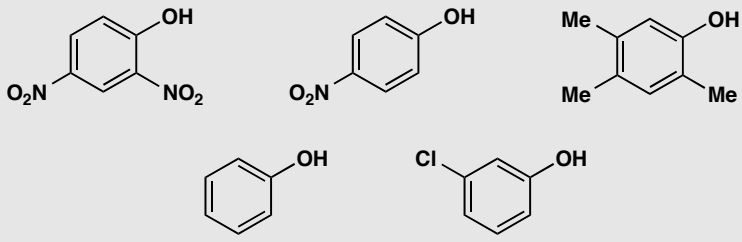




^{13}C NMR spectrum run in NaOD/D_2O

PROBLEM 8

These phenols have approximate pK_a values of 4, 7, 9, 10 and 11. Suggest with explanations which pK_a value belongs to which phenol.



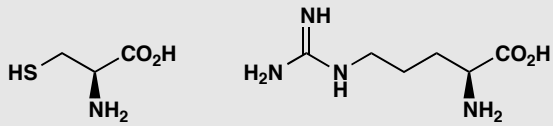
PROBLEM 9

The pK_a values of these two amino acids are as follows:

(a) cysteine: 1.8, 8.3, and 10.8

(b) arginine: 2.2, 9.0, and 13.2.

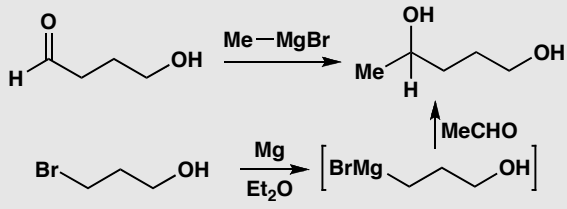
Assign these pK_a values to the functional groups in each amino acid and draw the most abundant structure that each molecule will have at pH 1, 7, 10, and 14.



cysteine arginine

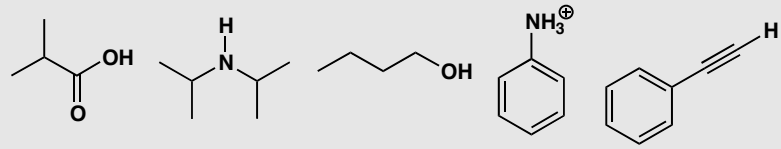
PROBLEM 10

Neither of these two methods for making pentan-1,4-diol will work. What will happen instead?



PROBLEM 11

Which of these bases would you choose to deprotonate the following molecules? Very strong bases are more challenging to handle so you should aim to use a base which is just strong enough for the job, but not unnecessarily so.



Choice of bases:

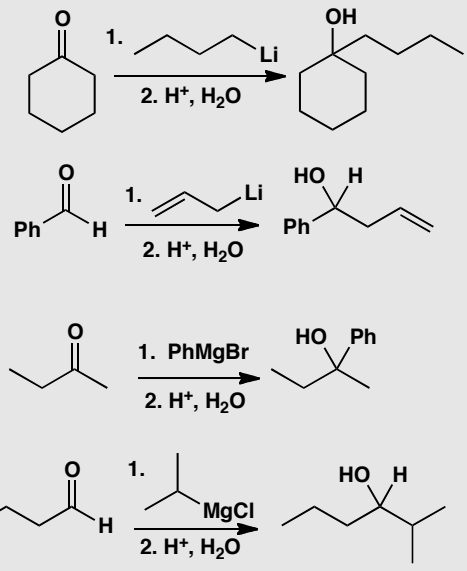
KOH NaH BuLi $NaHCO_3$

Problems for Chapter 9

9

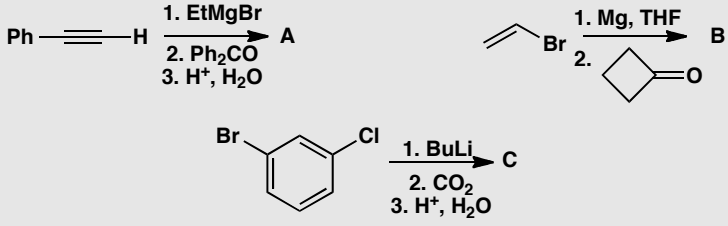
PROBLEM 1

Propose mechanisms for the first four reactions in the chapter.



PROBLEM 2

What products would be formed in these reactions?



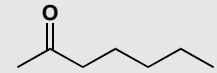
PROBLEM 3

Suggest alternative routes to fenarimol different from the one in the textbook

on p. 192. Remind yourself of the answer to problem 2 above.

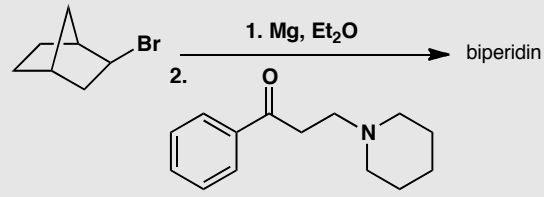
PROBLEM 4

Suggest two syntheses of the bee pheromone heptan-2-one.

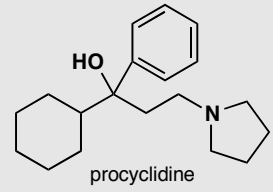


PROBLEM 5

The antispasmodic drug biperidin is made by the Grignard addition reaction shown here. What is the structure of the drug? Do not be put off by the apparent complexity of the structure: just use the chemistry of Chapter 9.

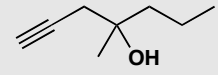


How would you suggest that the drug procyclidine should be made?



PROBLEM 6

The synthesis of the gastric antisecretory drug rioprostil requires this alcohol.

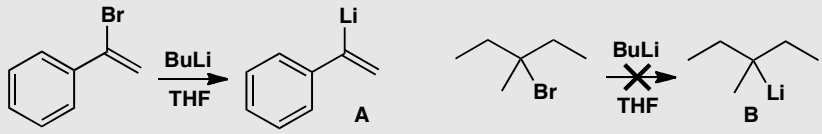


(a) Suggest possible syntheses starting from ketones and organometallics.
(b) Suggest possible syntheses of the ketones in part (a) from aldehydes and

organometallics (don't forget about CrO_3 oxidation).

PROBLEM 7

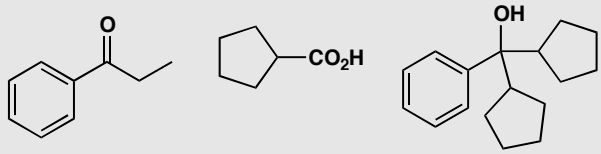
Why is it possible to make the lithium derivative A by Br/Li exchange, but not the lithium derivative B?



PROBLEM 8

How could you use these four commercially available starting materials

to make the following three compounds?

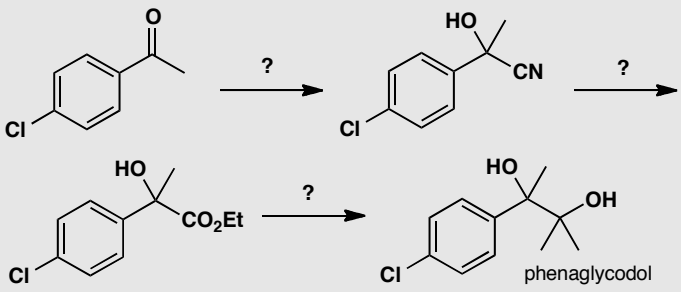


Problems for Chapter 10

10

PROBLEM 1

Suggest reagents to make the drug phenaglycodol by the route below.

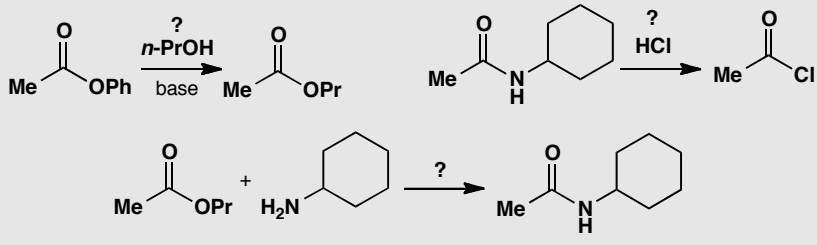


PROBLEM 2

Direct ester formation from carboxylic acids (R^1CO_2H) and alcohols (R^2OH) and works in acid solution but not in basic solution. Why not? By contrast, ester formation from alcohols (R^2OH) and acid anhydrides [$(R^1CO)_2O$)] or chlorides (R^1COCl) is commonly carried out in basic solution in the presence of bases such as pyridine. Why does this work?

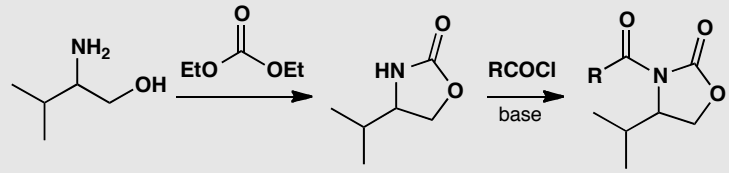
PROBLEM 3

Predict the success or failure of these attempted substitutions at the carbonyl group. You should use estimated pK_a values in your answer and, of course, draw mechanisms.



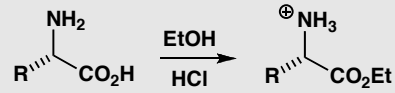
PROBLEM 4

Suggest mechanisms for these reactions.



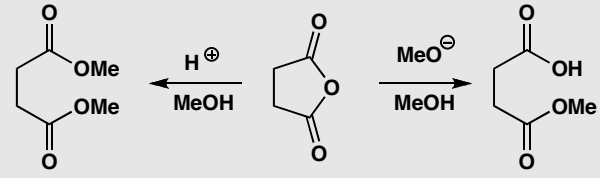
PROBLEM 5

In making esters of the naturally occurring amino acids (general structure below) it is important to keep them as their hydrochloride salts. What would happen to these compounds if they were neutralised?



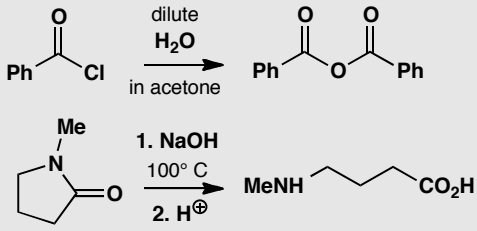
PROBLEM 6

It is possible to make either the diester or the monoester of butanedioic acid (succinic acid) from the cyclic anhydride as shown. Why does one method give the diester and one the monoester?



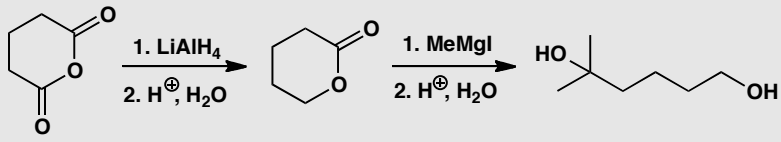
PROBLEM 7

Suggest mechanisms for these reactions, explaining why these particular products are formed.



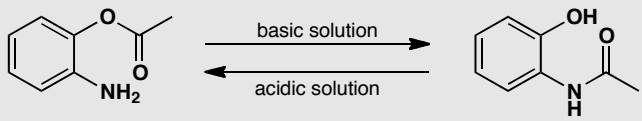
PROBLEM 8

Give mechanisms for these reactions, explaining the selectivity (or lack of it!) in each case.



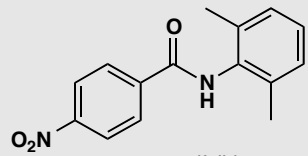
PROBLEM 9

This reaction goes in one direction in acid solution and in the other direction in basic solution. Draw mechanisms for the reactions and explain why the product depends on the conditions.

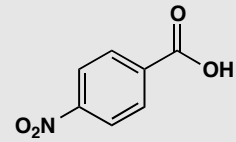


PROBLEM 10

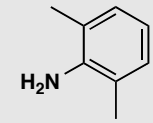
Amelfolide is a drug used to treat cardiac arrhythmia. Suggest how it could be made from 4-nitrobenzoic acid and 2,5-dimethylaniline.



amelfolide



4-nitrobenzoic acid

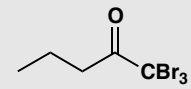


2,6-dimethylaniline

A reminder to avoid a common error in proposed reactions of carboxylic

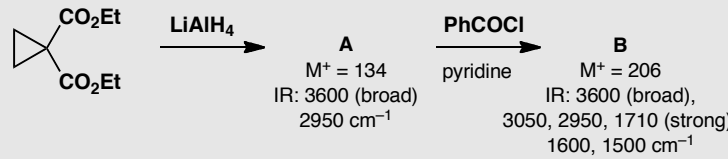
PROBLEM 11

Given that the pK_a of tribromomethane, $CHBr_3$ (also known as bromoform) is 13.7, suggest what will happen when this ketone is treated with sodium hydroxide.



PROBLEM 12

This sequence of reactions is used to make a precursor to the anti-asthma drug montelukast (Singulair). Suggest structures for compounds **A** and **B**.

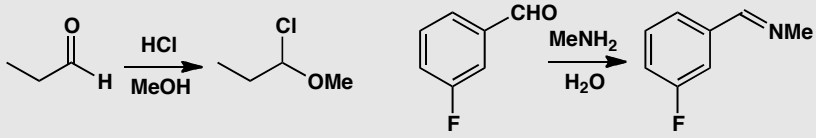


Problems for Chapter 11

11

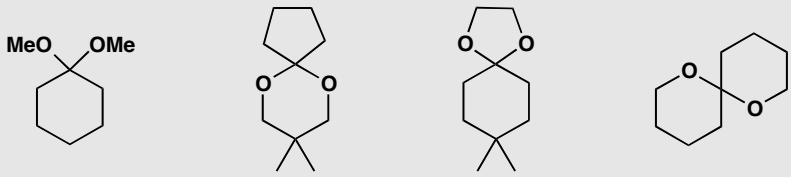
PROBLEM 1

Draw mechanisms for these reactions, both of which involve loss of carbonyl oxygen.



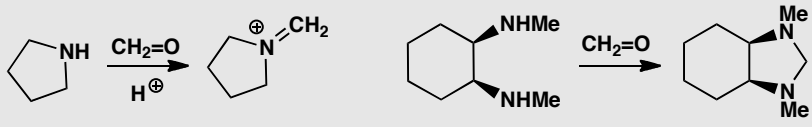
PROBLEM 2

Each of these compounds is an acetal, that is a molecule made from an aldehyde or ketone and two alcohol groups. Which compounds were used to make these acetals?



PROBLEM 3

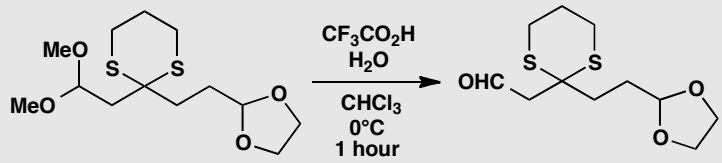
Suggest mechanisms for these two reactions of the smallest aldehyde, formaldehyde (methanal $CH_2=O$).



PROBLEM 4

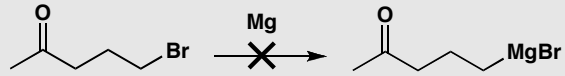
In the textbook (p. 104) we showed you a selective hydrolysis of an acetal. Why

were the other acetals (one is a thioacetal) not affected by this treatment? How would you hydrolyse them? Chloroform ($CHCl_3$) is the solvent.



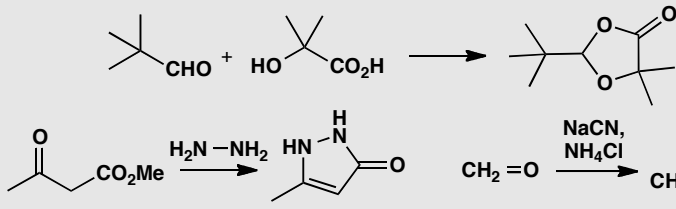
PROBLEM 5

In the textbook (p. 228) we say that the Grignard reagent below is 'an unstable structure – impossible to make.' Why is this? What would happen if you tried to make it?



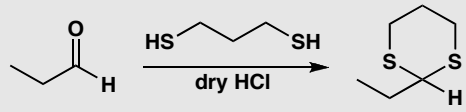
PROBLEM 6

Suggest mechanisms for these reactions.



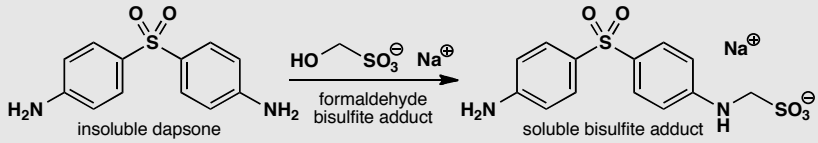
PROBLEM 7

Don't forget the problem in the summary on p.238 of the textbook: suggest a mechanism for the formation of this thioacetal.



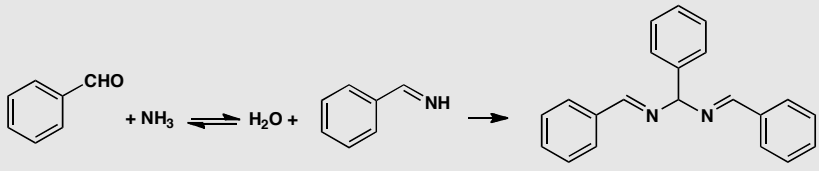
PROBLEM 8

In chapter 6 we described how the antileprosy drug dapsone could be made soluble by the formation of a 'bisulfite adduct'. Now that you know about the reactions described in chapter 11, you should be able to draw a mechanism for this reaction. The adduct is described as a 'prodrug', meaning that it is not the drug but gives rise to the drug by chemistry within the body. How might this happen?



PROBLEM 9

This stable product can be isolated from the reaction between benzaldehyde and ammonia. Suggest a mechanism.

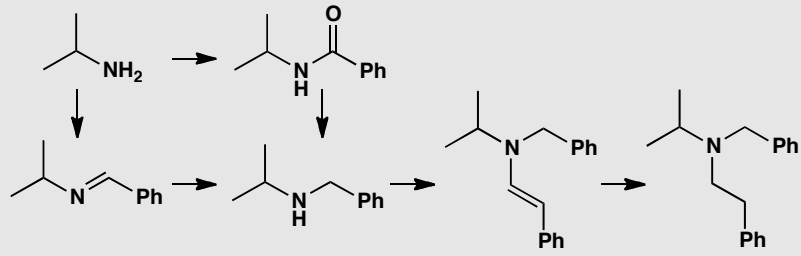


PROBLEM 10

In the following scheme

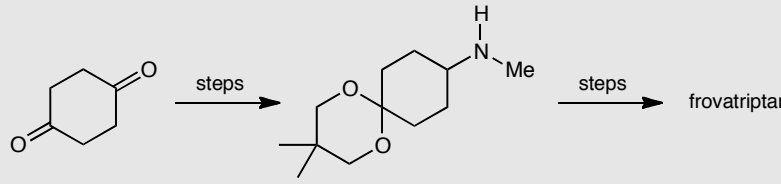
(a) Identify the functional group in each molecule

(b) Suggest a reagent or reagents for carrying out each transformation represented by an arrow.



PROBLEM 11

Three chemical steps convert cyclohexane-1,4-dione into a compound which is used for the synthesis of the anti-migraine drug frovatriptan. Suggest how this transformation is carried out.

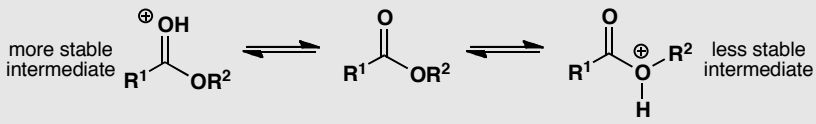


Problems for Chapter 12

12

PROBLEM 1

In the comparison of stability of the last intermediates in the substitution at the carbonyl group of acid chlorides or anhydrides to make esters (chapter 10) we preferred one of these intermediates to the other:



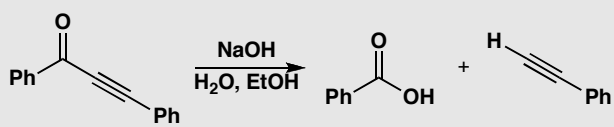
Why is the one more stable than the other? If you were to treat an ester with acid, which of the two would be formed?

PROBLEM 2

This reaction shows third-order kinetics as the rate expression is

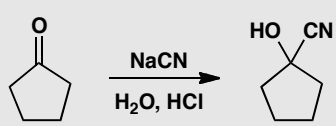
$$\text{rate} = [\text{ketone}][HO^-]^2$$

Suggest a mechanism for the reaction.



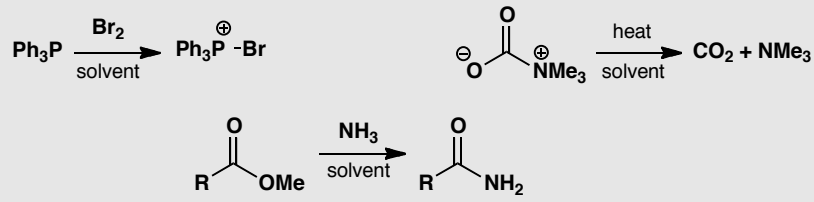
PROBLEM 3

Draw an energy profile diagram for this reaction. You will of course need to draw the mechanism first. Suggest which step in this mechanism is likely to be the slow step and what kinetics would be observed



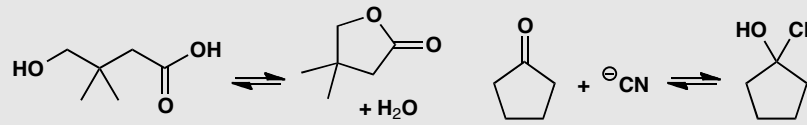
PROBLEM 4

What would be the effect of solvent changes on these reactions? Would the reactions be accelerated or retarded by a change from a polar to a non-polar solvent?



PROBLEM 5

Comment on the effect of acid and base on these equilibria.

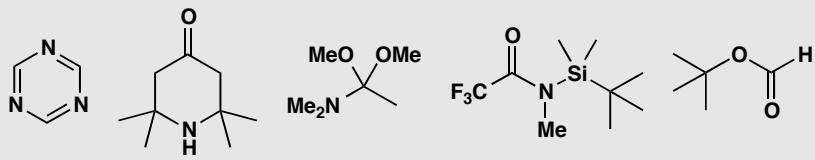


Problems for Chapter 13

13

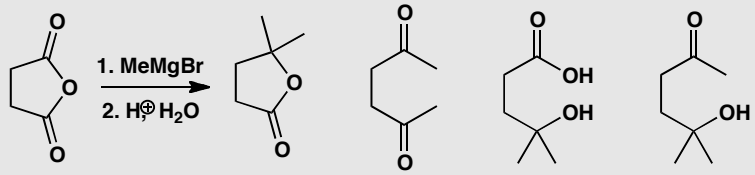
PROBLEM 1

How many signals will there be in the 1H NMR spectrum of each of these compounds? Estimate the chemical shifts of the signals.



PROBLEM 2

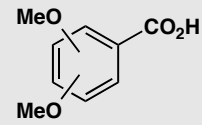
The following products might possibly be formed from the reaction of MeMgBr with the cyclic anhydride shown. How would you tell the difference between these compounds using IR and ^{13}C NMR? With ^{1}H NMR available as well, how would your task be easier?

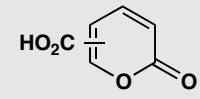


PROBLEM 3

One isomer of dimethoxybenzoic acid has the ^{1}H NMR spectrum δ_H (ppm) 3.85 (6H, s), 6.63 (1H, t, *J* 2 Hz), and 7.17 (2H, d, *J* 2 Hz). One isomer of coumalic acid has the ^{1}H NMR spectrum δ_H (ppm) 6.41 (1H, d, *J* 10 Hz), 7.82 (1H, dd, *J* 2, 10 Hz), and 8.51 (1H, d, *J* 2Hz). In each case, which isomer is it? The bonds sticking into the centre of the ring can be to any carbon atom.

dimethoxy benzoic acid

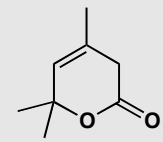


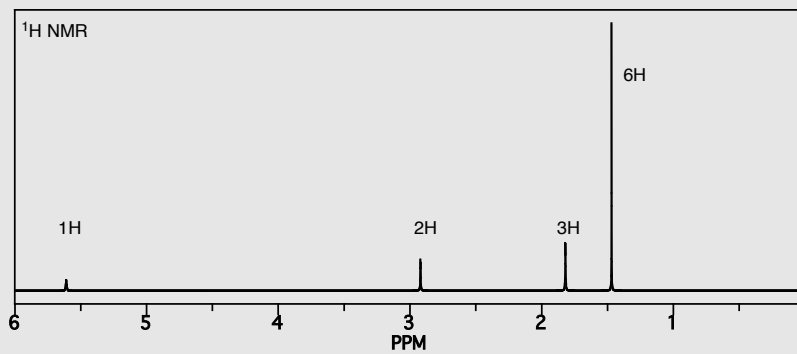


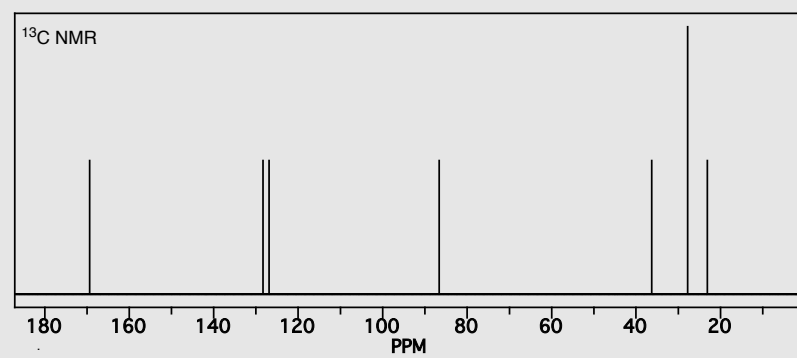
coumalic acid

PROBLEM 4

Assign the NMR spectra of this compound and justify your assignments. 'Assign' means 'say which signal belongs to which atom'.

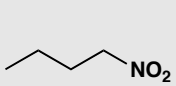




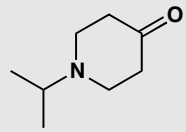


PROBLEM 5

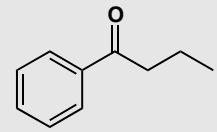
Assign the ^{1}H NMR spectra of these compounds and explain the multiplicity of the signals



δ 0.97 (3H, t, *J* 7 Hz)
δ 1.42 (2H, sextuplet, *J* 7 Hz)
δ 2.00 (2H, quintet, *J* 7 Hz)
δ 4.40 (2H, t, *J* 7 Hz)



δ 1.08 (6H, d, *J* 7 Hz)
δ 2.45 (4H, t, *J* 5 Hz)
δ 2.80 (4H, t, *J* 5 Hz)
δ 2.93 (1H, sextuplet *J* 7 Hz)



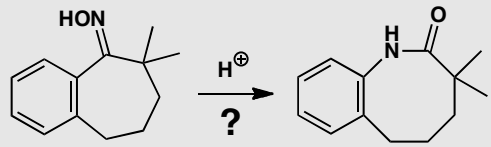
δ 1.00 (3H, t, *J* 7 Hz)
δ 1.75 (2H, sextuplet, *J* 7 Hz)
δ 2.91 (2H, t, *J* 7 Hz)
δ 7.4-7.9 (5H, m)

PROBLEM 6

The reaction below was expected to give the product A and did indeed give a compound with the correct molecular formula by its mass spectrum. However the NMR spectrum of this product was:

δ_H (ppm) 1.27 (6H, s), 1.70 (4H, m), 2.88 (2H, m), 5.4-6.1 (2H, broad s, exchanges with D_2O) and 7.0-7.5 (3H, m).

Though the detail is missing from this spectrum, how can you already tell that this is not the expected product?



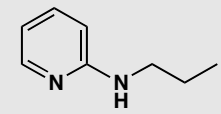
PROBLEM 7

Assign the 400 MHz ^{1}H NMR spectrum of this enynone as far as possible, justifying both chemical shifts and coupling patterns.

Spectrum from 1e p276 Q7

PROBLEM 8

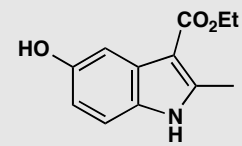
A nitration product ($C_8H_{11}N_3O_2$) of this pyridine has been isolated which has a nitro group somewhere in the molecule. From the spectrum deduce where the nitro group is and give a full analysis of the spectrum.



insert spectrum from p276 of 1e Q8

PROBLEM 9

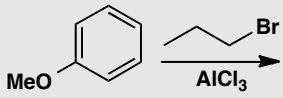
Interpret this ^{1}H NMR spectrum.



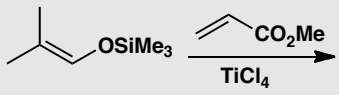
insert spectrum from 1e p 277 Q10

PROBLEM 10

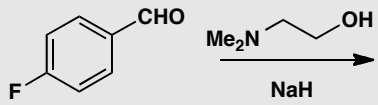
Suggest structures for the products of these reactions, interpreting the spectroscopic data. Most of the reactions will be new to you, and you should aim solve the structures from the data, not by guessing what might happen.



A, $C_{10}H_{14}O$
ν_{max} (cm^{-1}) C–H and fingerprint only
δ_C (ppm) 153, 141, 127, 115, 59, 33, 24
δ_H (ppm) 1.21 (6H, d, *J* 7 Hz), 2.83 (1H, septuplet, *J* 7 Hz), 3.72 (3H, s), 6.74 (2H, d, *J* 9 Hz) and 7.18 (2H, d, *J* 9 Hz)



B, $C_8H_{14}O_3$
ν_{max} (cm^{-1}) 1745, 1730
δ_C (ppm) 202, 176, 62, 48, 34, 22, 15
δ_H (ppm) 1.21 (6H, s), 1.8 (2H, t, *J* 7 Hz), 2.24 (2H, t, *J* 7 Hz), 4.3 (3H, s) and 10.01 (1H, s)



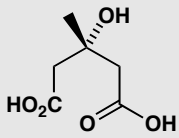
C, $C_{14}H_{15}NO_2$
ν_{max} (cm^{-1}) 1730
δ_C (ppm) 191, 164, 132, 130, 115, 64, 41, 29
δ_H (ppm) 2.32 (6H, s), 3.05 (2H, t, *J* 6 Hz) 4.20 (2H, t, *J* 6 Hz), 6.97 (2H, d, *J* 7 Hz), 7.82 (2H, d, *J* 7 Hz) and 9.97 (1H, s)

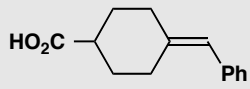
Problems for Chapter 14

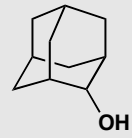
14

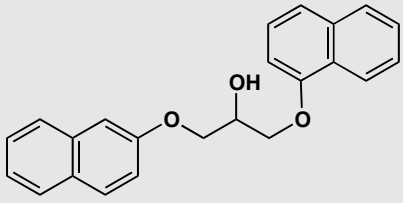
PROBLEM 1

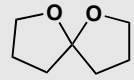
Are these molecules chiral? Draw diagrams to justify your answer.











PROBLEM 2

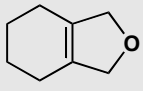
If a solution of a compound has an optical rotation of +12, how could you tell if this was actually +12 or really –348 or +372?

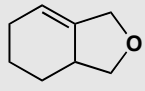
PROBLEM 3

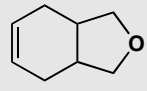
Cinderella's glass slipper was undoubtedly a chiral object. But would it have rotated the plane of polarized light?

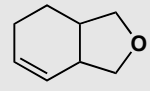
PROBLEM 4

Discuss the stereochemistry of these compounds. *Hint:* this means saying how many diastereoisomers there are, drawing clear diagrams of each, and stating whether they are chiral or not.



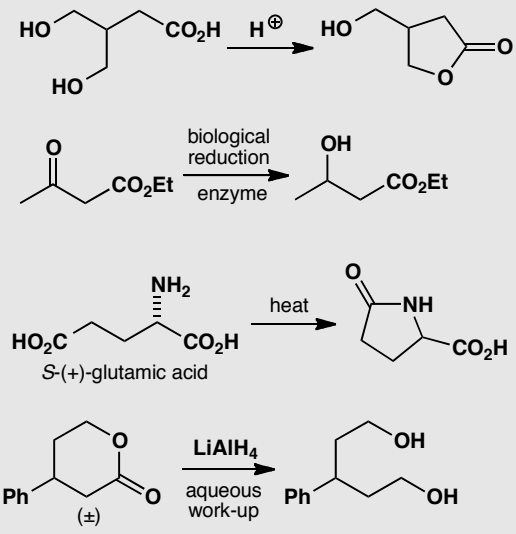






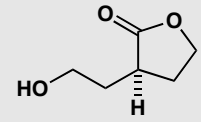
PROBLEM 5

In each case state, with explanations, whether the products of these reactions are chiral and/or enantiomericaly pure.



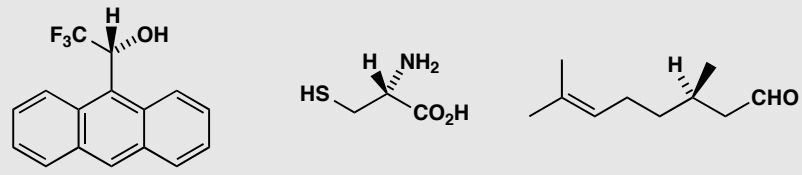
PROBLEM 6

This compound racemizes in base. Why is that?



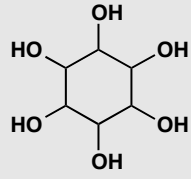
PROBLEM 7

Assign a configuration (*R* or *S*) to each of these compounds.



PROBLEM 8

Just for fun, you might try and work out just how many diastereoisomers there are of inositol and how many of them are chiral.



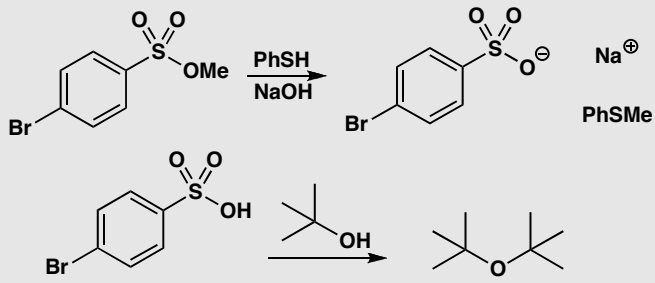
inositol

Problems for Chapter 15

15

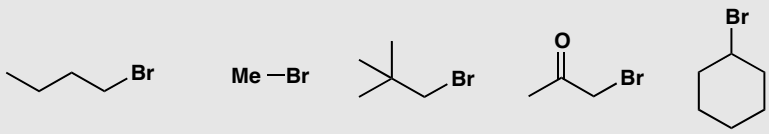
PROBLEM 1

Suggest mechanisms for the following reactions, commenting on your choice of S_N1 or S_N2.



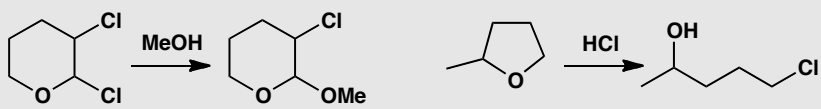
PROBLEM 2

Arrange the following in order of reactivity towards the nucleophile sodium azide. Give a brief comment for each compound to explain what factor influences its place in the reactivity scale.



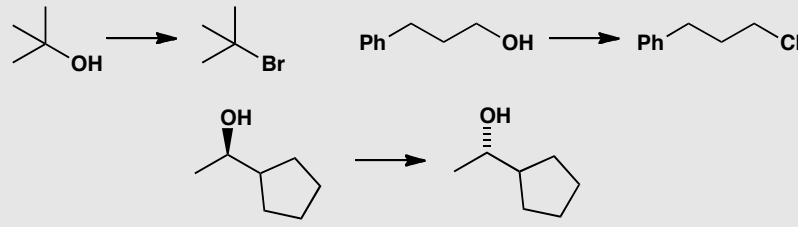
PROBLEM 3

Draw mechanisms for these reactions, explaining why these particular products are formed.



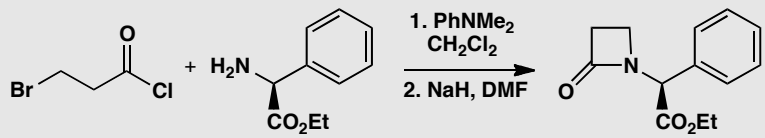
PROBLEM 4

Suggest how to carry out the following transformations.



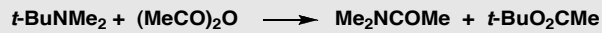
PROBLEM 5

Draw mechanisms for these reactions and give the stereochemistry of the product.



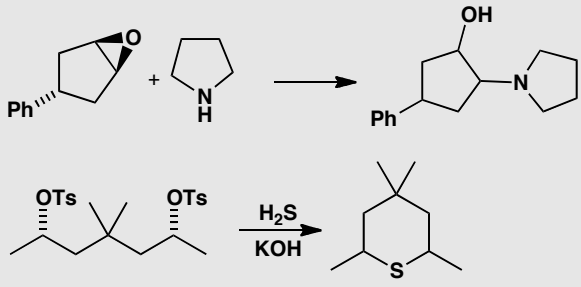
PROBLEM 6

Suggest a mechanism for this reaction. You will find it helpful first of all to draw good diagrams of reagents and products.



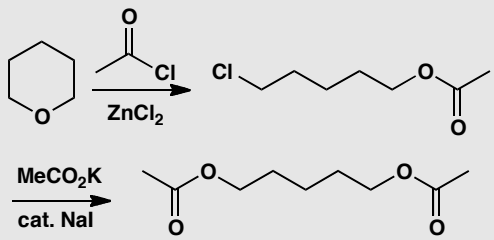
PROBLEM 7

Predict the stereochemistry of these products. Are they diastereoisomers, enantiomers, racemic or what?



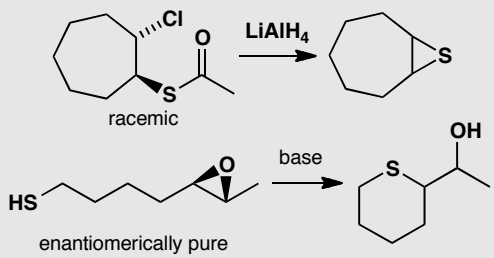
PROBLEM 8

What are the mechanisms of these reactions, and what is the role of the $ZnCl_2$ in the first step an the NaI in the second?



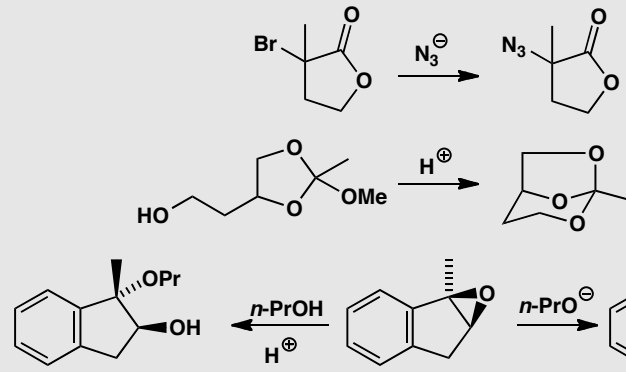
PROBLEM 9

Describe the stereochemistry of the products of these reactions.



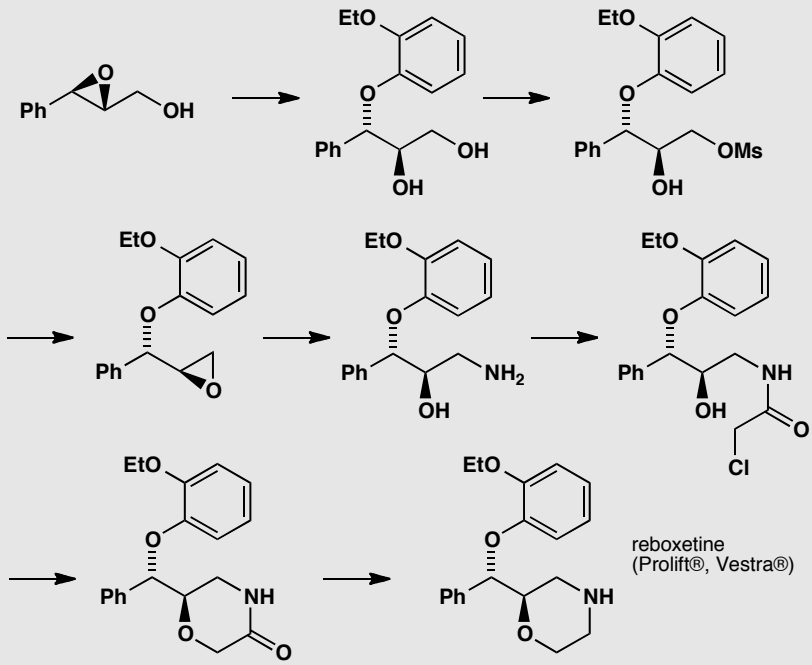
PROBLEM 10

State with reasons whether these reactions will be S_N1 or S_N2.



PROBLEM 11

The pharmaceutical company Pfizer made the antidepressant reboxetine by the following sequence of reactions. Suggest a reagent for each step, commenting on aspects of stereochemistry or reactivity.



Problems for Chapter 16

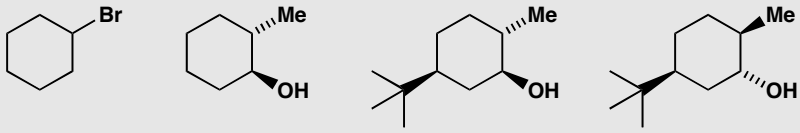
16

PROBLEM 1

Identify the chair or boat rings in the following structures and say why this particular structure is adopted.

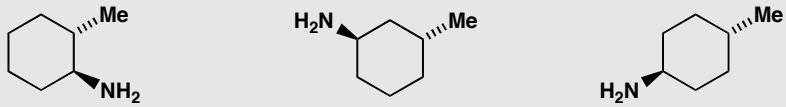
PROBLEM 2

Draw clear conformational drawings of these molecules, labelling each substituent as axial or equatorial.



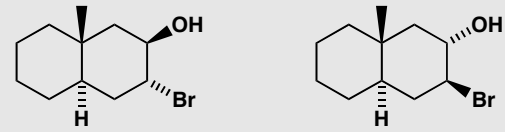
PROBLEM 3

Would the substituents in these molecules be axial, equatorial, or a mixture between the two?



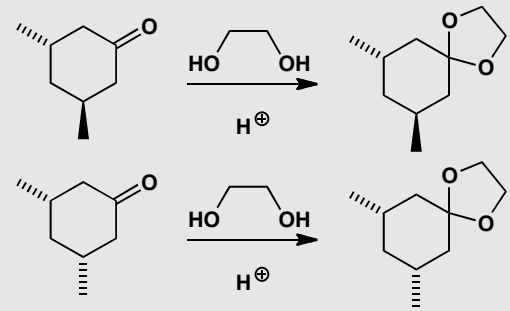
PROBLEM 4

Which of these two compounds would form an epoxide on treatment with base?



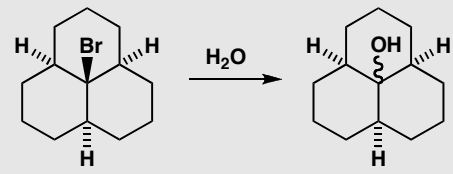
PROBLEM 5

It is more difficult to form an acetal from the first of these compounds than from the second. Why is this?



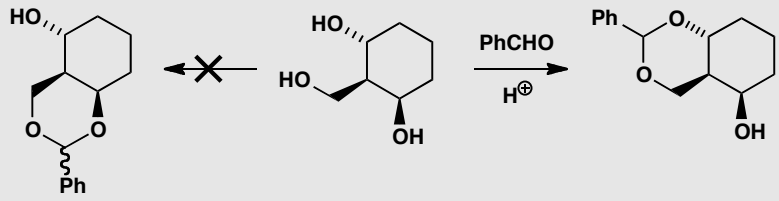
PROBLEM 6

Hydrolysis of the tricyclic bromide below in water gives an alcohol. What is the conformation of the bromide and what will be the stereochemistry of the alcohol?



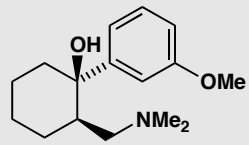
PROBLEM 7

Treatment of the triol below with benzaldehyde in acid solution produces one diastereoisomer of of an acetal but none of the alternative acetal. Why is one acetal preferred? (*Hint*: what controls acetal formation?) What is the stereochemistry of the undefined centre in the acetal that is formed?



PROBLEM 8

The compound below is the painkiller tramadol. Draw the most likely conformation of its six-membered ring.

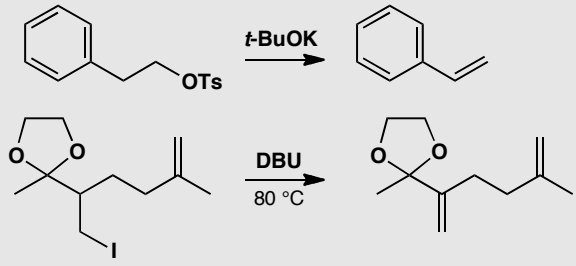


Problems for Chapter 17

17

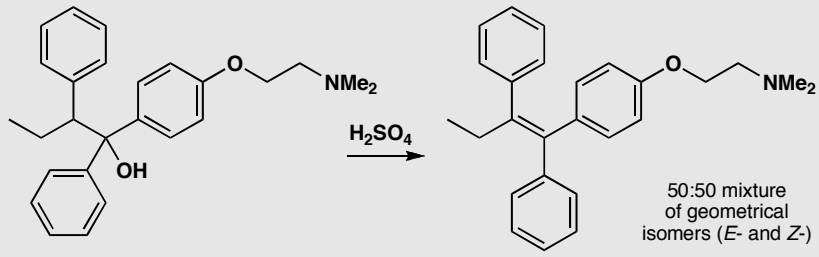
PROBLEM 1

Draw mechanisms for these elimination reactions.



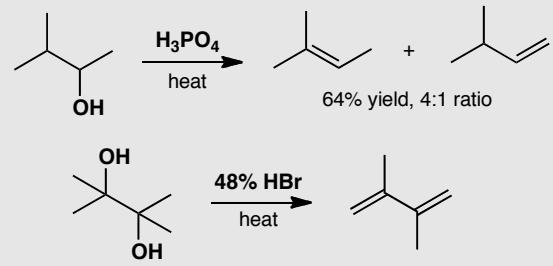
PROBLEM 2

Give a mechanism for the elimination reaction in the formation of tamoxifen, a breast cancer drug, and comment on the roughly 50:50 mixture of geometrical isomers (*cis*- and *trans*-alkenes)



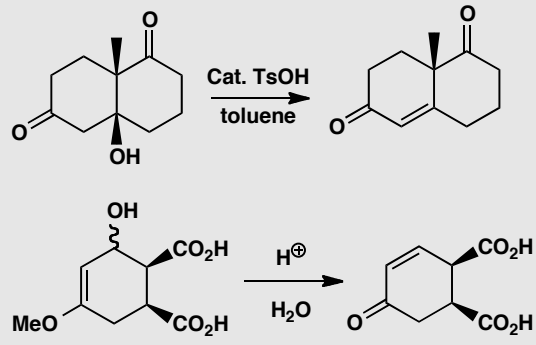
PROBLEM 3

Suggest mechanisms for these eliminations. Why does the first give a mixture and the second a single product?



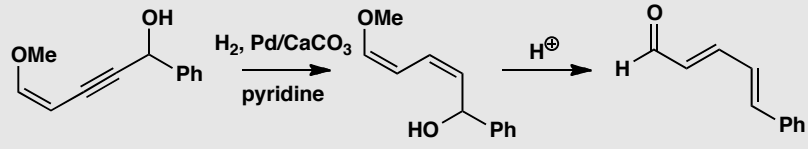
PROBLEM 4

Explain the position of the alkene in the products of these reactions. The starting materials are enantiomerically pure. Are the products also enantiomerically pure?



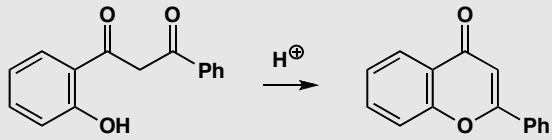
PROBLEM 5

Explain the stereochemistry of the alkenes in the products of these reactions.



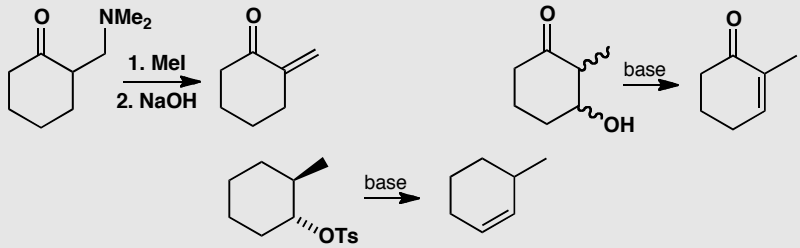
PROBLEM 6

Suggest a mechanism for this reaction and explain why the product is so stable.



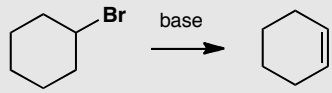
PROBLEM 7

Comment on the position taken by the alkene in these eliminations.



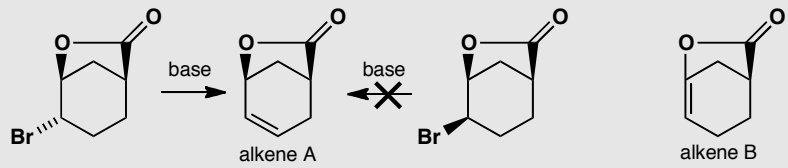
PROBLEM 8

Why is it difficult (though not impossible) for cyclohexyl bromide to undergo an E2 reaction? What conformational changes must occur during this reaction?



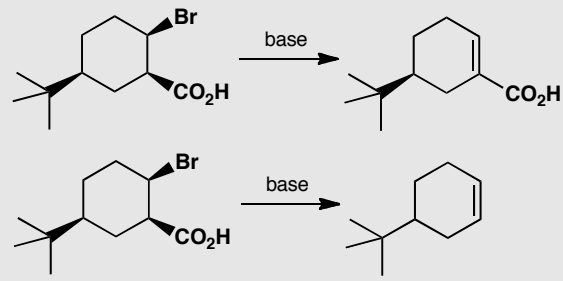
PROBLEM 9

Only one of these bromides eliminates to give alkene A. Why? Neither alkene eliminates to give alkene B. Why not?



PROBLEM 10

Account for the constrasting results of these two reactions.



Problems for Chapter 18

18

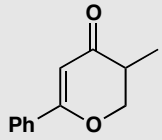
PROBLEM 1

A compound C_6H_5FO has a broad peak in the infrared at about 3100-3400 cm^{-1} and the following signals in its (proton decoupled) ^{13}C NMR spectrum. Suggest a structure for the compound and interpret the spectra.

δ_C (ppm) 157.4 (d, *J* 229 Hz), 151.2 (s), 116.3 (d *J* 7.5 Hz), and 116.0 (d, *J* 23.2 Hz).

PROBLEM 2

The natural product bullatenone was isolated in the 1950s from a New Zealand myrtle and assigned the structure A. Then authentic compound A was synthesised and found not to be identical to natural bullatenone. Predict the expected ^1H NMR spectrum of A. Given the full spectroscopic data, not available in the 1950s, say why A is definitely wrong and suggest a better structure for bullatenone.



A: alleged bullatenone

Spectra of isolated bullatenone:

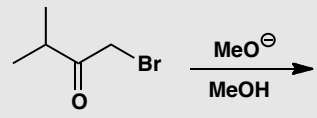
Mass spectrum: m/z 188 (10%) (high resolution confirms $C_{12}H_{12}O_2$), 105 (20%), 102 (100%), and 77 (20%)

Infrared: 1604 and 1705 cm^{-1}

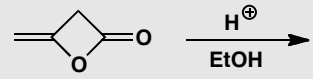
^1H NMR: δ_H (ppm) 1.43 (3H, s), 5.82 (1H, s), 7.35 (3H, m), and 7.68 (2H, m).

PROBLEM 3

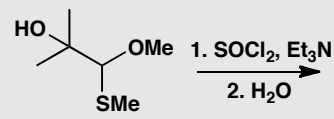
Suggest structures for each of these reaction products, interpreting the spectroscopic data. You are *not* expected to give mechanisms for the reactions and you must resist the temptation to say what 'ought to happen'. These are all unexpected products.



A, $C_6H_{12}O_2$
ν_{max} (cm^{-1}) 1745
δ_C (ppm) 179, 52, 39, 27
δ_H (ppm) 1.20 (9H, s) and 3.67 (3H, s)



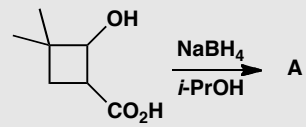
B, $C_6H_{10}O_3$
ν_{max} (cm^{-1}) 1745, 1710
δ_C (ppm) 203, 170, 62, 39, 22, 15
δ_H (ppm) 1.28 (3H, t, *J* 7 Hz), 2.21 (3H, s)
3.24 (2H, s) and 4.2 (2H, q, *J* 7 Hz)

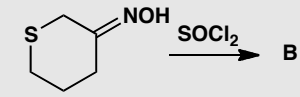


C, m/z 118
ν_{max} (cm^{-1}) 1730
δ_C (ppm) 202, 45, 22, 15
δ_H (ppm) 1.12 (6H, s), 2.28 (3H, s)
and 9.8 (1H, s)

PROBLEM 4

Suggest structures for the products of these reactions.



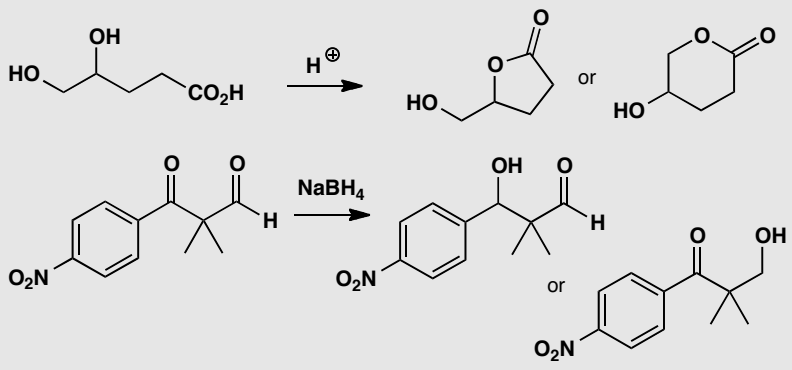


Compound **A**: $C_7H_{12}O_2$; IR 1725 cm^{-1}; δ_H (ppm) 1.02 (6H, s), 1.66 (2H, t, *J* 7 Hz), 2.51 (2H, t, *J* 7 Hz), and 4.6 (2H, s).

Compound **B**: m/z 149/151 (M^+ ratio 1:3); IR 2250 cm^{-1}; δ_H (ppm) 2.0 (2H, quintet, *J* 7 Hz), 2.5 (2H, t, *J* 7 Hz), 2.9 (2H, t, *J* 7 Hz), and 4.6 (2H, s).

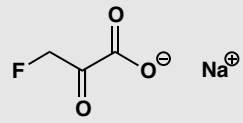
PROBLEM 5

Two alternative structures are shown for the products of these reactions. Explain in each case how you would decide which product is actually formed. Several pieces of evidence will be required and estimated values are better than general statements.



PROBLEM 6

The NMR spectra of sodium fluoropyruvate in D_2O are given below. Are these data compatible with the structure shown? If not, suggest how the compound might exist in this solution.



δ_H (ppm) 4.43 (2H, d, *J* 47 Hz);

δ_C (ppm) 83.5 (d, *J* 22 Hz), 86.1 (d, *J* 171 Hz), and 176.1 (d, *J* 2 Hz).

PROBLEM 7

An antibiotic isolated from a microorganism was crystallized from water and formed different crystalline salts in either acid or base. The spectroscopic data were:

Mass spectrum 182 (M^+, 9%), 109 (100%), and 74 (15%).

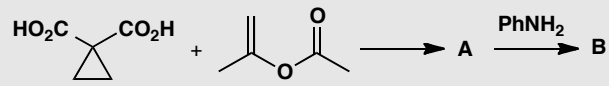
δ_H (ppm in D_2O at pH<1) 3.67 (2H, d, *J* 7), 4.57 (1H, t, *J* 7), 8.02 (2H, m), and 8.37 (1H, m).

δ_C (ppm in D_2O at pH<1) 33.5, 52.8, 130.1, 130.6, 130.9, 141.3, 155.9, and 170.2.

Suggest a structure for the antibiotic.

PROBLEM 8

Suggest structures for the products of these two reactions.



Compound **A:**

m/z 170 (M^+, 1%), 84 (77%), and 66 (100%);

IR 1773, 1754 cm^{-1};

δ_H (ppm, $CDCl_3$) 1.82 (6H, s) and 1.97 (4H, s);

δ_C (ppm, $CDCl_3$) 22, 23, 28, 105, and 169.

Compound **B:**

m/z 205 (M+, 40%), 161 (50%), 160 (35%), 105 (100%), and 77 (42%);

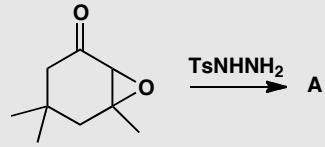
IR 1670, 1720 cm^{-1};

δ_H (ppm, $CDCl_3$) 2.55 (2H, m), 3.71 (1H, t, *J* 6 Hz), 3.92 (2H, m), 7.21 (2H, d, *J* 8 Hz), 7.35 (1H, t, *J* 8 Hz), and 7.62 (2H, d, *J* 8 Hz);

δ_C (ppm, $CDCl_3$) 21, 47, 48, 121, 127, 130, 138, 170, and 172.

PROBLEM 9

Treatment of this epoxy-ketone with tosyl hydrazine gives a compound with the spectra shown below. What is its structure?



m/z 128 (M+, 12%), 109 (56%), 95 (100%), 81 (83%), 82 (64%), and 79 74%);

IR 3290, 2115, 1710 cm^{-1};

δ_H (ppm in $CDCl_3$) 1.12 (6H, s), 2.02 (1H, t, *J* 3 Hz), 2.15 (3H, s), 2.28 (2H, d, *J* 3 Hz), and 2.50 (2H, s);

δ_C (ppm in $CDCl_3$) 26, 31, 32, 33, 52, 71, 82, 208.

PROBLEM 10

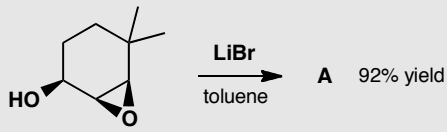
Reaction of the epoxy-alcohol below with LiBr in toluene gave a 92% yield of compound A. Suggest a structure for this compound from the data:

mass spectrum gives $C_8H_{12}O$;

ν_{max} (cm^{-1}) 1685, 1618;

δ_H (ppm) 1.26 (6H, s), 1.83, 2H, t, *J* 7 Hz), 2.50 (2H, dt, *J* 2.6, 7 Hz), 6.78 (1H, t (*J* 2.6 Hz), and 9.82 (1H, s);

δ_C (ppm) 189.2, 153.4, 152.7, 43.6, 40.8, 30.3, and 25.9.



PROBLEM 11

Female boll weevils (a cotton pest) produce two isomeric compounds that aggregate the males for food and sex. A few mg of two isomeric active compounds, grandisol and *Z*-ochtodenol, were isolated from 4.5 million insects. Suggest structures for these compounds from the data below. Signals marked * exchange with D_2O.

Z-ochtodenol:

m/z 154 ($C_{10}H_{18}O$), 139, 136, 121, 107, 69 (100%);

ν_{max} (cm^{-1}) 3350, and 1660;

δ_H (ppm) 0.89 (6H, s), 1.35-1.70 (1H, broad m), 1.41* (1H, s), 1.96 (2H, s), 2.06 (2H, t, *J* 6 Hz), 4.11 (2H, d, *J* 7 Hz), and 5.48 (1H, t, *J* 7 Hz).

Grandisol:

m/z 154 ($C_{10}H_{18}O$), 139, 136, 121, 109, 68 (100%);

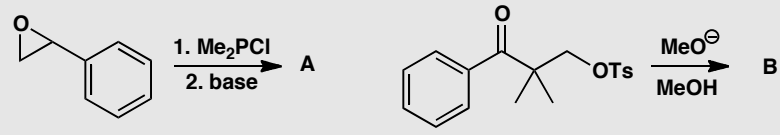
ν_{max} (cm^{-1}) 3630, 3520, 3550, and 1642;

δ_H (ppm) 1.15 (3H, s), 1.42 (1H, dddd, *J* 1.2, 6.2, 9.4, 13.4 Hz), 1.35-1.45 (1H, m), 1.55-1.67 (2H, m), 1.65 (3H, s), 1.70-1.81 (2H, m), 1.91-1.99 (1H, m), 2.52* (1H, broad t, *J* 9.0 Hz), 3.63 (1H, ddd, *J* 5.6, 9.4, 10.2 Hz), 3.66 (1H, ddd, *J* 6.2, 9.4, 10.2 Hz), 4.62 (1H, broad s), and 4.81 (1H, broad s);

δ_C (ppm) 19.1, 23.1, 28.3, 29.2, 38.8, 41.2, 52.4, 59.8, 109.6, and 145.1.

PROBLEM 12

Suggest structures for the products of these reactions.



Compound **A**:

$C_{10}H_{13}OP$, IR (cm^{-1}) 1610, 1235;

δ_H (ppm) 6.5-7.5 (5H, m), 6.42 (1H, t, *J* 17 Hz), 7.47 (1H, dd, *J* 17, 23 Hz), and 2.43 (6H, d, *J* 25 Hz).

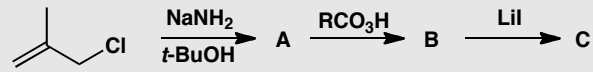
Compound **B**:

$C_{12}H_{17}O_2$, IR (cm^{-1}) C-H and fingerprint only;

δ_H (ppm) 7.25 (5H, s), 4.28 (1H, d, *J* 4.8 Hz), 3.91 (1H, d, *J* 4.8 Hz), 2.96 (3H, s), 1.26 (3H, s) and 0.76 (3H, s).

PROBLEM 13

Identify the compounds produced in these reactions. Warning! Do not attempt to deduce the structures from the starting materials, but use the data. These molecules are so small that you can identify them from ^1H NMR alone.



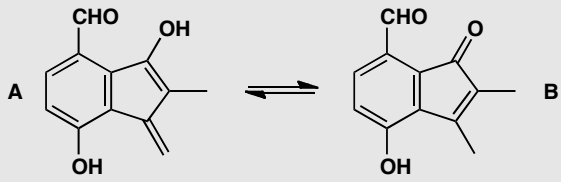
Data for **A**: C_4H_5; δ_H (ppm) 5.35 (2H, s) and 1.00 (4H, s)

Data for **B**: C_4H_6O; δ_H (ppm) 3.00 (2H, s), 0.90 (2H, d, *J* 3 Hz) and 0.80 (2H, d, *J* 3 Hz)

Data for **C**: C_4H_6O; δ_H (ppm) 3.02 (4H, d, *J* 5 Hz) and 1.00 (2H, quintet, *J* 5 Hz).

PROBLEM 14

The yellow crystalline antibiotic frustulosin was isolated from a fungus in 1978 and it was suggested the structure was an equilibrium mixture of A and B. Apart from the difficulty that the NMR spectrum clearly shows one compound and not an equilibrium mixture of two compounds, what else makes you unsure of this assignment? Suggest a better structure. Signals marked * exchange with D_2O.



Frustulosin:

m/z 202 (100%), 174 (20%);

ν_{max} (cm^{-1}) 3279, 1645, 1613, and 1522;

δ_H (ppm) 2.06 (3H, dd, *J* 1.0, 1.6 Hz), 5.44 (1H, dq, *J* 2.0, 1.6 Hz), 5.52 (1H, dq, *J* 2.0, 1.0 Hz), 4.5* (1H, broad s), 7.16 (1H, d, *J* 9.0 Hz), 6.88 (1H, dd, *J* 9.0, 0.4 Hz), 10.31 (1H, d, *J* 0.4 Hz), and 11.22* (1H, broad s);

δ_C (ppm) 22.8, 80.8, 100.6, 110.6, 118.4, 118.7, 112.6, 125.2, 129.1, 151.8, 154.5, and 196.6.

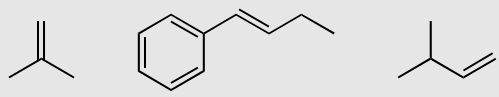
Warning! This is difficult – after all, the original authors got it wrong initially.
Hint: How might the DBEs be achieved without a second ring?

Problems for Chapter 19

19

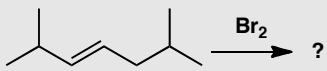
PROBLEM 1

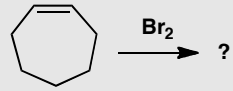
Predict the orientation of HCl addition to these alkenes.



PROBLEM 2

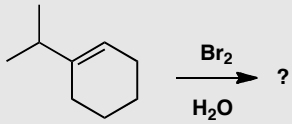
Suggest mechanism and products for these reactions.

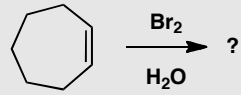




PROBLEM 3

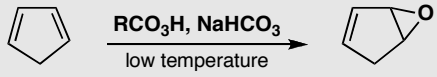
What will be the products of the addition of bromine water to these alkenes?





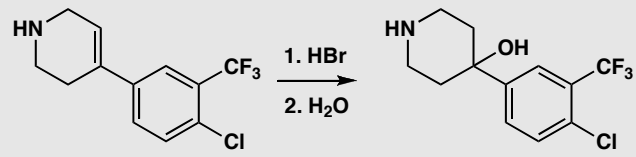
PROBLEM 4

By working at low temperature with one equivalent of buffered solution of a peroxy-acid, it is possible to prepare the monoepoxide of cyclopentadiene. Why are these precautions necessary and why does a second epoxidation not occur under these conditions?



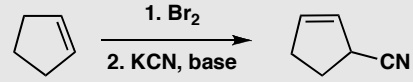
PROBLEM 5

The synthesis of a tranquilizer uses this step. Give mechanisms for the reactions.



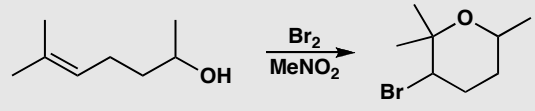
PROBLEM 6

Explain this result:



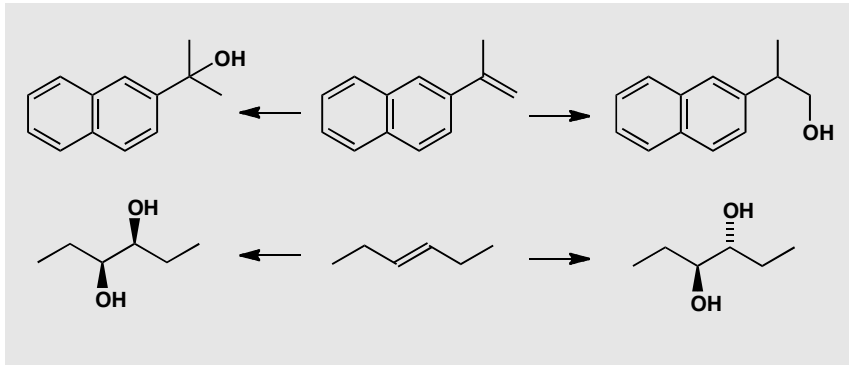
PROBLEM 7

Suggest a mechanism for the following reaction. What is the stereochemistry and conformation of the product? The product has these signals in its ^{1}H NMR spectrum: δ_H 3.9 (1H, ddq, *J* 12, 4, 7) and δ_H 4.3 (1H, dd, *J* 11, 3).



PROBLEM 8

The two alkenes below can be converted to two regioisomers or two diastereoisomers as shown. Suggest reagents to achieve these transformations. What alternative starting material could you use to make the *trans* diol (bottom right)?

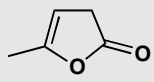

OH
OH
OH
OH
OH
OH

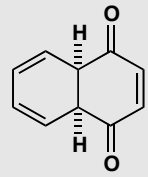
Problems for Chapter 20

20

PROBLEM 1

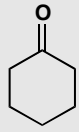
Draw all possible enol forms of these carbonyl compounds and comment on their stability.



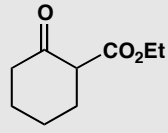


PROBLEM 2

The proportions of enol in a neat sample of the two ketones below are rather different. Why is this?



0.0004% enol

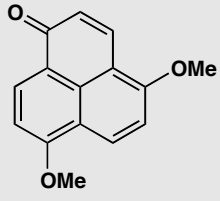


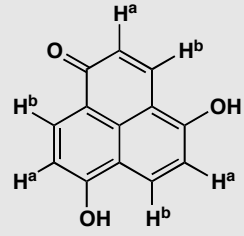
62% enol

PROBLEM 3

The NMR spectrum of this dimethyl ether is complicated: the two MeO groups are different as are all the hydrogen atoms on the rings. However the diphenol has a very simple NMR spectrum – there are only two types of proton on the rings marked 'a' and 'b' on the diagram. Explain.

dimethyl ether

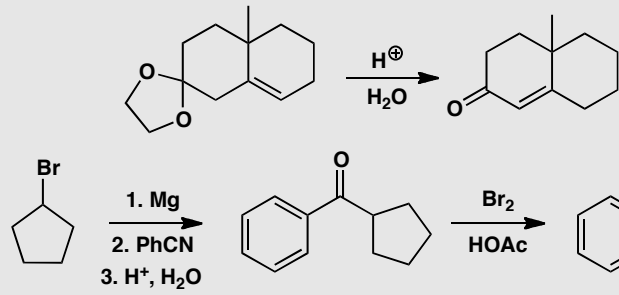




diphenol

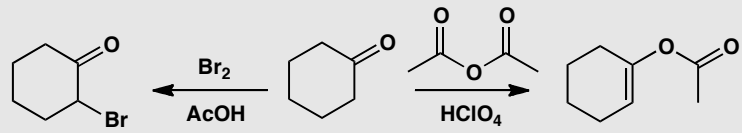
PROBLEM 4

Suggest mechanisms for these reactions:



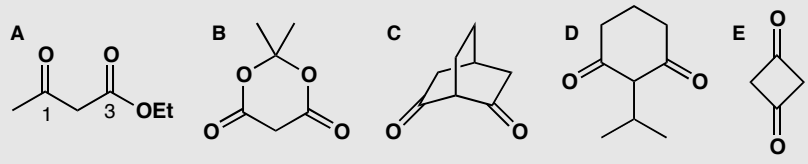
PROBLEM 5

Suggest mechanisms for these reactions and explain why these products are formed.



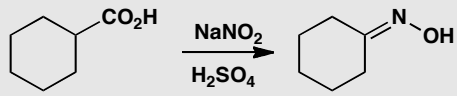
PROBLEM 6

1,3–Dicarbonyl compounds such as **A** are usually mostly enolized. Why is this? Draw the enols available to compounds **B**-**E** and explain why **B** is 100% enol but **C**, **D**, and **E** are 100% ketone.



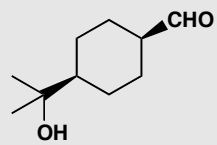
PROBLEM 7

Attempted nitrosation of this carboxylic acid leads to formation of an oxime with loss of CO_2. Why?



PROBLEM 8

This molecule is a perfumery compound with an intense flowery odour, but it isomerises rapidly in base to its odourless diastereoisomer. Why?

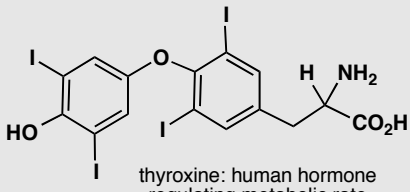


Problems for Chapter 21

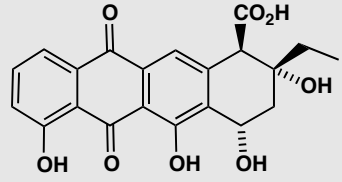
21

PROBLEM 1

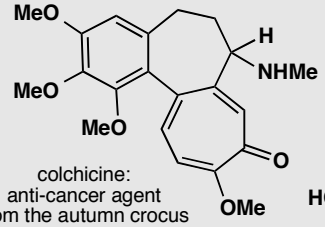
All you have to do is to spot the aromatic rings in these compounds. It may not be as easy as you think and you should give some reasons for questionable decisions.



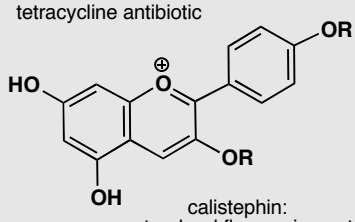
thyroxine: human hormone regulating metabolic rate



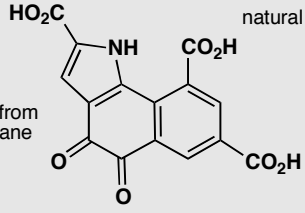
aklavinone: tetracycline antibiotic



colchicine: anti-cancer agent from the autumn crocus



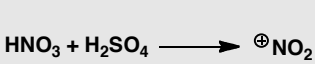
calistephin: natural red flower pigment

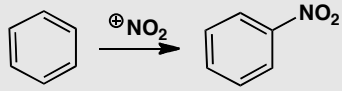


methoxatin: coenzyme from bacteria living on methane

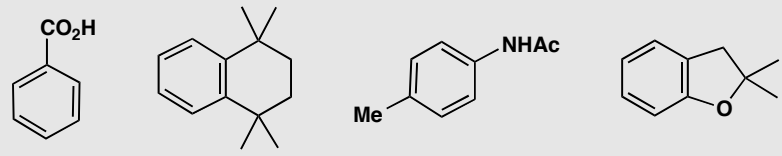
PROBLEM 2

First, as some revision, write out the detailed mechanism for these steps.



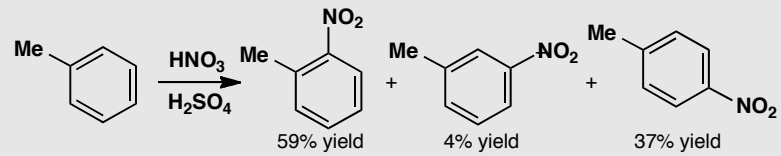


In a standard nitration reaction with, say, HNO_3 and H_2SO_4, each of these compounds forms a single nitration product. What is its structure? Explain your answer with at least a partial mechanism.



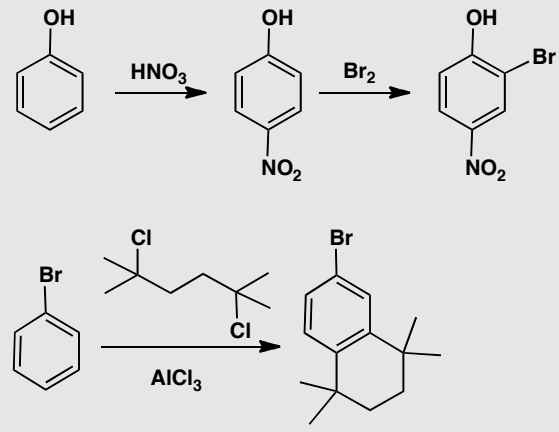
PROBLEM 3

How reactive are the different sites in toluene? Nitration of toluene produces the three possible products in the ratios shown. What would be the ratios if all the sites were equally reactive? What is the actual relative reactivity of the three sites? You could express this as x:y:1 or as a:b:c where a+b+c = 100. Comment on the ratio you deduce



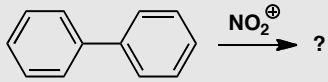
PROBLEM 4

Draw mechanisms for these reactions and explain the positions of substitution.

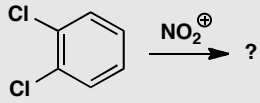


PROBLEM 5

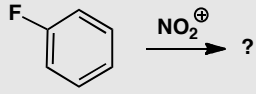
Nitration of these compounds gives products with the ^{1}H NMR spectra shown. Deduce the structures of the products and explain the position of substitution. **WARNING**: do not decide the structure by saying where the nitro group 'ought to go'! Chemistry has many surprises and it is the evidence that counts.



δ_H
7.77 (4H, d, *J* 10)
8.26 (4H, d, *J* 10)



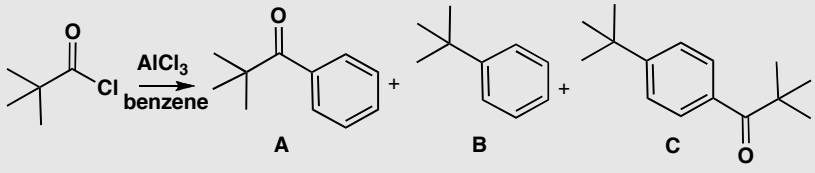
δ_H
7.6 (1H, d, *J* 10)
8.1 (1H, dd, *J* 10,2)
8.3 (1H, d, *J* 2)



δ_H
7.15 (2H, dd, *J* 7,8)
8.19 (2H, dd, *J* 6,8)

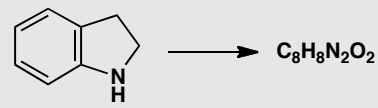
PROBLEM 6

Attempted Friedel-Crafts acylation of benzene with *t*-BuCOCl gives some of the expected ketone **A** as a minor product, as well as some *t*-butylbenzene **B**, but the major product is the substituted ketone **C**. Explain how these compounds are formed and suggest the order in which the two substituents are added to form compound **C**.



PROBLEM 7

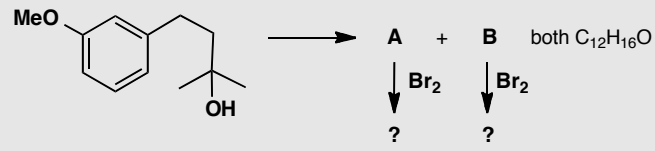
Nitration of this heterocyclic compound with the usual HNO_3/H_2SO_4 mixture gives a single nitration product with the ^{1}H NMR spectrum shown below. Suggest which product is formed and why.



δ_H
3.04 (2H, t, *J* 7 Hz)
3.68 (2H, t, *J* 7 Hz)
6.45 (1H, d, *J* 8 Hz)
7.28 (1H, broad s)
7.81 (1H, d, *J* 1 Hz)
7.90 (1H, dd, *J* 8, 1 Hz)

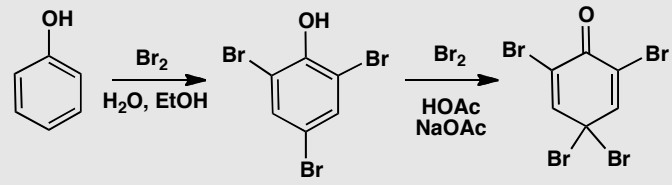
PROBLEM 8

What are the two possible isomeric products of this reaction? Which structure do you expect to predominate? What would be the bromination product from each?

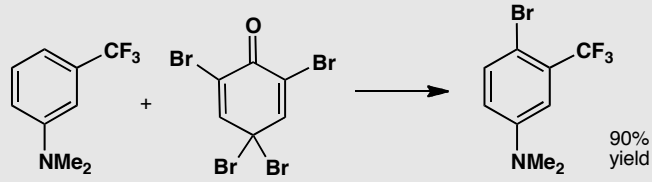


PROBLEM 9

On p. 479 of the textbook we explain the formation of 2,4,6-tribromophenol by bromination of phenol in water. It looks as though we can go no further as all the *ortho* and *para* positions are brominated. But we can if we treat the tribromo-compound with bromine in an organic solvent. Account for the formation of the tetrabromo-compound.

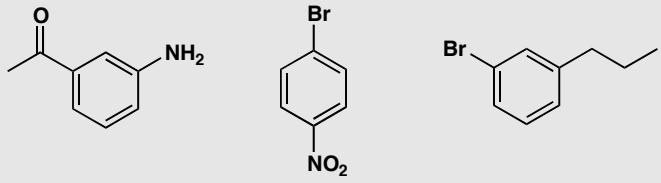


The product is useful in brominations as it avoids using unpleasant Br_2. Suggest a mechanism for the following bromination and account for the selectivity.



PROBLEM 10

How would you make each of the following compounds from benzene?

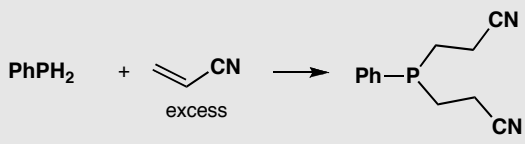


Problems for Chapter 22

22

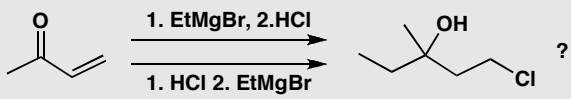
PROBLEM 1

Draw a mechanism for this reaction. Why is base unnecessary?



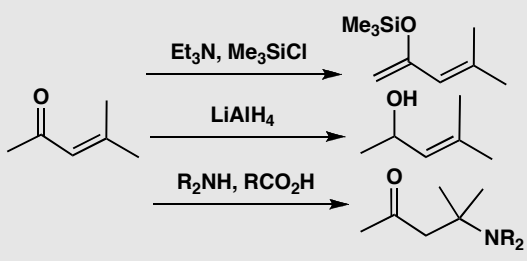
PROBLEM 2

Which of the two routes suggested here would actually lead to the product?



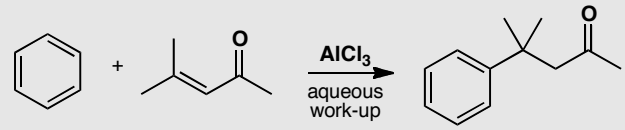
PROBLEM 3

Suggest reasons for the different outcome of each of these reactions. Your answer must of course be mechanistically based.



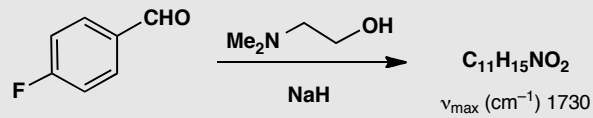
PROBLEM 4

Suggest a mechanism for this reaction.



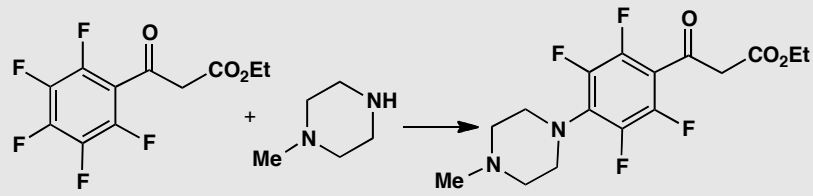
PROBLEM 5

What is the structure of the product of this reaction and how is it formed? It has δ_C 191, 164, 132, 130, 115, 64, 41, 29 and δ_H 2.32 (6H, s), 3.05 (2H, t, *J* 6 Hz), 4.20 (2H, t, *J* 6 Hz), 6.97 (2H, d, *J* 7 Hz), 7.82 (2H, d, *J* 7 Hz), 9.97 (1H, s). You should obviously interpret the spectra to get the structure.



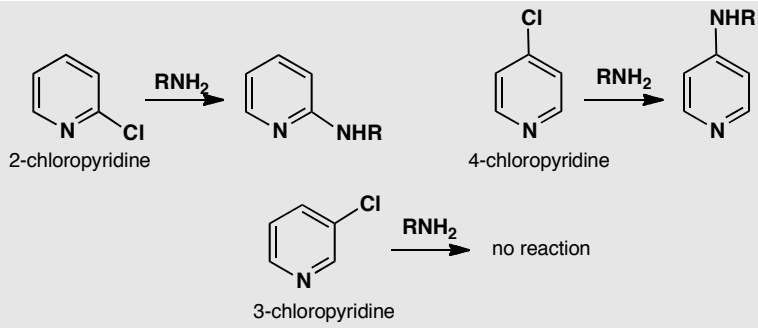
PROBLEM 6

Suggest a mechanism for this reaction, explaining the selectivity.



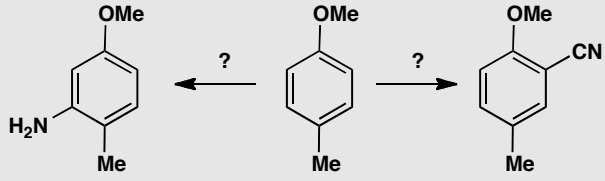
PROBLEM 7

Pyridine is a six-electron aromatic system like benzene. You have not yet been taught anything systematic about pyridine (that will come in chapter 29) but see if you can work out why 2- and 4-chloropyridines react with nucleophiles but 3-chloropyridine does not.



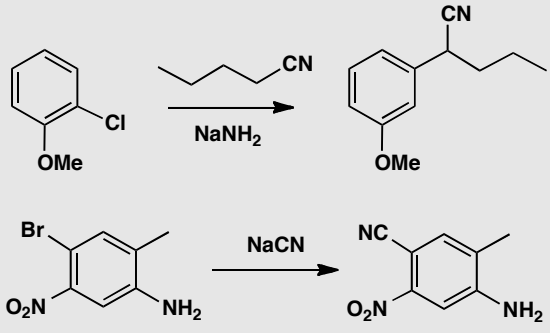
PROBLEM 8

How would you carry out these two conversions?



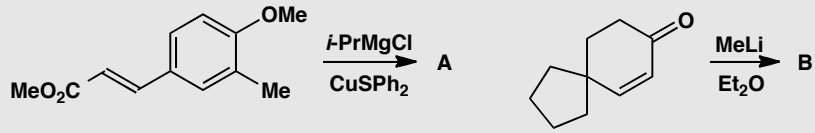
PROBLEM 9

Suggest mechanisms for these reactions, pointing out why you chose the pathways.



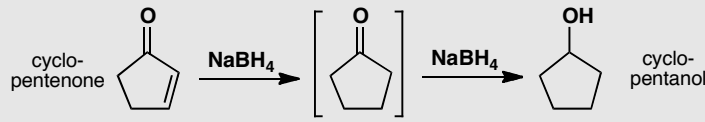
PROBLEM 10

Predict the products of these reactions.



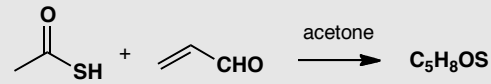
PROBLEM 11

When we discussed reduction of cyclopentenone to cyclopentanol, we suggested that conjugate addition of borohydride must occur before direct addition of borohydride: in other words, the scheme below must be followed. What is the alternative scheme? Why is the scheme shown definitely correct?



PROBLEM 12

Stirring thioacetic acid with acrolein (propenaldehyde) in acetone gives a compound with the NMR data shown below. Suggest the identity of this compound.



δ_H: 2.28 (3H, s), 3.58 (2H, d, *J* 8), 4.35 (1H, td, *J* 8, 6), 6.44 (1H, t, *J* 6, 7.67 (1H, d, *J* 6).

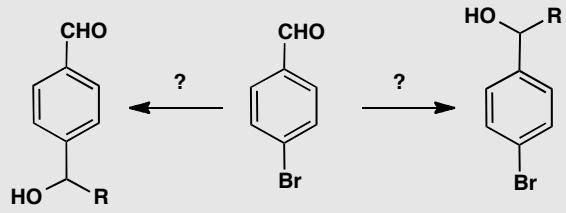
δ_C: 23.5, 31.0, 99.3, 144.2, 196.5.

Problems for Chapter 23

23

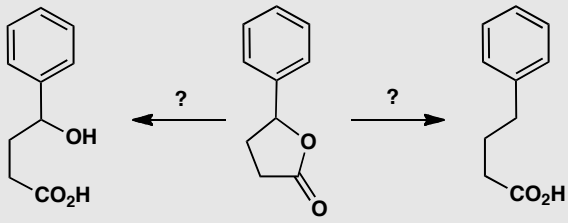
PROBLEM 1

How would you convert this bromo-aldehyde chemoselectively into the two products shown?



PROBLEM 2

How would you convert this lactone selectively into either the hydroxyacid or the unfunctionalised acid?

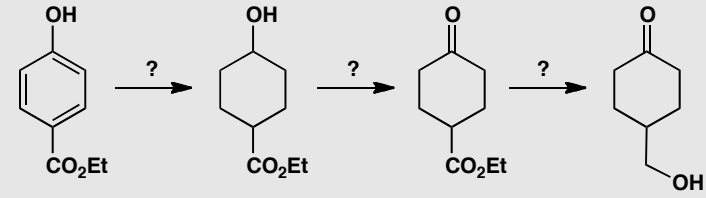


PROBLEM 3

Predict the products of Birch reduction of these aromatic compounds.

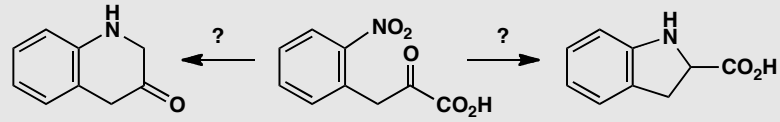
PROBLEM 4

How would you carry out these reactions? In some cases more than one step may be required.



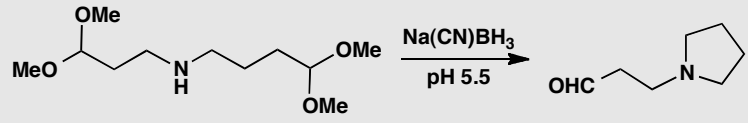
PROBLEM 5

How would you convert this nitro compound into the two products shown? Explain the order of events with special regard for reduction steps.



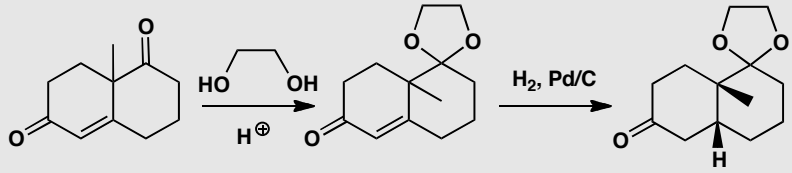
PROBLEM 6

Why is this particular amine formed by reductive amination here?.



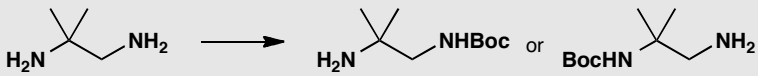
PROBLEM 7

Account for the chemoselectivity of the first reaction and the stereoselectivity of the second. A conformational drawing of the intermediate is essential.



PROBLEM 8

How would you convert this diamine to either of these two protected derivatives?

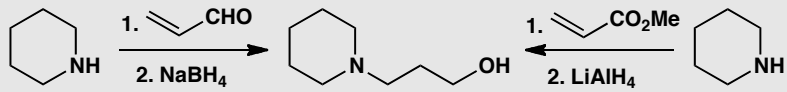


Problems for Chapter 24

24

PROBLEM 1

Two routes are proposed for the preparation of this amino-alcohol. Which do you think is more likely to succeed and why?

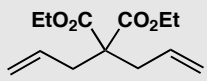


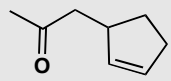
Problems for Chapter 25

25

PROBLEM 1

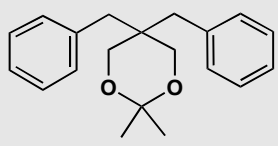
Suggest how these compounds might be made by alkylation of an enol or enolate.

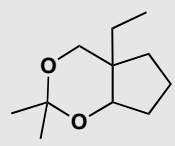




PROBLEM 2

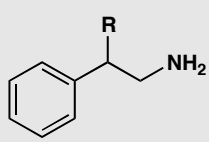
How might these compounds be made using alkylation of an enol or enolate as one step in the synthesis?

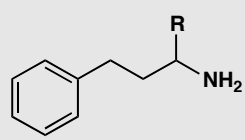




PROBLEM 3

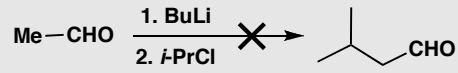
How might these amines be prepared using enolate-style alkylation as part of the synthesis?





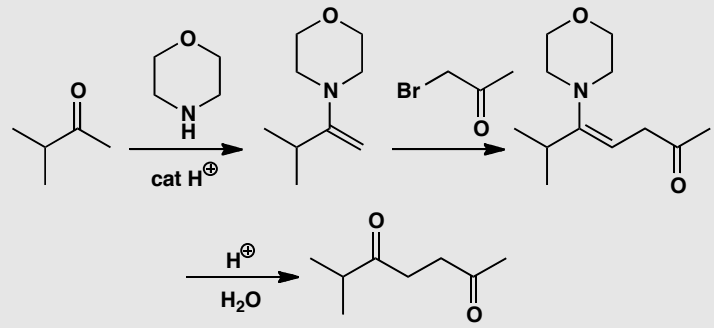
PROBLEM 4

This attempted enolate alkylation does not give the required product. What has gone wrong? What products would actually be formed? How would you make the required product?



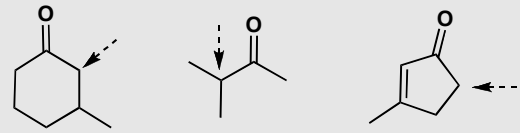
PROBLEM 5

Draw mechanisms for the formation of this enamine, its reaction with the alkyl halide, and the hydrolysis of the product.



PROBLEM 6

How would you produce specific enols or enolates at the points marked with the arrows (not necessarily starting with the ketones themselves)?

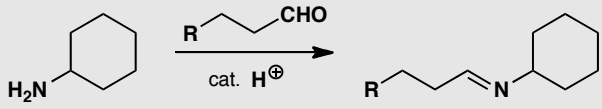


PROBLEM 7

How would the enol(ate) equivalents we have just made react with (a) bromine and (b) a primary alkyl halide RCH_2Br?

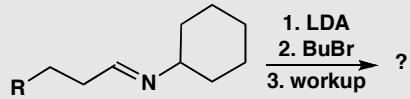
PROBLEM 8

Draw a mechanism for the formation this imine:



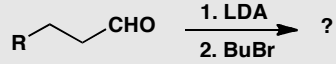
PROBLEM 9

How would the imine from problem 8 react with the reagents below? Draw mechanisms for each step: the reaction with LDA, the addition of BuBr, and the work-up.



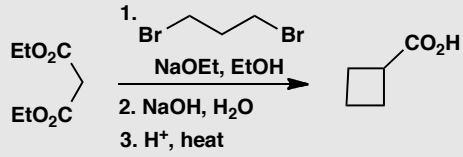
PROBLEM 10

What would happen if you tried this short cut for the reactions in problems 8 and 9?



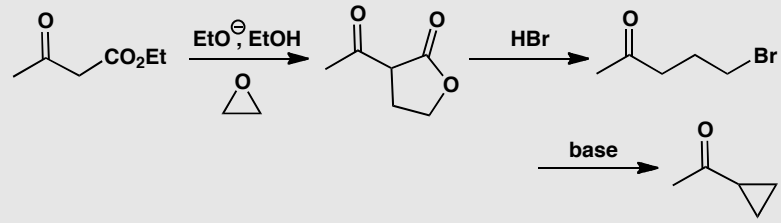
PROBLEM 11

Suggest mechanisms for these reactions.



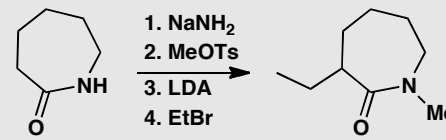
PROBLEM 12

How does this synthesis of a cyclopropyl ketone work?



PROBLEM 13

Give the structures of the intermediates in the following reaction sequence and mechanisms for the reactions.

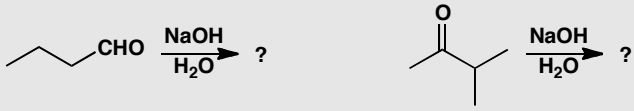


Problems for Chapter 26

26

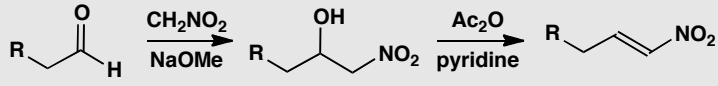
PROBLEM 1

The aldehyde and the ketone below are self-condensed with aqueous NaOH so that an unsaturated carbonyl compound is the product in both cases. Give a structure for each product and explain why you think this product is formed.



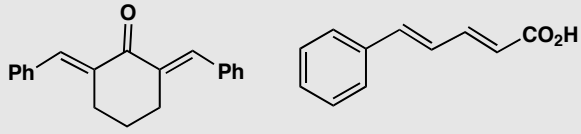
PROBLEM 2

Propose mechanisms for the 'aldol' and dehydration steps in the termite defence compound presented on p. 623 in the textbook.



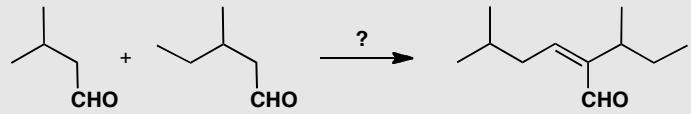
PROBLEM 3

How would you synthesise the following compounds?



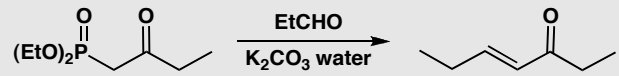
PROBLEM 4

How would you use a silyl enol ether to make this aldol product? Why is it necessary to use this particular intermediate? What would be the products be if the two carbonyl compounds were mixed and treated with base?



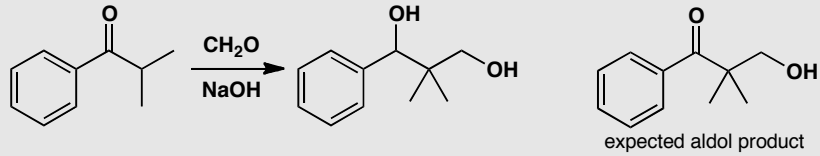
PROBLEM 5

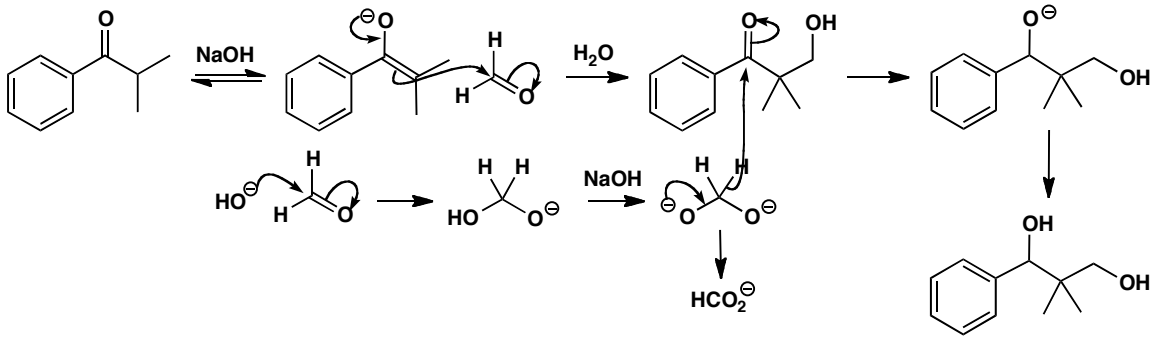
In what way does this reaction resemble an aldol reaction? Comment on the choice of base. How can the same product be made without using phosphorus chemistry?



PROBLEM 6

Suggest a mechanism for this attempted aldol reaction. How could the aldol product be made?

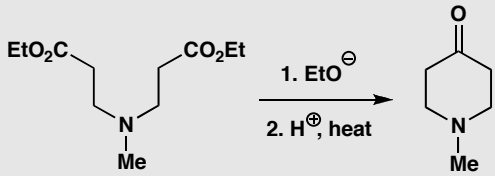




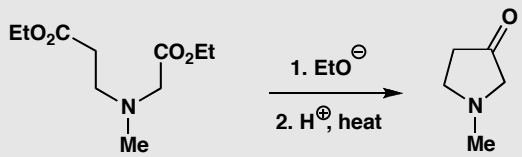
PROBLEM 7

The synthesis of six-membered ketones by intramolecular Claisen condensation was described in the chapter where we pointed out that it doesn't matter which

way round the cyclisation happens as the product is the same.

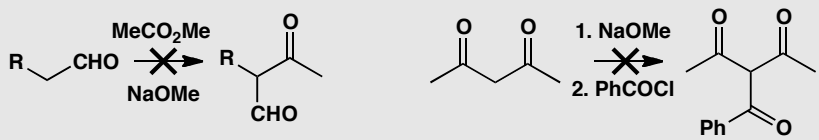


Strangely enough, five-membered heterocyclic ketones can be made by a similar sequence. The starting material is not symmetrical and two cyclized products are possible. Draw structures for these products and explain why it is unimportant which is formed.



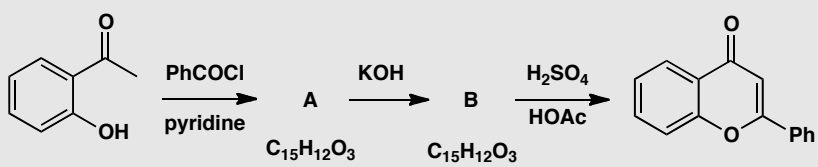
PROBLEM 8

Attempted acylation at carbon often fails. What would be the actual products of these attempted acylations and how would you successfully make the target molecules?



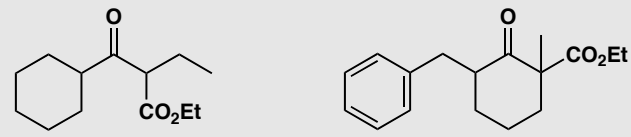
PROBLEM 9

Acylation of the phenolic ketone gives compound **A**, which is converted into an isomeric compound **B** in base. Cyclization of **B** gives the product shown. Suggest mechanisms for the reactions and structures for **A** and **B**.



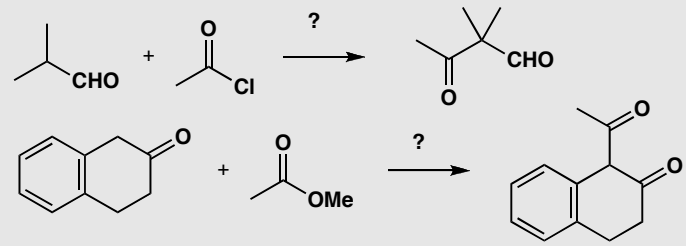
PROBLEM 10

How could these compounds be made using the acylation of an enol or enolate as a key step?



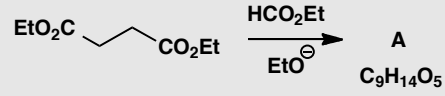
PROBLEM 11

Suggest how the following reactions might be made to work. You will probably have to select a specific enol equivalent.

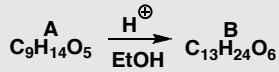


PROBLEM 12

Base-catalysed reaction between these two esters allows the isolation of a product **A** in 82% yield.



The NMR spectrum of this product shows that two species are present. Both show two 3H triplets at about $\delta_H = 1$ and two 2H quartets at about $\delta_H = 3$ ppm. One has a very low field proton and an ABX system at 2.1–2.9 with J_{AB} 16 Hz, J_{AX} 8 Hz, and J_{BX} 4 Hz. The other has a 2H singlet at 2.28 and two protons at 5.44 and 8.86 coupled with J 13 Hz. One of these protons exchanges with D_2O. Any attempt to separate the mixture (for example by distillation or chromatography) gives the same mixture. Both compounds, or the mixture, on treatment with ethanol in acid solution give the same product B.



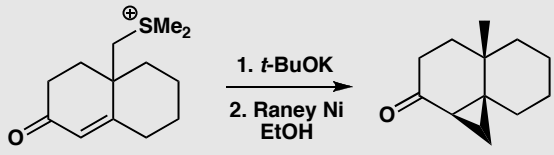
Compound B has IR 1740 cm^{-1}, δ_H 1.15-1.25 (four t, each 3H), 2.52 (2H, ABX system J_{AB} 16 Hz), 3.04 (1H, X of ABX split into a further doublet by *J* 5 Hz), and 4.6 (1H, d, *J* 5 Hz). What are the structures of **A** and **B**?

Problems for Chapter 27

27

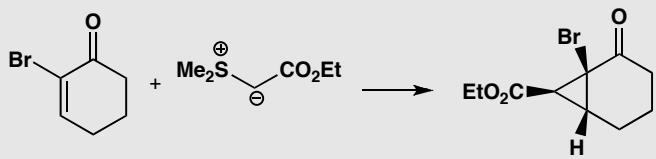
PROBLEM 1

Suggest a mechanism for this reaction, commenting on the selectivity and the stereochemistry.



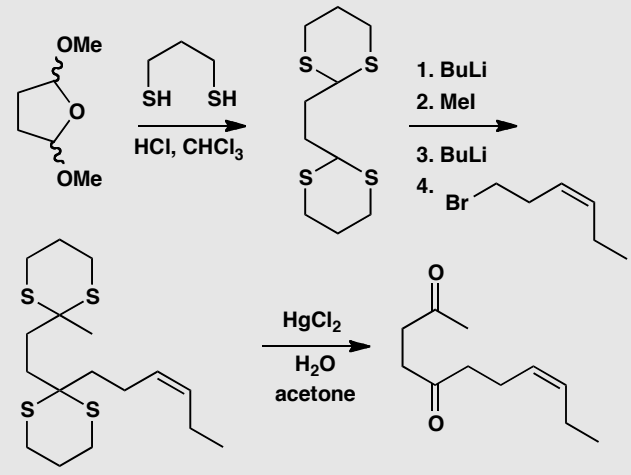
PROBLEM 2

Explain the regiochemistry and stereochemistry of this reaction..



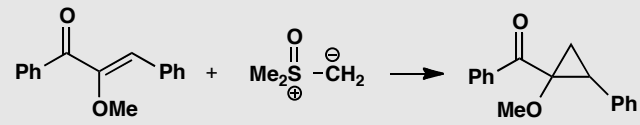
PROBLEM 3

Give mechanisms for these reactions, explaining the role of sulfur.

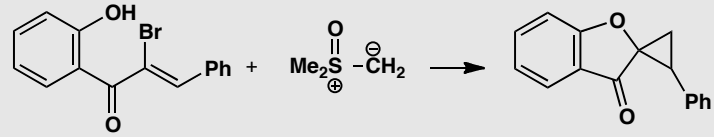


PROBLEM 4

Suggest a mechanism by which this cyclopropane might be formed.

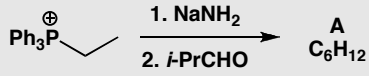


Attempts to repeat this synthesis on the related compound below led to a different type of product. What is different this time?



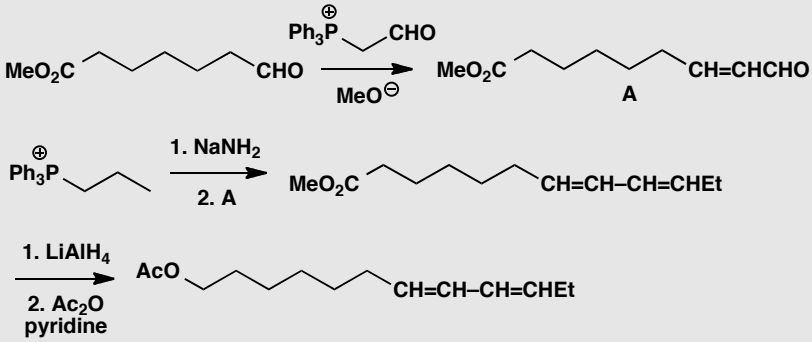
PROBLEM 5

Deduce the structure of the product of this reaction from the NMR spectra and explain the stereochemistry. Compound A has δ_H 0.95 (6H, d, *J* 7 Hz), 1.60 (3H, d, *J* 5), 2.65 (1H, double septuplet, *J* 4 and 7), 5.10 (1H, dd, *J* 10 and 4), and 5.35 (1H, dq, *J*, 10 and 5).



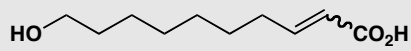
PROBLEM 6

A single geometrical isomer of an insect pheromone was prepared in the following way. Which isomer is formed and why?



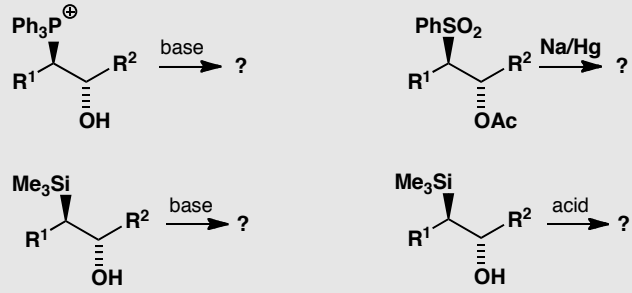
PROBLEM 7

How would you prepare samples of both geometrical isomers of this compound?



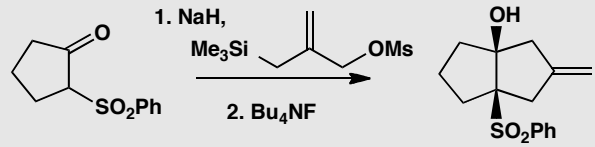
PROBLEM 8

Which alkene would be formed in each of these elimination reactions? Explain your answer mechanistically.



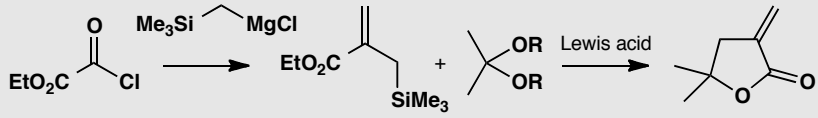
PROBLEM 9

Give mechanisms for these reactions, explaining the role of silicon.



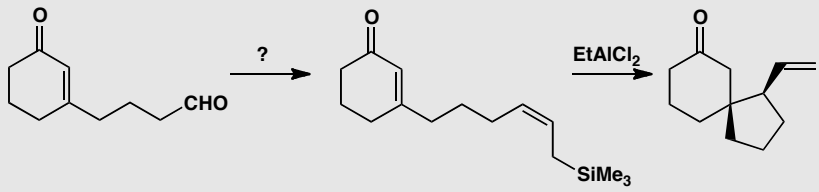
PROBLEM 10

Give mechanisms for these reactions, explaining the role of silicon. Why is this type of lactone difficult to make by ordinary acid- or base-catalysed reactions?



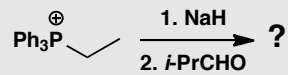
PROBLEM 11

How would you carry out the first step in this sequence? Give a mechansims for the second step and suggest an explanation for the stereochemistry. You may find that a Newman projection helps.



PROBLEM 12

The following reaction between a phosphonium salt, base, and an aldehyde gives a hydrocarbon C_6H_{12} with the 200 MHz 1H NMR spectrum shown (p. 278 of 1e). Give a structure for the product and comment on its stereochemistry.

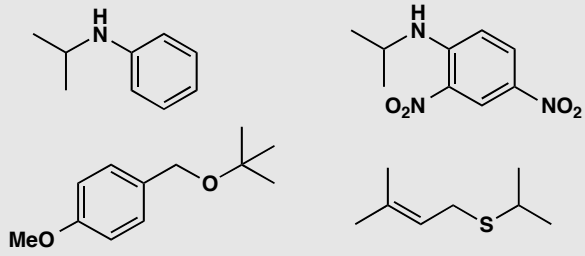


Problems for Chapter 28

28

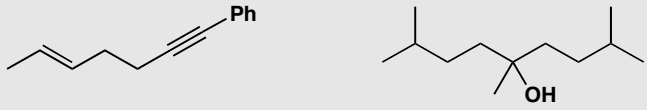
PROBLEM 1

How would you make these four compounds? Give your disconnections, explain why you chose them and then give reagents for the synthesis.



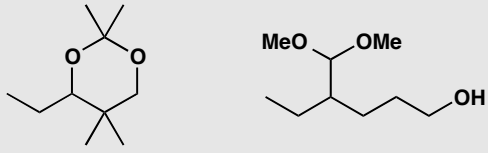
PROBLEM 2

How would you make these compounds? Give your disconnections, explain why you chose them and then give reagents for the synthesis.



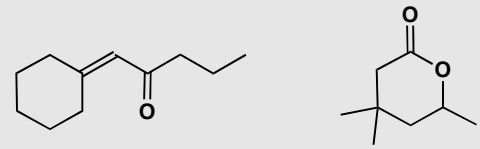
PROBLEM 3

Suggest ways to make these two compounds. Show your disconnections and make sure you number the functional group relationships.



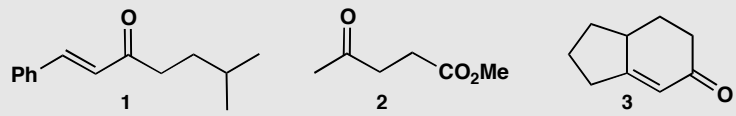
PROBLEM 4

Propose syntheses of these two compounds, explaining your choice of reagents and how any selectivity is achieved.

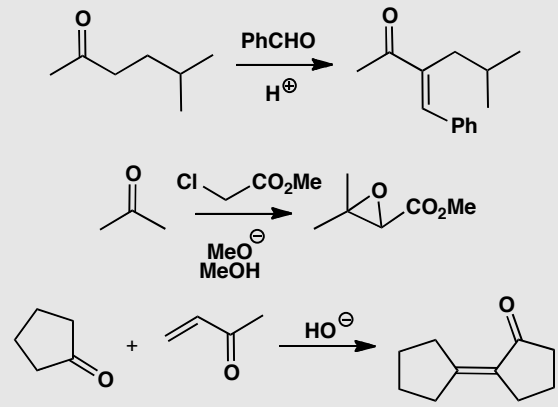


PROBLEM 5

The reactions to be discussed in this problem were planned to give syntheses of these three molecules.

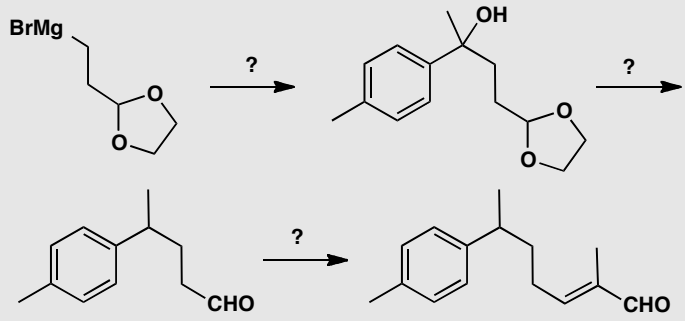


In the event each reaction gave a different product from what was expected, as shown below. What went wrong? Suggest syntheses that would give the target molecules above.



PROBLEM 6

The natural product nuciferal was synthesised by the route summarised here.



(a) Suggest a synthesis of the starting material.

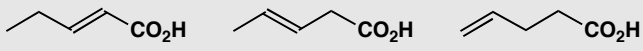
(b) Suggest reagents for each step.

(c) Draw the retrosynthetic analysis giving the disconnections that you consider the planners may have used and label them suitably.

(d) Which synthon does the starting material represent?

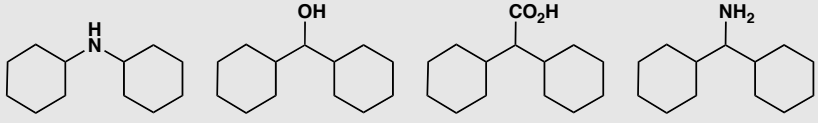
PROBLEM 7

Show how the relationship between the alkene and the carboxylic acid influences your suggestions for a synthesis of these three compounds.



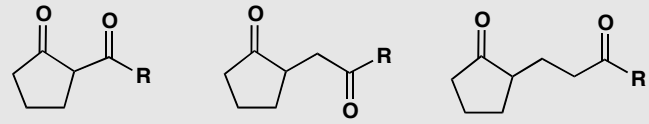
PROBLEM 8

How would you make these compounds?



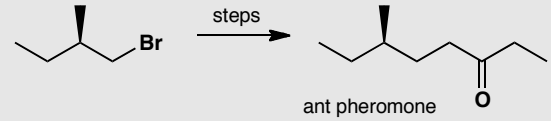
PROBLEM 9

Show how the relationship between the two carbonyl groups influences your choice of disconnection when you design a synthesis for each of these ketones.



PROBLEM 10

A synthesis of this enantiomerically pure ant pheromone was required for the purposes of pest control. Given a supply of the enantiomerically pure alkyl bromide as a starting material, suggest a synthesis of the pheromone.

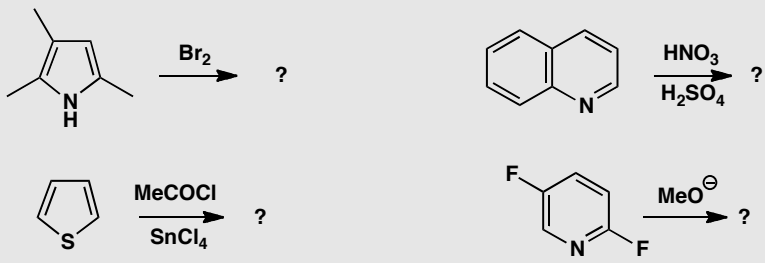


Problems for Chapter 29

29

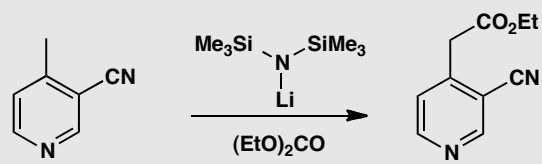
PROBLEM 1

For each of the following reactions (a) state what kind of substitution is suggested and (b) suggest what product might be formed if monosubstitution occured.



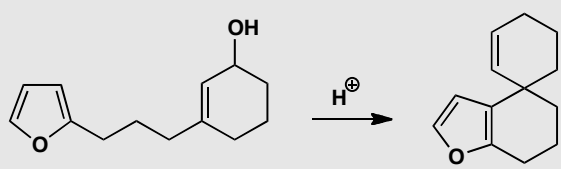
PROBLEM 2

Give a mechanism for this side-chain extension of a pyridine.



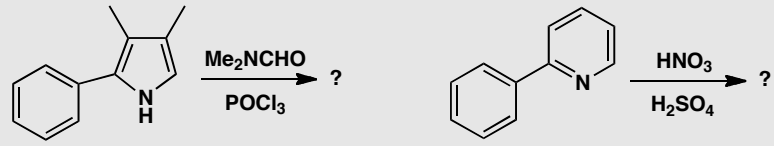
PROBLEM 3

Give a mechanism for this reaction, commenting on the position in the furan ring that reacts.



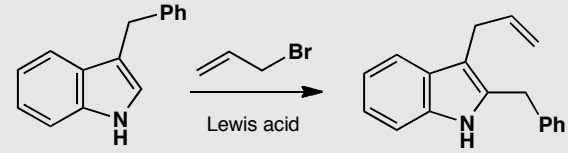
PROBLEM 4

Suggest which product might be formed in these reactions and justify your choice.



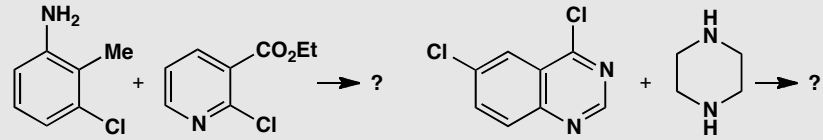
PROBLEM 5

Explain the formation of the product in this Friedel-Crafts alkylation of an indole.



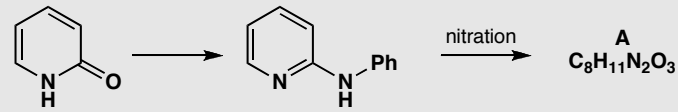
PROBLEM 6

Suggest what the products of these nucleophilic substitutions might be.



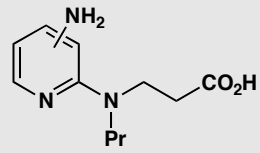
PROBLEM 7

Suggest how 2-pyridone might be converted into the amine shown. This amine undergoes nitration to give compound A with the NMR spectrum given. What is the structure of A? Why is this isomer formed?



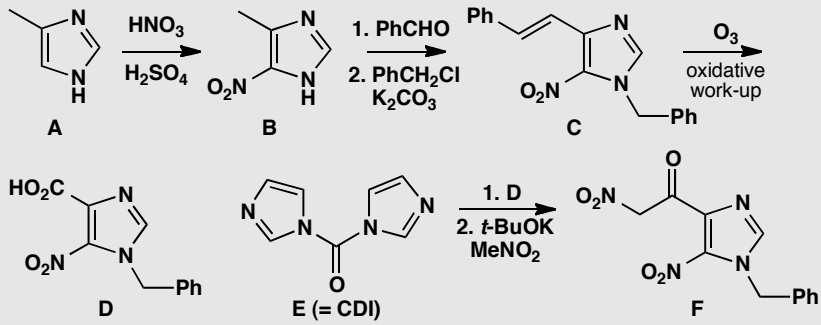
NMR of A: δ_H 1.0 (3H, t, *J* 7 Hz), 1.7 (2H, sextet, *J* 7 Hz), 3.3 (2H, t, *J* 7 Hz), 5.9 (1H, broad s), 6.4 (1H, d, *J* 8 Hz), 8.1 (1H, dd, *J* 8 and 2 Hz), and 8.9 (1H, d, *J* 2 Hz). Compound A was needed for conversion into the enzyme inhibitor below. How

might this be achieved?



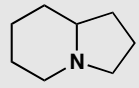
PROBLEM 8

The reactions outlined in the chart below were the early stages in a synthesis of an antiviral drug by the Parke-Davis company. Consider how the reactivity of imidazoles is illustrated in these reactions, which involve not only the skeleton of the molecule but also the reagent D. You will need to draw mechanisms for the reactions and explain how they are influenced by the heterocycles.



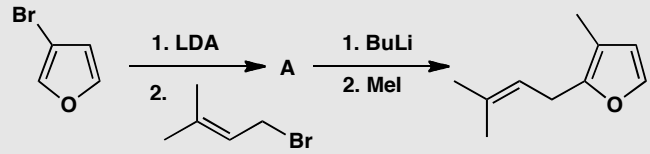
PROBLEM 9

What aromatic system might be based on this ring system? What sort of reactivity might it display?



PROBLEM 10

Explain the order of events and the choice of bases in this sequence.

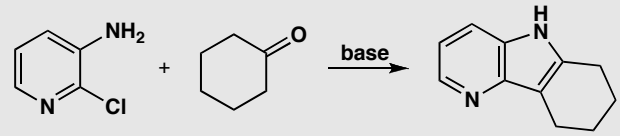


■ The product is related to a
constituent of the perfume of r
and was made by N. D. Ly and M
Schlosser, *Helv. Chim. Acta* 1977
2085.

Problems for Chapter 30

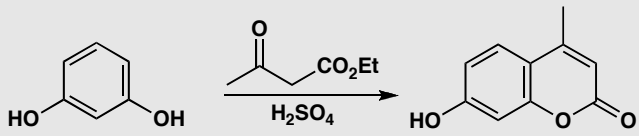
PROBLEM 1

Suggest a mechanism for this synthesis of a tricyclic aromatic heterocycle.



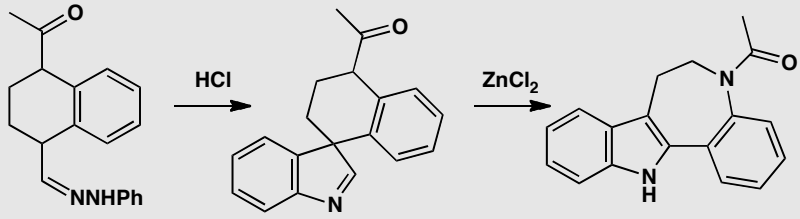
PROBLEM 2

Is the heterocyclic ring created in this reaction aromatic? How does the reaction proceed? Comment on the regioselectivity of this cyclisation.



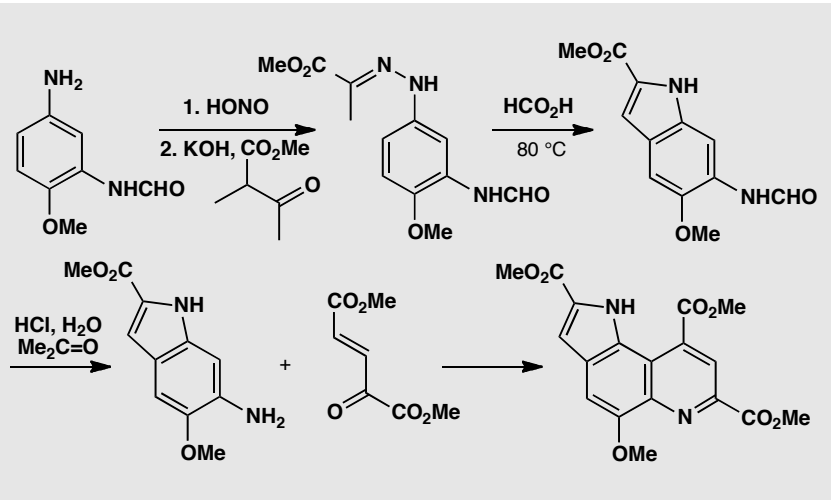
PROBLEM 3

Suggest mechanisms for this unusual indole synthesis. How does the second mechanism relate to electrophilic substitution on indoles (p. 746) ?



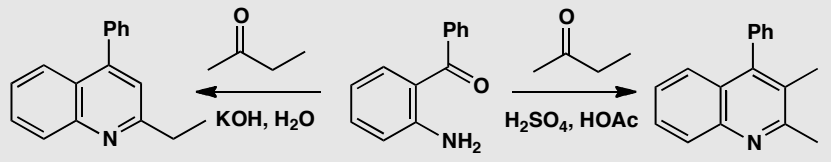
PROBLEM 4

Explain the reactions in this partial synthesis of methoxatin, the coenzyme of bacteria living on methanol.



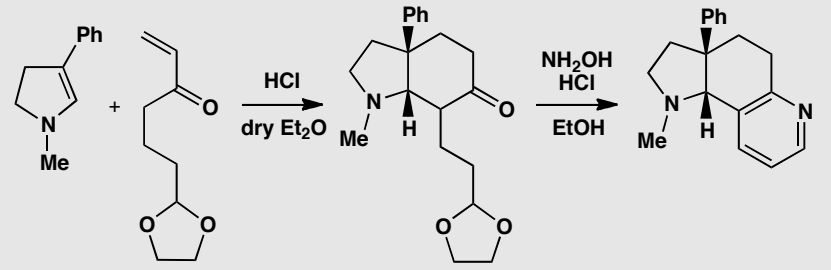
PROBLEM 5

Explain why these two quinoline syntheses from the same starting materials give (mainly) different products.



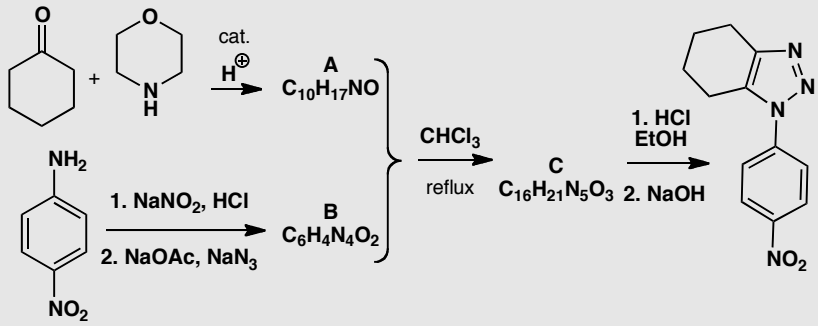
PROBLEM 6

Give mechanisms for these reactions used to prepare a fused pyridine. Why is it necessary to use a protecting group?



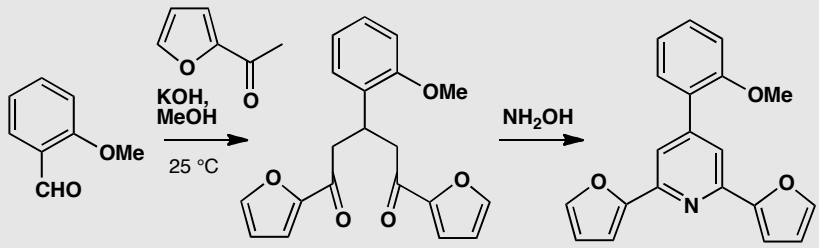
PROBLEM 7

Identify the intermediates and give mechanisms for the steps in this synthesis of a triazole.



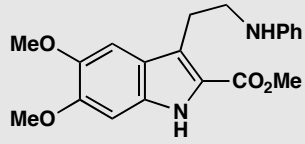
PROBLEM 8

Give detailed mechanisms for this pyridine synthesis.



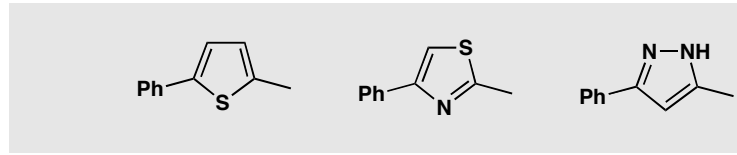
PROBLEM 9

Suggest a synthesis for this compound.



PROBLEM 10

How would you synthesise these aromatic heterocycles?

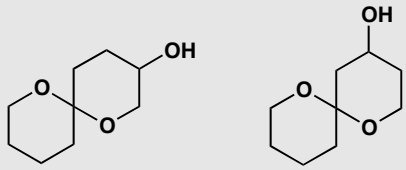

Ph
S
Ph
S
N
Ph
N—NH

Problems for Chapter 31

31

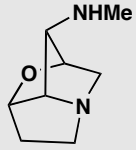
PROBLEM 1

Predict the most favourable conformation for these insect pheromones.

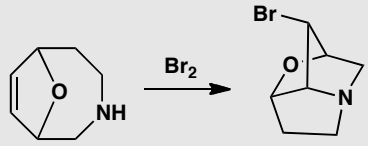


PROBLEM 2

The *Lolium* alkaloids have a striking saturated heterocyclic skeleton. One way to make this skeleton appears below. Suggest a mechanism and explain the stereochemistry.

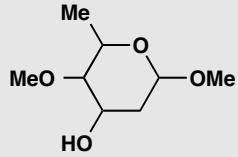


Lolium alkaloid skeleton



PROBLEM 3

One of the sugar components of the antibiotic kijanimycin has the basic structure shown here and NMR spectrum given below. What is the stereochemistry? When you have deduced the structure, suggest which conformation the molecule will prefer.

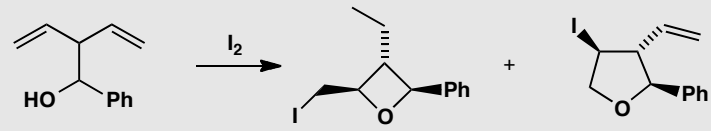


δ_H 1.33 (3H, d, *J* 6 Hz), 1.61* (1H, broad s), 1.87 (1H, ddd, *J* 14, 3, 3.5 Hz), 2.21 (1H, ddd, *J* 14, 3, 1.5 Hz), 2.87 (1H, dd, *J* 10, 3 Hz), 3.40 (3H, s), 3.99 (1H, dq, *J* 10, 3 Hz),

3.40 (3H, s), 1.33 (3H, d, *J* 6 Hz), 4.24 (1H, ddd, *J* 3, 3, 3.5 Hz) and 4.79 (1H, dd, *J* 3.5, 1.5 Hz). The signal marked * exchanges with D_2O.

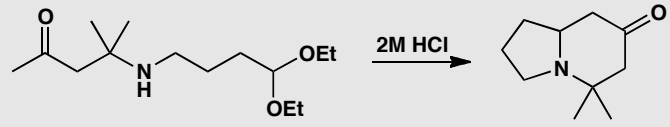
PROBLEM 4

Explain why this cyclization gives a preponderance (3:1) of the oxetane, though the tetrahydrofuran is much more stable.



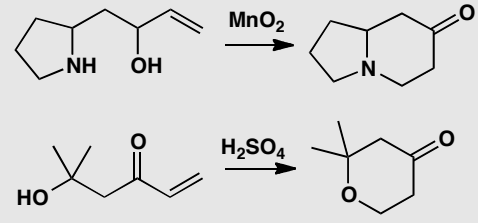
PROBLEM 5

Draw a mechanism for the following multistep reaction. Do the cyclisation steps follow Baldwin's rules?



PROBLEM 6

Consider the question of Baldwin's rules for each of these reactions. Why do you think they are both successful?



PROBLEM 7

A revision problem in spectroscopy. A Pacific sponge contains 2.8% dry weight of a sweet-smelling oil with the following spectroscopic details. What is its structure and stereochemistry?

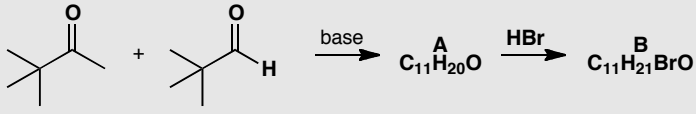
Mass spectrum gives formula: $C_9H_{16}O$. IR 1680 and 1635 cm^{-1}.

δ_H 0.90 (6H, d, *J* 7), 1.00 (3H, t, *J* 7), 1.77 (1H, m), 2.09 (2H, t, *J* 7), 2.49 (2H, q, *J* 7), 5.99 (1H, d, *J* 16), and 6.71 (1H, dt, *J* 16, 7).

δ_C 8.15 (q), 22.5 (two qs), 28.3 (d), 33.1 (t), 42.0 (t), 131.8 (d), 144.9 (d), and 191.6 (s).

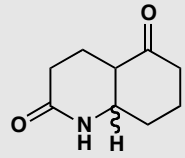
PROBLEM 8

Reaction between this aldehyde and ketone in base gives a compound A with the proton NMR spectrum: δ_H 1.10 (9H, s), 1.17 (9H, s), 6.4 (1H, d, *J* 15), and 7.0 (1H, d, *J* 15). What is its structure? (Don't forget stereochemistry!). When this compound reacts with HBr it gives compound B with this NMR spectrum: δ_H 1.08 (9H, s), 1.13 (9H, s), 2.71 (1H, dd, *J* 1.9, 17.7), 3.25 (dd, *J* 10.0, 17.7), and 4.38 (1H, dd, *J* 1.9, 10.0). Suggest a structure, assign the spectrum, and give a mechanism for the formation of B.



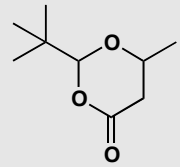
PROBLEM 9

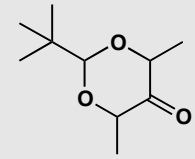
Two diastereoisomers of this cyclic keto-lactam have been prepared. The NMR spectra have many overlapping signals but the marked proton can be seen clearly. In isomer A it is at δ_H 4.12 (1H, q, *J* 3.5) and in isomer B it is δ_H 3.30 (1H, dt, *J* 4, 11). Which isomer has which stereochemistry?



PROBLEM 10

Given a sample of each of these two compounds, how would you determine the stereochemistry?





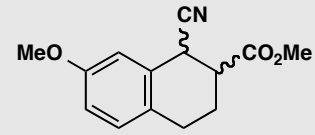
PROBLEM 11

The structure and stereochemistry of the antifungal antibiotic ambrucitin was in part deduced from the NMR spectrum of this simple cyclopropane which forms part of its structure. Interpret the NMR and show how it gives definite information on the stereochemistry.

δ_H 1.21 (3H, d, *J* 7 Hz), 1.29 (3H, t, *J* 9), 1.60 (1H, t, *J* 6), 1.77 (1H, ddq, *J* 13, 6, 7), 2.16 (1H, dt, *J* 6, 13), 4.18 (2H, q, *J* 9), 6.05 (1J, d, *J* 20), and 6.62 (1H, dd, *J* 20, 13).

PROBLEM 12

A reaction produces two diastereoisomers of the product below: isomer **A** has δ_H 3.08 (1H, dt, *J* 4, 9, 9) and 4.32 (1H, d, *J* 9), while isomer **B** has δ_H 4.27 (1H, d, *J* 4). All other protons (except those of the Me groups) overlap in the NMR. Isomer **B** is converted into isomer **A** in base. What is the stereochemistry of **A** and **B**?

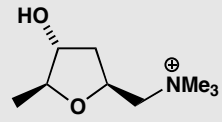


PROBLEM 13

Muscarine, the poisonous principle of the death cap mushroom, has the structure below. We give the proton NMR spectrum. Can you see any definite evidence for the stereochemistry? Couplings are in Hz, m stands for multiplet, and * means that the proton exchanges with D_2O.

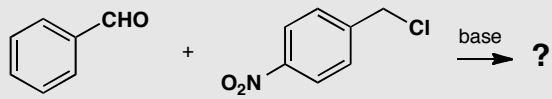
δ_H 1.16 (3H, d, *J* 6.5), 1.86 (1H, ddd, *J* 12.5, 9.5, 9.5), 2.02 (1H, ddd, *J* 12.5, 6.0, 2.0),

3.36 (9H, s), 3.54 (1H, dd, *J* 13, 9.0), 3.92 (1H, dq, *J* 2.5, 6.5), 4.03 91H, m), 4.30* (1H, d, *J* 3.5), and 4.68(1H, m).



PROBLEM 14

Treatment of the two compounds shown here with base gives an unknown compound with the spectra given below. What is its structure?



m/z: 241 (M^+, 60%), 90 (100%), 89 (62%)

δ_H (ppm in $CDCl_3$) 3.89 (1H, d, *J* 3 Hz), 4.01 (1H, d, *J* 3 Hz), 7.31 (5H, s), 7.54 (2H, d, *J* 10 Hz) and 8.29 (2H, d, *J* 10 Hz)

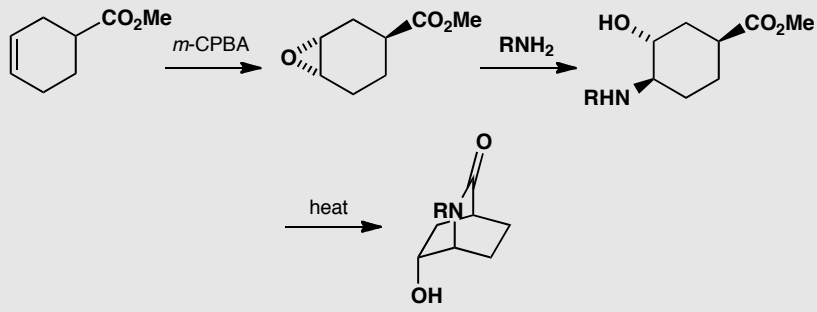
δ_C (ppm in $CDCl_3$) 62, 64, 122, 125, 126, 127, 130, 136, and 148 (the last three are weak).

Problems for Chapter 32

32

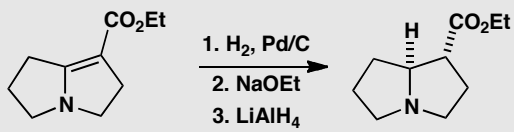
PROBLEM 1

Explain how the stereo- and regio-chemistry of these reactions are controlled. Why is the epoxidation only moderately diastereoselective, and why does the amine attack where it does?



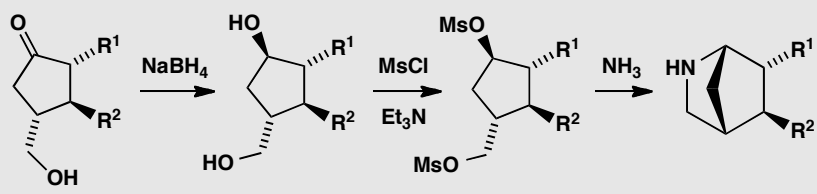
PROBLEM 2

Explain the stereochemistry of this sequence of reactions, noting the second step in particular.



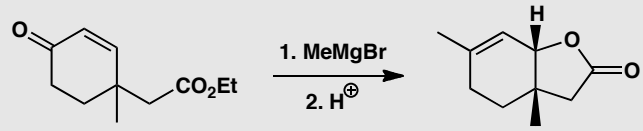
PROBLEM 3

Comment on the control over stereochemistry achieved in this sequence.



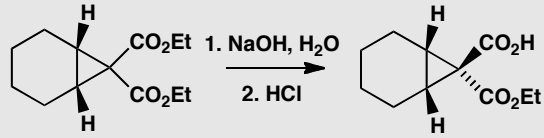
PROBLEM 4

What controls the stereochemistry of this product? You are advised to draw the mechanism first and then consider the stereochemistry.



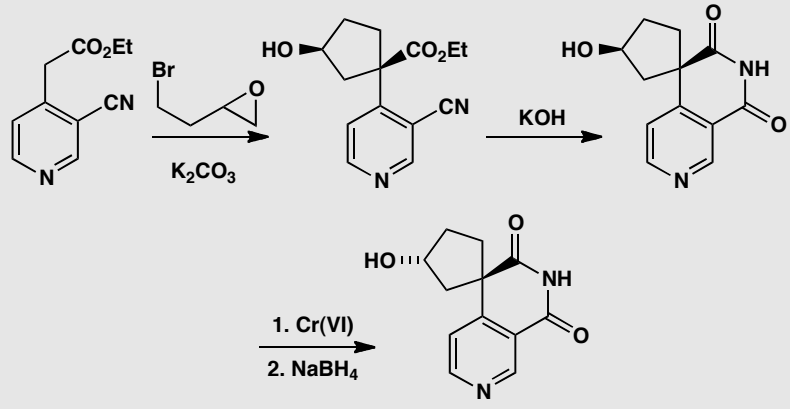
PROBLEM 5

Why is one of these esters more reactive than the other?



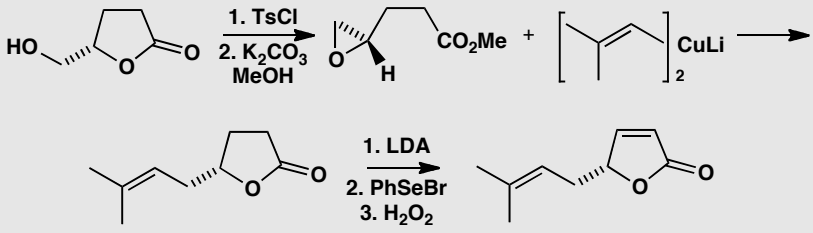
PROBLEM 6

Explain the stereoselectivity in these reactions.



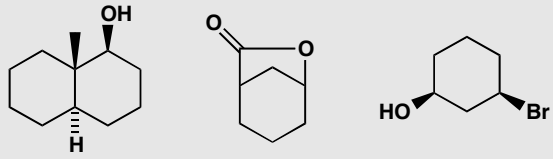
PROBLEM 7

The synthesis of a starting material used in chapter 32 (p. 834) is a good example of how cyclic compounds can be used in a simple way to control stereochemistry. Draw mechanisms for each reaction and explain the stereochemistry.



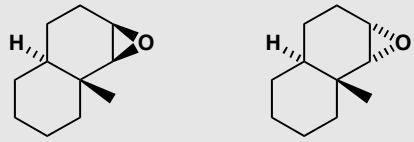
PROBLEM 8

Draw conformational drawings for these compounds. State in each case why the substituents have the positions you give. To what extent could you confirm your predictions experimentally?



PROBLEM 9

Predict which products would be formed on opening these epoxides with a nucleophile, say cyanide ion.

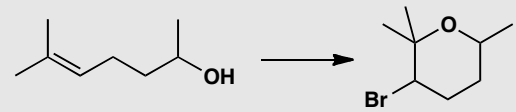


PROBLEM 10

These two sugar analogues are part structures of two compounds used to treat poultry diseases. Which conformation will they prefer?

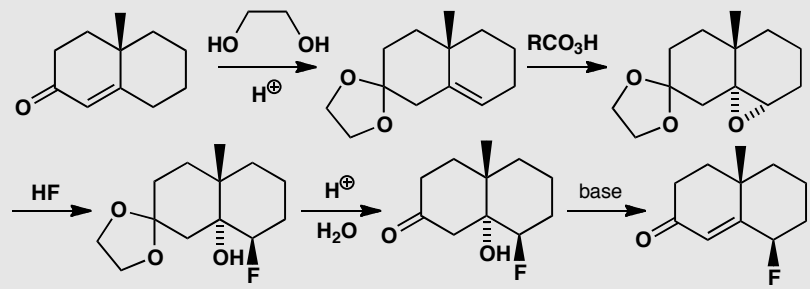
PROBLEM 11

Suggest a mechanism for the following reaction. The product has the following signals in its 1H NMR spectrum: δ_H 3.9 (1H, ddq, *J* 12, 4, 7) and 4.3 (1H, dd, *J* 11, 3). What is the stereochemistry and conformation of the product?



PROBLEM 12

Revision problem. Give mechanisms for each step in this synthesis and explain any regio- or stereochemistry.

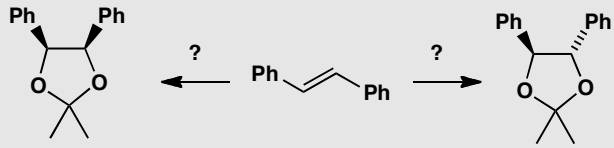


Problems for Chapter 33

33

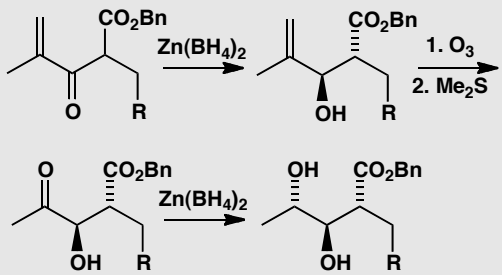
PROBLEM 1

How would you make each diastereoisomer of this product from the same alkene?



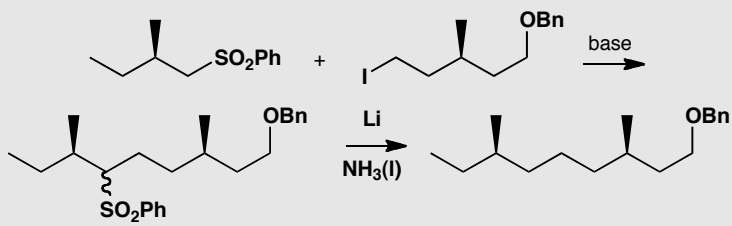
PROBLEM 2

Explain the stereochemistry shown in this sequence of reactions.



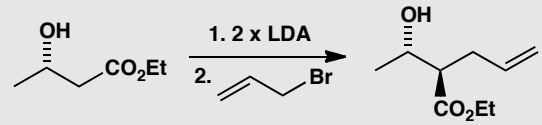
PROBLEM 3

How is the relative stereochemistry of this product controlled? Why was this method chosen?



PROBLEM 4

When this hydroxy-ester is treated with a two-fold excess of LDA and then alkylated, one diastereoisomer of the product predominates. Why?

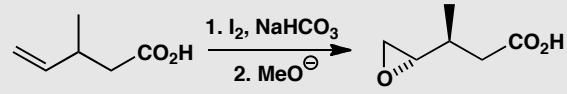


PROBLEM 5

Explain the stereochemical control in this reaction, drawing all the intermediates.

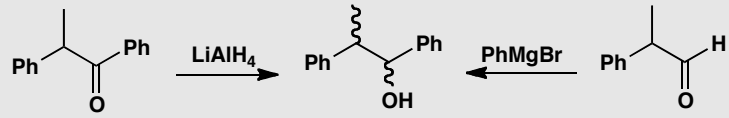
PROBLEM 6

Explain how the stereochemistry of this epoxide is controlled.



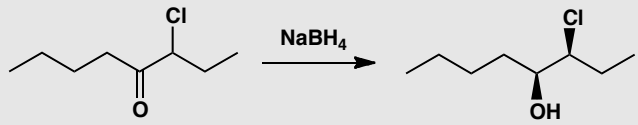
PROBLEM 7

Explain how these reactions give different isomers of the same product.



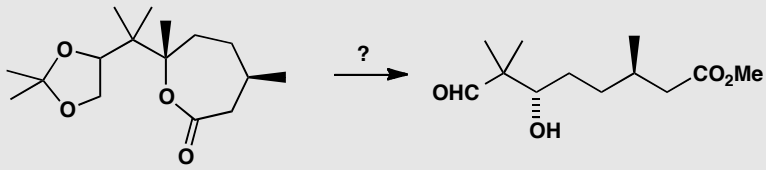
PROBLEM 8

Explain the stereoselectivity of this reaction. What isomer of the epoxide would be produced by treatment of the product with base?



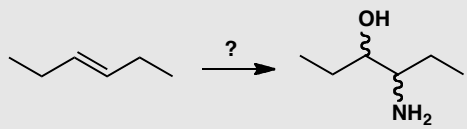
PROBLEM 9

How could this cyclic compound be used to produce the open-chain compound with correct relative stereochemistry?



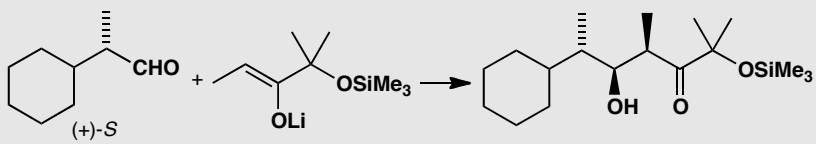
PROBLEM 10

How would you transform this alkene stereoselectively into either of the diastereoisomers of the amino alcohol?



PROBLEM 11

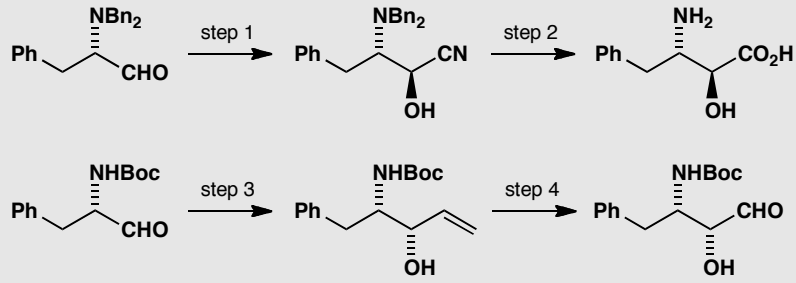
Explain the formation of essentially one stereoisomer in this reaction.



PROBLEM 12

The following sequences show parts of the syntheses of two different HIV protease inhibitors. What reagents are required for steps 1-4? (For steps 1 and 3,

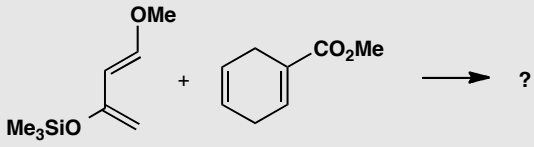
consider carefully how the stereochemistry of the product might be controlled.)



Problems for Chapter 34

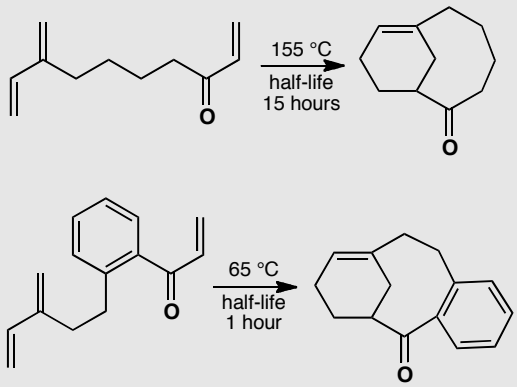
PROBLEM 1

Predict the structure of the product of this Diels-Alder reaction.



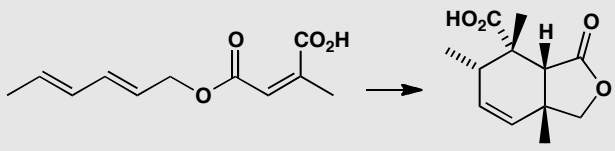
PROBLEM 2

Comment on the difference in rate between these two reactions.



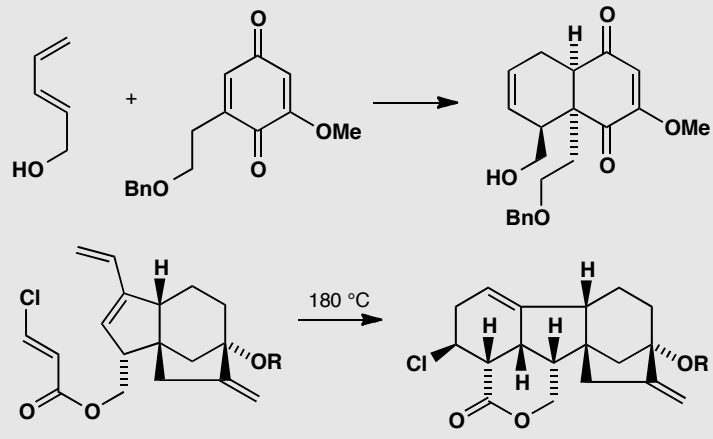
PROBLEM 3

Justify the stereoselectivity in this intramolecular Diels-Alder reaction.



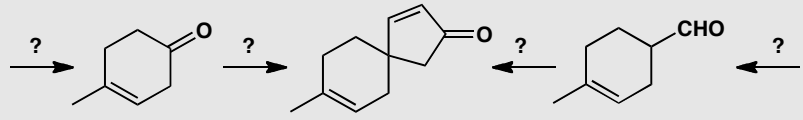
PROBLEM 4

Explain the formation of single adducts in these reactions.



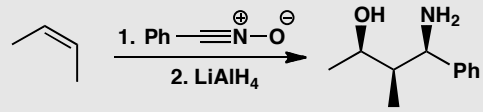
PROBLEM 5

Suggest two syntheses of this spirocyclic ketone from the starting materials shown. Neither starting material is available.



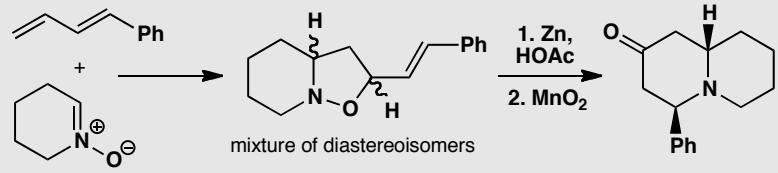
PROBLEM 6

Draw mechanisms for these reactions and explain the stereochemistry.



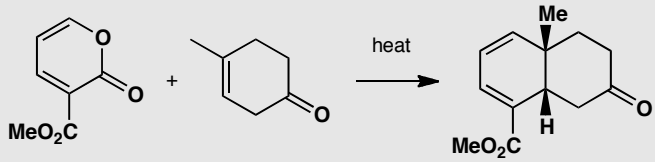
PROBLEM 7

Give mechanisms for these reactions and explain the regio- and stereochemical control (or lack of it!). [Note that MnO_2 oxidises allylic alcohols to enones]



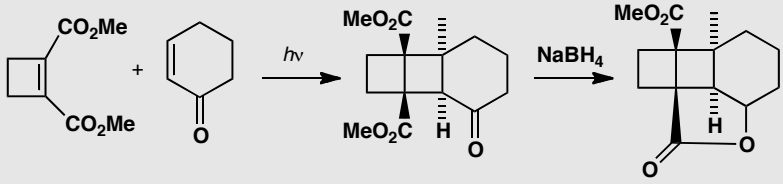
PROBLEM 8

Suggest a mechanism for this reaction and explain the stereo- and regiochemistry.



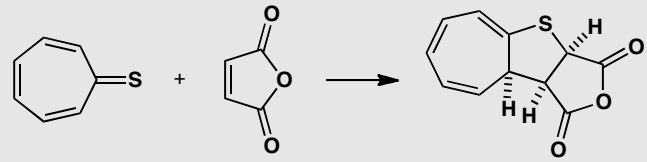
PROBLEM 9

Photochemical cycloaddition of these two compounds is claimed to give the diastereoisomer shown. The chemists who did this work claimed that the stereochemistryof the adduct is simply proved by its conversion to a lactone on reduction. Comment on the validity of this deduction and explain the stereochemistry of the cycloaddition.



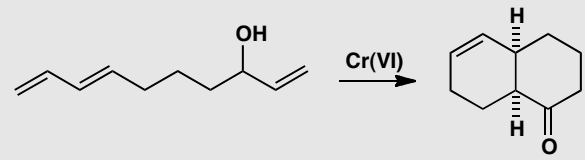
PROBLEM 10

Thioketones, with a C=S bond, are not usually stable. However, this thioketone is quite stable and undergoes reaction with maleic anhydride to give an addition product. Comment on the stability of the thioketone, the mechanism of the reaction, and the stereochemistry of the product.



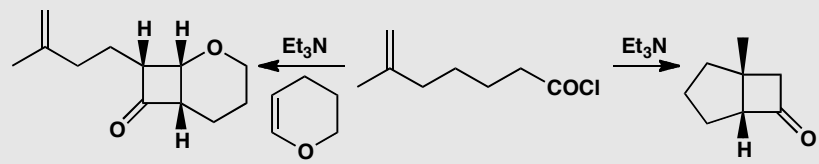
PROBLEM 11

This unsaturated alcohol is perfectly stable until it is oxidised with Cr(VI): it then cyclises to the product shown. Explain.



PROBLEM 12

Give mechanisms for these reactions, explaining the stereochemistry.

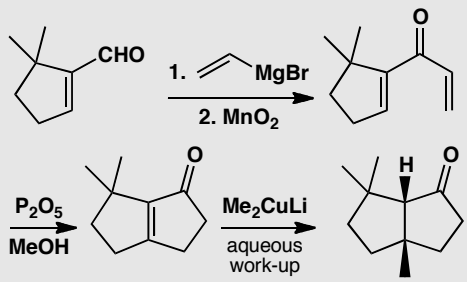


Problems for Chapter 35

35

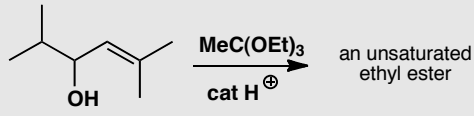
PROBLEM 1

Give mechanisms for these steps, commenting on the regioselectivity of the pericyclic step and the different regioselectivity of the two metals.



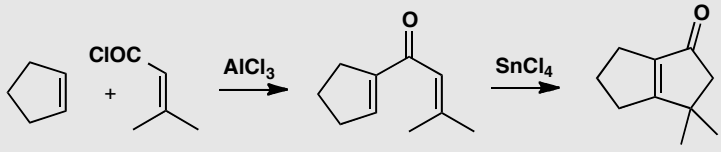
PROBLEM 2

Predict the product of this reaction.



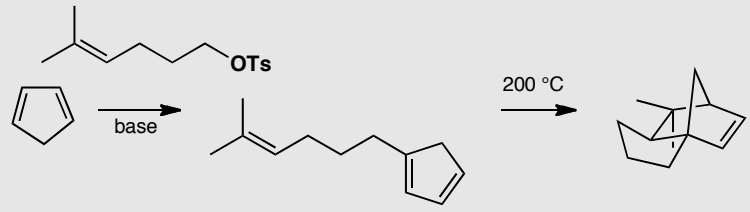
PROBLEM 3

Give mechanisms for this alternative synthesis of two fused five-membered rings.



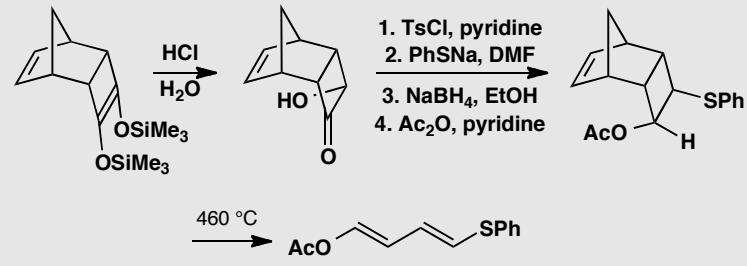
PROBLEM 4

Explain what is going on here.



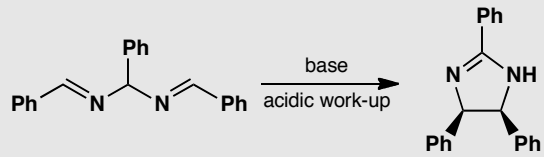
PROBLEM 5

A tricyclic hydroxyketone was made by hydrolysis of a *bis* silyl ether. Further reaction gave a new compound. Explain these reactions including the stereochemistry. The diene has the proton NMR spectum: δ_H 6.06 (1H, dd, *J* 10.3, 12.1), 6.23 (1H, dd, *J* 10.3, 14.7), 6.31 (1H, d, *J* 14.7), and 7.32 (1H, d, *J* 12.1). Does this agree with the structure given?



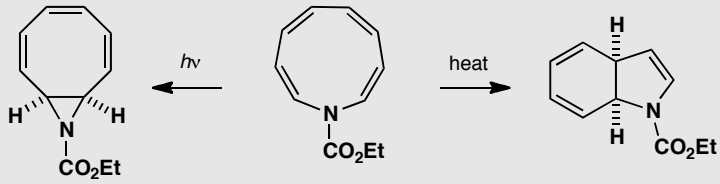
PROBLEM 6

Treatment of this imine with base followed by an acidic work-up gives a cyclic product with two phenyl groups *cis* to one another. Why is this?



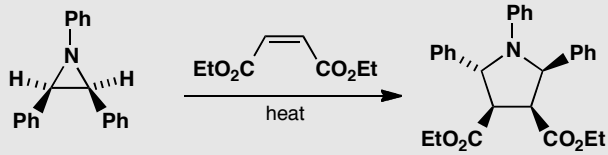
PROBLEM 7

This problem concerns the structure and chemistry of an unsaturated nine-membered ring. Comment on the structure. Explain its different behaviour under thermal or photochemical conditions.



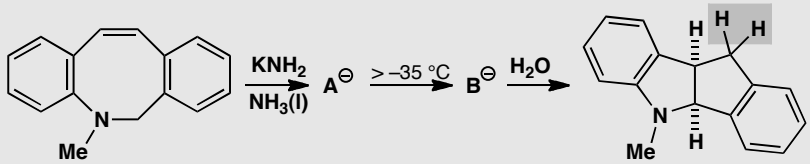
PROBLEM 8

Propose a mechanism for this reaction that accounts for the stereochemistry of the product.



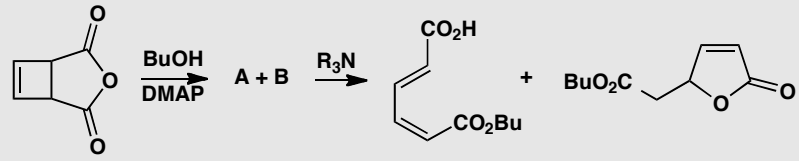
PROBLEM 9

Treatment of this amine with base at low temperature gives an unstable anion that isomerizes to another anion above –35 °C. Aqueous work-up gives a bicyclic amine. What are the two anions? Explain the stereochemistry of the product. In the NMR spectrum of the product the two protons in the grey box appear as an ABX system with J_{AB} 15.4 Hz. Comment.



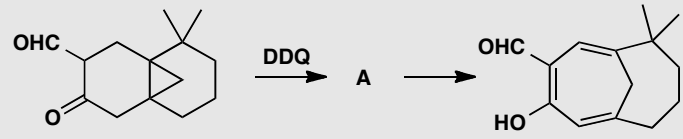
PROBLEM 10

How would you make the starting material for these reactions? Treatment of the anhydride with butanol gives an ester that in turn gives two indeparable compounds on heating. On treatment with an amine, an easily separable mixture of an acidic and a neutral compound is formed. What are the components of the first mixture and how are they formed?



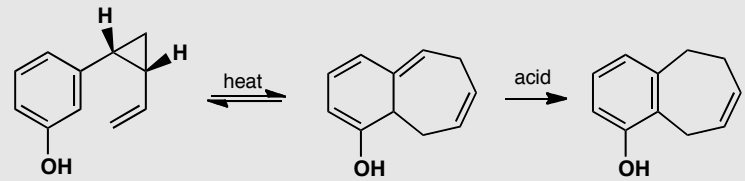
PROBLEM 11

Treatment of this keto-aldehyde (which exists largely as an enol) with the oxidizing agent DDQ (a quinone—see p. 764) gives an unstable compound that turns into the product shown. Explain the reactions and comment on the stereochemistry.



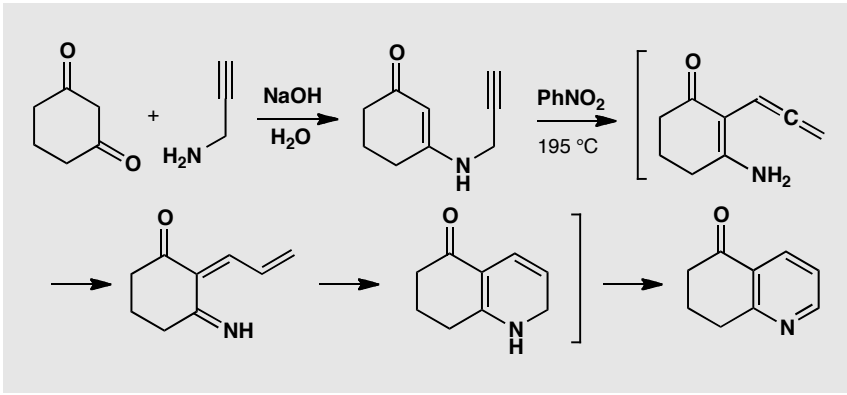
PROBLEM 12

Explain the following observations. Heating this phenol brings it into rapid equilibrium with a bicyclic compound that does not spontaneously give the final product unless treated with acid.



PROBLEM 13

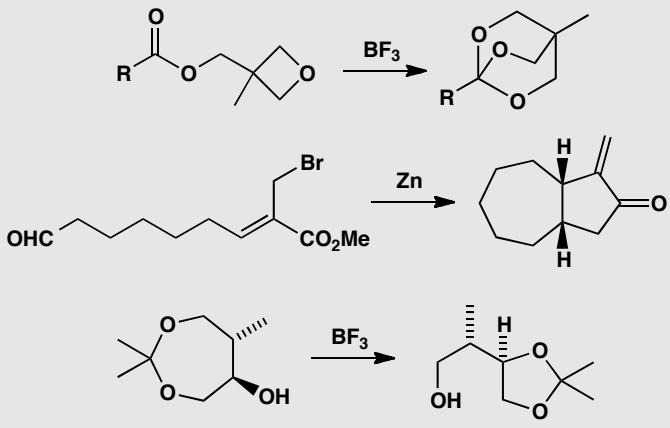
Treatment of cyclohexa-1,3-dione with this acetylenic amine gives a stable enamine in good yield. Refluxing the enamine in nitrobenzene gives a pyridine after a remarkable series of reactions. Fill in the details, give mechanisms for the reaction, structures for the intermediates, and suitable explanations for each pericyclic step. A mechanism is not required for the last step as nitrobenzene simply acts as an oxidant.


O
O
+
H2N
NaOH
H2O
O
N
H
PhNO2
195 °C
O
C
NH2
O
NH
O
N
H
O
N

Problems for Chapter 36

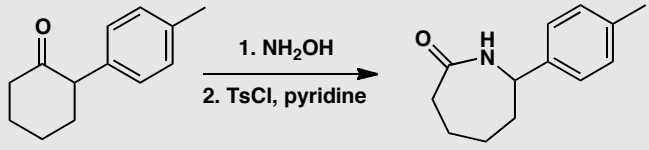
PROBLEM 1

Rearrangements by numbers: just draw a mechanism for each reaction.



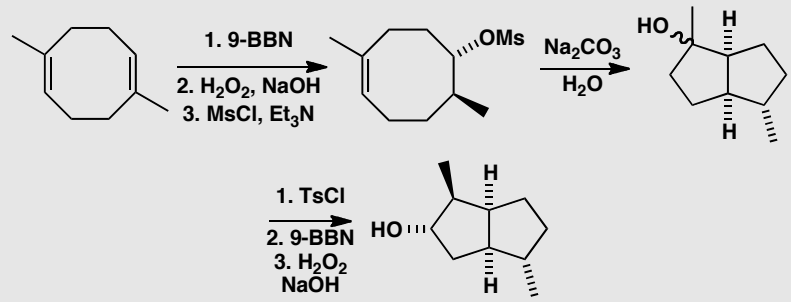
PROBLEM 2

Explain this series of reactions.



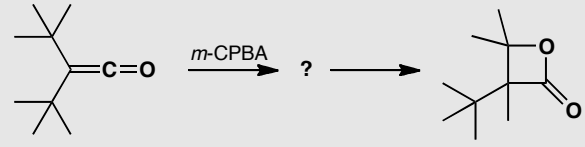
PROBLEM 3

Draw mechanisms for the reactions and structures for the intermediates. Explain the stereochemistry, especially of the reactions involving boron. Why was 9-BBN chosen as the hydroborating agent?



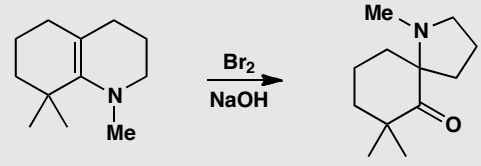
PROBLEM 4

It is very difficult to prepare three-membered lactones. One attempted preparation, by the epoxidation of di-*t*-butyl ketone, gave an unstable compound with an IR stretch at 1900 cm^{-1}. This compound decomposed rapidly to a four-membered ring lactone that could be securely identified. Do you think they made the three-membered ring?



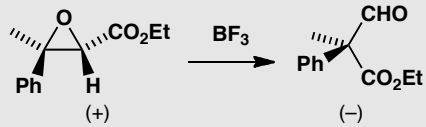
PROBLEM 5

Suggest a mechanism for this rearrangement.



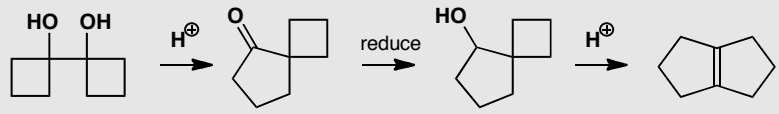
PROBLEM 6

A single enantiomer of the epoxide below rearranges with Lewis acid catalysis to give a single enantiomer of the product. Suggest a mechanism and comment on the stereochemistry.



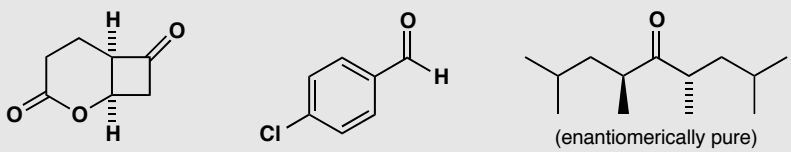
PROBLEM 7

The 'pinacol' dimer of cyclobutanone rearranges with expansion of one of the rings in acid solution to give a cyclopentanone fused *spiro* to the remaining four-membered ring. Draw a mechanism for this reaction. Reduction of the ketone gives an alcohol that rearranges to a bicyclic alkene also in acid. Suggest a mechanism for this reaction and suggest why the rearrangements happen.



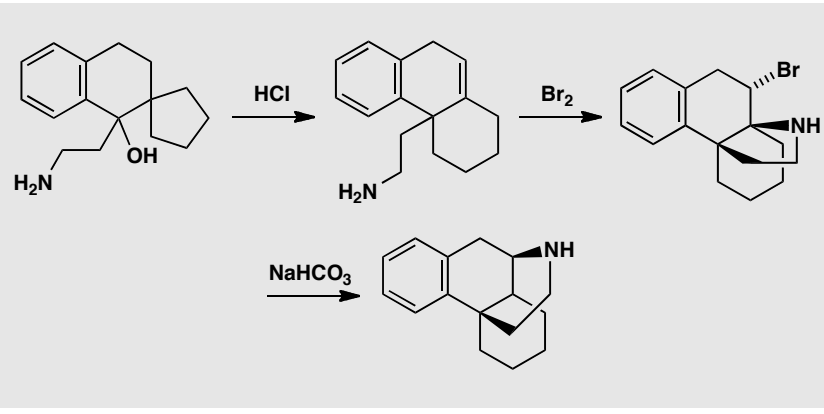
PROBLEM 8

Give the products of Baeyer-Villiger rearrangements on these compounds, with reasons.



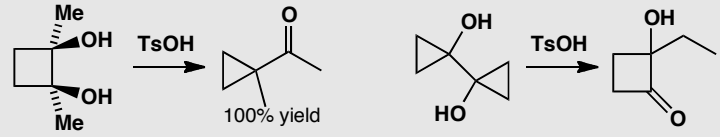
PROBLEM 9

Suggest mechanisms for these rearrangements, explaining the stereochemistry in the second reaction.



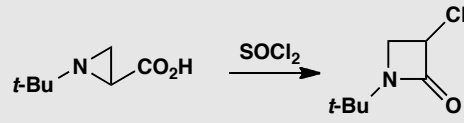
PROBLEM 10

Give mechanisms for these reactions that explain any selectivity.



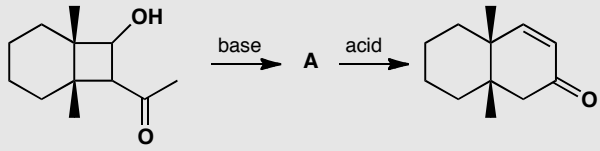
PROBLEM 11

Attempts to produce the acid chloride from this unusual amino acid by treatment with $SOCl_2$ gave instead a β-lactam. What has happened?



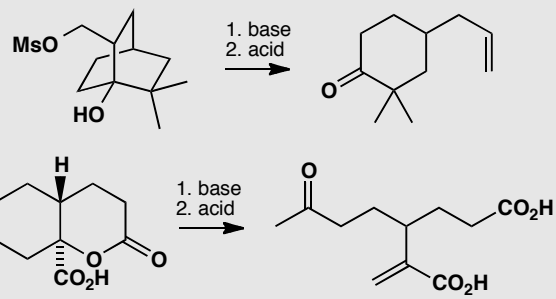
PROBLEM 12

Treatment of this hydroxy-ketone with base followed by acid gives the enone shown. What is the structure of intermediate **A**, how is it formed, and what is the mechanism of its conversion to the final product?



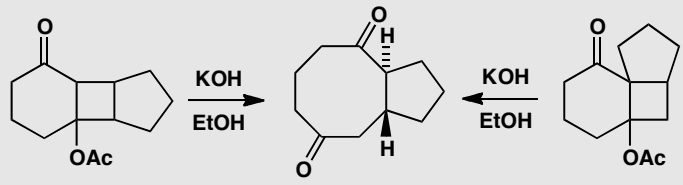
PROBLEM 13

Just to check your skill at finding fragmentations by numbers, draw the mechanism for each of these one-step fragmentations in basic solution with acidic work-up.



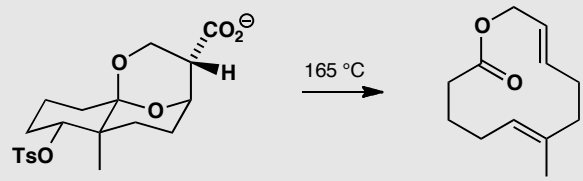
PROBLEM 14

Explain why both these tricyclic ketones fragment to the same diastereoisomer of the same cyclo-octane.



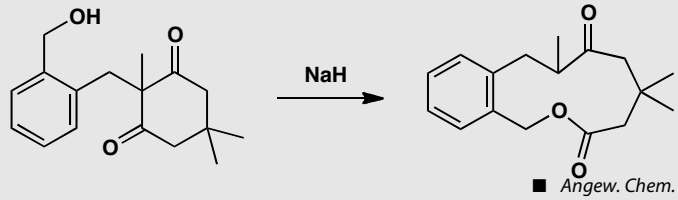
PROBLEM 15

Suggest a mechanism for this fragmentation and explain the stereochemistry of the alkenes in the product. This is a tricky problem, but find the mechanism and the stereochemistry will follow.



PROBLEM 16

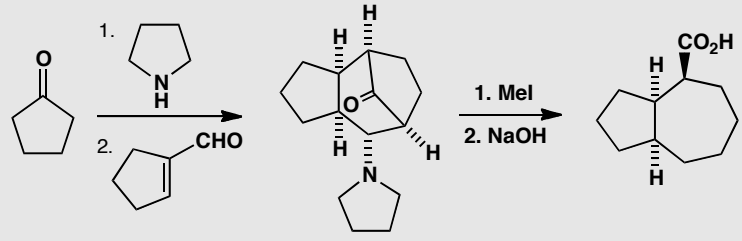
Suggest a mechanism for this reaction and explain why the molecule is prepared to abandon a stable six-membered ring for a larger ring.



■ *Angew. Chem. Int. Ed. Engl.*, 1979, **18**, 634, 636.
■ *Angew. Chem. Int. Ed. Engl.*, 1979, **18**, 634, 636..

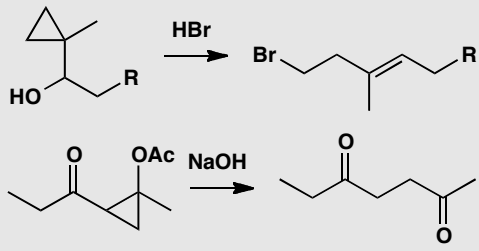
PROBLEM 17

Give mechanisms for these reactions, commenting on the fragmentation.



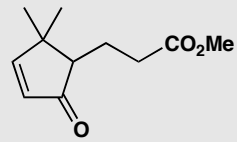
PROBLEM 18

Suggest mechanisms for these reactions, explaining the alkene geometry in the first case. Do you consider that they are fragmentations?



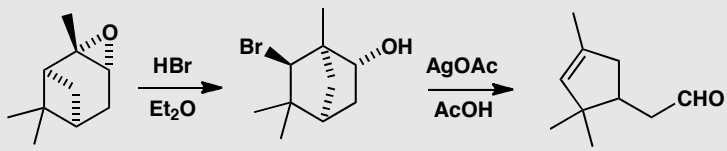
PROBLEM 19

What steps would be necessary to carry out an Eschenmoser fragmentation on this ketone, and what products would be formed?



PROBLEM 20

Revision content. Suggest mechanisms for these reactions to explain the stereochemistry.

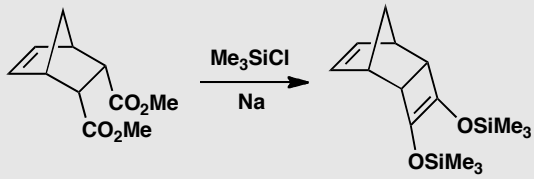


Problems for Chapter 37

37

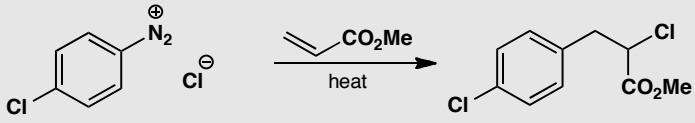
PROBLEM 1

Give a mechanism for the formation of this silylated ene-diol and explain why the Me_3SiCl is necessary.



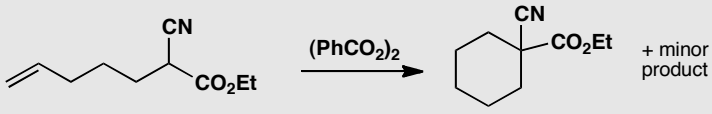
PROBLEM 2

Heating the diazonium salt below in the presence of methyl acrylate gives a reasonable yield of a chloroacid. Why is this unlikely to be nucleophilic aromatic substitution by the S_N1 mechanism (p. 520)? Suggest an alternative mechanism that explains the regioselectivity.



PROBLEM 3

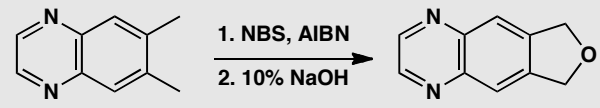
Suggest a mechanism for this reaction and comment on the ring size formed. What is the minor product likely to be?



PROBLEM 4

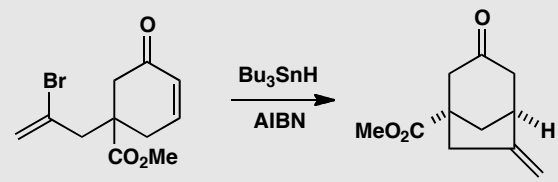
Treatment of this aromatic heterocycle with NBS (*N*-bromosuccinimide) and AIBN gives mainly one product but this is difficult to purify from minor impurities

containing one or three bromine atoms. Further treatment with 10% aqueous NaOH gives one easily separable product in modest yield (50%). What are the mechanisms for the reactions?



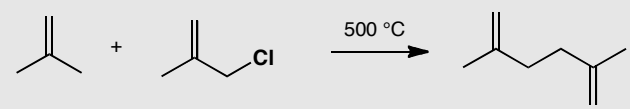
PROBLEM 5

Propose a mechanism for this reaction accounting for the selectivity. Include a conformational drawing of the product.



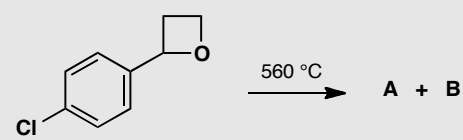
PROBLEM 6

An ICl process for the manufacture of the diene used to make pyrethroid insecticides involved heating these compounds to 500 °C in a flow system. Propose a radical chain mechanism for the reaction.



PROBLEM 7

Heating this compound to 560 °C gives two products with the spectroscopic data shown below. What are they and how are they formed?

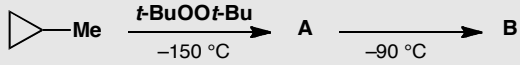


A has IR 1640 cm^{-1}; *m/z* 138 (100%) and 140 (33%), δ_H (ppm) 7.1 (4H, s), 6.5 (1H, dd,

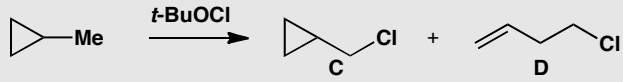
J 17, 11 Hz), 5.5 (1H, dd, *J* 17, 2 Hz), and 5.1 (1H, dd, *J* 11, 2 Hz).
B has IR 1700 cm^{-1}; *m/z* 111 (45%), 113 (15%), 139 (60%), 140 (100%), 141 (20%), and 142 (33%), δ_H (ppm) 9.9 (1H, s), 7.75 (2H, d, *J* 9 Hz), and 7.43 (2H, d, *J* 9 Hz).

PROBLEM 8

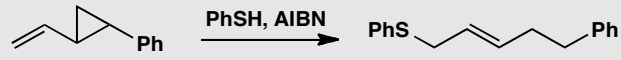
Treatment of methylcyclopropane with peroxides at very low temperature (–150°C) gives an unstable species whose ESR spectrum consists of a triplet with coupling of 20.7 gauss and fine splitting showing dtt coupling of 2.0, 2.6, and 3.0 gauss. Warming to a mere –90 °C gives a new species whose ESR spectrum consists of a triplet of triplets with coupling 22.2 and 28.5 gauss and fine splitting showing small ddd coupling of less than 1 gauss.



If methylcyclopropane is treated with *t*-BuOCl, various products are obtained but the two major products are **C** and **D**. At lower temperatures more of **C** is formed and at higher temperatures more of **D**.

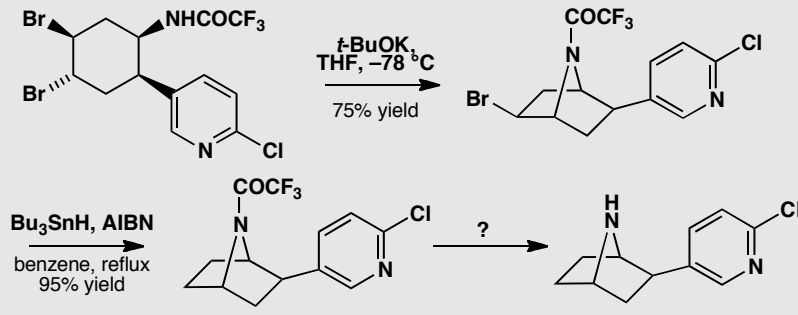


Treatment of the more substituted cyclopropane below with PhSH and AIBN gives a single product in quantitative yield. Account for all these reactions, identifying **A** and **B** and explaining the differences between the various experiments.



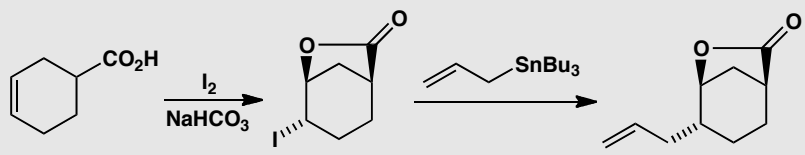
PROBLEM 9

The last few stages of Corey's epibatidine synthesis are shown here. Give mechanisms for the first two reactions and suggest a reagent for the last step.



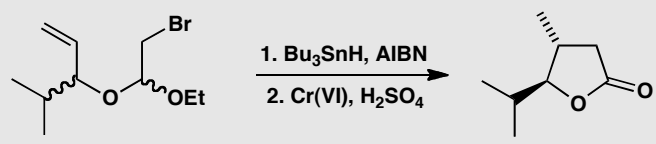
PROBLEM 10

How would you make the starting material for this sequence of reactions? Give a mechanism for the first reaction that explains its regio- and stereoselectivity. Your answer should include a conformational drawing of the product. What is the mechanism of the last step? Attempts to carry out this last step by iodine/lithium exchange and reaction with allyl bromide failed. Why? Why is the alternative shown here successful?



PROBLEM 11

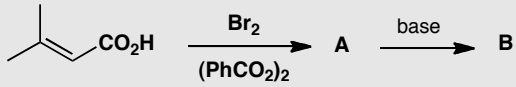
Suggest a mechanism for this reaction explaining why a mixture of diastereoisomers of the starting material gives a single diastereoisomer of the product. Is there any other form of selectivity?



PROBLEM 12

Reaction of this carboxylic acid ($C_5H_8O_2$) with bromine in the presence of

dibenzoyl peroxide gives an unstable compound **A** ($C_5H_6Br_2O_2$) that gives a stable compound **B** ($C_5H_5BrO_2$) on treatment with base. Compound **B** has IR 1735 and 1645 cm^{-1} and NMR δ_H 6.18 (1H, s), 5.00 (2H, s) and 4.18 (2H, s). What is the structure of the stable product **B**? Deduce the structure of the unstable compound **A** and mechanisms for the reactions.



Problems for Chapter 38

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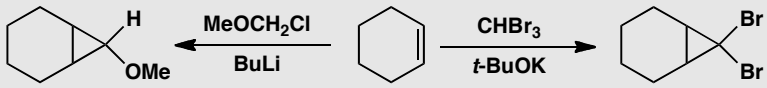
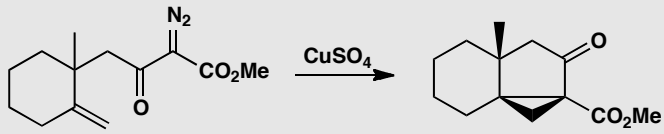
PROBLEM 1

Suggest mechanisms for these reactions.



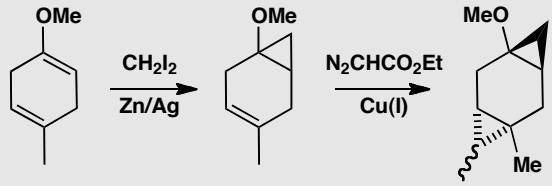
PROBLEM 2

Suggest a mechanism for this reaction and explain the stereochemistry.



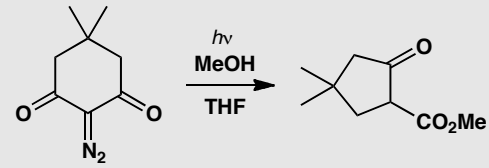
PROBLEM 3

Comment on the selectivity shown in these reactions.



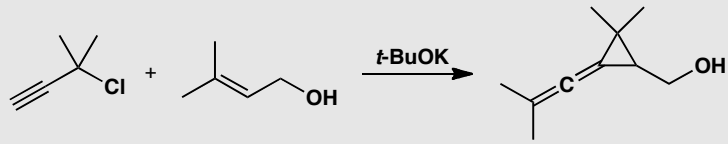
PROBLEM 4

Suggest a mechanism for this ring contraction.



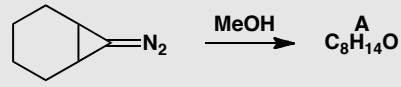
PROBLEM 5

Suggest a mechanism for the formation of this cyclopropane.

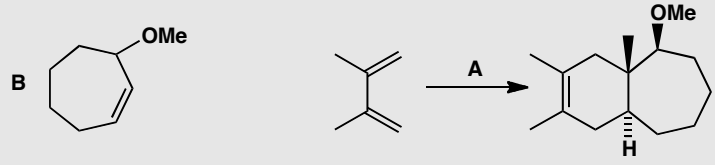


PROBLEM 6

Decomposition of this diazo compound in methanol gives an alkene **A** ($C_8H_{14}O$) whose NMR spectrum contains two signals in the alkene region: δ_H 3.50 (3H, s), 5.50 (1H, dd, *J* 17.9, 7.9), 5.80 (1H, ddd, *J* 17.9, 9.2, and 4.3), 4.20 (1H, m) and 1.3-2.7 (8H, m). What is its structure and geometry?



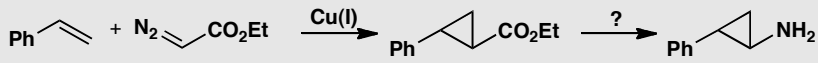
When you have done that, suggest a mechanism for the reaction using this extra information: Compound **A** is unstable and even at 20 °C isomerizes to **B**. If the diazo compound is decomposed in methanol containing a diene, compound **A** is trapped as the adduct shown. Account for all these reactions.



PROBLEM 7

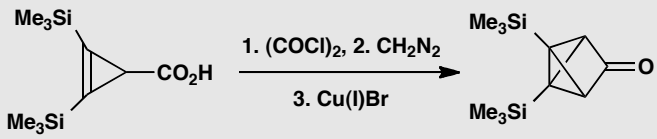
Give a mechanism for the formation of the three-membered ring in the first of

these reactions and suggest how the ester might be converted into the amine with retention of configuration



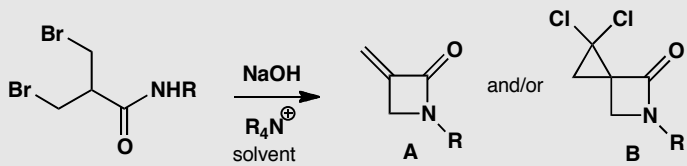
PROBLEM 8

Explain how this highly strained ketone is formed, albeit in very low yield, by these reactions. How would you attempt to make the starting material?



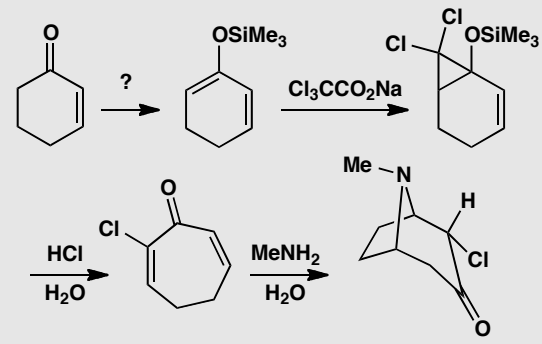
PROBLEM 9

Attempts to prepare compound **A** by phase-transfer catalysed cyclization required a solvent immiscible with water. When chloroform ($CHCl_3$) was used, compound **B** was formed instead and it was necessary to use the more toxic CCl_4 for success. What went wrong?



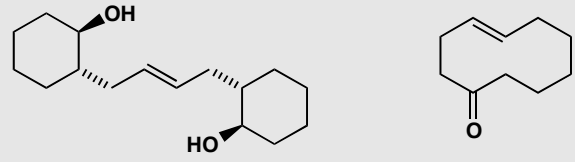
PROBLEM 10

Revision content. How would you carry out the first step in this sequence? Propose mechanisms for the remaining steps explaining any selectivity.



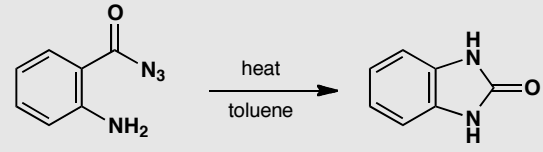
PROBLEM 11

How would you attempt to make these alkenes by metathesis?



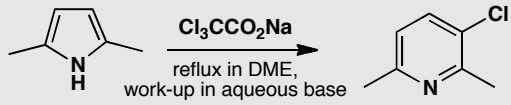
PROBLEM 12

Heating this acyl azide in dry toluene under reflux for three hours gives a 90% yield of a heterocycle. Suggest a mechanism, emphasizing the role of any reactive intermediates.



PROBLEM 13

Give mechanisms for the steps in this conversion of a five- into a six-membered aromatic heterocycle.


Cl3CCO2Na
reflux in DME,
work-up in aqueous base
N
H
Cl
N

Problems for Chapter 39

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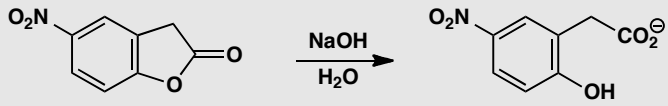
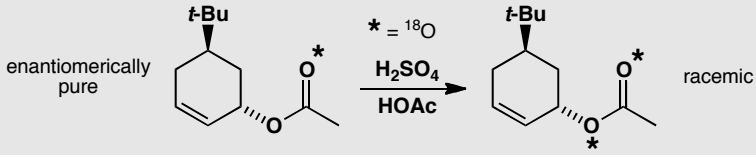
PROBLEM 1

Propose three fundamentally different mechanisms (other than variations of the same mechanism with different kinds of catalysis) for this reaction. How would (a) D labelling and (b) ^{18}O labelling help to distinguish the mechanisms? What other experiments would you carry out to rule out some of these mechanisms?



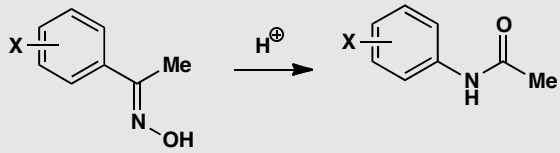
PROBLEM 2

Explain the stereochemistry and labelling pattern in this reaction.



PROBLEM 3

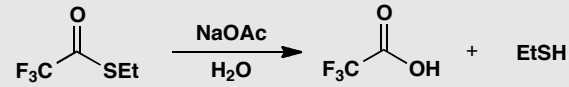
The Hammett ρ value for migrating aryl groups in the acid-catalysed Beckmann rearrangement is –2.0. What does that tell us about the rate-determining step?



PROBLEM 4

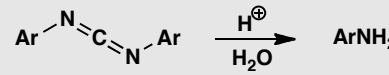
Between pH 2 and 7 the rate of hydrolysis of this ester is independent of pH. At pH 5 the rate is proportional to the concentration of acetate ion (AcO^-) in the buffer

solution and the reaction goes twice as fast in H_2O as in D_2O. Suggest a mechanism for the pH-independent hydrolysis. Above pH 7 the rate increases with pH. What kind of change is this?



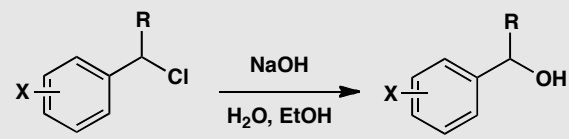
PROBLEM 5

In acid solution, the hydrolysis of this carbodiimide has a Hammett ρ value of –0.8. What mechanism might account for this?



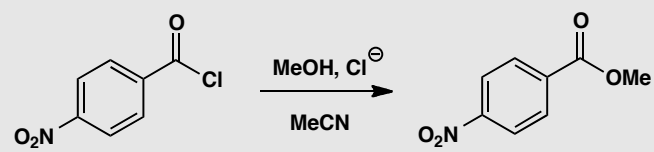
PROBLEM 6

Explain the difference between these Hammett ρ values by mechanisms for the two reactions. In both cases the ring marked with the substituent X is varied. When R = H, ρ = –0.3 but when R = Ph, ρ = –5.1.



PROBLEM 7

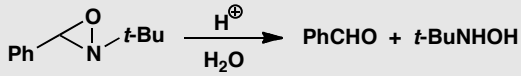
Explain how chloride catalyses this reaction.



PROBLEM 8

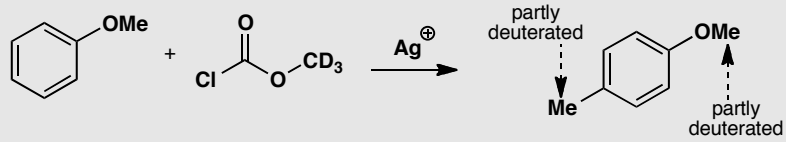
The hydrolysis of this oxaziridine in 0.1M sulfuric acid has $k(H_2O)/k(D_2O) = 0.7$ and

an entropy of activation of $\Delta S = -76$ J mol^{-1}K^{-1}. Suggest a mechanism.



PROBLEM 9

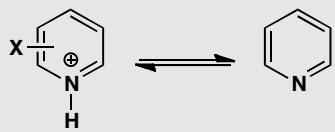
Explain how both methyl groups in the product of this reaction come to be labelled. If the starting material is reisolated at 50% reaction, its methyl group is also labelled.



PROBLEM 10

The pK_a values of some protonated pyridines are as follows:

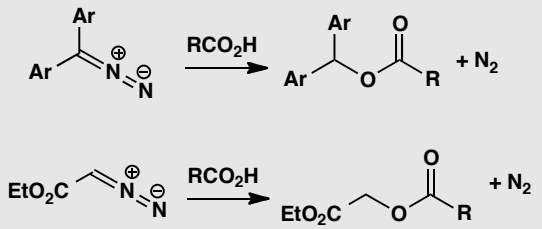
X	H	3-Cl	3-Me	4-Me	3-MeO	4-MeO	3-NO_2
pK_a	5.2	2.84	5.68	6.02	4.88	6.62	0.81



Can the Hammett correlation be applied to pyridines using the σ values for benzene? What equilibrium ρ value does it give and how do you interpret it? Why are no 2-substituted pyridines included in the list?

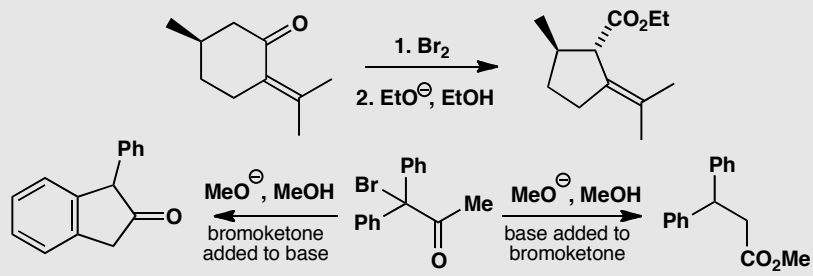
PROBLEM 11

These two reactions of diazo compounds with carboxylic acids give gaseous nitrogen and esters as products. In both cases the rate of reaction is proportional to [diazo compound][RCO_2H]. Use the data for each reaction to suggest mechanisms and comment on the difference between them.



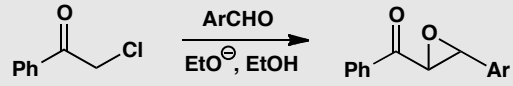
PROBLEM 12

Suggest mechanisms for these reactions and comment on their relevance to the Favorskii family of mechanisms.



PROBLEM 13

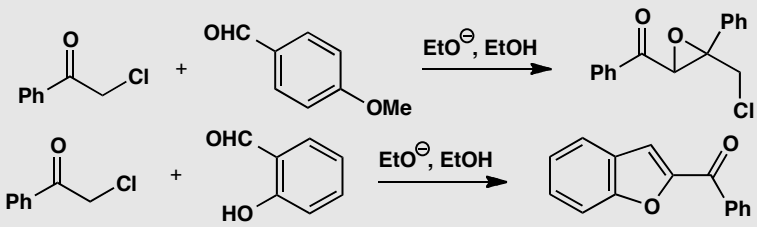
A typical Darzens reaction involes the base-catalysed formation of an epoxide from an α-haloketone and an aldehyde. Suggest a mechanism consistent with the data below.



(a) The rate expression is: rate = k_3[PhCOCH$_2$Cl][ArCHO][EtO$^-$]

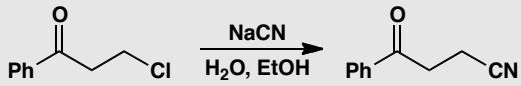
(b) When Ar is varied, the Hammett ρ value is +2.5.

(c) The following attempted Darzens reactions produced unexpected results:



PROBLEM 14

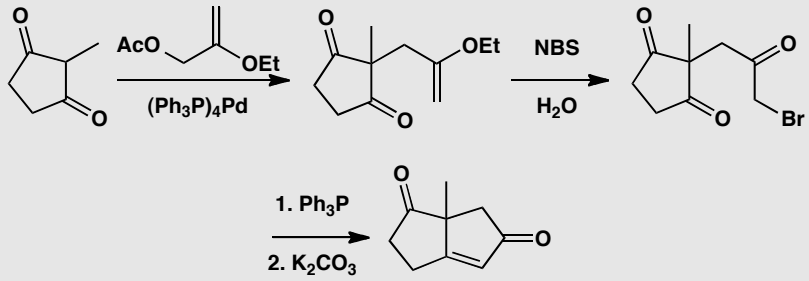
If you believed that this reaction went by elimination followed by conjugate addition, what experiments would you carry out to try and prove that the enone is an intermediate?



Problems for Chapter 40

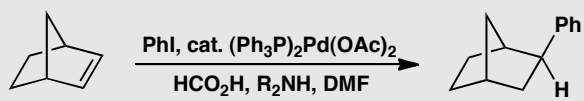
PROBLEM 1

Suggest mechanisms for these reactions, explaining the role of palladium in the first step.



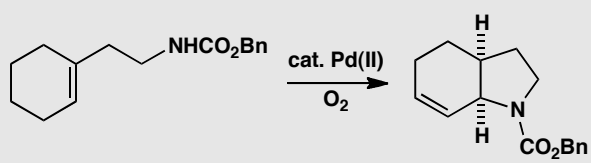
PROBLEM 2

This Heck-style reaction does not lead to regeneration of the alkene. Why not? What is the purpose of the formic acid (HCO_2H) in the reaction mixture?



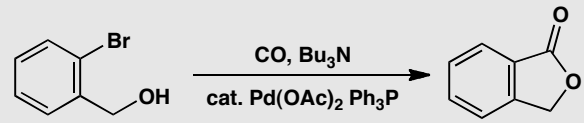
PROBLEM 3

Cyclization of this unsaturated amine with catalytic Pd(II) under an atmosphere of oxygen gives a cyclic unsaturated amine in 95% yield. How does the reaction work? Why is the atmosphere of oxygen necessary? Explain the stereochemistry and regiochemistry of the reaction. How would you remove the CO_2Bn group from the product?



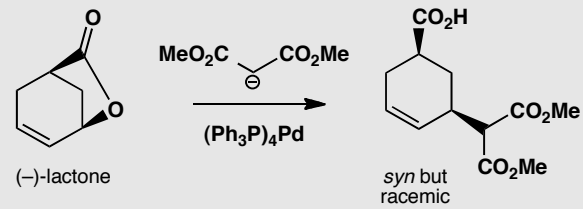
PROBLEM 4

Suggest a mechanism for this lactone synthesis.



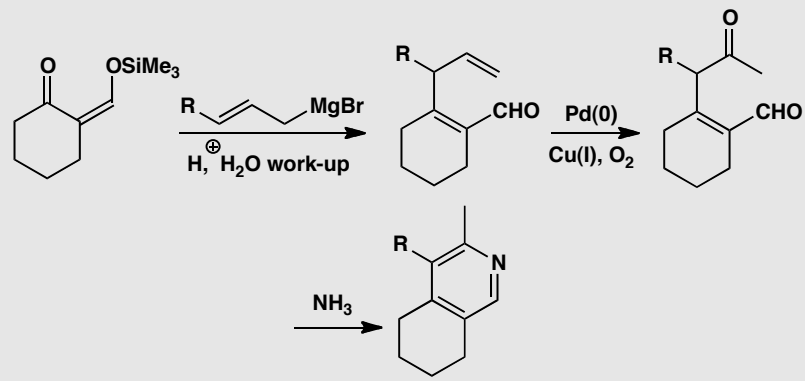
PROBLEM 5

Explain why enantiomerically pure lactone gives *syn* but racemic product in this palladium-catalysed reaction.



PROBLEM 6

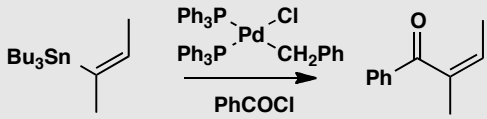
Explain the reactions in this sequence, commenting on the regioselectivity of the organometallic steps.



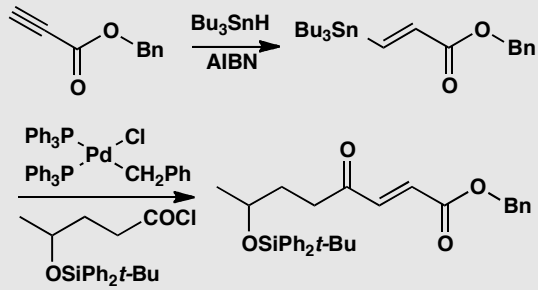
PROBLEM 7

Give a mechanism for this carbonylation reaction. Comment on the

stereochemistry and explain why the yield is higher if the reaction is carried out under a carbon monoxide atmosphere.

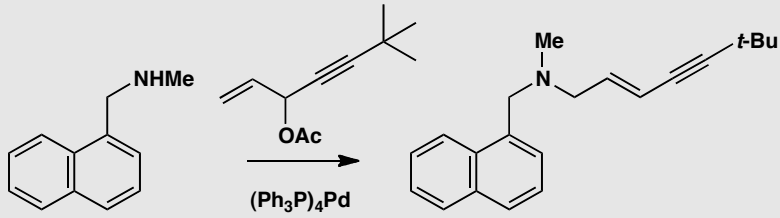


Hence explain this synthesis of part of the antifungal compound pyrenophorin.



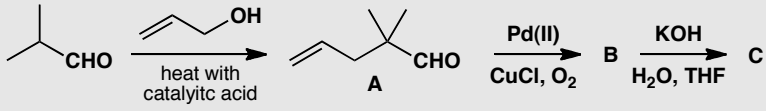
PROBLEM 8

The synthesis of an antifungal drug was completed by this palladium-catalysed reaction. Give a mechanism, explaining the regio- and stereochemistry.



PROBLEM 9

Work out the structures of the compounds in this sequence and suggest mechanisms for the reactions, explaining any selectivity.



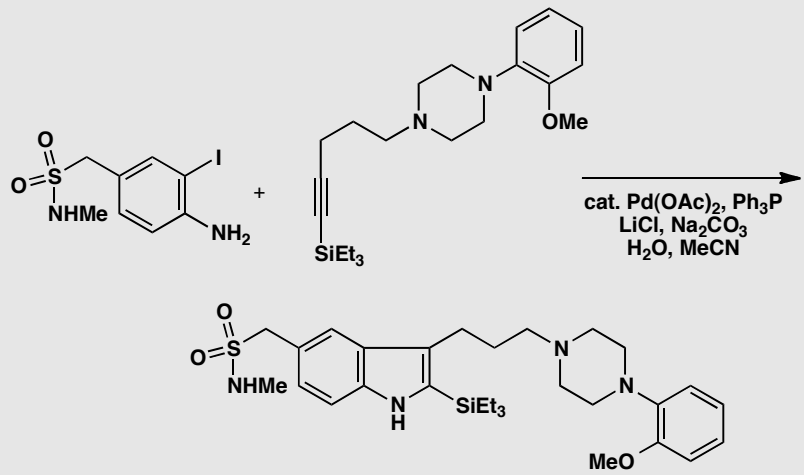
B has IR: 1730, 1710 cm^{-1}, δ_H 9.4 (1H, s), 2.6 (2H, s), 2.0 (3H, s), and 1.0 (6H, s).

C has IR: 1710 cm^{-1}, δ_H 7.3 (1H, d, *J* 5.5 Hz), 6.8 (1H, d, *J* 5.5 Hz), 2.1 (2H, s), and 1.15 (6H, s).

■ This is the Larock indole synthesis (R. C.Larock and E. K. Yum, *J. Am. Chem. Soc.*, 1991, **113**, 6689) and its usedin the synthesis of Avitriptan is described in P. D. Brod fuehrer *et al*, *J. Org. Chem.*, 1997, **62**, 9192).

PROBLEM 10

A synthesis of the Bristol-Meyers Squibb anti-migraine drug Avitriptan (a 5-HT receptor antagonist) involves this palladium-catalysed indole synthesis. Suggest a mechanism and comment on the regioselectivity of the alkyne attachment.

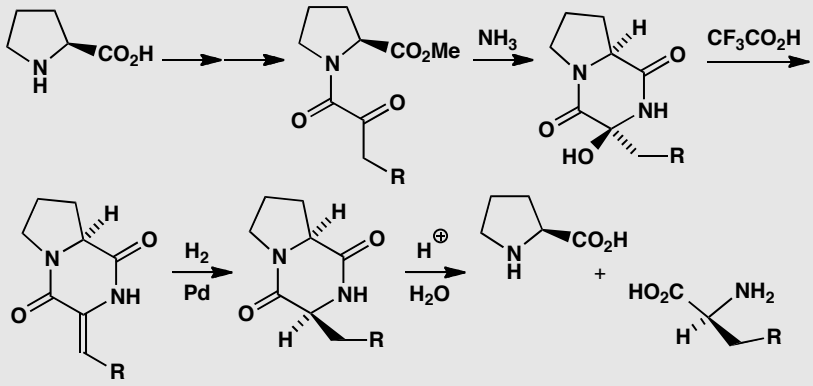


Problems for Chapter 41

41

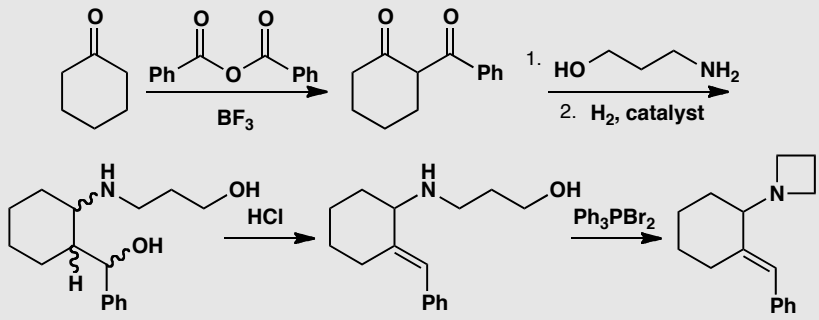
PROBLEM 1

Explain how this synthesis of amino acids, starting with natural proline, works. Explain the stereoselectivity of each step after the first.



PROBLEM 2

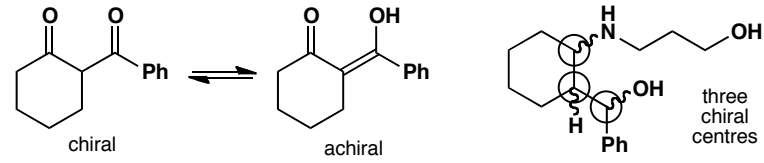
This is a synthesis of the racemic drug tazodolene. If the enantiomers of the drug are to be evaluated for biological activity, they must be separated. At which stage would you recommend separating the enantiomers and how would you do it?



First steps in planning an asymmetric synthesis by resolution.

Suggested solution

You meed to ask: which is the first chiral intermediate? Can it be conveniently resolved? Will the chirality survive subsequent steps? The first intermediate is chiral but it enolizes very readily and the enol is achiral, so that's no good. The second intermediate is chiral but it has three chiral centres and these are evidently not controlled. We would have to separate the diastereoisomers before resolution and that would be a waste of time and material since all of them give the next intermediate anyway.

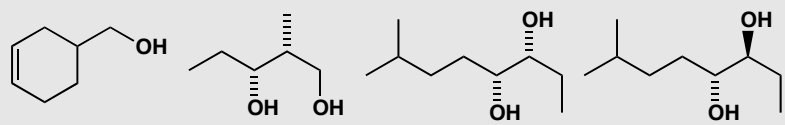


The next intermediate, the amino alcohol is ideal: it has only one chiral centre and that is not affected by the last reaction. It has two 'handles' for resolution – the amine and the alcohol. We might make a salt with tartaric acid or an ester of the alcohol with some chiral acid. Alternatively we could resolve tazadolene itself: it still has an amino group and we could form a salt with a suitable acid.

■ This synthesis is from the Up company and is in only the pat literature (*Chem. Abstr.*, 1984, **1** 6311.

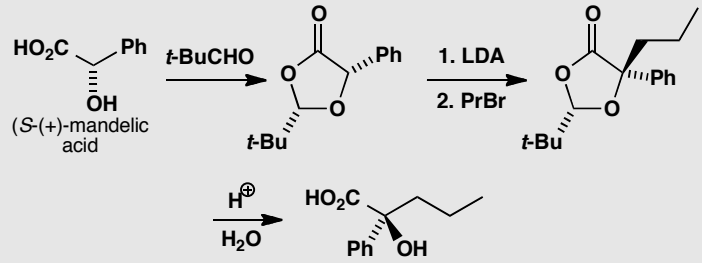
PROBLEM 3

How would you make enantiomerically enriched samples of these compounds (either enantiomer)?



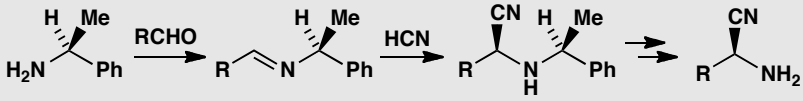
PROBLEM 4

In the following reaction sequence, the stereochemistry of mandelic acid is transmitted to a new hydroxy-acid by stereochemically controlled reactions. Give mechanisms for each reaction and state whether it is stereospecific or stereoselective. Offer some rationalization for the creation of new stereogenic centres in the first and last reactions.



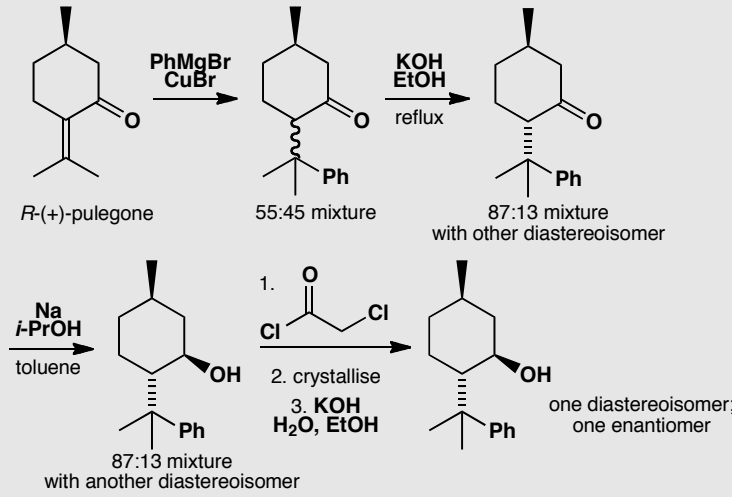
PROBLEM 5

This reaction squence can be used to make enantiomerically enriched amino acids. Which compound is the origin of the chirality and how is it made? Suggest why this particular enantiomer of the product amino acid might be formed. Suggest reagents for the last stages of the process. Would the enatiomerically enriched starting material be recovered?



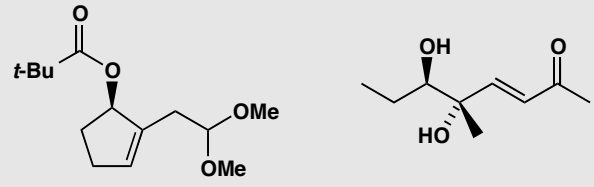
PROBLEM 6

Explain the stereochemistry and mechanism in the synthesis of the chiral auxiliary 8-phenylmenthol from (+)-pulegone. After the reaction with Na in *i*-PrOH, what is the minor (13%) component of the mixture?



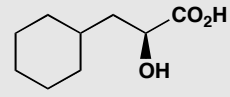
PROBLEM 7

Suggest syntheses for single enantiomers of these compounds.



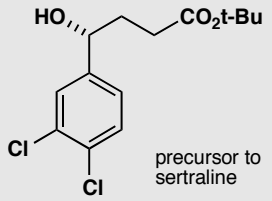
PROBLEM 8

This compound is a precirsor to a Novartis drug used for the control of inflammation. How can it be made from a chiral pool starting material?

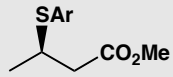


PROBLEM 9

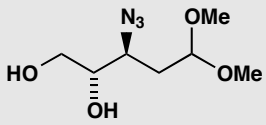
Propose catalytic methods for the asymmetric synthesis of these three precursors to drug molecules.



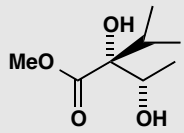
precursor to sertraline



precursor to MK-0507



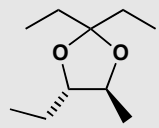
precursor to AZT



precursor to indicine

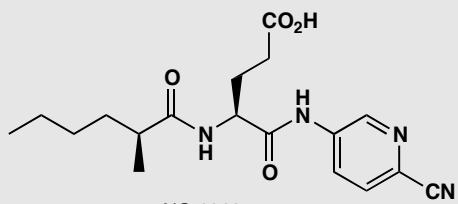
PROBLEM 10

The triatomine bug which causes Chagas' disease can be trapped by using synthetic samples of its communication pheromone, which consists of a 4:1 mixture of the enantiomers of this heterocycle. How would you synthesise the required mixture of enantiomers? Why would the other diastereoisomer of this compound be more of a challenge to make?



PROBLEM 11

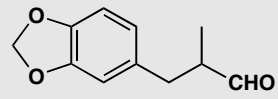
This compound was developed by the Nutrasweet company as an artifical sweetener. Propose a strategy for its synthesis. Would your proposed approach still be suitable if the compound had turned out to be a successful product, required in muti-tonne quantities?



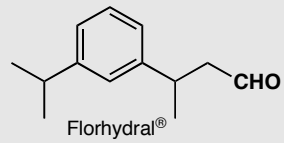
NC-00637

PROBLEM 12

The two aldehydes below are valuable products in the perfumery industry (Tropional® is a component of Issey Miyake's *L'Eau d'Issey* and Florhydral® is a component of *Allure* by Chanel). How would you make them as single enantiomers?



Tropional®



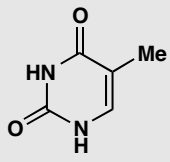
Florhydral®

Problems for Chapter 42

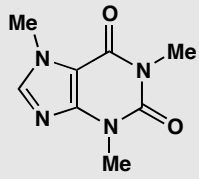
42

PROBLEM 1

Do you consider that thymine and caffeine are aromatic compounds? Explain.



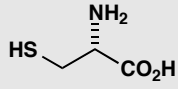
thymine



caffeine

PROBLEM 2

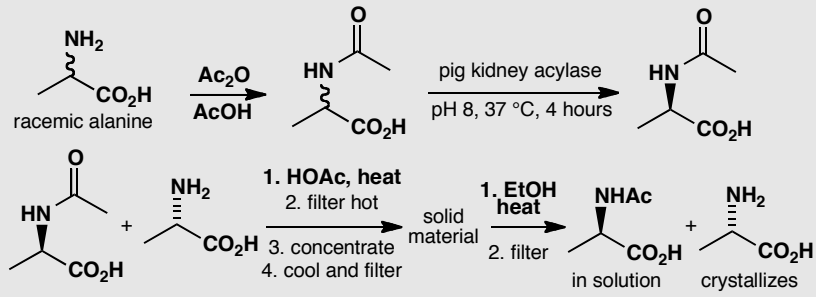
Human hair is a good source of cystine, the disulfide dimer of cysteine. Hair is boiled with aqueous HCl and HCO_2H for a day, the solution concentrated, and a large amount of sodium acetate added. About 5% of the hair by weight crystallises out as pure cystine $[\alpha]_D$ –216. How does the process work? Why is such a high proportion of hair cystine? Why is no cysteine isolated by this process? Make a drawing of cystine to show why it is chiral. How would you convert the cystine to cysteine?



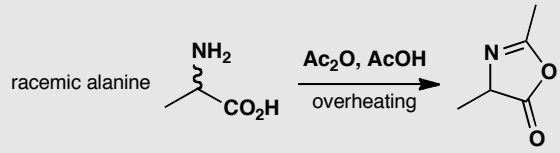
(*S*)-cysteine

PROBLEM 3

The amide of alanine can be resolved by pig kidney acylase. Which enantiomer of alanine is acylated faster with acetic anhydride? In the enzyme-catalysed hydrolysis, which enantiomer hydrolyses faster? In the separation, why is the mixture heated in acid solution, and what is filtered off? How does the separation of the free alanine by dissolution in ethanol work?

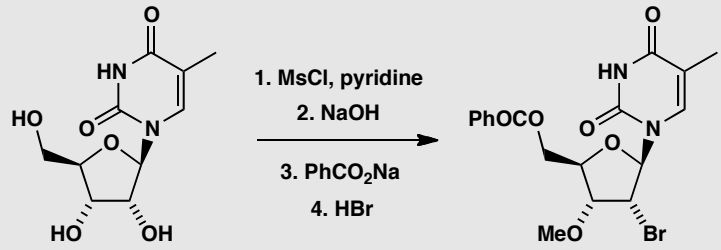


If the acylation is carried out carelessly, particularly if the heating is too long or too strong, a by-product is fomed that is not hydrolysed by the enzyme. How does this happen?

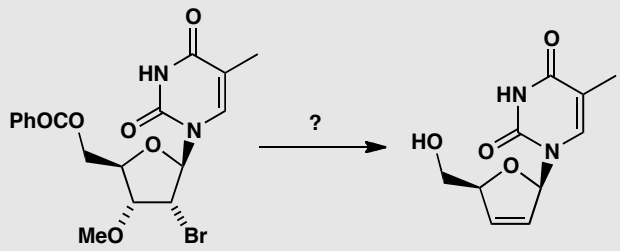


PROBLEM 4

A patent discloses this method of making the anti-AIDS drug d4T. The first few stages involve differentiating the three hydroxyl groups of 5-methyluridine as we show below. Explain the reactions, especially the stereochemistry at the position of the bromine atom.

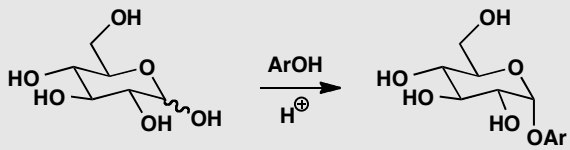


Suggest how the synthesis might be completed.



PROBLEM 5

How are phenyl glycosides formed from phenols (in nature or in the laboratory)? Why is the configuration of the glycoside not related to that of the original sugar?

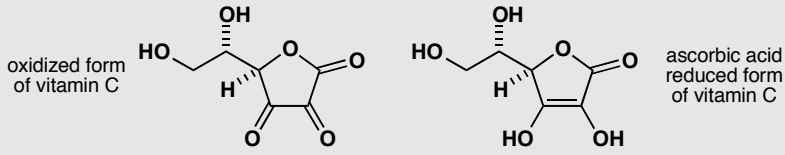


PROBLEM 6

'Caustic soda' (NaOH) was used to clean ovens and blocked drains. Many commercial products for these jobs still contain NaOH. Even concentrated sodium carbonate (Na_2CO_3) does quite a good job. How do these cleaners work? Why is NaOH so dangerous to humans especially if it gets into the eye?

PROBLEM 7

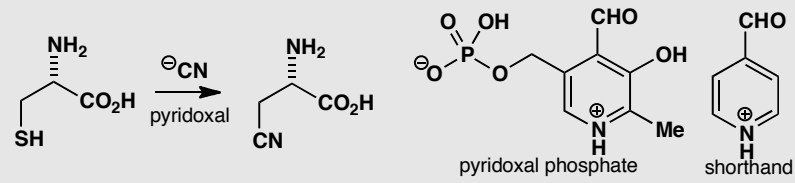
Draw all the keto- and enol forms of ascorbic acid (the reduced form of vitamin C). Why is the one shown here the most stable?



PROBLEM 8

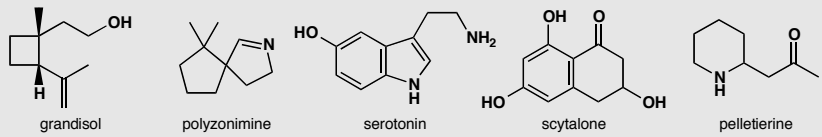
The amino acid cyanoalanine is found in leguminous plants (*Lathyrus spp.*) but not

in proteins. It is made in the plant from cysteine and cyanide by a two-step process catalysed by pyridoxal phosphate. Suggest a mechanism. We suggest you use the shorthand form of pyridoxal phosphate shown here.



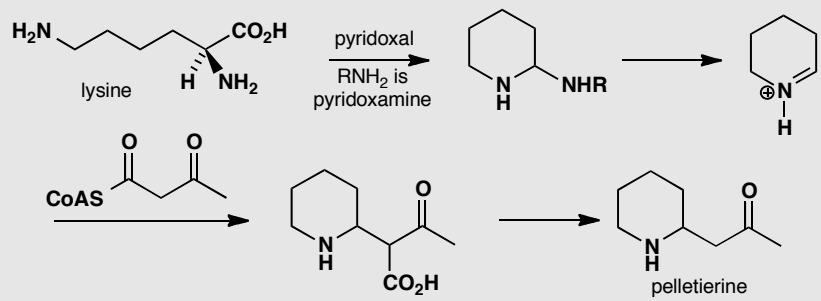
PROBLEM 9

Assign each of these natural products to a general class (such as amino acid metabolite, terpene, polyketide) explaining what makes you choose that class. Then assign them to a more specific part of the class (such as pyrrolidine alkaloid).



PROBLEM 10

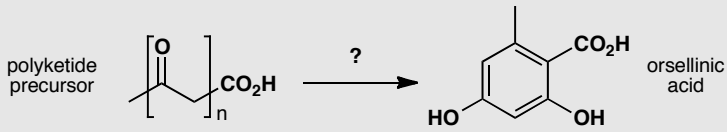
The piperidine alkaloid pelletierine, mentioned in problem 9, is made in nature from the amino acid lysine by pyridoxal chemistry. Fill in the details from this outline:



PROBLEM 11

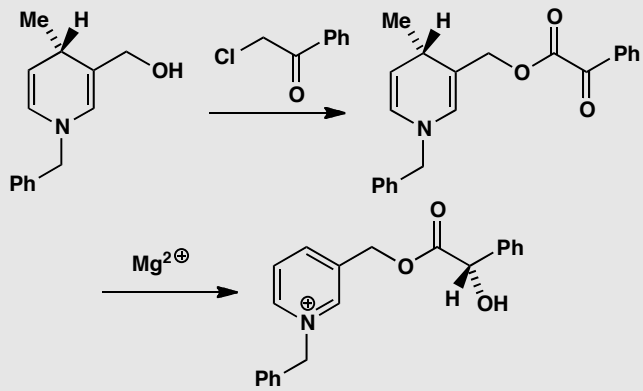
Aromatic polyketides are typically biosynthesised from linear ketoacids with a

carboxylic acid terminus. Suggest what polyketide starting material might be the precursor of orsellinic acid and how the cyclisation might occur.



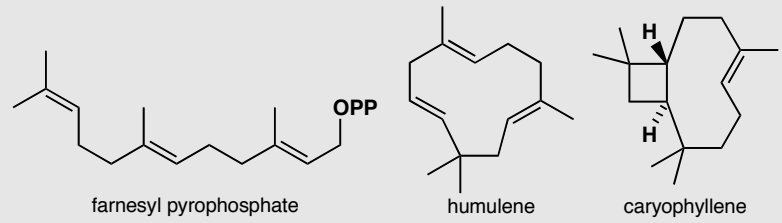
PROBLEM 12

Chemists like to make model compounds to see whether their ideas about mechanisms in nature can be reproduced in simple organic compounds. Nature's reducing agent is NADPH and, unlike $NaBH_4$, it reduces stereopecifically (p. 1150). A model for a proposed mechanism uses a much simpler molecule with a close resemblance to NADH. Acylation and treatment with Mg(II) causes stereospecific reduction of the remote ketone. Suggest a mechanism for this stereochemical control. How would you release the reduced product?



PROBLEM 13

Both humulene, a flavouring substance in beer, and caryophylene, a flavour principle of cloves, are made in nature from farnesyl pyrophosphate. Suggest detailed pathways. How do the enzymes control which product will be formed?



farnesyl pyrophosphate humulene caryophyllene

PROBLEM 14

This experiment aims to imitate the biosynthesis of terpenes. A mixture of products results. Draw a mechanism for the reaction. To what extent is it biomimetic, and what can the natural system do better?