WORKBOOK FOR ORGANIC CHEMISTRY

Supplemental Problems and Solutions

JERRY JENKINS

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SUPPLEMENTAL PROBLEMS AND SOLUTIONS

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Otterbein College

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PREFACE

WORKBOOK FOR ORGANIC CHEMISTRY
SUPPLEMENTAL PROBLEMS AND SOLUTIONS

Organic Chemistry is mastered by *reading* (textbook), by *listening* (lecture), by *writing* (outlining, notetaking), and by *experimenting* (laboratory). But perhaps most importantly, it is learned by *doing, i.e.*, solving problems. It is not uncommon for students who have performed below expectations on exams to explain that they honestly *thought* they understood the text and lectures. The difficulty, however, lies in *applying, generalizing,* and *extending* the specific reactions and mechanisms they have "memorized" to the solution of a very broad array of related problems. In so doing, students will begin to "internalize" Organic, to develop an intuitive feel for, and appreciation of, the underlying logic of the subject. Acquiring that level of skill requires but goes far beyond rote memorization. It is the ultimate process by which one learns to manipulate the myriad of reactions and, in time, gains a predictive power that will facilitate solving new problems.

Mastering Organic is challenging. It demands memorization (*an organolithium reagent will undergo addition to a ketone*), but then requires application of those facts to solve real problems (*methyllithium and androstenedione dimethyl ketal will yield the anabolic steroid methyltestosterone*). It features a highly logical structural hierarchy (like mathematics) and builds upon a cumulative learning process (like a foreign language). The requisite investment in time and effort, however, can lead to the development of a sense of self-confidence in Organic, an intellectually satisfying experience indeed.

Many excellent first-year textbooks are available to explain the theory of Organic; all provide extensive exercises. Better performing students, however, consistently ask for additional exercises. It is the purpose of this manual, then, to provide *Supplemental Problems and Solutions* that reinforce and extend those textbook exercises.

Workbook organization and coverage. Arrangement is according to classical functional group organization, with each group typically divided into *Reactions*, *Syntheses*, and *Mechanisms*. To emphasize the vertical integration of Organic, problems in later chapters heavily draw upon and integrate reactions learned in earlier chapters.

It is desirable, but impossible, to write a workbook that is *completely* text-independent. Most textbooks will follow a similar developmental sequence, progressing from alkane/alkene/alkyne to aromatic to aldehyde/ketone to carboxylic acid to enol/enolate to amine chemistry. But within the earlier domains placement of stereochemistry, spectroscopy, S_N/E, and other functional groups (*e.g.*, alkyl halides, alcohols, ethers) varies considerably. The sequence is important because it establishes the concepts and reactions that can be utilized in subsequent problems. It is the intent of this workbook to follow a *consensus* sequence that complements a broad array of Organic textbooks. Consequently, instructors utilizing a specific textbook may on occasion need to offer their students guidance on workbook chapter and problem selection.

Most Organic textbooks contain later chapters on biochemical topics (proteins, lipids, carbohydrates, nucleic acids, *etc.*). This workbook does not include separate chapters on such subjects. However, consistent with the current trend to incorporate biochemical relevance into Organic textbooks, numerous problems with a bioorganic, metabolic, or medicinal flavor are presented throughout all chapters.

To produce an error-free manual is certainly a noble, but unrealistic, goal. For those errors that remain, I am solely responsible. I encourage the reader to please inform me of any inaccuracies so that they may be corrected in future versions.

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Grindstones sharpen knives; problem-solving sharpens minds!

ABOUT THE AUTHOR

Jerry A. Jenkins received his BA degree *summa cum laude* from Anderson University and PhD in Organic from the University of Pittsburgh (*T Cohen*). After an NSF Postdoctoral Fellowship at Yale University (*JA Berson*), he joined the faculty of Otterbein College where he has taught Organic, Advanced Organic, and Biochemistry, and chaired the Department of Chemistry & Biochemistry. Prof. Jenkins has spent sabbaticals at Oxford University (*JM Brown*), The Ohio State University (*LA Paquette*), and Battelle Memorial Institute, represented liberal arts colleges on the Advisory Board of Chemical Abstracts Service, and served as Councilor to the American Chemical Society. He has published in the areas of oxidative decarboxylations, orbital symmetry controlled reactions, immobilized micelles, chiral resolving reagents, nonlinear optical effects, and chemical education. Prof. Jenkins has devoted a career to challenging students to appreciate the logic, structure, and aesthetics of Organic chemistry through a problem-solving approach.

ACKNOWLEDGMENTS

I wish to express gratitude to my students, whose continued requests for additional problems inspired the need for this book; to Mark Santee, Director of Marketing, WebAssign, for encouraging and facilitating its publication; to Dave Quinn, Media and Supplements Editor, W. H. Freeman, for invaluable assistance in bringing this project to completion; to the production team at W.H. Freeman, specifically Jodi Isman, Project Editor, for all their assistance with the printing process; to Diana Blume, Art Director, and Eleanor Jaekel for their assistance in the cover design; and to my wife Carol, for her endless patience and support.

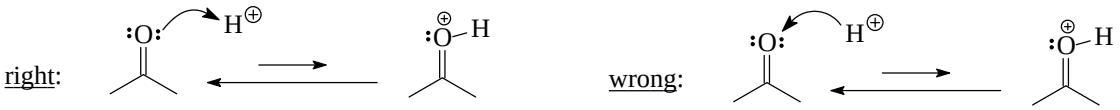
SELECTED CONCEPTS/REACTIONS LOCATOR

The location of problems relating to the majority of concepts and reactions in most Organic textbooks will be generally predictable: pinacol rearrangements will be found under *ALCOHOLS*, benzynes under *AROMATICS*, acetals under *ALDEHYDES AND KETONES*, etc. Placement of others, however, may vary from one text to another: diazonium ions may be under *AROMATICS* or *AMINES*, thiols may be under *ALCOHOLS* or *ETHERS*, the Claisen rearrangement may be under *ETHERS* or *AROMATICS*, etc. The following indicates where problems on several of these often variably placed concepts or reactions are *initially* encountered in *Workbook for Organic Chemistry*.

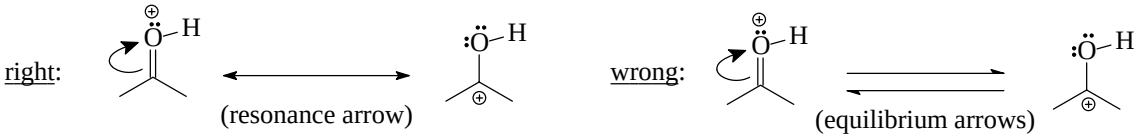
Selected concept/reaction	Chapter
Active methylene chemistry (*e.g.*, malonic/acetoacetic ester syntheses)	18
Brønsted-Lowry/Lewis equations	1
Carbocation rearrangements	5
cis-, *trans*- (geometric) isomers	3
Claisen, Cope, oxy-Cope rearrangements	14
Conformational analysis	2, 3
Curved arrow notation	*vi*, 1
Degrees of unsaturation (units of hydrogen deficiency)	5
Diazonium ions	20
Diels-Alder reaction	11
Enamines, synthesis of	15
Enamines, reactions of	19
Epoxides, synthesis of	5
Epoxides, reactions of	14
Free radical additions	5
Free radical substitutions	8
Hydrogens, distinguishing different	2
Isocyanates, ketenes	17
Kinetic isotope effects	9
Kinetics, thermodynamics	4
Neighboring group participation	9
Nitriles	16
Organometallics (Grignard, organolithium, Gilman), synthesis of	8
Phenols	12
Polymers	5
Reaction coordinate diagrams	4
Reaction types/mechanisms	4
Resonance	1
Thiols, (di)sulfides	14
UV/VIS spectroscopy	11

TIPS (TO IMPROVE PROBLEM SOLVING)

Mechanism arrows. All reactions (except nuclear) involve the flow of electrons. Arrows are used to account for that movement. They originate at a site of *higher* electron density (*e.g.*, lone pairs, π bond) and point to an area of *lower* electron density (*e.g.*, positively or partially positively charged atoms).



Equilibrium *vs*. resonance arrows. Equilibrium arrows interrelate real species (as above). Resonance arrows interrelate imaginary valence bond structures. Do not interchange them.

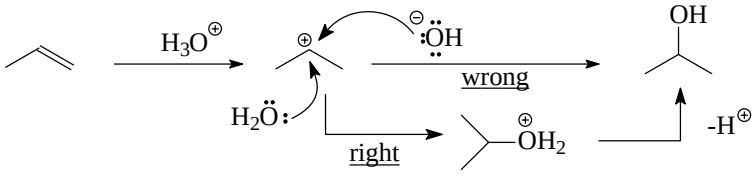


Hydrogen nomenclature. The word "hydrogen" is commonly misused. Be more specific.

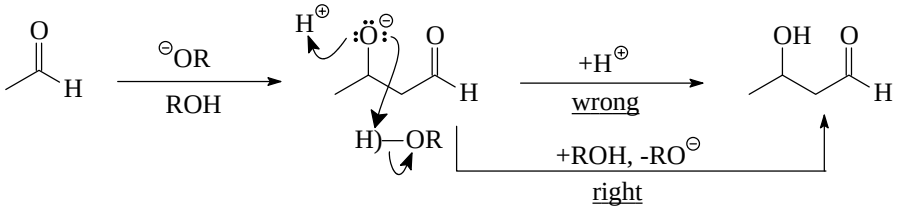
A <u>proton</u> ($H^{\oplus}$) is removed by <u>hydride</u> ($H:^{\ominus}$) to form <u>hydrogen</u> (H_2).

A <u>hydrogen atom</u> ($H\cdot$) is removed by a free radical species.

State of association/dissociation. Correct identification of the appropriate charge state on a species in a particular environment is important. Generally speaking, alkoxides (hydroxide), carboxylates, carbanions, enolates, amines, *etc*., exist under *alkaline* conditions. Protons, carboxylic acids, carbocations, enols, *etc*., exist under *acidic* conditions. For example, hydroxide does not exist in an acidic solvent



and a proton is not *directly* available in base.



COMMON ABBREVIATIONS

The following abbreviations and symbols are used throughout this workbook:

Ac	acetyl (CH_3CO-)
AcOH	acetic acid
*	chiral center or isotopic label
B:	base
Bn	benzyl ($PhCH_2$-)
Bu	butyl (C_4H_9-)
CA	conjugate acid
CB	conjugate base
Δ	heat energy
D-A or (4+2)	Diels-Alder
DB	double bond(s)
DCC	dicyclohexylcarbodiimide
DIBAH	diisobutylaluminum hydride
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
EAS	electrophilic aromatic substitution
ee	enantiomeric excess
equiv	equivalent(s)
Et	ethyl (CH_3CH_2-)
F-C	Friedel-Crafts
[H]	reduction
$\sim H^+$	proton shift
HMPA	hexamethylphosphoramide
HSCoA	coenzyme A
$h\nu$	light energy
H-V-Z	Hell-Volhard-Zelinsky reaction
inv	inversion of configuration
L	leaving group
LDA	lithium diisopropylamide
mCPBA	*m*-chloroperbenzoic acid
Me	methyl (CH_3-)
NAS	nucleophilic acyl (or aryl) substitution
NBS	N-bromosuccinimide
NGP	neighboring group participation
NR	no reaction
Nu:	nucleophile
[O]	oxidation
PCC	pyridinium chlorochromate
Ph	phenyl (C_6H_5-)
Pr	propyl (C_3H_7-)
py	pyridine
Ra-Ni	Raney nickel
ret	retention of configuration
rds	rate determining step
taut	tautomerization
THF	tetrahydrofuran
TMS	tetramethylsilane or trimethylsilyl
Ts	tosyl (*p*-toluenesulfonyl)
TsOH	tosyl acid (*p*-toluenesulfonic acid)
TS	transition state
W-K	Wolff-Kishner reduction
X	halogen
(XS)	excess

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PROBLEMS

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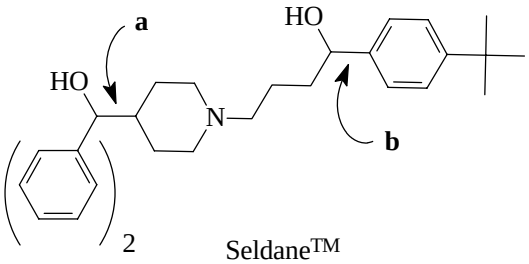
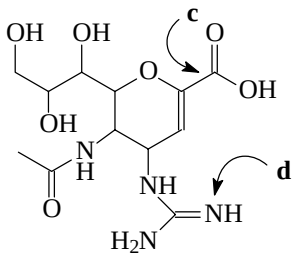
CHAPTER 1
THE BASICS

1.1 Hybridization, formulas, physical properties

1. Seldane™ is a major drug for seasonal allergies; Relenza™ is a common antiviral.



Seldane™



Relenza™

a. Complete the molecular formula for each. Seldane™: C___H___NO_2 Relenza™: C___H___N_4O_7

b. Draw all the lone electron pairs in both structures.

c. Which orbitals overlap to form the covalent bonds indicated by arrows **a, b,** and **c**?

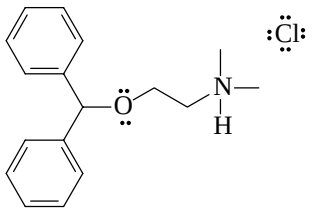
a _____ **b** _____ **c** _____

d. What is the hybridization state of both oxygens in Seldane™ and of nitrogen **d** in Relenza™?

2. Place formal charge over any atom that possesses it in the following structures:

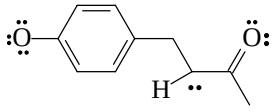
a. :C≡C: b. H–C≡O: c. :O=N=O: d. the *conjugate base* of $:NH_2CH_3$

e.



Benadryl™ (antihistamine)

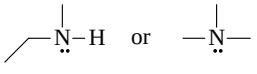
f.

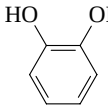


zingerone (a constituent of the spice ginger)

3. a. One type of carbene, [$:CH_2$], a very reactive species, has the two unshared electrons in the *same* orbital and is called "singlet" carbene. Identify the orbital and predict the HCH bond angle.

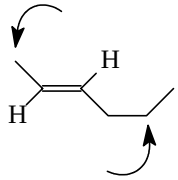
b. Another type of carbene is called "triplet" carbene and has a linear HCH bond angle. Identify the orbitals housing the two lone electrons.

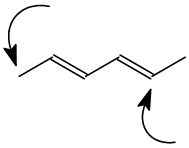
4. a. Which has the *higher* bp?  or

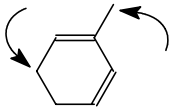
b. *lower* mp?  or 

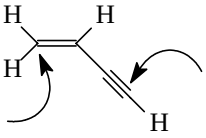
catechol *hydroquinone*

5. Must the indicated carbon atoms in each of the following structures lie in the same plane?

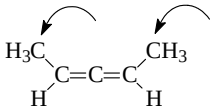
a. 

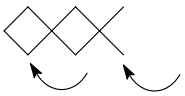
b. 

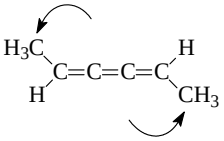
c. 

d. 

e. $(CH_3)_3C^{\oplus}$
all four carbons

f. 

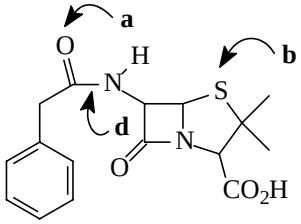
g. 

h. 

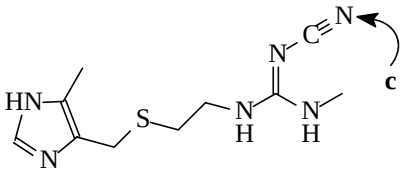
6. Which species in each pair has the *higher* molecular dipole moment (μ)?

a. $CHCl_3$ or $CFCl_3$ b. CH_3NH_2 or CH_3NO_2 c. CO_2 or SO_2

7. *Penicillin V* and the antiulcerative *cimetidine* (Tagamet™ – the first billion dollar ethical drug) have the structures below:



penicillin V



cimetidine

a. Complete the molecular formulas for each.

penicillin V: C_____H_____N_____O_____S *cimetidine*: C_____H_____N_____S

b. Identify the type of orbital (s, p, sp, sp^2, sp^3) that houses the lone electron pairs on the atoms indicated by arrows **a**, **b**, and **c** in the above structures.

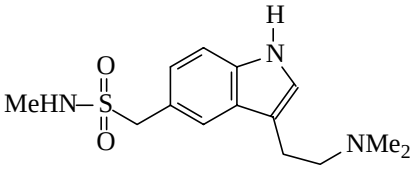
a _____ **b** _____ **c** _____

c. The bond between the carbonyl carbon and nitrogen (indicated by arrow **d**) is somewhat *stronger* than a single but *weaker* than a double bond. Given that fact, what type of orbital houses the lone pair of electrons on that nitrogen? (Suggestion: do this problem after studying *resonance*.)

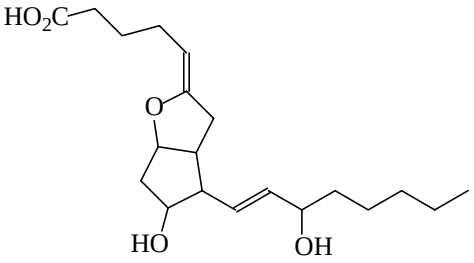
d. How many lone pairs of electrons are in each structure?

penicillin V: _____ *cimetidine*: _____

8. *Sumatriptan* is often prescribed for the treatment of migraines. *Prostacyclin* is a platelet aggregation inhibitor.



sumatriptan



prostacyclin

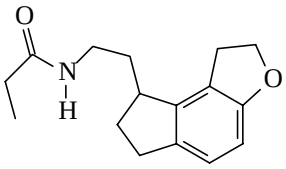
a. Complete the molecular formulas for each.

sumatriptan: C____H____N____O____S *prostacyclin*: C____H____O____

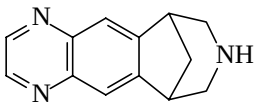
b. *Sumatriptan* contains _____ sp^2 and _____ sp^3 carbons; p*rostacyclin* contains _____ sp^2 and _____ sp^3 carbons.

c. *Sumatriptan* and *prostacyclin* possess _____ and _____ lone pairs of electrons, respectively.

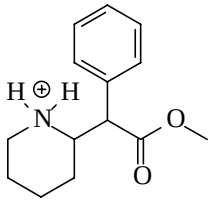
9. Rozerem™ is prescribed for the treatment of insomnia, Chantix™ for smoking cessation, and Ritalin™ for ADHD.



Roserem™



Chantix™



Ritalin™

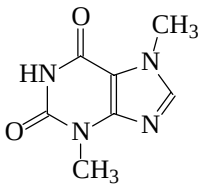
a. What is the molecular formula for each?

Rozerem™ _____ Chantix™ _____ Ritalin™ _____

b. How many *lone pairs* of electrons are there in each?

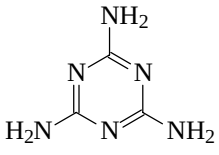
Rozerem™ _____ Chantix™ _____ Ritalin™ _____

10. *Theobromine* (Greek *theobroma* – "food of the gods") is a constituent of cocoa. How many lone pairs of electrons are in its structure? How many lone pairs of electrons are in the plasticizer *melamine*?



theobromine

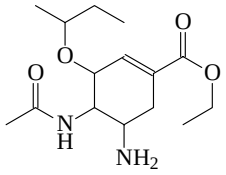
_____



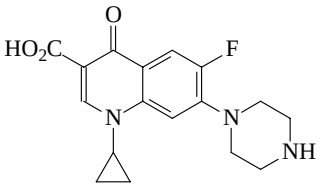
melamine

_____

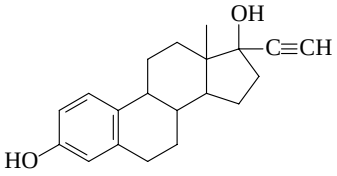
11. Which functional groups are present in each of the following medicines?

a. 

Tamiflu™ (antiviral)

b. 

Cipro™ (antibiotic)

c. 

Yasmin™ component (OCP)

1.2 Acids and bases

1. What is the *strongest* base that can exist in ammonia?

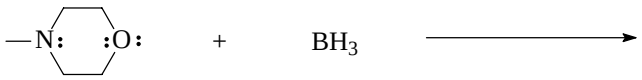
Sodium hydride (NaH) is, in fact, a stronger base than the above answer. Write a reaction to describe what happens when NaH is added to NH_3. Use arrows to show the flow of electrons.

2. Which is the *stronger* base: $(CH_3)_2NH$ or $CH_3\text{-}O\text{-}CH_3$?

3. Using curved arrow notation, write Lewis acid/base equations for each of the following. Remember to place formal charge on the appropriate atoms.

a. 

b. $Ph_3P: + BF_3 \longrightarrow$

c. 

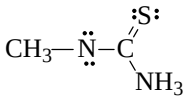
4. Place formal charge on all appropriate atoms. Label the reactants on the left of the arrow as Lewis acids (LA) or Lewis bases (LB) and draw curved arrows to show the movement of electron pairs in each reaction.

a. $H_3C\text{—}\ddot{O}: + CH_3CH_2\text{—}\ddot{Cl}: \longrightarrow CH_3\text{—}\ddot{O}\text{—}CH_2CH_3 + :\ddot{Cl}:$

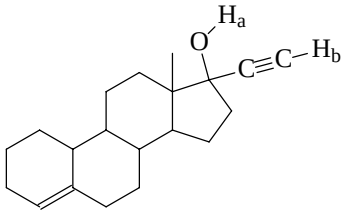
b. $H_2C{=}CH_2 + BF_3 \longrightarrow CH_2\text{—}CH_2\text{—}BF_3$

c. $H_3C{-}\ddot{O}{-}H + :CH_2{-}CH_3 \longrightarrow H_3C{-}\ddot{O}: + H_3C{-}CH_3$

d. $:\ddot{Cl}{-}\ddot{Cl}: + AlCl_3 \longrightarrow :\ddot{Cl} + AlCl_4$

e. $CH_3{-}\ddot{N}{=}C{=}\ddot{S}: + :NH_3 \longrightarrow$ 

5. *Lynestrenol*, a component of certain oral contraceptives, has the structure

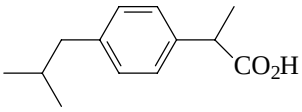


a. Calculate the molecular formula: C___H___O.

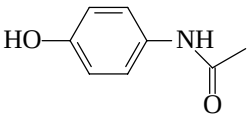
b. The pK_as of hydrogens *a* and *b* are about 16 and 25, respectively, and the pK_a of ammonia is about 35. Write a Brønsted-Lowry equation for the reaction of the *conjugate base* of lynestrenol with ammonia.

c. Is the K_{eq} for the above reaction about equal to, greater than, or less than 1?

6. The structure of *ibuprofen* (A) and *acetaminophen* (B) are drawn below.



A



B

a. Write a reaction for the *conjugate base* of A with B.

b. Identify the weak and strong acids and bases.

c. Is K_{eq} about equal to, less than, or greater than 1?

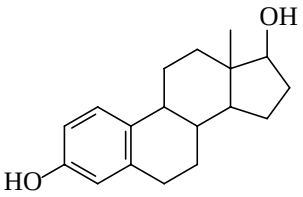
7. Which compound has the *lowest* pK_a?

a. EtOH b. HOAc c. H_2O d. PhOH e. H_2 f. NH_3

8. Which species has the ability to quantitatively (completely) remove the proton H_a (pK_a 22) from $R{-}C{\equiv}C{-}H_a$?

a. hydroxide b. *CB* of NH_3 c. *CA* of hydride d. *CB* of EtOH

9. Stress levels in horses may be monitored by measuring urine *estradiol*. Comment on the K_{eq} for the reaction of the *conjugate base* of nitromethane (pK_a 10.3) with estradiol.

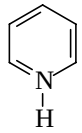


estradiol

CH_3NO_2

nitromethane

10. *Pyridinium chloride* is drawn below.
a. Place the appropriate formal charge on the atoms that bear it.



Cl

b. The pK_as for pyridinium chloride and sodium bicarbonate ($NaHCO_3$) are 5.2 and 10.2, respectively. Write a Brønsted-Lowry equation for the reaction of pyridinium chloride with the *conjugate base* of bicarbonate. Use curved arrow notation to show the flow of electrons.

c. Is K_{eq} greater than, less than, or about one?

1.3 Resonance

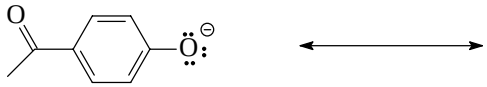
1. Identify the type of orbital housing the electrons specified by the arrows.

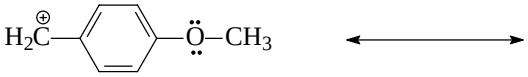
2. Which species has the lower pK_a, H–C≡N: or H–O–C≡N:?

3. How many nuclei can *reasonably* bear the charge in each of these ions?

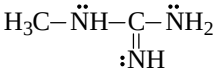
a. 

b. 

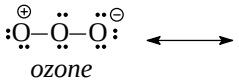
c. 

d. 

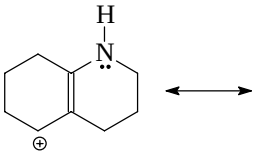
4. The compound below can be protonated at any of the three nitrogen atoms to give a *guanidinium* ion derivative (creatine phosphate and the amino acid arginine possess this moiety). One of these nitrogens is much more basic than the others, however. Draw the conjugate acids resulting from such protonation, then identify the conjugate acid which is most stable. Why?

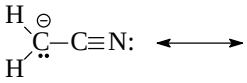


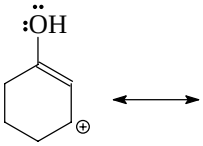
5. Draw a resonance structure that is *more stable* than the one given. Use curved arrows to derive.

a. 

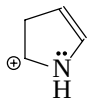
ozone

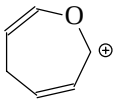
b. 

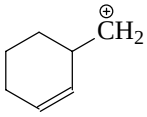
c. 

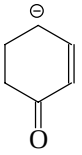
d. 

6. How many nuclei can *reasonably* bear the charge in each of the following ions?

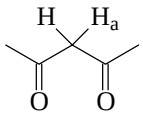
a. 

b. 

c. 

d. 

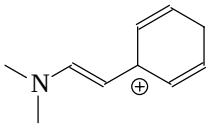
7. Recalling that resonance is a stabilizing force, explain why the pK_a of H_a in **A** is (only!) about 10.

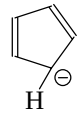


A

8. Either oxygen in acetic acid (HOAc) could, in theory, be protonated to produce two different conjugate acid forms. Draw each and explain which is more favored.

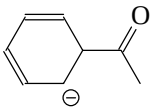
9. How many nuclei can *reasonably* bear the charge or odd electron in each of the following?

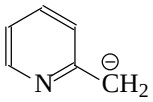
a. 

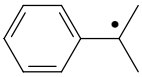
b. 

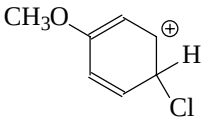
c. 

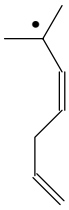
d. 

e. 

f. 

g. 

h. 

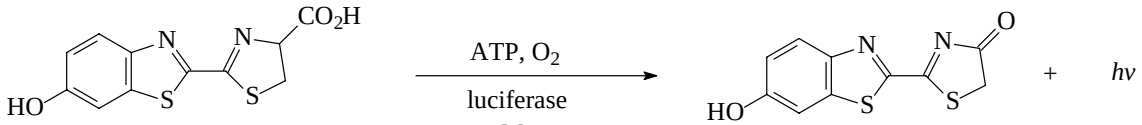
i. 

10. **B**'s molecular dipole moment (μ) is larger than **A**'s. Explain.

A

B

11. Bioluminescence in fireflies is a result of the conversion of chemical energy (in ATP) to light energy. Specifically, ATP, O_2, and the enzyme luciferase cause *luciferin* (~ 9 mg can be collected from about 15,000 fireflies!) to be oxidatively decarboxylated to an electronically excited *oxyluciferin*. Relaxation of the latter to its ground state is accompanied by the emission of light (fluorescence). Subsequent regeneration reactions then recycle oxyluciferin back to luciferin. Draw the two resonance structures of the CB of oxyluciferin in which either oxygen bears the negative charge.



luciferin *oxyluciferin*

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CHAPTER 2
ALKANES

2.1 General

1. Which compound has the *highest* mp?

   1. *n*-octane 2. 2,5-dimethylhexane 3. 2,3,4-trimethylpentane

   4. bicyclo[2.2.2]octane 5. all have the same number of carbons and would melt at the same T

2. Which compound has the *highest* bp?

   1. *n*-pentane 2. neopentane (dimethylpropane) 3. isopentane

3. Dodecahedrane, one of the three Platonic solids (tetrahedron, hexahedron, and dodecahedron), is a regular polyhedron consisting of twelve cyclopentane rings (think soccer ball). Eicosane is a straight-chain compound. Although both are C_{20} hydrocarbon alkanes, one melts at 420^0 and the other at 37^0. Explain.

4. How many *constitutional* (structural) isomers exist for

   a. C_6H_{14}? b. C_7H_{16}?

5. How many *different kinds* (constitutional) of hydrogens are in

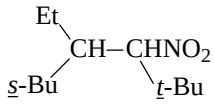
   a. 2,3-dimethylpentane? b. 2,4-dimethylpentane?

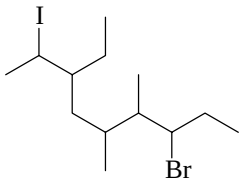
   c. 3-ethylpentane? d. 2,2,4-trimethylpentane?

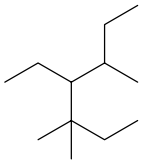
   e. 2,5,5-trimethylheptane? f. 4-ethyl-3,3,5-trimethylheptane?

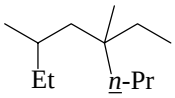
2.2 Nomenclature

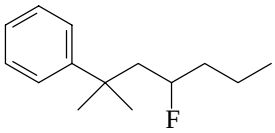
Give the IUPAC name for each of the following. Be certain to specify stereochemistry when relevant.

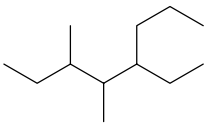
1. 

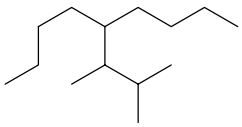
2. 

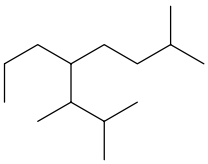
3. 

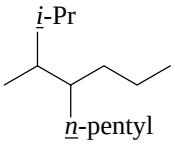
4. 

5. 

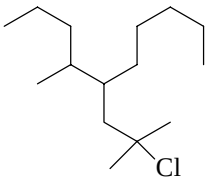
6. 

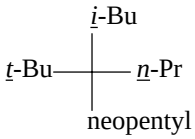
7. 

8. 

9. 

10. isohexyl iodide

11. 

12. 

Give the *correct* IUPAC names for problems 13 – 16.

13. 2-isopropyl-4-methylheptane

14. 3-(1-methylbutyl)octane

15. 3-*s*-butyl-7-*t*-butylnonane

16. tetraethylmethane

17. Draw structural formulas, using bond line notation, for the following:

a. neopentyl alcohol (R-OH) b. isobutyl *n*-pentyl ether (R-O-R') c. allyl bromide (R-X)

2.3 Conformational analysis, acyclic

1. The rotational energy barrier about the C-C bond in EtBr is 3.7 kcal/mole. What is the energy cost of eclipsing a C-H and C-Br bond?

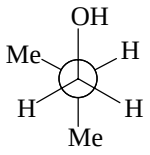
2. Draw Newman projections of the

a. *most stable* conformer , looking down the C_2-C_3 bond, of 2-cyclopentyl-6-methylheptane

b. *gauche* conformer of 1-phenylbutane, looking down the C_1-C_2 bond (use two-letter abbreviations for R groups).

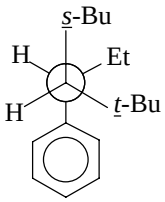
3. Give the *common* name for (a) and the *IUPAC* name for (b).

a.

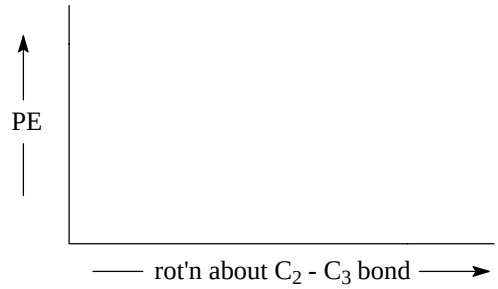


(R-OH = alkyl alcohol)

b.



4. Draw the *conformer* of isopentane that corresponds to the *highest minimum* in a plot of the potential energy *vs*. rotation about the C_2-C_3 bond (use a Newman projection).

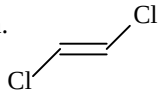


5. The molecular dipole moment (μ) for FCH_2CH_2OH is much larger than that for FCH_2CH_2F. Use conformational analysis to explain.

CHAPTER 3
CYCLOALKANES

3.1 General

1. Which compound has the *highest* molecular dipole moment (u)?

a.  b. *anti* conformer of 2,3-dichlorobutane c. C_2Cl_2 d. *cis*-1,3-dichlorocyclobutane

2. How many *constitutional* (structural) isomers exist for

   a. dichlorocyclopentane?

   b. C_6H_{12} that have a cyclopropyl ring in their structure?

3. How many *cis/trans* stereoisomers exixt for

   a. dichlorocyclopentane?

   b. diphenylcyclohexane?

   c. 2-chloro-4-ethyl-1-methylcyclohexane?

4. How many *different kinds* [constitutional and geometric (*cis*/*trans*)] of hydrogens are there in

   a. 1-ethyl-1-methylcyclopropane?

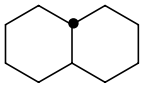
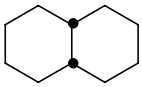
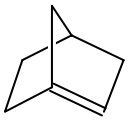
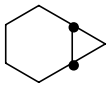
   b. allylcyclobutane?

   c. methylcyclobutane?

d. chlorocyclopentane?

e. vinylcyclopentane?

5. Which bicyclic compound is *least* strained?

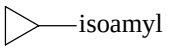
a.  b.  c.  d. 

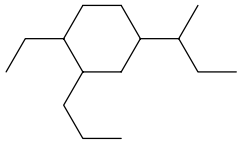
6. Three structural isomers are possible for methylbicyclo[2.2.1]heptane. One of them has two stereoisomeric forms. Draw structures for all four isomers.

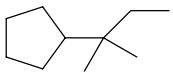
7. In view of the previous problem, how many structural and geometric isomers exist for methylbicyclo[2.2.2]octane?

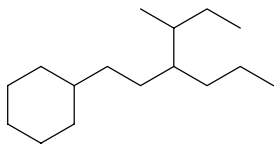
3.2 Nomenclature

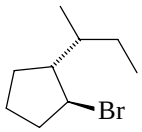
Give the IUPAC name for each of the following. Be certain to specify stereochemistry when relevant.

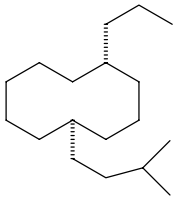
1. 

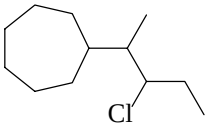
2. 

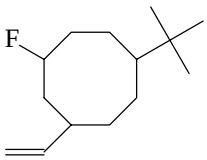
3.  (three names!)

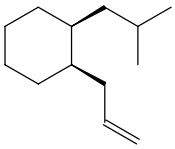
4. 

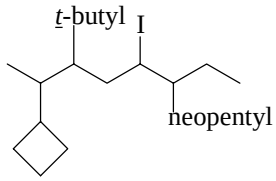
5. 

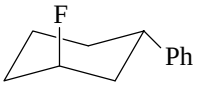
6. 

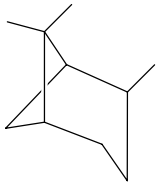
7. 

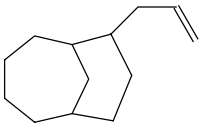
8. 

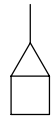
9. 

10. 

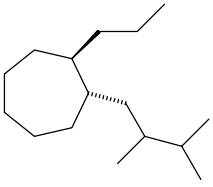
11. 

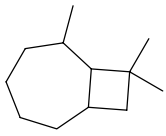
12. 

13. 

14. 

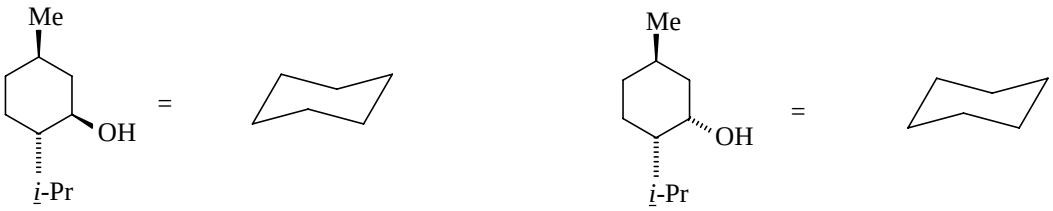
roof-methylhausane (!)

15. 

16. 

3.3 Conformational analysis, cyclic

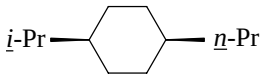
1. Draw the *most stable* conformer of



menthol *neomenthol*

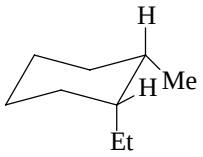
2. In each of the following predict whether K_{eq} is about *equal to*, *greater than*, or *less than* one:

a. *trans*-1,3-diphenylcyclohexane ⇌ "flipped" conformer

b. 

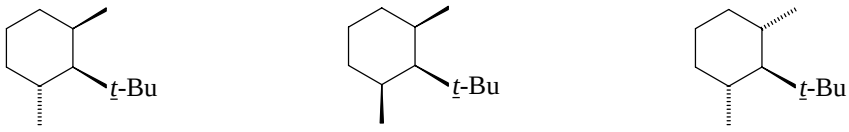
⇌ "flipped" conformer

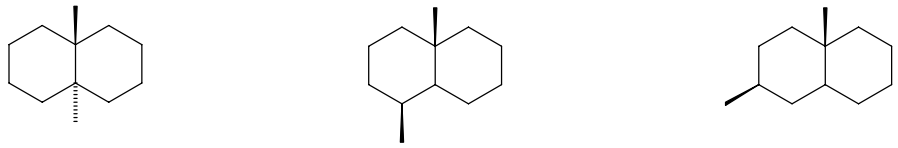
(if *i*-Pr is equatorial)

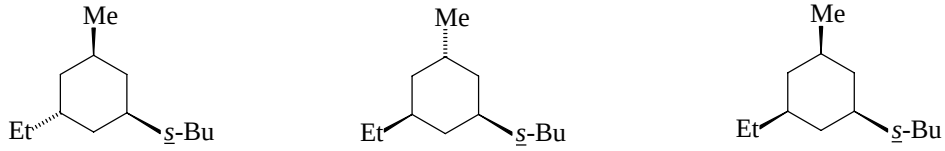
c. 

⇌ "flipped" conformer

3. Which has the *most* negative heat of combustion (ΔH_{comb}) in each of (a), (b), or (c)?

a. 

b. 

c. 

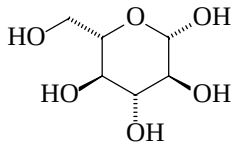
4. a. Which has the *least* negative heat of combustion (ΔH_{comb})?

b. Which two structures in (a) are the same compound?

5. Many alkyl halides undergo loss of HX in the presence of base. For example, chlorocyclohexane gives cyclohexene when treated with sodium hydroxide. The reaction mechanism generally requires both the leaving proton and halide to occupy axial positions, a process known as a *trans*-diaxial elimination. Therefore, which do you think would react faster, *cis*-1-chloro-2-*t*-butylcyclohexane or *trans*-1-chloro-2-*t*-butylcyclohexane?

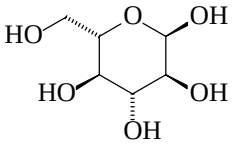
6. *Trans*-4-fluorocyclohexanol exists largely in a chair conformation, whereas the *cis*-isomer favors a twist-boat conformation. Explain.

7. Glucose, like cyclohexane, exists in a chair conformation. Two configurations of glucose are possible; they are drawn below:



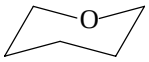
1

and

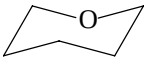


2

a. Complete the chair conformations below to show the *most stable* conformer of **1** and **2**.



1



2

b. Which configuration would you predict would be *less* stable, *i.e.*, burn with a *more negative* heat of combustion?

8. One of the chair conformations of *cis*-1,3-dimethylcyclohexane is 5.4 kcal/mol more stable than the other. If the steric strain of 1,3-diaxial interactions between hydrogen and methyl is 0.9 kcal/mol, what is the strain cost of a 1,3-diaxial interaction between the two methyl groups?

9. a. How many *cis*/*trans* stereoisomers exist for 1,2,3,4,5,6-hexamethylcyclohexane?

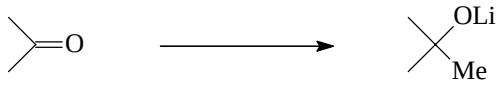
b. For three of those stereoisomers, $K_{eq} = 1$ for conformational chair-chair flipping. Draw them.

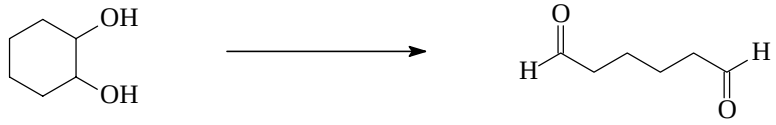
c. Of those three, which is the *least* stable?

d. Which stereoisomer would be *least* likely to undergo conformational flipping?

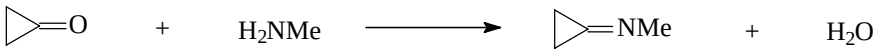
CHAPTER 4
REACTION BASICS

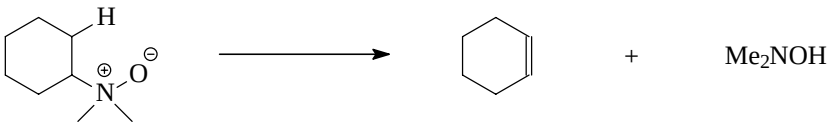
1. Which type of reaction – *addition, elimination, rearrangement, substitution, reduction* [H], or *oxidation* [O] – best describes each of the following?

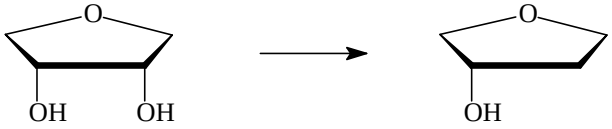
a. MeLi + 

b. 

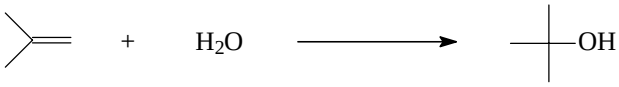
c. $RCO_2R + NH_2R \longrightarrow RCONHR + HOR$

d. 

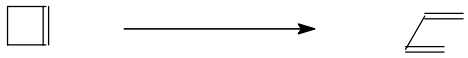
e. 

f. 

g. $RHC{=}CHR \longrightarrow RC{\equiv}CR$

h. 

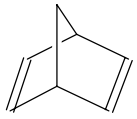
i. $PhCO_2H \longrightarrow PhCHO$

j. 

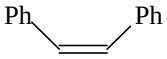
k. BnOH ⟶ PhCHO

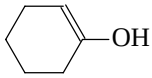
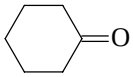
l. Ac_2O + H_2O ⟶ 2 AcOH

m. $CHCl_3$ + KO-*t*-Bu ⟶ $:CCl_2$ + *t*-BuOH + KCl

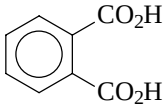
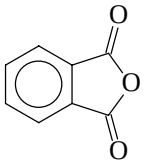
n.  + HC≡CH ⟶ 

o. Br_2 ⟶ 2 $Br^{\ominus}$

p.  ⟶ 

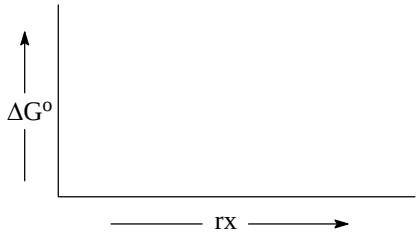
q.  ⟶ 

r. vinyl chloride ⟶ C_2H_2

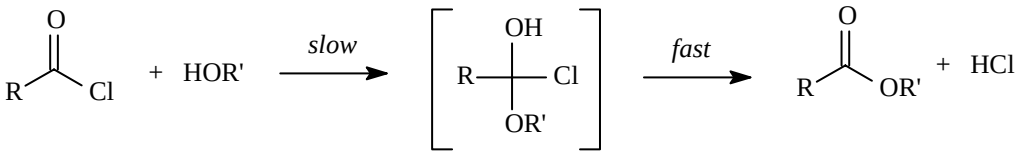
s.  ⟶  + H_2O

t. isohexyl alcohol ⟶ isohexane

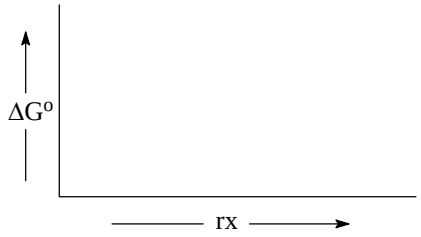
2. Imagine a 2-step (**A** to **B** and **B** to **C**) endothermic reaction for which ΔG^o values for each step are, respectively, +3 and +7 kcal/mole. The $\Delta G^{\pm}$ value for the rate determining step is 11 kcal/mole. (a) Draw a potential energy diagram for this reaction. (b) What is the $\Delta G^{\pm}$ value for the conversion of **C** to **B**?



3. A simplified mechanism for the exothermic substitution reaction below involves two steps:



a. Draw an overall energy diagram and label the transition state(s), intermediate, $\Delta G^{\pm}$ for the rate determining step, and ΔG^{o}.



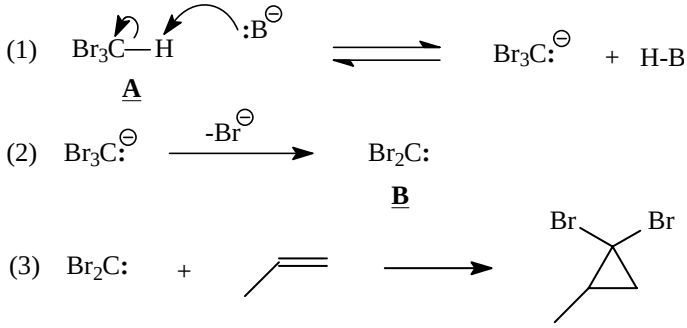
b. The overall K_{eq} for the conversion of RCOCl to RCO_2R' could be calculated from ΔG^{o} according to the equation:

K_{eq} = _____

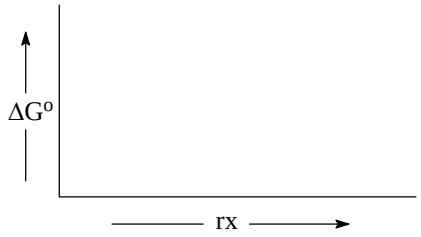
c. If $\Delta G^{\pm}$ is known, the rate of the reaction could be calculated according to the equation:

rate = _____

4. Bromoform (**A**) in the presence of base ($:B^-$) can form a very reactive intermediate, dibromocarbene (**B**), which can rapidly add to olefins to produce *gem*-dibromocyclopropane derivatives. The following summarizes the two-step mechanism:

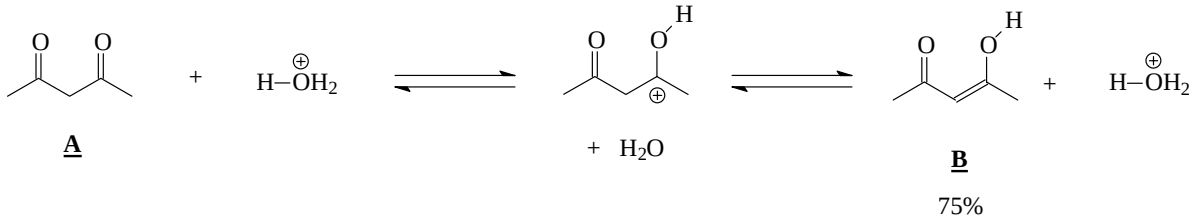


a. Assuming that ΔG^{o} for the overall reaction is +2.5 kcal/mol and that step (2) is rate-determining, draw a reaction energy diagram that depicts all three steps.



b. Calculate K_{eq} for this reaction (R = 2 *cal*/mol·K, T = 300).

5. Consider the following reaction mechanism for **A** in equilibrium with **B**:



A **B**

75%

a. The overall reaction is an example of a(n) _____ (type) reaction that occurs by a(n) _____ mechanism.

b. Draw curved arrows to show the electron flow that has occurred in each step.

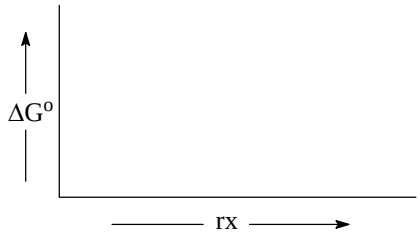
c. Calculate K_{eq}, assuming only **A** and **B** are present (note: **B** is formed in 75% yield).

K_{eq} = _____

If K_{eq} is known, then ΔG^o = _____.

d. Which species is (are) nucleophilic in this reaction?

e. Draw a qualitative energy diagram for the reaction (assume the first step is slower than the second). Label the transition state(s) and intermediate.

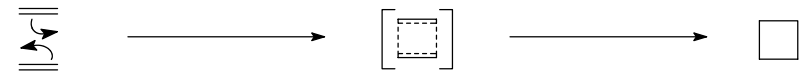


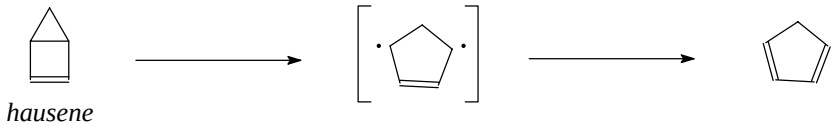
6. Consider the following reaction:

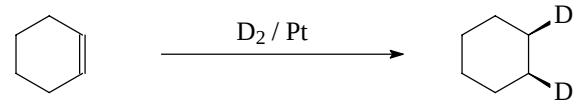
A

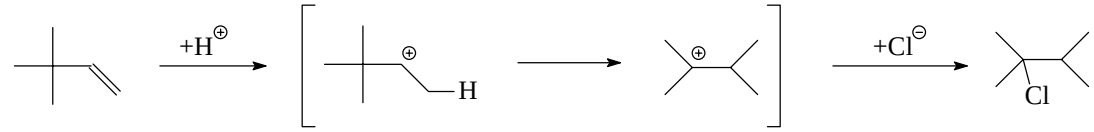
The rate law for the reaction may be expressed as: rate = k[**A**]. Given that methyl alcohol is *not* in the rate law, propose a reaction for the rate determining step.

7. Below are reactions we shall examine in more detail later. Classify the mechanisms as *polar/ionic, free radical,* or *pericyclic* (concerted).

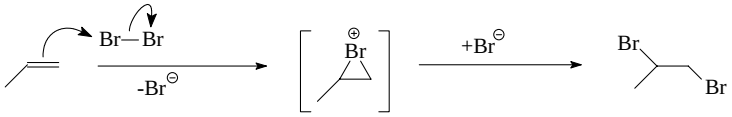
a. 

b. 

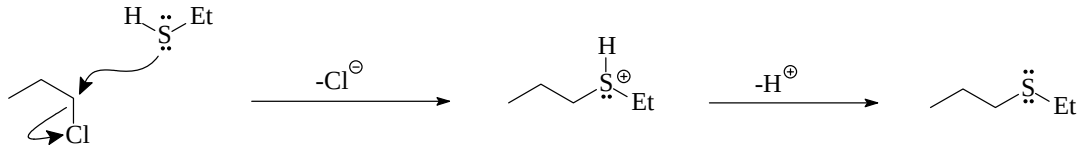
c. 

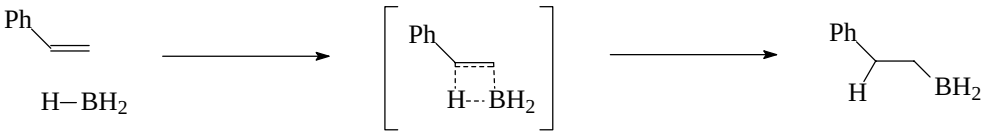
d. 

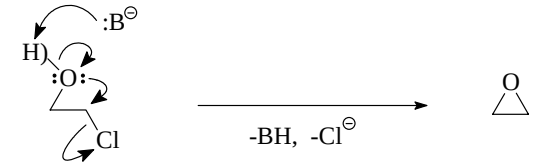
e. 

f. 

g. 

h. 

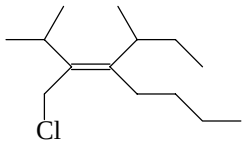
i. 

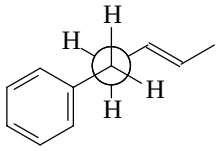
j. 

CHAPTER 5
ALKENES AND CARBOCATIONS

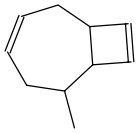
5.1 General

1. Nomenclature. Give the complete IUPAC name for the following:

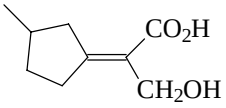
a. 

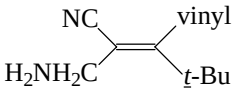
b. 

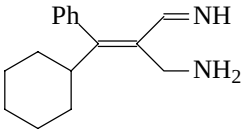
c. 4-vinyldecane (an *incorrect* name!)

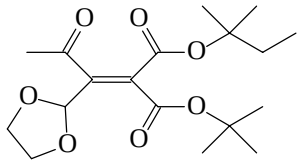
d. 

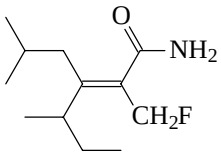
2. Identify each of the olefins below as (E)- or (Z)-:

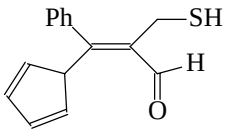
a. 

b. 

c. 

d. 

e. 

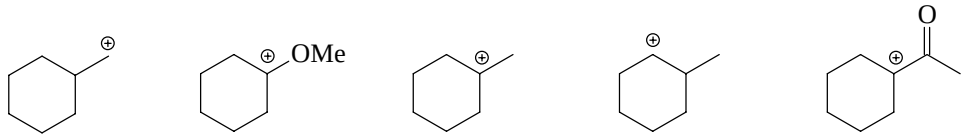
f. 

3. a. How many alkenes, C_7H_{12}, could you treat with H_2 / Pt to prepare methylcyclohexane?

b. Which would have the *least negative* heat of hydrogenation?

4. How many *geometric* isomers exist for 2,4-heptadiene?

5. Which carbocation is the most stable?



6. Degrees of unsaturation (units of hydrogen deficiency).
a. The antidepressant *fluoxetine* (Prozac™), $C_{17}H_{18}F_3NO$, when treated with H_2 / Ni gives a structure with molecular formula $C_{17}H_{30}F_3NO$. It contains no triple bonds. How many rings are in fluoxetine?

b. Cipro™ is an antibacterial that is used to treat anthrax. Its molecular formula is $C_{17}H_{18}FN_3O_3$. The drug has four rings and no triple bonds. How many double bonds does it contain?

c. *RU 486* is an abortion medication. Its molecular formula is $C_{28}H_{35}NO_2$. Its structure contains five double bonds and one triple bond. How many rings are in *RU 486*?

d. The COX-2 inhibitor *rofecoxib* (Vioxx™), an anti-inflammatory agent, has been taken off the market because of potential increased cardiovascular risk. Its molecular formula is $C_{17}H_{14}O_4S$. There are three rings and no triple bonds in rofecoxib. How many double bonds are there? (Note: for each sulfur atom, subtract four hydrogen atoms to arrive at the equivalent hydrocarbon formula.)

e. The antibiotic *floxacillin*, $C_{19}H_{17}ClFN_3O_5S$, contains eight double bonds. How many rings are present? (In this case, treat sulfur as you would oxygen.)

f. The antidepressant Paxil™ has the molecular formula $C_{19}H_{20}FNO_3$. Upon exhaustive hydrogenation (H_2/Pt) a compound $C_{19}H_{32}FNO_3$ is formed. How many double bonds and how many rings are in Paxil™?

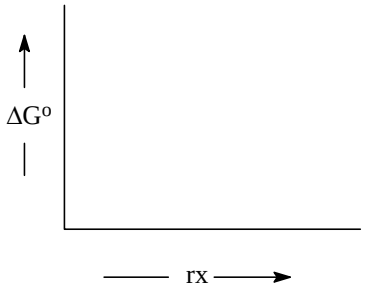
7. How many stereoisomers exist for 2,4-hexadiene? for 2-chloro-2,4-hexadiene?

8. Draw structural formulas for each of the following:

a. (Z)-3-methyl-2-phenyl-2-hexene b. propylene dichloride

c. styrene bromohydrin d. *trans*-cyclohexene glycol e. isobutylene epoxide

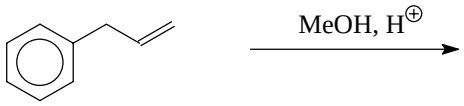
9. Draw an energy *vs*. progress of reaction diagram for the *exothermic* reaction of vinylcyclobutane with HCl to yield 1-chloro-1-methylcyclopentane. Be certain the number of intermediates is clearly indicated.



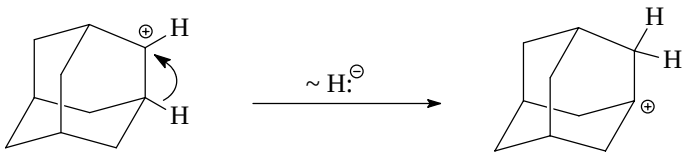
10. Draw the *most*

a. *important* contributing resonance structure of the conjugate acid of 6-methyl-1,3,5-heptatriene

b. *stable intermediate* in the following reaction:



11. The following 1,2-hydride shift does not occur. Why?



adamantyl carbocation

12. Which reaction demonstrates NEITHER *regiospecificity* nor *stereospecificity*?

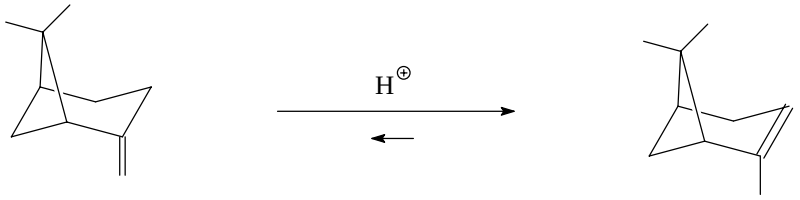
a. *trans*-2-pentene $\xrightarrow{HF}$

b. 1-pentene $\xrightarrow[(XS)\ NaBr]{Cl_2}$

c. cyclobutene $\xrightarrow[H_2O]{Cl_2}$

d. 1-ethylcyclopropene $\xrightarrow{D_2 / Pt}$

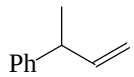
13. Why, and how, does *β-pinene* readily isomerize to *α-pinene* in the presence of an acid catalyst?



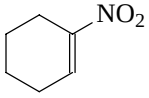
β-pinene α-pinene

5.2 Reactions

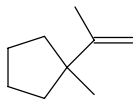
Draw the structural formula of the major organic product(s). Show stereochemistry where appropriate.

1. 

$\xrightarrow{HCl}$

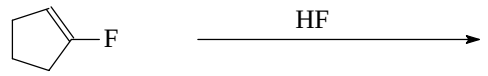
2. 

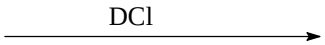
$\xrightarrow{HI}$

3. 
$\xrightarrow{H_3O^{\oplus}}$

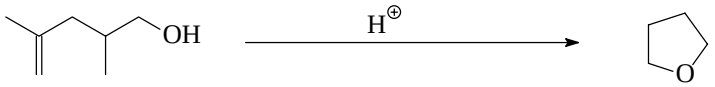
4. cyclopentane $\xrightarrow[2.\ KOMe,\ MeOH\ \ 3.\ Br_2,\ CHCl_3]{1.\ Cl_2 / \Delta}$

5. 

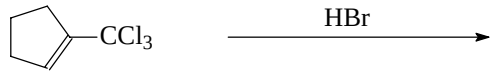
6. 

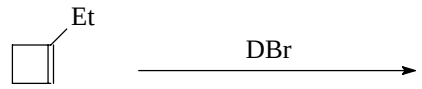
7. vinylcyclohexane 

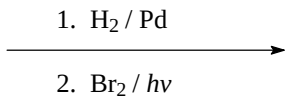
8. 

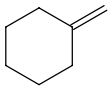
9. 

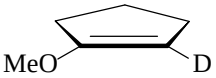
(complete)

10. 

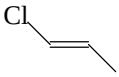
11. 

12. cyclopentene 

13.  $\xrightarrow{H^{\oplus},\ EtOH}$

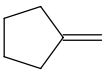
14. 

$\xrightarrow{HF}$

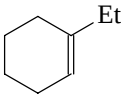
15. 

$\xrightarrow{HI}$

16.  $\xrightarrow{Cl_2 / H_2O}$

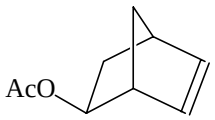
17.  $\xrightarrow[2.\ H_2O_2,\ ^{\ominus}OH]{1.\ B_2D_6}$

18. propylene $\xrightarrow[(XS)\ NaI]{Cl_2}$

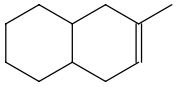
19. 

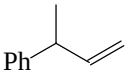
$\xrightarrow[2.\ NaBH_4]{1.\ Hg(OAc)_2,\ PhOH}$

20. $H_2C{=}C{=}CH_2$ *allene* $\xrightarrow[Zn(Cu)]{(XS)\ CH_2I_2}$

21. 

1. $KMnO_4$, $^{\ominus}OH$
2. HIO_4

22. 
1. O_3
2. $H_3O^{\oplus}$, Zn

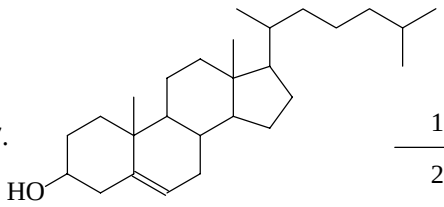
23. 

HBr, di-*t*-butyl peroxide

24. (E)-3-hexene
diazomethane
$h\nu$

25. cyclopentyl bromide
1. base
2. OsO_4
3. $NaHSO_3$

26. 3-methyl-1-butene
IN_3

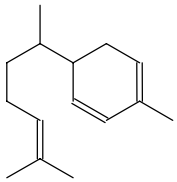
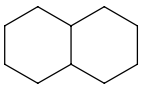
27. 

1. BD_3, THF
2. H_2O_2, $^{\ominus}OH$

cholesterol

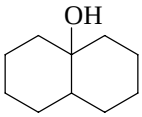
28. 

$H^{\oplus}$, MeOH

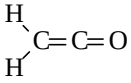
29.  $\xrightarrow{H^{\oplus}}$ 

(complete)

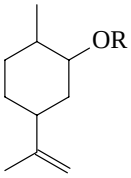
30. styrene glycol $\xrightarrow{HIO_4}$

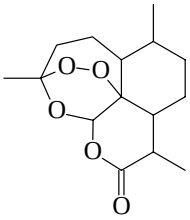
31. 

$\xrightarrow[2.\ KMnO_4,\ ^{\ominus}OH]{1.\ H_2SO_4}$

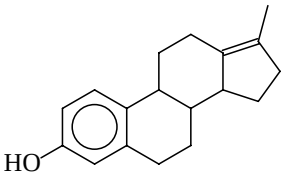
32. 

$\xrightarrow{HCl}$

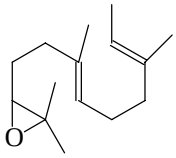
33. 

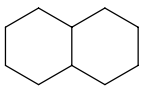
$\xrightarrow[2.\ H_2O_2,\ ^{\ominus}OH]{1.\ BH_3,\ THF}$ [ ] $\Longrightarrow$ 

artemisinin (antimalarial)

34. 

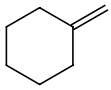
$\xrightarrow[2.\ base]{1.\ Br_2,\ H_2O}$ [ ] $\Longrightarrow$ *estrone*

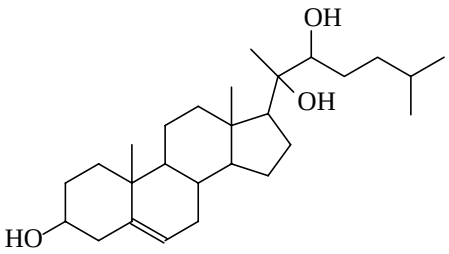
35. 

$\xrightarrow{H^{\oplus}}$ 

(complete)

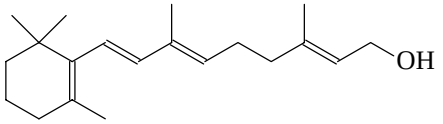
36. chlorocyclopentane $\xrightarrow[2.\ mCPBA\ \ 3.\ EtOH,\ H^{\oplus}]{1.\ {}^{\ominus}OR}$

37.  $\xrightarrow{Br_2,\ \underline{s}\text{-BuOH}}$

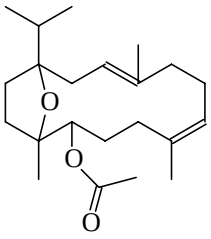
38.  $\xrightarrow{HIO_4}$

pregnenolone

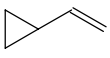
39. Draw the structure of the *largest* carbon-containing product in the following reaction:

 $\xrightarrow{KMnO_4,\ H^{\oplus}}$

vitamin A

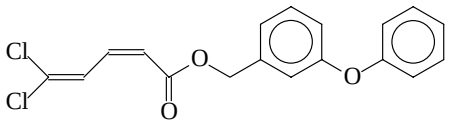
40.  $\xrightarrow[3.\ HIO_4]{1.\ OsO_4\ \ 2.\ NaHSO_3}$

incensole acetate
(found in frankincense)

41.  $\xrightarrow[\text{two 1,2-shifts}]{HCl}$ $\square$

(complete)

42. $PhCH_2Cl$ + *n*-BuLi (*a very strong base*) $\xrightarrow[-HCl]{\text{1,1-elimination}}$ [ ] $\xrightarrow{\text{cyclohexene}}$

43. 

$\xrightarrow[Zn(Cu)]{(CH_3)_2CI_2 \text{ (1 equiv)}}$

permethrin (insect repellent)

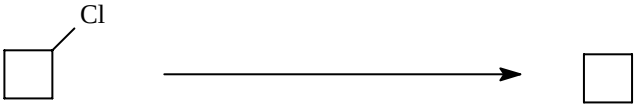
5.3 Syntheses

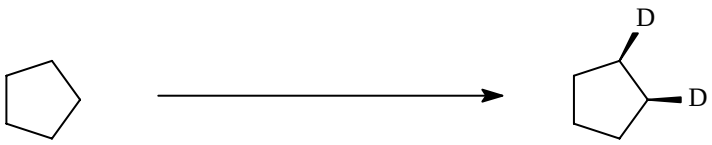
Supply a reagent or sequence of reagents that will effect the following conversions.

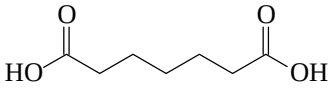
1. 

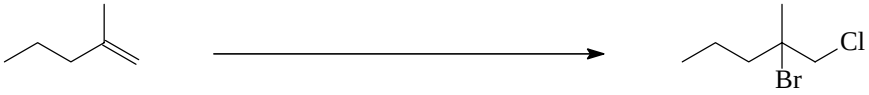
2. cyclohexyl alcohol ⟶ cyclohexyl chloride

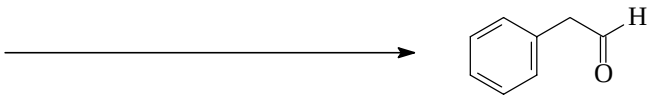
3. *t*-BuCl ⟶ *t*-BuF

4. 

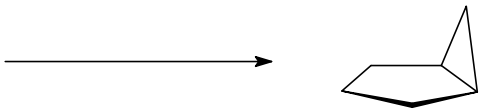
5. 

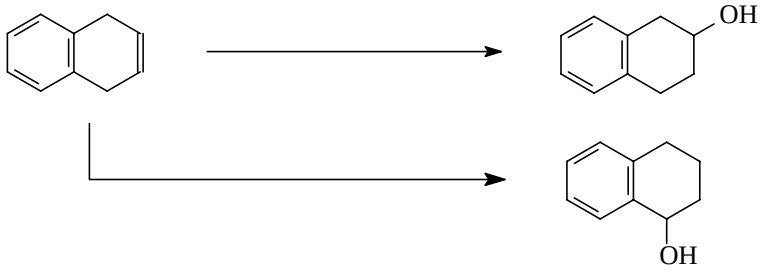
6. cycloheptane 

7. 

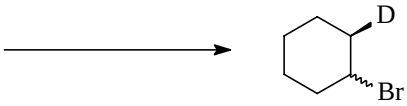
8. allylbenzene 

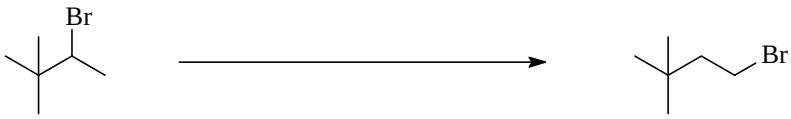
9. ethylene ⟶ bromocyclopropane

10. cyclopentyl alcohol 

11. 

12. 

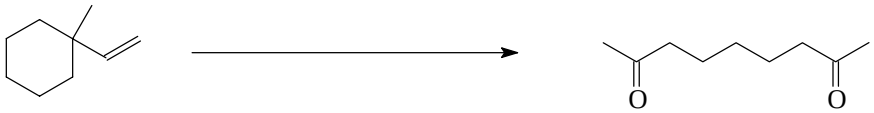
13. cyclohexane 

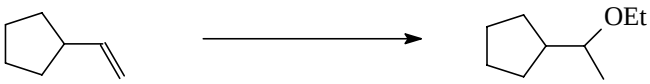
14. 

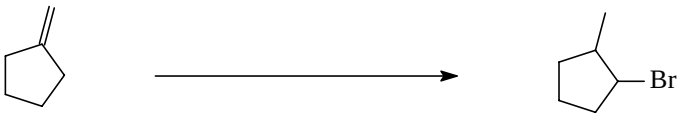
15. isobutane ⟶ isobutyl alcohol

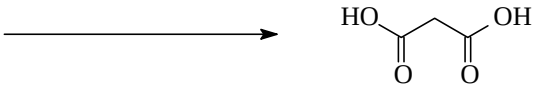
16. 

17. *t*-butyl chloride ⟶ isobutylene chlorohydrin

18. 

19. 

20. 

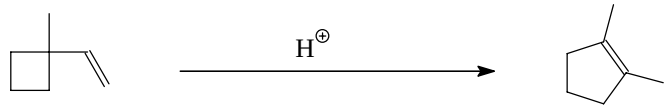
21. ethylene 

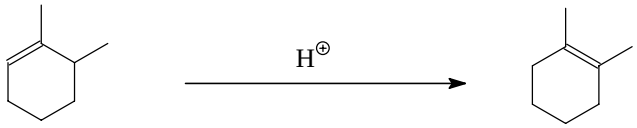
22. *t*-butyl bromide (*only source of carbon*) ⟶ di-*t*-butyl ether

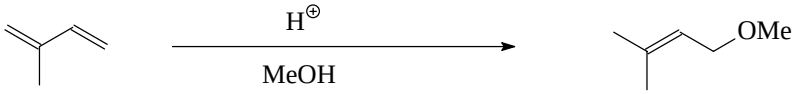
23. cyclobutyl alcohol ⟶ hausane (bicyclo[2.1.0]pentane)

5.4 Mechanisms

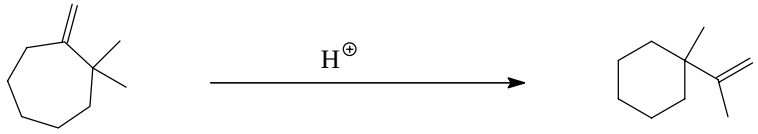
Outline a detailed mechanism for each of the following. No other reagents than those given are necessary. Use arrows to explain the flow of electrons and show all intermediates. NO WORDS!

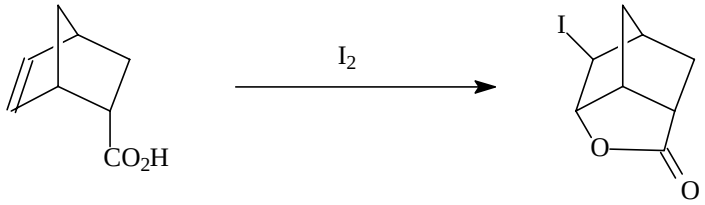
1. 

2. 

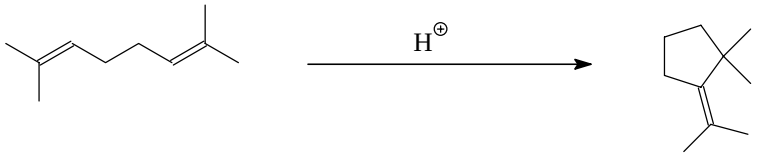
3. 

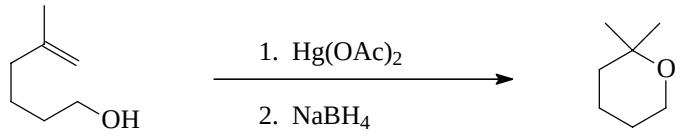
isoprene

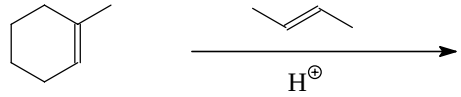
4. 

5. 

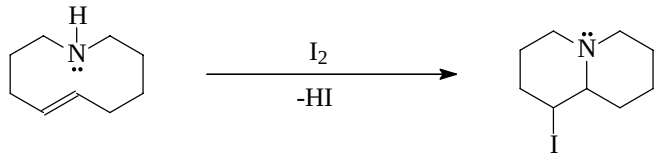
6. Isobutylene in the presence of excess propylene and a trace of acid yields C_7H_{14}. Deduce this product.

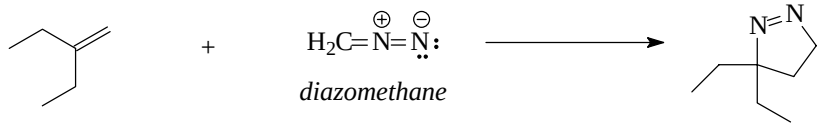
7. 

8. 

9. 

(*a C_{11} olefin*)

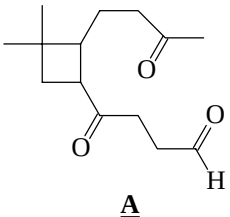
10. 

11. 

diazomethane

12. The reaction of 3-bromocyclohexene with HBr yields only *trans*-cyclohexene dibromide, *i.e.*, no *cis*-product is formed. In contrast, 3-methylcyclohexene reacts with HBr to yield a mixture of *cis*- and *trans*-stereoisomers, as well as a tertiary alkyl halide. Explain with appropriate structures and arrows.

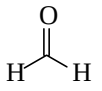
13. The natural products c*aryophyllene* and *isocaryophyllene* (odor somewhere between cloves and turpentine) are stereoisomers that differ in the configuration of a double bond. They have the molecular formula $C_{15}H_{24}$. Catalytic hydrogenation of either yields the same compound, $C_{15}H_{28}$. Ozonolysis, followed by zinc and aqueous acid, yields **A** and an other aldehyde. Suggest structures for the caryophyllenes.



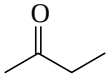
A

14. Treatment of an unknown alkene with $Hg(OAc)_2$ in H_2O/THF, followed by a $NaBH_4$ workup, produces an alcohol isomeric to one obtained by hydroboration-oxidation of the same alkene. Reduction of the alkene affords the compound C_5H_{12}, while ozonolysis yields an aldehyde, CH_3CHO, as one of the products. Deduce the structure of the alkene.

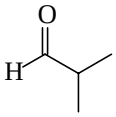
15. *Partial* catalytic hydrogenation of C_5H_8 (**A**) yields a mixture of **B**, **C**, and **D**. Ozonolysis, followed by a reductive work-up (Zn, H_3O^+), of **B** gives no new products. When treated in the same way, **C** gives formaldehyde and 2-butanone and **D** gives formaldehyde and isobutyraldehyde. Provide structures for compounds **A through D**. What is the *common* name of **A**?



formaldehyde



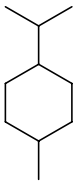
2-butanone



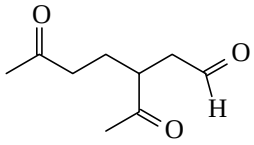
isobutyraldehyde

16. *β-Myrcene*, $C_{10}H_{16}$, found in bayleaves and hops, is an intermediate in the manufacture of perfumes. When treated with H_2/Pt, 2,6-dimethyloctane is formed (β-myrcene has no triple bonds). Treatment of β-myrcene with ozone, followed by an acidic zinc work-up, yields **A** ($C_5H_6O_3$), acetone (Me_2CO), and two equivalents of formaldehyde. What are the structures of β-myrcene and **A**?

17. Reaction of **A**, $C_{10}H_{16}$, with H_2/Pd yields **B**. When treated with $KMnO_4$, a brown precipitate forms. When **A** is treated with ozone followed by zinc in acid, compound **C** and another product are produced. What are the structures of **A** and the other ozonolysis product?

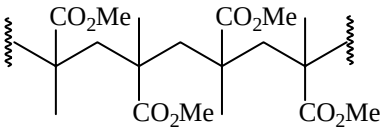


B



C

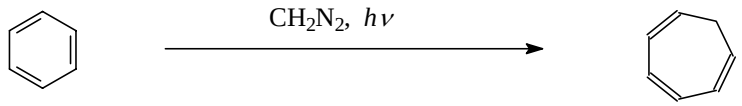
18. Draw
a. the structure of the *monomer* that would give the following polymer by an addition mechanism:

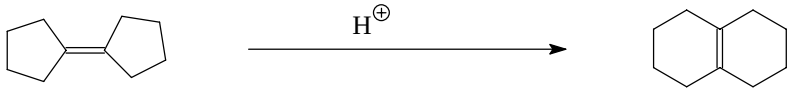


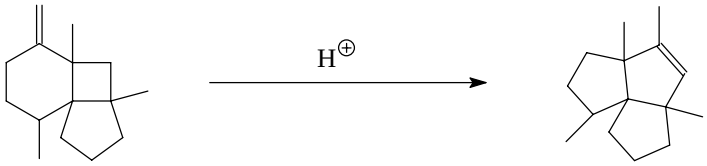
b. a segment (three or four repeating units) of poly(styrene).

19. *t*-Butyl vinyl ether is polymerized commercially by a cationic process for use in adhesives. Show the mechanism for linking three monomeric units.

20. $2\ CH_2N_2 \xrightarrow{\Delta}$ ethylene + $2\ N_2$

21. 

22. 

23. 

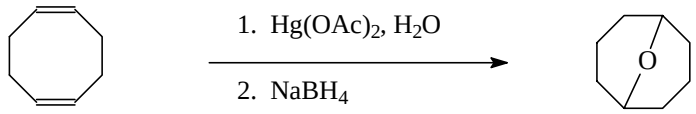
isocomene (from goldenrod)

24. Hydride shifts and alkyl migrations occur in many enzyme-catalyzed reactions in all living species – *including you as you are working these problems!* Below is one such biochemical reaction (see 14.3, 6 for perhaps the very best example). Account for the formation of all intermediates leading to the product. (Hint: positive sulfur, like positive oxygen, is a good leaving group, *i.e.*, it easily leaves a carbon to which it is attached, taking with it both bonding electrons.)

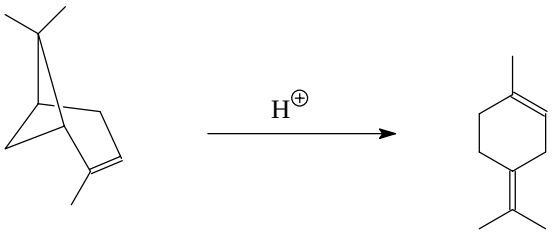
SAM (S-adenosylmethionine, a common methylating agent in all of us)

oleic acid (a fatty acid)

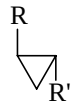
25.



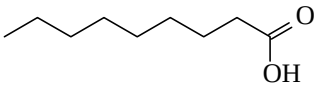
26.



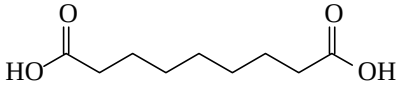
27. *Elaidic acid* ($C_{18}H_{34}O_2$), a fatty acid, is present in processed foods such as margarine and *may* contribute to elevated levels of cholesterol. Reaction of elaidic acid with Simmons-Smith reagent produces compound **I**, whereas reaction with acidic permanganate yields **II** and **III**. What is the structure of elaidic acid? Indicate stereochemistry.



I



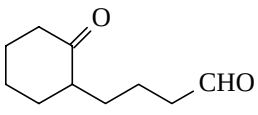
II



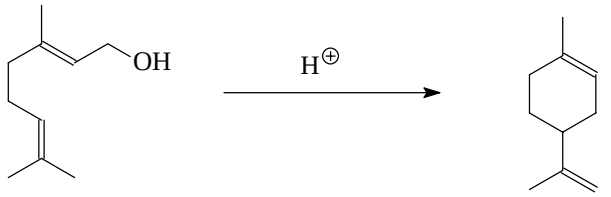
III

28. Compound **A** ($C_{10}H_{18}O$) reacts with H_2SO_4 to give **B** ($C_{10}H_{16}$) and an isomer **C**. Ozonolysis of **B** yields a diketone; ozonolysis of **C** yields **D**. (a) Draw structures for **A**, **B**, and **C.** (b) Describe a simple chemical color test that would differentiate **A** from **B** or **C**.

A **B** **C**



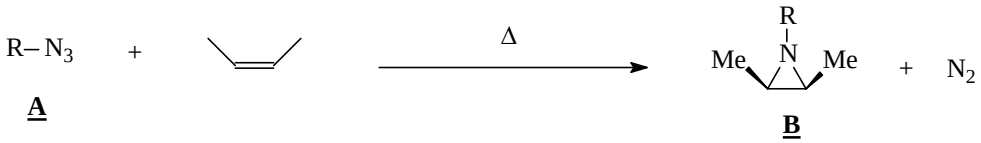
D

29. 

limonene (volatile in lemons and oranges)

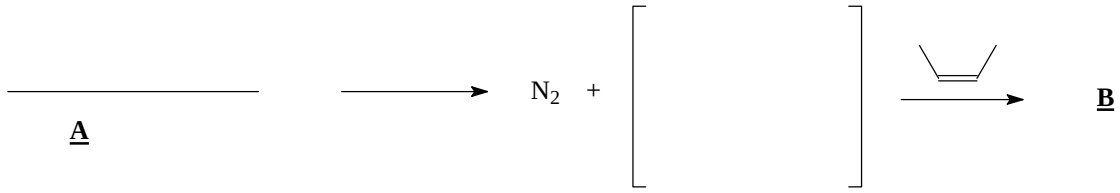
Hint: some alcohols can be protonated to form oxonium ions which may then "leave" as water to give a carbocation.

30. Aziridines (**B**) are nitrogen analogs of epoxides and can be made from azides (**A**) by the following reaction:



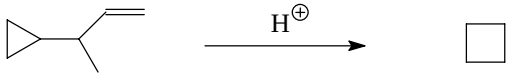
A **B**

Recalling the mechanism of generating carbene from diazomethane, and the fact that nitrogen is an excellent "leaving group," (a) draw the resonance structure of **A** that *best* illustrates how it can decompose to extrude N_2 and (b) supply electron flow arrows to show the *structure of the reactive intermediate* derived from **A** that reacts with *cis*-2-butene to give **B**.



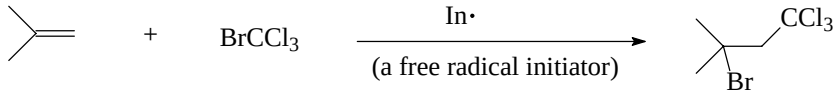
A

(c) Given the observed stereochemistry, what *type* of mechanism does this addition reaction illustrate?

31. 

(an olefin - complete)

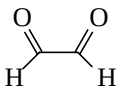
32. styrene (vinylbenzene) $\xrightarrow[\text{2. base}\\\text{3. } \textit{dry}\text{ HCl}]{\text{1. } Cl_2,\ H_2O}$

33. 

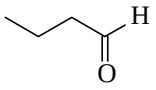
34. Compound **A**, $C_{16}H_{30}O$, is a sex attractant (pheremone) for the male silkworm moth. Given the data from the following three experiments, deduce the structure of **A**, clearly showing its stereochemistry.

a. Catalytic hydrogenation of **A** yields $C_{16}H_{34}O$.

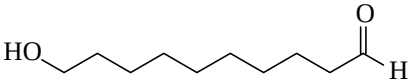
b. Ozonolysis of **A**, followed by treatment with zinc and acid, yields compounds **B**, **C**, and **D**.



B



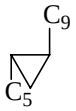
C



D

c. *Incomplete* reaction of **A** with diazomethane (CH_2N_2) gives a mixture of **E** and **F** (the C_{11} and C_9 substituents contain one oxygen atom). Note: this experiment establishes the stereochemistry of **A**.

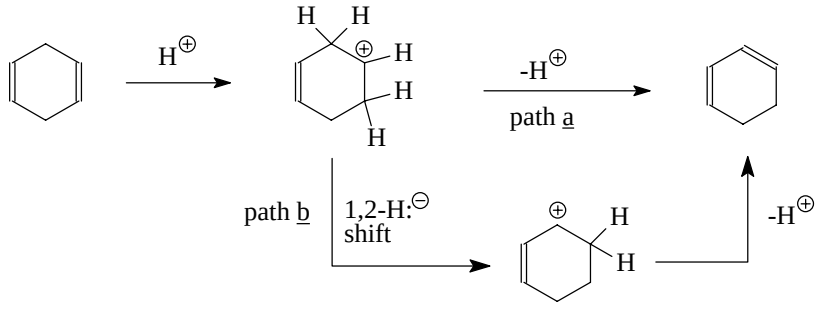
E



F

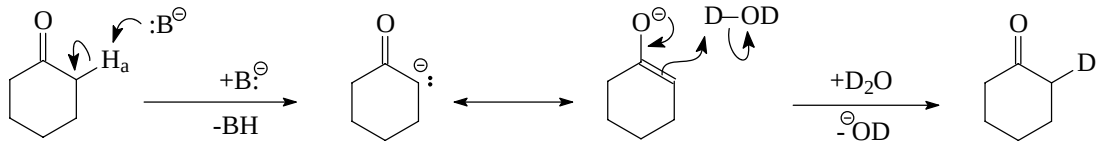
A = _____

35. 1,4-Cyclohexadiene undergoes isomerization to 1,3-cyclohexadiene in the presence of acid. Two mechanisms are possible: protonation followed by deprotonation (path a) *vs*. protonation followed by a 1,2-hydride shift and subsequent deprotonation (path b):



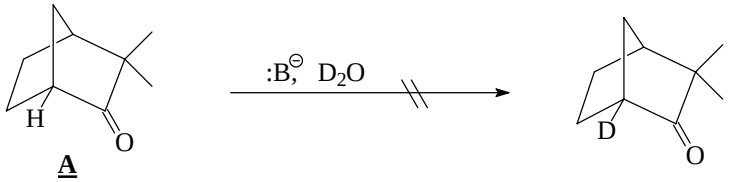
If 3,3,6,6-tetradeuterio-1,4-cyclohexadiene is treated with acid, 1,2,5,5-tetradeuterio-1,3-cyclohexadiene is formed. Which path is favored? (Note: C-H bonds are *slightly* weaker than C-D bonds.)

36. Carbonyl groups greatly affect the acidity of nearby (α-) protons. For example, the pK_a of cyclohexane is about 60, but the pK_a of H_a in cyclohexanone is about 20. This dramatic increase in acidity is largely a consequence of resonance stabilization of the conjugate base of the latter (for an example of the additive effect on pK_as of 1,3-dicarbonyls, see problem 1.3, 7), and allows an easy exchange of α-hydrogen for deuterium atoms by the following mechanism:



cyclohexanone

Under the same conditions, however, species **A** does not undergo hydrogen-deuterium exchange. Explain. Hint: consider the geometric constraints of olefinic moieties.



A

CHAPTER 6
ALKYNES

6.1 Reactions

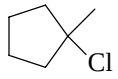
Draw the structural formula of the major organic product(s). Show stereochemistry where appropriate.

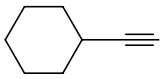
1. 3-penten-1-yne $\xrightarrow[2.\ D_2O]{1.\ NaH}$

2. 1-octyne $\xrightarrow{H^{\oplus},\ HgSO_4,\ PhOH}$

3. phenylacetylene $\xrightarrow[2.\ H_2O_2,\ ^{\ominus}OH]{1.\ B_2H_6}$

4. *n*-BuCl $\xrightarrow[2.\ Cl_2]{1.\ ^{\ominus}OMe,\ HOMe}$ $\xrightarrow[4.\ BH_3{\cdot}THF]{3.\ (XS)\ NaNH_2}$ $\xrightarrow{5.\ H_2O_2,\ ^{\ominus}OH}$

5.  $\xrightarrow{RC{\equiv}C{:}^{\ominus}}$

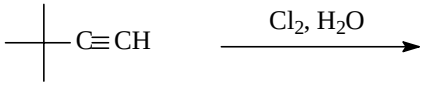
6.  $\xrightarrow[2.\ HBr,\ di\text{-}t\text{-}butyl\ peroxide]{1.\ Li\ /\ NH_3}$

7. isopropylacetylene $\xrightarrow[2.\ BH_3]{1.\ H_2\ /\ Pd(Pb)}$ $\xrightarrow{3.\ H_2O_2,\ ^{\ominus}OH}$

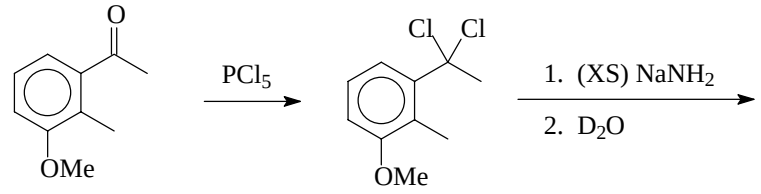
8. 1-decyne $\xrightarrow[2.\ CH_3(CH_2)_{12}Cl]{1.\ NaH}$ $\xrightarrow{3.\ Lindlar\ catalyst}$

muscalure (pheremone for house fly)

9. 1,1-dichlorobutane $\xrightarrow{1.\ (XS)\ NaNH_2}$ $\xrightarrow{2.\ H_3O^{\oplus},\ HgSO_4}$

10. 

11. PhC≡CH
1. (XS) HI
2. Zn(Cu), cyclopentene

12. 

13. H–C≡C–CH_2OH
1. $LiNH_2$ (2 equiv)
2. *n*-$C_5H_{11}Br$ (1 equiv)
3. $H^{\oplus}$

14. acetylene
1. $NaNH_2$ (1 equiv)
2. *n*-Pr-I
3. $NaNH_2$
4. *t*-Bu-Cl

6.2 Syntheses

Supply a reagent or sequence of reagents that will effect the following conversions.

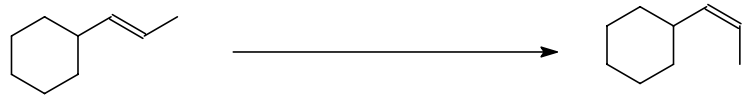
1. 

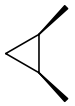
2. acetylene ⟶ *n*-pentyl bromide

3. vinyl chloride ⟶ methyl vinyl ether

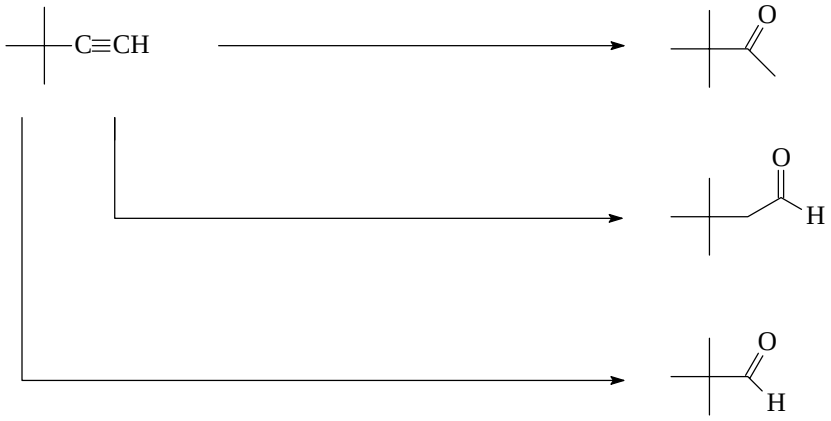
4. acetylene ⟶ (E)-3-octene

5. *t*-butylacetylene ⟶ 2-chloro-2,3-dimethylbutane

6. 

7. propyne ⟶ 

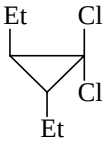
8. propyne ⟶ *n*-propyl bromide

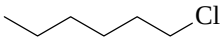
9. 

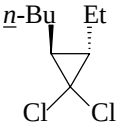
10. styrene ⟶ (E)-1-phenyl-1-butene

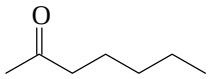
11. diphenylacetylene ⟶ *cis*-1,2-diphenylcyclopropane

⟶ PhCHO

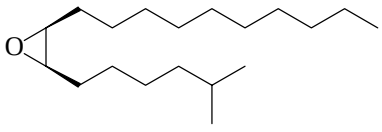
12. 3-hexyne ⟶ 

13. 

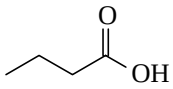
⟶ 

14. acetylene ⟶ 

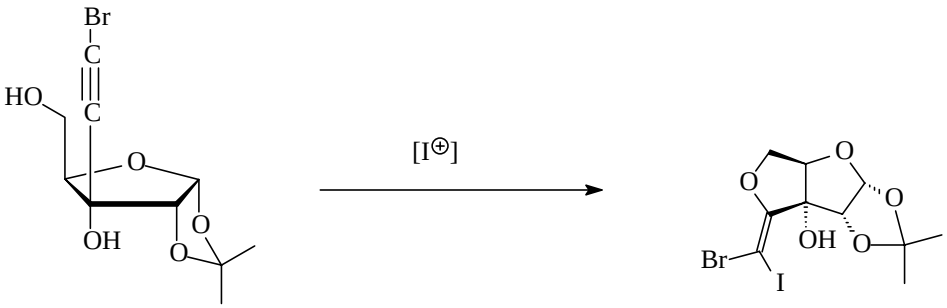
(odor of cheddar cheese)

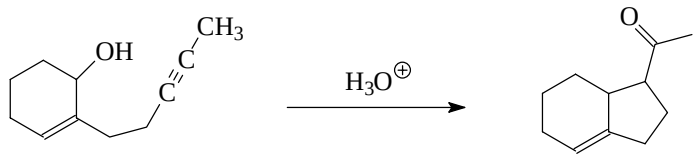
15. acetylene ⟶ 

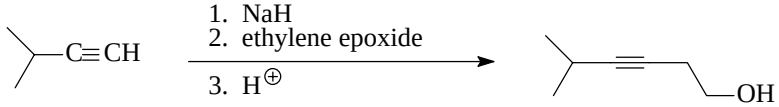
disparlure (pheremone for female gypsy moth)

16. 1-pentyne ⟶ 2 

6.3 Mechanisms

1. 

2. 

3. 

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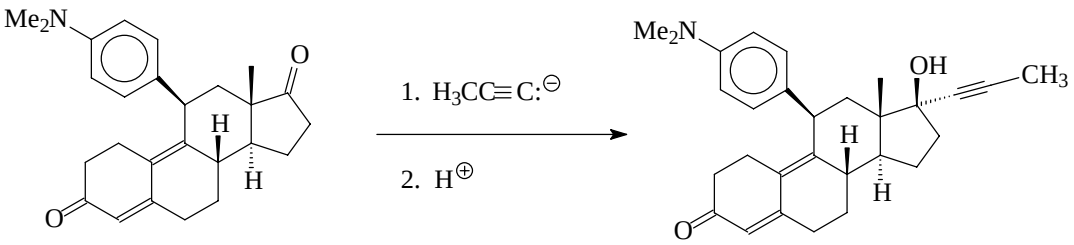
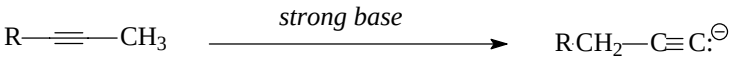


mifepristone (RU-486)

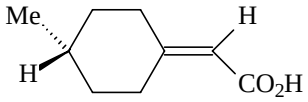
5. In the presence of *very* strong base an internal triple bond in *any* position of a straight chain alkyne will shift to the terminus of the chain, a process known as the *acetylene zipper reaction*:

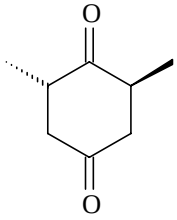


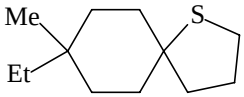
CHAPTER 7
STEREOCHEMISTRY

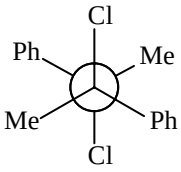
7.1 General

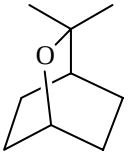
1. Which of the following molecules are chiral?

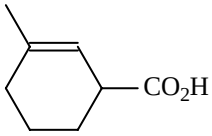
a. 

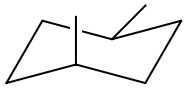
b. 

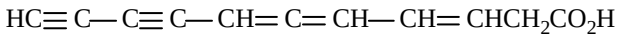
c. 

d. 

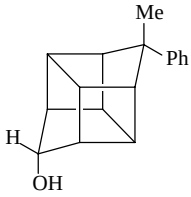
e. 

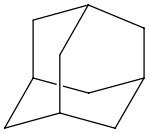
f. 

g. 

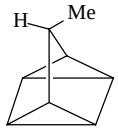
h. 

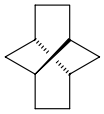
(an antibiotic)

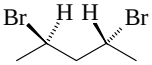
i. 

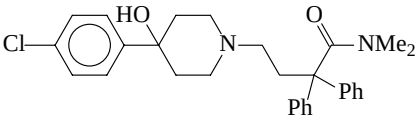
j. 

adamantane (an anti-viral agent)

k. 

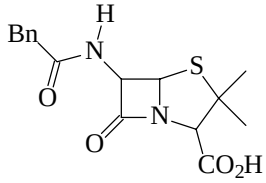
l. 

m. the C_2-epimer of 

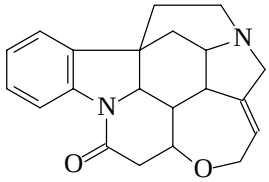
n. 

loperamide (Imodium™ - antidiarrheal)

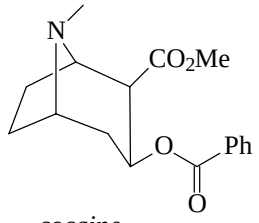
2. How many chiral carbons are there in each of the following molecules?

a. 

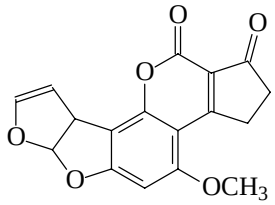
penicillin G

b. 

strychnine

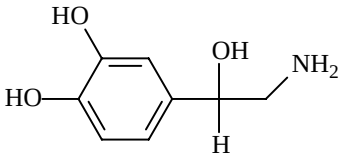
c. 

cocaine

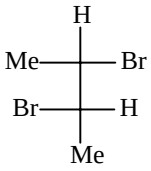
d. 

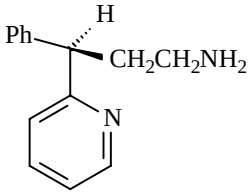
aflatoxin B_1

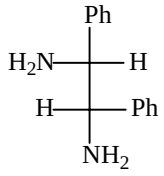
3. Identify each chiral center as (R)- or (S)-.

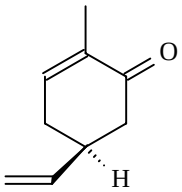
a. 

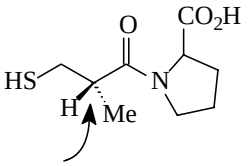
(-)-norepinephrine

b. 

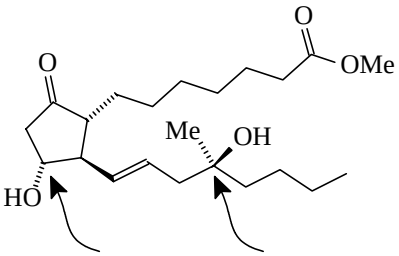
c. 

d. 

e. 

f. 

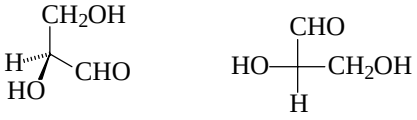
captopril (antihypertensive)

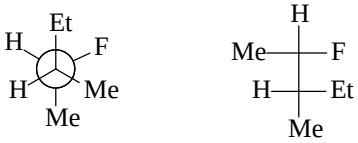
g. 

misoprostol (Cytotec™ - promotes cervical ripening)

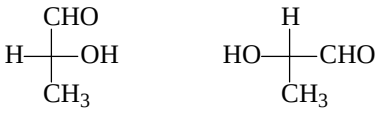
4. Identify each of the following pairs of structures as identical, enantiomers, or diastereomers.

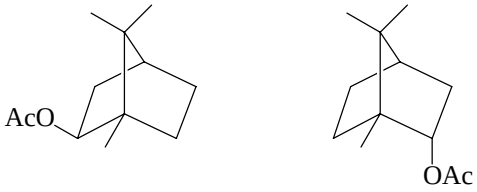
a. 

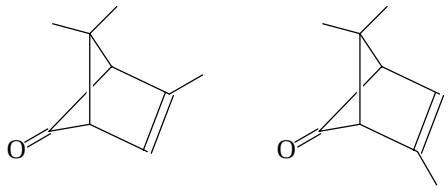
b. 

c. 

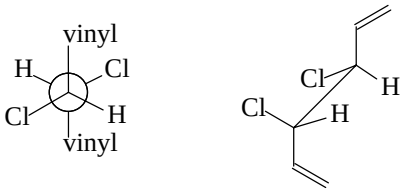
d. 

e. 

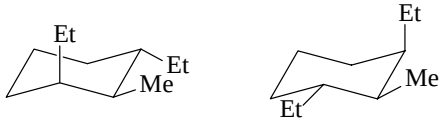
f. 

g. 

α-*pinene* (from pine resin)

h. 

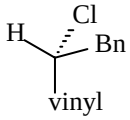
i. 

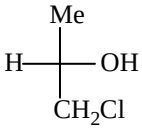
j. 

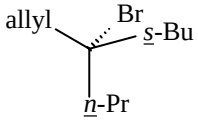
5. How many "kinds" of hydrogens (enantiomeric and diastereomeric hydrogens are different!) are there in

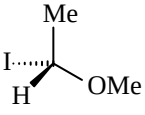
a. isohexane? b. (R)-2-chloropentane? c. (S)-4-chloro-1-pentene?

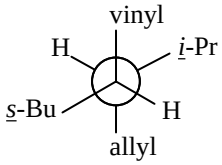
6. Nomenclature. Give the complete IUPAC name for the following:

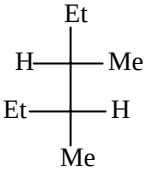
a. 

b. 

c. 

d. 

e. 

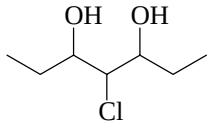
f. 

7. How many

a. *pairs of enantiomers* exist for bromochlorocyclopentane?

b. *geometric diastereomers* exist for 1,3-dichloro-2,4-dimethylcyclobutane?

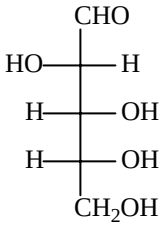
c. *pairs of enantiomers* are possible for chlorofluorocyclobutane?

d. *meso* stereoisomers and how many *enantiomeric pairs* exist for 

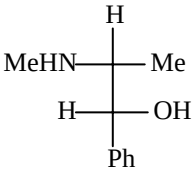
?

e. *meso* stereoisomers exist for 2,3,4,5-tetrachlorohexane?

8. a. *D-Xylose* is a common sugar found in maple trees. Because it is much less likely to cause tooth decay than sucrose, D-xylose is often used in the manufacture of candy and gum. D-Xylose is the C_4-epimer of the enantiomer of **A**. Draw its structure.



A



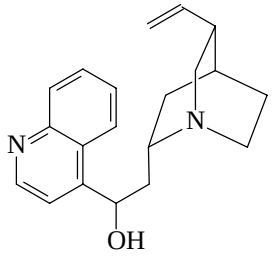
(-)-ephedrine

b. E*phedrine*, a very potent dilator of the air passages in the lungs, has been used to treat asthma. The naturally occurring stereoisomer, isolable from the plant *Ephedra sinica*, is levorotatory ($[\alpha] = -40^0$) and has the configuration above.

(i) Assign (R)- or (S)- configuration to each chiral center.

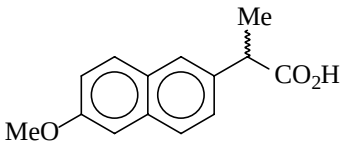
(ii) If a solution of (+) and (-) ephedrine has a specific rotation of $+10^0$, what percentage of the mixture is *dextrorotatory* enantiomer?

9. Optically pure *quinine* has a specific rotation of -170^0. What percent of levorotatory form is present in an optically impure sample whose [α] is $+68^0$? How many chiral carbons are there in quinine?



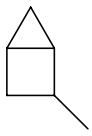
quinine

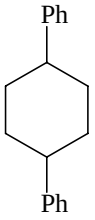
10. (*S*)-*Naproxen* is an active non-steroidal anti-inflammatory drug (NSAID), but the (R)-enantiomer is a harmful liver toxin. Assign the configuration for the (S)-enantiomer.

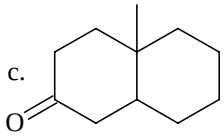


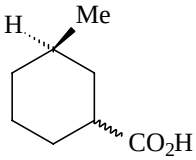
naproxin

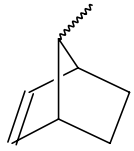
11. For each of the molecules below, indicate whether it is capable of *enantiomerism only* (**E**), *diastereomerism only* (**D**), or *both enantiomerism and diastereomerism* (**ED**).

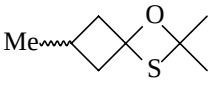
a. 

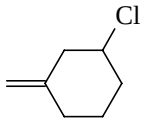
b. 

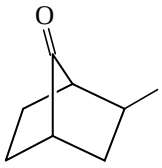
c. 

d. 

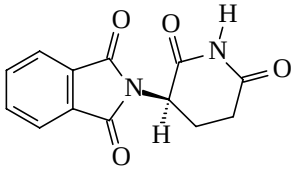
e. 

f. 

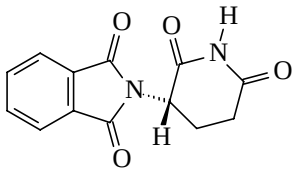
g. 

h. 

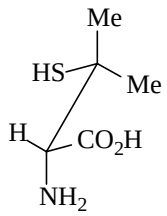
12. *Thalidomide* was used as a sedative and anti-nausea drug for pregnant women in Europe (1959-62). Unfortunately, it was sold as a racemate and each enantiomer has a different biochemical activity. One enantiomer, the (S)-form, is a teratogen that was responsible for thousands of serious birth defects. Which of the following is (R)-thalidomide?



vs.

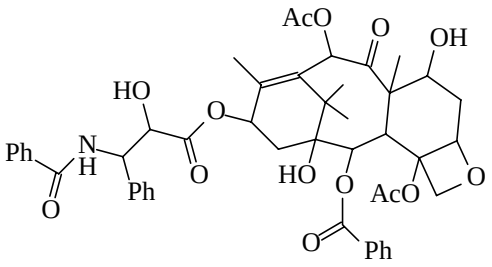


13. Another example of different enantiomers having remarkably different biochemical activities is *penicillamine*. The (S)-form has anti-arthritic properties, whereas the (R)-form is toxic. Which form is the following configuration?



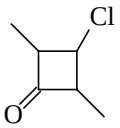
penicillamine

14. *Taxol* is an anticancer agent active against ovarian and breast tumors. (a) How many chiral carbons are in taxol? (b) If the specific rotation of optically pure taxol is -120°, and a synthetic preparation of taxol containing only its two enantiomers shows a specific rotation of +24°, what is the percentage of *dextrorotatory* enantiomer in the mixture?

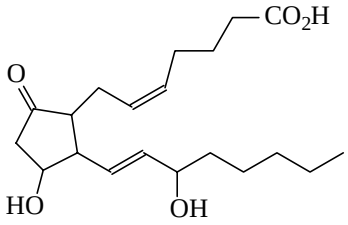


taxol

15. Compound **A** below has _____ chiral carbons, _____ *meso* stereoisomers, and _____ *pair*(s) of enantiomers.



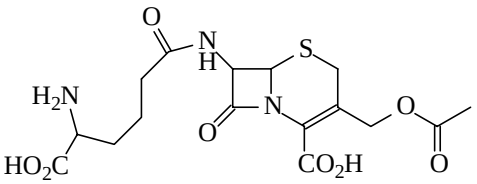
A



B *PGE_2* (a prostaglandin)

The number of stereoisomers possible for **B** is _____ (do not change *cis/trans* configurations of the olefins).

16. The antibiotic *cephalosporin C* has a specific rotation of +103° in water.



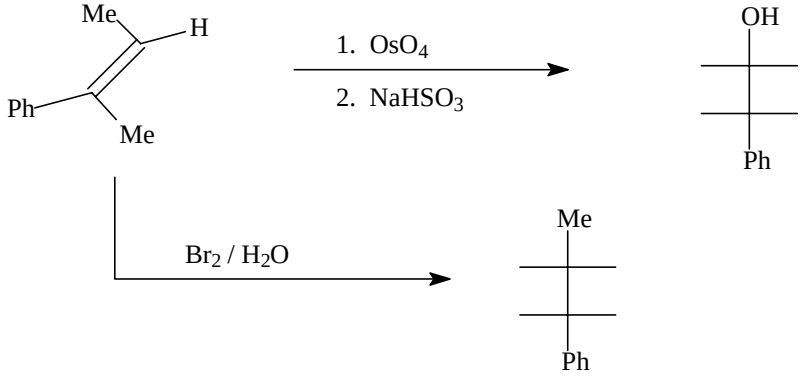
cephalosporin C

a. What is the maximum number of stereoisomers for the above structure?

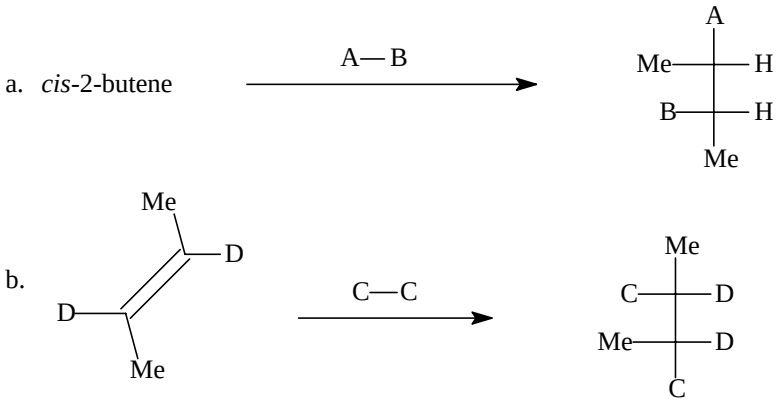
b. If a synthetic sample of cephalosporin C has an optical rotation of +82°, what percent of the enantiomers is levorotatory?

7.2 Reactions and stereochemistry

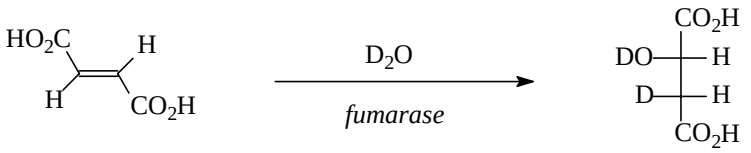
1. Draw the stereochemical formula for the major organic product(s) in the following reactions by completing the Fisher projections.



2. Have the following reactions proceeded with *syn*- or *anti*- stereochemistry?

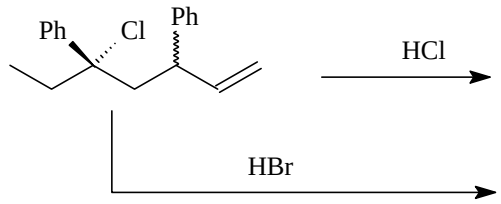


c. *Fumarase* catalyzes the following reaction in mitochondria:

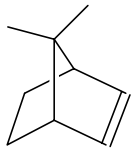


malic acid

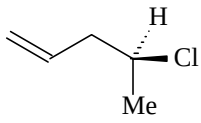
3. For each of the following reactions, (a) how many fractions could be collected by fractional distillation or recrystallization, and (b) for each fraction describe whether it is one enantiomer (**E**), a racemate (**R**), or a meso compound (**M**).

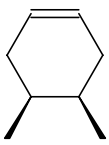
a. 

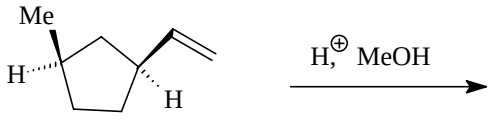
b. (Z)-3-hexene $\xrightarrow{Br_2}$

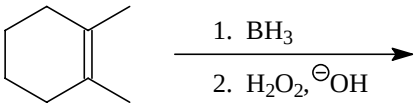
c. 

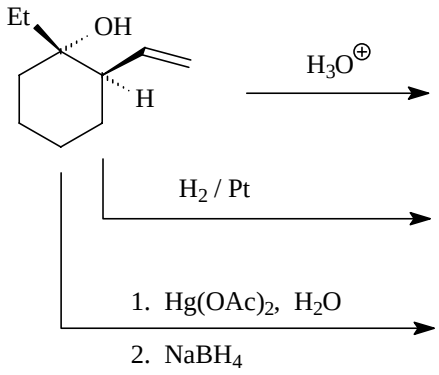
d. (S)-3-phenyl-1-butene $\xrightarrow{HI}$

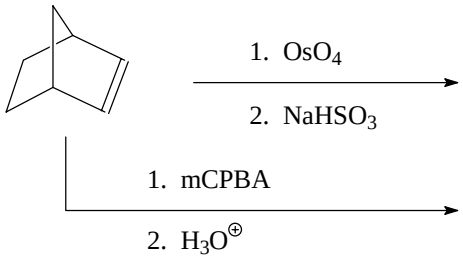
e. 

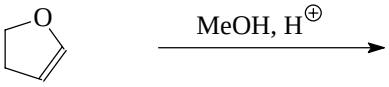
f. 

g. 

h. 

i. 

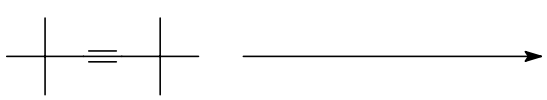
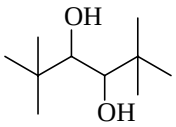
j. 

k. 

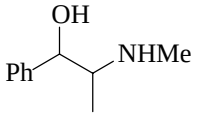
4. Outline syntheses for the following conversions that ensure the indicated stereochemical outcomes.

a. 

b. 2-butyne ⟶ *meso*-2,3-dibromobutane

c.  ⟶ *racemic* 

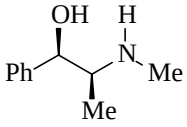
d. *trans*-2-butene ⟶ *meso*-glycol only

5. Consider the structure 

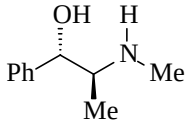
, and answer the following:

a. How many stereoisomers are possible?

b. Two of the structures are the decongestants *ephedrine* and *pseudoephedrine*:



ephedrine



pseudoephedrine

Which stereochemical term best describes their structural relationship?

c. The HCl salt of ephedrine has a specific rotation of -34^{o}. What would you predict for the specific rotation of the HCl salt of pseudoephedrine?

d. Both ephedrine and pseudoephedrine can be dehydrated to an olefin, which upon hydrogenation produces methamphetamine (“speed,” “meth”).

i. How many stereoisomers exist for the olefin?

ii. How many stereoisomers are possible for “meth”?

CHAPTER 8
ALKYL HALIDES AND RADICALS

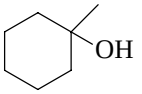
8.1 Reactions

Draw the structural formula of the major organic product(s). Show stereochemistry where appropriate.

1. How many different dichlorides could be isolated by ordinary physical methods (*e.g.*, fractional distillation) from the following reaction? Would each, as collected, be optically active or inactive?

2. Calculate the maximum % of (R)-2-bromopentane that could be formed from the reaction of bromine with *n*-pentane.

3. 2,3-dimethylbutane
   1. Br_2, Δ
   2. Mg
   3. D_2O

4. 

   1. conc HCl
   2. Li
   3. CuI
   4. allyl iodide

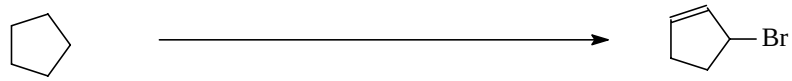
5. cyclobutane
   1. Cl_2, *hν* 2. Li
   3. CuI
   4. vinyl iodide 5. HI

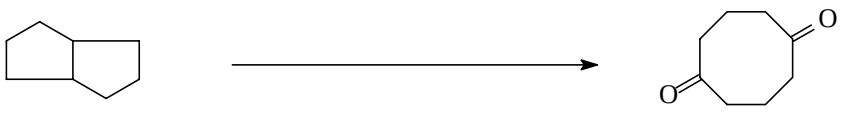
6. propane
   1. Br_2, Δ
   2. Mg
   3. phenylacetylene

7. bromobenzene
   1. Li 2. CuI
   3. *n*-PrBr 4. NBS, peroxides
   5. KOH 6. Br_2 / H_2O

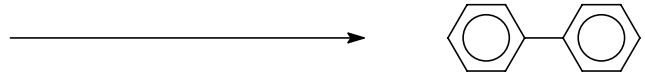
8.2 Syntheses

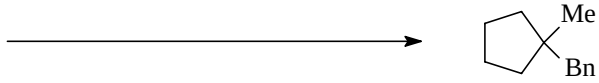
Supply a reagent or sequence of reagents that will effect the following conversions.

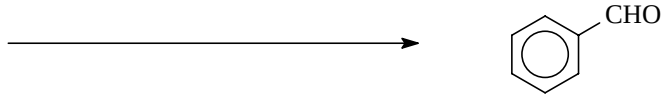
1. 

2. 

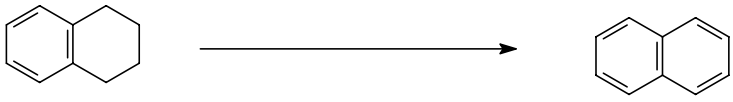
3. isopentane 

4. iodobenzene 

5. cyclopentane 

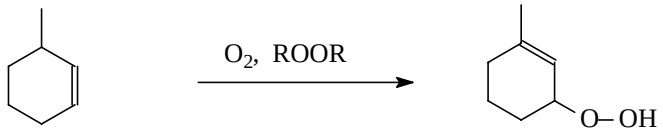
6. chlorobenzene 

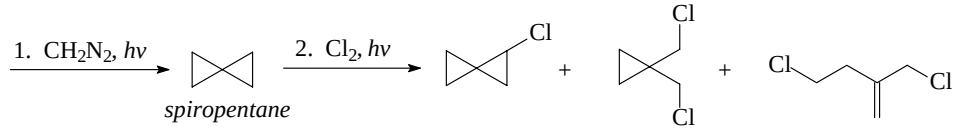
7. cyclohexene —(3 ways!)→ deuteriocyclohexane

8. 

8.3 Mechanisms

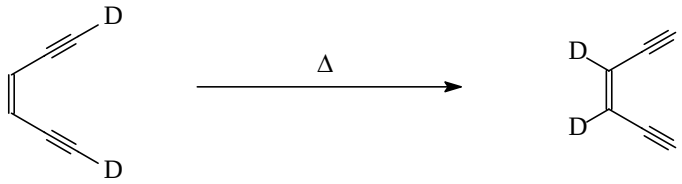
Outline a detailed mechanism for each of the following. No other reagents than those given are necessary. Use arrows to explain the flow of electrons and show all intermediates.

1. 

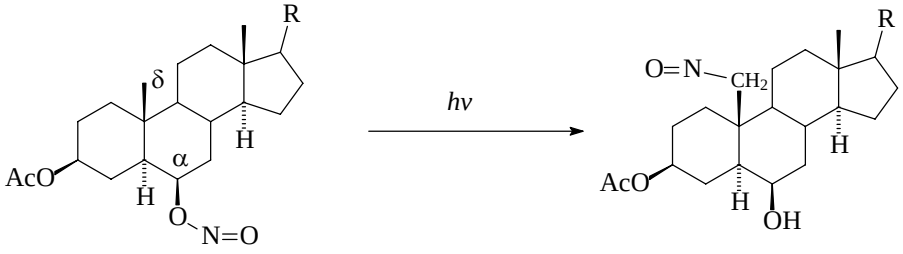
2. $H_2C{=}C{=}CH_2$ (*allene*) 

(propose a mechanism for step 2)

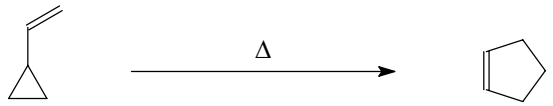
3. *Bergman reaction*:



4. Alkyl nitrite esters (RO-NO) readily undergo photolytic homolysis. The *Barton reaction* utilizes this fact to functionalize the remote δ-position of steroids. Use conformational analysis to explain.

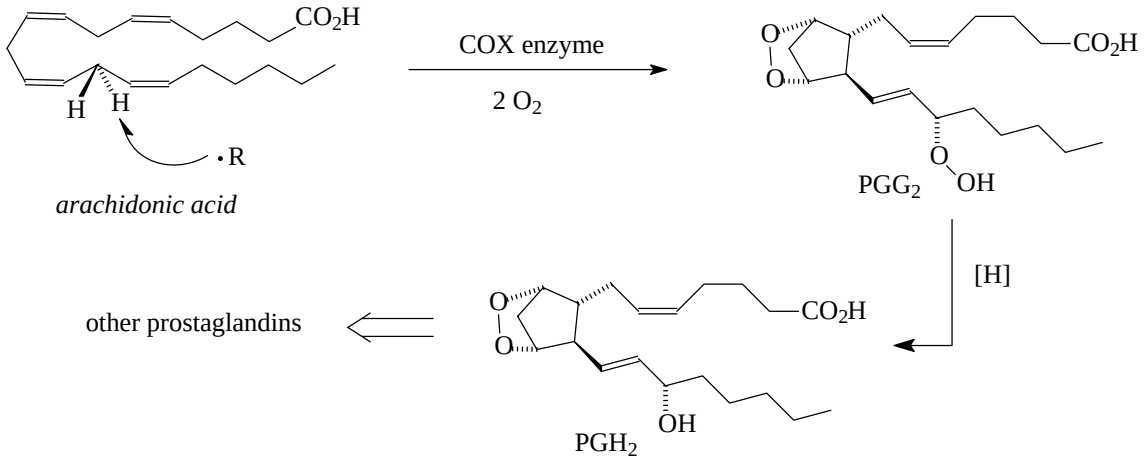


5. a. The *vinylcyclopropane – cyclopentene rearrangement* proceeds by a free radical mechanism. Explain. Hint: the cyclopropyl C-C bond is easily homolyzed.



b. Predict the product:

6. Aspirin, as well as other non-steroidal anti-inflammatory drugs (NSAIDS), blocks the synthesis of certain inflammation-mediating prostaglandins by inhibiting the enzyme cyclooxygenase (COX – see 5.1, 6d). COX converts arachidonic acid to the prostaglandin PGG_2, which subsequently undergoes reduction to give PGH_2. Other prostaglandins derive from the latter. Outline a mechanism for the synthesis of PGG_2. Hint: begin by a free radical removal of one of the doubly allylic hydrogen atoms.



CHAPTER 9

S_N1, S_N2, E1, AND E2 REACTIONS

9.1 General

For problems 1 – 9, circle the

1. reaction that will go *faster*:

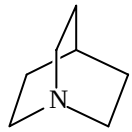
a. $AcO^{\ominus}$ + allyl chloride $\xrightarrow{\text{ethanol}}$

b. $AcO^{\ominus}$ + allyl chloride $\xrightarrow{\text{HMPA}}$

2. structure with the *poorest* leaving group:

a. R-SH b. R-NH_2 c. R-OAc d. R-OH

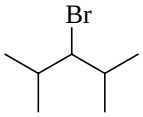
3. *stronger* nucleophile:

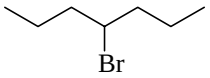
a. 

b. Et_3N

4. alkyl halide most reactive by an S_N2 pathway:

a. 

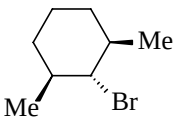
b. 

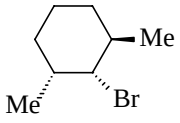
c. 

5. solvent that will *maximize* the rate of the reaction of Et_3N with *n*-BuBr:

a. DMSO b. MeOH c. PhH d. chloroform

6. halide that will react *more rapidly* by an E2 pathway:

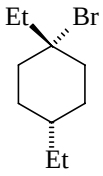
a. 

b. 

7. approximate value of k_H / k_D when $PhCHBrCH_3$, *vs.* $PhCDBrCD_3$, is allowed to react with potassium *t*-butoxide:

a. 1 b. <1 c. >1

8. reaction that will yield the more stereochemically pure product(s):

a. 

(or diastereomer) $\xrightarrow{\text{methanolysis } (S_N)}$

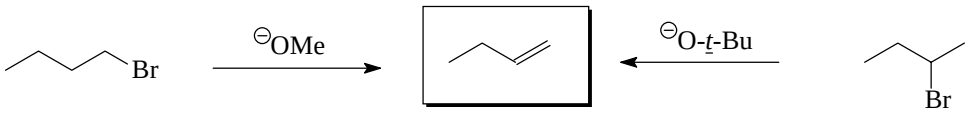
b. (R)-2-bromopentane (or enantiomer) $\xrightarrow{MeO^{\ominus},\ MeOH\ (S_N)}$

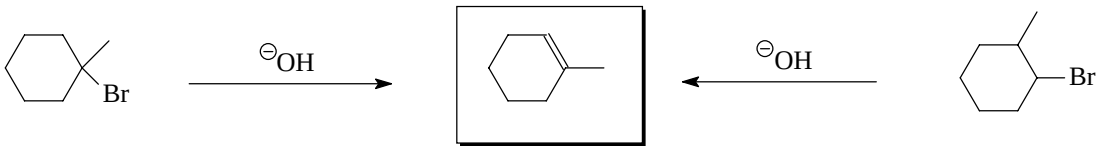
9. *change* in rate of reaction if the concentration of Ph_2CHBr is *tripled* and the concentration of ethanol is *doubled*:

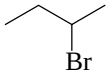
a. rate is unaffected b. rate triples c. rate doubles
d. rate increases 5-fold e. rate increases 6-fold

---

10. Which would be the *reaction of choice* (higher yielding) for each of these syntheses?

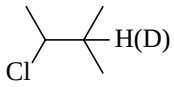
a. 

b. 

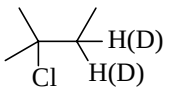
c. 

+ $^{\ominus}OR$ *vs.* $^{\ominus}SR$ (which?) to maximize S_N

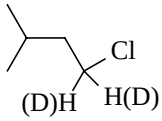
11. Which reaction would be expected to show a *primary hydrogen kinetic isotope effect*?

a. 

$\xrightarrow[t\text{-BuOH}]{\text{KO-}t\text{-Bu}}$

b. 

$\xrightarrow[\text{MeOH}]{\text{KOH}}$

c. 

$\xrightarrow[\text{MeOH}]{\text{KOMe}}$

12. The following reaction might be envisioned as occurring by an intramolecular S_N2 process. However, kinetic evidence indicates a bimolecular mechanism. Explain.

9.2 Reactions

Identify (if not already stated) each reaction as largely S_N1, S_N2, E1, or E2 – then draw the structural formula of the major organic product(s). Show stereochemistry where appropriate.

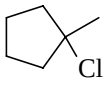
1. *n*-octyl bromide + $KOCH_3$ —MeOH→

2. 3-iodo-3-methylpentane + sodium ethoxide / EtOH →

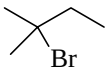
3. potassium *t*-butoxide + *sec*-BuCl →

4. 2-bromo-3-methylbutane + lithium diisopropylamide →

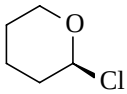
5. *n*-hexyl iodide —KCN / DMF→

6. 

—methanolysis (RT)→

7. 

—refluxing EtOH→

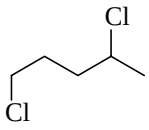
8. 

—acetolysis (S_N)→

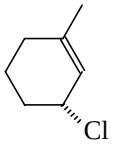
9. *n*-propyl bromide + Me_2NH ⟶

10. isopropyl bromide + sodium *t*-butoxide ⟶

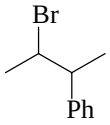
11. 3-iodopentane —sodium acetate / DMF→

12. 

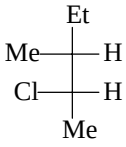
—NaSH (1 equiv)→

13. 

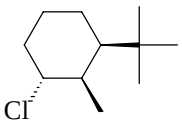
—ethanolysis (S_N)→

14. 

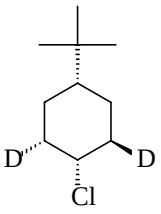
—$^{\ominus}$OAc / $Ag^{\oplus}$→

15. 

—$^{\ominus}$OEt (E)→

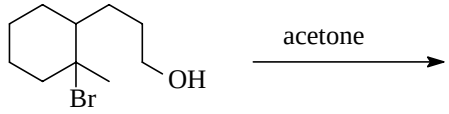
16. 

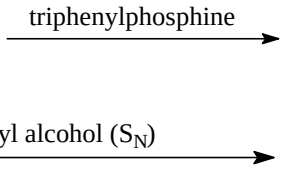
—$^{\ominus}$OMe / MeOH→

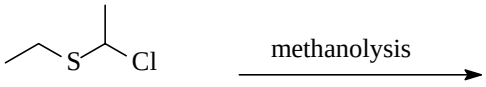
17. 

—E2→

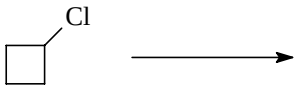
18. 

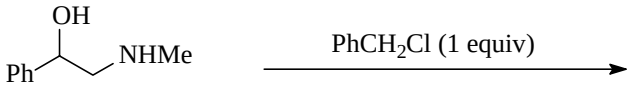
19. 

20. 4-iodo-1-pentane 

21. 

22. 

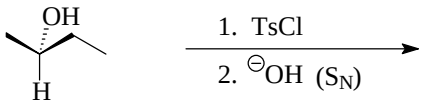
23. conjugate base of H_2Se + 

24. 

ephedrine

25. 

choline

26. 

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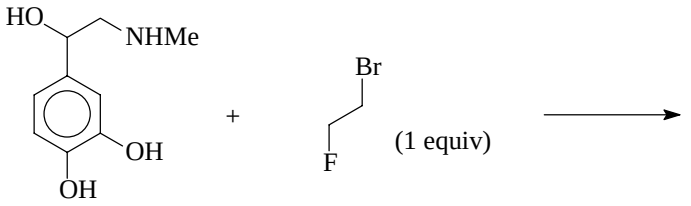
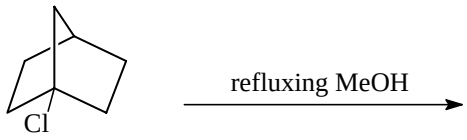
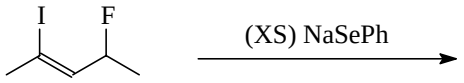
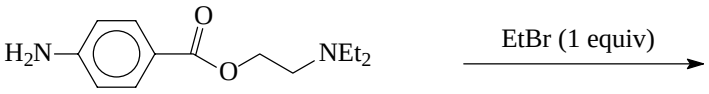
28. 

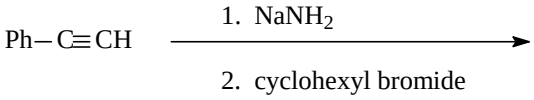
epinephrine

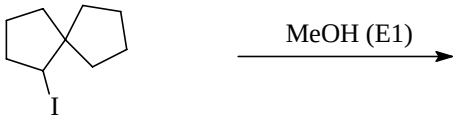
29. 

30. 

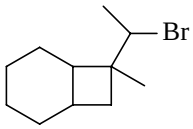
31. 

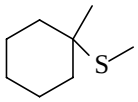
Novocaine™

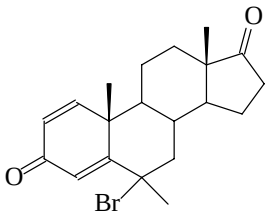
32. 

33. 

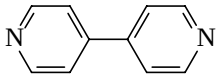
34. Ph–OTs $\xrightarrow{\text{KSCN}}$

35.  $\xrightarrow[\text{RT}]{\textit{acetolysis}}$

36.  $\xrightarrow[\text{2. refluxing EtOH}]{\text{1. MeI}}$

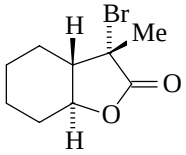
37.  $\xrightarrow{\text{KO-}t\text{-Bu / }t\text{-BuOH}}$

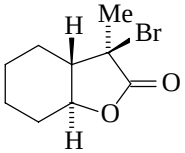
Aromasin™ (an aromatase inhibitor used in breast cancer therapy)

38.  $\xrightarrow{\text{(XS) MeI}}$

paraquat (an herbicide)

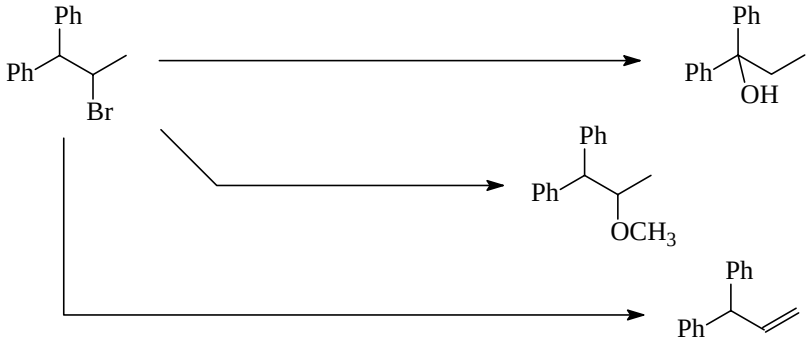
39.

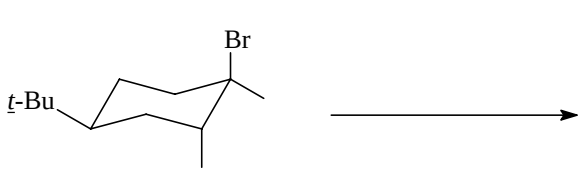
a.  $\xrightarrow[\text{EtOH}]{\text{EtO}^{\ominus}}$

b.  $\xrightarrow[\text{EtOH}]{\text{EtO}^{\ominus}}$

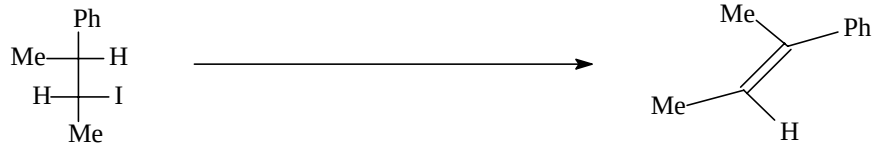
9.3 Syntheses

Supply a reagent or sequence of reagents that will effect the following conversions.

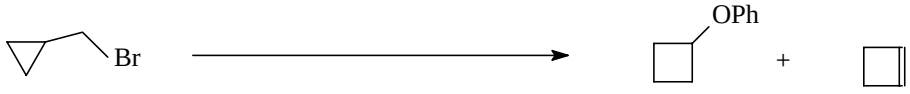
1. 

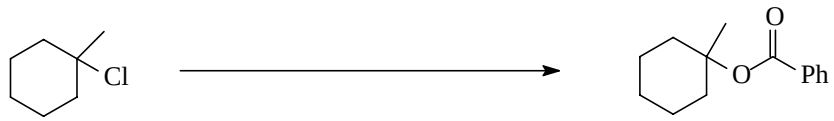
2. 

3. 

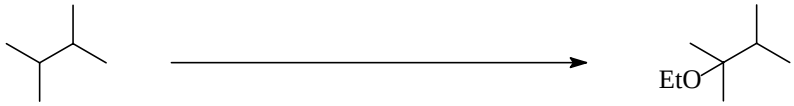
4. 

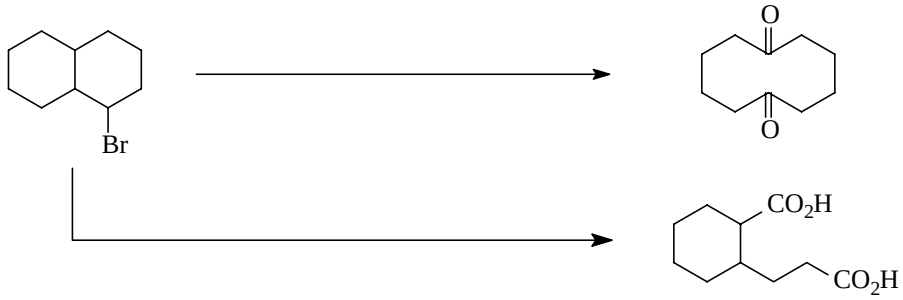
5. 

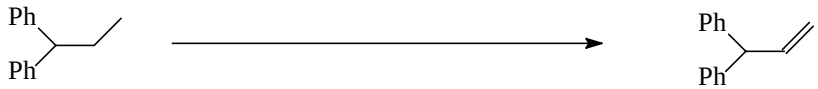
6. 

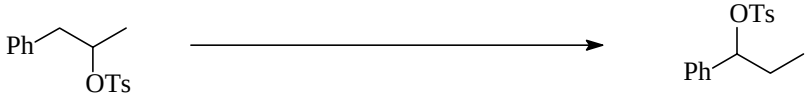
7. 

8. 

9. 

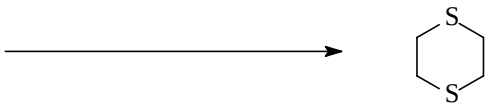
10. 

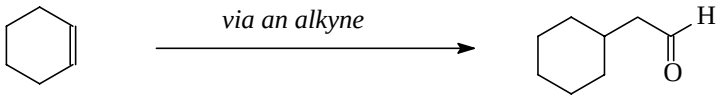
11. 

12. 

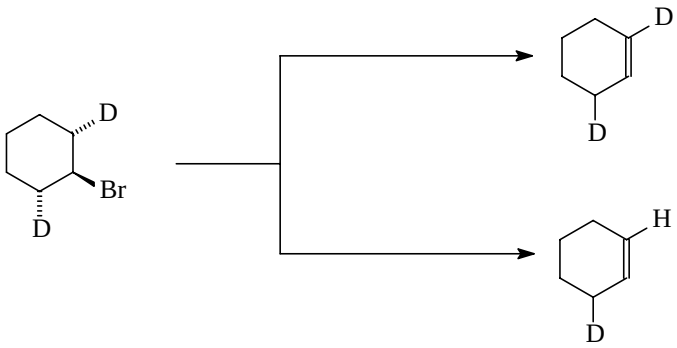
13. 

14. 

15. ethylene 

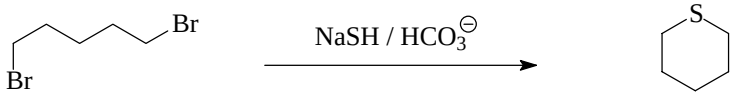
16. 

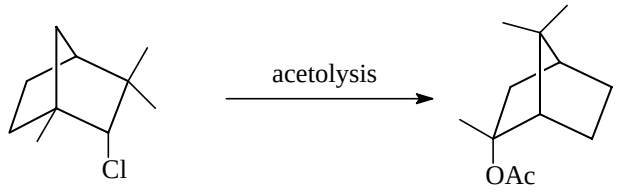
17. 

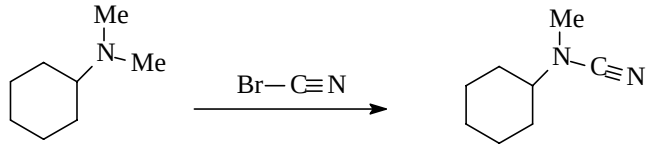
18. 

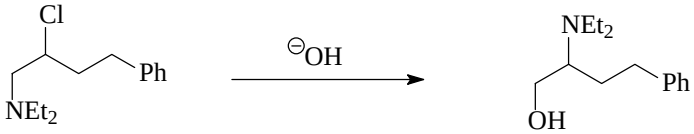
9.4 Mechanisms

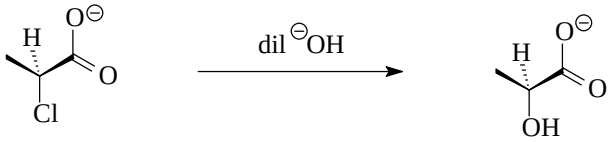
Outline a detailed mechanism for each of the following. No other reagents than those given are necessary. Use arrows to explain the flow of electrons and show all intermediates.

1. 

2. 

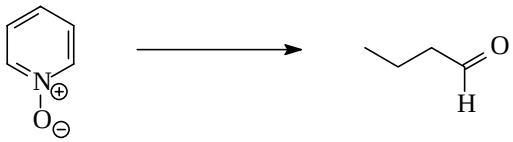
3. 

4. 

5. 

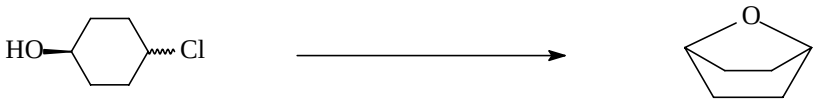
(Note: *retention* of configuration!)

6. 

7. <u>*n*</u>-butyl bromide + 

pyridine N-oxide

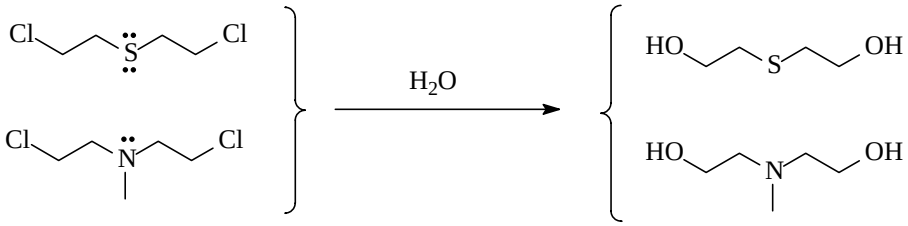
8. When treated with hydroxide, *trans*-**A** yields **B**. However, when *cis*-**A** is treated with hydroxide, no **B** is observed. Explain.



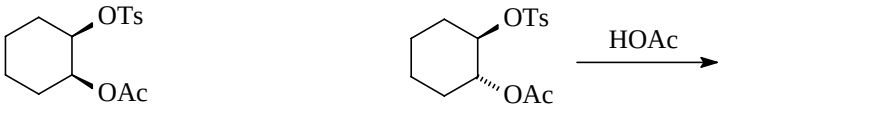
A **B**

Problems 4 and 5 above illustrate the concept of "*neighboring group participation*" (NGP), wherein an *internal* nucleophilic atom (*e.g.*, N and O, respectively, in those examples) facilitates the ejection of the leaving group by an intramolecular S_N2 attack to form an unstable intermediate. This type of mechanism is often evidenced by (1) *rearrangement* (problem 4), (2) *stereochemistry* (problem 5), or (3) *kinetic data* (problem 9 below). Problems 9 – 16 are additional examples. Account for the observations mechanistically.

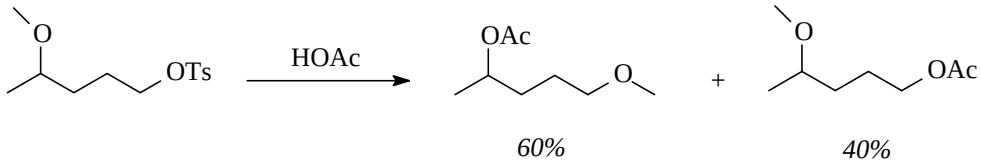
9. Unlike most primary alkyl halides the molecules below, types of sulfur and nitrogen mustard gases, do NOT undergo second order hydrolysis, but rather first order: $-d[RX]/dt = k[RX]$. Yet their rates of hydrolysis are *enormously faster* than those of most primary alkyl halides.



10. Compound **II** undergoes acetolysis at 75° about 10^3 times more rapidly than **I** and yields a racemate. Explain. What stereochemical outcome would you predict for the product from **I**?

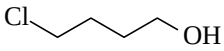


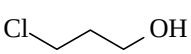
I **II**

11. 

12. Paquette (*OSU*) observed that **II** undergoes solvolysis, *e.g.*, acetolysis about 10^4 times more rapidly than **I**.

I **II**

13. 

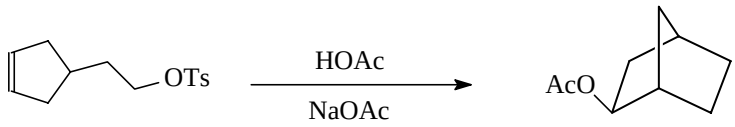
undergoes ethanolysis 5,700 times more rapidly than 

.

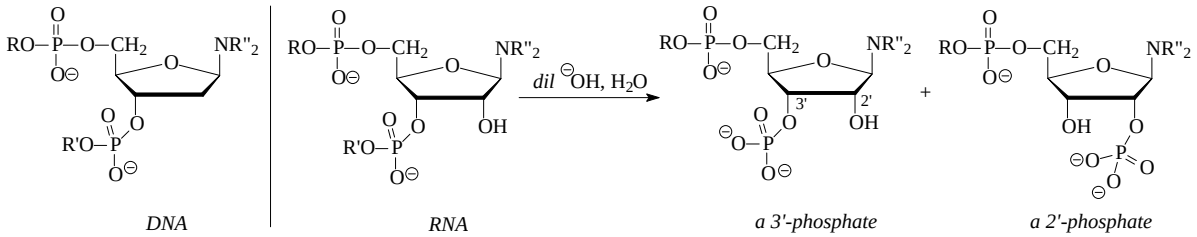
14. Sometimes a carbon-carbon double bond can act as a neighboring group nucleophile. For example, **II** undergoes acetolysis ~ 10^{11} times faster than **I** and does so with *retention of configuration*. Explain.

I **II**

15. In view of the previous problem, account for the following:

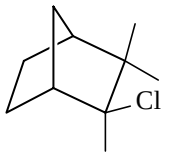


16. DNA is stable in dilute aqueous hydroxide solution, but RNA rapidly hydrolyzes. A mechanistic clue is provided in the observation that hydrolysis of the latter yields not only 3'-phosphates but also 2'-phosphates. Explain.



DNA *RNA* *a 3'-phosphate* *a 2'-phosphate*

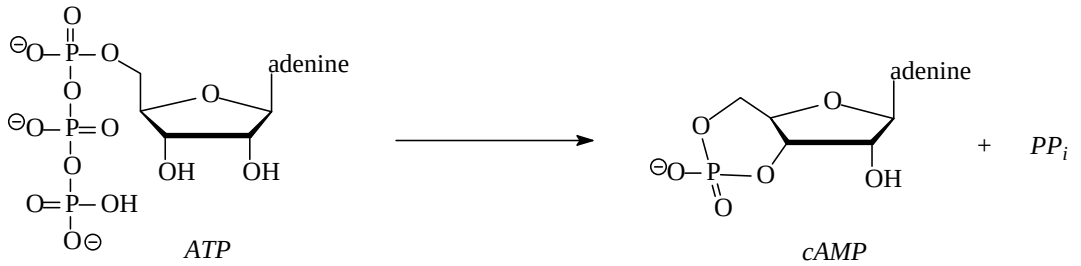
17.



$\xrightarrow{\Delta}$ *racemic* camphene + HCl

camphene hydrochloride

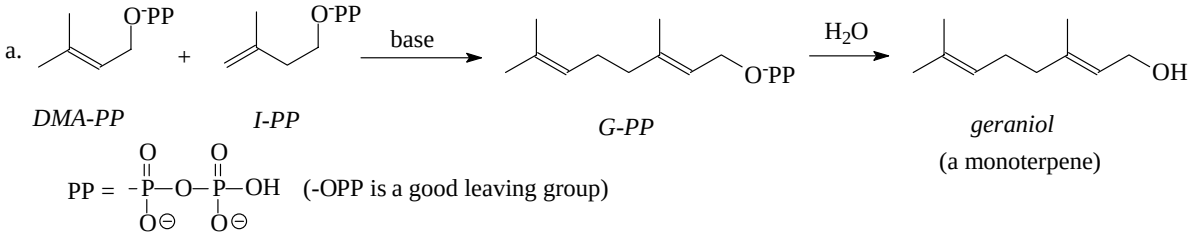
18.

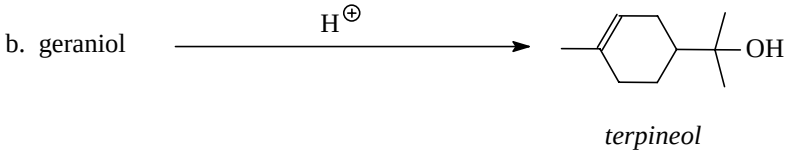


ATP *cAMP* + PP_i

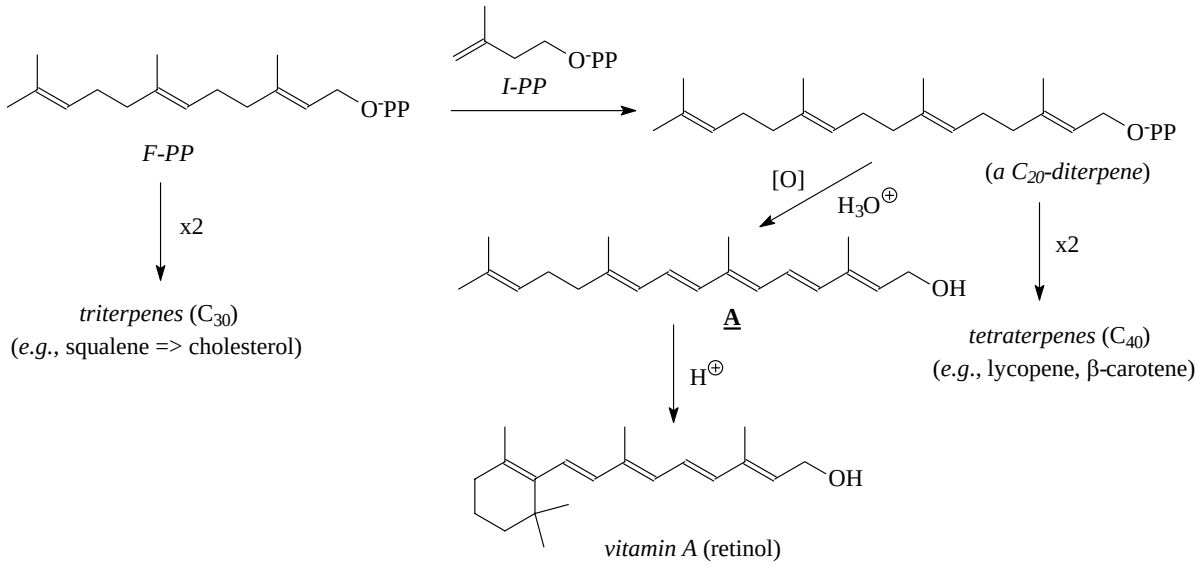
Some terpene chemistry…

19. The biosynthesis of *terpenes* (natural products constructed from the essence of *n* units of isoprene) begins with a "head-to-tail" coupling of two derivatives of isoprene, dimethylallyl pyrophosphate (*DMA-PP*) and isopentenyl pyrophosphate (*I-PP*) to form geranyl pyrophosphate (*G-PP*):



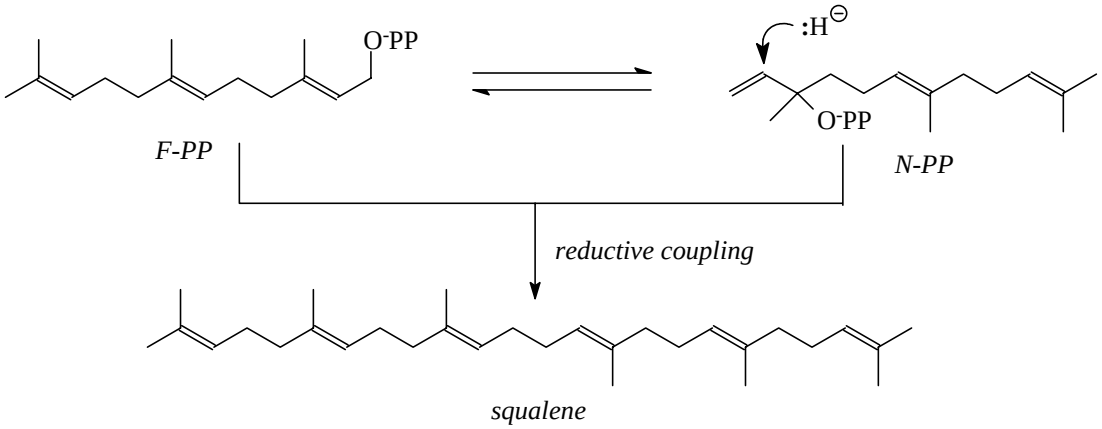


c. A similar coupling of *G-PP* with *I-PP* yields the C_{15}-sesquiterpene farnesyl pyrophosphate (*F-PP*) to produce a C_{20}-diterpene:

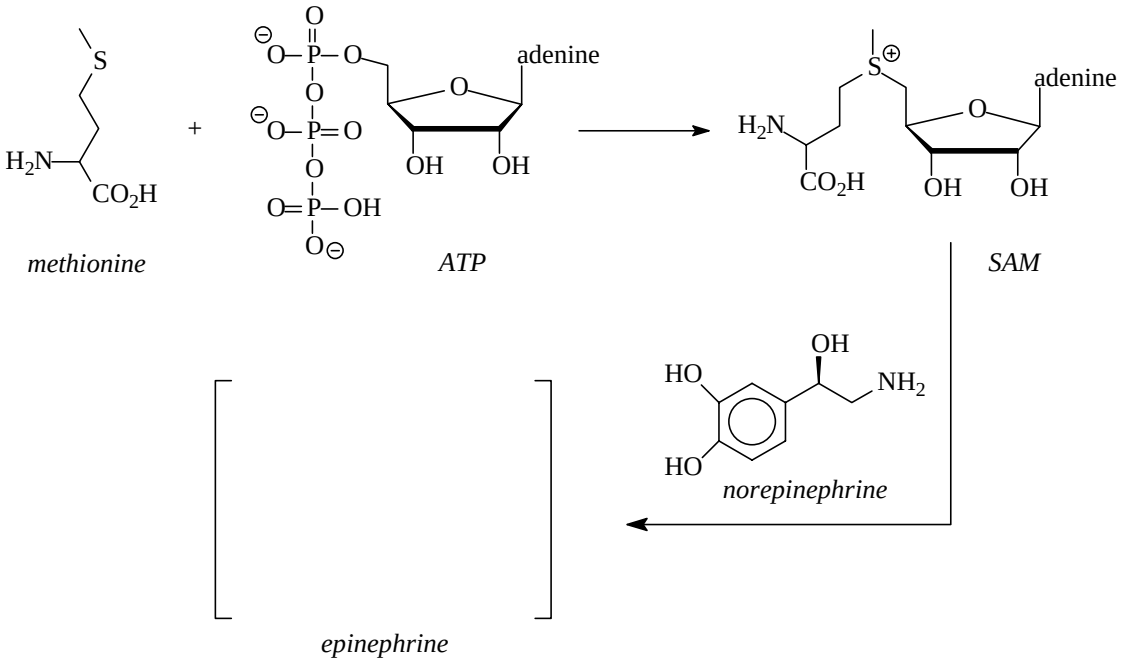


Outline a mechanism for the coupling and for the conversion of the diterpene **A** to vitamin A.

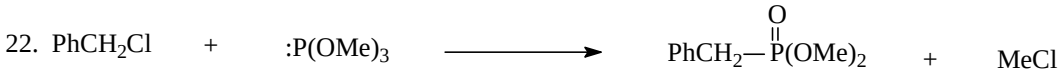
d. *F-PP* can isomerizes to nerolidol pyrophosphate (*N-PP*). *F-PP* and *N-PP* undergo a "head-to-head" reductive coupling by an E1 reaction to form the C_{30}-triterpene *squalene*. Outline the mechanisms for each of these events. Hint: reductive coupling is initiated by hydride attack on *N-PP* as shown below.

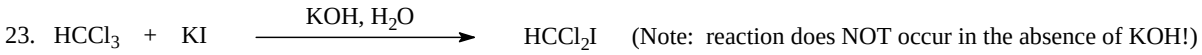


20. The most common methylating agent in biochemistry is *SAM* (S-adenosylmethionine), formed by an S_N reaction between the amino acid methionine and ATP. An example of a metabolic methylation is the conversion of *norepinephrine* (the prefix "*nor*" means one-less-carbon-than) to *epinephrine*. Formulate a mechanism for producing SAM and draw the structure of epinephrine.



21. 

22. 

23. 

(Note: reaction does NOT occur in the absence of KOH!)

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CHAPTER 10

NMR

Deduce the structures in problems 1 - 17 from the ^{1}H NMR and IR information.

1. **C_6H_{12}**: δ 0.9 (t, 3H), 1.6 (s, 3H), 1.7 (s, 3H), 2.0 (p, 2H), 5.1 (t, 1H); no long-range coupling evident.

2. **$C_6H_{12}Cl_2O_2$**: δ 1.3 (t, 6H), 3.6 (q, 4H), 4.4 (d, 1H), 5.4 (d, 1H).

3. **$C_8H_{18}O_2$**: IR (3405 cm^{-1}). ^{1}H NMR δ 1.3 (s, 12H), 1.5 (s, 4H), 1.9 (s, 2H).

4. **$C_{10}H_{14}O$**: IR (3200 cm^{-1}). ^{1}H NMR δ 1.2 (s, 6H), 1.6 (s, 1H), 2.7 (s, 2H), 7.2 (s, 5H).

5. **$C_5H_{10}O_4$**: δ 3.2 ((s, 6H), 3.8 (s, 3H), 4.8 (s, 1H).

6. **C_8H_9BrO**: δ 1.4 (t, 3H), 3.9 (q, 2H), 6.7 (d, 2H), 7.4 (d, 2H).

7. **$C_3H_5ClF_2$**: δ 1.75 (t, 3H), 3.63 (t, 2H).

8. **C_9H_{10}**: δ 2.04 (m, 2H), 2.91 (t, 4H), 7.17 (s, 4H).

9. **C_8H_9Br**: δ 2.0 (d, 3H), 5.3 (q, 1H), 7.6 (m, 5H).

10. **$C_4H_6Cl_2$**: δ 2.18 (s, 3H), 4.16 (d, 2H), 5.71 (t, 1H).

11. **$C_9H_{11}Br$**: δ 2.15 (m, 2H), 2.75 (t, 2H), 3.38 (t, 2H), 7.22 (s, 5H).

12. **$C_9H_{10}O_3$**: δ 2.3 (t, 2H), 4.1 (t, 2H), 7.3 (m, 5H), 11.0 (br s, 1H).

13. **$C_6H_{11}Br$**: δ 1.0 (s, 9H), 5.5 (d, 1H, J = 17 Hz), 6.6 (d, 1H, J = 17 Hz).

14. **C_8H_{14}**: δ 1.7 (s, 6H), 1.8 (s, 6H), 6.0 (s, 2H).

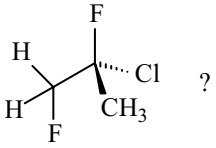
15. **$C_6H_{11}FO_2$**: IR (3412 cm^{-1}). ^1H NMR δ 1.2 (s, 6H), 2.2 (s, 3H), 3.8 (d, 1H), 4.1 (s, 1H).

16. **$C_7H_{14}O_2$**: IR (1610 cm^{-1}). ^1H NMR δ 1.0 (s, 9H), 2.1 (m, 2H), 3.8 (br s, 1H), 4.0 (t, 1H), 8.6 (t, 1H).

17. **$C_{11}H_{12}O_2$**: IR (1705 cm^{-1}). ^1H NMR δ 2.2 (s, 3H), 2.5 (s, 3H), 5.8 (m, 1H), 7.1 (d, 2H), 7.9 (d, 2H), 9.8 (s, 1H).

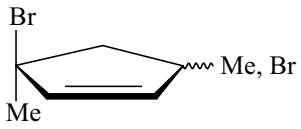
---

18. What is the *maximum* multiplicity for either of the methylene protons in the proton NMR for



?

19. The structure below represents two diastereomeric compounds, **A** and **B.** Compound **A** gives a *singlet* proton NMR for the methylene group, but **B** gives a *multiplet* for the same group. What are the structures of **A** and **B**?

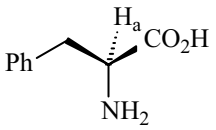


20. *Trans*-3-bromo-1-phenyl-1-propene shows a spectrum in which the vinylic proton at C_2 is coupled with the C_1 proton (J = 16 Hz) and the C_3 protons (J = 8 Hz). What is the expected multiplicity for that proton? Use a spin tree diagram to explain.

21. a. What is the multiplicity of the chemical shift at *highest* field in the proton NMR of (R)-1,2-dichloro-2-fluoropropane?

b. Use a spin tree diagram to explain why the *lowest* field chemical shift appears as a *triplet*.

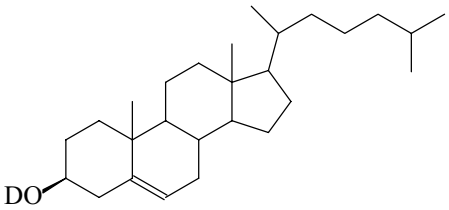
22. What is the *maximum* multiplicity for H_a in the amino acid phenylalanine?



phenylalanine

23. A compound has only two singlets in its ^{1}H NMR spectrum: δ 1.4 and 2.0 with relative intensities of 3:1. Its ^{13}C NMR spectrum has chemical shifts at δ 22, 28, 80, and 170. A strong absorption in its IR occurs at 1740 cm^{-1}. Draw a possible structure for the compound.

24. The following questions relate to deuterated cholesterol, drawn below:

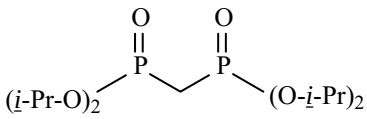


a. Predict the theoretical multiplicity of the *lowest field* proton.

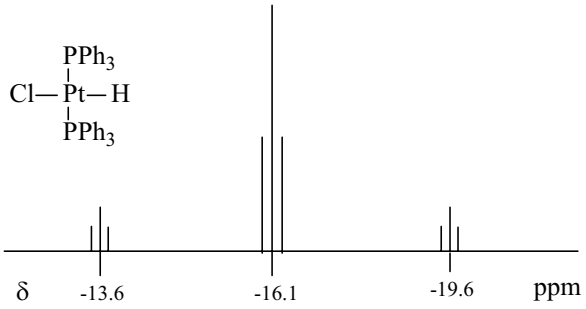
b. What is the maximum number of ^{13}C chemical shifts that would be expected for the C_8H_{17} alkyl side chain?

25. Treatment of 2,3-dibromo-2,3-dimethylbutane with SbF_5 (a very strong Lewis acid) in SO_2 at -60^0 yields SbF_6^- and a substance whose ^{1}H NMR shows only a singlet at δ 2.9. Draw the structure of that substance.

26. What is the *multiplicity* of the methylene group in the following compound?



27. Below is the structure and partial ^{1}H NMR for an organoplatinum compound. Platinum has three isotopes: ^{195}Pt (I = ½, 34% natural abundance), ^{194}Pt (I = 0), and ^{196}Pt (I = 0) – the latter two account for the remaining 66% natural abundance. (Note: aromatic proton resonances are not shown.)

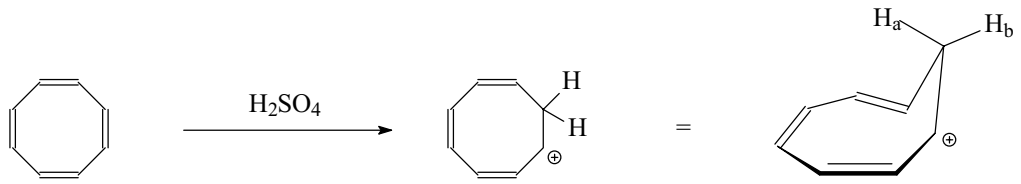


a. Explain the relative *amplitude* and *multiplicity* of the signal at δ -16.6. Clearly explain $J_{H,?}$ by using a spin tree diagram.

b. Explain the *amplitude* and *multiplicity* of the two signals at δ -13.6 and -19.6. Again, clearly explain $J_{H,?}$ by using a spin tree diagram.

c. What do the very negative chemical shift values of the signals suggest about the magnetic environment of the resonating proton?

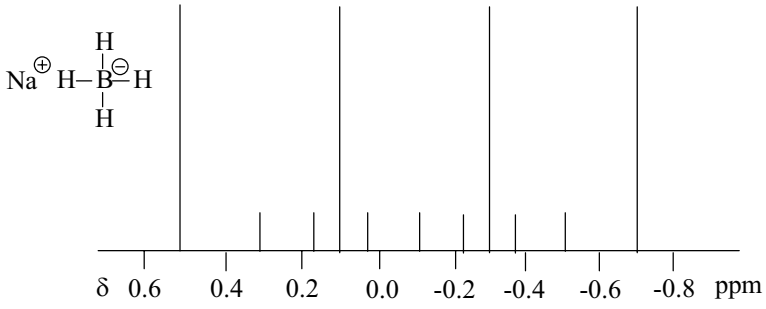
28. Pettit (*UT*) observed that the protonation of cyclooctatetraene (*COT*) yields a carbocation (*homotropylium ion*) that possesses *homoaromatic* stabilization. (*Homoaromatics* refers to π systems that are interrupted by a saturated center but in which the geometry still permits significant overlap of the *p* orbitals across a gap.)



COT *homotropylium ion*

The ^{1}H NMR of the homotropylium ion shows a remarkable chemical shift difference of 5.5 ppm for geminal protons H_a (δ 0.5) and H_b (δ 5.0). Each appears as a pseudoquartet. Explain both the location of the chemical shifts and multiplicities of these protons.

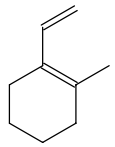
29. The ^{1}H NMR spectrum of $NaBH_4$ is shown below. Boron has two isotopes: ^{10}B (I = 3) and ^{11}B (I = 3/2) whose natural abundances are 20% and 80%, respectively. Interpret the spectrum.

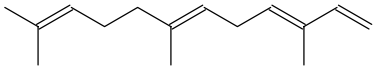


CHAPTER 11
CONJUGATED SYSTEMS

11.1 Reactions

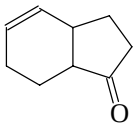
Draw the structural formula of the major organic product(s). Show stereochemistry where appropriate.

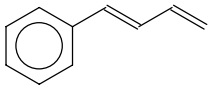
1.  HBr (1 equiv) → (1,4-addition)

2.  DCl (1 equiv) → (1,4-addition)

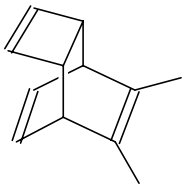
α-farnesene (in waxy coatings of apple skins)

3. isoprene + $MeO_2C—\equiv—CO_2Me$ ⟶

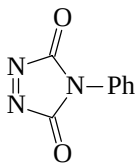
4.  retro D-A, Δ

5.  HBr (1 equiv) →

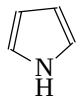
(*product of thermodynamic control*)

6.  Δ → 2-butyne +

7. 3-methyl-1,3,5-hexatriene → DBr (1 equiv), ROOR (1,4-addition)

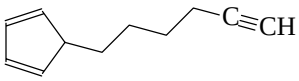
8.  +  ⟶

Cookson's dienophile

9.  + (Z)-1,2-diphenylethene ⟶

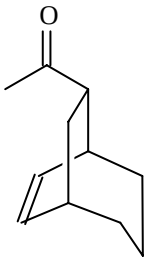
10. cyclohexene ⟶ (1. NBS, ROOR; 2. KOMe (E2); 3. phenylacetylene)

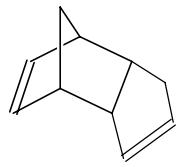
11. 4-vinylcyclohexene ⟶ (1. Δ (retro D-A); 2. *trans*-2-butene)

12.  ⟶ (*intra* D-A)

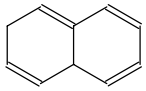
13.  ⟶ (1. vinyl chloride; 2. KO-*t*-Bu)

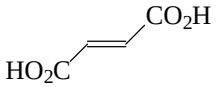
14. 1,3-cyclohexadiene ⟶ (1.  2. O_3 3. Zn, $H^{\oplus}$)

15.  ⟶ (Δ (retro 4+2))

16. 

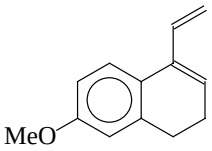
1. Δ (retro D-A)
2. *cis*-1,2-diphenylethylene

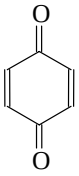
17. 

+ 

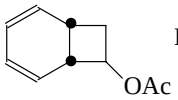
Δ

fumaric acid

18. 

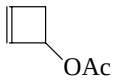
+ 

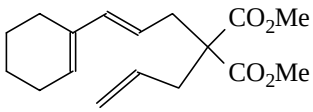
⟹ *estrone*

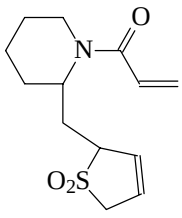
19. 

$HO_2C{\equiv}CO_2H$, Δ

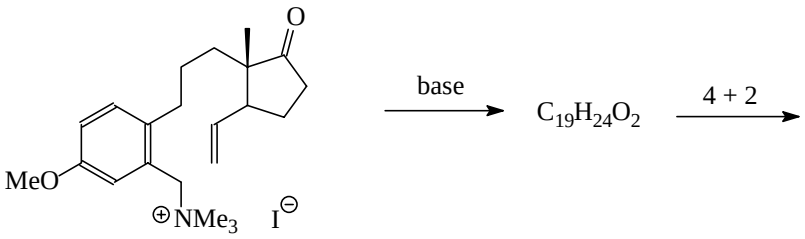
Δ

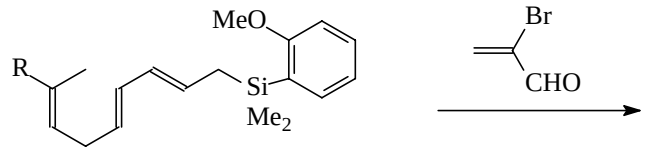
+ 

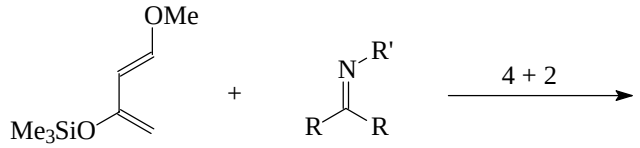
20. 

21. 

Δ → SO_2 +

22. 

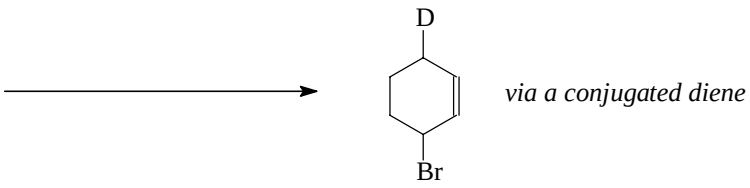
23. 

24. 

Danishefsky's diene

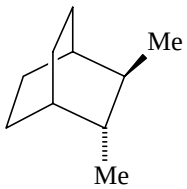
11.2 Syntheses

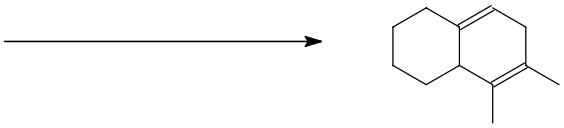
Supply a reagent or sequence of reagents that will effect the following conversions.

1. cyclohexane 

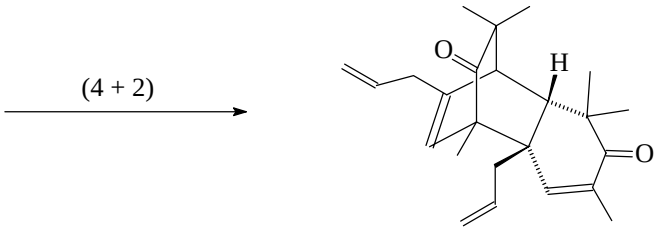
via a conjugated diene

2. cyclohexane ⟶ bicyclo[2.2.2]octane

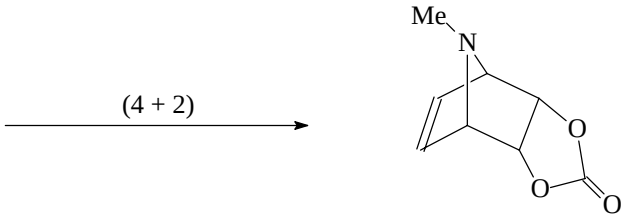
3. cyclohexene ⟶ 

4. vinylcyclohexane 

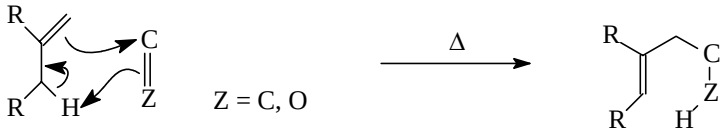
5. A Diels-Alder dimerization of **A** gives the indicated product. Draw the structure of **A**.

A 

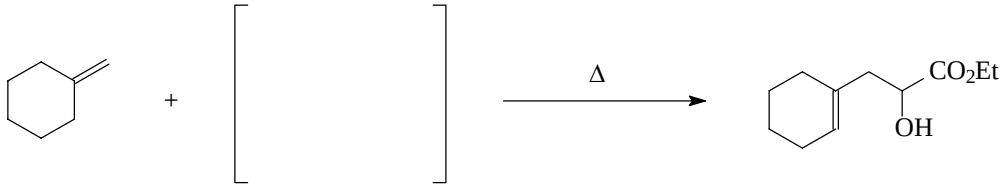
6. Draw the structures of the starting materials that may be used to synthesize the following product:

? 

7. The *Alder-ene reaction*, like the Diels-Alder, is a concerted (pericyclic) reaction:



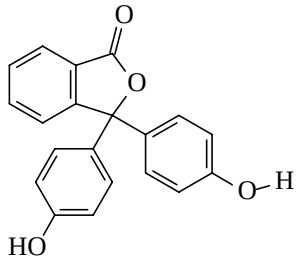
How could the following compound be prepared by an ene reaction?



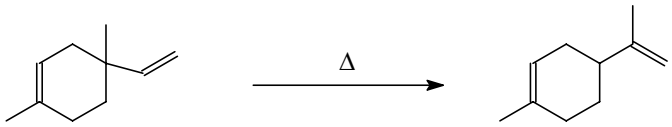
11.3 Mechanisms

Outline a detailed mechanism for each of the following. No other reagents than those given are necessary. Use arrows to explain the flow of electrons and show all intermediates.

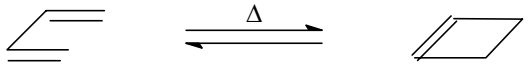
1. *Phenolphthalein* in solutions below pH 8.5 is colorless, but in solutions above pH 8.5 is a deep red-purple color. Explain.



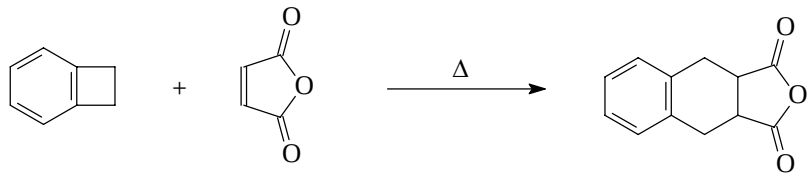
phenolphthalein

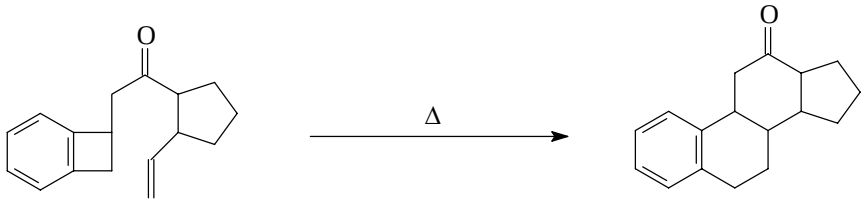
2. 

3. Similar to the Diels-Alder the following *electrocyclic reaction* is generally concerted (pericyclic) and readily reversible.

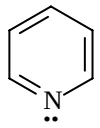


Explain the observed conversions:

a. 

b. 

4. The structure of *pyridine* is shown below:



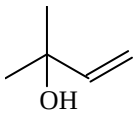
pyridine

a. Describe the *longest* wavelength λ_{max} electronic transition in terms of σ, σ*, π, π*, or n.

b. Comment on the *probability* of that transition. What term in the Beer-Lambert equation reflects this probability?

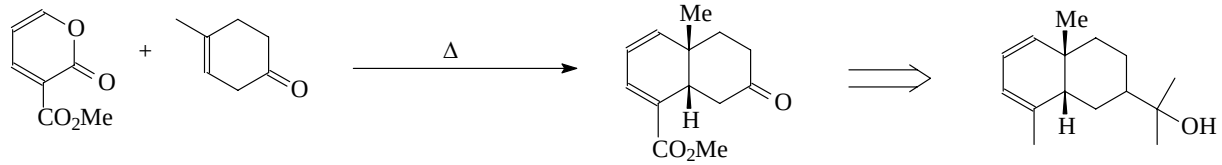
c. Draw the conjugate acid of pyridine. How would that transition in (a) be affected?

5. Compound **A**, upon standing in acid, yields a new isomeric compound **B** whose ^{1}H NMR is δ 1.7 (s, 3H), 1.8 (s, 3H), 2.3 (br s, 1H), 4.1 (d, J = 8 Hz, 2H), 5.5 (t, J = 8 Hz, 1H). Draw the structure of compound **B** and give its mechanism of formation.



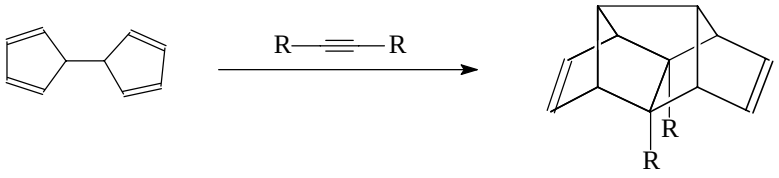
A

6. One approach to synthesizing the sesquiterpene *occidentalol*, found in New England white cedar trees, begins with a forward Diels-Alder reaction, followed by a retro-Diels-Alder, to form **A**. Explain.

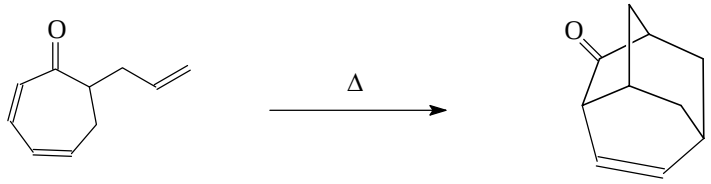


A *occidentalol*

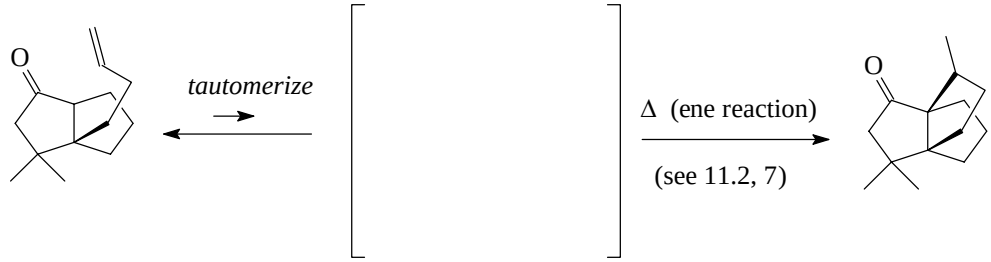
7. An early stage reaction in Paquette's (*OSU*) total synthesis of dodecahedrane employed the following "domino" Diels-Alder:



8.

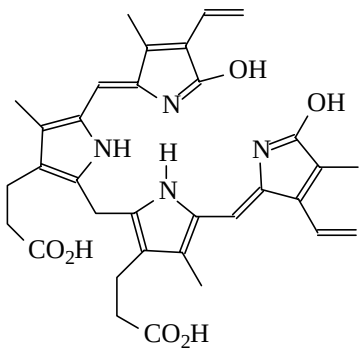


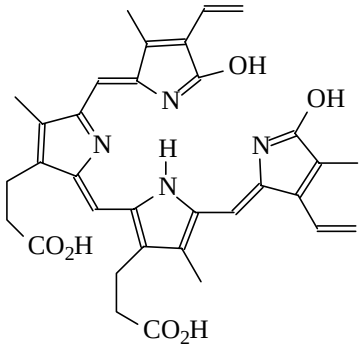
9.



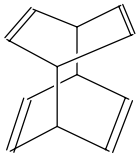
10.

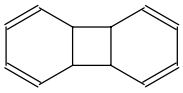
11. The degradation of heme proceeds by way of the bile pigments *biliverdin* and *bilirubin*, green and red, respectively. Elevated levels of the latter produce jaundice. Bilirubin, a principal antioxidant in blood plasma, is formed by reducing biliverdin. Label the structures below as biliverdin or bilirubin and identify the site of reduction in the former. Explain the difference in color of the two pigments.

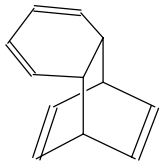




12. Depending upon the number of π electrons in a pericyclic process, reversible cycloaddition reactions may be classified as *thermally* "allowed" or "forbidden" (a theoretical prediction of the probability that such a reaction will occur). The Diels-Alder reaction is the most common example of a *thermally allowed* (4+2) cycloaddition. Examples of *thermally forbidden* reactions include (2+2) and (4+4) cycloadditions (they do occur, however, under photochemical conditions). Formation of the dibenzenes below could be envisioned by a cycloaddition mechanism. Identify each as (2+2), (4+2), or (4+4). Which would be expected to undergo a thermal *retro*-cycloaddition to benzene most rapidly?

a. 

b. 

c. 

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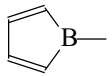
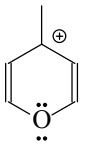
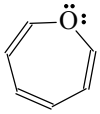
CHAPTER 12
AROMATICS

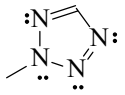
12.1 General

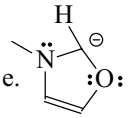
1. Circle the compounds that would be expected to have aromatic character.

a. 

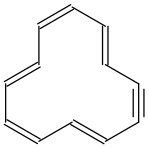
b. 

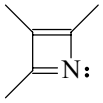
c. 

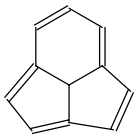
d. 

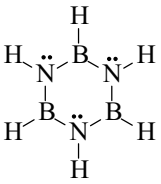
e. 

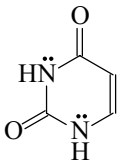
f. 

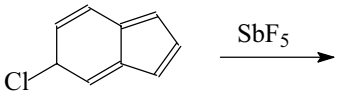
g. 

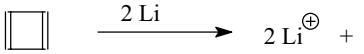
h. 

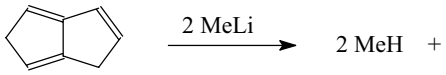
i. 

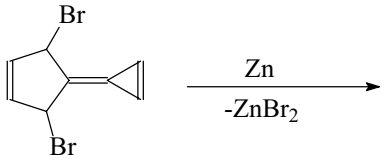
j. 

k. 

l. carbocation in the reaction of 

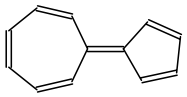
m. product in the reaction of 

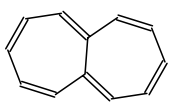
n. product in the reaction of 

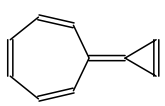
o. product in the reaction of 

calicene

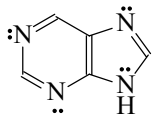
2. Which would have the *largest* molecular dipole moment (μ)?

a. 

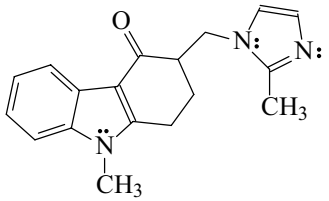
b. 

c. 

3. Which nitrogen atom is *least basic* in purine and *most basic* in Zofran™?



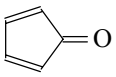
purine

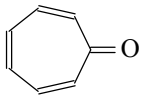


Zofran™ (antiemetic)

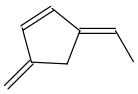
4. One of the following ketones is *unstable* and undergoes a Diels-Alder reaction rapidly. Which?

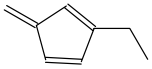
a. 

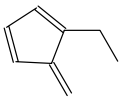
b. 

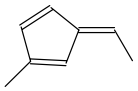
c. 

5. Which of the following compounds would most easily form its conjugate base?

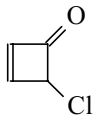
a. 

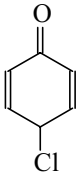
b. 

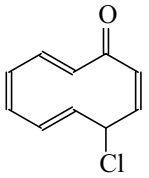
c. 

d. 

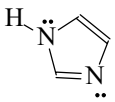
6. Which would undergo an S_N1 reaction most readily?

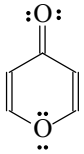
a. 

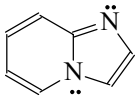
b. 

c. 

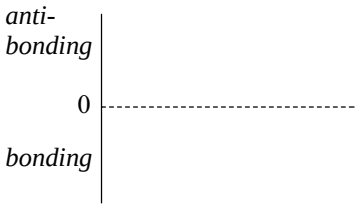
7. Circle the *more(most) basic* electron pair in each of the following:

a. 

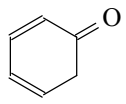
b. 

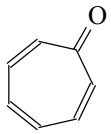
c. 

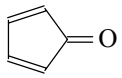
8. Use a Frost mnemonic to explain why 7-chloro-1,3,5-cycloheptatriene gives a *singlet* ^{1}H NMR spectrum when dissolved in a solvent containing a Lewis acid.



9. Which ketone has the *largest* molecular dipole moment (μ)?

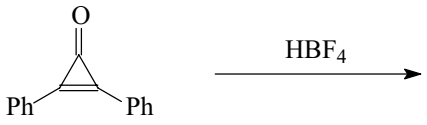
a. 

b. 

c. 

d. 

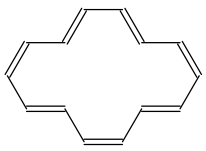
10. **A** in the presence of HBF_4 forms a salt. Explain.



A

11. Explain the regioselectivity of the following addition:

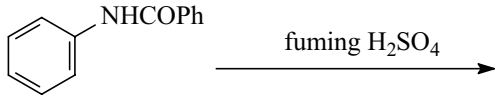
12. The ^1H NMR spectrum for the following [14]annulene compound shows two major chemical shifts. Simulate their approximate location and predict the integration of each.



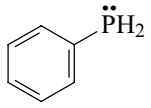
a [14]annulene

12.2 Reactions

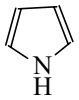
Draw the structural formula of the major organic product(s). Show stereochemistry where appropriate.

1. 

2. *o*-methylphenol $\xrightarrow{HONO_2 / H_2SO_4}$

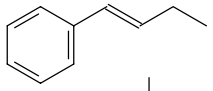
3. 

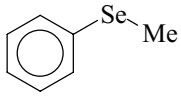
H_2SO_4, SO_3 →

4. 

Cl_2 / Fe →

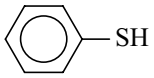
5. benzene
1. $PhCH_2CH_2Br$, $AlCl_3$
2. NBS, R_2O_2
3. KOMe, MeOH →

6. 
Br_2 / CCl_4 →
Br_2, Fe →
NBS, R_2O_2 →

7. 

ICl, Fe →

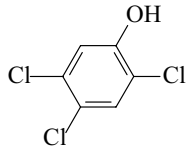
8. Ph—N=O
Br_2, $FeBr_3$ →

9. 

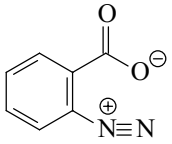
Cl_2, $FeCl_3$ →

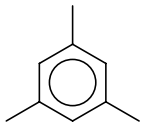
10. 

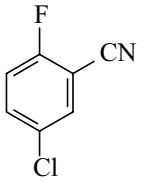
Cl_2, BF_3 →

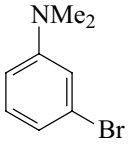
11. 2  + formaldehyde $\xrightarrow{H_2SO_4}$

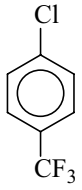
($C_{13}H_6Cl_6$ - *hexachlorophene*, a disinfectant)

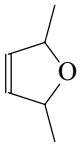
12.  $\xrightarrow[2.\ 1,3\text{-cyclohexadiene}]{1.\ \Delta\ (-CO_2,\ -N_2)}$

13.  $\xrightarrow{\text{picric acid}}$

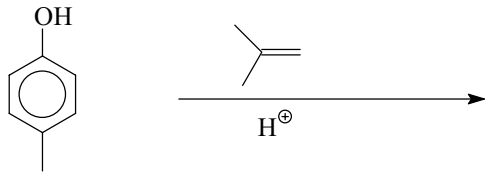
14.  $\xrightarrow{NH_3}$

15.  $\xrightarrow[2.\ H^{\oplus}]{1.\ \text{MeLi}}$

16.  $\xrightarrow[2.\ \text{NaOMe, MeOH}]{1.\ HNO_3,\ H_2SO_4}$

17. toluene +  $\xrightarrow[-H_2O]{H^{\oplus}}$

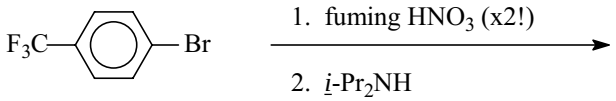
(*a bicyclic C_{13} compound*)

18. 

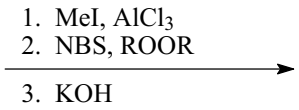
BHT ($C_{15}H_{22}O$ - a food preservative)

19. 

α-pyrone

20. 

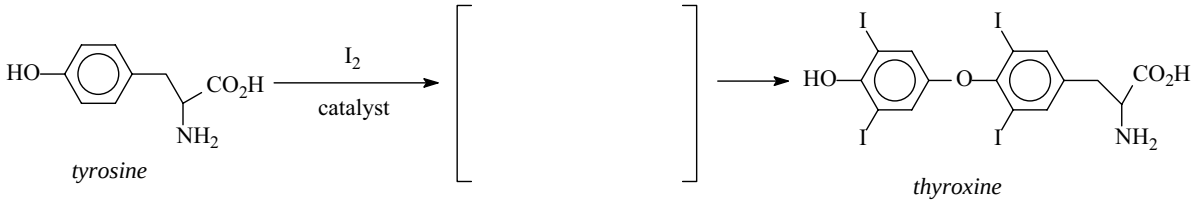
Trifluralin B™ (a pre-emergent herbicide)

21. anisole 

(flavor in licorice)

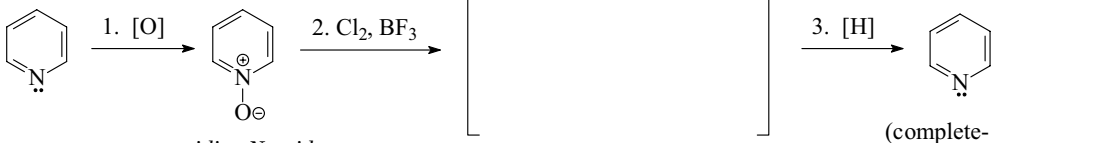
partial ^{1}H NMR: δ 7.2 (d, 2H), 7.9 (d, 2H)

22. Although iodination of aromatic rings does not occur as readily as bromination, it can be observed when activating substituents are present, *e.g.*, in the biosynthesis of the hormone *thyroxine*:



tyrosine *thyroxine*

12.2 Reactions

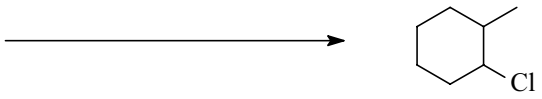
23. 

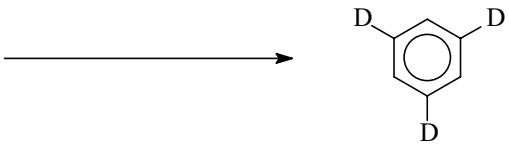
pyridine N-oxide

(complete-contrast to 12.2, 10)

12.3 Syntheses

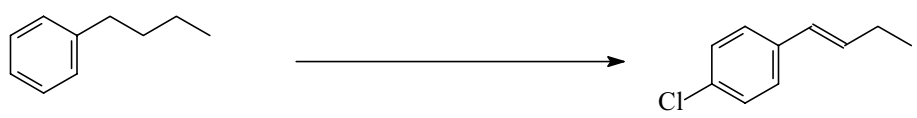
Supply a reagent or sequence of reagents that will effect the following conversions.

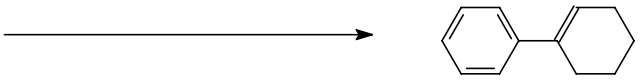
1. benzene 

2. benzene 

3. benzene 

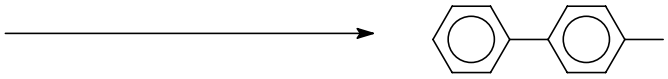
4. benzene ⟶ 1,2-diphenylethane

5. 

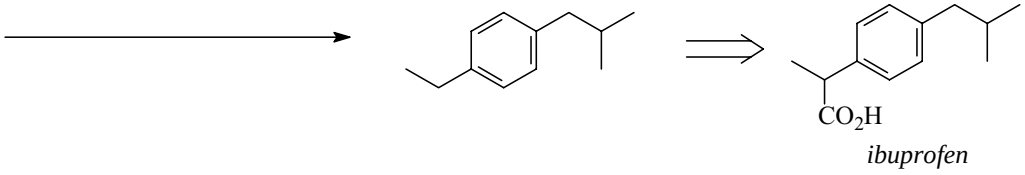
6. PhH 

7. 

8. benzene ⟶ *o*-nitrobenzoic acid

9. benzene 

10. 

11. benzene 

ibuprofen

12. acetone, phenol 

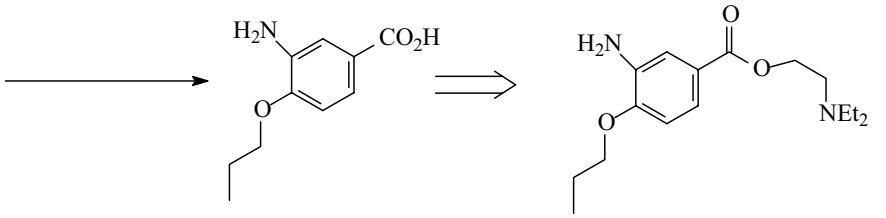
13. *2,4-D* and *2,4,5-T* are the active agents in the defoliant Agent Orange™. How could they be prepared from the indicated starting materials?

2,4-D *2,4,5-T*

14.

Tylenol™

15. *p*-hydroxybenzoic acid

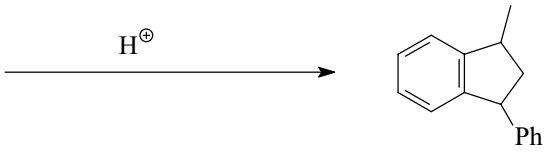


proparacaine (a local anesthetic)

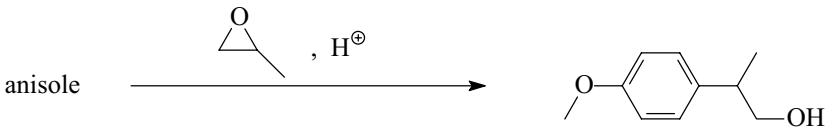
12.4 Mechanisms

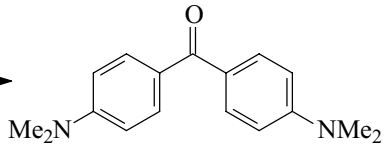
Outline a detailed mechanism for each of the following. No other reagents than those given are necessary. Use arrows to explain the flow of electrons and show all intermediates.

1. styrene



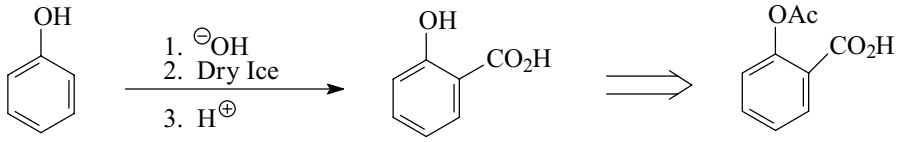
2. Epoxides, because of ring strain, are much more reactive than most ethers. Account for the following:



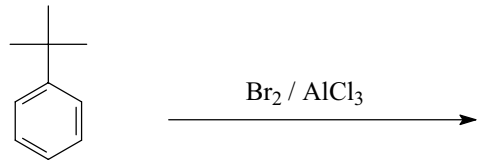
3. (XS) N,N-dimethylaniline + $COCl_2$ (*phosgene*) $\xrightarrow{AlCl_3}$ 

Michler's ketone

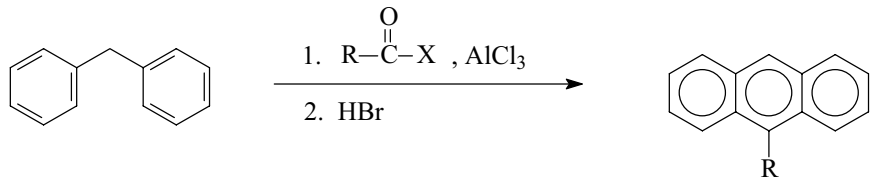
4. The *Kolbe reaction* is used industrially to convert phenol to salicylic acid, an immediate precursor to aspirin.

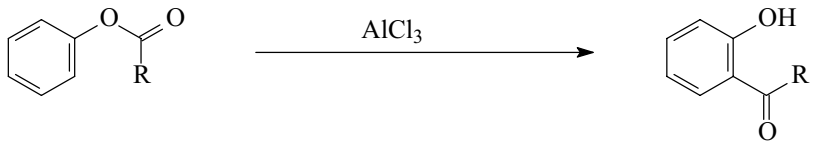


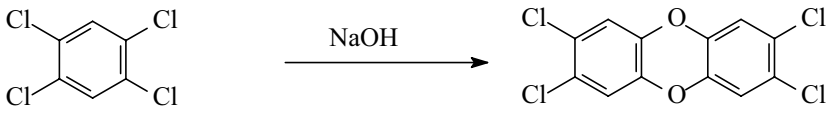
salicylic acid *aspirin*

5. 

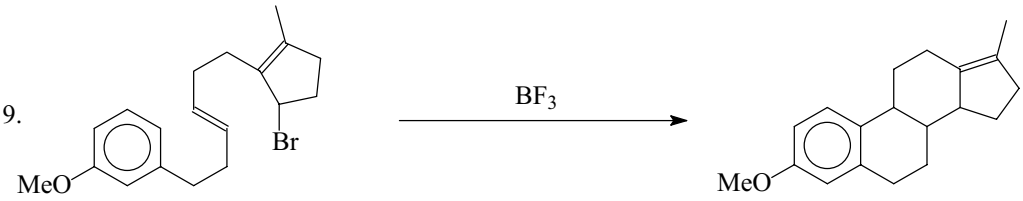
+ isobutylene

6. 

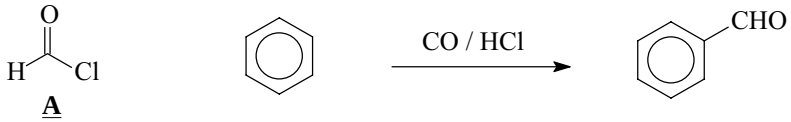
7. 

8. 

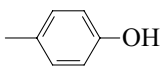
dioxin

9. 

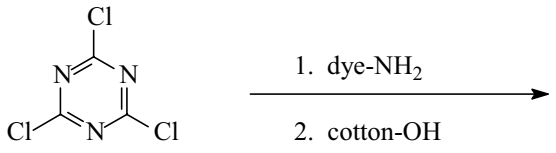
10. Formyl chloride, **A**, does NOT exist; therefore, one cannot do a Friedel-Crafts type acylation to produce benzaldehyde. However, the latter can by synthesized by the reaction of benzene with carbon monoxide and HCl (a process known as the *Gatterman-Koch reaction*). Outline a mechanism.



A

11. toluene $\xrightarrow[CF_3SO_3H]{H_2O_2}$  (*a convenient way to substitute an hydroxyl group onto an aromatic ring*)

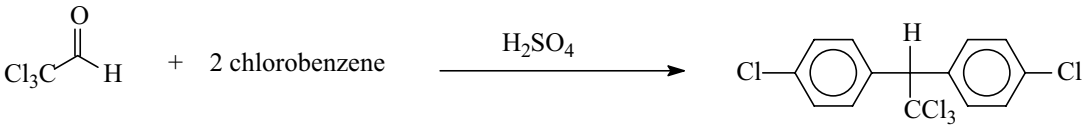
12. Dyes such as indigo blue (see 19.1, 34) do not bond well to cotton and tend to wash off after repeated laundering; they are known as *surface* dyes. On the other hand, *reactive* dyes bind covalently to cotton, resulting in greater color retention ('fastness'). The following process illustrates the latter. An amino-containing dye is initially bound to cyanuryl chloride to give a product that subsequently is allowed to react with the hydroxyl groups of cotton. Show a mechanism for this process that illustrates how cyanuryl chloride serves to crosslink the dye with cotton. What type of reaction describes each step?



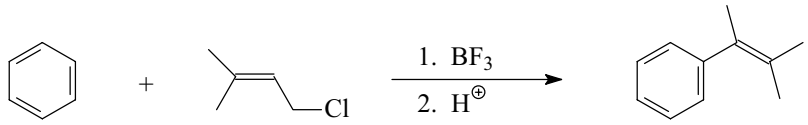
cyanuryl chloride

13. Malaria, which claims over one million lives *per year*, mostly children and largely in Africa, could be eradicated with the judicious use of *DDT*. Banned in the US in 1972, in large part because of Rachael Carson's 1962 book *The Silent Spring*, exhaustive scientific review has since shown DDT, *in moderation*, not only to be safe for humans and the environment, but also the single most effective anti-malarial agent ever formulated. Although the World Health Organization and the US have now reversed their anti-DDT stance, emotional opposition to the pesticide remains so fierce that its use continues to be resisted – at the cost of millions of unnecessary deaths.

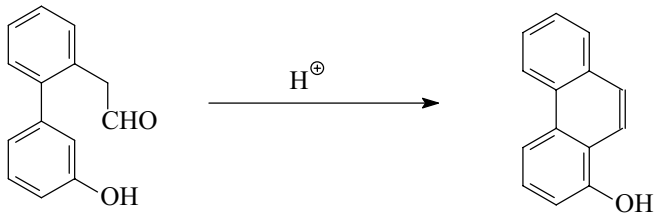
DDT is easily prepared as follows:



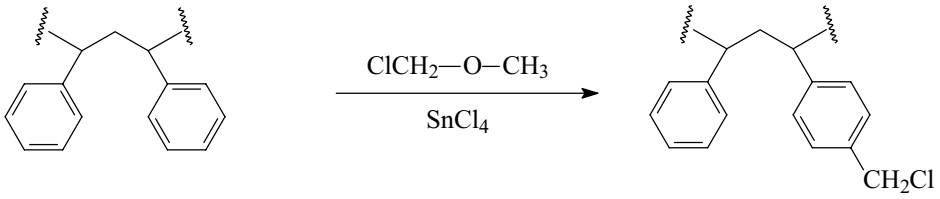
DDT

14. 

15.

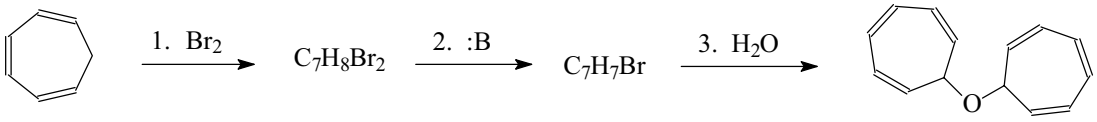


16. When poly(styrene) is treated with chloromethyl methyl ether and $SnCl_4$ (a strong Lewis acid), Merrifield resin (named after Nobel laureate Bruce Merrifield who pioneered *in vitro* peptide syntheses) is formed.



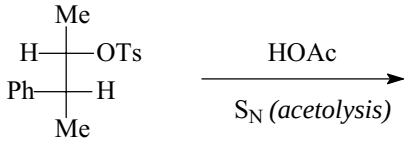
poly(stryene) *Merrifield resin*

17.



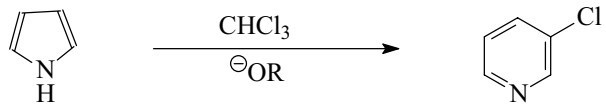
ditropyl ether

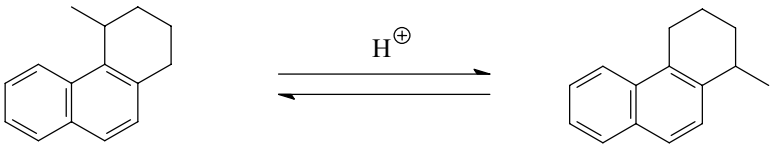
18.

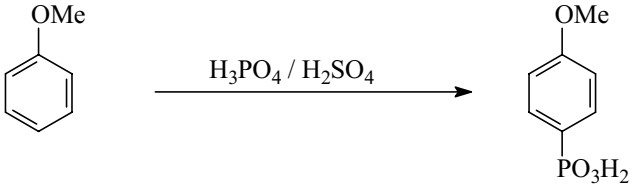


(a *racemate)*

Hint: recall the concept of neighboring group participation (9.4, 9-16) in some nucleophilic substitution reactions; even aromatic rings are sometimes capable of acting as a "neighboring group."

19. 

20. 

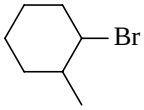
21. 

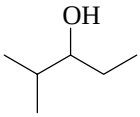
CHAPTER 13
ALCOHOLS

13.1 Reactions

Draw the structural formula of the major organic product(s). Show stereochemistry where appropriate.

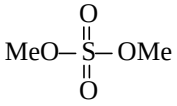
1. benzyl methyl ketone
   - 1. $NaBH_4$
   - 2. NH_4Cl (a weak acid)
   - 3. PCl_3
   - 4. KO-*t*-Bu
   - 1. H_2 / Pd
   - 2. H_2SO_4

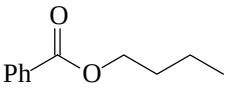
2. 3-ethyl-3-pentanol
   - 1. *i*-PrMgBr
   - 2. 

3. 

   - 1. H_2SO_4
   - 2. $H_3O^{\oplus}$
   - HCl

4. 5-hydroxy-2-heptanone
   - 1. TsCl
   - 2. NaOAc

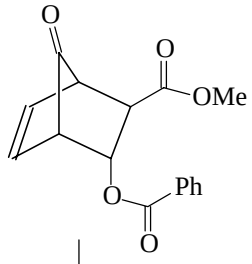
5. 1-hexen-3-ol
   - 1. NaH
   - 2. 

6. 

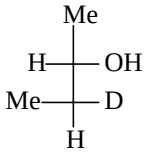
   - 1. PhMgCl
   - 2. $H^{\oplus}$
   - 1. $LiAlH_4$
   - 2. $H^{\oplus}$

7. iodomethane $\xrightarrow[3.\ H^{\oplus}]{1.\ Li \\ 2.\ \text{diisopropyl ketone}}$

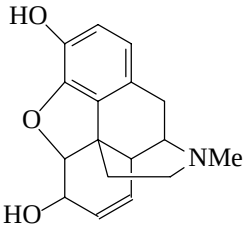
8. 2-butanol $\xrightarrow[4.\ H_2O_2,\ HO^{\ominus}]{1.\ HBr \\ 2.\ LDA \\ 3.\ BH_3{\cdot}THF}$

9. 

$\xrightarrow[2.\ H^{\oplus}]{1.\ NaBH_4}$
$\xrightarrow[2.\ H^{\oplus}]{1.\ LiAlH_4}$
$\xrightarrow{H_2 / Pt}$

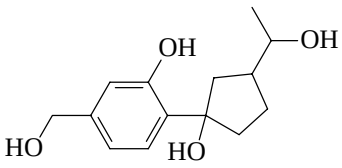
10. 

$\xrightarrow[\text{pyridine}]{POCl_3}$

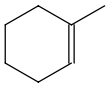
11. 

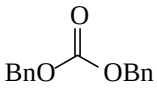
$\xrightarrow[2.\ CH_3I\ (1\ \text{equiv})]{1.\ NaOH}$

morphine *codeine*

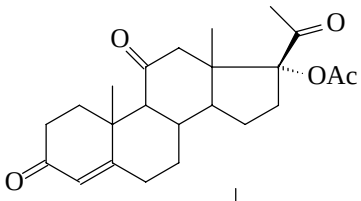
12. 

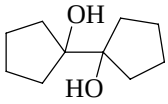
$\xrightarrow{\text{Jones reagent}}$

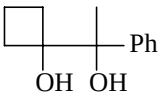
13. 
1. Br_2, H_2O
2. Me_3SiCl
3. Li
4. acetone
5. $H_3O^{\oplus}$

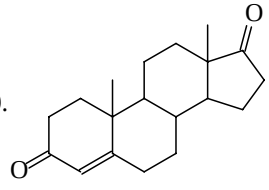
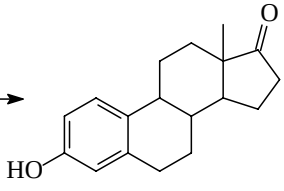
14. 
1. (XS) MeLi
2. $H^{\oplus}$

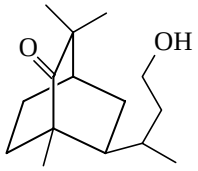
15. *p*-hydroxybenzoic acid
1. $LiAlH_4$
2. (XS) HBr

16. 
cortisone acetate
1. $NaBH_4$
2. $H^{\oplus}$
1. $LiAlH_4$
2. $H^{\oplus}$

17. 
$H^{\oplus}$
(*pinacol rx*)

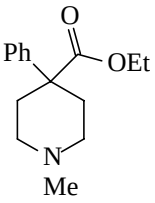
18. 
$H^{\oplus}$

19. 
andostenedione
aromatase

estrone
1. $NaBH_4$
2. $H^{\oplus}$
estradiol

20. 

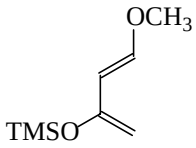
1. $SOCl_2$, Et_2O
2. Mg
3. $H^{\oplus}$

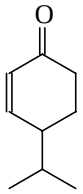
patchouli alcohol (used as a fragrance)

21. 

1. *n*-PrMgCl
2. $H^{\oplus}$

Demerol™ (narcotic analgesic)

22. 

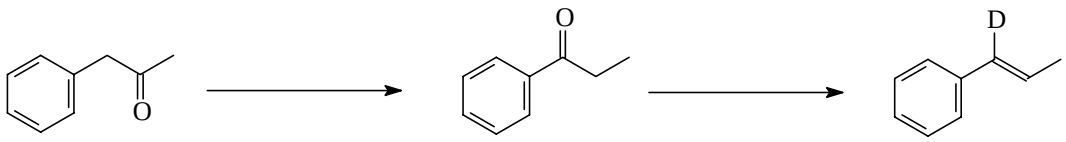
+ 

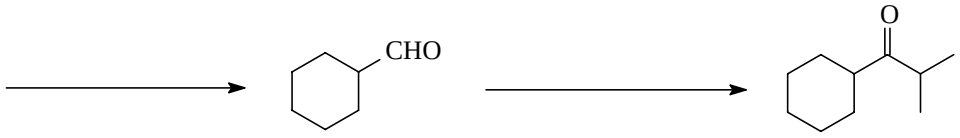
1. toluene, Δ
2. $H^{\oplus}$

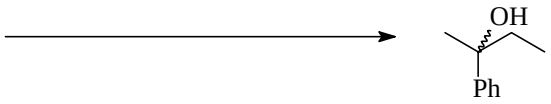
Danishefsky's diene

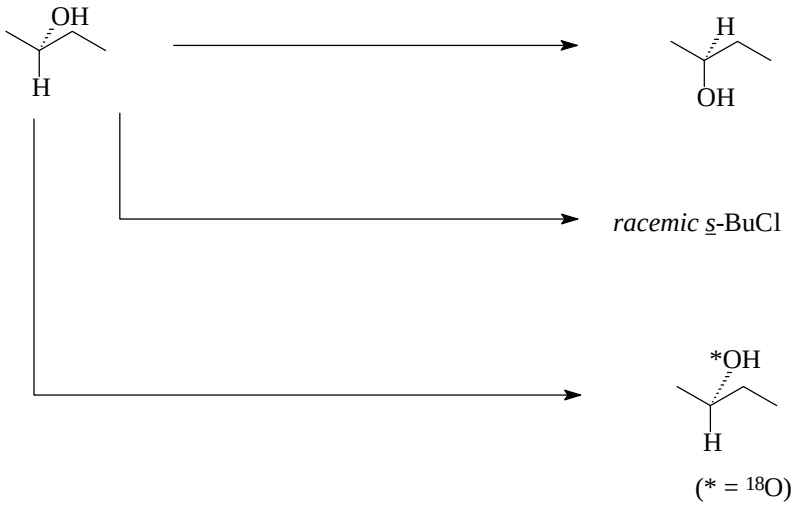
13.2 Syntheses

Supply a reagent or sequence of reagents that will effect the following conversions.

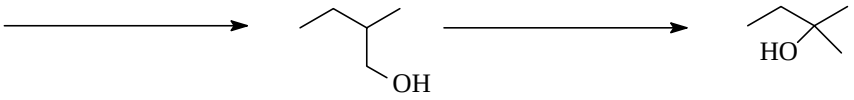
1. 

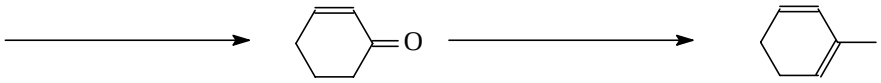
2. cyclohexanol 

3. 1-butene 

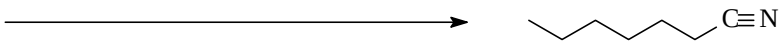
4. 

(* = ^{18}O)

5. *n*-butane 

6. cyclohexane 

7. vinyl chloride ⟶ 1,3,5-hexatriene

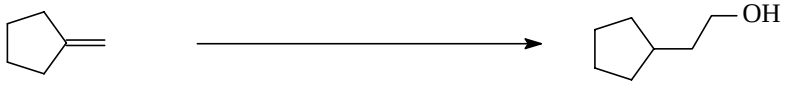
8. *n*-hexyl alcohol 

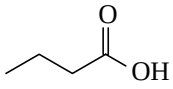
9. 

10. *p*-chlorophenol ⟶ *p*-hydroxybenzaldehyde (*via a Grignard*)

11. 

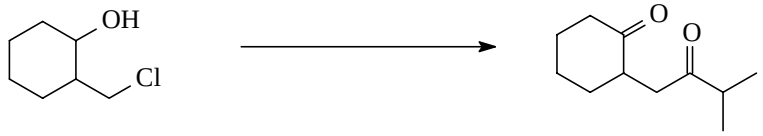
estradiol

12. 

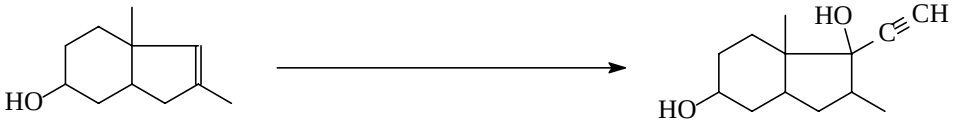
13. *n*-butane ⟶ 

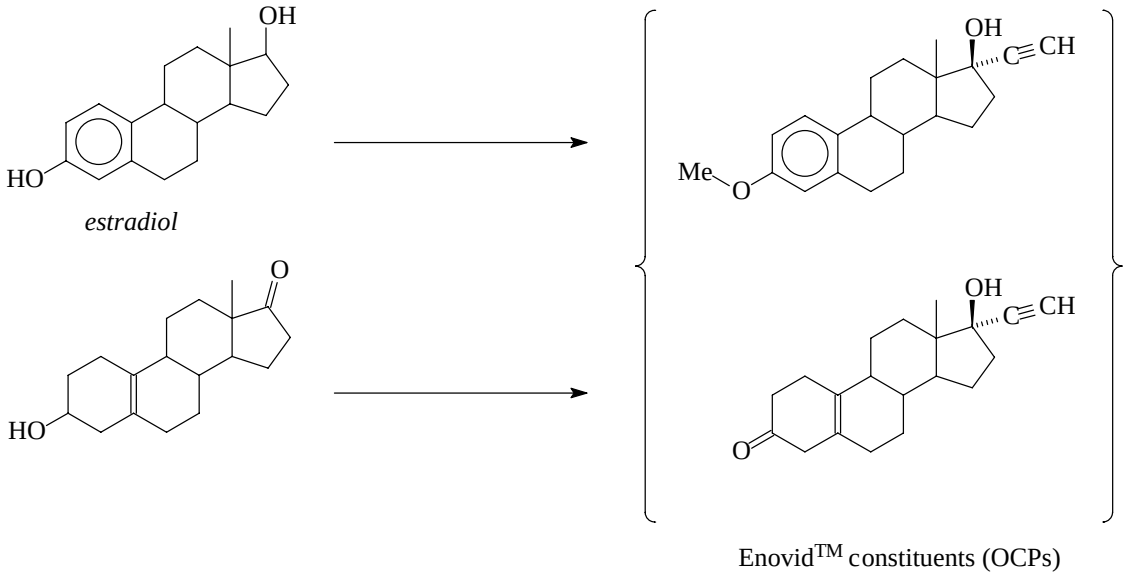
14. 

15. 

16. 

17. 

18. 

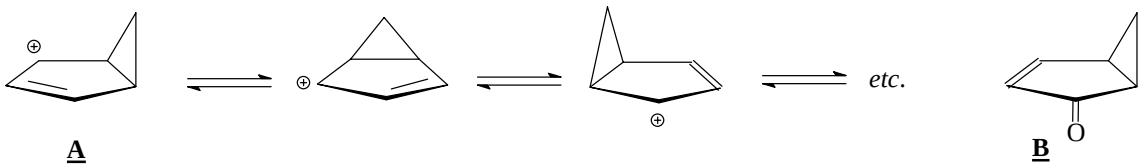
19. 

estradiol

Enovid™ constituents (OCPs)

20. 

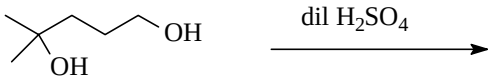
21. Berson (*Yale*) discovered that the bicyclic carbocation **A** undergoes a clever rearrangement in which the cyclopropyl ring circumambulates around the cyclopentenium ring. Beginning with **B**, synthesize a deuterium-labeled species that would support this observation.



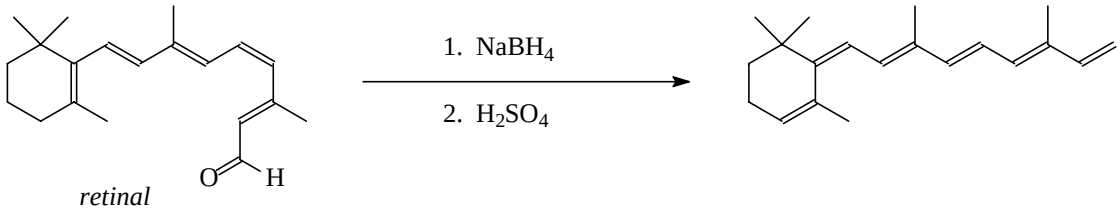
A **B**

13.3 Mechanisms

Outline a detailed mechanism for each of the following. No other reagents than those given are necessary. Use arrows to explain the flow of electrons and show all intermediates.

1. 

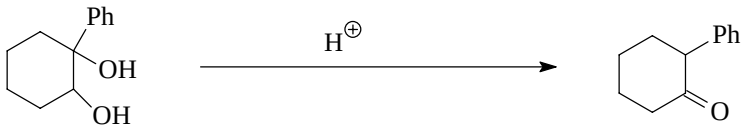
(*a cyclic ether*)

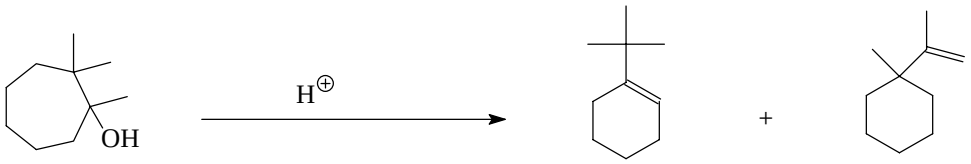
2. 

retinal

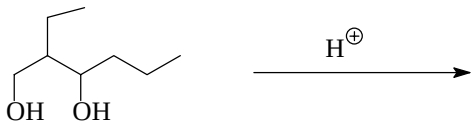
3. cycloheptene glycol $\xrightarrow{H^{\oplus}}$

$C_7H_{12}O$
IR: 1729 cm^{-1}
^1H NMR: δ 9.5 (d, 1H),
plus other chemicals shifts

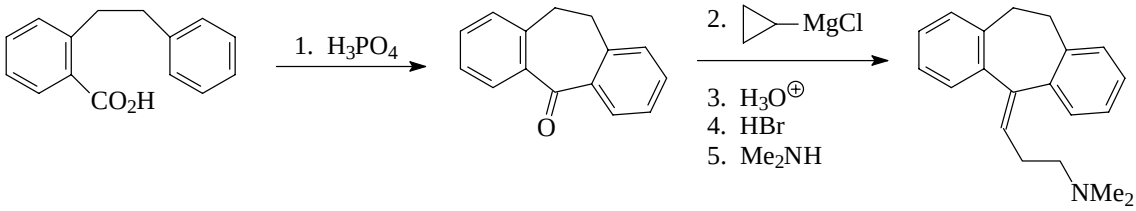
4. 

5. 

6. glycerol 

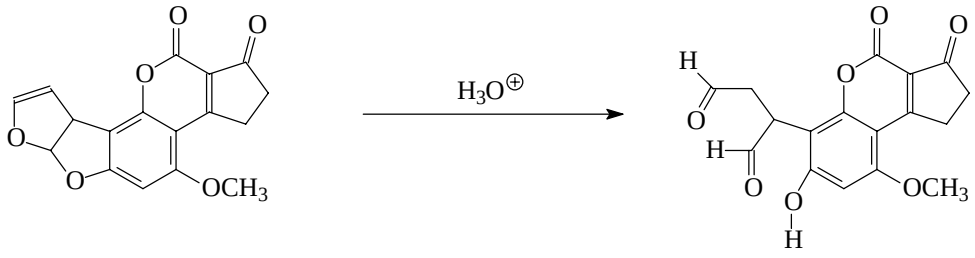
7. 

(*an aldehyde*)

8. 

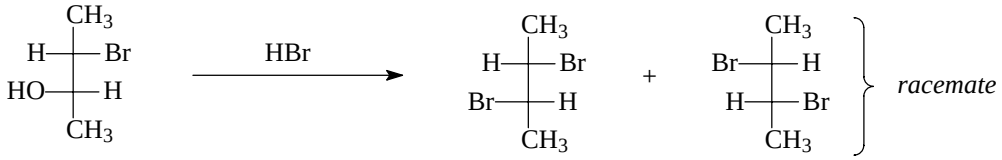
amitriptyline
(an antidepressant)

9. *Aflatoxin B_1* is one of the most potent carcinogens known. In the presence of water and acid, compound **A** is formed.



aflatoxin B_1 **A**

10.

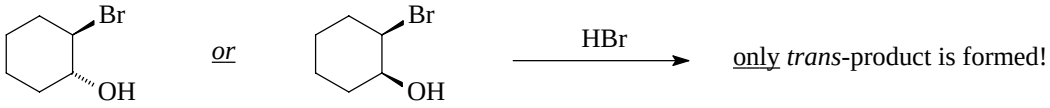


Note: *retention at* $C_{2,3}$ *inversion at BOTH* $C_{2,3}$!

This observation by Winstein (*UCLA*) provided stereochemical support for the concept of neighboring group participation (see 9.4, 9-16).

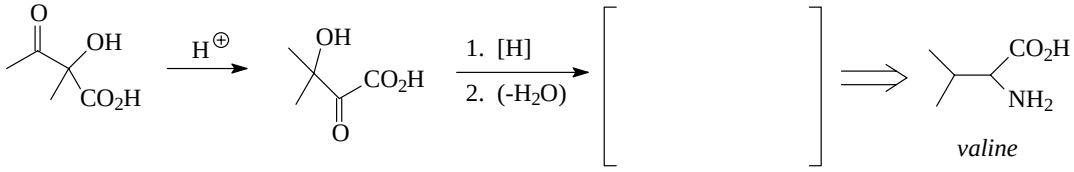
Similarly,

11.

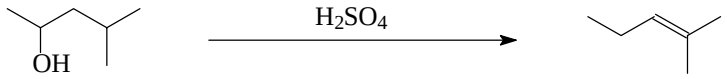


only *trans*-product is formed!

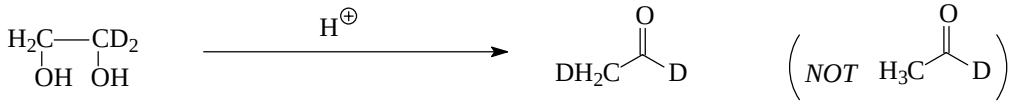
12. A step in the biosynthesis of the amino acid *valine:*



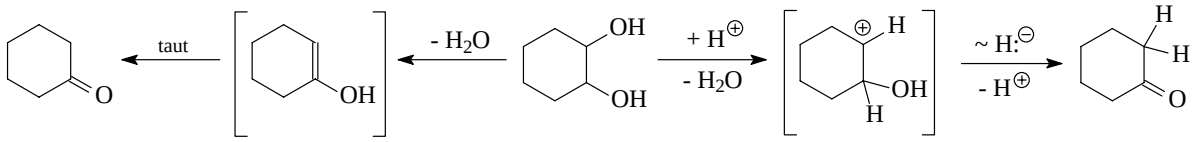
valine

13. 

14. The conversion of ethylene glycol to acetaldehyde under acidic conditions could occur by one of two pathways: (1) dehydration to an enol followed by tautomerization, or (2) a pinacol-like rearrangement. In view of the following experiment, which pathway is suggested?

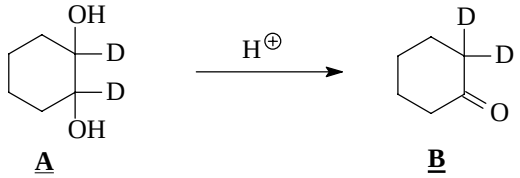


15. Cyclohexene glycol in the presence of acid forms cyclohexanone. Similar to problem 14, two pathways are possible: dehydration/tautomerization *vs.* a pinacol-like rearrangement:



cyclohexene glycol

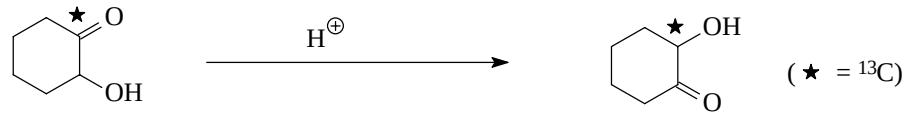
Synthesis of deuterium-labeled glycol **A**, when treated with acid, yields **B**:



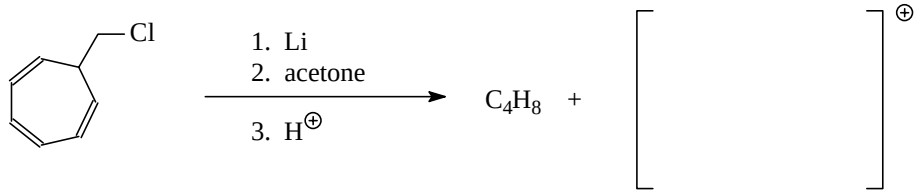
A **B**

a. Which pathway is consistent with this observation?

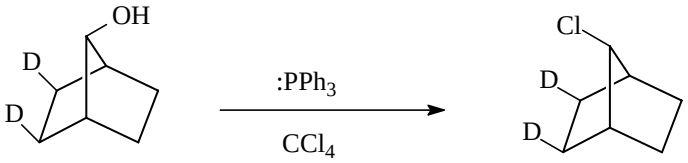
b. Suggest a preparation of **A** from cyclohexene.

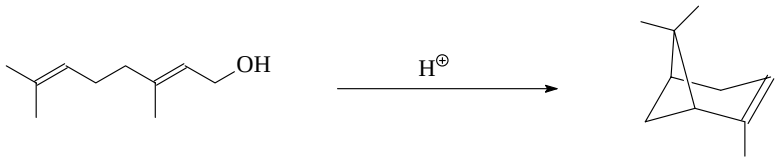
16. 

(★ = ^{13}C)

17. 

(*^1H NMR shows only a singlet at δ 8.2*)

18. 

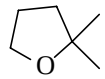
19. 

α-pinene (a constituent in oil of turpentine - interestingly, the dextrorotatory form is found in North American oils and the levorotatory form in European oils)

CHAPTER 14
ETHERS

14.1 Reactions

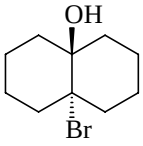
Draw the structural formula of the major organic product(s). Show stereochemistry where appropriate.

1. 

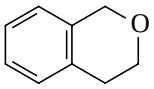
1. HBr (1 equiv)
2. TsCl
3. KOAc, 18-crown-6

2. benzyl phenyl ether $\xrightarrow{\text{(XS) HI}}$

3. phenyl mercaptan + $Me_3S^{\oplus}\ I^{\ominus}$ $\longrightarrow$

4. 

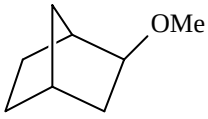
$\xrightarrow{\text{KOH}}$

5. 

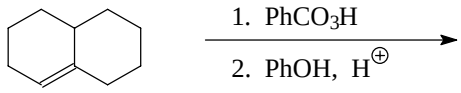
1. HF
2. PCC

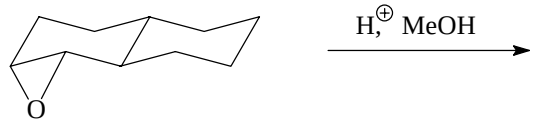
6. 2-isopropyloxirane $\xrightarrow[\text{MeOH}]{\text{NaCN}}$

7. PhLi $\xrightarrow[\text{2. } H_2SO_4]{\text{1. styrene epoxide}}$

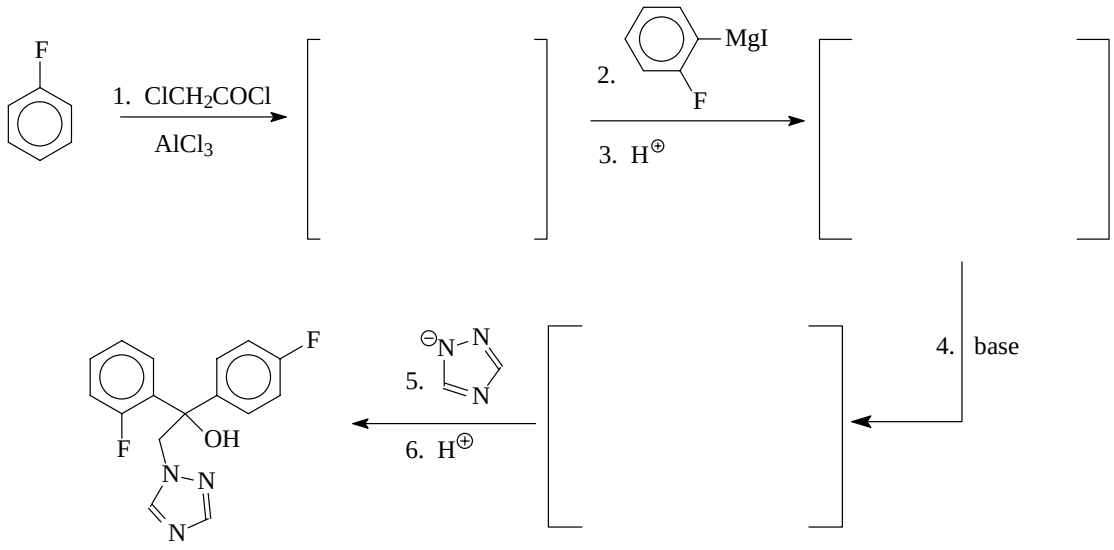
8. 

1. HI (1 equiv)
2. CrO_3, $H^{\oplus}$
3. $NaBD_4$
4. $H^{\oplus}$

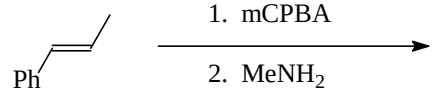
9. 

10. 

11. The fungicide *flutriazole* can be synthesized by the following scheme:

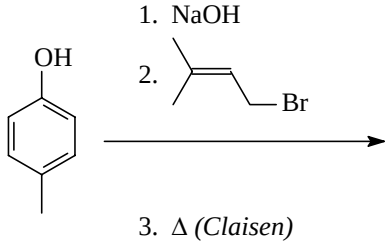


flutriazole

12. 

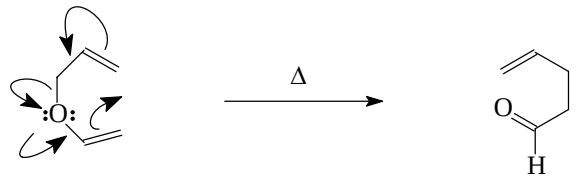
ephedrine (bronchodilator)

13. The *Claisen rearrangement* of allyl phenyl ethers:



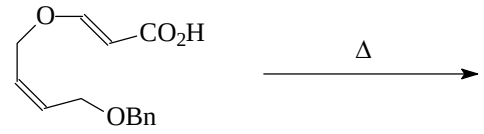
14.1 Reactions

14. The Claisen rearrangement can be generalized to include *allyl vinyl ethers*:

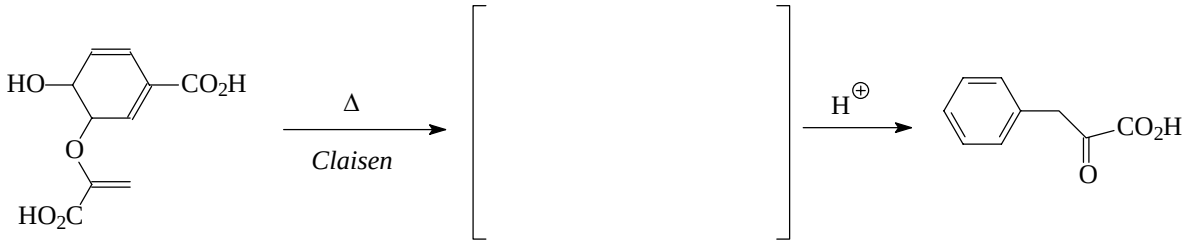


Draw the expected Claisen rearrangement product for each of the following:

a.

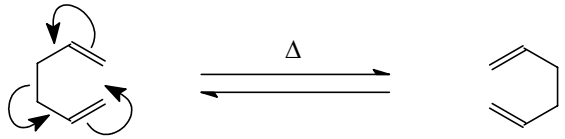


b. A stage in the biosynthesis of aromatic amino acids (draw the structure of prephenic acid and give a mechanism for its conversion to phenylpyruvic acid):

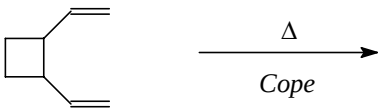


chorismic acid *prephenic acid* *phenylpyruvic acid*

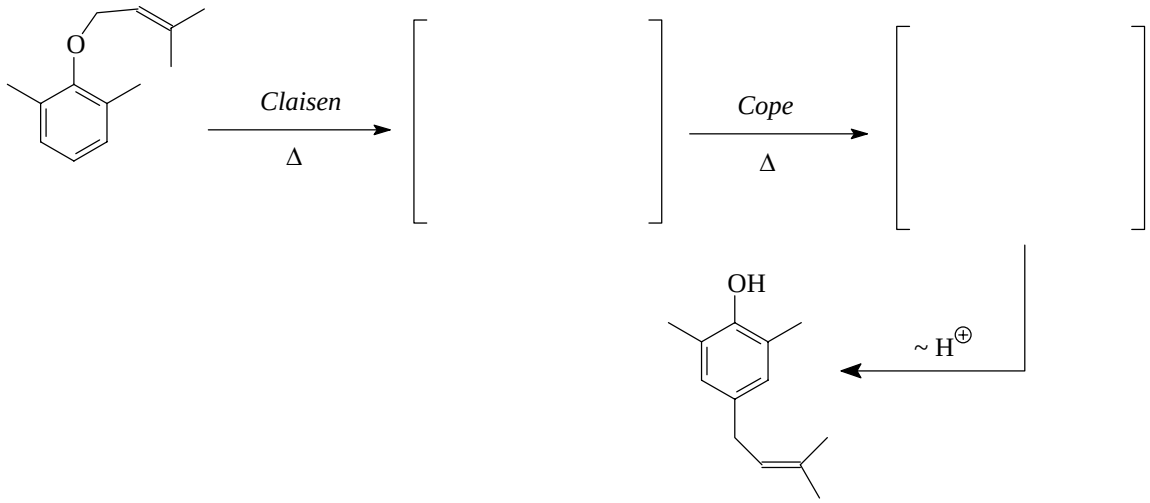
15. Mechanistically similar to the Claisen rearrangement is the *Cope rearrangement*:



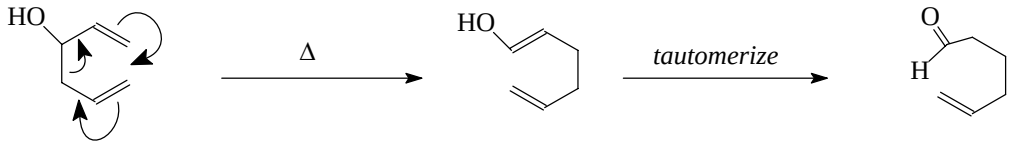
This specific example became known as the "degenerate Cope," a moniker that did not particularly please its discoverer, Prof. A. Cope! Of course, the degeneracy can be removed:



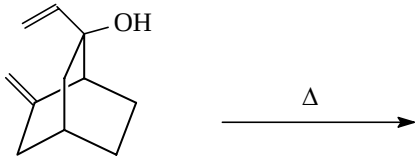
16. Going back to problem 14.1, 13, if the *ortho* positions are blocked the initial Claisen rearrangement product may be followed by a Cope rearrangement. Fill in the brackets.

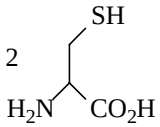


17. A slight variation of problem 14.1, 15 is the *oxy-Cope rearrangement*:



Predict the oxy-Cope product for the reaction below:

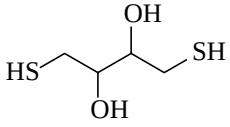


18. 2 

[O] →

cysteine

cystine [crystallization in kidneys can lead to one type of calculi (stone)]

19. 

[O] →

dithiothreitol

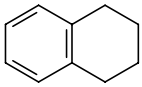
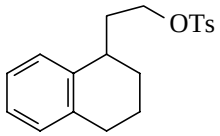
$C_4H_8O_2S_2$

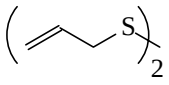
14.2 Syntheses

Supply a reagent or sequence of reagents that will effect the following conversions.

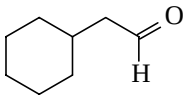
1. 3-methylpentane ⟶ 3-methoxy-3-methylpentane

2. cyclohexene ⟶ *trans*-cyclohexene glycol

3.  ⟶ 

4. propylene ⟶ 

diallyldisulfide (found in garlic)

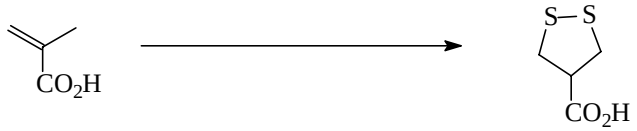
5. cyclohexane ⟶ 

via an epoxide

6. cyclohexene oxide ⟶ cyclohexane

7. 

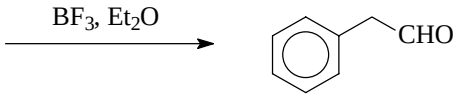
captopril (antihypertensive)

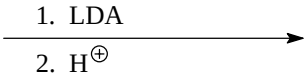
8. 

asparagusic acid (isolable from asparagus)

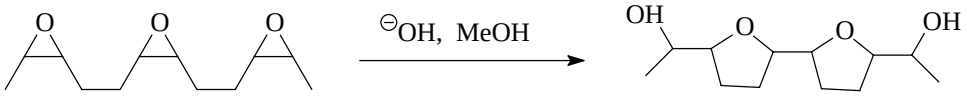
14.3 Mechanisms

Outline a detailed mechanism for each of the following. No other reagents than those given are necessary. Use arrows to explain the flow of electrons and show all intermediates.

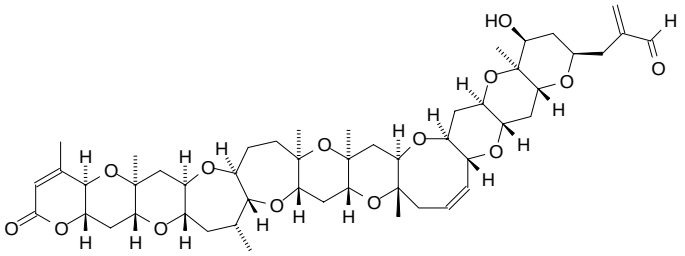
1. styrene epoxide 

2. methyloxirane  allyl alcohol

3. 

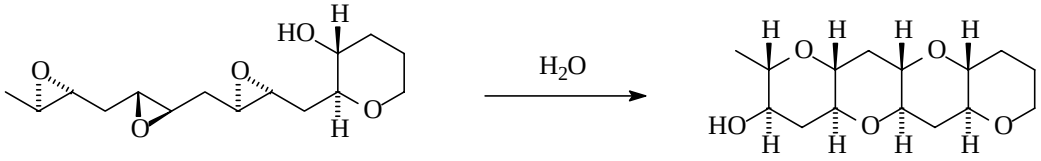
4. 

5. Complex ladder polyether natural products, so named for their rung-like structure, are the active toxins found in harmful algal blooms known as *red tides*, which cause devastating ecological damage. *Brevetoxin B* is an example.

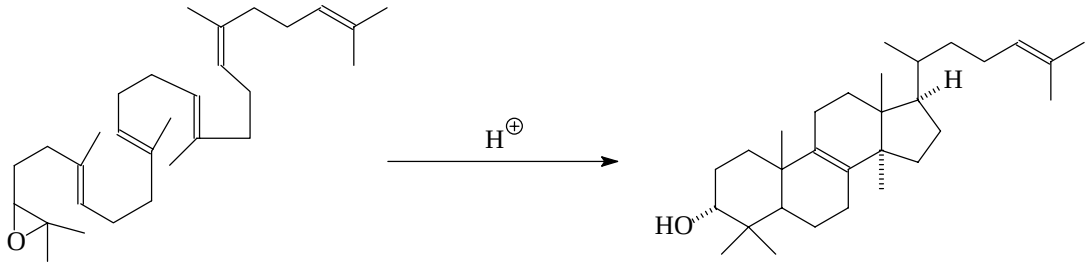


brevetoxin B

Twenty years ago Nakanishi (*Columbia*) proposed such products arise biosynthetically from an elaborate cascade of epoxide ring-opening reactions that zip up the polyether structure. The following reaction, discovered by Jamison (*MIT*) in 2007, supports this hypothesis.

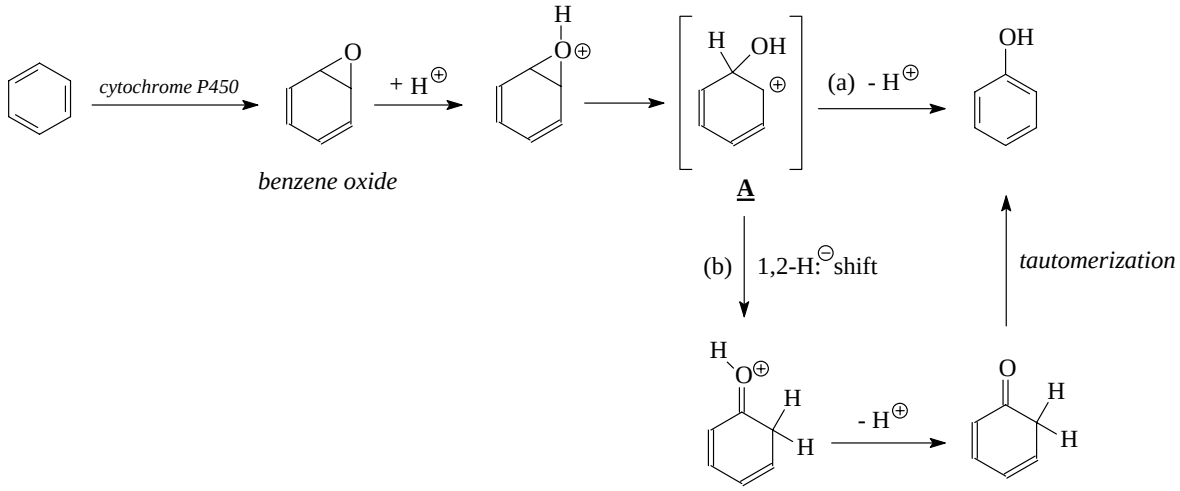


6. The biosynthesis of steroids involves an absolutely gorgeous (!) polycyclization reaction of *squalene epoxide*, followed by two sequential 1,2-hydride shifts and two 1,2-methide shifts to form *lanosterol* (lanosterol is then converted to *cholesterol*, the precursor to most other steroid hormones):

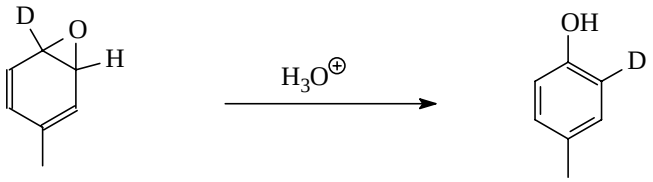


squalene epoxide *lanosterol*

7. Biochemical hydroxylation of aromatic compounds proceeds *via* arene oxides, which subsequently undergo ring opening to form phenols:

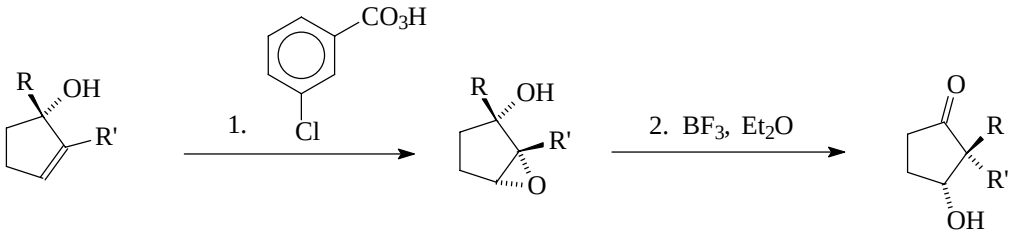


Phenol could be formed from intermediate **A** simply by an E1-like loss of a proton (*path a*) or, alternatively, by a pinacol-like rearrangement followed by tautomerization (*path b*). Support for *path b* was provided by chemists at the NIH who observed the following conversion:

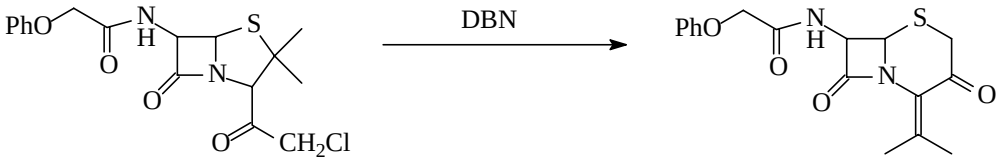


Explain. Account for the role of the methyl substituent. (This rearrangement of an arene oxide has now become known as the *NIH shift*!)

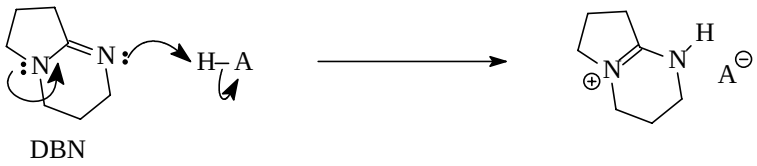
8.



Step 2 illustrates a semi-pinacol type rearrangement. Propose a mechanism for that step.

9. 

Note: DBN (1,5-diazabicyclo[4.3.0]non-5-ene) is a sterically hindered nitrogen base that favors elimination over substitution:



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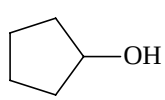
CHAPTER 15
ALDEHYDES AND KETONES

15.1 Reactions

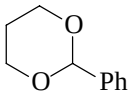
Draw the structural formula of the <u>major</u> organic product(s). Show <u>stereochemistry</u> where appropriate.

1. 

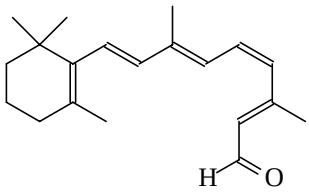
1. CrO_3, $H^{\oplus}$
2. hydrazine, $H^{\oplus}$

2. $PhOCH_2Br$
1. Ph_3P
2. MeLi
3. methyl ethyl ketone

a *vinyl ether* (see 15.1, 12, 13 and 15.3, 3, 33 for examples of their reactivity)

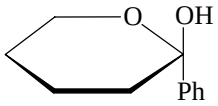
3. 

$H_3O^{\oplus}$

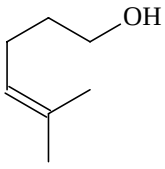
4. 

+ opsin-NH_2

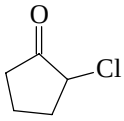
11-cis-retinal (*a protein*) *rhodopsin*

5. 

$H_3O^{\oplus}$

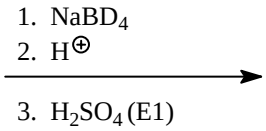
6. 

1. PCC
2. $H_3O^{\oplus}$
3. HOEt, $H^{\oplus}$

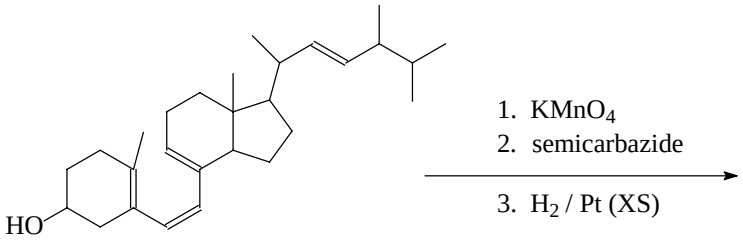
7. 

1. KO-*t*-Bu / *t*-BuOH
2. HCl

8. methyl *n*-propyl ketone

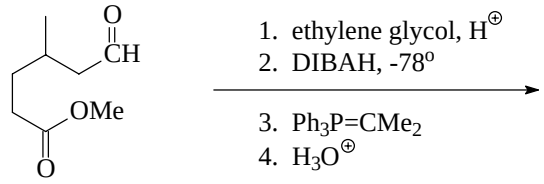


9.



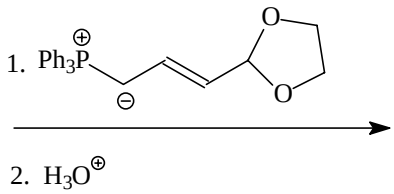
vitamin D

10.



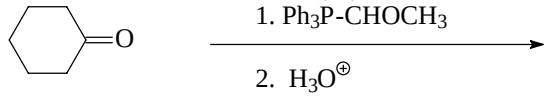
citronellal

11. *p*-nitrobenzaldehyde



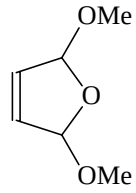
a fluorescent "spy dust" ingredient

12.



an aldehyde

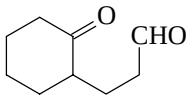
13. Using the above reaction (12) as a model, how could you prepare pentanal from butanal?

14. 

1. CH_2I_2 / Zn (Cu)
2. $H_3O^{\oplus}$
3. $Ph_3P{=}CHC{=}CH_2$

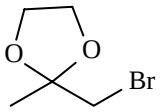
15. cyclopropanecarbaldehyde hydrazone
1. $H_3O^{\oplus}$
2. EtMgI
3. $H^{\oplus}$

16. acetophenone diphenyl ketal
1. $H_3O^{\oplus}$
2. H_2NOH

17. 

$H_3O^{\oplus}$

a heterocycle

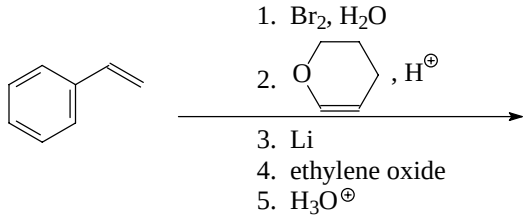
18. 

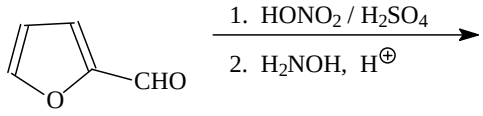
1. Ph_3P
2. *n*-BuLi
3. butanal
4. $H_3O^{\oplus}$

19. 

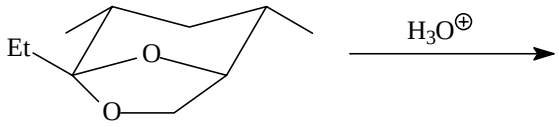
$H_3O^{\oplus}$

20. *t*-butylacetylene
1. $H_3O^{\oplus}$, Hg^{2+}
2. hydrazine, $^{\ominus}OH$

21. 

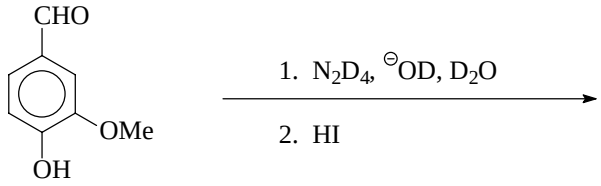
22. 

nitrofuroxime (used in treating urinary tract infections)

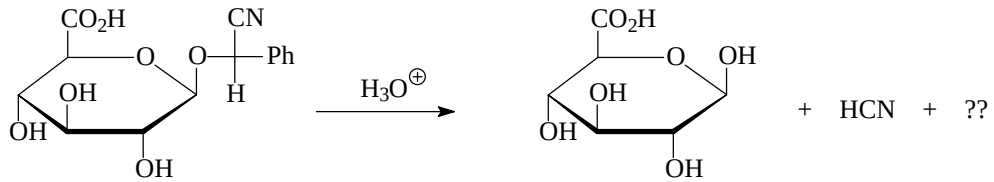
23. 

multistriatin
(European elm bark beetle pheremone)

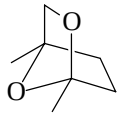
24. 2-oxopropanal $\xrightarrow[\text{(}intra\text{-}Cannizzaro\text{)}]{^{\ominus}OH \,/\, ROH}$

25. 

vanillin

26. 

This reaction, with the release of the very toxic HCN, provides a defense mechanism for millipedes.

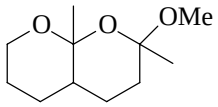
27. 

$H_3O^{\oplus}$ →

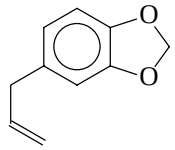
frontalin (insect pheremone)

28. 3-oxobutanal $\xrightarrow{MeOH,\ H^{\oplus}}$

$C_6H_{12}O_3$ IR: 1715 cm^{-1}
^1H NMR: δ 2.2 (s, 3H), 2.8 (d, 2H), 3.4 (s, 6H), 4.9 (t, 1H)

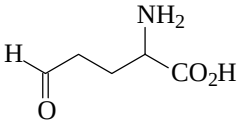
29. 

$\xrightarrow{H_3O^{\oplus}}$

30. 

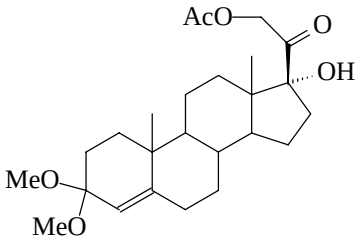
$\xrightarrow{H_3O^{\oplus}}$

safrole (odor of sassafras)

31. 

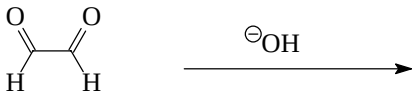
$\xrightarrow[2.\ H_2 / Pt]{1.\ H^{\oplus}}$

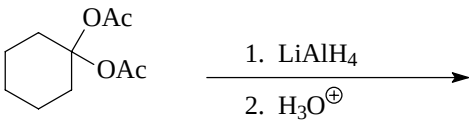
proline (an amino acid)

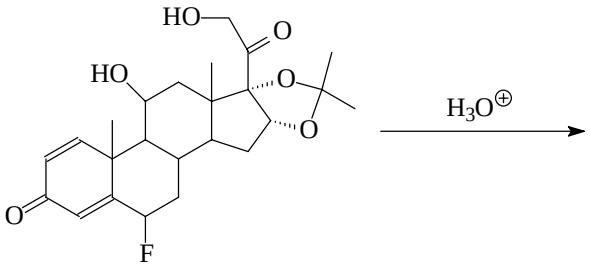
32. 

$\xrightarrow[2.\ H_3O^{\oplus}]{1.\ LiAlH_4}$

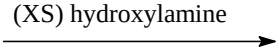
cortisone acetate dimethyl ketal

33. 

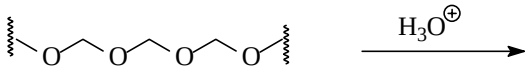
34. 

35. 

flunisolide (anti-inflammatory in allergy medication)

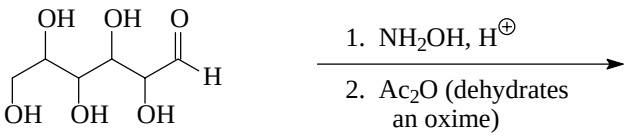
36. 1,2-cycloheptanedione 

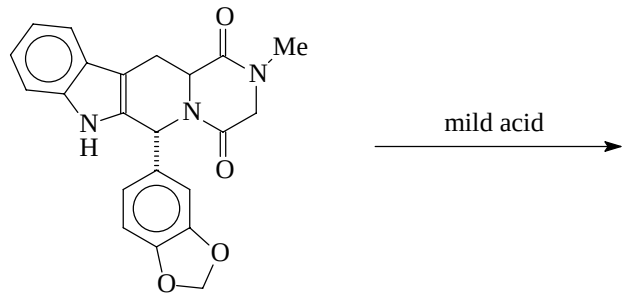
heptoxime (used in quantitative determination of Ni)

37. 

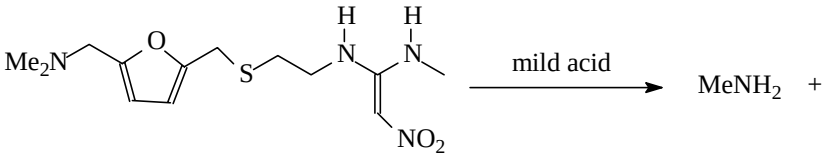
paraformaldehyde

38. Chain degradation of a hexose:

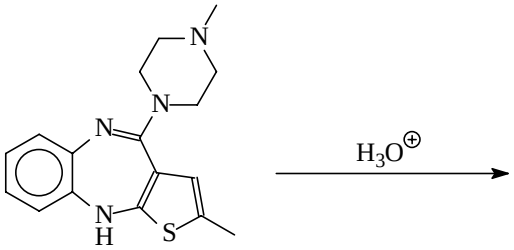


39. 

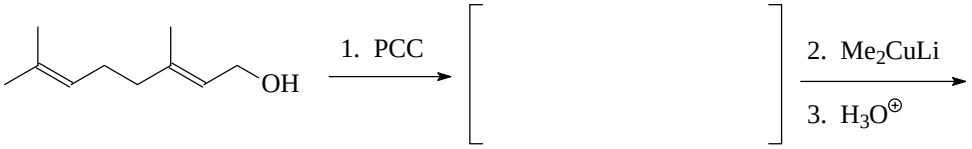
tadalafil (Cialis™)

40. 

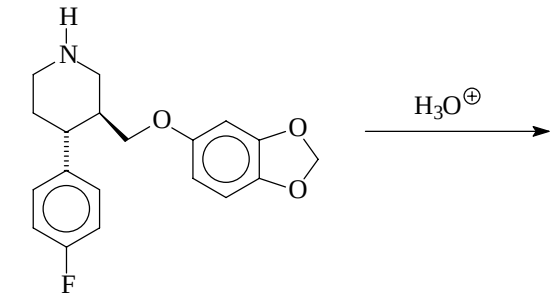
ranitidine (Zantac™ - antiulcerative)

41. 

olanzapine (Zyprexa™ - antipsychotic)

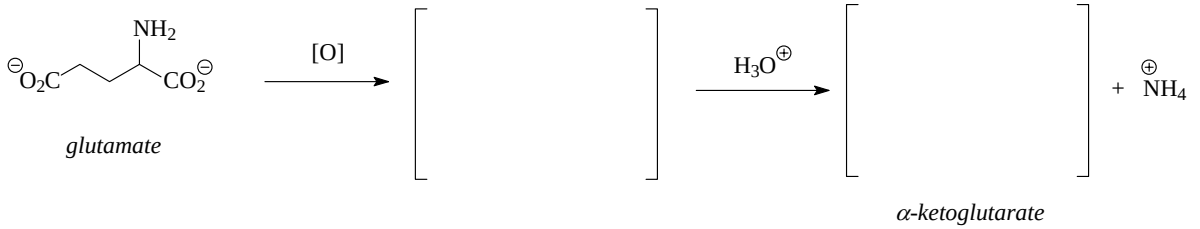
42. 

citral

43. 

paroxetine (Paxil™ - antidepressant)

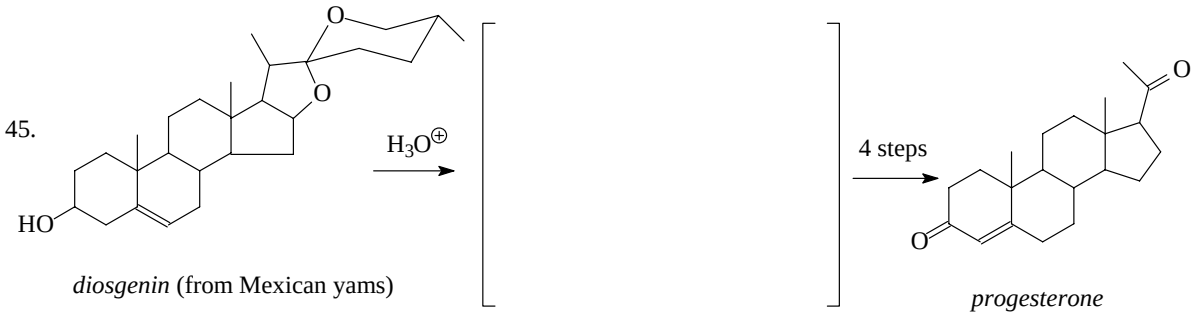
44. Ammonia is produced in the mitochondria primarily by the oxidation of *glutamate* to produce an imine, which is subsequently hydrolyzed:



glutamate

α-ketoglutarate

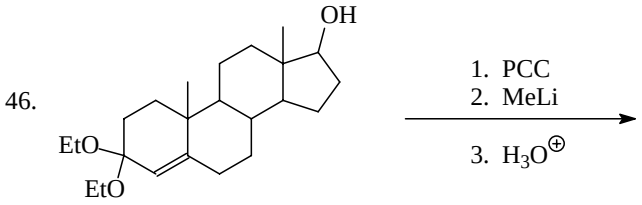
45.



diosgenin (from Mexican yams)

progesterone

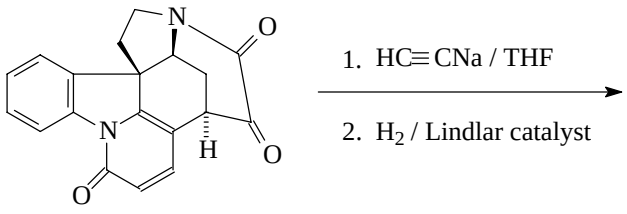
46.



testosterone diethyl ketal

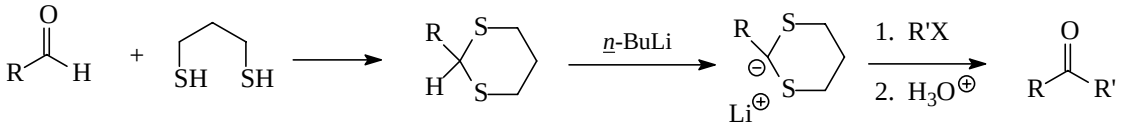
17-methyltestosterone (an anabolic steroid)

47. A step in Woodward's (*Harvard*) synthesis of strychnine:



dehydrostrychninone

48. Aldehyde protons are non-acidic. However, if the aldehyde is converted to a 1,3-dithiane (the sulfur analog of an acetal), the proton can then be quantitatively removed by $NaNH_2$ or organolithiuim bases. The resultant anion (Corey-Seebach reagent) readily undergoes S_N2 or carbonyl addition reactions. Subsequent hydrolysis of the product unmasks the starting carbonyl.



a dithiane *Corey-Seebach reagent*

Predict the products of the following reactions:

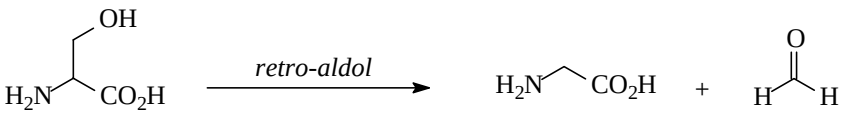
a. benzaldehyde
1. $HS(CH_2)_3SH$, $H^{\oplus}$
2. MeLi
3. EtI
4. $H_3O^{\oplus}$

b.

1. *n*-BuLi
2. *n*-decyl bromide
3. $H_3O^{\oplus}$

c. acetaldehyde
1. HS SH , $H^{\oplus}$
2. $NaNH_2$
3. cyclohexanone
4. $H_3O^{\oplus}$

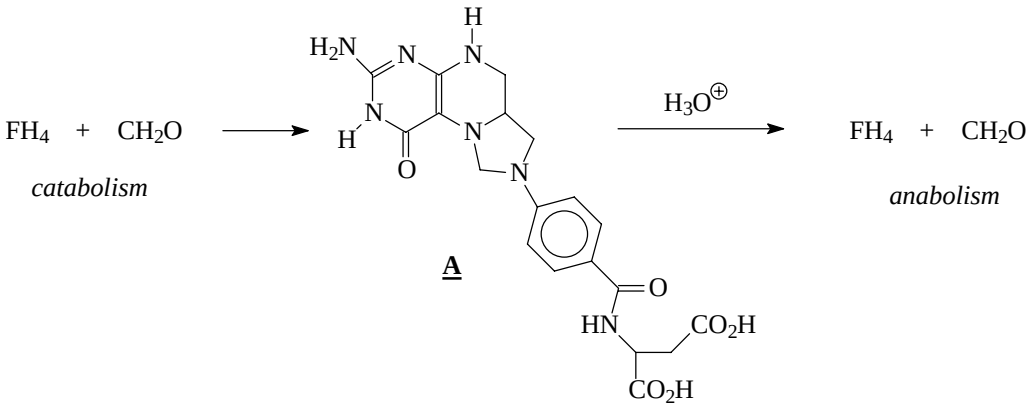
49. The amino acid *serine* can undergo a retro-aldol-like reaction (*see* *CARBONYL CONDENSATION REACTIONS*) to form glycine and formaldehyde; in cells this reaction is catalyzed by a derivative of pyridoxine (vitamin B6):



serine *glycine*

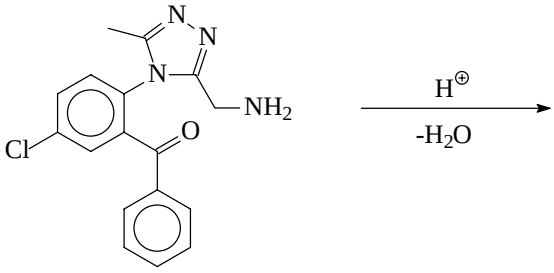
(*cont. on next page*)

Catabolic reactions that produce formaldehyde, as above, generally occur in the presence of another vitamin derivative, tetrahydrofolic acid (FH_4). The later detoxifies formaldehyde by reacting with it to produce **A**. On the other hand, many *anabolic* reactions require formaldehyde as a building block (*e.g.*, biosyntheses of the nucleoside bases). In those instances **A** undergoes hydrolysis to yield FH_4 and formaldehyde *in situ*. Draw the structure of FH_4.



[Note: Unlike us, bacteria can synthesize FH_4 *de novo* from precursors such as *p*-aminobenzoic acid (PABA). Sulfa drugs are effective competitive inhibitors to enzymes that utilize PABA, thus destroying the ability of the bacteria to synthesize FH_4.]

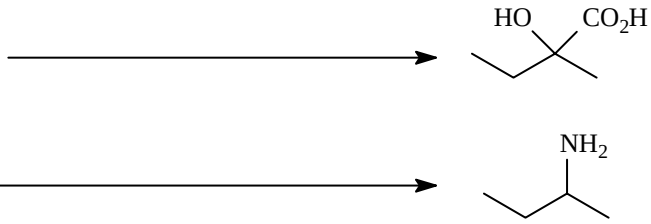
50.

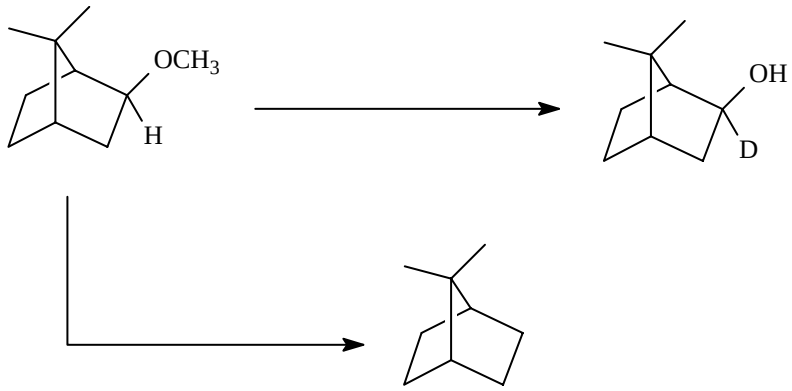


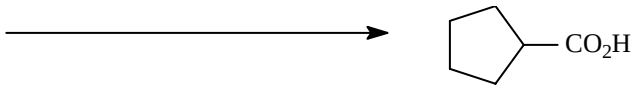
Xanax™ (anxiolytic)

15.2 Syntheses

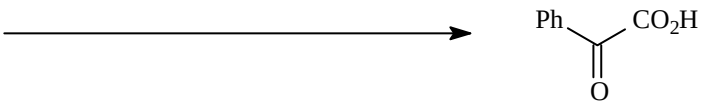
Supply a reagent or sequence of reagents that will effect the following conversions.

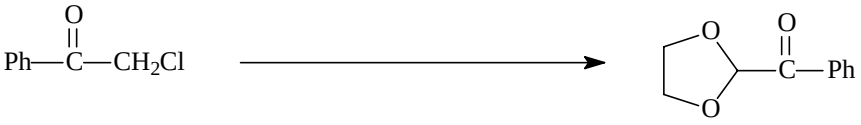
1. *cis*-2-butene 

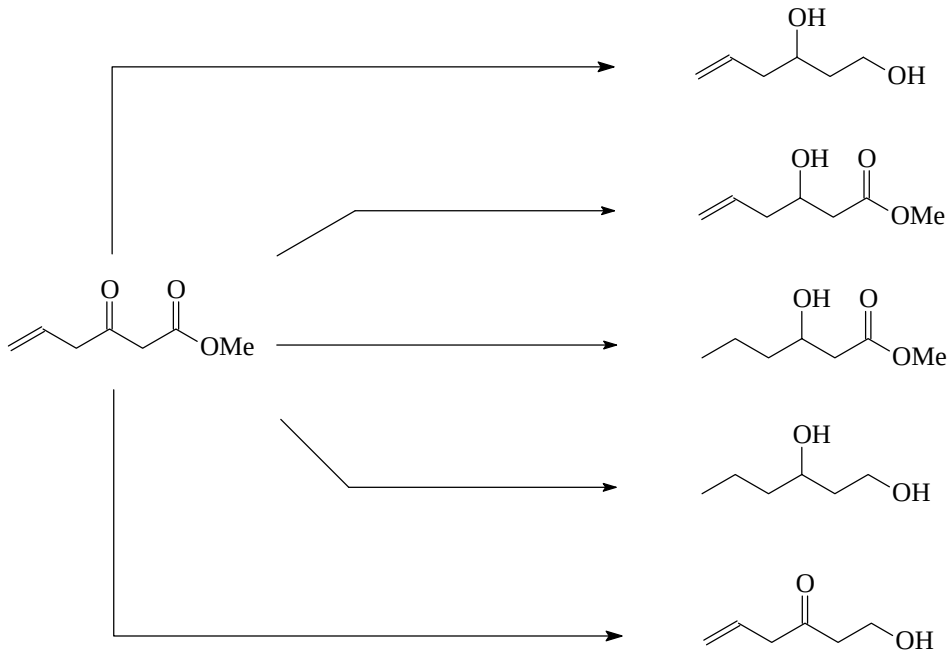
2. 

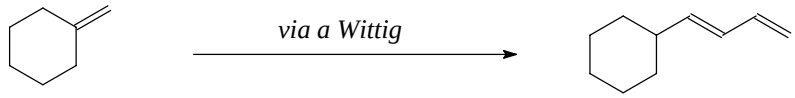
3. cyclopentanone 

4. 

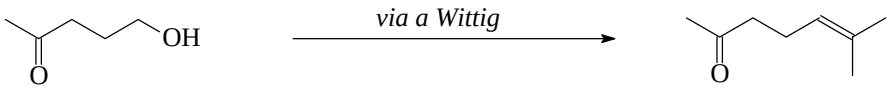
5. benzaldehyde 

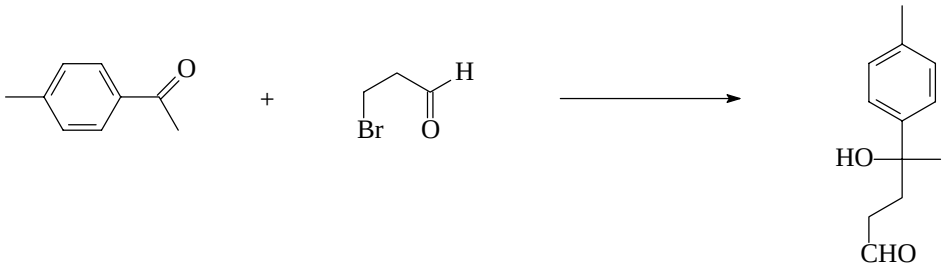
6. 

7. 

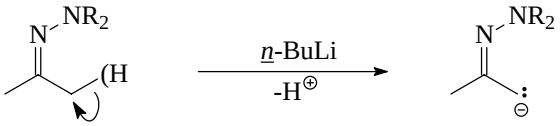
8. 

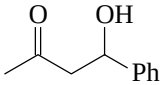
9. MVK (methyl vinyl ketone) 

10. 

11. 

12. Hydrazones can be deprotonated by strong bases to give carbanions that act as nucleophiles, *e.g.*,



How could this observation be used to form 

from acetone and benzaldehyde?

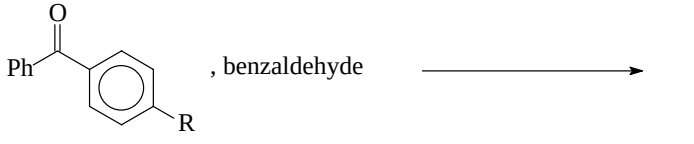
13. 

14. 

15.

major component in OCPs

16.

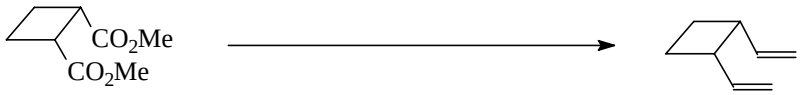


(R = $-OCH_2CH_2NMe_2$)

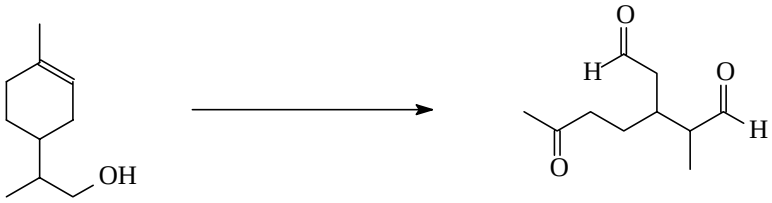
tamoxifen (Nolvadex^{TM} - antiestrogen)

17. 1-butene

18.

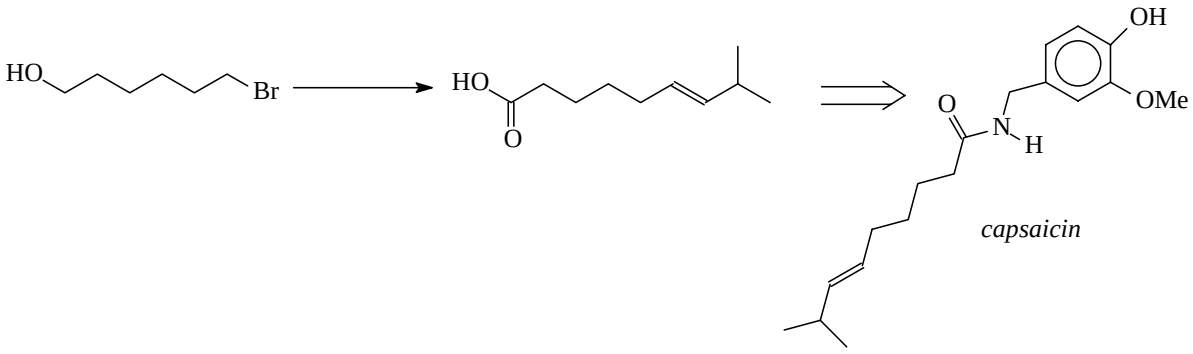


19.



chrysomelidial (secreted by larvae of some beetles in self-defense)

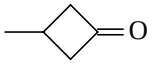
20. The hotness of chili peppers can be quantified by determining their *Scoville heat units* (SHUs). An SHU is the amount of dilution needed before the chili is undetectable. The hottest, according to the *Guinness Book of World Records*, is the *bhut jolokia* from India, firing up at around 1,041,427 SHU, *i.e.*, a drop of extract needs about a million drops of water! (Jalapeño and Tabasco range a mild 5,000 – 25,000 and 100,000 – 200,000, respectively, on the SHU scale.) The active ingredient is *capsaicin*. Formulate a synthesis of the carboxylic acid moiety from 6-bromo-1-hexanol.



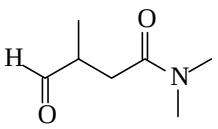
capsaicin

21. Similar to benzyl carbon-oxygen single bonds, carbon-sulfur single bonds readily undergo *hydrogenolysis*. This observation provides a more gentle reduction of aldehyde or ketone carbonyls than the highly alkaline Wolff-Kishner or acidic Clemmensen reductions. Complete the following illustration of this approach:

a *dithiane* (see 15.1, 48)
(*or thioketal*)

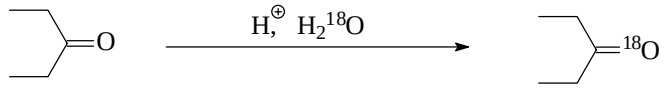
22. 

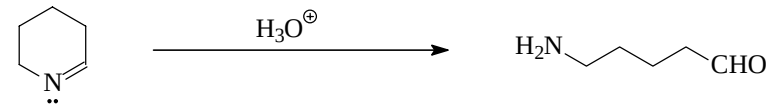
via an enamine



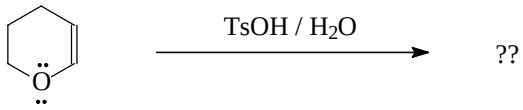
15.3 Mechanisms

Outline a detailed mechanism for each of the following. No other reagents than those given are necessary. Use arrows to explain the flow of electrons and show all intermediates.

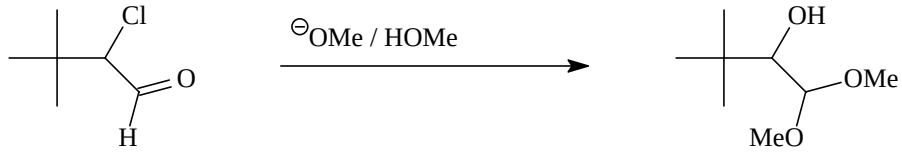
1. 

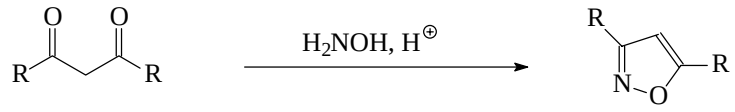
2. 

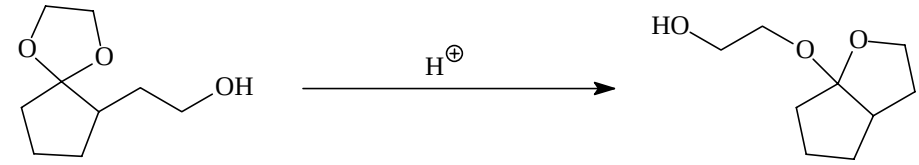
3. *Vinyl ethers*, unlike ordinary ethers, hydrolyze rapidly in water with just a trace of added acid. Draw the products and mechanism for



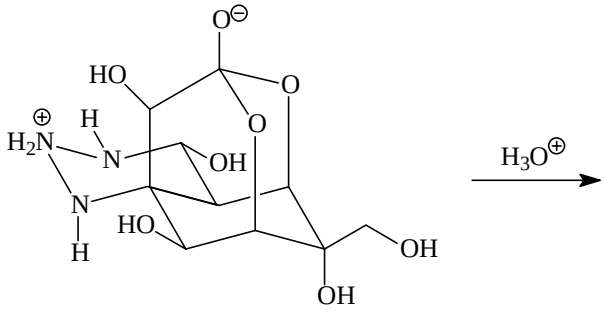
4. 

5. 

6. 

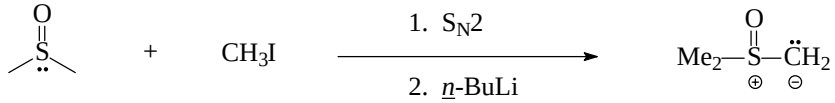
7. 

8. *Fugu*, a fish, is a Japanese delicacy. Unfortunately it produces a very toxic substance, tetrodotoxin (an adult fugu contains enough to kill 30 people), in organs that must be removed by a licensed chef. To become a fugu chef requires training for years with a master and culminates in a battery of state-administered exams, including eating a fugu prepared by oneself ! Though the risk of fugu poisoning is practically nil, *if prepared by a master*, a handful of diners succumb to fugu each year; perhaps that is why Japan's Imperial Family is forbidden from tasting one of their country's choicest dishes. Deduce the structure and outline the mechanism of the carboxylic acid produced when tetrodotoxin is treated with aqueous acid.

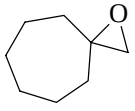


tetrodotoxin

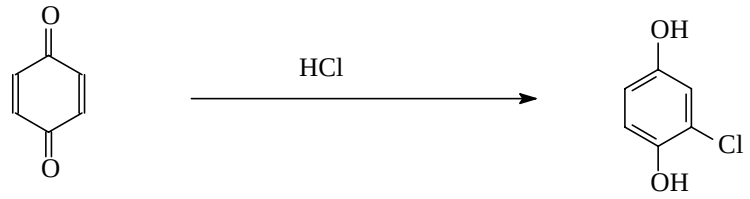
9. E. J. Corey (*Harvard*) found that sulfur ylids, similar to the Wittig reagent, can be prepared as follows:

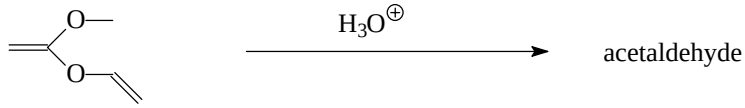


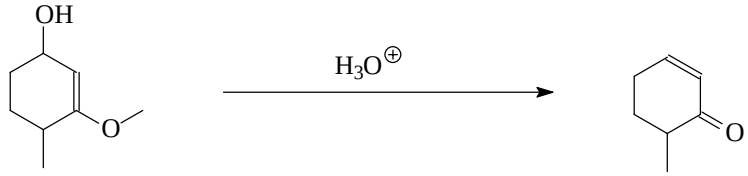
When treated with cycloheptanone a 70% yield of **A** is obtained. Explain, showing clearly how the intermediate betaine's behavior to form an epoxide differs from that of a typical Wittig intermediate.

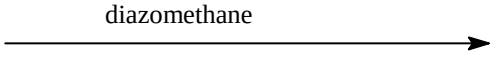


A

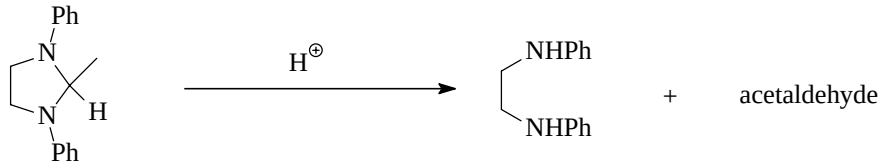
10. 

11. 

12. 

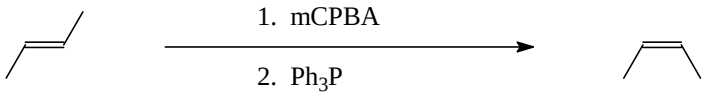
13. cyclohexanone 

cycloheptanone

14. 

15.3 Mechanisms

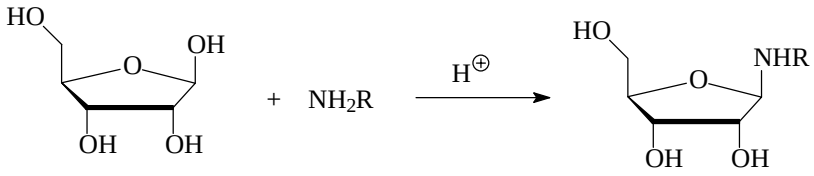
15. The *Vedejs olefin inversion reaction* readily converts *cis-to-trans* or *trans-to-cis* stereoisomers:



(Hint: think Wittig-like)

16. propylene epoxide $\xrightarrow{:P(OMe)_3}$ propylene

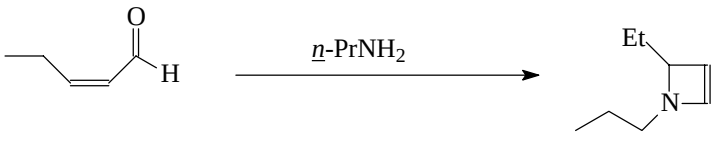
17.



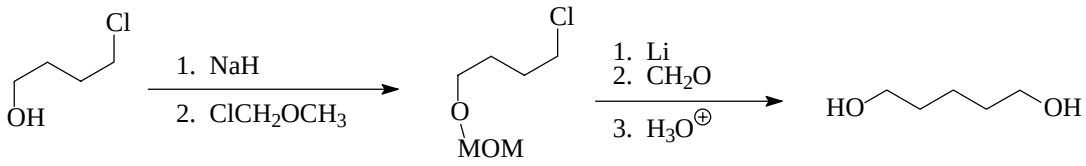
18. 2 phenol + acetone $\xrightarrow{H^{\oplus}}$ $C_{15}H_{16}O_2$

bisphenol A (a starting material in the synthesis of Lexan^{TM})

19.

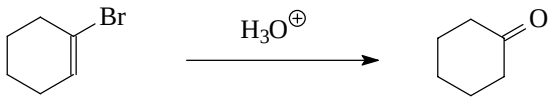


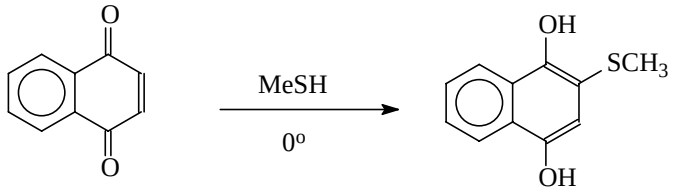
20. Another protecting group for alcohols (in addition to TMS or vinyl ether derivatives) is MOM (methoxymethyl). MOM is stable to base, but can be cleaved upon treatment with mild acid. The following sequence illustrates its use:

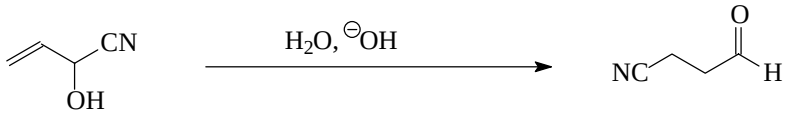


a. Draw the structure of the MOM derivative and explain its mechanism of formation.

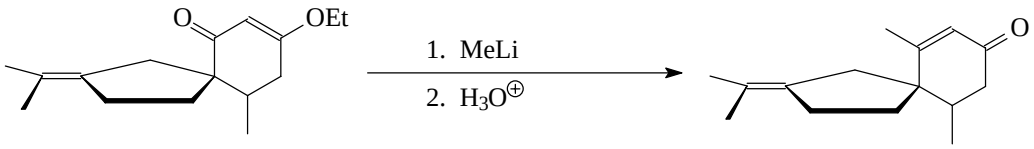
b. Outline the mechanism of the last step. What other two organic products are formed from the MOM group?

21. 

22. 

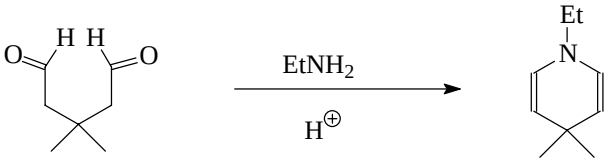
23. 

24.

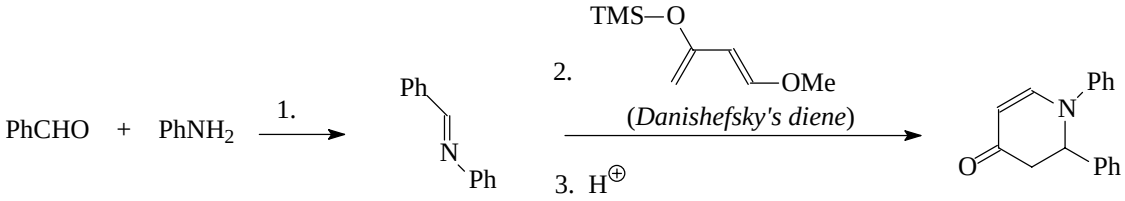


β-vetivone

25.

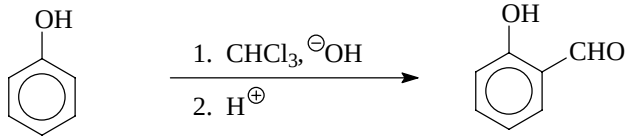


26. Outline the mechanism for steps 2 and 3.

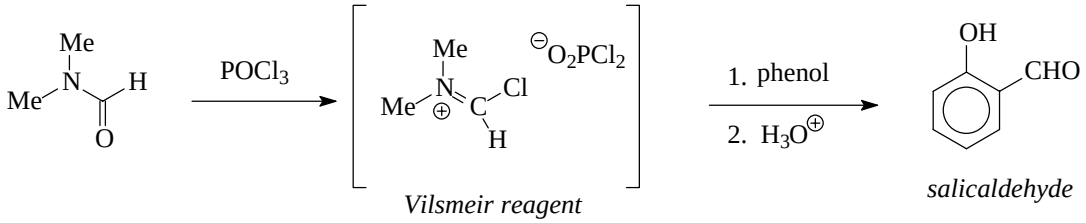


27. Aromatic aldehydes cannot be prepared by direct Friedel-Crafts acylation (formyl chloride is unstable). One alternative is the Gatterman-Koch reaction (12.4, 10). Other options include the following two reactions:

a. the *Reimer-Tiemann reaction*



b. the *Vilsmeier reaction* (outline a mechanism for *both* steps)



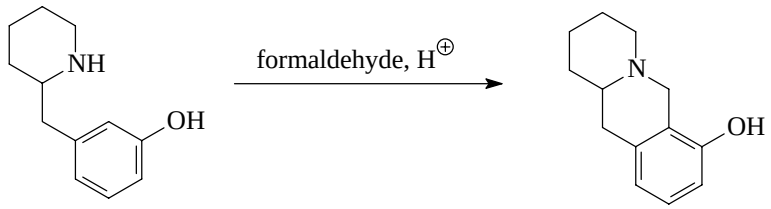
Vilsmeir reagent

salicaldehyde

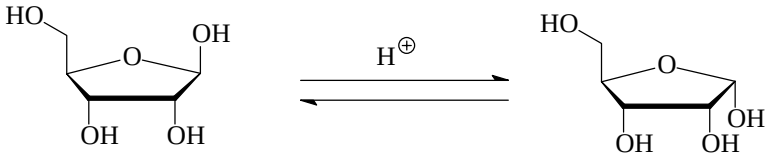
28. Another approach to enhancing the acidity of an aldehyde proton (see 15.1, 48 – Corey-Seebach reaction) is illustrated by the *benzoin condensation reaction*:

benzoin

29.



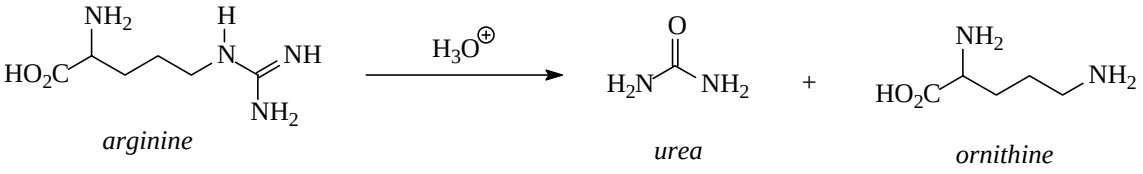
30.



β-D-ribose *α-D-ribose*

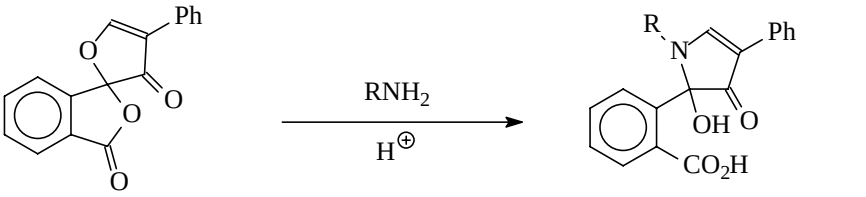
(Carbohydrate chemists call this process "mutarotation" and refer to the two epimeric diastereomers as "anomers.")

31. The final step in the *urea cycle*:



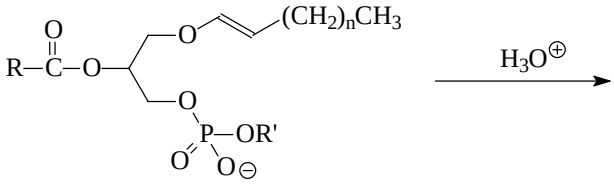
arginine *urea* *ornithine*

32. *Fluorescamine* reacts with amines to give a highly fluorescent derivative. As little as a nanogram of an amino acid, for example, can be detected by this method. (Warning: do not attempt this one alone!)



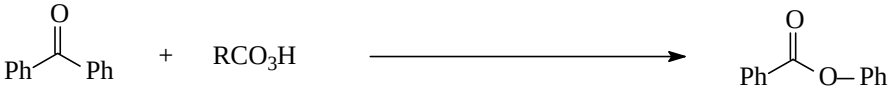
fluorescamine *highly fluorescent derivative*

33. Unlike other types of phospholipids, *plasmalogens* undergo hydrolysis to produce not only fatty acids but also fatty *aldehydes*. Explain the formation of the latter.

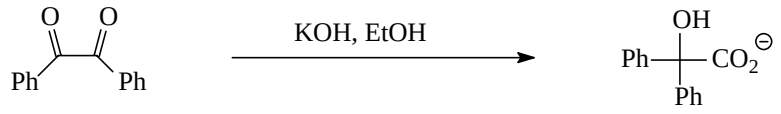


a *plasmalogen* (platelet activating factor)

34. Although ketones are generally not reactive with most oxidizing agents, they are readily oxidized to esters when treated with peracids (*Baeyer-Villager reaction*).



35. Many historians of chemistry credit the discovery of molecular rearrangements to the *benzilic acid rearrangement*:

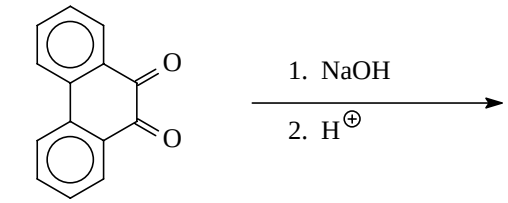


benzil *CB of benzilic acid*

Discovered by Liebig in 1838, it is a rare example of a rearrangement under alkaline conditions (most require acidic environments). Because of (1) disagreements over atomic weights at the time (the "conventional" weights for carbon and oxygen were thought to be 6 and 8!), and (2) the (erroneous as we now know) dogma propagated by Kekulé that carbon skeletal rearrangements could not occur in the course of chemical reactions, many wrong structures for benzilic acid were proposed -- until Baeyer finally got it right nearly forty(!) years later in 1877.

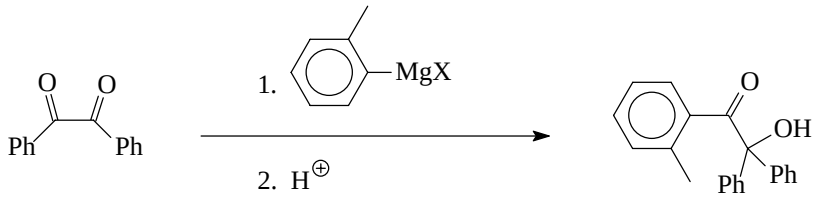
a. Propose a mechanism for the benzilic acid rearrangement.

b. Baeyer observed a benzilic acid-type rearrangement when phenanthrenequinone is treated with base. Draw the expected product.

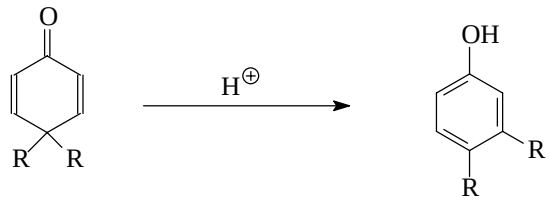


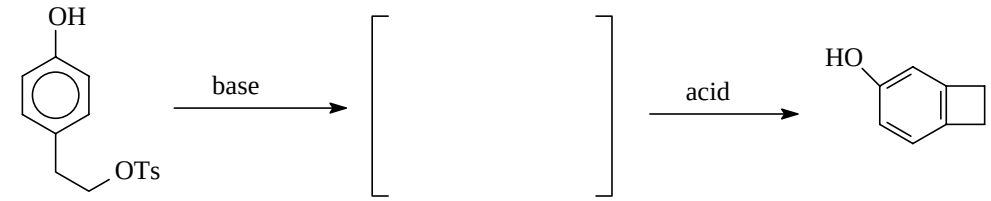
phenanthrenequinone

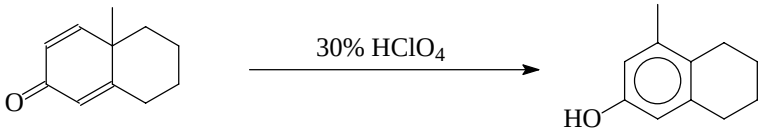
c. Another more modern benzilic acid-type rearrangement:



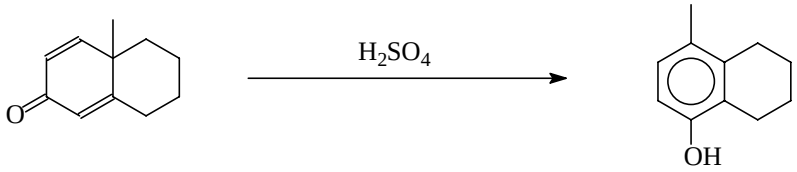
Problems 36 – 40 illustrate the *dienone – phenol-type rearrangements*.

36. 

37. 

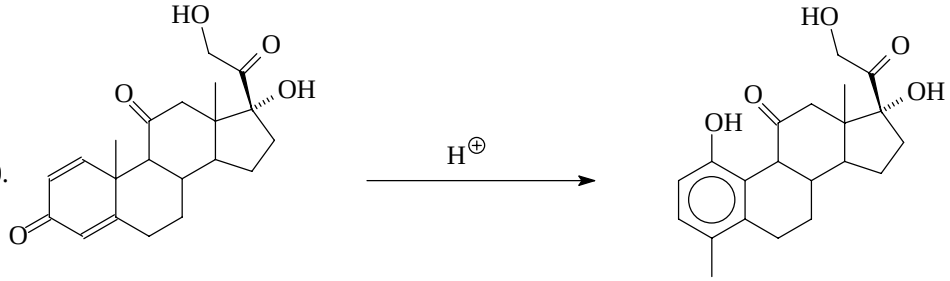
38. 

However (!),

39. 

And, lastly, a steroid dienone – phenol rearrangement:

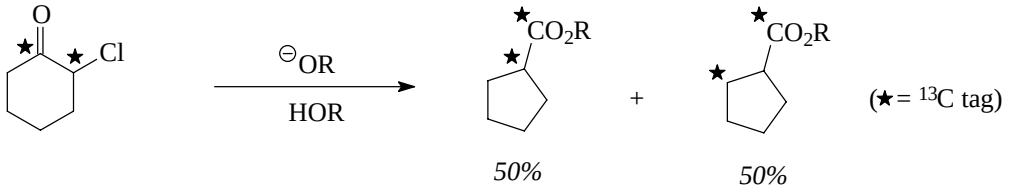
40.



prednisone (anti-inflammatory)

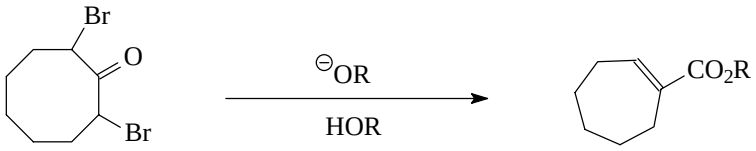
Problems 41 and 42 illustrate the *Favorskii-type rearrangement.*

41.

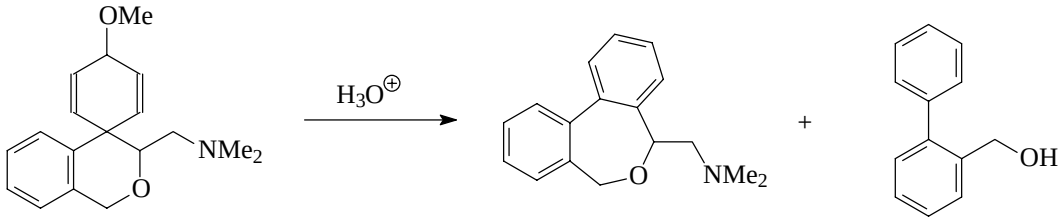


50% *50%*

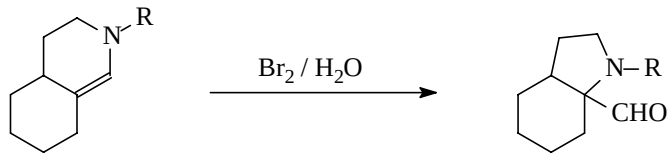
42.



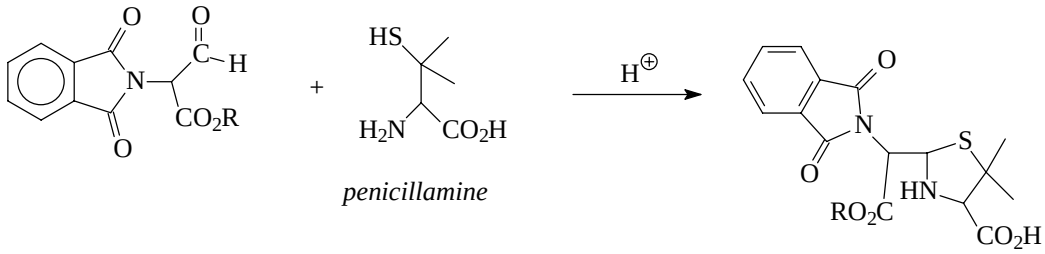
43.



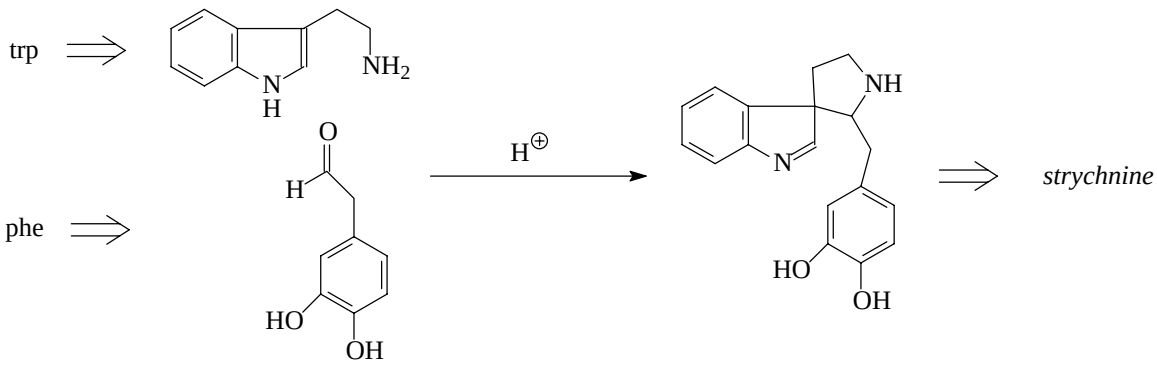
44.



45. Sheehan's (*MIT*) classic total synthesis of penicillin V involved a condensation step between the following reactants. Formulate a mechanism. (Note: the product is simply a nitrogen – sulfur analog of an acetal.)

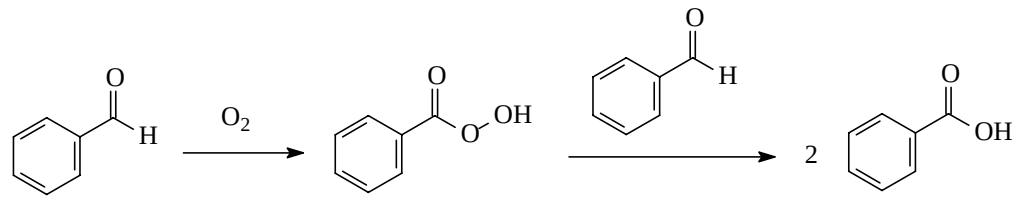


46. Woodward (*Harvard*) envisioned the biosynthesis of *strychnine* as beginning with a condensation of derivatives of the amino acids tryptophan (trp) and phenylalanine (phe). Sketch a likely sequence of events.

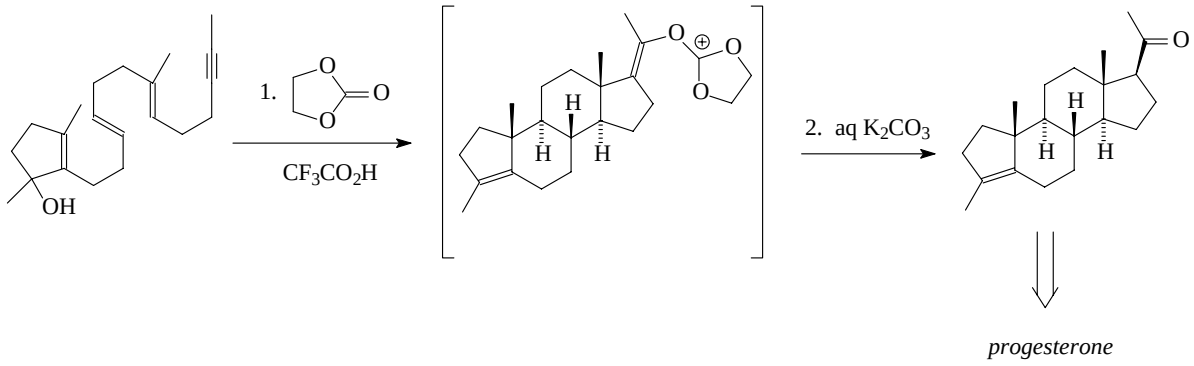


47. Thioketones, in the presence of aqueous acid, form hydrates *via* an intermediate ketone:

48. Many aldehydes autooxidize in air. For example, a white powder (benzoic acid) may often be seen around the cap of a bottle of previously opened benzaldehyde (liquid). Such autooxidation is thought to proceed by the addition of O_2 to a molecule of benzaldehyde *via* a free radical process to form perbenzoic acid. The perbenzoic acid then reacts with a second molecule of benzaldehyde to form two molecules of benzoic acid. Outline a mechanism for the second step. Hint: recall the Baeyer-Villager oxidation of ketones to esters (15.3, 34).



49. An impressive biomimetic conversion in Johnson's (*Stanford*) total synthesis of *progesterone* (see 19.3, 16 for the final stage):

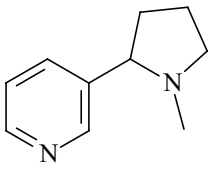


progesterone

CHAPTER 16
CARBOXYLIC ACIDS

16.1 Reactions

Draw the structural formula of the major organic product(s). Show stereochemistry where appropriate.

1. 

$KMnO_4,\ H^{\oplus}$ →

nicotine *niacin*

2. phenylacetic acid

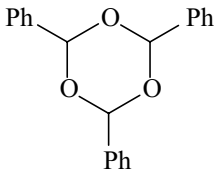
1. NaOH
2. $Me_3O^{\oplus}\ BF_4^{\ominus}$

→

3. 3-oxobutanoic acid

1. $NaBH_4$
2. $H^{\oplus}$

→

4. 

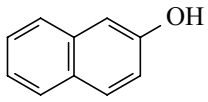
1. $H_3O^{\oplus}$
2. $CrO_3,\ H^{\oplus}$

→

5. γ-bromobutyric acid

1. NaOH (1 equiv)
2. Δ
3. $LiAlH_4$
4. $H_3O^{\oplus}$

→

6. 

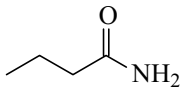
1. KOH
2. acrylic acid (propenoic acid)
3. BH_3
4. $H_3O^{\oplus}$

→

7. benzyl chloride

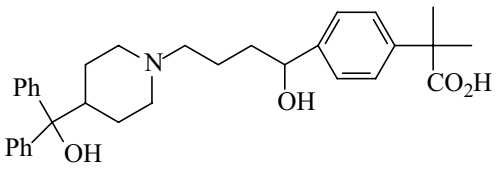
1. NaCN
2. PhMgCl
3. $H_3O^{\oplus}$

→

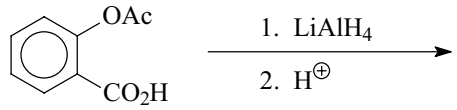
8. 

1. $SOCl_2$
2. DIBAH, -78°
3. $H_3O^{\oplus}$

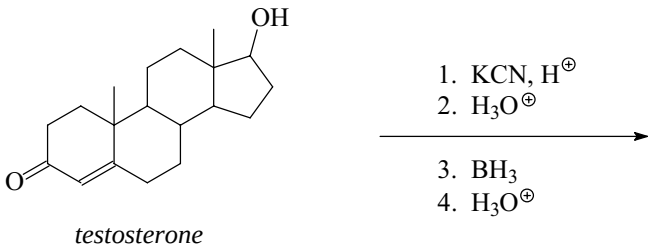
→

9. 

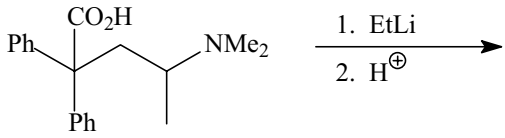
fexofenadine (Allegra™ - antihistaminic)

10. 

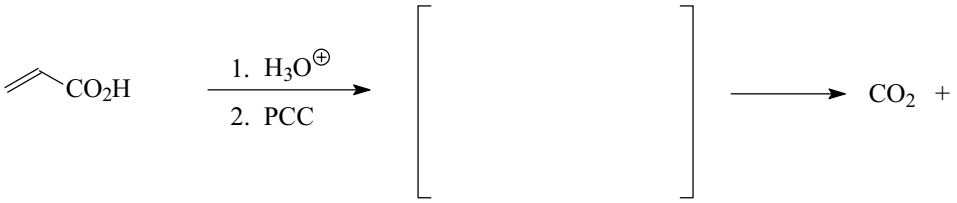
aspirin

11. 

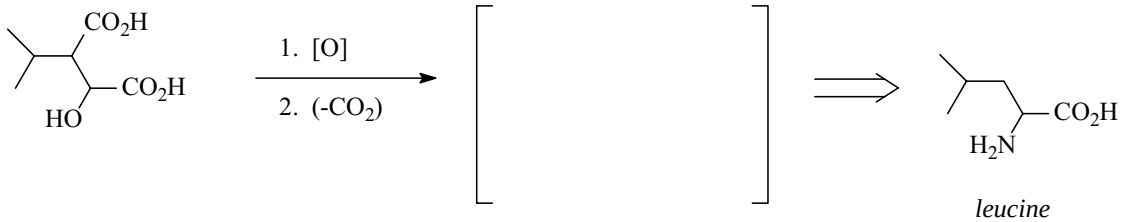
testosterone

12. 

methadone

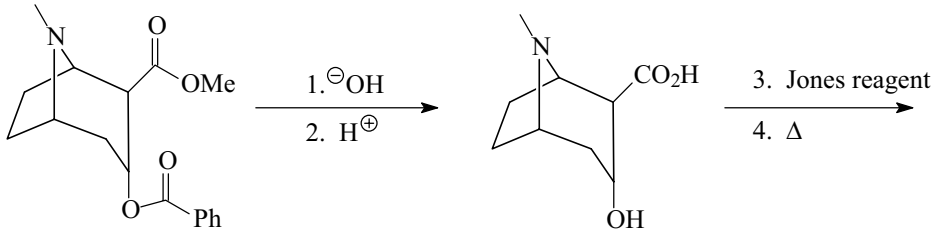
13. 

14. A reaction in the biosynthesis of the amino acid *leucine:*

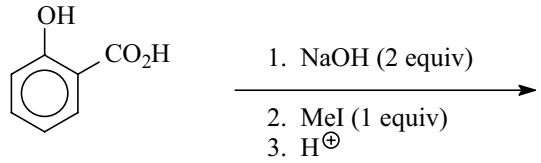


leucine

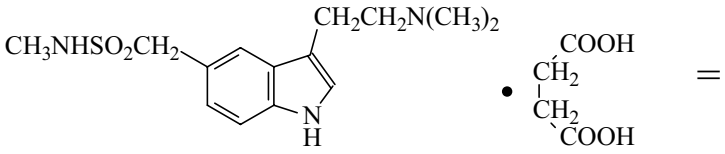
15. The alkaloid *cocaine*, isolable from coca leaves, can be converted to *tropinone*, a precursor to the antispasmodic *atropine* (see 20.3, 12). Deduce the structure of tropinone.



cocaine *ecgonine* *tropinone*

16. 

17. Chemical structures for medicinals that contain acid-base components are routinely drawn incorrectly in prescription information supplied by drug companies. For example, *sumatriptan succinate*, an active ingredient of Treximet™ (prescribed for migraines) is drawn as shown below. Draw its *correct* structure.

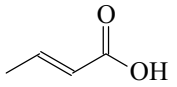


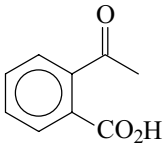
16.2 Syntheses

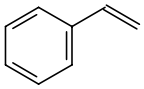
Supply a reagent or sequence of reagents that will effect the following conversions.

1. benzoic acid ⟶ $PhCH_2CO_2H$

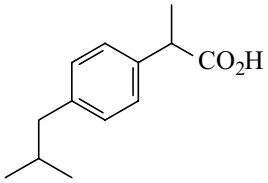
2. propylene ⟶ pentanedioic acid

3.  acetone + CO_2

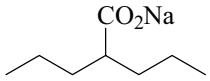
4. *o*-chloroacetophenone 

5. 

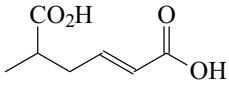
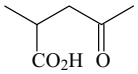
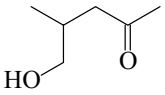
styrene

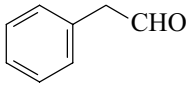


ibuprofen (Motrin™ - antipyretic)

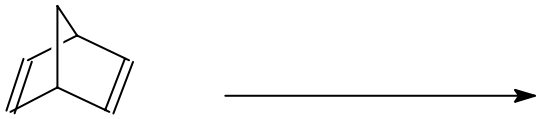
6. 1-butanol 

sodium valproate (used in the treatment of epilepsy)

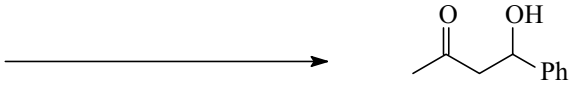
7.   

8. benzyl bromide *via a nitrile* 

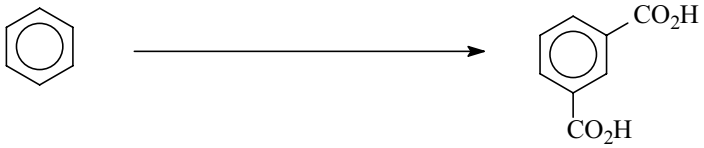
9. 

10. 
pentanedioic acid

11. RCO_2H 

12. 3-oxobutanoic acid 

13. ethanol
butanedioic acid (*succinic acid*)

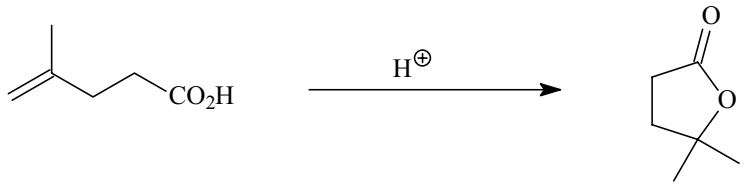
14. 

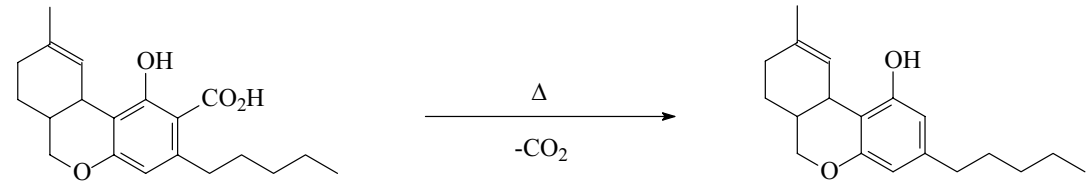
15. acetylene ⟶ hexanoic acid

16. 

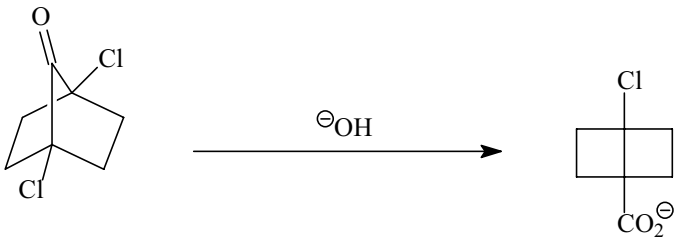
16.3 Mechanisms

Outline a detailed mechanism for each of the following. No other reagents than those given are necessary. Use arrows to explain the flow of electrons and show all intermediates.

1. 

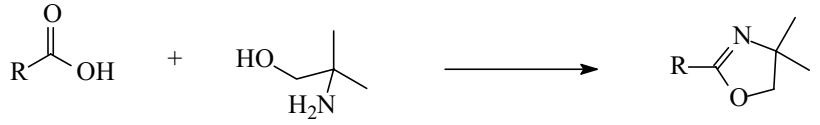
2. 

tetrahydrocannabinolic acid *THC*

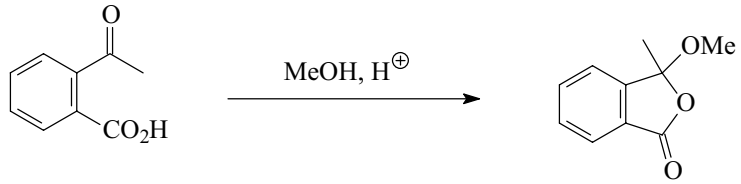
3. 

4. Isobutylene and carbon monoxide, in the presence of acid, give dimethylpropionic acid. Explain.

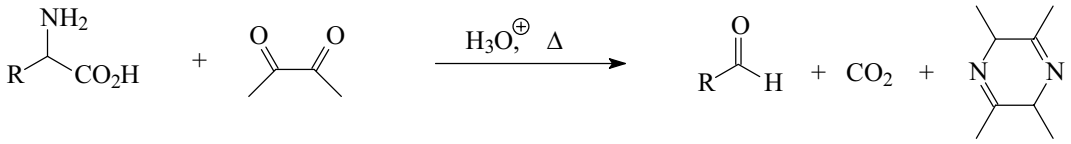
5. The carboxyl group may be protected by allowing it to react with 2-amino-2-methylpropanol to form an oxazoline derivative. Outline the mechanism. (Acid hydrolysis of the oxazoline regenerates the carboxylic acid.)



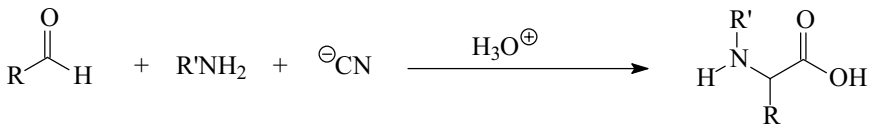
(an *oxazoline)*

6. 

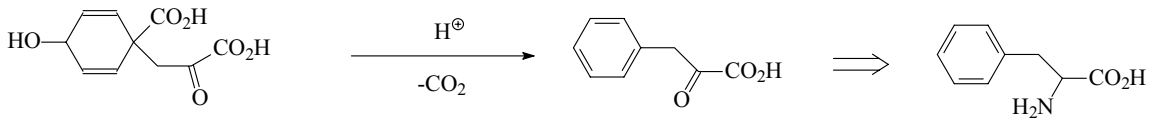
7. The aldehyde flavorings formed in the roasting of cocoa beans is caused by the *Strecker degradation* of amino acids:



8. Strecker also developed a synthesis of amino acids:

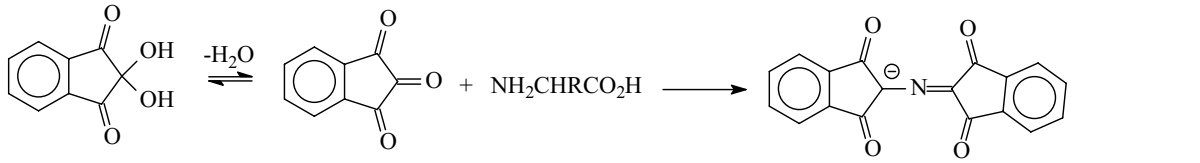


9. The biosynthesis of the amino acid phenylalanine involves an acid-catalyzed decarboxylation of *prephenic acid*:



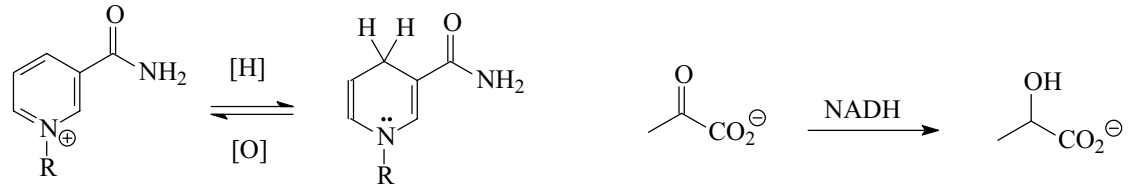
prephenic acid *phenylalanine*

10. *Ninhydrin* reacts with amino acids to give a blue dye which can be colorimetrically assayed. Sketch the intermediates.



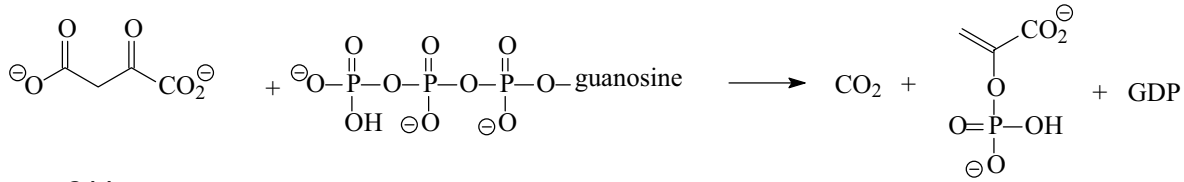
ninhydrin a blue dye

11. The vitamin *niacin* is used to form nicotinamide adenosine dinucleotide, which readily shuttles between its oxidized (NAD^+) and reduced (NADH) forms. The latter serves as a cellular equivalent to $NaBH_4$. The essential portions of the structures are shown below. Outline a mechanism for the cellular conversion of pyruvate to lactate. (Note: like $NaBH_4$, NADH cannot reduce carboxylic acid carbonyls.)



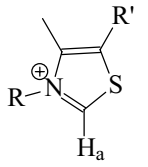
NAD+ *NADH* *pyruvate* *lactate*

12. The cellular biosynthesis of glucose (*gluconeogenesis*) begins with the conversion of oxaloacetate (OAA) to phosphoenolpyruvate (PEP!) *via* a decarboxylation-phosphorylation pathway. Provide arrows.

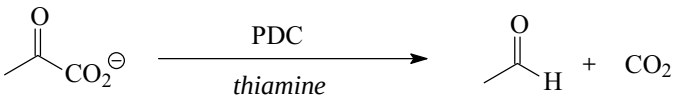


OAA *GTP* *PEP*

13. Unlike β-ketocarboxylic acids, α-ketocarboxylic acids do NOT undergo mild thermal decarboxylation. However, the enzyme pyruvate decarboxylase (PDC) gently converts pyruvate to acetaldehyde at 37°. The key is provided by an essential cofactor, a derivative of *vitamin B1* (thiamine). The activity of thiamine resides in the *thiazolium* ring, shown below. A mechanistic clue was offered by Breslow's (*Columbia*) discovery that H_a rapidly undergoes exchange with deuterium when thiamine is dissolved in D_2O, suggesting that H_a is relatively acidic. Propose a mechanism for thiamine-assisted decarboxylation of α-ketocarboxylic acids. (Hint: begin with the conjugate base of thiamine, then consider how the thiazolium nitrogen can serve as an 'electron sink' to accept the electrons from decarboxylation.)

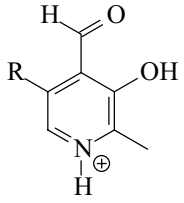


thiazolium ring

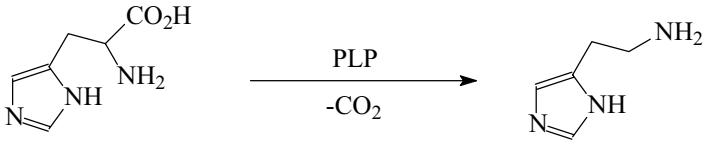


pyruvate

14. Another biochemical approach to decarboxylation:
Vitamin B6 (pyridoxine) is a precursor to the coenzyme PLP (pyridoxal phosphate), a catalyst for many reactions, such as decarboxylations, that involve amino acids. Outline a mechanism. (Hint: form an imine from PLP and the amino acid, then consider the role of the pyridinium nitrogen as an 'electron sink.')



PLP



histidine *histamine*

15. Determination of the molecular mass of acetic acid in a nonpolar solvent, *e.g.*, hexane, yields a value of 120. Explain.

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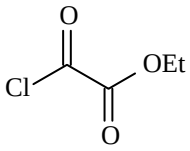
CHAPTER 17
CARBOXYLIC ACID DERIVATIVES

17.1 Reactions

Draw the structural formula of the <u>major</u> organic product(s). Show <u>stereochemistry</u> where appropriate.

1. 

Et_2NH (1 equiv) / pyridine →

2. butyric anhydride + methylamine →

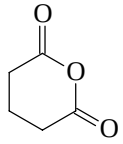
3. cyclopropyl cyclohexanecarboxylate —EtOH (XS), $H^{\oplus}$→

4. propane -1,3-diol —phosgene→

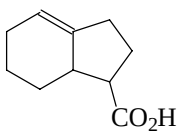
5. oxalic acid —1. PCl_3 2. $LiAlH(O\text{-}t\text{-}Bu)_3$ 3. $H^{\oplus}$→

6. N,N-diisopropylpropionamide —$H_3O^{\oplus}$→

7. phenyl hexanoate —1. isopropyl magnesium bromide 2. $H_3O^{\oplus}$→

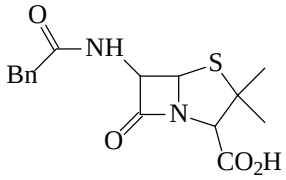
8. 

—MeOH, $H^{\oplus}$→

9. 

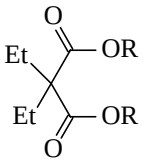
—1. $LiAlH_4$ 2. $H^{\oplus}$ 3. Ac_2O→

10. ε-caprolactone $\xrightarrow{\text{saponification}}$

11. 

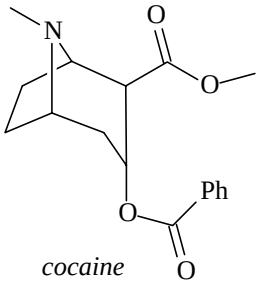
$\xrightarrow{H_2O,\ {}^{\ominus}OH}$

penicillin G

12. 

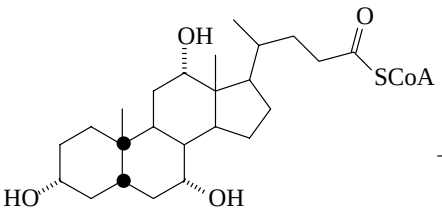
+ urea $\longrightarrow$

Veronal™ (a barbiturate, sedative)

13. 

cocaine

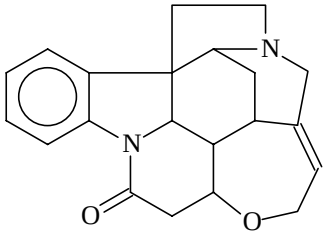
$\xrightarrow[\text{2. } H^{\oplus}]{\text{1. } {}^{\ominus}OH}$ $\xrightarrow[\text{4. } \Delta]{\text{3. Jones reagent}}$

14. 

$\xrightarrow{NH_2CH_2CO_2H\ (\textit{glycine})}$

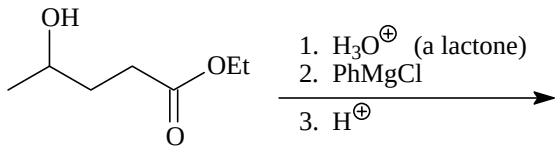
cholyl coenzyme A (a rare example of *cis*-fused A-B rings in steroids)

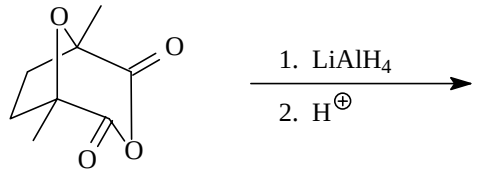
glycocholate (a major bile salt)

15. 

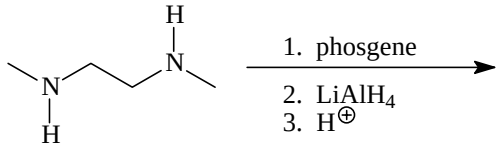
$\xrightarrow[\text{2. } CH_2N_2]{\text{1. } H_3O^{\oplus}}$

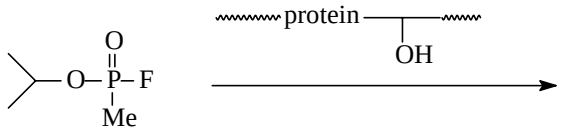
strychnine

16. 

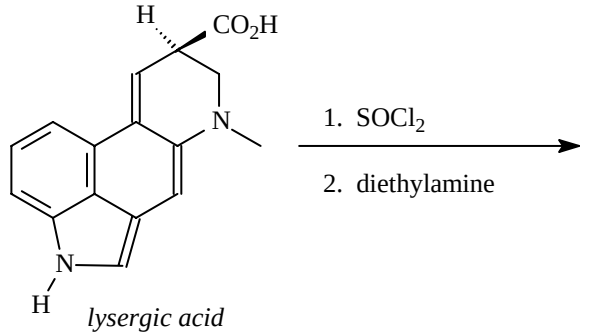
17. 

Spanish fly

18. 

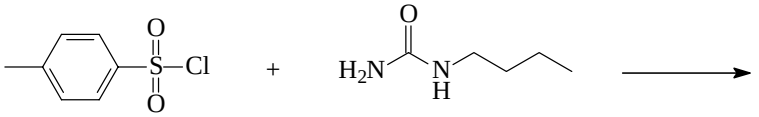
19. 

Sarin™ (a cholinesterase inhibitor)

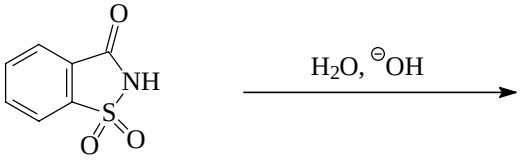
20. 

lysergic acid

LSD

21. 

Orinase™ (for diabetes)

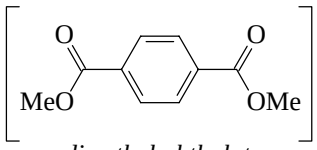
22. 

saccharin

23. *p*-hydroxyaniline $\xrightarrow[(1\ \text{equiv})]{\text{acetic anhydride}}$

acetaminophen (Tylenol™ - antipyretic)

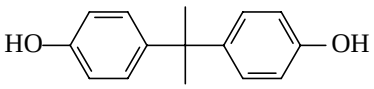
24. acetic acid $\xrightarrow[(-H_2O)]{Al_2O_3,\ \Delta}$ $H_2C{=}C{=}O$ *ketene* $\xrightarrow{\text{aniline}}$

25.  + [ethylene glycol]$_n$ $\xrightarrow{H^{\oplus}}$

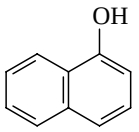
dimethyl phthalate

Dacron™

26. Lexan™, a high-molecular weight "polycarbonate," is manufactured by mixing *bisphenol A* (see 15.3, 18) with phosgene ($COCl_2$) in the presence of pyridine. Draw a partial structure for Lexan™.

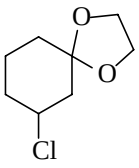


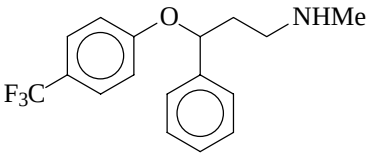
bisphenol A

27. $Me{-}N{=}C{=}O$ +  $\longrightarrow$

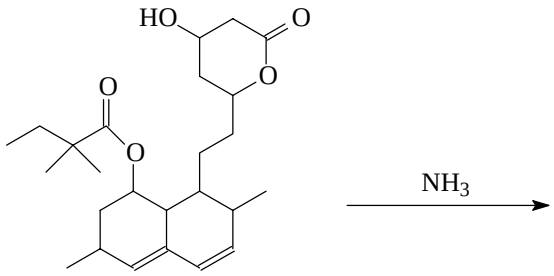
methyl isocyanate

(active ingredient in the insecticide Sevin™)

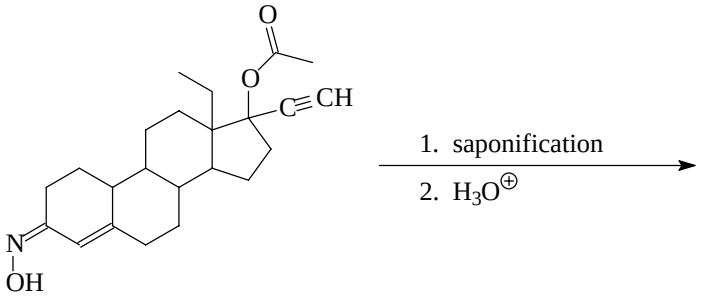
28.  $\xrightarrow[3.\ \text{benzoyl chloride}]{1.\ \text{Li}\ \ 2.\ \text{CuI}}$ $\xrightarrow{4.\ H_3O^{\oplus}}$

29.  $\xrightarrow[2.\ LiAlH_4]{1.\ \text{propionic anhydride}}$ $\xrightarrow{3.\ H^{\oplus}}$

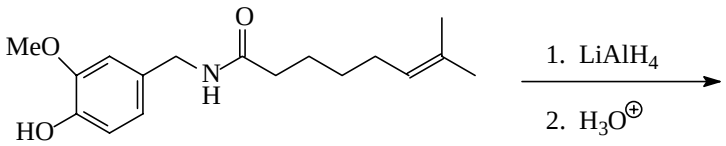
fluoxetine (Prozac™ - antidepressant)

30. 

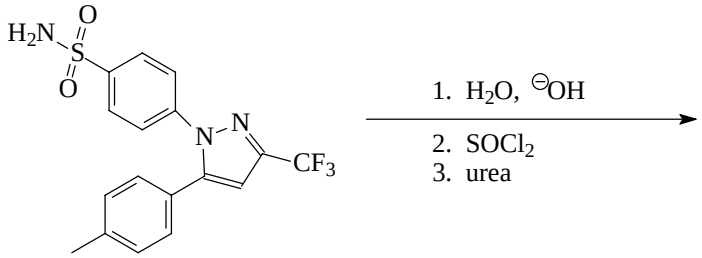
simvastatin (Zocor™ - antilipemic)

31. 

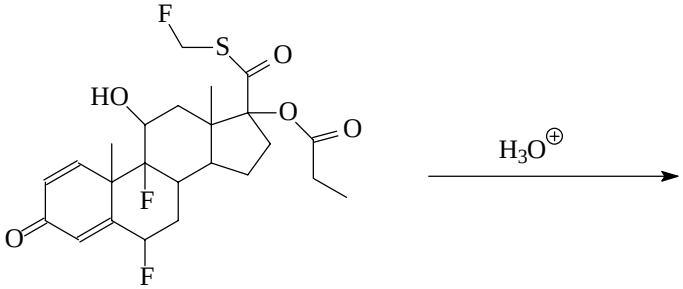
Ortho TriCyclin™ (OCPs)

32. 

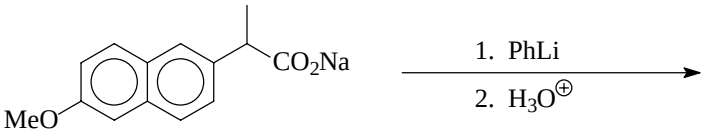
capsaicin (active agent in cayenne pepper)

33. 

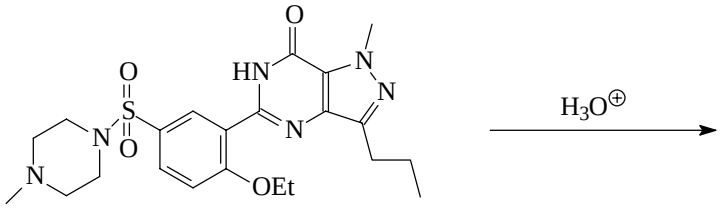
celecoxib (Celebrex™ - anti-inflammatory)

34. 

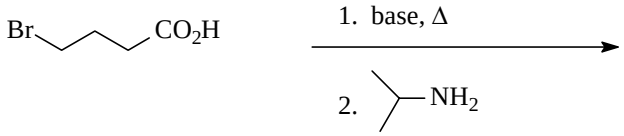
fluticasone propionate (Flonase™ - anti-inflammatory)

35. 

naproxen sodium (Aleve™ - anti-inflammatory)

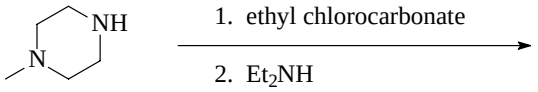
36. 

sildenafil (Viagra™ - treatment of ED)

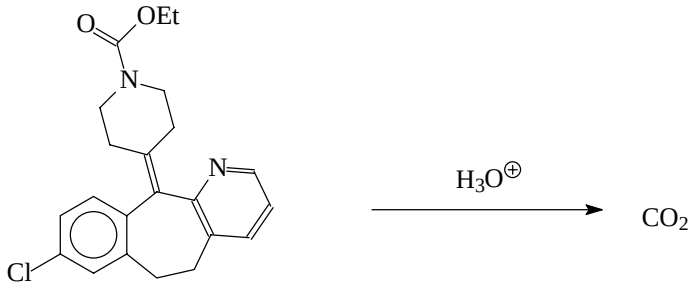
37. 

38. 

ε-caprolactam *Nylon 6* (a polyamide)

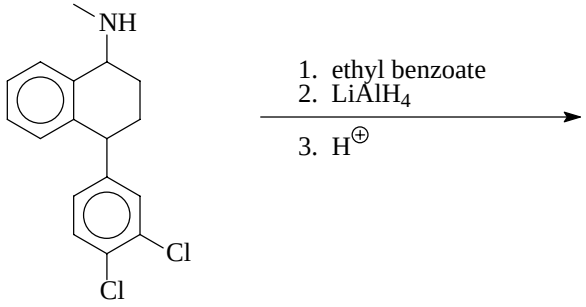
39. 

diethylcarbamazine (anthelmintic)

40. 

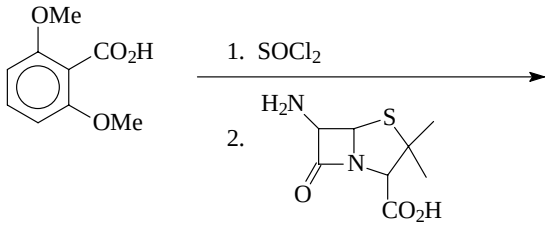
loratadine (Claritin™ - antihistaminic)

41.



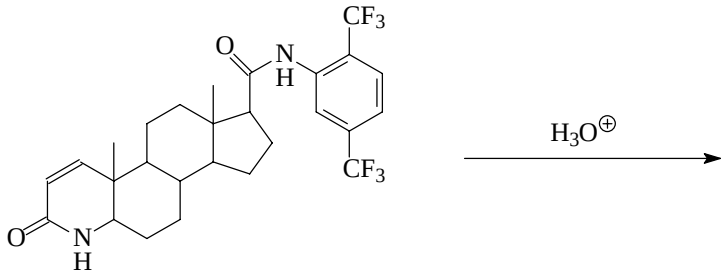
sertraline (Zoloft™ - antidepressant)

42.



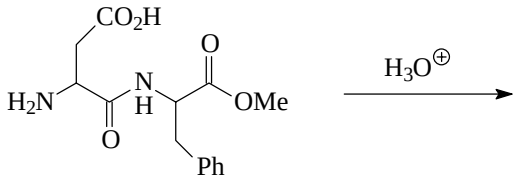
methicillin [an estimated 90,000 people in the US fall ill each year from MRSA (methicillin resistant *Staphylococcus aureus*)]

43.



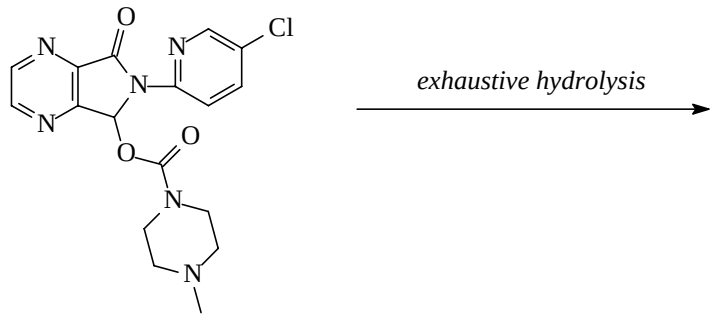
dutasteride (Avodart™ - treatment of BPH)

44.

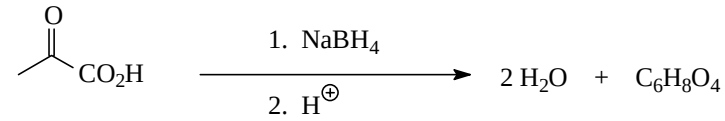


aspartame

45.

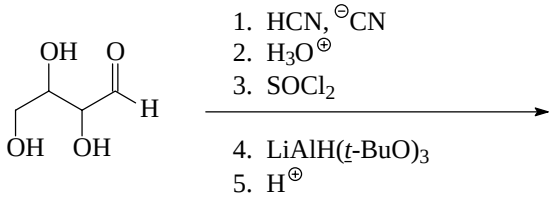


zopiclone (Lunesta™ - sedative, hypnotic)

46. 

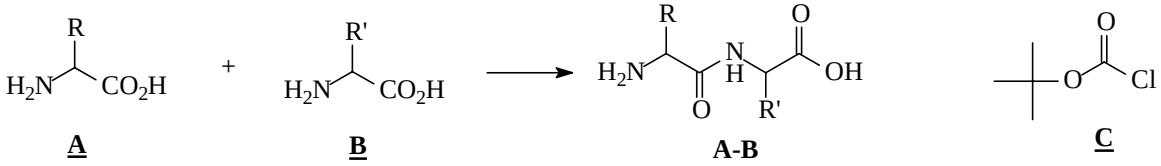
pyruvic acid

47. Chain *elongation* of a tetrose sugar:



(see chain *degradation* of a sugar, 15.1, 38)

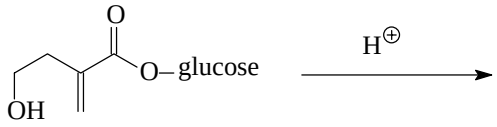
48. Consider the reaction of amino acid **A** with amino acid **B**. Four possible products are possible: **A-A**, **B-B**, **A-B**, and **B-A**, if simply **A** and **B** are heated together. A more rational synthesis of, for example, **A-B** is to first treat **A** with *t*-butyl chlorocarbonate (**C**), which has the effect of eliminating (blocking) the nucleophilicity of the nitrogen in **A**. The blocked species is termed a *t*-BOC amino acid (*t*-butoxy-carbonyl).



A **B** **A-B** **C**

a. Draw the product of the reaction of **A** with **C**.

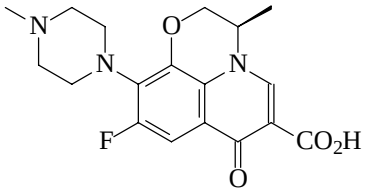
b. The *t*-BOC-**A** is then condensed with **B** to yield a derivative of **A-B**. **A-B** is formed by treating that derivative with mild acid. Show the mechanism of removing the blocking group to form **A-B**. (Hint: CO_2 and isobutylene are by-products.)

53. 

+ glucose

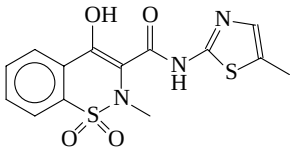
tuliposide
(found in tulip bulbs)

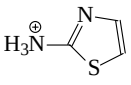
tulipaline (a γ-lactone)
(produced when bulbs are damaged - a fungicide)

54. 

1. $SOCl_2$
2. ammonia
3. $SOCl_2$

Levaquin™ (antibacterial)

55. 

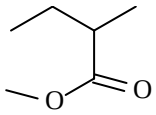
$H_3O^{\oplus}$, Δ → CO_2 + $MeNH_3^{\oplus}$ +  + ??

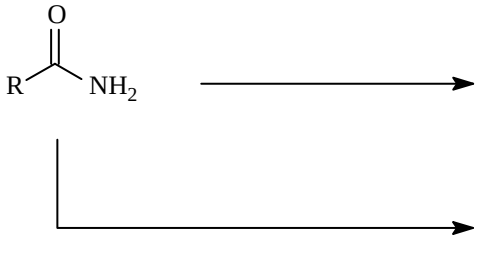
(gives a positive Tollens' test)

meloxicam (Metacam™ - anti-inflammatory)

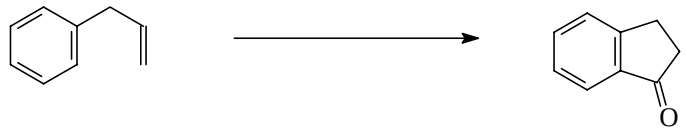
17.2 Syntheses

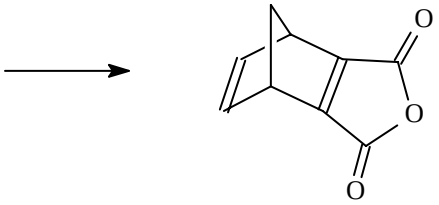
Supply a reagent or sequence of reagents that will effect the following conversions.

1. *sec*-butyl acetate → 

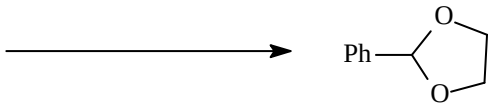
2. 

3. 

4. 

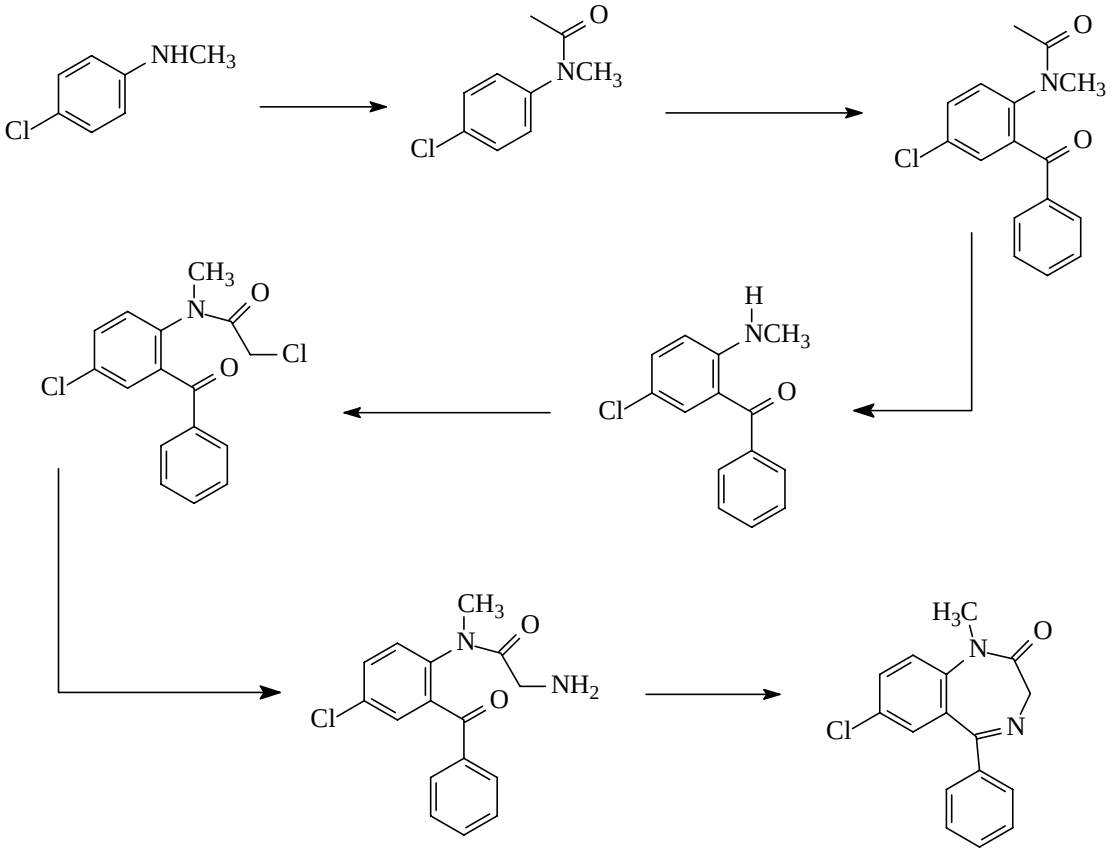
5. 1,3-cyclopentadiene, acetylenedicarboxylic acid 

6. 

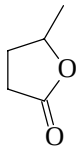
7. benzamide 

8. butanal ⟶ 2-pentanone

9. Following is an outline for the synthesis of *diazepam* (Valium™). Supply the appropriate reagents for each step.

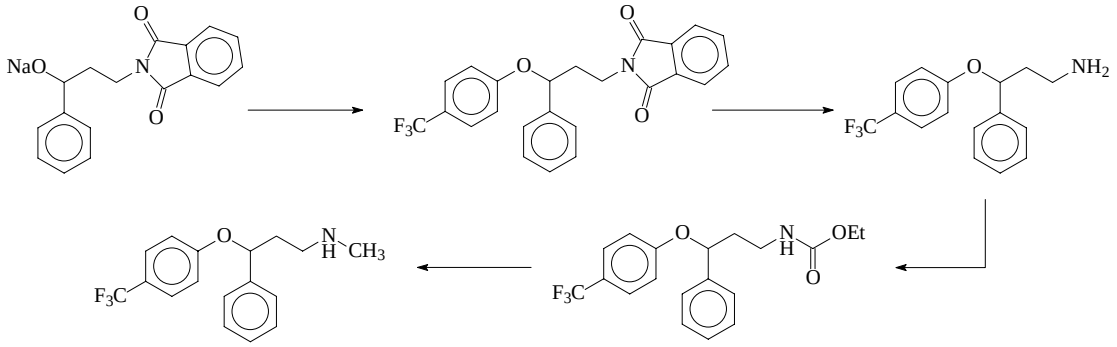


Valium™

10. 3-oxohexanedioic acid ⟶ 

11. methyl benzoate ⟶ methyl phenylacetate

12. Following is an outline for the synthesis of *fluoxetine* (Prozac™). Supply reagents for each step.

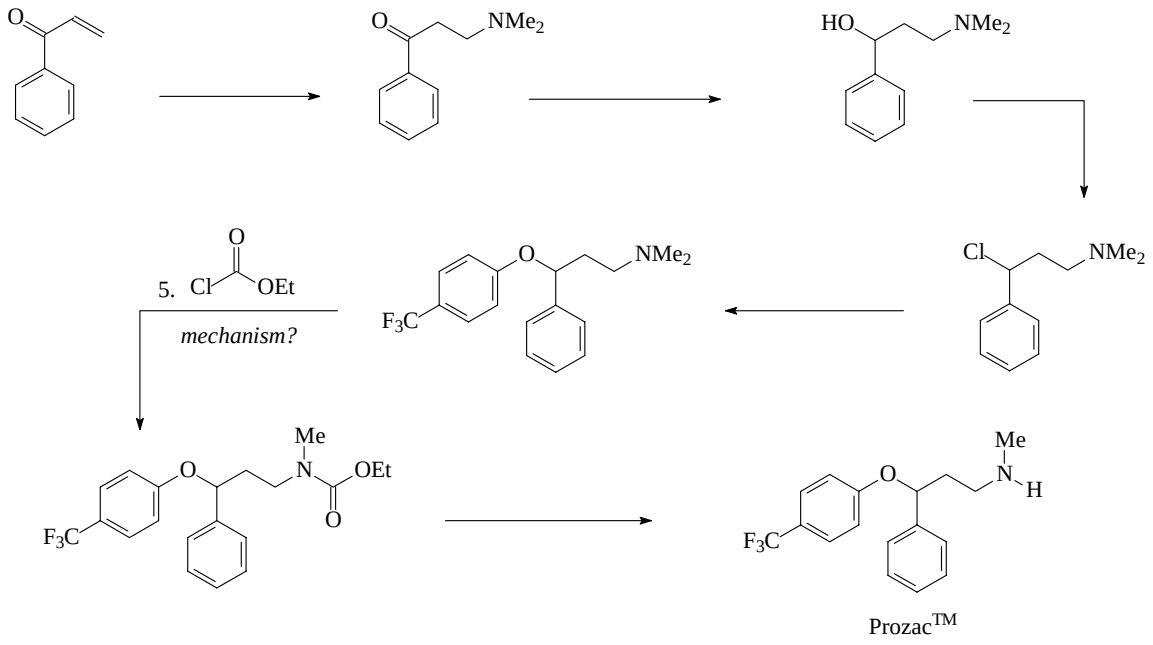


Prozac™ (antidepressant)

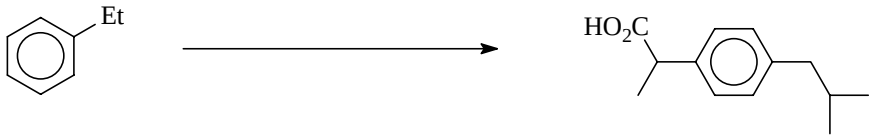
13.

Demerol™ (analgesic)

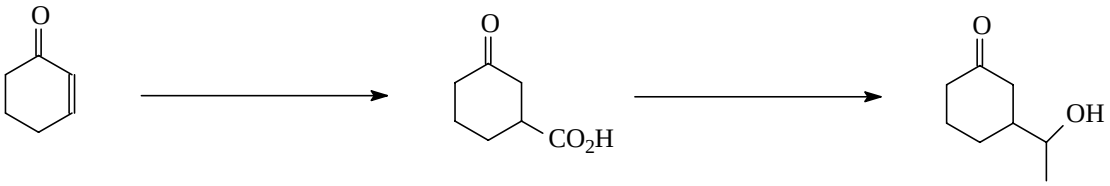
14. Following is an alternative synthesis of Prozac™ (see 17.2, 12). The reagent for step 5 is indicated; supply reagents for all the other steps. Outline a mechanism for step 5.

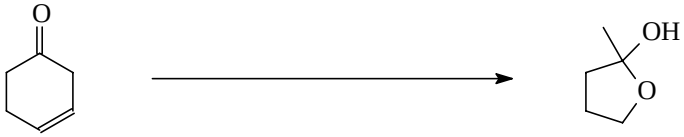


mechanism:

15. 

ibuprofen

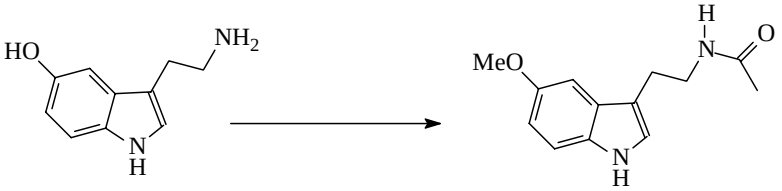
16. 

17. 

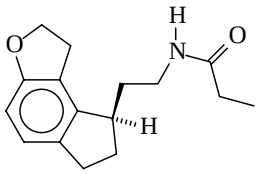
18. 

DEET (N,N-diethyl-*m*-toluamide - insect repellent)

19. *Melatonin* mediates circadian rhythm, the 24-hour sleep-wake cycle. Because its biosynthesis is inhibited by light, it is produced in the brain when the eye is not receiving light. Outline a synthesis from the neurotransmitter *serotonin*.



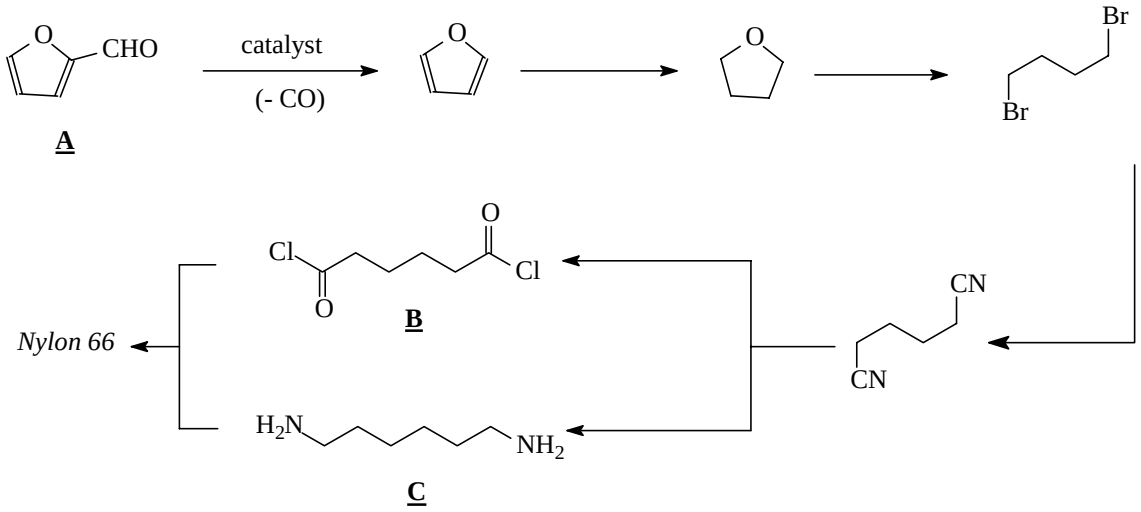
serotonin (5-HT) *melatonin*

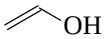


Roserem™

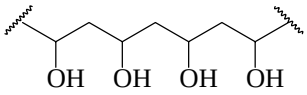
Insomnia affects one in every eight people. Roserem™, a selective melatonin receptor agonist, is an example of several drugs approved to treat short- and long-term insomnia.

20. The two monomers (**B** and **C**) for the synthesis of *Nylon 66* can be prepared from a sugar derivative **A**. Supply the necessary reagents.

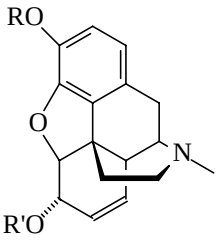


21. Name the following polymer and devise a synthesis for it. Remember, 

is not an appropriate starting monomer. Why?



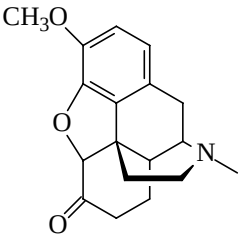
22. Some members of the morphine family of opium alkaloids…



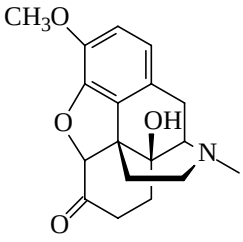
R, R' = H (*morphine*)

R = Me, R' = H (*codeine*)

R, R' = Ac (*heroin*)



hydrocodone (a component of Vicodin™)



oxycodone (HCl salt = OxyContin™, a component of Percoset™)

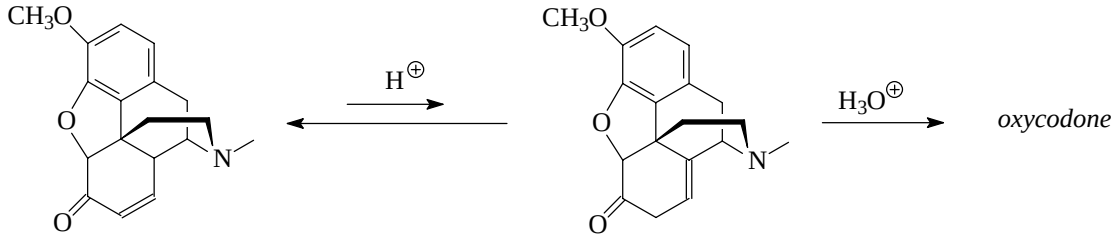
How can the following conversions be accomplished?

a. morphine ⟶ codeine

b. morphine ⟶ heroin

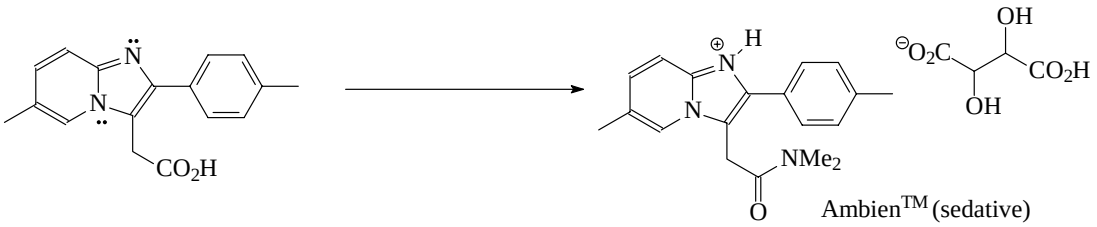
c. codeine ⟶ hydrocodone

d. In aqueous solution *codeinone* exists in dynamic equilibrium with its β,γ-unsaturated isomer, *neopinone*, hydration of which yields *oxycodone*. Write a mechanism for the equilibration.



codeinone *neopinone*

23.

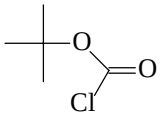


Ambien™ (sedative)

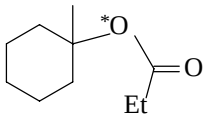
17.3 Mechanisms

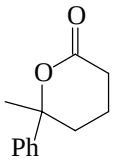
Outline a detailed mechanism for each of the following. No other reagents than those given are necessary. Use arrows to explain the flow of electrons and show all intermediates.

1. γ-butyrolactone $\xrightarrow{H_2{}^*O,\ H^{\oplus}}$ (show location of the labeled oxygen)

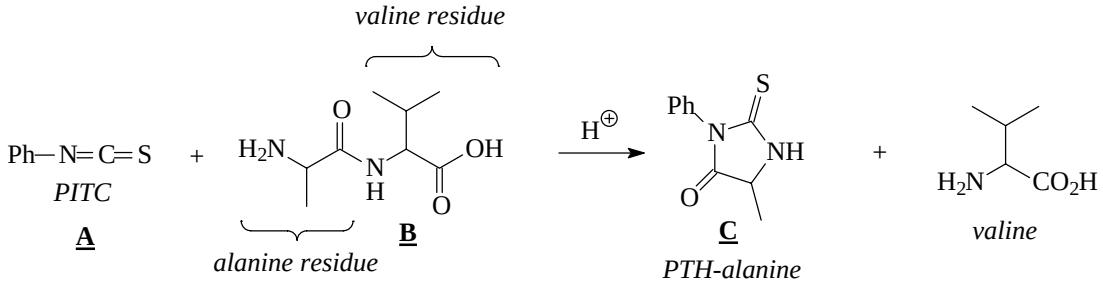
2.  $\xrightarrow[2.\ H^{\oplus}]{1.\ (XS)\ RMgX}$ *t*-BuOH + ??

3. Lactic acid (α-hydroxypropanoic acid) forms a cyclic compound, $C_6H_8O_4$. Formulate a structure for this compound. Why does lactic acid not form a simple α-lactone?

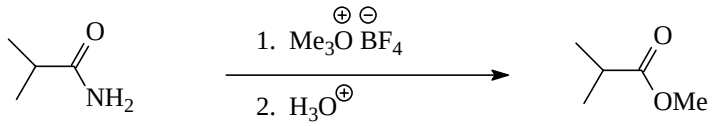
4.  $\xrightarrow{TsOH}$ an alkene + ?? (show location of the labeled oxygen)

5. ethyl 5-oxohexanoate $\xrightarrow{PhMgCl\ (1\ equiv)}$ 

6. Phenylisothiocyanate (**A**, *PITC*, *Edman reagent*) can be used to sequence proteins, *i.e.*, to determine the order of amino acids (primary structure). For example, treatment of dipeptide **B** with **A** in the presence of acid yields **C** (a phenylthiohydantoin, or PTH, derivative of the amino acid). Characterization of **C** identifies the first (from the N-terminal end) amino acid, in this case alanine.



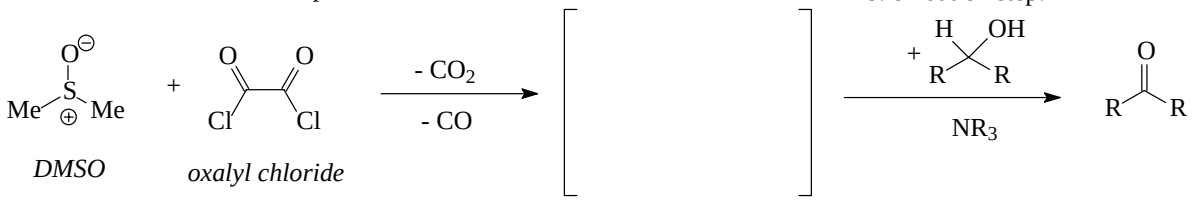
7.



8. The *Swern oxidation*:

a. "activation" of DMSO step:

b. oxidation step:



a chlorosulfonium salt

9. Similar to the Swern is the *Corey-Kim oxidation*:

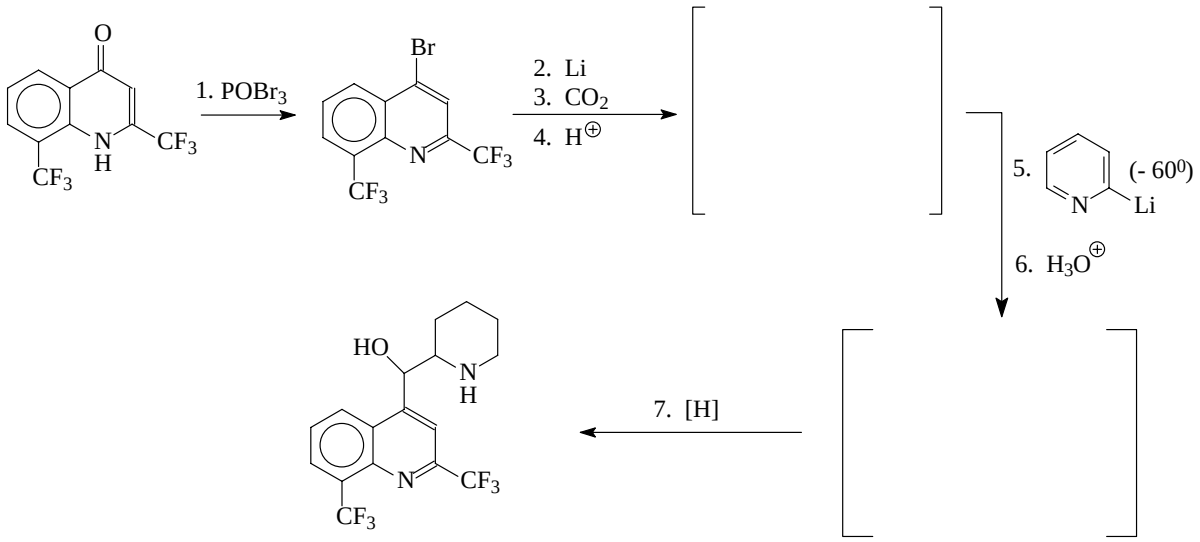
N-chlorosuccinimide

a chlorosulfonium salt

10. The biosynthesis of pyrimidine bases, *e.g.*, *uracil*, begins with the formation of dihydoorotic acid. Formulate a mechanism.

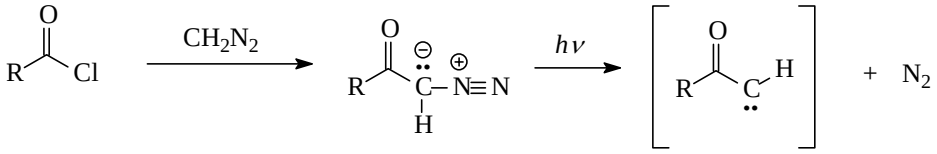
carbamoyl phosphate *aspantic acid* *dihydroorotic acid* *uracil*

11. The antimalarial *mefloquine* can be synthesized from substituted 4-quinolones by the following sequence of reactions. Outline a mechanism for step 1 and draw the structures in brackets.



mefloquine

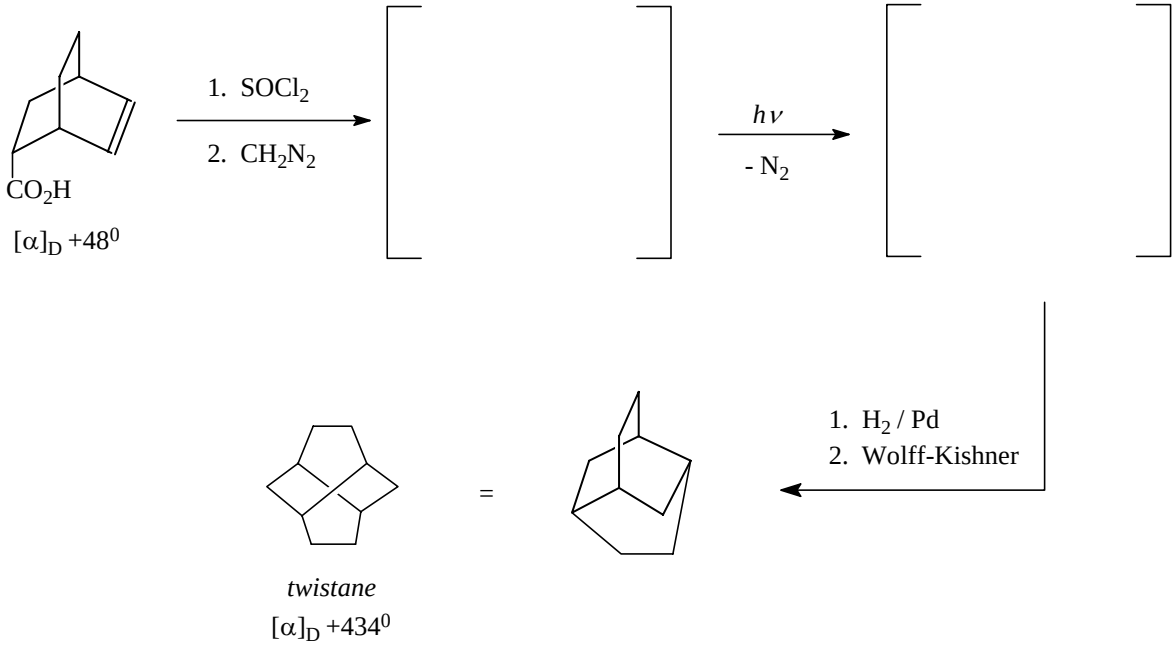
12. Acid halides react with diazomethane to give diazomethyl ketones, which, like diazomethane, decompose to give carbenes.



a diazomethyl ketone

a. Formulate a mechanism.

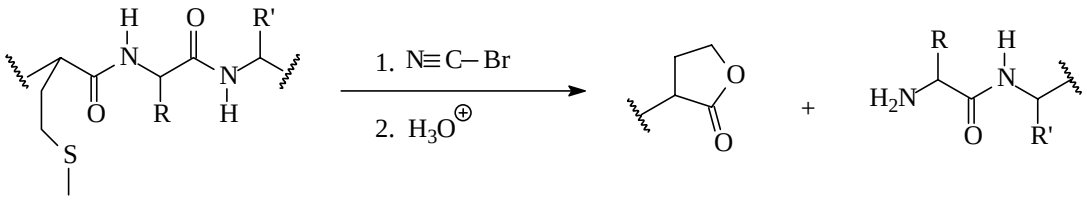
b. This reaction was used in the synthesis of *twistane*. Draw the structures in brackets.



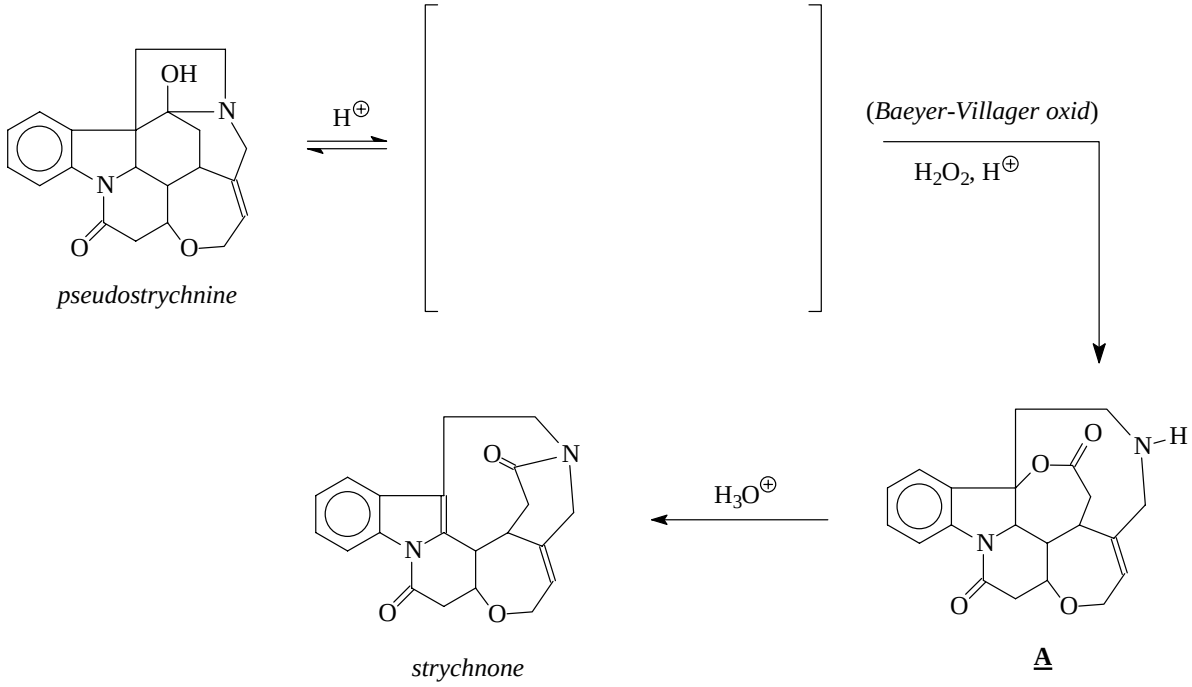
twistane

$[\alpha]_D$ +434⁰

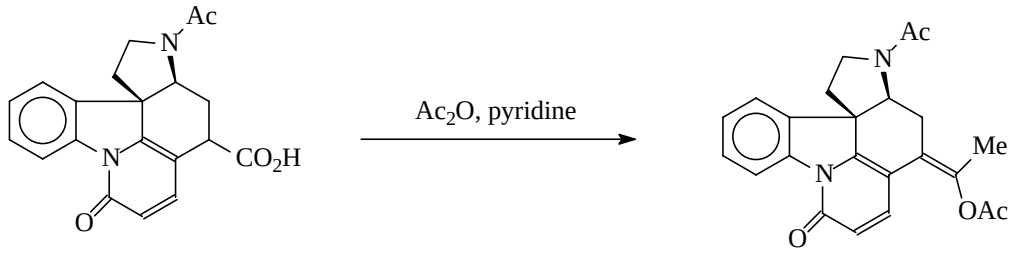
13. Cyanogen bromide (CNBr) specifically cleaves certain peptide (amide) bonds to yield a lactone:



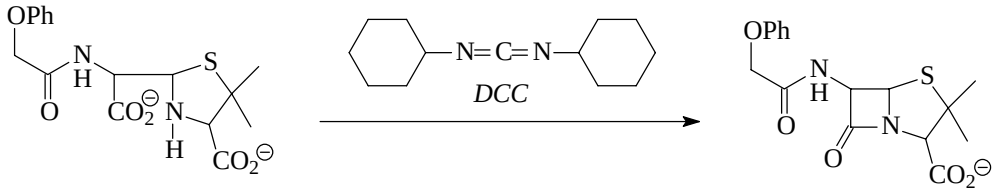
14. Draw the structure in brackets and give a mechanism for the conversion of **A** to strychnone.



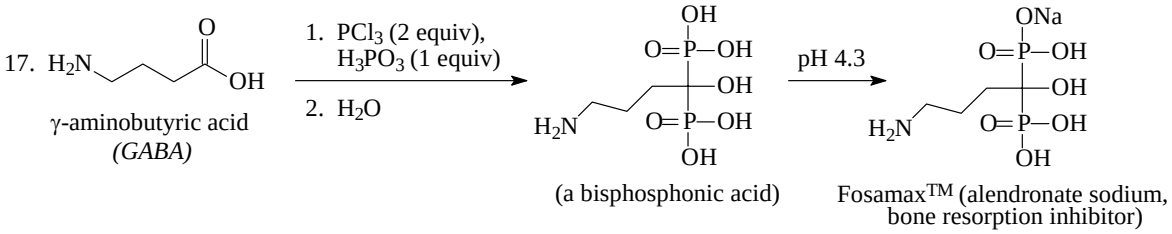
15. A step in Woodward's (*Harvard*) classic total synthesis of strychnine:



16. The final step in Sheehan's (*MIT*) total synthesis of *penicillin V* involved the formation of a strained β-lactam. To accomplish this he employed a new reagent, *dicyclohexylcarbodiimide* (DCC), first reported from his lab two years earlier to smoothly form amides from an aqueous mixture of a carboxylic acid and an amine at room temperature. [That important advance in the state of the art for forming amide bonds was subsequently utilized by Merrifield (*Rockefeller*) in his solid-phase approach to synthesizing proteins by linking amino acids together through amide (peptide) bonds.] Propose a mechanism for the lactamization reaction.



salt of penicillin V

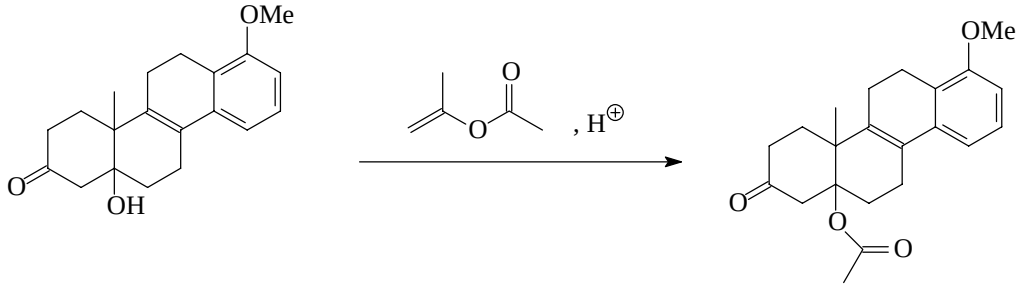


(a bisphosphonic acid)

Fosamax™ (alendronate sodium, bone resorption inhibitor)

Hint: phosphorous acid exists in two tautomeric forms; use the nucleophilic form to attack the product of the reaction of GABA with PCl_3. This one is rather challenging.

18. Tertiary alcohols are weakly nucleophilic because of steric hindrance near the hydroxyl group and, therefore, do not readily undergo Fischer esterification. One approach to form acetate esters of such alcohols is to allow them to react with isopropenyl acetate in the presence of an acid catalyst. Hint: the actual acetylation step involves an S_N1-like reaction of the alcohol with an acylium ion.



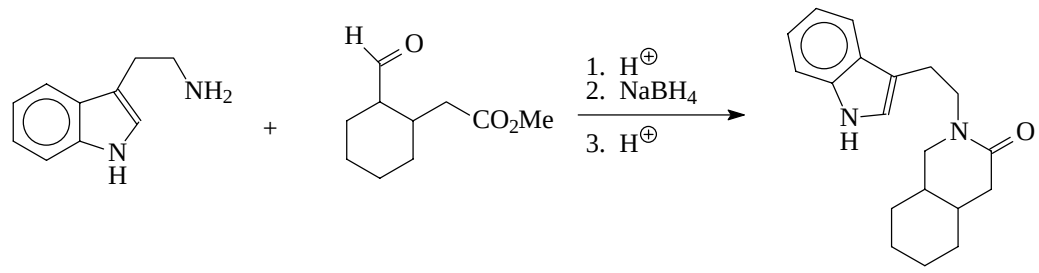
19. In contrast to phenyl acetate, the conjugate base of aspirin (acetylsalicylic acid) readily undergoes hydrolysis in water, suggesting kinetic enhancement by the latter's carboxylate moiety. Consider two possible pathways and outline a mechanism for each.

a. The carboxylate anion acts as a *nucleophile*, attacking the acetate ester to form a mixed anhydride, which is subsequently hydrolyzed by water:

b. The carboxylate anion acts as a *base*, removing a proton from water to form hydroxide, which subsequently attacks the ester:

c. Experimental evidence indicates that when the reaction is conducted in the presence of ^{18}O-labeled water, no label is found in the salicylic acid product. Which pathway is supported by this experiment?

20.



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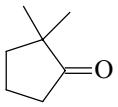
CHAPTER 18

CARBONYL α-SUBSTITUTION REACTION AND ENOLATES

18.1 Reactions

Draw the structural formula of the major organic product(s). Show stereochemistry where appropriate.

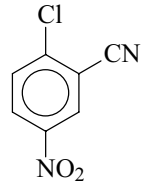
1. 

1. LDA
2. *n*-PrBr

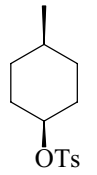
2. methyl 3-oxopentanoate
1. $^{\ominus}$OMe, MeOH
2. benzoyl bromide
3. $H_3O^{\oplus}$, Δ

3. cyclohexanone
1. $EtOCO_2Et$, LDA
2. $^{\ominus}$OEt
3. EtI
4. $H_3O^{\oplus}$, Δ

4. diethyl malonate
1. base
2. benzoic anhydride
3. $H_3O^{\oplus}$, Δ

5. 

+ $NC\text{-}CH_2\text{-}CO_2Et$
1. $^{\ominus}$OEt
2. $H_3O^{\oplus}$, Δ

6. 

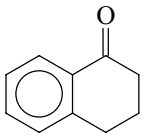
+ $NaCH(CO_2R)_2$

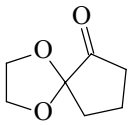
7. (E)-3-pentene-2-one
1. $H_3O^{\oplus}$
2. CrO_3, $H^{\oplus}$
3. NaH (2 equiv)
4. benzyl chloride (1 equiv)
5. $H^{\oplus}$

8. diethyl malonate
   1. $^{\ominus}$OEt
   2. isobutylene epoxide
   3. $H_3O^{\oplus}$, Δ

9. ethyl acetoacetate
   1. (XS) NaOEt
   2. $Br(CH_2)_4Br$
   3. $H_3O^{\oplus}$, Δ

($C_7H_{12}O$)

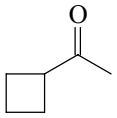
10. 
    1. LDA
    2. PhSeBr
    3. H_2O_2
    4. MeOH, $H^{\oplus}$

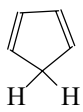
11. 
    1. Br_2, $H^{\oplus}$
    2. KO-*t*-Bu / *t*-BuOH
    3. $LiMe_2Cu$
    4. $H_3O^{\oplus}$

12. *t*-butyl methyl ketone
    1. Br_2, $H^{\oplus}$
    2. $(CN)_2CH:^{\ominus}$
    3. $H_3O^{\oplus}$, Δ

13. diethyl malonate
    1. $^{\ominus}$OEt, HOEt
    2. butanoyl chloride
    3. $H_3O^{\oplus}$, Δ

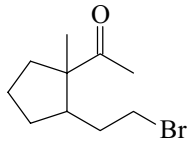
    $2\ CO_2$ +

14. 
    1. a. Br_2, $^{\ominus}$OH b. $H^{\oplus}$
    2. PCl_3, Br_2
    3. MeOH

15. 
    H H (pK_a 15)
    +
    
    NaOEt / HOEt

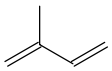
(C_8H_{10})

16.

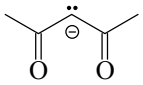


1. LDA
2. Cl_2, $H^{\oplus}$

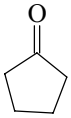
17.



isoprene

1. HCl (1,4-addition)
2. 
3. $H_3O^{\oplus}$, Δ

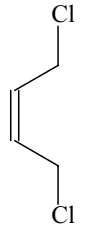
18.



1. Cl_2, $H^{\oplus}$
2. $^{\ominus}OH$ (S_N2)
3. $KMnO_4$

1. Cl_2, $H^{\oplus}$
2. KO-*t*-Bu
3. $H_3O^{\oplus}$
4. $KMnO_4$

19.



$CH_2(CO_2Me)_2$

LiH (XS)

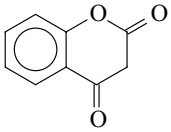
95%

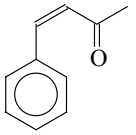
1. KOH, EtOH
2. Δ

91%

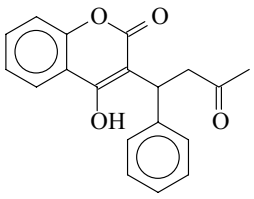
1. $SOCl_2$
2. Me_2NH
3. *m*-chloroperbenzoic acid

20.



1. base
2. 

tautomerize



coumadin (Warfarin™ - an anticoagulant)

18.2 Syntheses

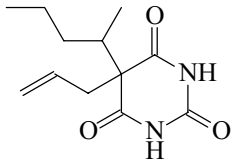
Supply a reagent or sequence of reagents that will effect the following conversions.

1. butyric acid ⟶ ethylpropanedioic acid

2. dimethyl malonate ⟶ δ-valerolactone
(valeric acid is a common name for pentanoic acid)

3. dimethyl malonate ⟶ butanedial

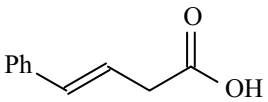
4. dimethyl malonate ⟶



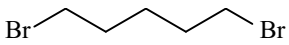
seconal (a sedative)

5. dimethyl malonate ⟶ 2-benzylbutanoic acid

6. dimethyl malonate + styrene ⟶

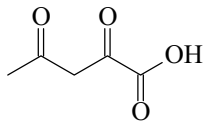


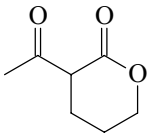
7. dimethyl malonate + methyl acrylate ⟶

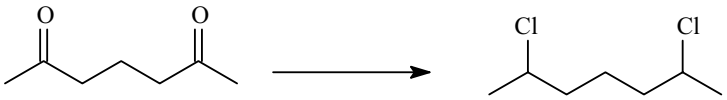


(acrylic acid is propenoic acid)

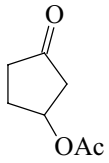
8. ethyl acetoacetate ⟶ s-Bu-$CONH_2$

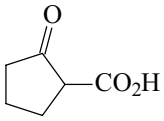
9. ethyl acetoacetate 

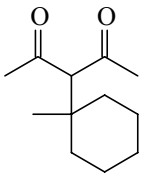
10. ethyl acetoacetate 

11. ethyl acetoacetate 

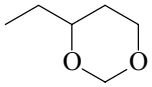
12. ethyl acetoacetate ⟶ s-butyl methyl ketone ⟶ 2-methylbutanoate

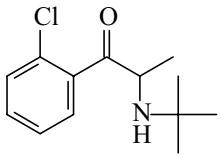
13. cyclopentanone 

14. cyclopentanol 

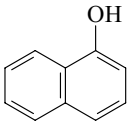
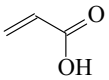
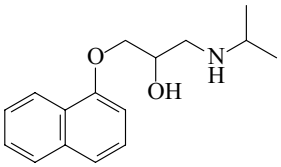
15. 2,4-pentanedione 

16. methyl acetoacetate ⟶ 2,4-pentanedione

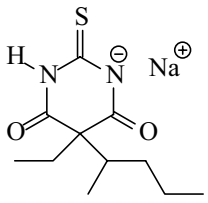
17. 3-pentanone —*via an organoselenium cmpd*→ ethyl vinyl ketone ⟶ 

18. chlorobenzene ⟶ 

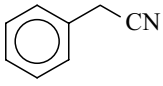
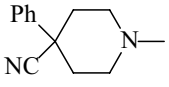
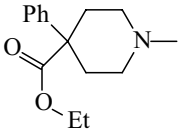
Wellbutrin™ (an antidepressant)

19.  ,  ⟶ 

propranolol (a β-adrenergic blocker, developed by Sir James Black, recipient of '88 Nobel Prize in medicine; greatest breakthrough in pharmaceuticals for heart illness since discovery of *digitalis* approximately 200 years ago)

20. dimethyl malonate ⟶ 

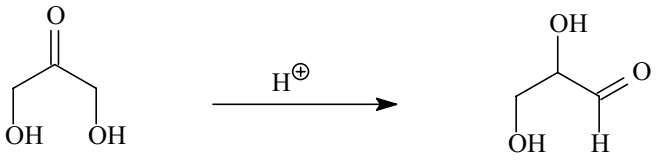
sodium pentothal
(used to induce pre-surgical anesthesia in combination with sedatives)

21.  ⟶  ⟶ 

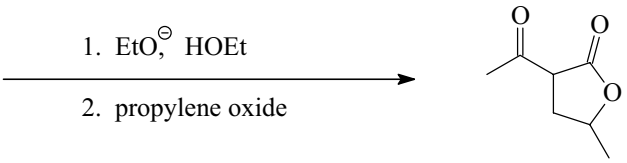
meperidine (an analgesic)

18.3 Mechanisms

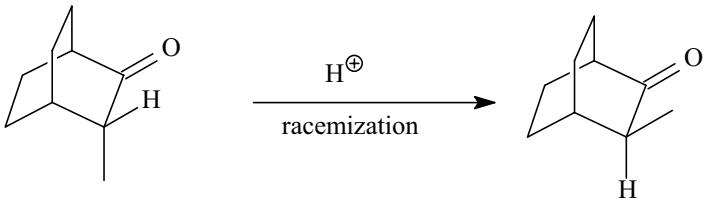
Outline a detailed mechanism for each of the following. No other reagents than those given are necessary. Use arrows to explain the flow of electrons and show all intermediates.

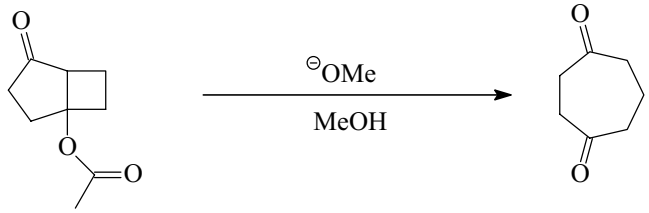
1. 

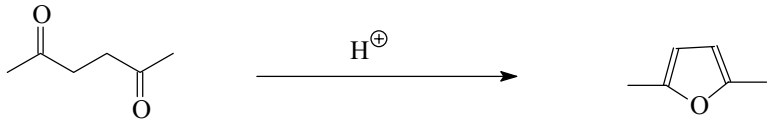
(a central reaction in glycolysis catalyzed by the enzyme *TIM*, triose isomerase)

2. ethyl acetoacetate 

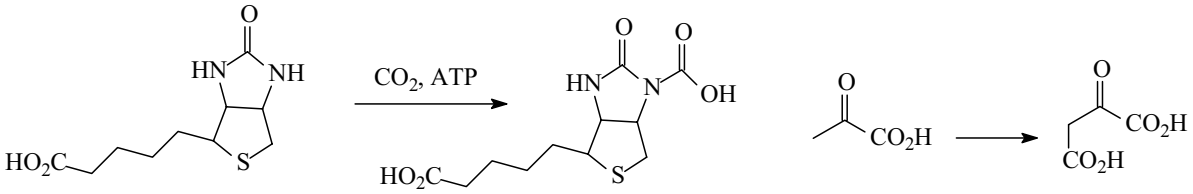
3. 1,3-Diphenyl-1,3-propanedione gives a positive iodoform test even though it is not a methyl ketone. In addition to CHI_3, two equivalents of benzoate are formed. Explain.

4. 

5. 

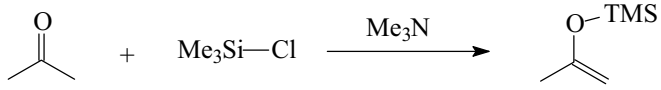
6. 

7. The vitamin *biotin* is necessary for many metabolic carboxylation reactions. It reacts initially with CO_2 to form unstable **A**, which then "donates" CO_2 to a substrate. Outline the mechanism for carboxylation of pyruvic acid to oxaloacetic acid (OAA).



biotin **A** *pyruvic acid* *OAA*

8. 

9. 

CHAPTER 19

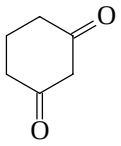
CARBONYL CONDENSATION REACTIONS

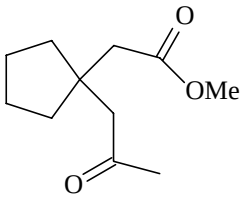
19.1 Reactions

Draw the structural formula of the <u>major</u> organic product(s). Show <u>stereochemistry</u> where appropriate.

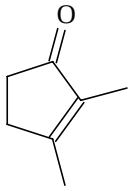
1. benzaldehyde + acetophenone $\xrightarrow[3.\ H_3O^{\oplus}]{1.\ {}^{\ominus}OH,\ (-H_2O)\ \ 2.\ NaCH(CO_2R)_2}$

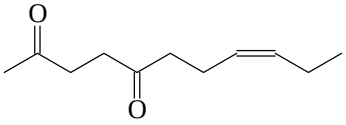
2. isobutryaldehyde $\xrightarrow{H^{\oplus}}$

3.  +  $\xrightarrow{{}^{\ominus}OEt,\ EtOH}$

4.  $\xrightarrow{{}^{\ominus}OMe,\ MeOH}$

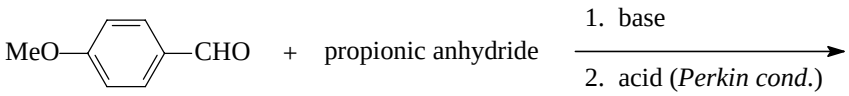
5. dimethyl heptanedioate $\xrightarrow[2.\ H_3O,^{\oplus}\ \Delta]{1.{}^{\ominus}OMe}$ CO_2 +

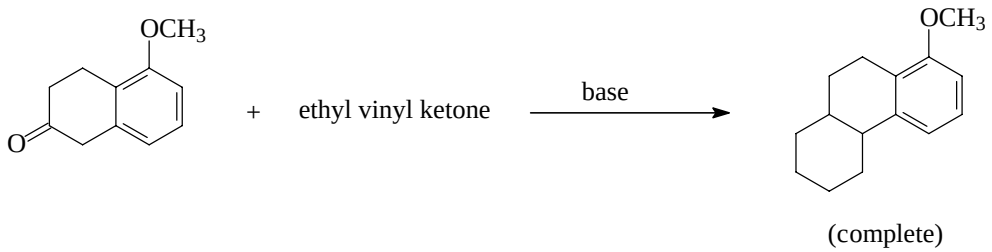
6.  $\xrightarrow[(conj.\ add'n\ +\ retro\text{-}aldol)]{{}^{\ominus}OH,\ ROH}$

7.  $\xrightarrow{{}^{\ominus}OH}$

cis-jasmone (a perfume)

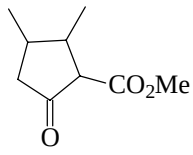
8. propionaldehyde $\xrightarrow[2.\ H_3O,^{\oplus}\ \Delta\ (Darzen's\ cond.)]{1.\ BrCH_2CO_2Me,\ t\text{-}BuO^{\ominus}}$

9. 

10. 

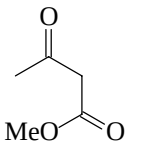
(complete)

11. benzaldehyde + CH_3NO_2 $\xrightarrow{\ominus OH}$

12. 

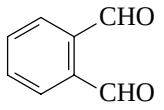
$\xrightarrow{\ominus OMe,\ MeOH\ (\textit{retro-Claisen})}$

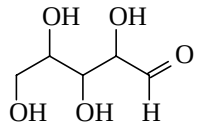
13. cyclopentanone $\xrightarrow[2.\ NH_2NHPh]{1.\ NaOEt\ /\ EtOH\ (-H_2O)}$

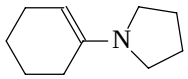
14. 

$\xrightarrow[2.\ \text{  }\ \ 3.\ H_3O^{\oplus}]{1.\ {}^{\ominus}OMe,\ MeOH}$ CO_2 + C_5H_6O

15. acetone $\xrightarrow[(aldol)]{\ominus OH}$ $C_6H_{10}O$ $\xrightarrow[2.\ H_3O^{\oplus},\ \Delta]{1.\ CH_2(CO_2Me)_2,\ {}^{\ominus}OMe}$ $C_8H_{12}O_2$

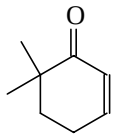
16.  + 3-pentanone $\xrightarrow{^{\ominus}OH\ (-H_2O)}$

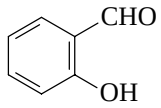
17.  $\xrightarrow{\textit{retro-aldol}}$

18.  $\xrightarrow[2.\ H_3O^{\oplus}\quad 3.\ NaOH\ (\textit{aldol})]{1.\ \text{methyl vinyl ketone}}$

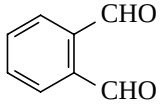
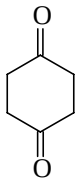
19. acetaldehyde + (XS) formaldehyde $\xrightarrow{^{\ominus}OH}$

$C(CH_2OH)_4$ -- *pentaerythritol*

20.  $\xrightarrow{PhCHO,\ H^{\oplus}}$

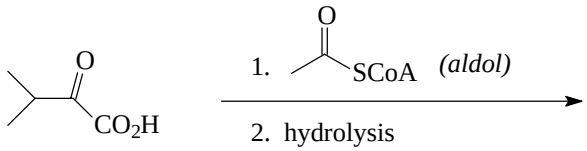
21.  + $CH_2(CO_2Et)_2$ $\xrightarrow[2.\ H^{\oplus}]{1.\ \text{base}}$

$C_{12}H_{10}O_4$

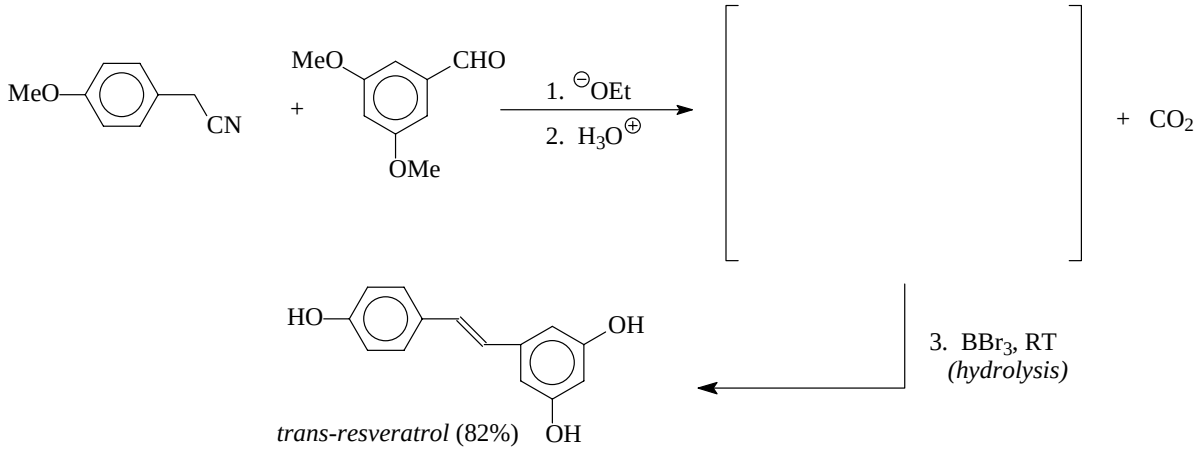
22.  +  $\xrightarrow{KOH}$

(a pentacyclic dione)

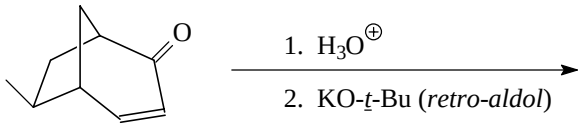
23. A reaction in the biosynthesis of the amino acid *leucine*:



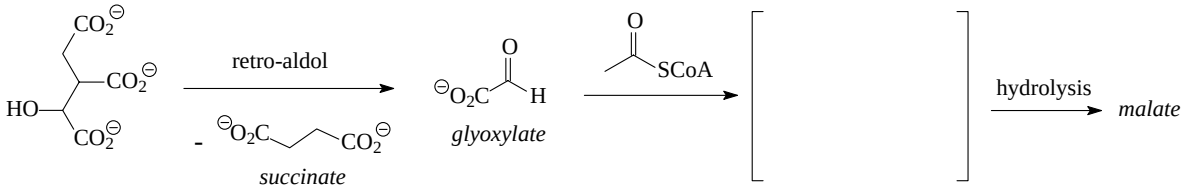
24. *Trans-resveratrol*, isolable from red wine, has been implicated as a cardioprotective and can be synthesized as follows:

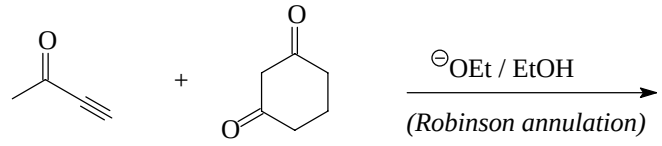


25.

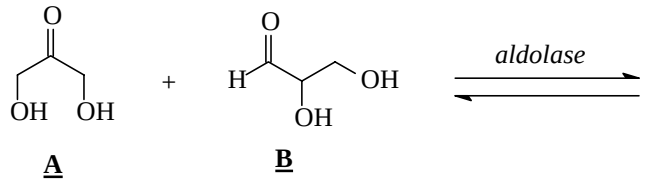


26. Forward and retro-aldol-like reactions that occur in plants:



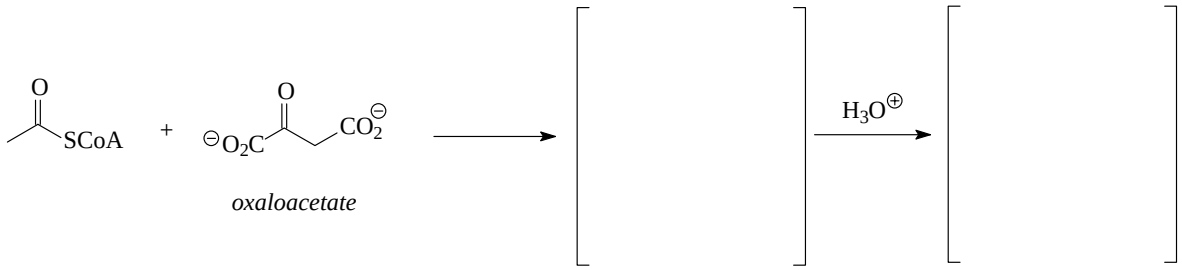
27. 

28. The biosynthesis of glucose involves *aldolase*, an enzyme that catalyzes both forward and retro-aldol reactions. The forward process illustrates a mixed aldol wherein the enzyme initially binds with **A**, promoting its tautomerization and subsequent reaction with **B** to form a ketohexose:



A **B**

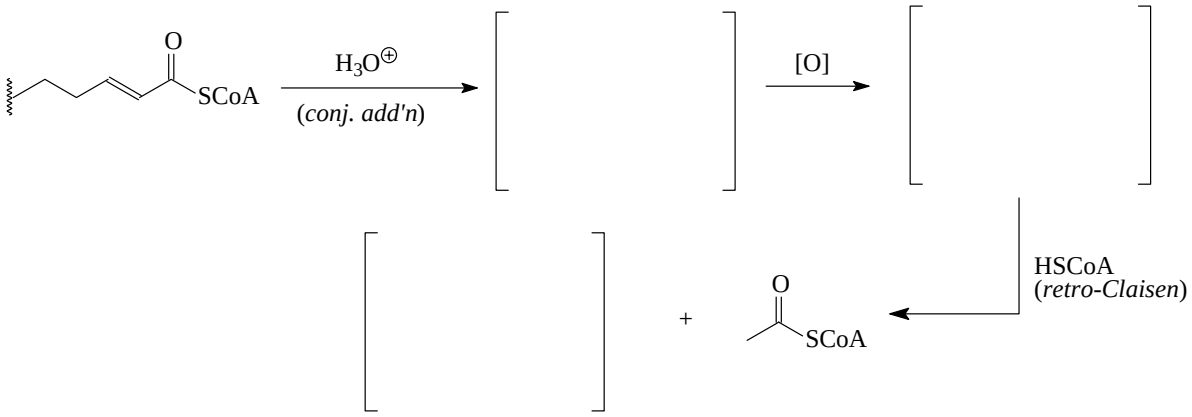
29. The *Krebs Cycle* begins with an aldol-like condensation of a thioester (acetyl coenzyme A) with oxaloacetate, followed by hydrolysis:



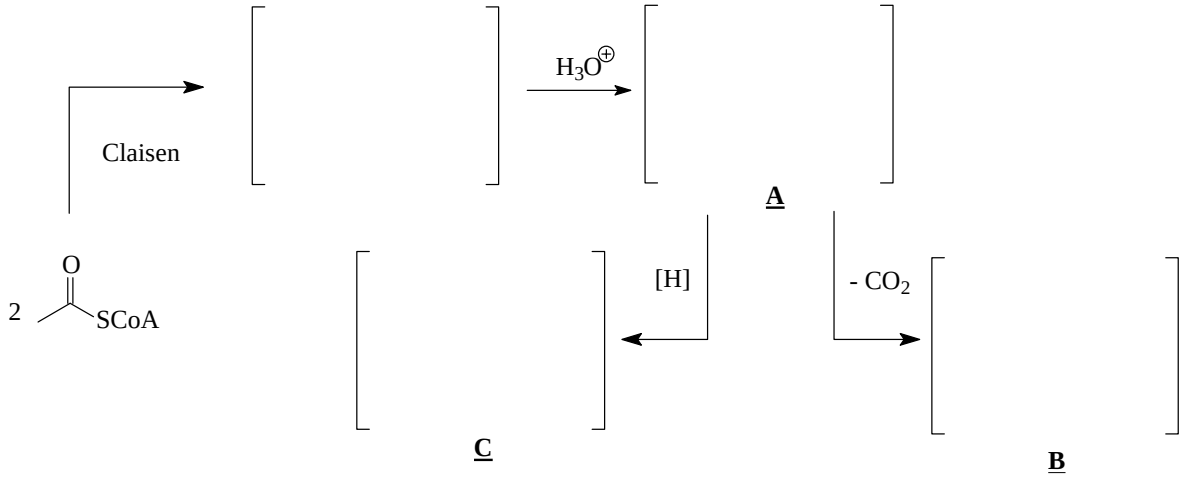
oxaloacetate

citric acid

30. The following sequence illustrates how fatty acids are catabolized to acetyl coenzyme A, a process known as β-oxidation. Fill in the brackets.



31. Excessive accumulation of acetyl CoA can lead to metabolic *ketosis* by the following pathway:



[**A**, **B**, and **C** (unfortunately!) are referred to as "*ketone bodies*;" accumulation of acids **A** and **C** lowers blood pH (*acidosis*).]

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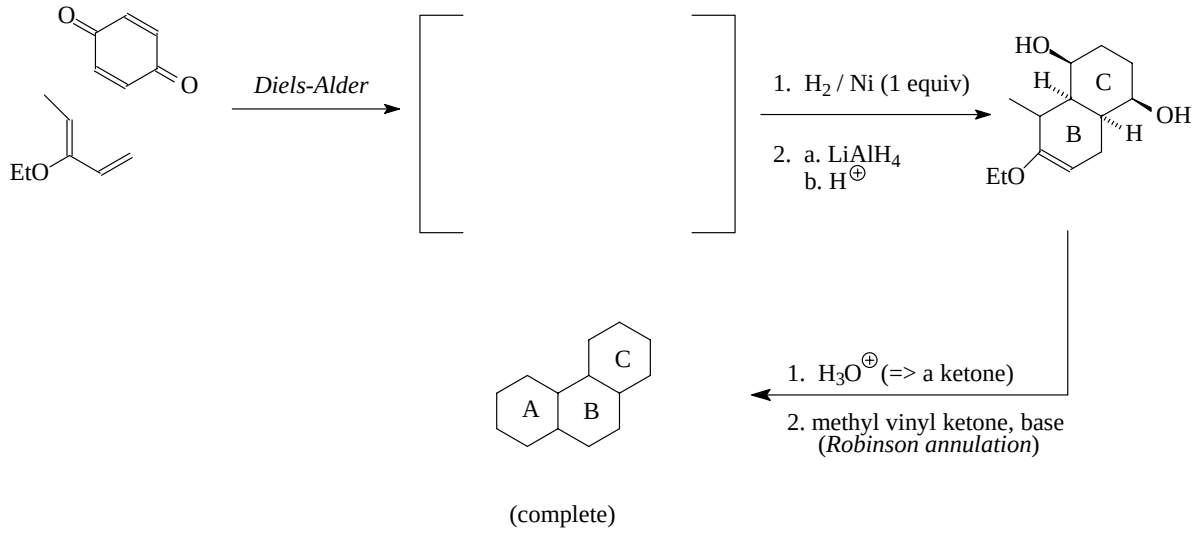
32. A *cortisone story…*

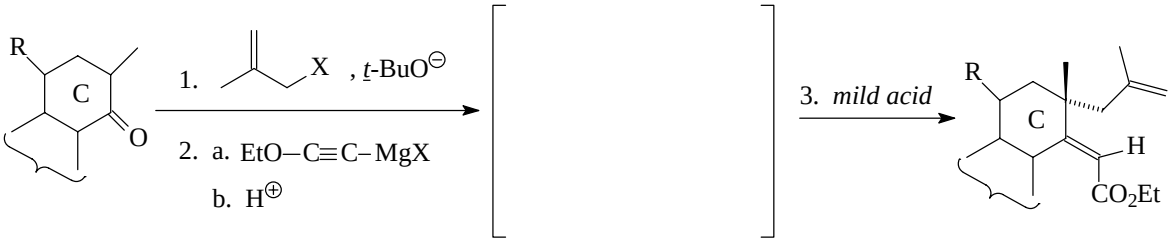
Cortisone is one of 43 steroids found in adrenal cortical glands. It was first isolated by Kendall (*Mayo Clinic*) in 1934 (extraction of ~ 1,000 lbs of beef adrenal glands yielded only 85 – 200 mg of cortisone). One of the earliest total syntheses of cortisone was published by Sarett (*Merck*) in 1952. The following reactions illustrate his strategy.

a. The initial sequence of reactions formed the A-B-C rings. Draw the missing structures.

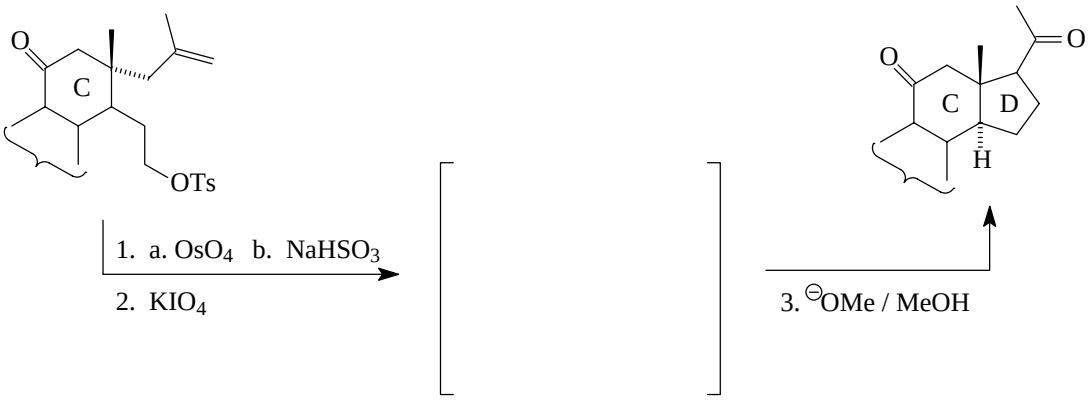


(complete)

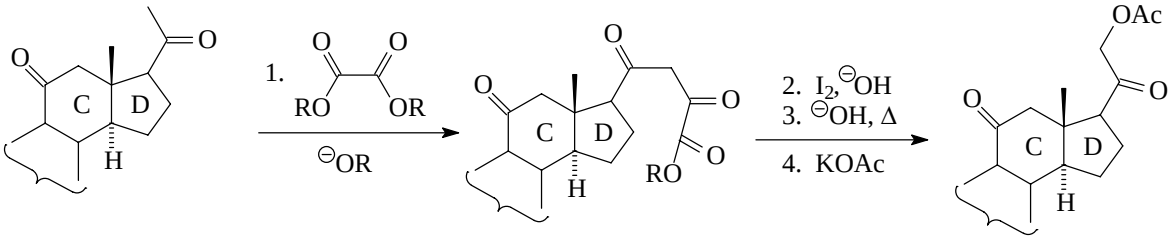
b. Construction of the D ring began as follows. Fill in the bracketed structure and outline the mechanism for step 3.



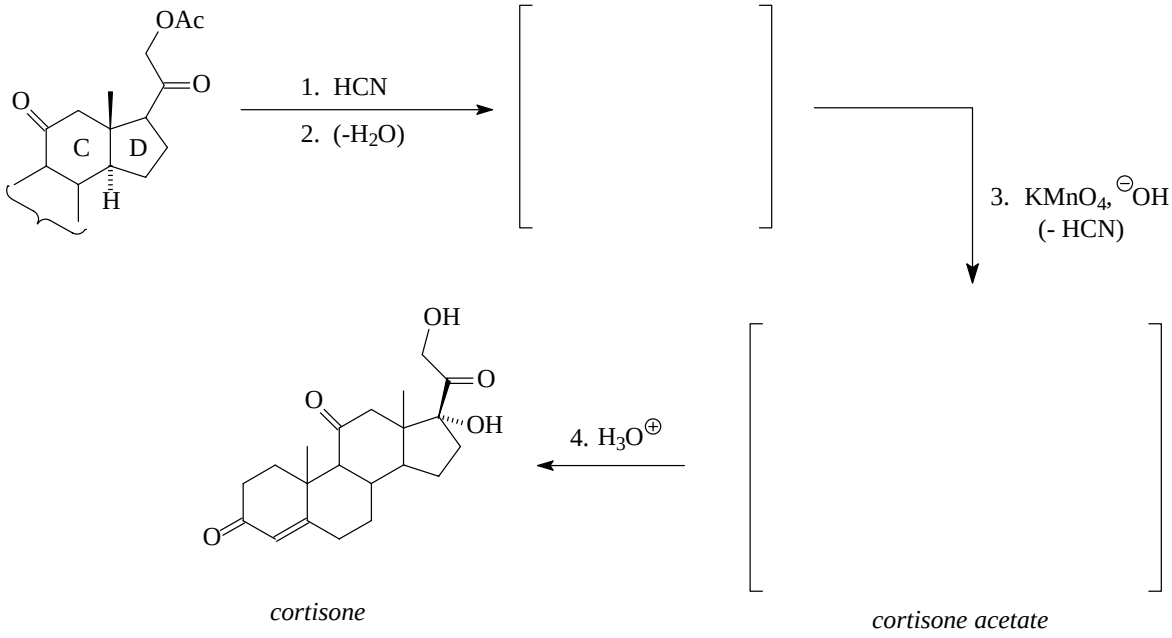
c. Subsequent selective reduction followed by tosylation produced the indicated structure, which was then treated with the sequence of reagents shown. Draw the product of step 2 and give the mechanism for step 3.



d. The above product was then subjected to the following steps. Draw structures for the critical intermediates in steps 2 -4.

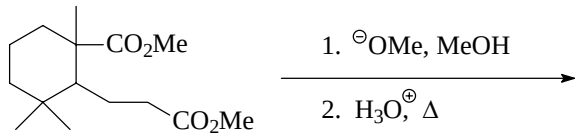


e. The final four steps yielded *cortisone*. Deduce the structure of cortisone acetate.



cortisone *cortisone acetate*

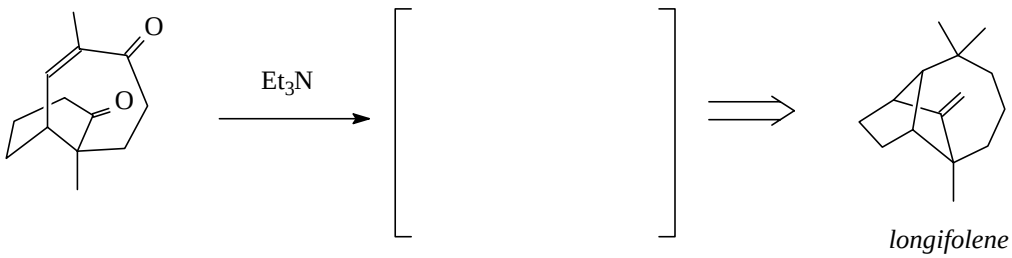
33.



34.

indigo blue (probably oldest known coloring agent - used to dye bluejeans)

35. A step involving an intra-Michael reaction in Corey's (*Harvard*) synthesis of *longifolene*, a component of Indian turpentine oil:

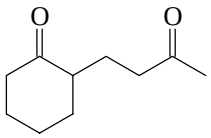


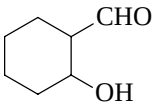
longifolene

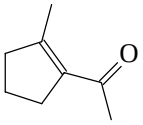
19.2 Syntheses

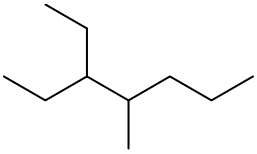
Supply a reagent or sequence of reagents that will effect the following conversions.

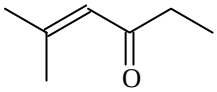
1. ? + ? —*via an aldol*→ 1,3-diphenyl-1-propanol

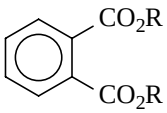
2. cyclohexanone —*via an enamine*→ 

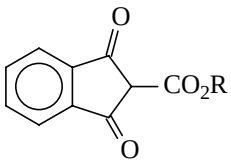
3. ? —*via an aldol*→ 

4. ? —*via an aldol*→ 

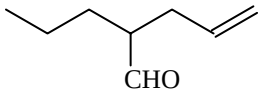
5. diethyl ketone → 

6. acetone → 

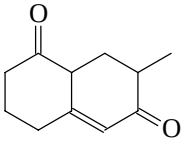
7. 

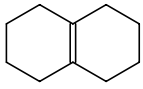
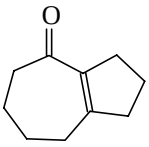
→ 

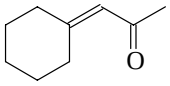
8. cyclohexanone ⟶ 4-benzyl-1,3-cyclohexadione

9. 1-pentene ⟶ 

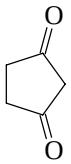
10. phenylacetaldehyde ⟶ $PhCH(CH_2OH)_2$

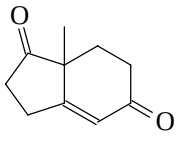
11. ? + ? —*via a Robinson annulation*→ 

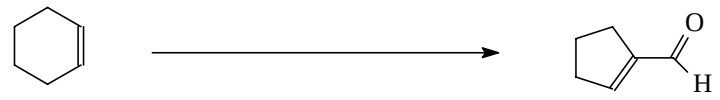
12.  ⟶ 

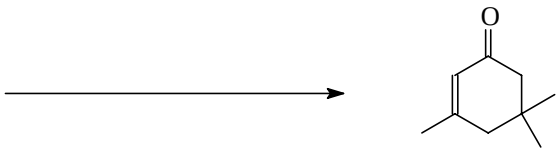
13. cyclohexanone, acetone —*via a Wittig**→ 

*Why not *via* an aldol?

14. 

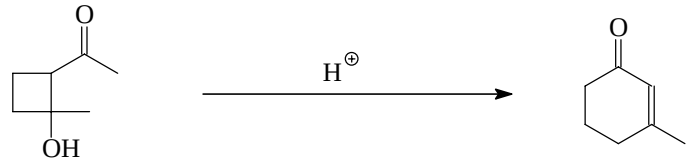
—*via a Robinson annulation*→ 

15. 

16. acetone 

19.3 Mechanisms

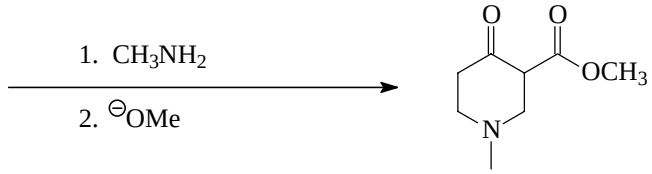
Outline a detailed mechanism for each of the following. No other reagents than those given are necessary. Use arrows to explain the flow of electrons and show all intermediates.

1. 

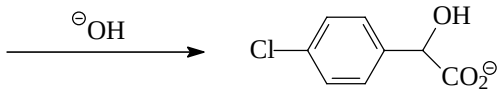
2. 

3. 

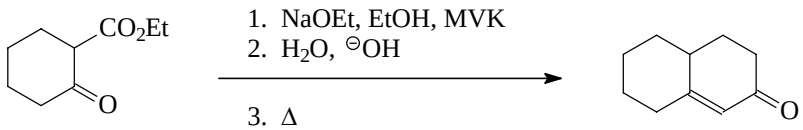
4. 2 methyl acrylate



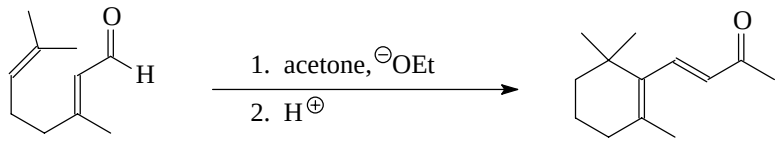
5. *p*-chlorobenzaldehyde + $CHBr_3$



6.



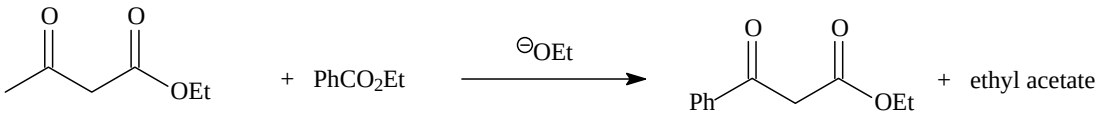
7.

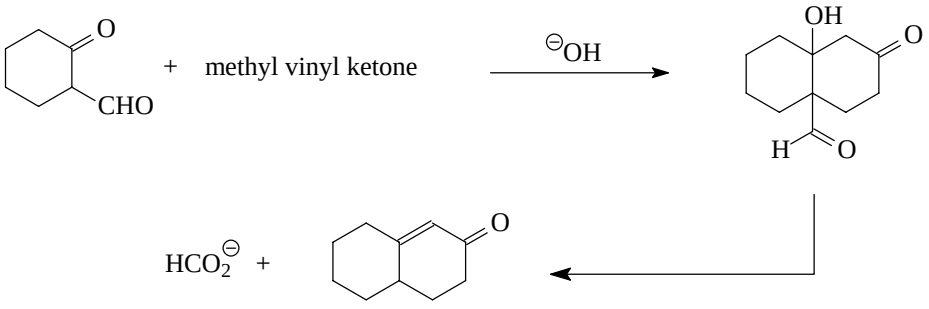


geranial

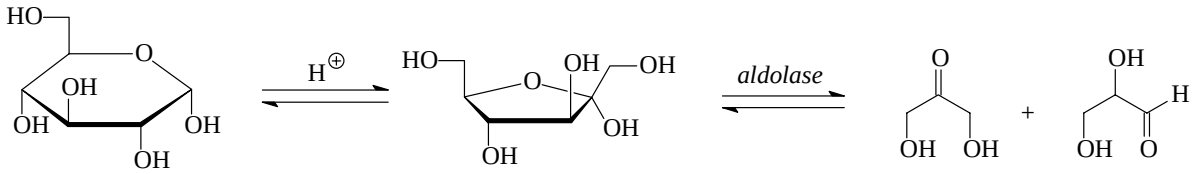
(*a step in the commercial synthesis of vitamin A*)

8.

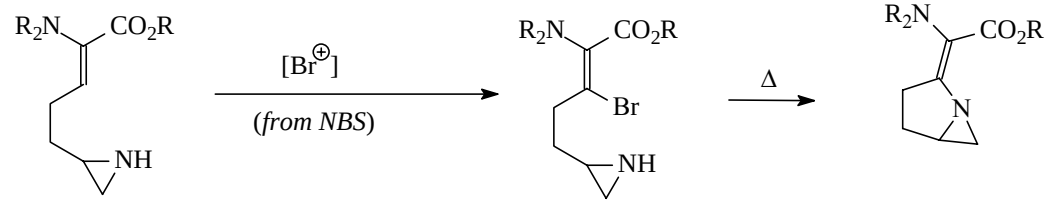


9. 

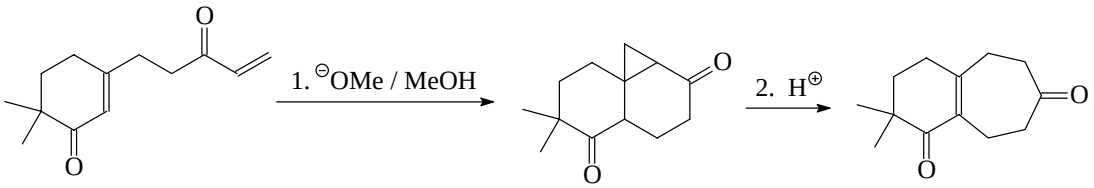
10. The anaerobic breakdown of glucose (glycolysis) involves the following isomerization and retro-aldol:

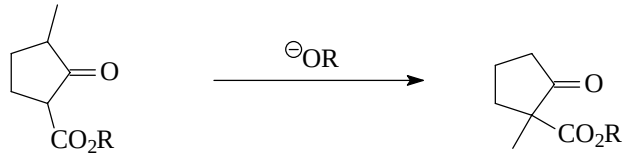


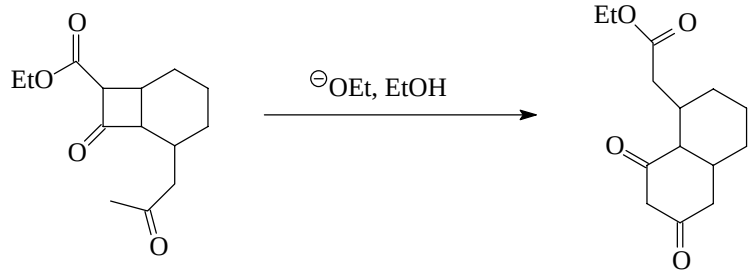
α-D-glucose *α-D-fructose*

11. 

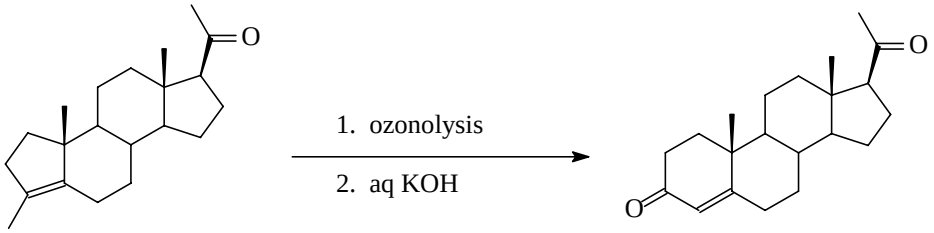
12. The following illustrates the *Stobbe reaction*. Hint: a key intermediate is a γ-lactone.

13. 

14. 

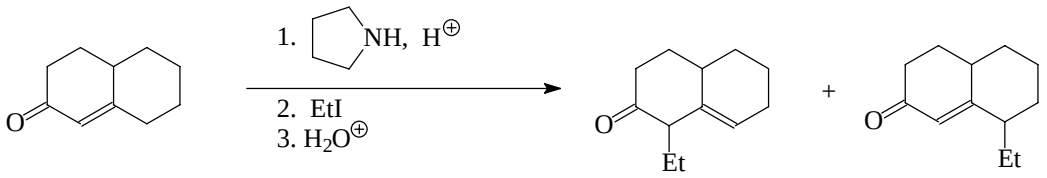
15. 

16. The final stage of Johnson's (*Stanford*) historic total synthesis of *progesterone* (give a mechanism for step 2):

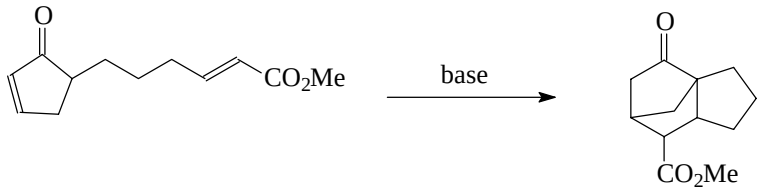


progesterone

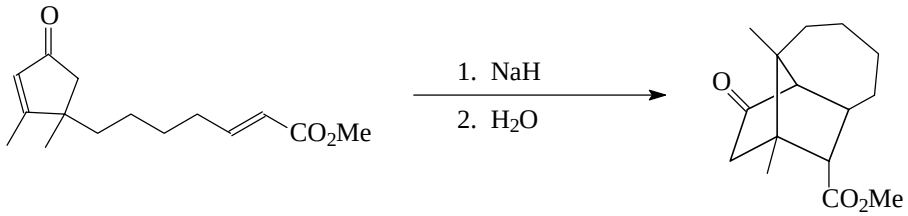
17.



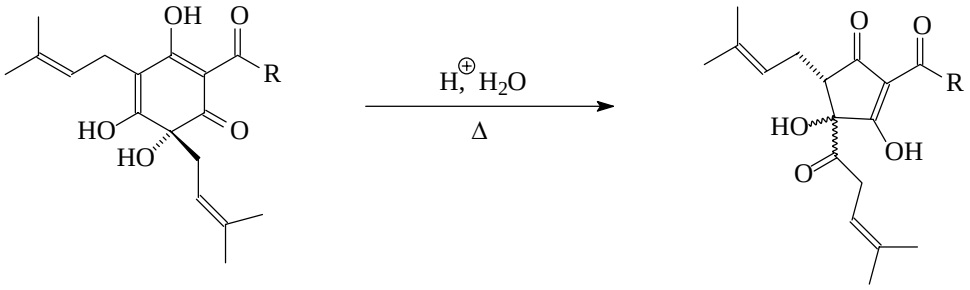
18.



19.



20. *Humulones* are found in hops. When boiled, the insoluble humulones isomerize to the soluble *isohumulones*, which give beer its distinctive bitterness. (Caution: difficult!)



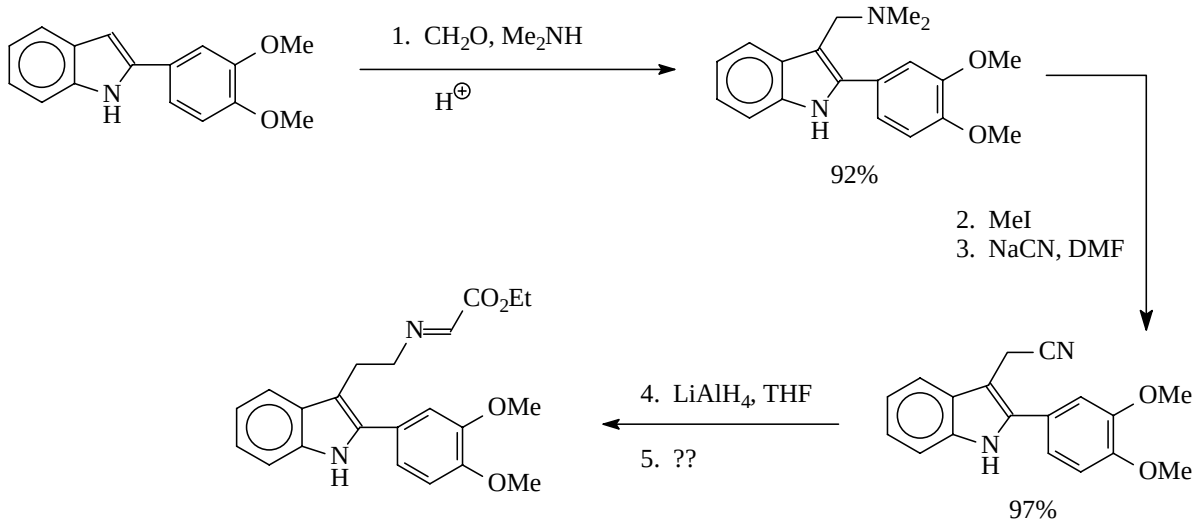
humulone: R = *i*-Bu

cohumulone: R = *i*-Pr

adhumulone: R = *s*-Bu

cis- and trans-isohumulones

21. Woodward's (*Harvard*) total synthesis of the alkaloid *strychnine* included the following steps:

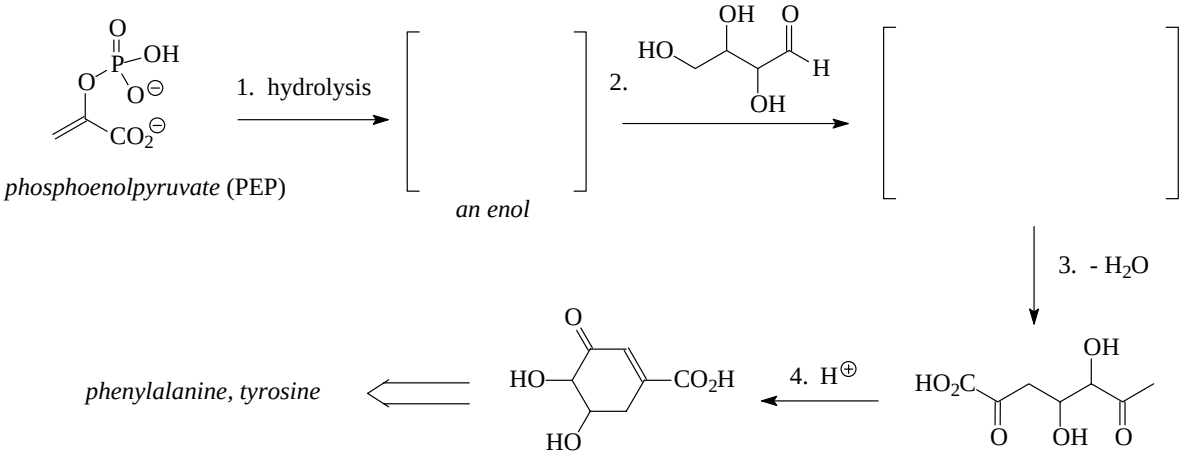


a. Step 1 is an example of the (name) _____ *reaction*.

b. Outline the mechanism for steps 2 and 3.

c. Supply the missing reagent in step 5.

22. Enzyme-catalyzed mixed aldol reactions are very common in metabolism. The beginning sequence in the *de novo* synthesis of aromatic amino acids, for example involves the following steps. Fill in the structures and write a mechanism for step 4.

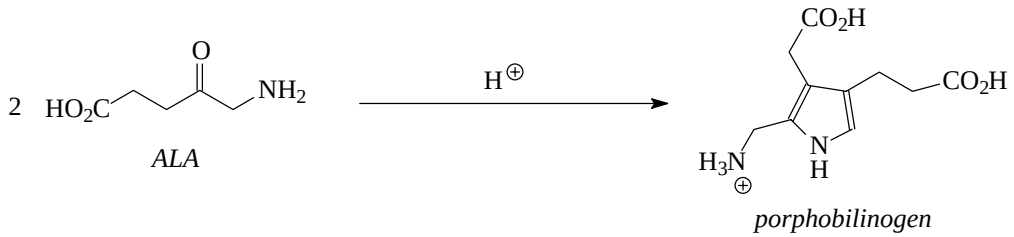


phosphoenolpyruvate (PEP)

an enol

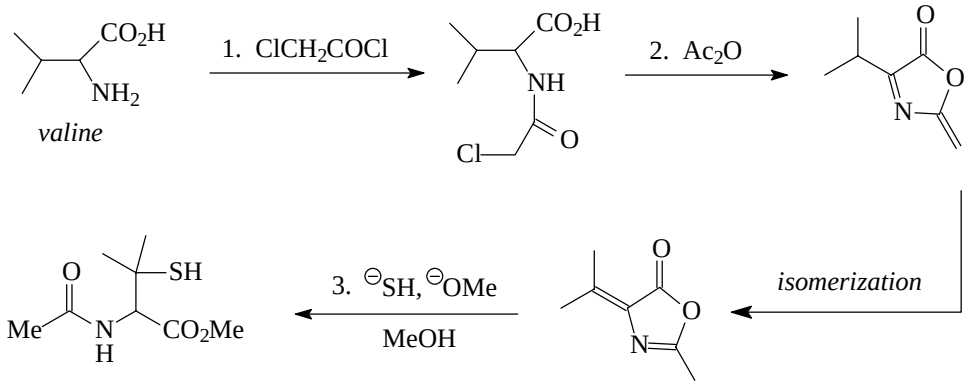
phenylalanine, tyrosine

23. The biosynthesis of porphyrin rings (*e.g.*, *heme*) begins with an annulation reaction that involves an aldol reaction and imine formation in the dimerization of δ-aminolevulinic acid (ALA) to form *porphobilinogen*.



ALA *porphobilinogen*

24. Several steps in Sheehan's (*MIT*) total synthesis of *penicillin V* are shown below.

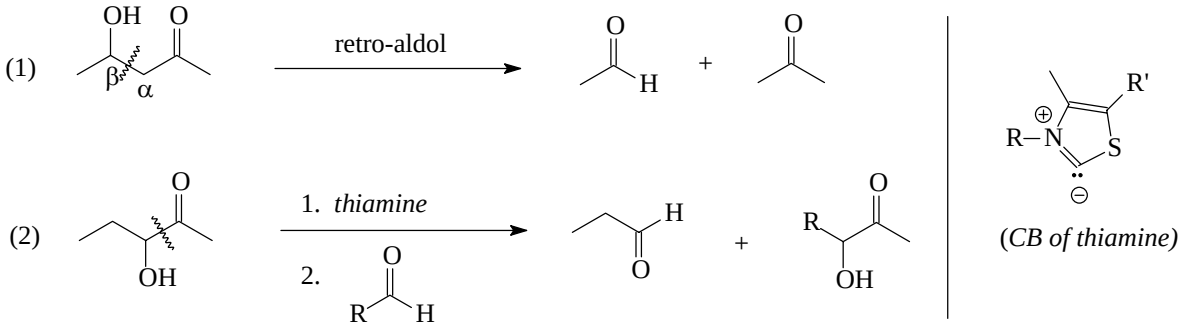


a. Propose a mechanism for step 2.

b. Propose a mechanism for step 3.

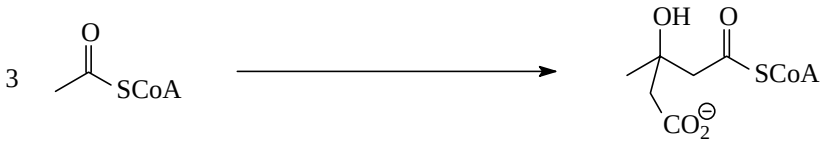
25. The biosynthesis of fatty acids begins with a Claisen-like reaction:

26. The $C_\alpha - C_\beta$ bond in β-hydroxyketones is easily cleaved via a retro-aldol reaction; the carbonyl – C_α bond is unreactive. In α-hydroxyketones, however, the $C_\alpha - C_\beta$ bond is unreactive; but, <u>in the presence of *thiamine*</u>, the carbonyl – C_α bond can be cleaved (2).



Recalling the mechanism for *thiamine*-assisted decarboxylation of α-ketocarboxylic acids (problem 16.3, 13), formulate a mechanism for reaction (2).

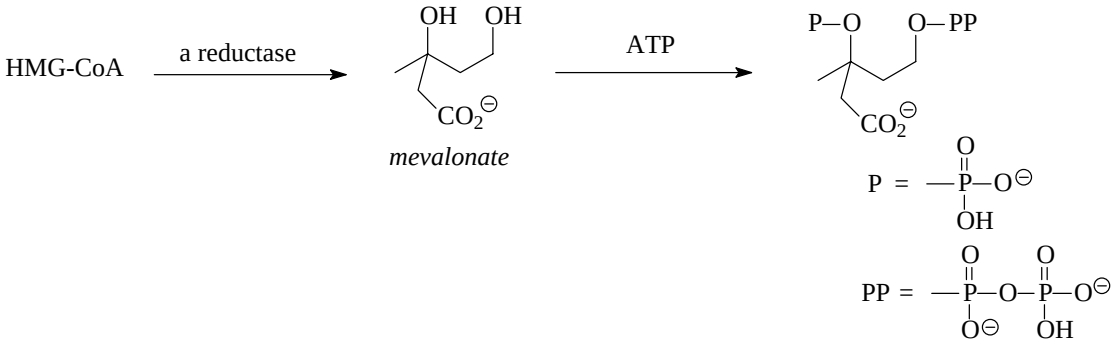
27. The biosynthesis of cholesterol begins with the formation of HMG-CoA (3-<u>h</u>ydroxy-3-<u>m</u>ethylglutaryl coenzyme A):



HMG-CoA

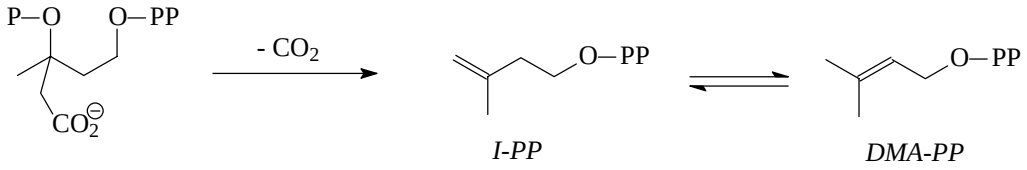
a. Formulate a mechanism.

b. HMG-CoA is subsequently reduced to *mevalonate* by an enzyme, HMG-CoA reductase. Because this reaction is the major control (rate-limiting) step, considerable research has been devoted toward developing a class of medicines that inhibits the action of this enzyme, notably the statins [*e.g.*, *atorvastatin* (Lipitor^{TM})].

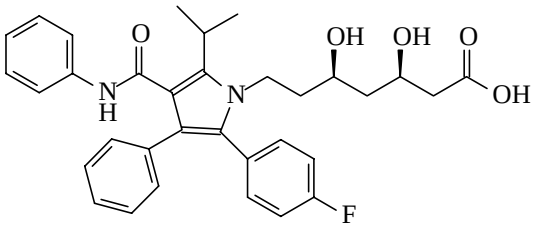


mevalonate

Mevalonate then undergoes phosphorylation and decarboxylation to form *I-PP* (isopentenyl pyrophosphate) and *DMA-PP* (dimethylallyl pyrophosphate) – recall problem 9.4, 19a. Outline the mechanisms for decarboxylation to form *I-PP* and isomerization of the latter to form *DMA-PP*.



I-PP *DMA-PP*



Lipitor^{TM}

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CHAPTER 20
AMINES

20.1 Reactions

Draw the structural formula of the <u>major</u> organic product(s). Show <u>stereochemistry</u> where appropriate.

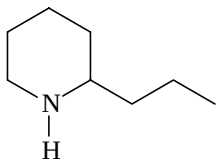
1. phthalimide
   1. base
   2. $ClCH(CO_2Et)_2$
   3. base
   4. isopropyl chloride
   5. $H_3O^{\oplus}$

   → *alanine*

2. 2-methyl-2-hexylamine
   1. (XS) CH_3I
   2. Ag_2O, H_2O, Δ
   3. OsO_4
   4. $NaHSO_3$
   5. (XS) $COCl_2$
   6. NH_3

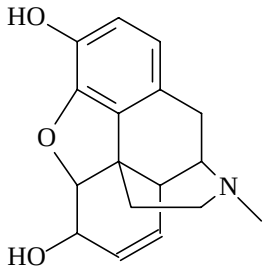
   → $C_9H_{18}N_2O_4$ - Miltown™

3. N-ethylcyclohexylamine
   1. (XS) MeI
   2. Ag_2O, H_2O
   3. Δ

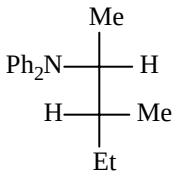
4. 

   1. (XS) MeI
   2. Ag_2O, H_2O
   3. Δ

   coniine (toxin in hemlock, killed Socrates)

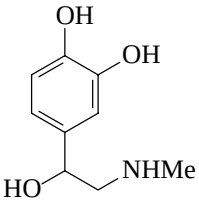
5. 

   morphine
   1. (XS) CH_3I
   2. Ag_2O, H_2O, Δ

6. 

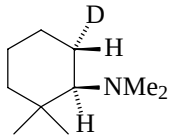
   1. H_2O_2
   2. Δ

7. cyclopropanecarboxylic acid $\xrightarrow[3.\ \Delta,\ H_2O]{1.\ SOCl_2\ \ 2.\ NaN_3}$

8. 

$\xrightarrow[2.\ Ag_2O,\ H_2O,\ \Delta]{1.\ (XS)\ MeI}$

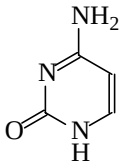
epinephrine

9. 

Hofmann elimination

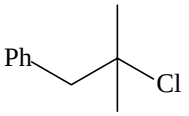
Cope elimination

10. 3-pentanone + dimethylamine + formaldehyde $\xrightarrow[(Mannich\ rx)]{H^{\oplus}}$

11. 

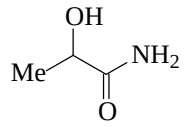
$\xrightarrow[H_2O]{HONO}$

cytosine *uracil*

12. 

$\xrightarrow[4.\ SOCl_2\ \ 5.\ NH_3\ \ 6.\ Br_2,\ {}^{\ominus}OH,\ H_2O]{1.\ Li\ \ 2.\ CO_2\ \ 3.\ H^{\oplus}}$

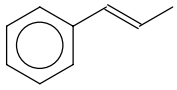
phentermine (a diet drug)

13. 

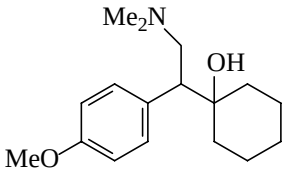
Br_2, $^{\ominus}OH$ / H_2O → NH_3 +

14. Ph_2CHOH
1. $NaNH_2$
2. ethylene oxide
3. PBr_3
4. Me_2NH

diphenhydramine (Benadryl™ - antihistamine)

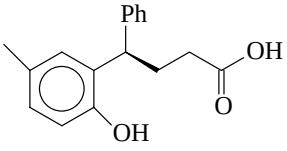
15. 
1. HBr, ROOR
2. potassium phthalimide
3. hydrazine

amphetamine (CNS stimulant)

16. 

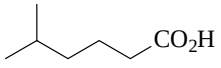
1. MeI
2. Ag_2O, H_2O, Δ
3. $H^{\oplus}$

Effexor™ (antidepressant) (gives a positive DNP test)

17. 

1. $SOCl_2$
2. NH_3
3. Br_2, $^{\ominus}OH$, H_2O
4.  (2 equiv)

Detrol™ (treatment of urinary incontinence)

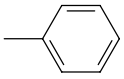
18. 

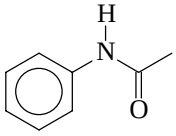
1. a. Br_2, PBr_3 b. H_2O
2. KO-*t*-Bu
3. HCN, $^{\ominus}CN$
4. H_2 / Pt

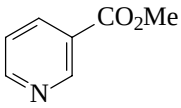
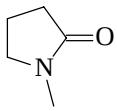
pregabalin (Lyrica™ - first treatment approved for fibromyalgia)

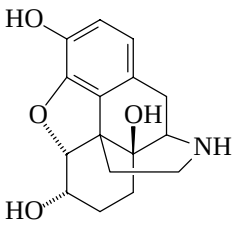
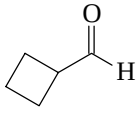
19. *p*-toluidine (*p*-aminotoluene) $\xrightarrow[3.\ KI]{1.\ Br_2;\ 2.\ NaNO_2,\ HCl}$

20. benzonitrile $\xrightarrow[3.\ KNO_2,\ H^{\oplus};\ 4.\ CuCN;\ 5.\ H_3O^{\oplus}]{1.\ Cl_2,\ FeCl_3;\ 2.\ NaNH_2\ /\ NH_3}$

21.  $\xrightarrow[4.\ NaNO_2,\ HCl;\ 5.\ HBF_4]{1.\ KMnO_4,\ H^{\oplus};\ 2.\ fuming\ nitric\ acid;\ 3.\ Fe,\ HCl}$

22.  $\xrightarrow[4.\ I\text{-}Cl,\ Fe;\ 5.\ HONO;\ 6.\ H_3PO_2]{1.\ Br_2,\ Fe;\ 2.\ Cl_2,\ Fe;\ 3.\ H_2O,\ {}^{\ominus}OH}$

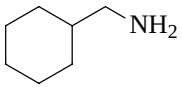
23.  +  $\xrightarrow[4.\ HBr\ (S_N1);\ 5.\ \Delta\ (-HBr)]{1.\ NaH;\ 2.\ H_3O^{\oplus};\ 3.\ NaBH_4}$ *nicotine*

24.  $\xrightarrow[2.\ HCl]{1.\ \text{  };\ NaBH_3CN,\ EtOH}$ Nubain™ (narcotic)

20.2 Syntheses

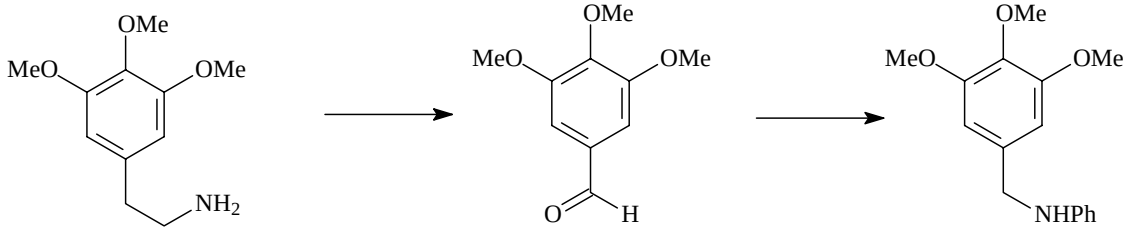
Supply a reagent or sequence of reagents that will effect the following conversions.

1. methylcyclohexane ⟶ 1-methyl-1-cyclohexylamine

2. cyclohexane ⟶ 

3. isopentane ⟶ 3-methyl-1-butene (*via a Hofmann elimination*)

4. 3-methyl-1-butene ⟶ isopropylamine

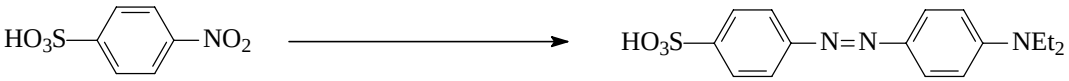
5. 

mescaline (from peyote cactus)

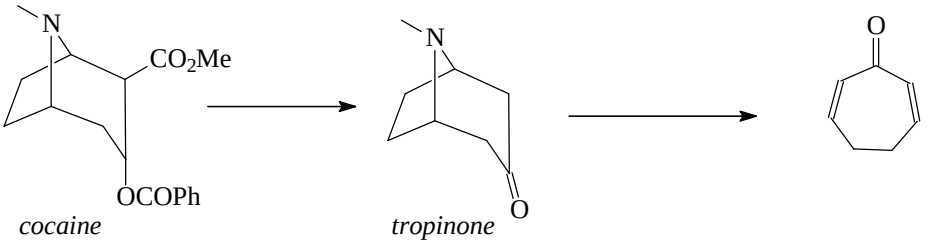
6. *p*-nitrotoluene ⟶ *p*-nitrobenzylamine

7. *p*-nitrotoluene ⟶ *p*-nitroaniline

8. 

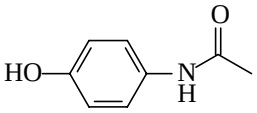
9. 

methyl orange

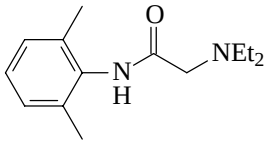
10. 

cocaine *tropinone*

11. toluene ⟶ 2,6-dichlorotoluene

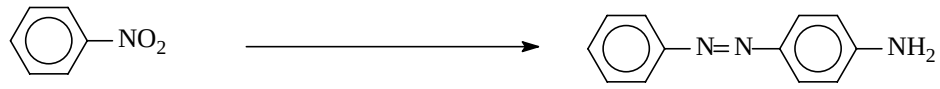
12. *p*-nitroaniline ⟶ 

acetaminophen (Tylenol™)

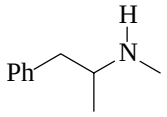
13. 1-nitro-2,6-dimethylbenzene, ethylene oxide, diethylamine ⟶ 

lidocaine

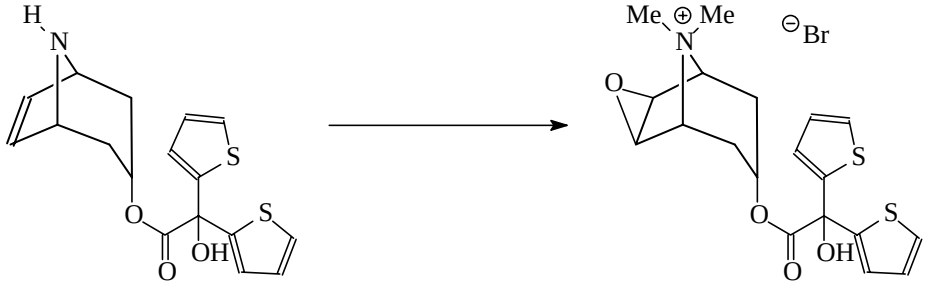
14. benzene ⟶ anisole

15. 

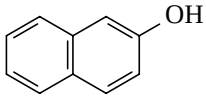
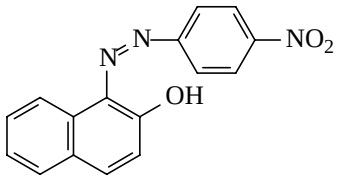
butter yellow

16. benzyl methyl ketone 

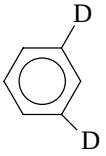
methamphetamine

17. 

tiotropium bromide (Spireva™ - bronchodilator)

18.  , benzene 

para-red dye

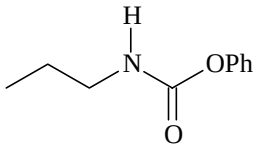
19. benzene 

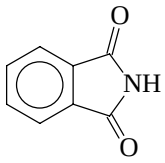
20. 

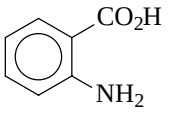
propofol (intravenous anesthetic)

20.3 Mechanisms

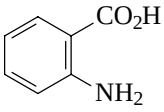
Outline a detailed mechanism for each of the following. No other reagents than those given are necessary. Use arrows to explain the flow of electrons and show all intermediates.

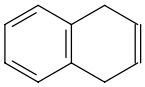
1. butanamide + phenol + Br_2 $\xrightarrow{{}^{\ominus}OH}$ 

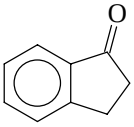
2. 

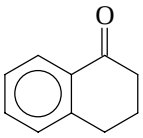
$\xrightarrow[2.\ H^{\oplus}]{1.\ Cl_2,\ H_2O,\ {}^{\ominus}OH}$ 

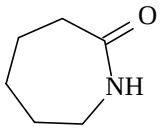
anthranilic acid

3. 

$\xrightarrow[3.\ 1,3\text{-butadiene}]{1.\ HONO;\ 2.\ \text{adjust to pH 8}}$ 

4. 

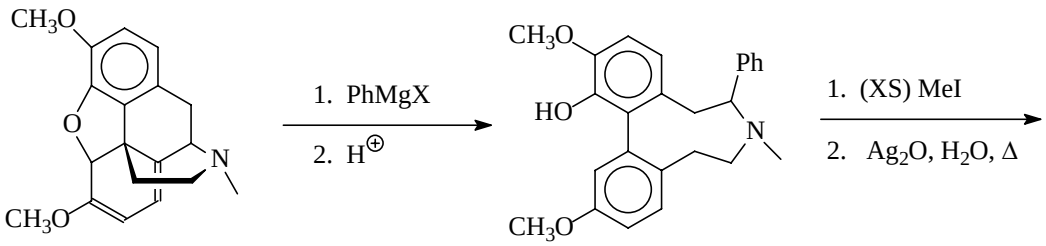
$\xrightarrow[3.\ NaNO_2,\ HCl]{1.\ HCN,\ {}^{\ominus}CN;\ 2.\ H_2 / Pt}$ 

5. cyclohexanone $\xrightarrow[2.\ H^{\oplus}]{1.\ NH_2OH}$ 

ε-caprolactam

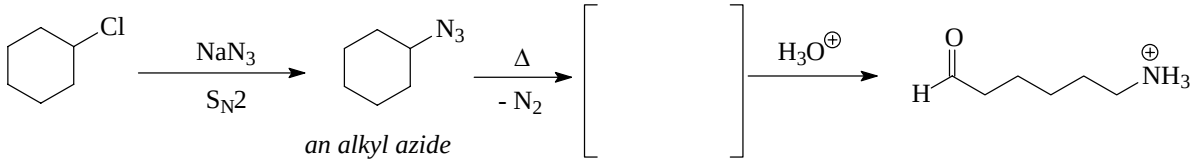
(This is an example of the *Beckmann rearrangement*, similar to the Hofmann and Curtius rearrangements.)

6. Sir Robert Robinson (*Oxford*) observed that *thebaine* (a dimethylated derivative of the alkaloid morphine) forms phenyldihydrothebaine when treated with phenylmagnesium halide. Formulate a mechanism and draw the Hofmann elimination product.



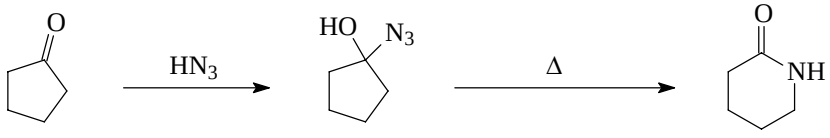
thebaine *phenyldihydrothebaine*

7. The *Curtius rearrangement* not only occurs with *acyl* halides but also *alkyl* azides. Draw the bracketed structure and deduce a mechanism for its formation.

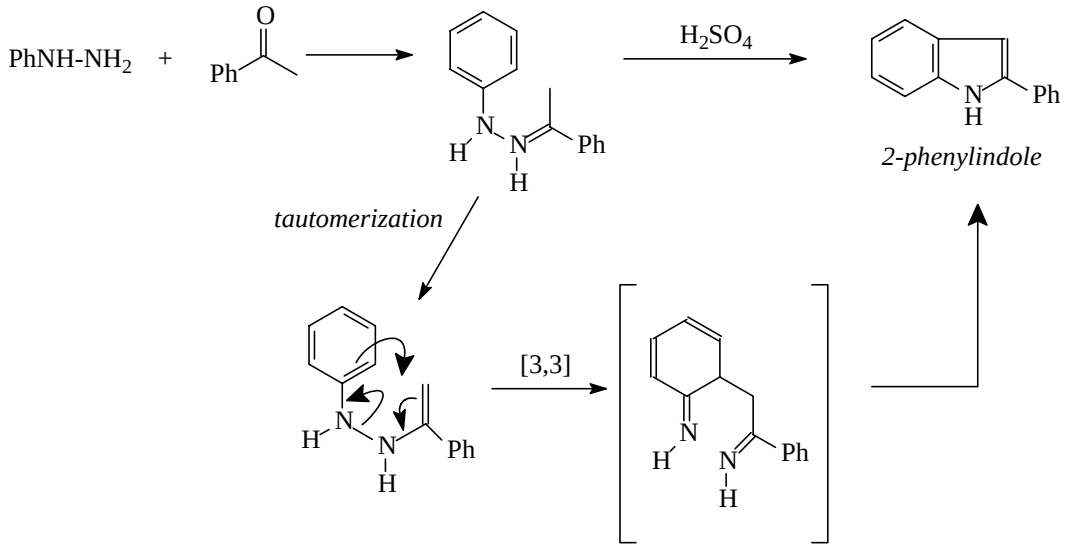


an alkyl azide

8. Hydrazoic acid (HN_3) undergoes addition to ketones to form a product that readily rearranges to an amide (*Schmidt reaction*):

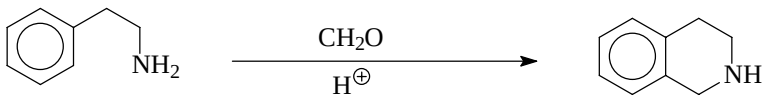


9. The *Fischer indole synthesis* involves an isomerization known as a [3,3] sigmatropic rearrangement, shown by the arrows below:

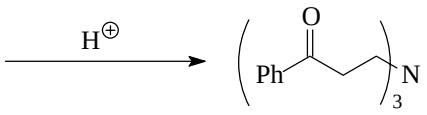


Outline a mechanism for conversion of the intermediate in brackets to the indole product.

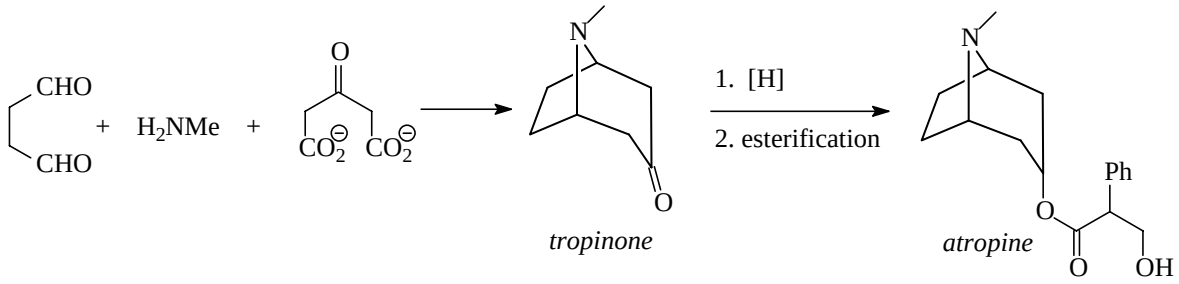
10.



11. acetophenone + CH_2O + NH_3

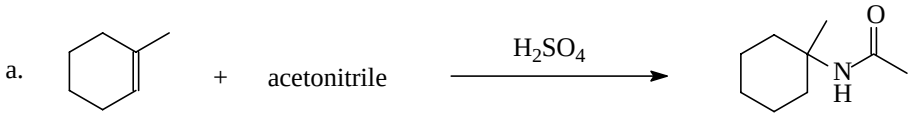


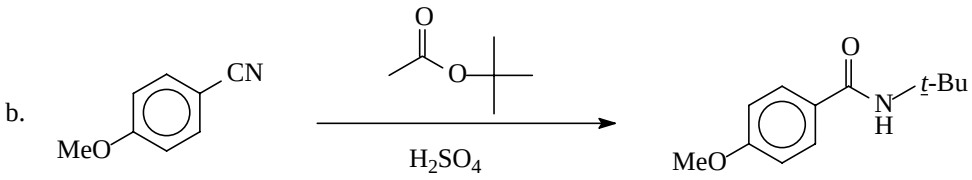
12. *Atropine*, an antidote to cholinesterase inhibitors (*e.g.*, nerve gases), can be easily synthesized from tropinone. The first total synthesis of tropinone required 17 steps. Years later Robinson (*Oxford*) accomplished its synthesis in a one-step, one-pot reaction (*Robinson-Schopf condensation*)! Sketch the critical intermediates in this synthesis.



tropinone *atropine*

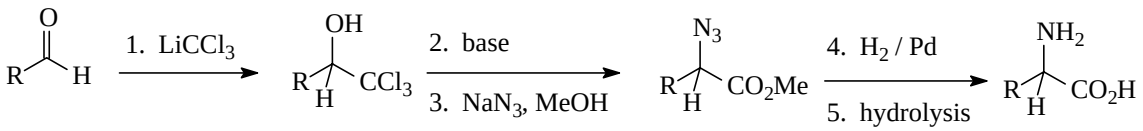
13. The *Ritter reaction* offers a way to prepare amides (or, by subsequent hydrolysis, amines) from good precursors to carbocations:





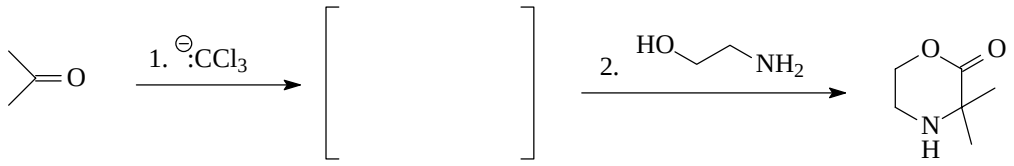
14. A convenient method of synthesizing pure *secondary* amines involves (1) treating the sulfonamide of a *primary* amine with hydroxide, followed by (2) an alkyl halide, then (3) hydrolysis. Outline such an approach to preparing N-methylaniline.

15. The *Corey-Link reaction* (step 2) may be used to prepare α-amino acids:

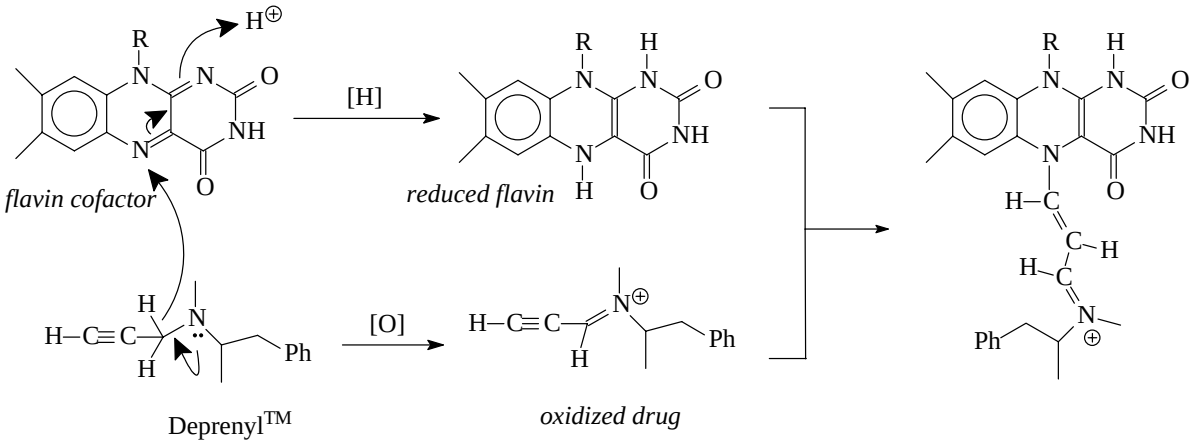


a. Outline a mechanism for steps 2 and 3.

b. Account for the product in a mechanistically similar reaction:



16. *Parkinson's disease* is associated with low levels of dopamine, a neurotransmitter. The enzyme monoamine oxidase (MAO) deaminates dopamine, thereby decreasing its concentration. One approach to treating Parkinson's utilizes (-)-Deprenyl™, a "suicide inhibitor" to MAO. The mechanism first involves oxidation of the drug by a flavin cofactor of MAO, followed by a conjugate addition reaction between the reduced flavin and oxidized drug to irreversibly "kill" any future normal activity by the MAO enzyme. Outline the mechanism for formation of the adduct.



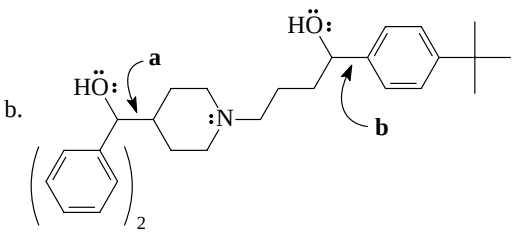
SOLUTIONS TO PROBLEMS

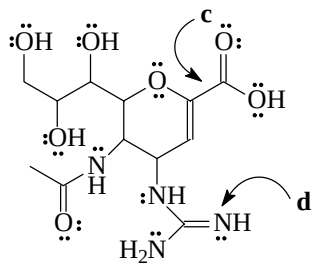
CHAPTER 1
THE BASICS

1.1 Hybridization, formulas, physical properties

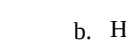
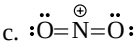
1. a. Seldane™: $C_{32}H_{42}NO_2$ Relenza™: $C_{12}H_{20}N_4O_7$

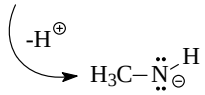
b.

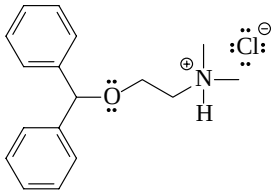
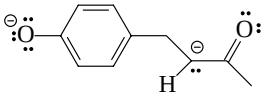


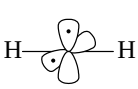


c. **a**: $sp^3 - sp^3$; **b**: $sp^3 - sp^2$; **c**: $sp^2 - sp^2$ d. Seldane™ oxygens: sp^3; nitrogen **d**: sp^2

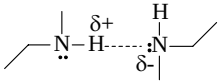
2. a.  b.  c.  d. the *conjugate base* of $:NH_2CH_3$



e.  f. 

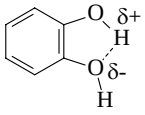
3. a.  sp^2 => bond angle ~ 120^0 b.  = 

a linear HCH bond angle implies sp hybridization; therefore, each lone electron lies in an un-hybridized p orbital with spins aligned (Hund's rule)

4. a. higher bp: 

this isomer is capable of *intermolecular* H-bonding, thereby increasing intermolecular attractive forces and raising its bp relative to the other amine

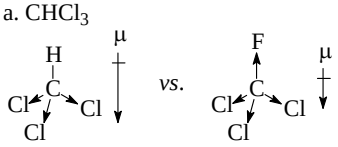
b. lower mp: catechol



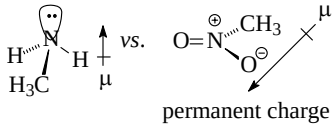
catechol, unlike hydroquinone, can undergo *intramolecular* H-bonding, which decreases intermolecular attractions and results in lowering its mp relative to hydroquinone

5. a. no b. no c. yes d. yes e. yes f. no g. yes h. yes

6. a. $CHCl_3$

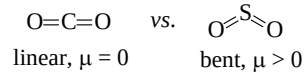


b. CH_3NO_2



permanent charge separation (> ε)

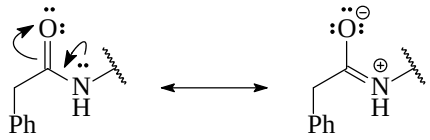
c. SO_2



linear, μ = 0 bent, μ > 0

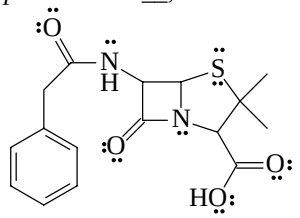
7. a. *penicillin V*: $C_{16}H_{18}N_2O_4S$ *cimetidine*: $C_{10}H_{16}N_6S$

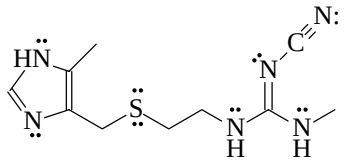
b. arrow **a**: sp^2 **b**: sp^3 **c**: sp

c. 

this resonance structure suggests *some* double bond character;
electrons must be in a p orbital in order to resonate

d. lone pairs: *penicillin V*: 12; *cimetidine*: 8.

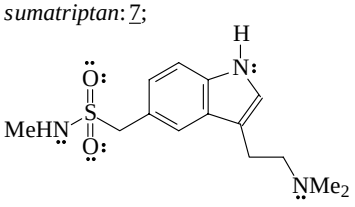


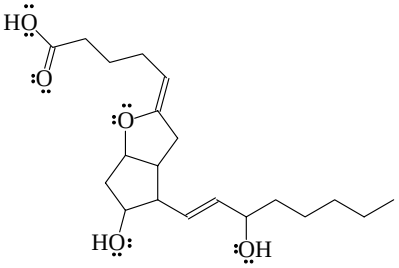


8. a. *sumatriptan*: $C_{14}H_{21}N_3O_2S$ *prostacyclin*: $C_{20}H_{32}O_5$

b. *Sumatriptan* contains 8 sp^2 and 6 sp^3 carbons; *prostacyclin* contains 5 sp^2 and 15 sp^3 carbons.

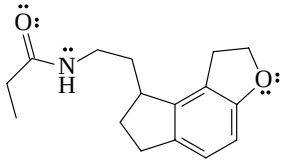
c. lone pairs: *sumatriptan*: 7; *prostacyclin*: 10.

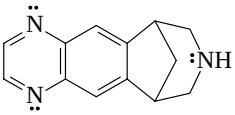


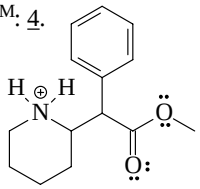


9. a. Rozerem™: $C_{16}H_{21}NO_2$ Chantix™: $C_{13}H_{13}N_3$ Ritalin™: $C_{14}H_{20}NO_2$

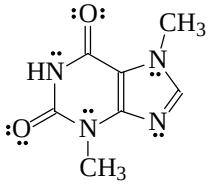
b. lone pairs: Rozerem™: 5; Chantix™: 3; Ritalin™: 4.

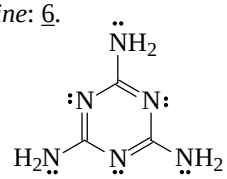






10. lone pairs: *theobromine*: 8; *melamine*: 6.



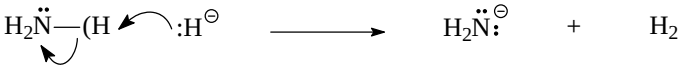


11. a. alkene, amide, amine, ester, ether b. alkene, amine, arene, carboxylic acid, halide, ketone

c. alcohol, alkyne, arene.

1.2 Acids and bases

1. strongest base in ammonia: $H_2\ddot{N}^{\ominus}$ amide anion - the CB of ammonia



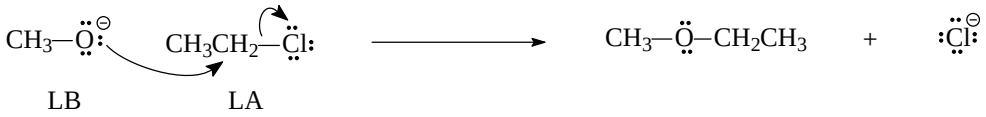
2. stronger base: $(CH_3)_2NH$ nitrogen is more electron-releasing than oxygen

3. a.

b. $Ph_3P: + BF_3 \longrightarrow Ph_3\overset{\oplus}{P}-\overset{\ominus}{B}F_3$

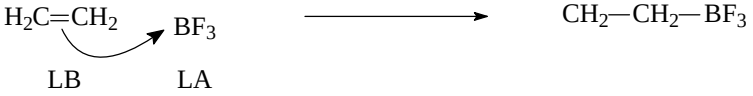
c.

4. a.



LB LA

b.



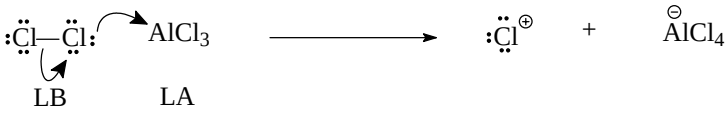
LB LA

c.

LA LB

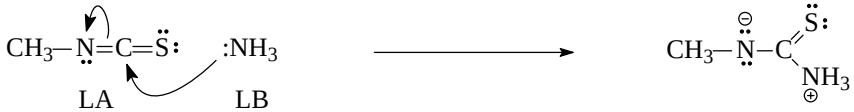
(also Bronsted-Lowry acid-base, respectively)

d.



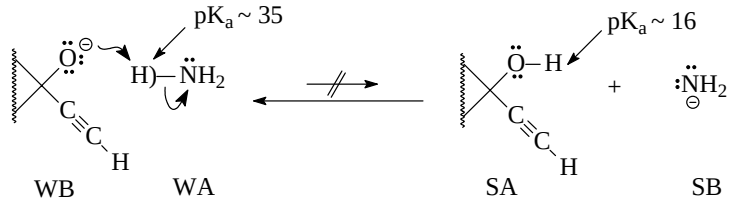
LB LA

e.



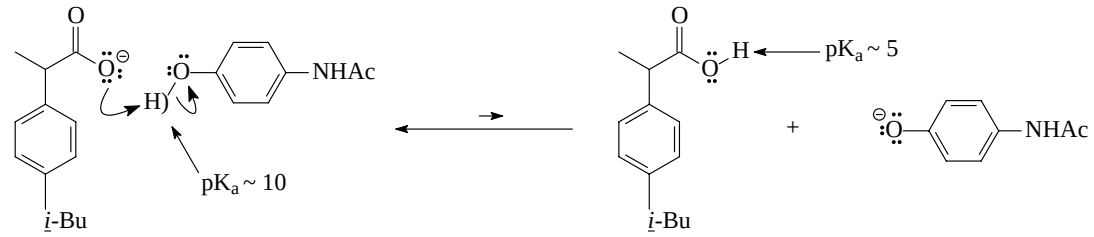
LA LB

5. a. $C_{20}H_{28}O$ b.



WB WA SA SB

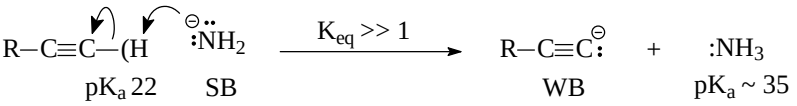
c. $K_{eq} << 1$ (Δ pK_as > 4)

6. a. 

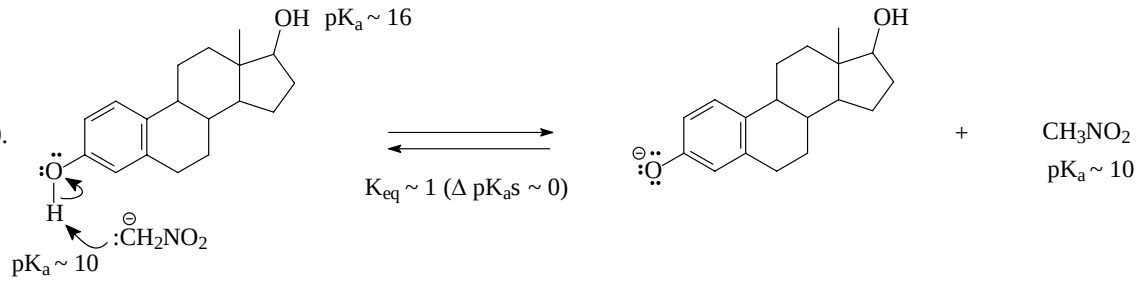
b. WB WA SA SB

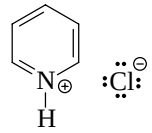
c. $K_{eq} << 1$ (Δ pK_as > 4)

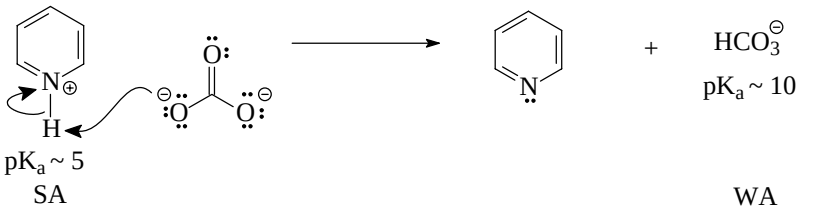
7. lowest pK_a: b. a. ~ 16 b. ~ 5 c. ~ 16 d. ~ 10 e. ~ 38 f. ~ 35

8. quantitative rx: b. 

a. hydroxide ($K_{eq} << 1$) c. H_2 (NR) d. EtO^- ($K_{eq} << 1$)

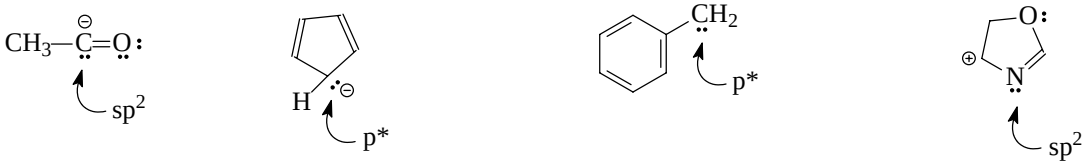
9. 

10. a. 

b. 

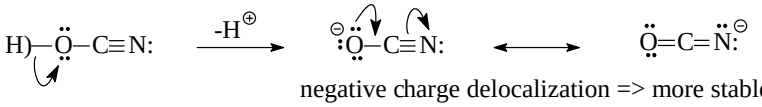
c. $K_{eq} >> 1$ (Δ pK_as > 4)

1.3 Resonance

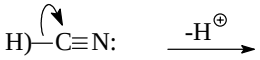
1. 

* not sp^3 per VSEPR; electrons may resonate if housed in a p orbital

2. lower pK_a: H-O-CN

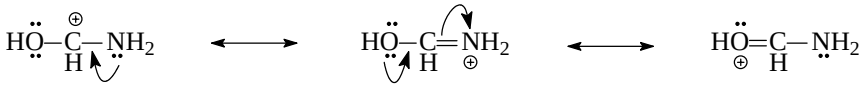


negative charge delocalization => more stable CB

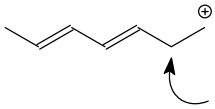


negative charge localized on C

3. a. 3.



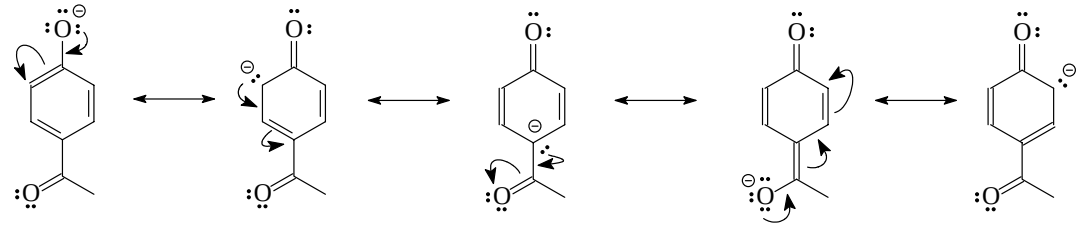
b. 1.



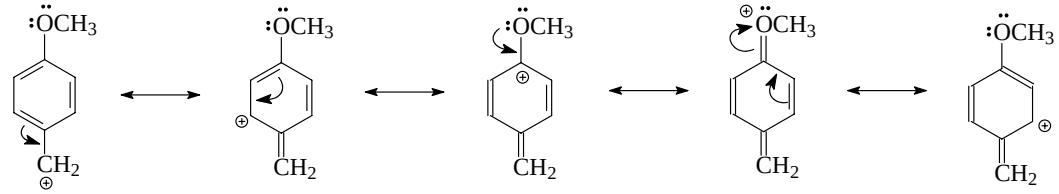
localized charge

saturated, no p orbital

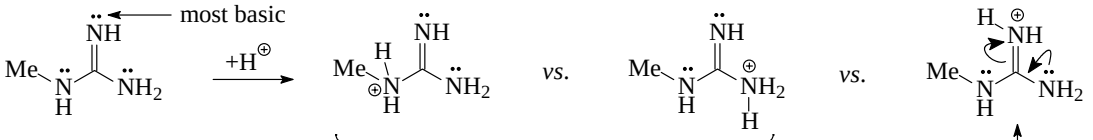
c. 5.



d. 5.

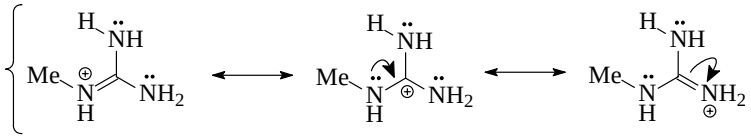


4.

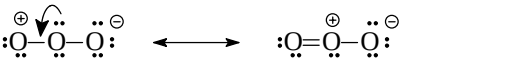


no important resonance contributions

4 resonance structures
=> a more stable CA

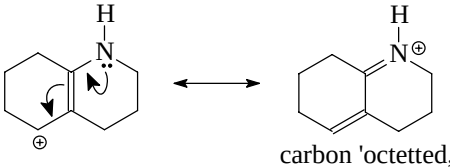


5. a.

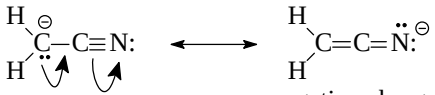


oxygen 'octetted,'
closer charge separation

b.



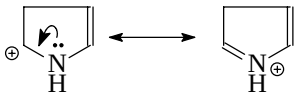
carbon 'octetted,'
additional π bond

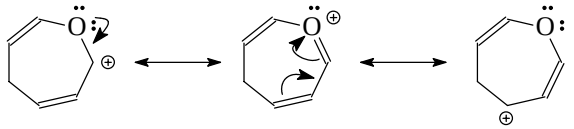
c. 

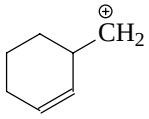
negative charge is borne by more electronegative atom

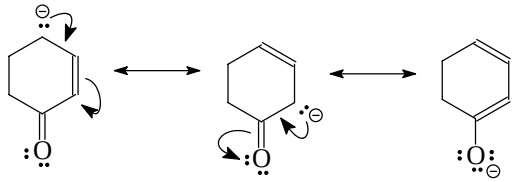
d. 

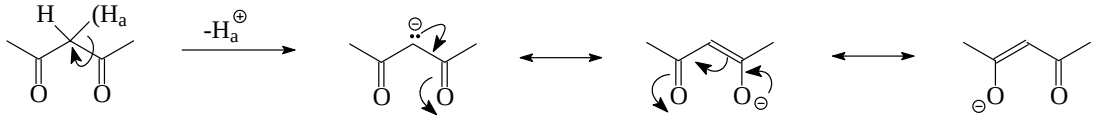
carbon 'octetted,' additional π bond

6. a. 2. 

b. 3. 

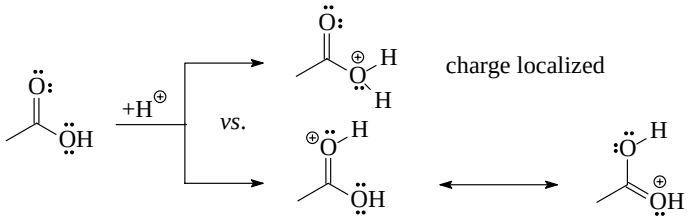
c. 1. 

d. 3. 

7. 

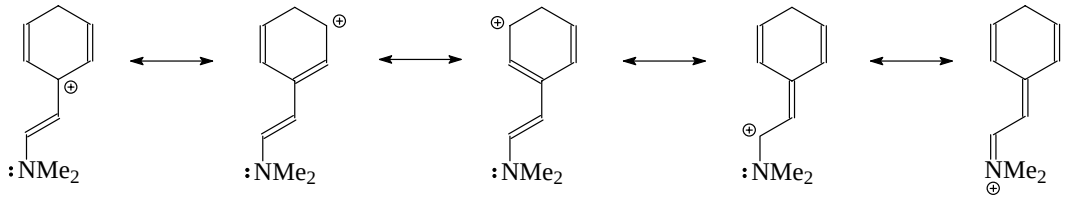
A

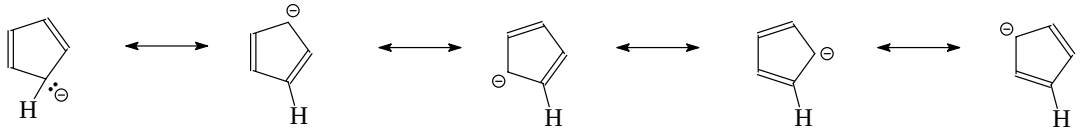
CB of **A** is stabilized by charge delocalization over three nuclei and, therefore, more easily formed => pK_a of H_a is lowered

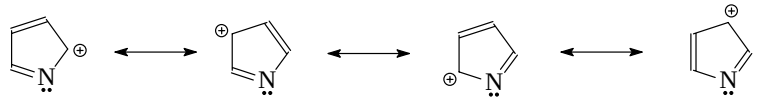
8. 

charge localized

charge delocalized, => > stability
therefore, more favored CA species

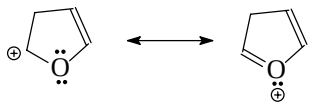
9. a. 5. 

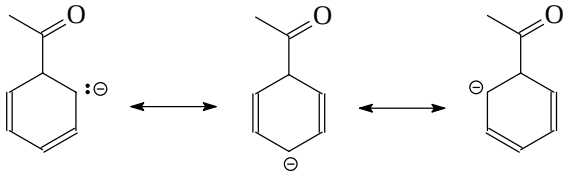
b. 5. 

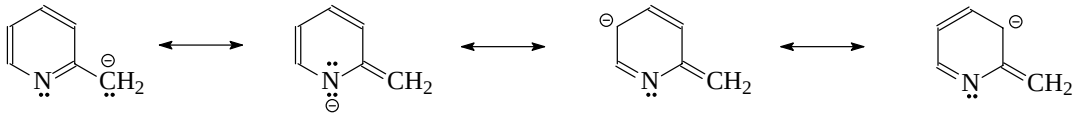
c. 4. 

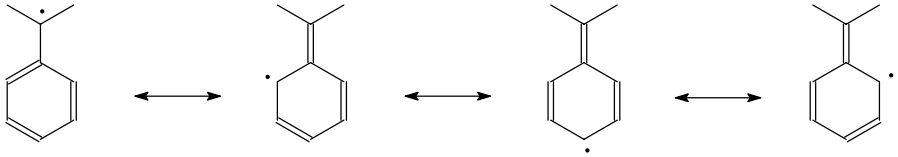
not 

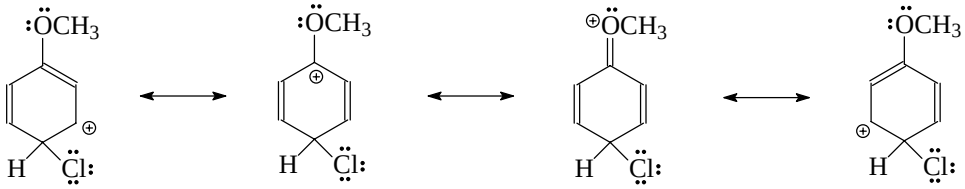
nitrogen 'sextetted'

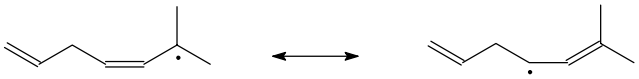
d. 2. 

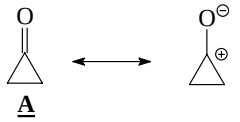
e. 3. 

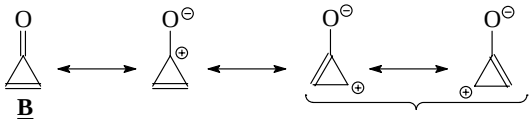
f. 4. 

g. 4. 

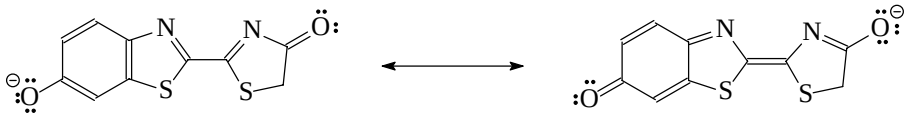
h. 4. 

i. 2. 

10. 
A

vs. 
B

these additional resonance structures increase both $\underline{\varepsilon}$ and $\underline{d}$ ($\mu = \varepsilon \times d$); therefore, $\mu_B > \mu_A$

11. 

CB of oxyluciferin

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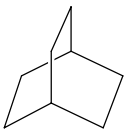
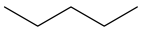
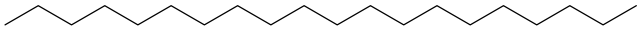
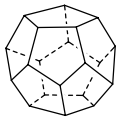
CHAPTER 2
ALKANES

2.1 General

1. highest mp: 4.  bicyclo[2.2.2]octane (most spherical)

2. highest bp: 1.  *n*-pentane (least branched)

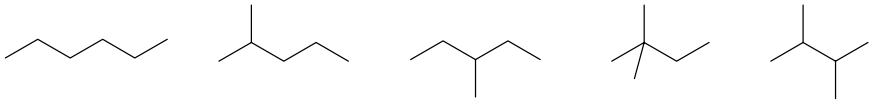
3. 

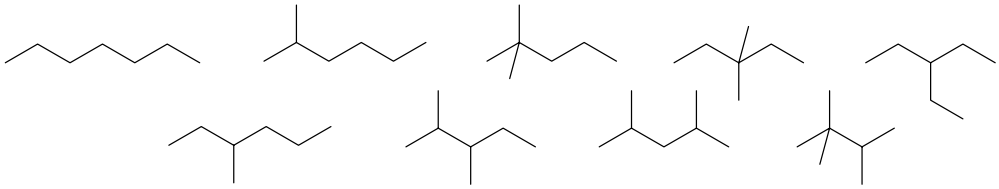


eicosane, mp 37^0 dodecahedrane, mp 420^0

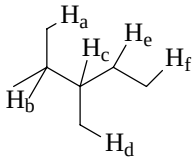
spherical molecules (dodecahedrane) pack more closely in the solid state than linear (eicosane) ones, therefore requiring more energy to separate (melt) them

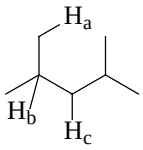
4. constitutional isomers for

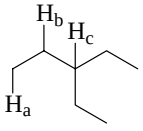
a. C_6H_{14}: 5. 

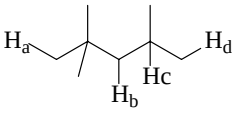
b. C_7H_{16}: 9. 

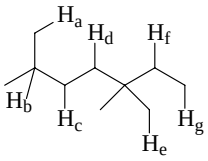
5. different kinds (constitutional) of hydrogens in

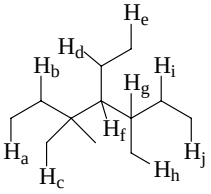
a. 2,3-dimethylpentane: 6. 

b. 2,4-dimethylpentane: 3. 

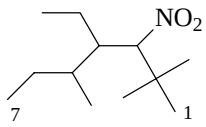
c. 3-ethylpentane: 3. 

d. 2,2,4-trimethylpentane: 4. 

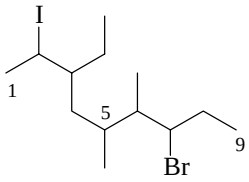
e. 2,5,5-trimethylheptane: 7. 

f. 4-ethyl-3,3,5-trimethylheptane: 10. 

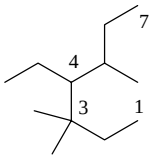
2.2 Nomenclature

1. 

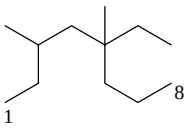
3-nitro-4-ethyl-2,2,5-trimethylheptane

2. 

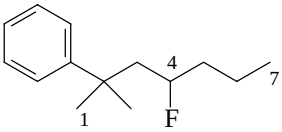
7-bromo-2-iodo-3-ethyl-5,6-dimethylnonane

3. 

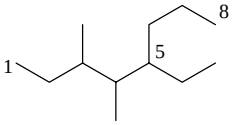
4-ethyl-3,3,5-trimethylheptane

4. 

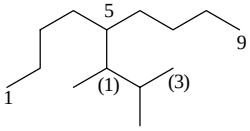
5-ethyl-3,5-dimethyloctane

5. 

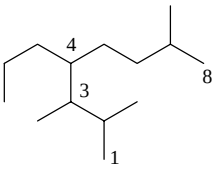
4-fluoro-2-methyl-2-phenylheptane

6. 

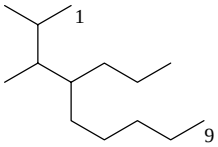
5-ethyl-3,4-dimethyloctane

7. 

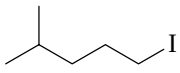
5-(1,2-dimethylpropyl)nonane

8. 

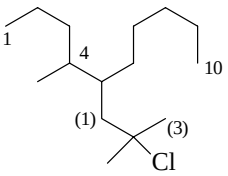
2,3,7-trimethyl-4-*n*-propyloctane
(choose path with more branching)

9. 

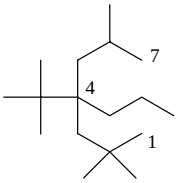
2,3-dimethyl-4-*n*-propylnonane

10. 

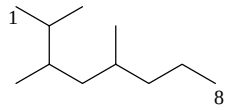
1-iodo-4-methylpentane

11. 

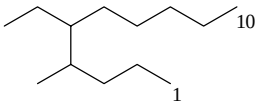
5-(2-chloro-2-methylpropyl)-4-methyldecane

12. 

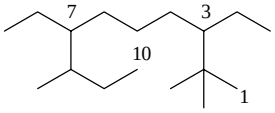
4-*t*-butyl-2,2,6-trimethyl-4-*n*-propylheptane
not 4-*t*-butyl-4-isobutyl-2,2-dimethylheptane
(less branching)

13. 

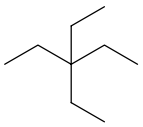
2,3,5-trimethyloctane

14. 

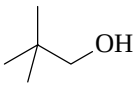
5-ethyl-4-methyldecane

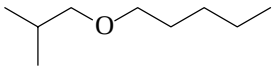
15. 

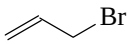
3,7-diethyl-2,2,8-trimethyldecane

16. 

diethylpentane
(3,3- not necessary!)

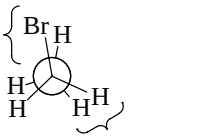
17. a. 

b. 

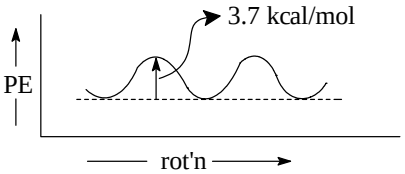
c. 

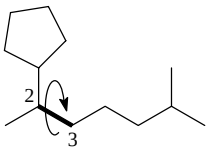
2.3 Conformational analysis, acyclic

1. 3.7 kcal/mol
-2.0 (2 x 1.0 kcal/mol)
1.7 kcal/mol

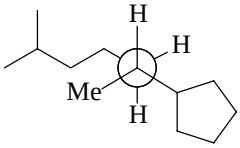


1.0 kcal/mol

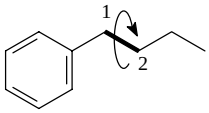


2. a. 

=



largest R-groups are *anti*

b. 

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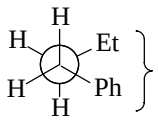
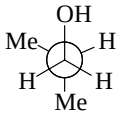
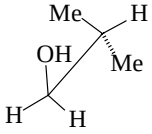


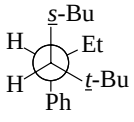
gauche: dihedral angle ~ 60^0

3. a. 

=



isobutyl alcohol

b. 

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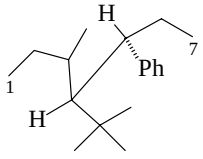
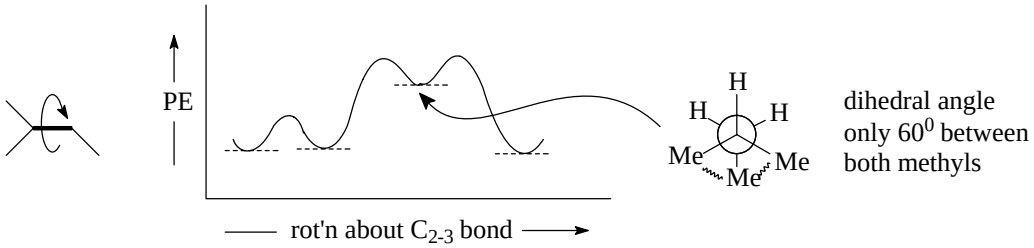
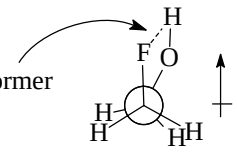


4-*t*-butyl-3-methyl-5-phenylheptane

4. 

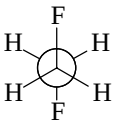
dihedral angle only 60^0 between both methyls

5. intramolecular hydrogen-bond stabilizes a nearly eclipsed conformer for FCH_2CH_2OH



$\mu >> 0$

vs.

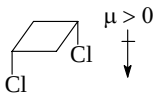


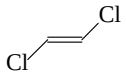
$\mu \sim 0$

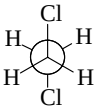
CHAPTER 3
CYCLOALKANES

3.1 General

1. highest molecular dipole moment: d.



a. 

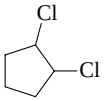
b. 

c. Cl—C≡C—Cl

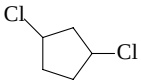
μ = 0

2. constitutional isomers for
a. dichlorocyclopentane: 3.

1,1-

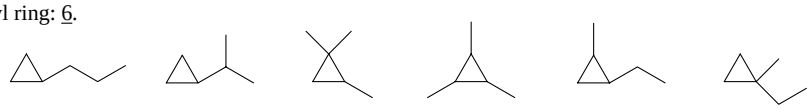


1,2-

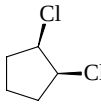


1,3-

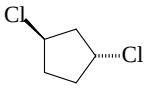
b. C_6H_{12} that contain a cyclopropyl ring: 6.



3. *cis/trans* stereoisomers for
a. dichlorocyclopentane: 2 pairs.

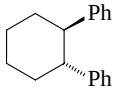


1,2- + *trans-*

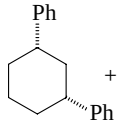


1,3- + *cis-*

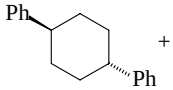
b. diphenylcyclohexane: 3 pairs.



1,2- + *cis-*

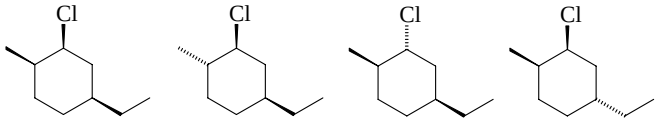


1,3- + *trans-*



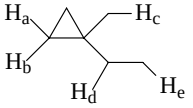
1,4- + *cis-*

c. 2-chloro-4-ethyl-1-methylcyclohexane: 4.



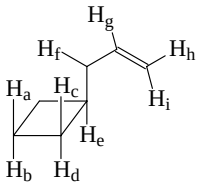
4. different kinds (constitutional and geometric) of hydrogens in

a. 1-ethyl-1-methylcyclopropane: 5.

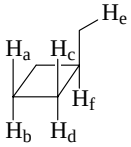


H_a and H_b are *cis-* and *trans-* to methyl, and so are 'different'

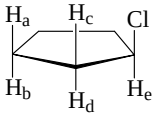
b. allylcyclobutane: 9.



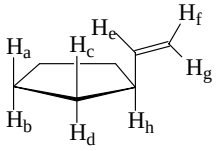
c. methylcyclobutane: 6.



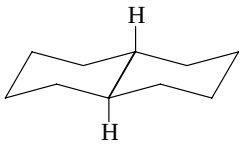
d. chlorocyclopentane: 5.



e. vinylcyclopentane: 8.

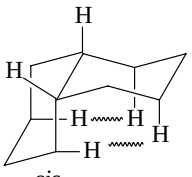


5. least strained: a.



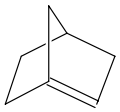
trans-
no strain

b.



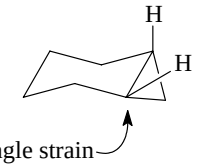
cis-
diaxial strain

c.



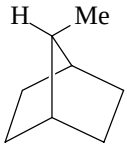
ring strain prevents
alkene from being planar -
violates Bredt's rule

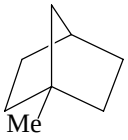
d.

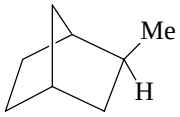


angle strain

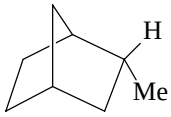
6.







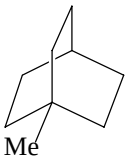
exo-



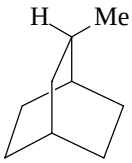
endo-

stereoisomers

7. only 2.



+



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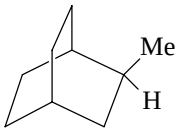

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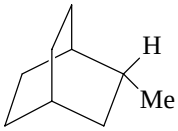
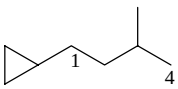


identical structures (*for now*!)

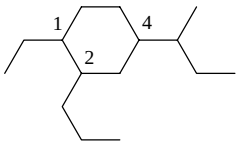
3.2 Nomenclature

1.



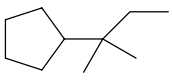
1-cylclopropyl-3-methylbutane

2.



4-*s*-butyl-1-ethyl-2-*n*-propylcyclohexane

3.

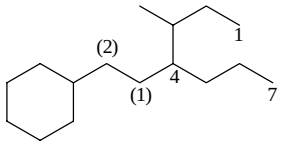


t-pentylcyclopentane

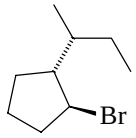
(1,1-dimethylpropyl)cyclopentane

2-cyclopentyl-2-methylbutane

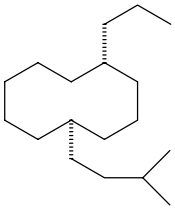
4.



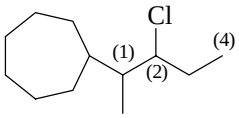
4-(2-cyclohexylethyl)-3-methylheptane

5. 

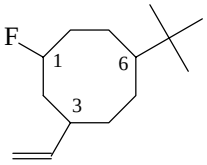
trans-1-bromo-2-s-butylcyclopentane

6. 

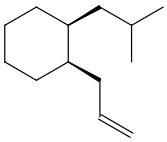
cis-1-isopentyl-5-*n*-propylcyclodecane

7. 

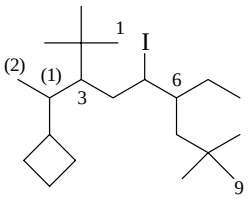
(2-chloro-1-methylbutyl)cycloheptane

8. 

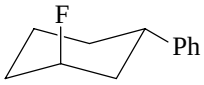
1-fluoro-6-*t*-butyl-3-vinylcyclooctane

9. 

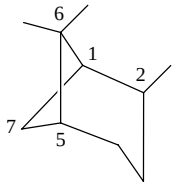
cis-1-allyl-2-isobutylcyclohexane

10. 

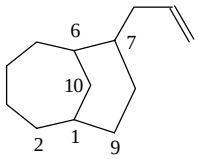
5-iodo-3-(1-cyclobutylethyl)-6-ethyl-2,2,8,8-tetramethylnonane

11. 

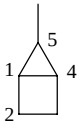
trans-1-fluoro-3-phenylcyclohexane

12. 

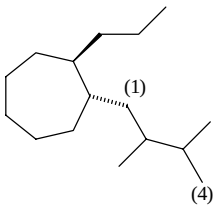
2,6,6-trimethylbicyclo[3.1.1]heptane

13. 

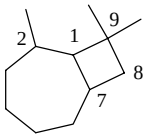
7-allylbicyclo[4.3.1]decane

14. 

5-methylbicyclo[2.1.0]pentane

15. 

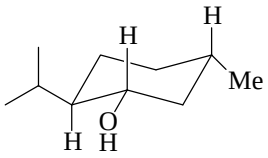
trans-1-(2,3-dimethylbutyl)-2-*n*-propylcycloheptane

16. 

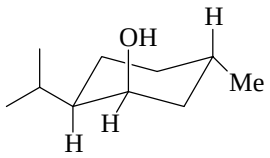
2,9,9-trimethylbicyclo[5.2.0]nonane

3.3 Conformational analysis, cyclic

1. most stable conformer:

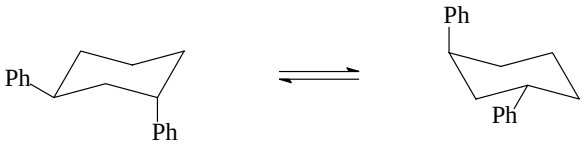


menthol



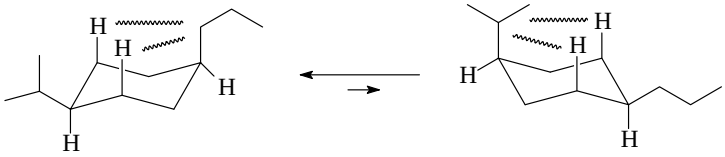
neomenthol

2. a.



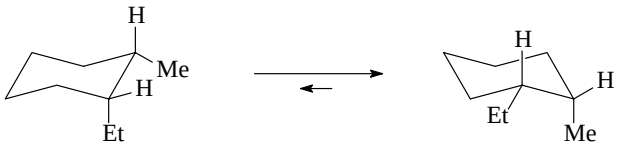
degenerate structures (same energy)
therefore, $K_{eq} = 1$

b.



> 1,3-diaxial interactions => less stable conformer
therefore, $K_{eq} < 1$

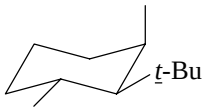
c.

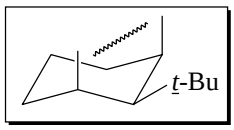


larger ethyl group in more stable equatorial position
therefore, $K_{eq} > 1$

3. most negative ΔH_{comb} (=> least stable):

a.

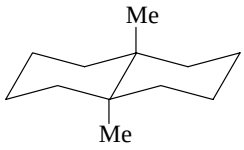


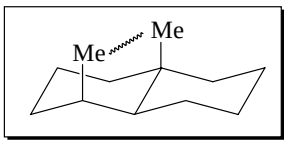


least stable

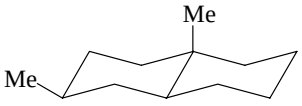
(most stable, therefore,
least negative ΔH_{comb})

b.

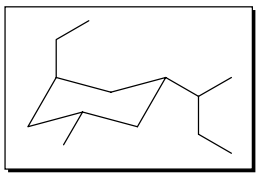




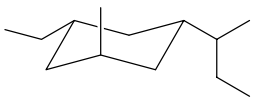
> dimethyl repulsion
therefore, least stable



c.

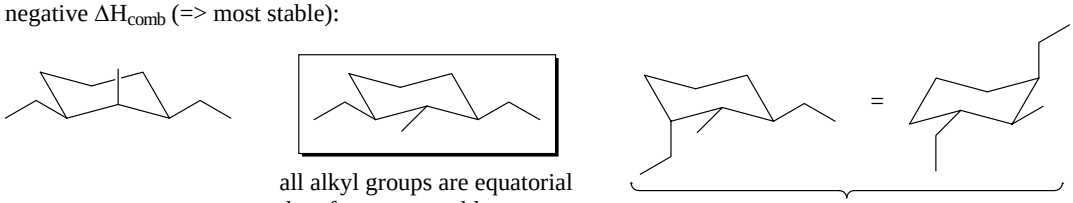


least stable



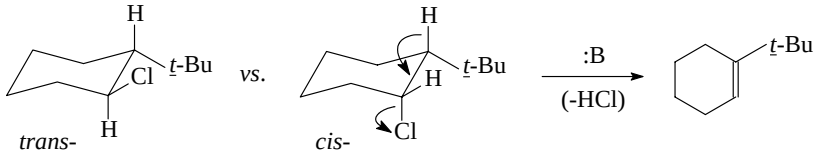
(most stable)

4. least negative ΔH_{comb} (=> most stable):

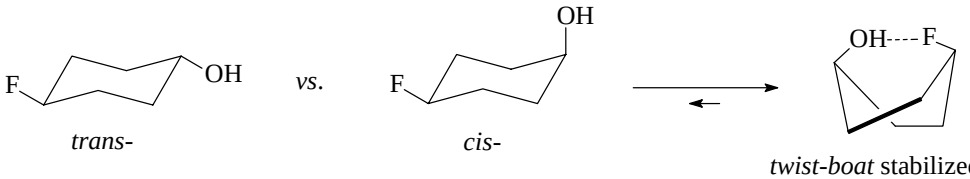
a. 

all alkyl groups are equatorial
therefore, most stable

b. same compound!

5. most stable conformer for: 

t-butyl group prevents 'flipping,' so chlorine cannot assume the axial position in the *trans*-isomer
therefore, the *cis*-isomer would react more rapidly

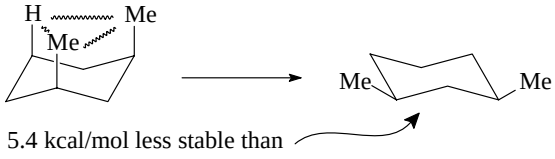
6. 

twist-boat stabilized by intramolecular hydrogen-bonding; not possible in chair conformer (or in *trans*-isomer)

7. a. 

1 **2**

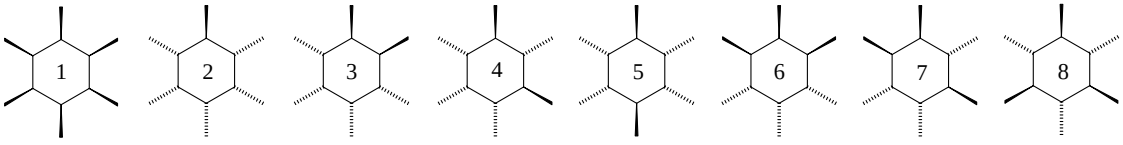
b. configuration **2** is less stable (one substituent must be axial) and would burn with a more negative ΔH_{comb}

8. 

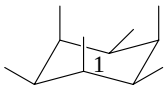
5.4 kcal/mol less stable than

5.4 kcal/mol
-0.9
-0.9 } (2 Me-H 1,3-diaxial strain interactions)
3.6 kcal/mol (Me-Me 1,3-diaxial strain interaction)

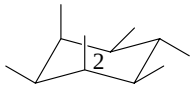
9. a. number of *cis/trans* stereoisomers: 8.



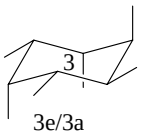
b. for conformational chair-chair flipping, $K_{eq} = 1$ for configurations 1, 3, and 5: 3e/3a ⇌ 3a/3e



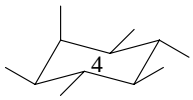
3e/3a



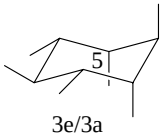
4e/2a



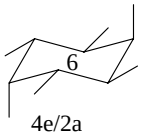
3e/3a



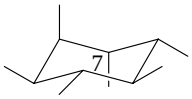
5e/1a



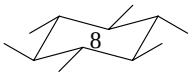
3e/3a



4e/2a

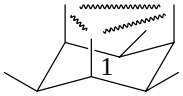


4e/2a



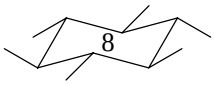
6e/0a

c. least stable: 1.

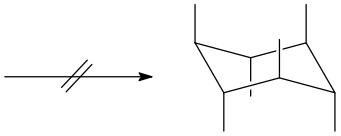


three 1,3-diaxial steric interactions exist between two methyl groups (only *one* such interaction exists in configurations 3 and 5)

d. least likely to flip: 8.



all methyls are equatorial

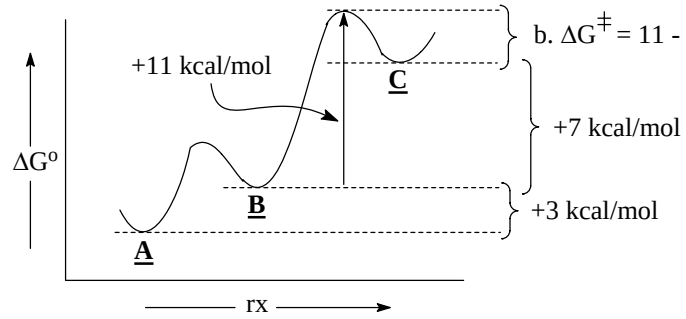


all axial!

CHAPTER 4
REACTION BASICS

1.	a. addition	b. oxidation [O]	c. substitution	d. substitution
	e. elimination	f. reduction [H]	g. oxidation [O]	h. addition
	i. reduction [H]	j. rearrangement	k. oxidation [O]	l. substitution
	m. elimination	n. addition	o. reduction [H]	p. reduction [H]
	q. rearrangement	r. elimination	s. substitution	t. reduction [H]

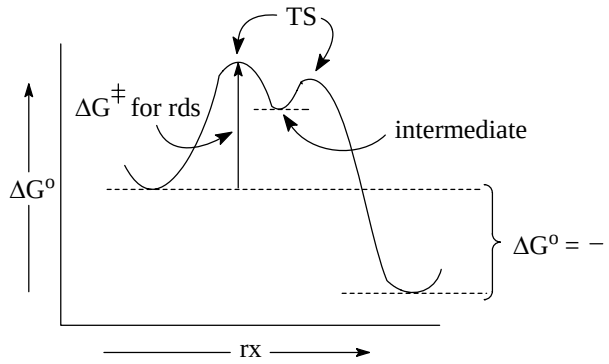
2. a.



b. $\Delta G^{\ddagger}$ = 11 - 7 = +4 kcal/mol

A	→	**B**	+3 kcal/mol
B	→	**C**	+7
A	→	**C**	+10 kcal/mol

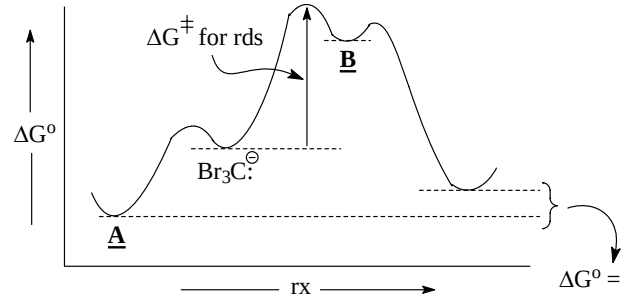
3. a.



b. $K_{eq} = e^{-\Delta G^{o} / RT}$

c. rate = k[conc. term(s)] = $k_o e^{-\Delta G^{\ddagger} / RT}$

4. a.



b. $\Delta G^{o} = -RT \ln K_{eq}$

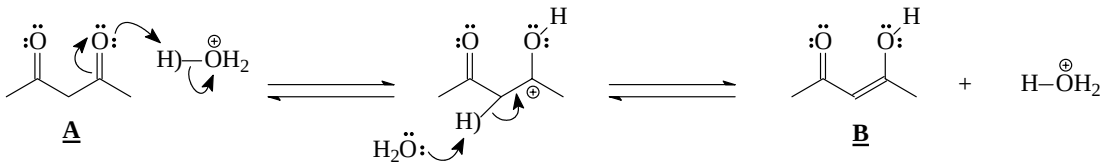
$K_{eq} = e^{-\Delta G^{\ddagger} / RT} = e^{-2,500 / (2)(300)}$

$K_{eq} = \underline{1.6 \times 10^{-2}}$

ΔG^{o} = +2.5 kcal/mol

5. a. type of reaction: rearrangement; mechanism: polar / ionic.

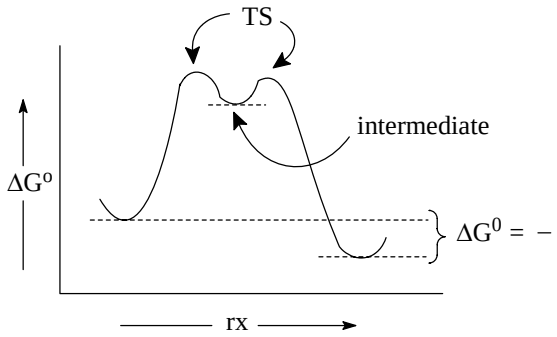
b.



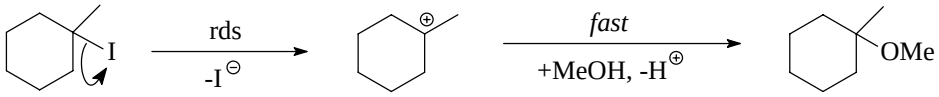
c. K_{eq} = [**B**] / [**A**] = 75% / 25% = 3.0; $\Delta G^o = -RT \ln K_{eq}$.

d. nucleophiles: **A**, H_2O, and **B**.

e.



6.

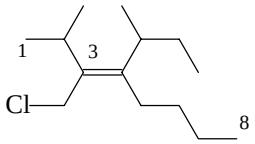


7.

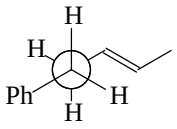
a. pericyclic	b. free radical	c. pericyclic	d. polar / ionic
e. pericyclic	f. polar / ionic	g. free radical	h. polar / ionic
i. pericyclic	j. polar / ionic		

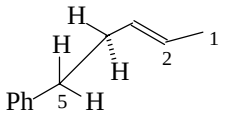
CHAPTER 5
ALKENES AND CARBOCATIONS

5.1 General

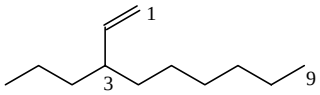
1. a. 

(E)-3-chloromethyl-4-*s*-butyl-2-methyl-3-octene

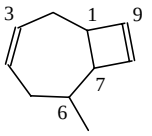
b. 

=


trans-5-phenyl-2-pentene

c. 

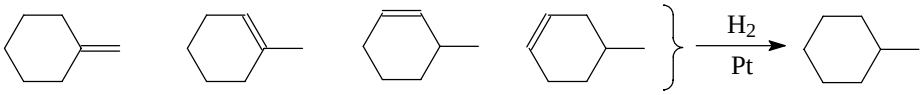
3-*n*-propyl-1-nonene

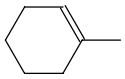
d. 

6-methylbicyclo[5.2.0]-3,8-nonadiene

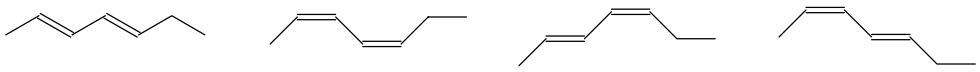
2. a. (Z)- b. (E)- c. (Z)- d. (Z)- e. (Z)- f. (Z)-

3. a. number of alkenes: 4.

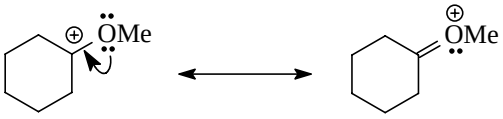


b. least negative $\Delta H_{hydrogenation}$:  most stable (trisubstituted)

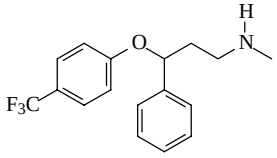
4. number of *geometric* isomers: 4.



trans, trans- *cis, cis*- *trans, cis*- *cis, trans*-

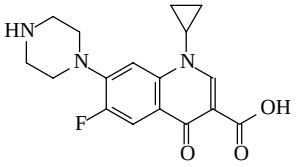
5. most stable carbocation: 

6. a. no. deg. unsat: $C_{17}H_{36}$ - $C_{17}H_{20(18+3-1)}$ = H_{16} => $H_{16}/2$ = 8 deg.
hydrogenation: $C_{17}H_{30}F_3NO$ - $C_{17}H_{18}F_3NO$ = H_{12} => $H_{12}/2$ = 6 DB
no. rings = 8 - 6 DB = 2.



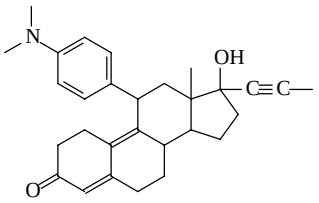
fluoxetine

b. no. deg. unsat: $C_{17}H_{36}$ - $C_{17}H_{16(18+1-3)}$ = H_{20} => $H_{20}/2$ = 10 deg.
no. DB = 10 - 4 rings = 6.



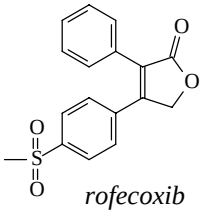
Cipro™

c. no. deg. unsat: $C_{28}H_{58}$ - $C_{28}H_{34(35-1)}$ = H_{24} => $H_{24}/2$ = 12 deg.
no. rings = 12 - 5 DB -1 TB(= 2 DB!) = 5.



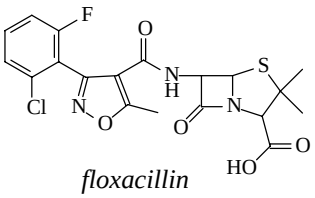
RU 486

d. no. deg. unsat: $C_{17}H_{36}$ - $C_{17}H_{10(14-0-4)}$ = H_{26} => $H_{26}/2$ = 13 deg.
no. DB = 13 - 3 rings = 10.



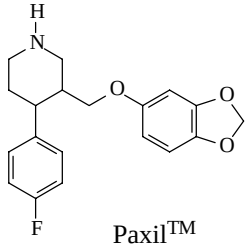
rofecoxib

e. no. deg. unsat: $C_{19}H_{40}$ - $C_{19}H_{16(17+2-3)}$ = H_{24} => $H_{24}/2$ = 12 deg.
no. rings = 12 - 8 DB = 4.



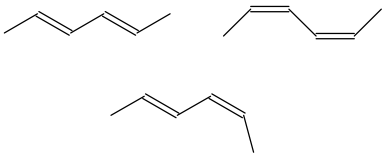
floxacillin

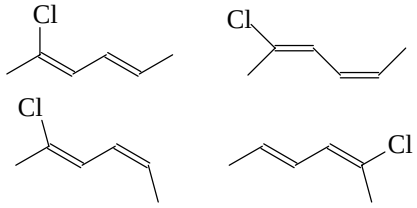
f. no. deg. unsat: $C_{19}H_{40}$ - $C_{19}H_{20(20+1-1)}$ = H_{20} => $H_{20}/2$ = 10 deg.
hydrogenation: $C_{19}H_{32}FNO_3$ - $C_{19}H_{20}FNO_3$ = H_{12} => $H_{12}/2$ = 6 DB
no. rings = 10 - 6 DB = 4.



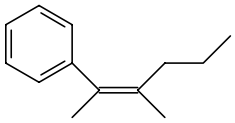
Paxil™

7. number of stereoisomers for 2,4-hexadiene: 3; for 2-chloro-2,4-hexadiene: 4.



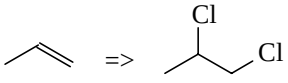


8. a.



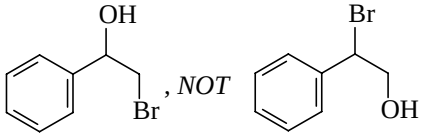
(Z)-3-methyl-2-phenyl-2-hexene

b.



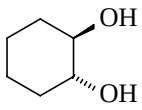
propylene dichloride
(note: *no* double bond)

c.



styrene bromohydrin

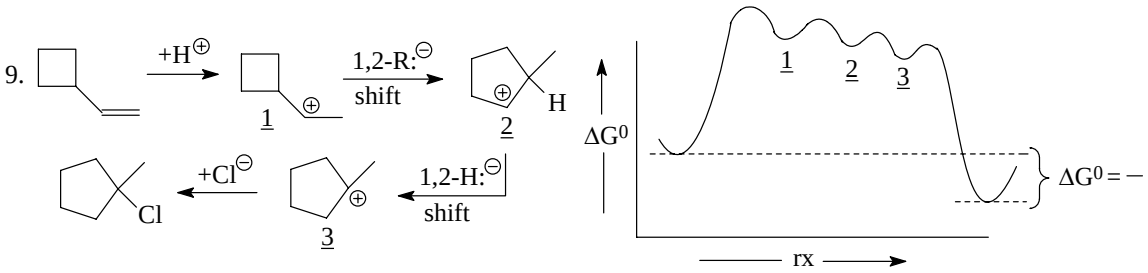
d.

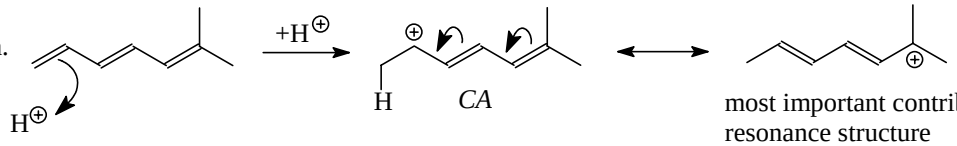


trans-cyclohexene glycol

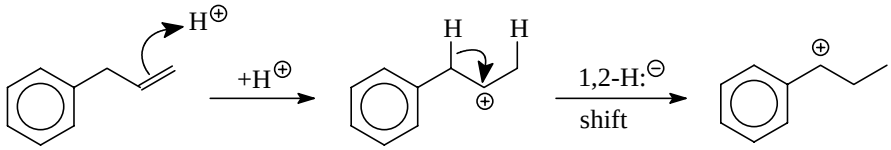
e.

isobutylene epoxide

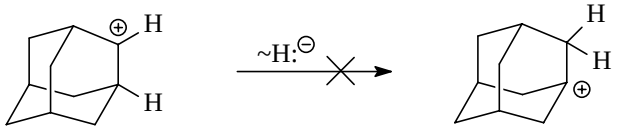
9. 

10. a. 

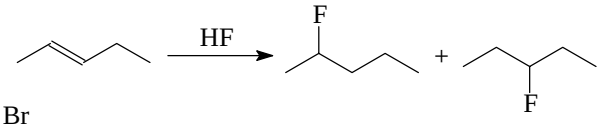
most important contributing resonance structure

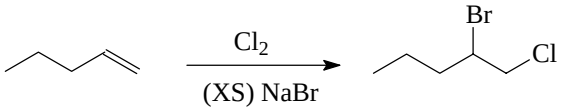
b. 

most stable intermediate: benzylic carbocation

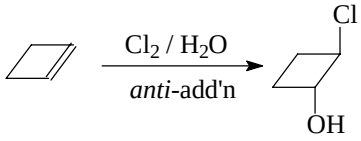
11. 

rigidity of the carbon skeleton prevents carbocation from being planar

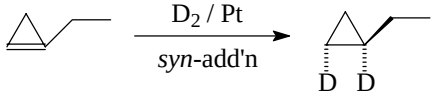
12. neither regiospecificity nor stereospecificity: a. 

b. 

regiospecific

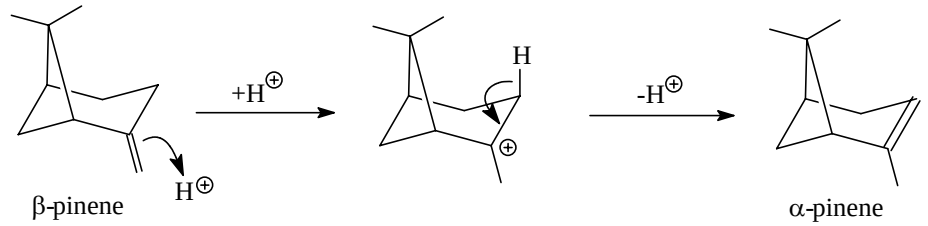
c. 

stereospecific

d. 

stereospecific

13.



β-pinene

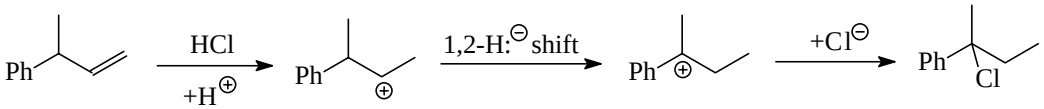
α-pinene

more highly substituted double bond => more stable olefin

therefore, $K_{eq} >> 1$

5.2 Reactions

1.



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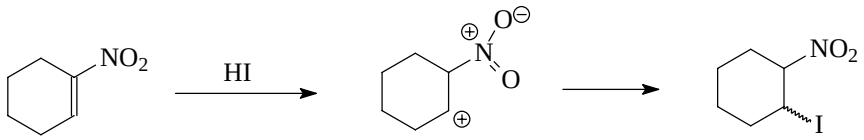

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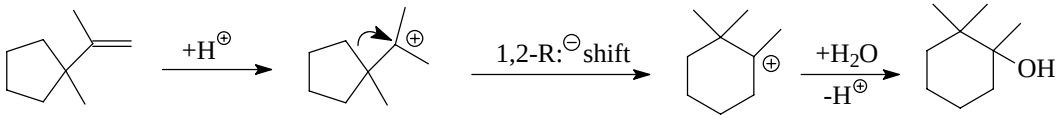

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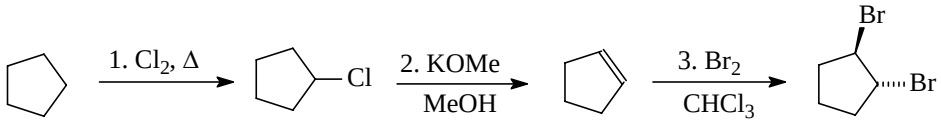

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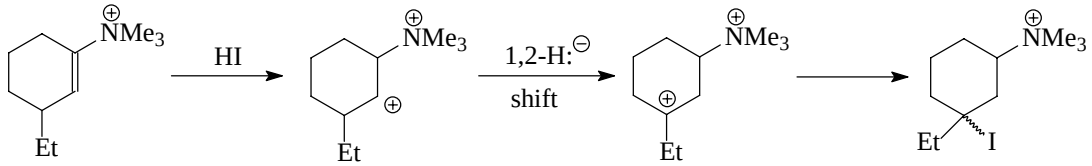

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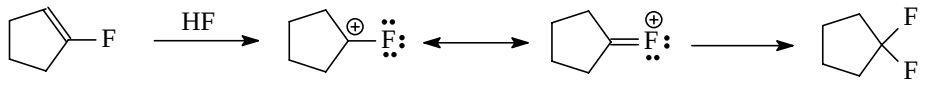

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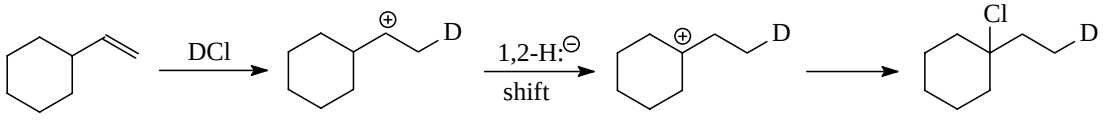
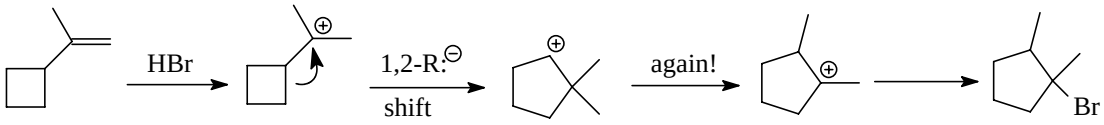
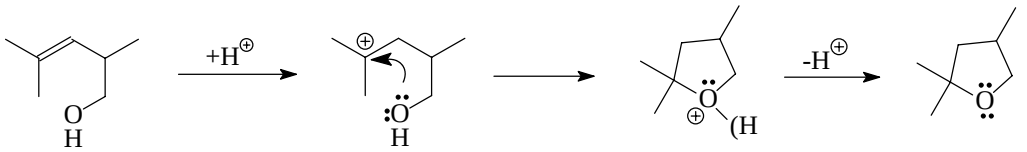
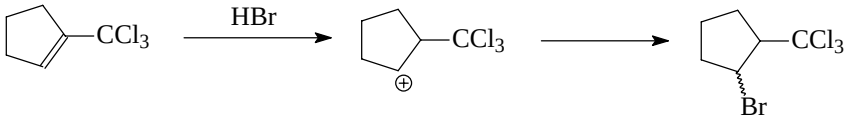
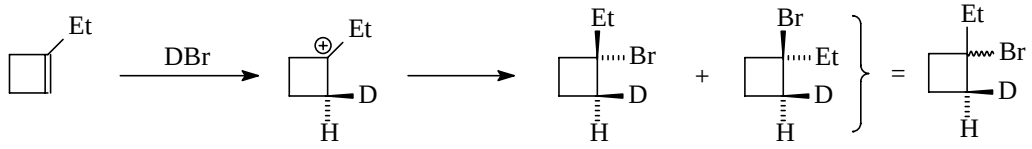
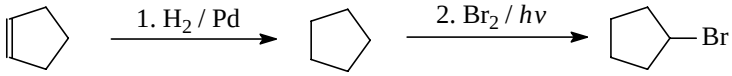


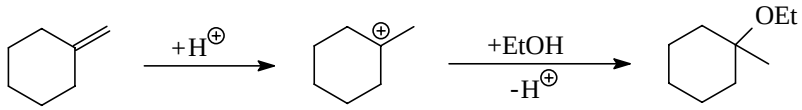
8. 

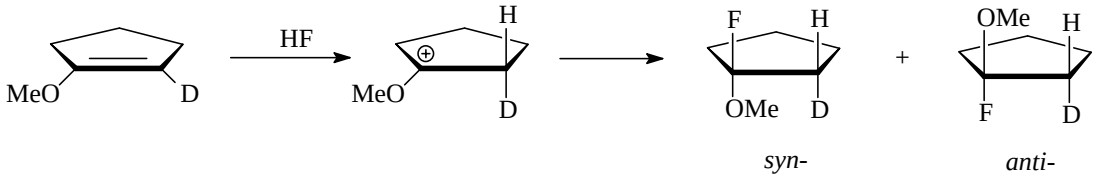
9. 

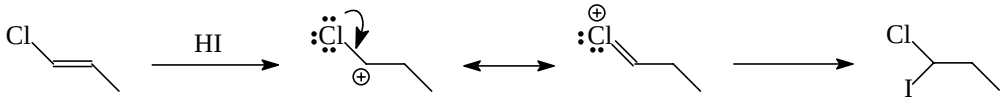
10. 

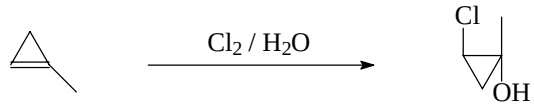
11. 

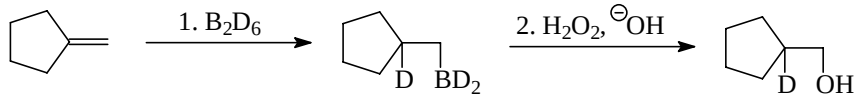
12. 

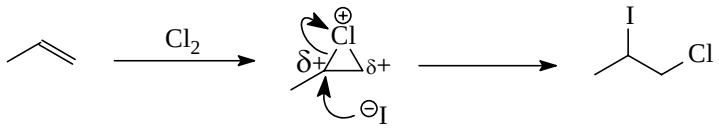
13. 

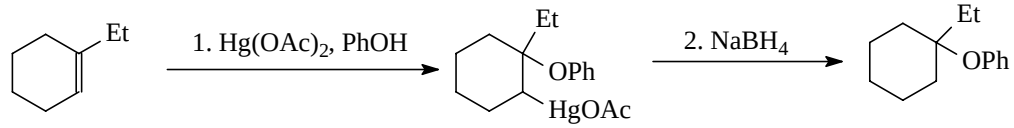
14. 

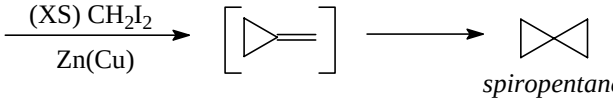
15. 

16. 

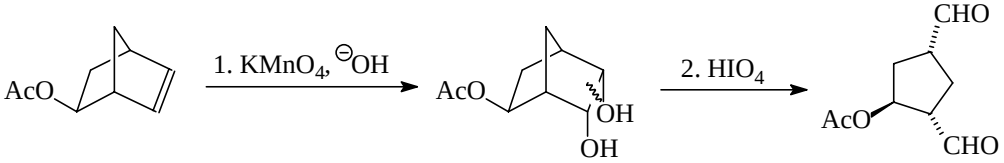
17. 

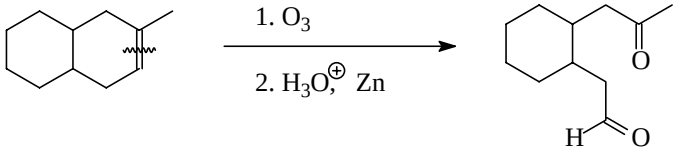
18. 

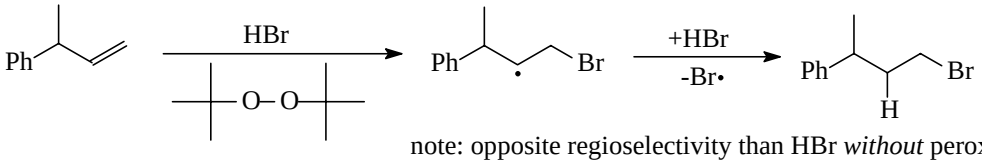
19. 

20. $H_2C{=}C{=}CH_2$ 

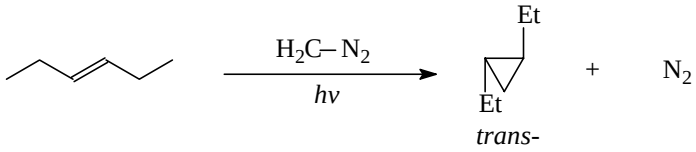
spiropentane

21. 

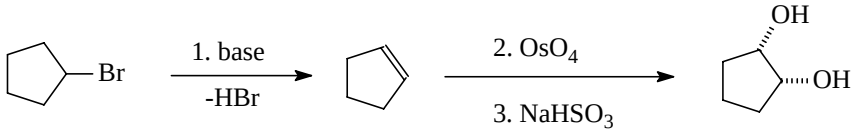
22. 

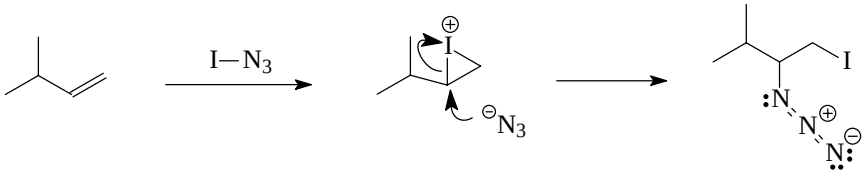
23. 

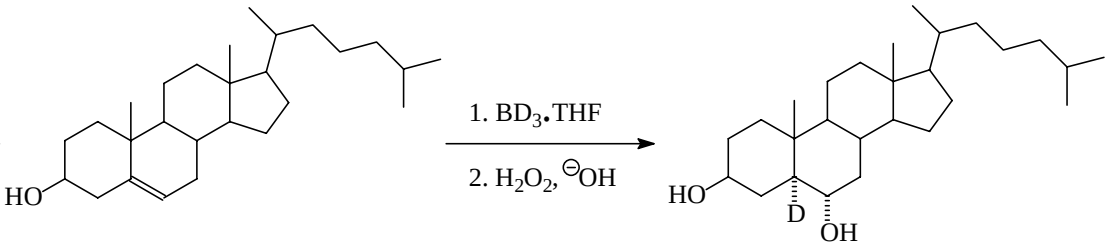
note: opposite regioselectivity than HBr *without* peroxide - and no rearrangement

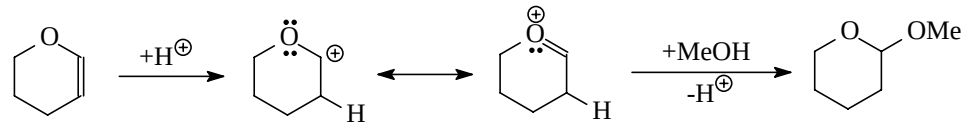
24. 

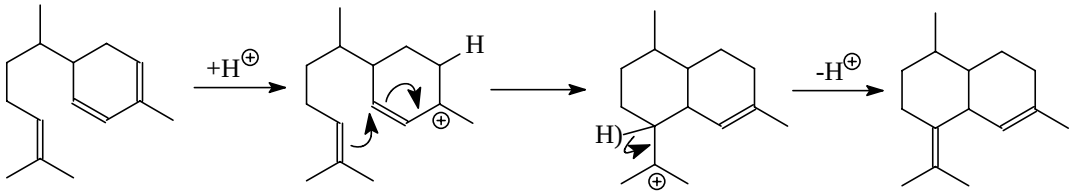
trans-

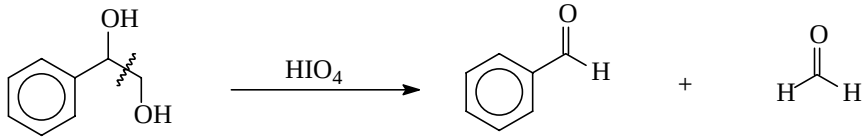
25. 

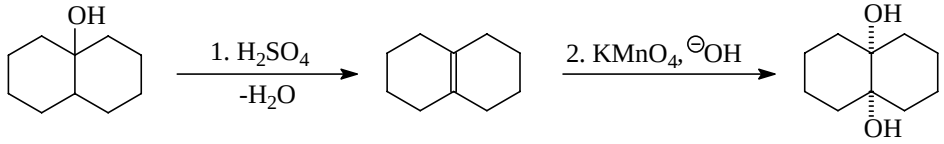
26. 

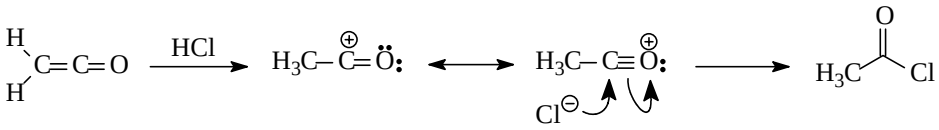
27. 

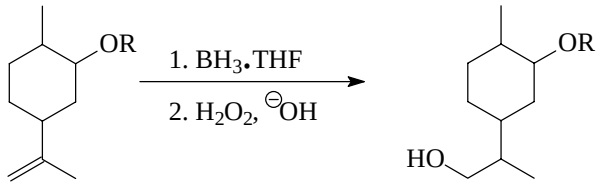
28. 

29. 

30. 

31. 

32. 

33. 

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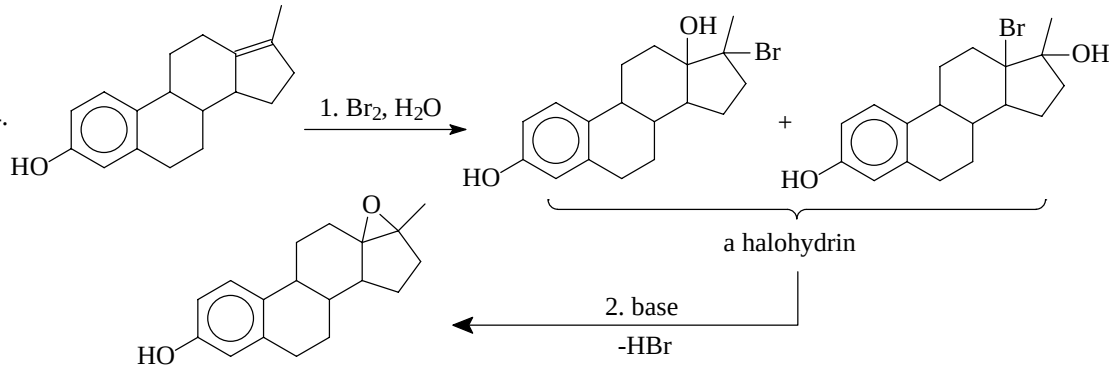

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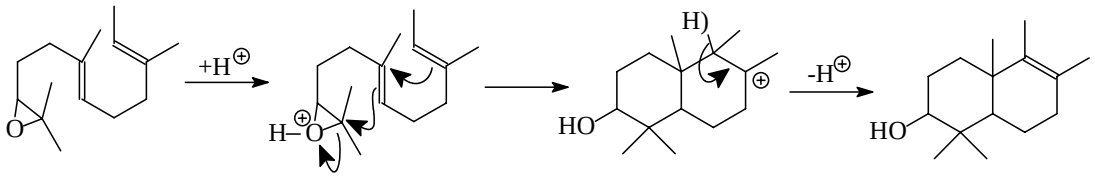

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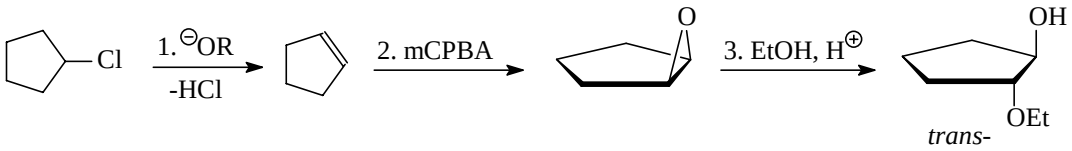
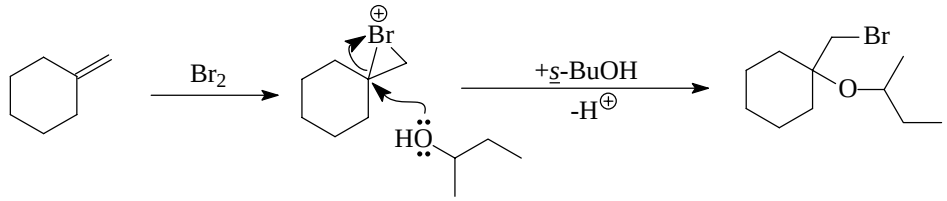


trans-

37.



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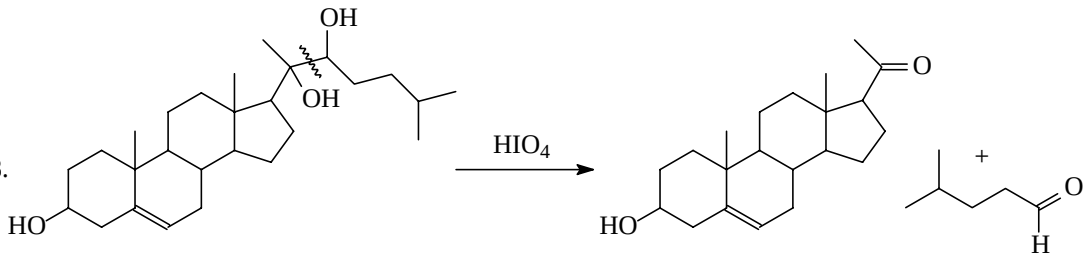

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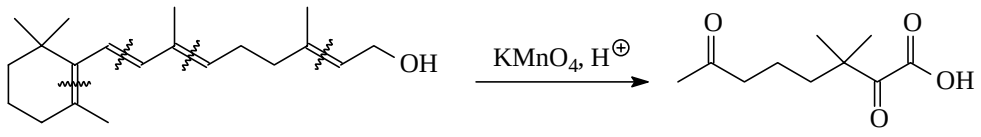
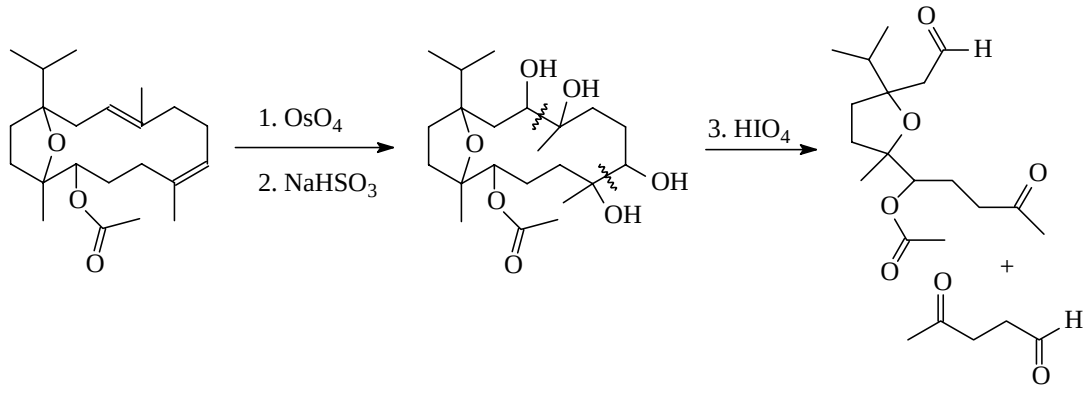
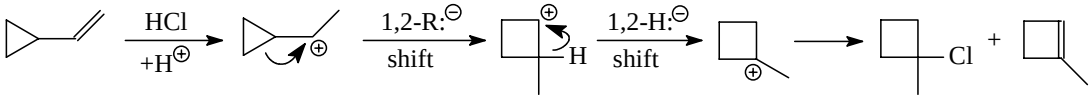
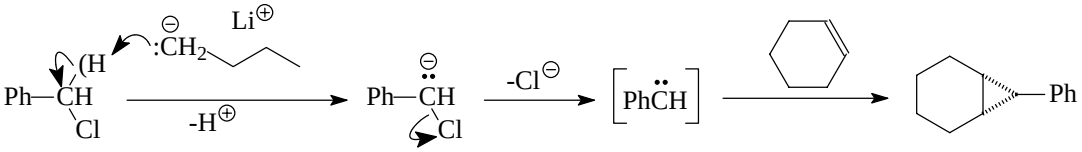


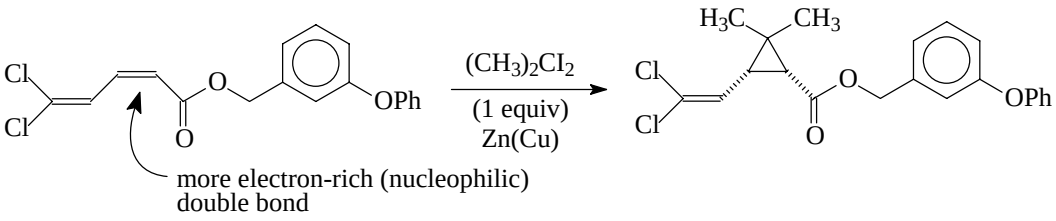
largest C-containing product

40. 

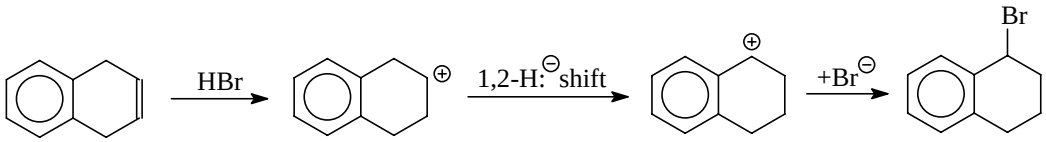
41. 

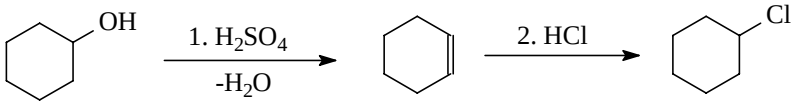
42. 

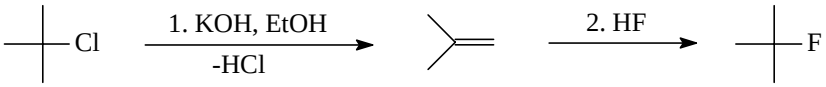
a 1,1- (or α-) elimination to produce a carbene

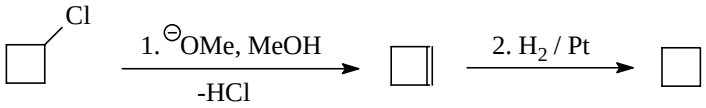
43. 

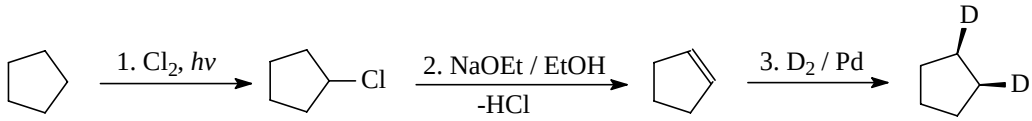
5.3 Syntheses

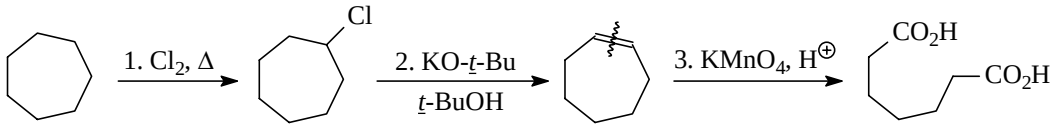
1. 

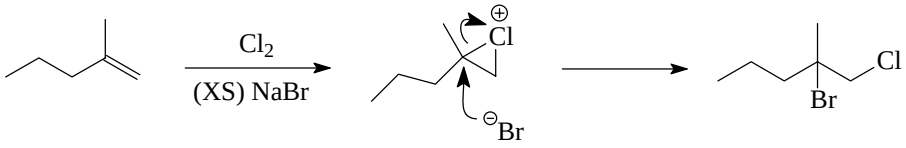
2. 

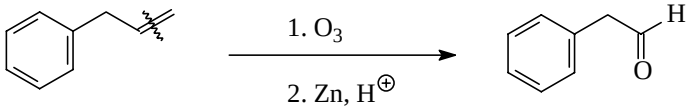
3. 

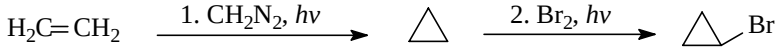
4. 

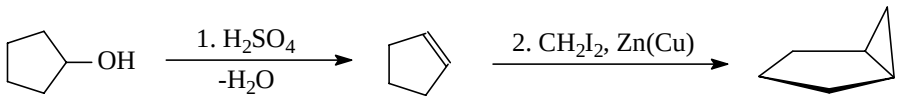
5. 

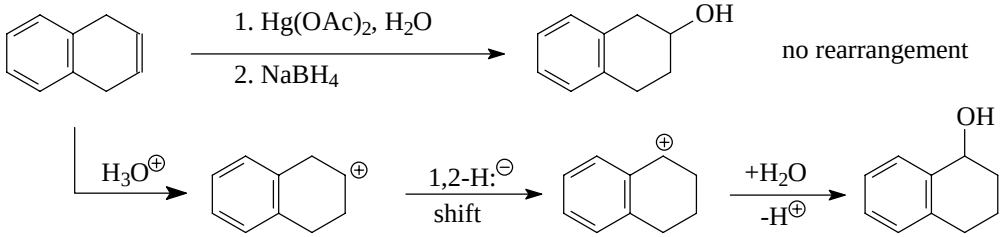
6. 

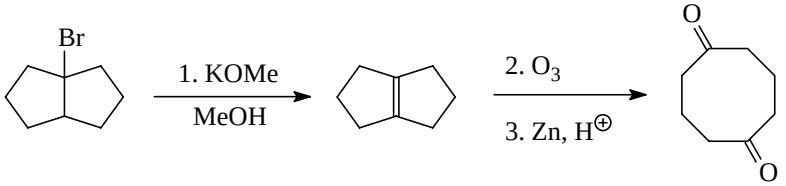
7. 

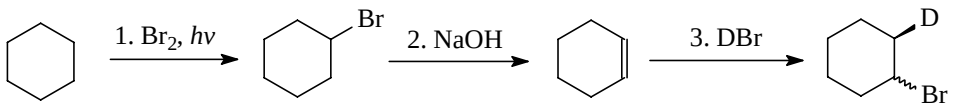
8. 

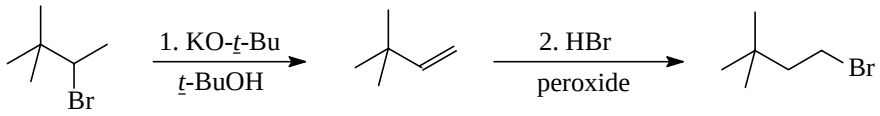
9. 

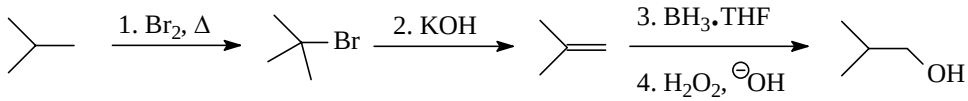
10. 

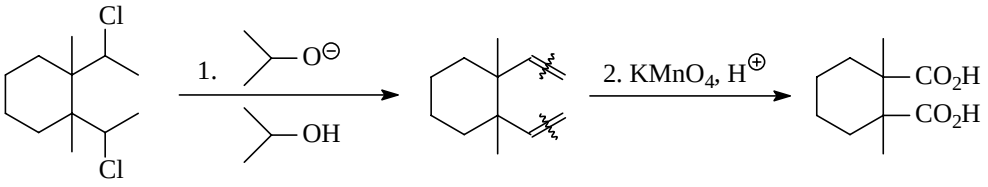
11. 

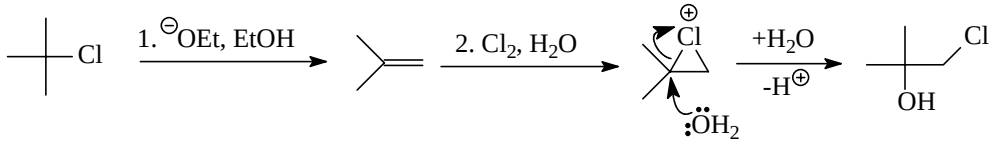
12. 

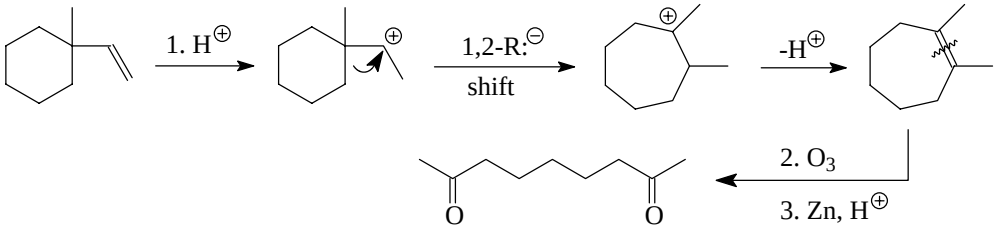
13. 

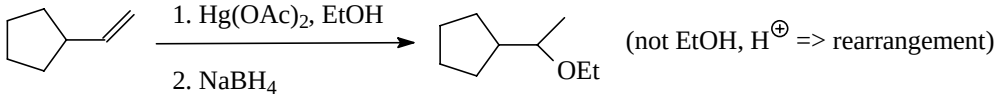
14. 

15. 

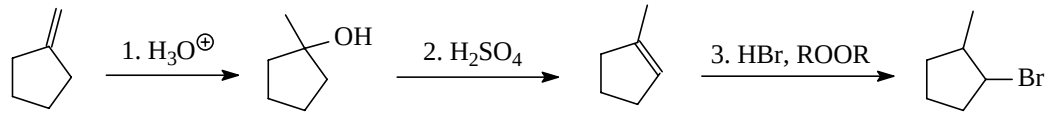
16. 

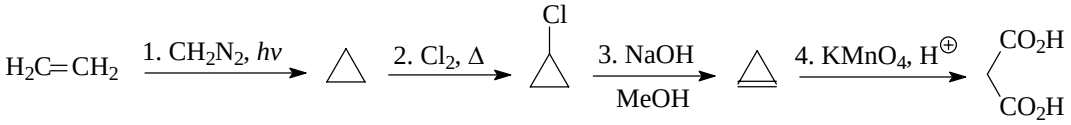
17. 

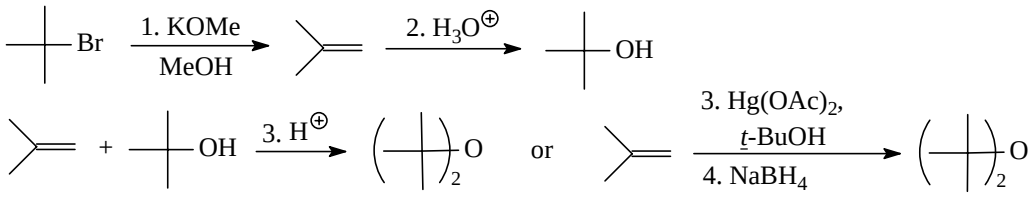
18. 

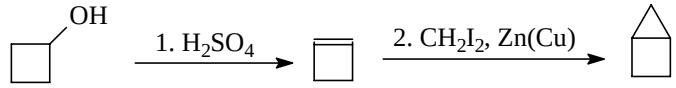
19. 

(not EtOH, $H^{\oplus}$ => rearrangement)

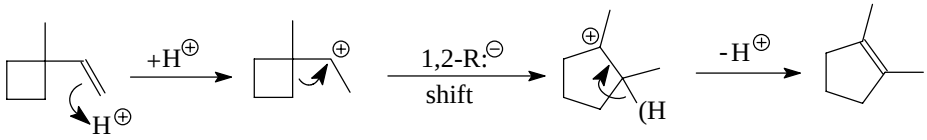
20. 

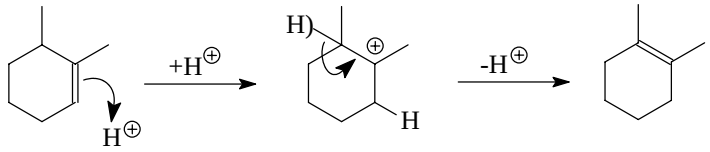
21. 

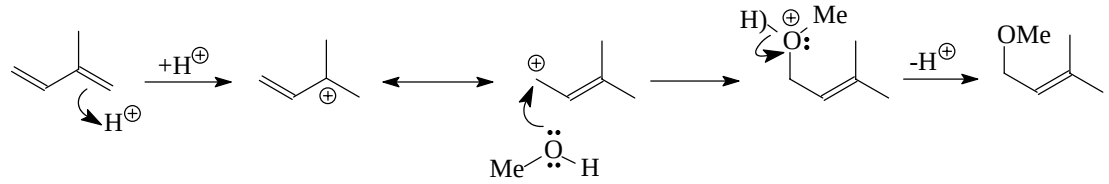
22. 

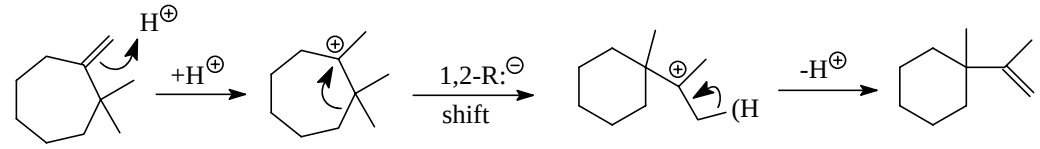
23. 

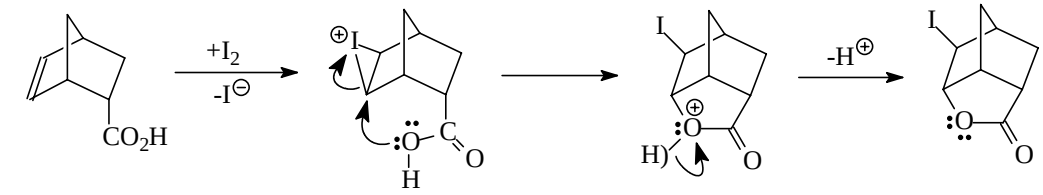
5.4 Mechanisms

1. 

2. 

3. 

4. 

5. 

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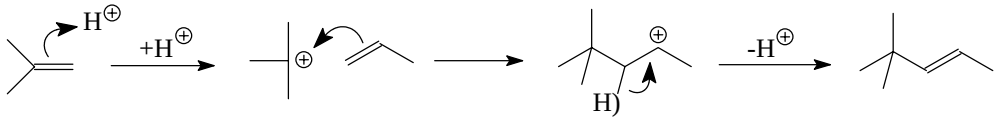
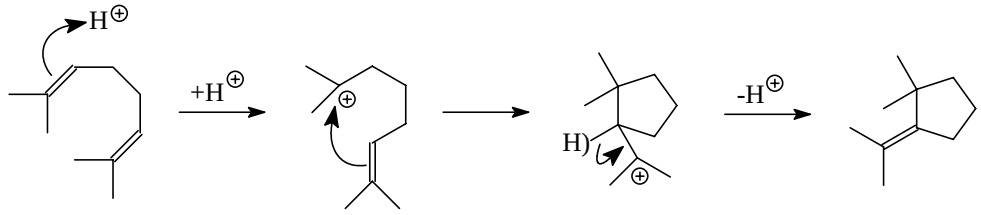
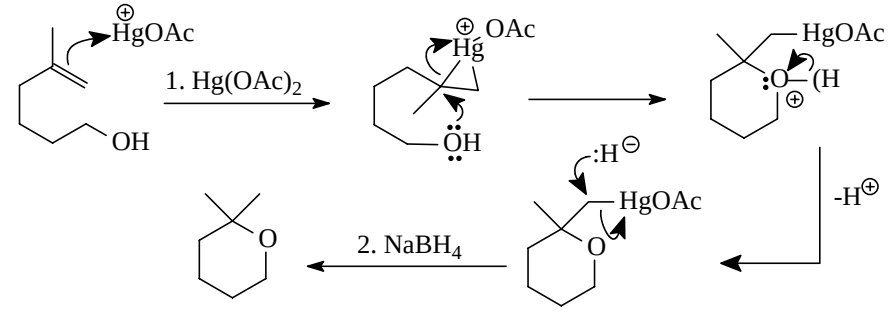

H⊕
+H⊕
H)
-H⊕

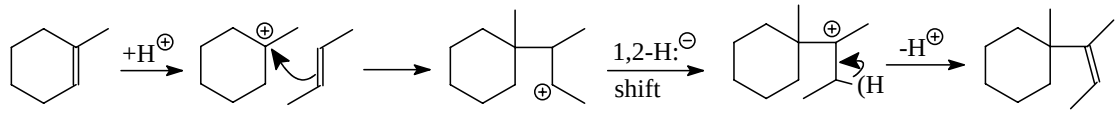
7.


H⊕
+H⊕
H)
-H⊕

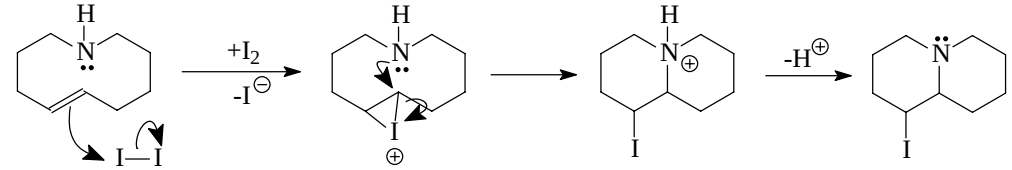
8.


HgOAc
1. Hg(OAc)2
OAc
Hg
OH
HgOAc
O
(H
:H⊖
HgOAc
-H⊕
O
2. NaBH4
O

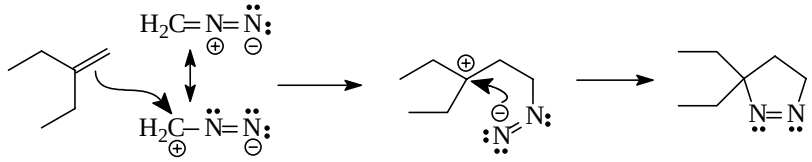
9.


+H⊕
1,2-H:⊖
shift
(H
-H⊕

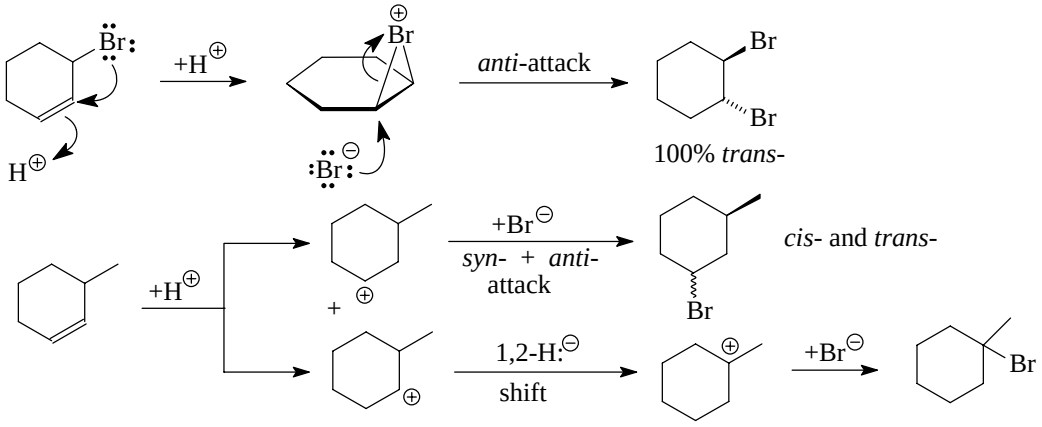
10.


H
N
I—I
+I2
-I⊖
-H⊕
I

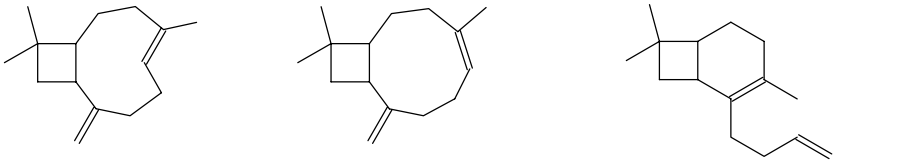
11.


H2C=N=N:
H2C–N=N:
N=N

12.

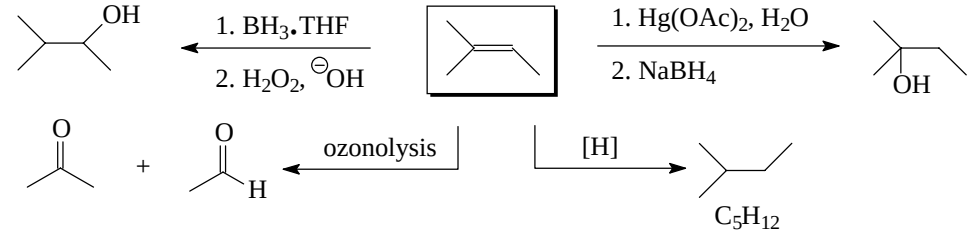


13. **A** is C_{14} => other aldehyde is CH_2O; no. deg. unsat: $C_{15}H_{32}$ - $C_{15}H_{24}$ = H_8 => $H_8/2$ = 4 deg.
hydrogenation: $C_{15}H_{28}$ - $C_{15}H_{24}$ = H_4 => $H_4/2$ = 2 DB; therefore, 2 rings are present

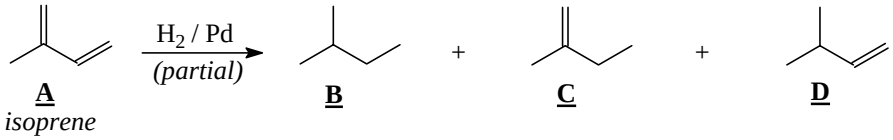


caryophyllene *isocaryophyllene* incorrect: cannot exist in *cis*/*trans* forms

14.

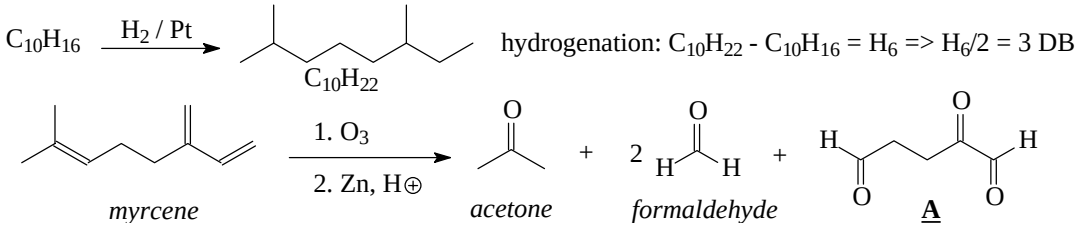


15.



A *isoprene* **B** **C** **D**

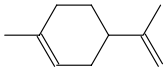
16. no. deg. unsat: $C_{10}H_{22}$ - $C_{10}H_{16}$ = H_6 => $H_6/2$ = 3 deg.

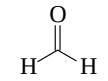


myrcene *acetone* *formaldehyde* **A**

17. hydrogenation: $C_{10}H_{20}$ - $C_{10}H_{16}$ = H_4 => $H_4/2$ = 2 DB **A** =

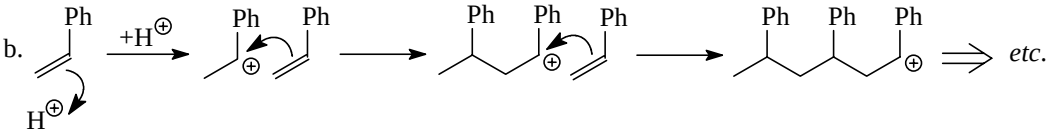
B **A**

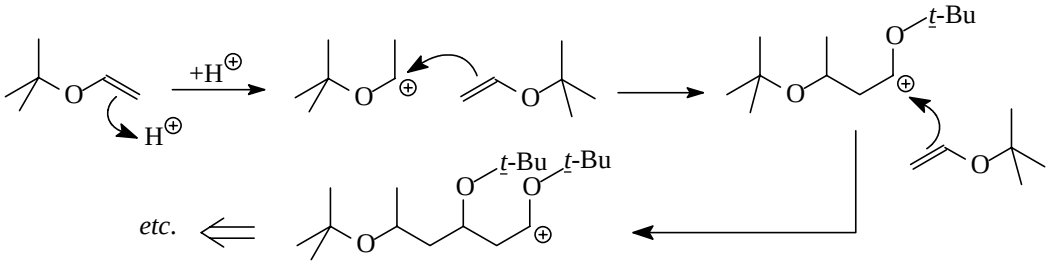


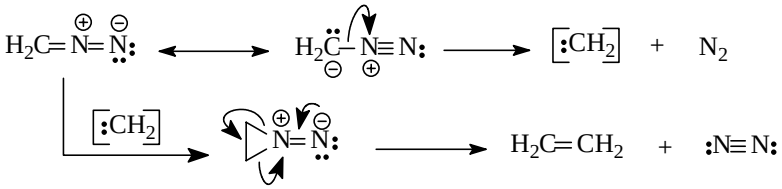


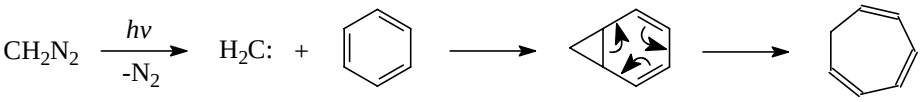
other ozonolysis product

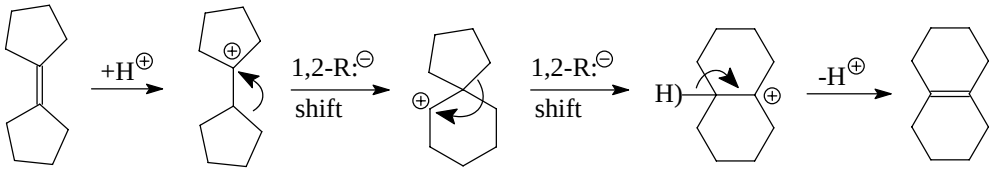
18. a. *n*  *poly(methyl methacrylate)*

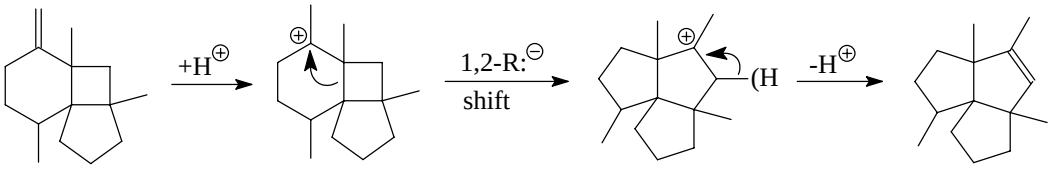
b. 

19. 

20. 

21. 

22. 

23. 

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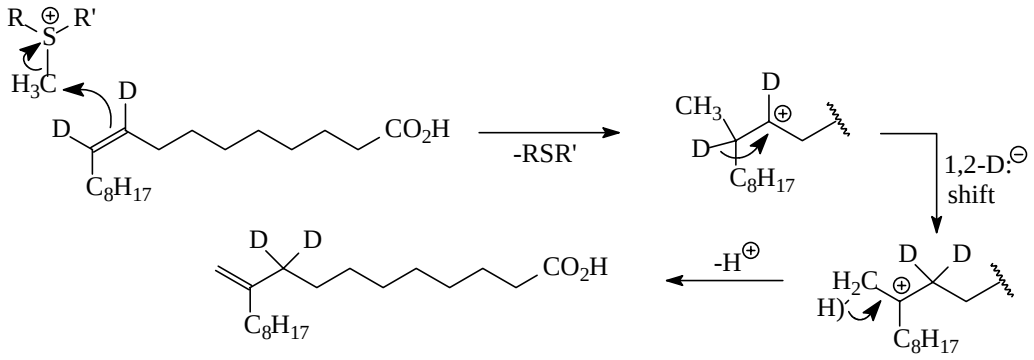

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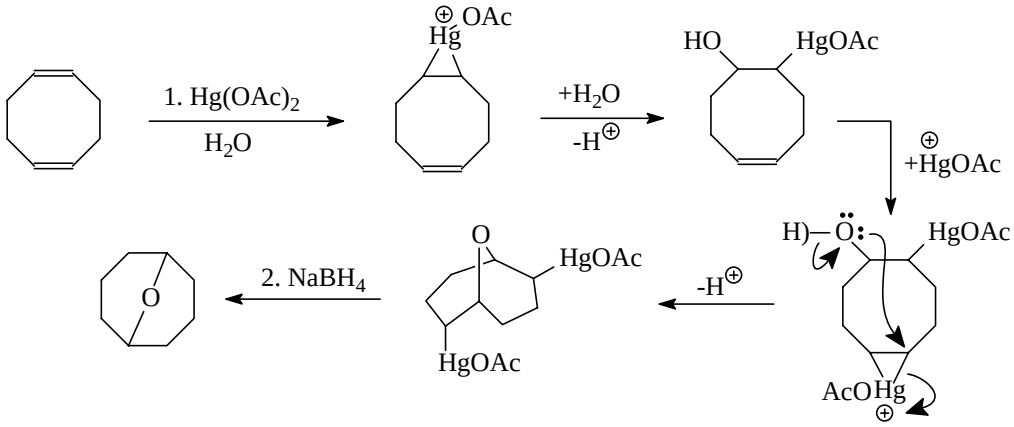
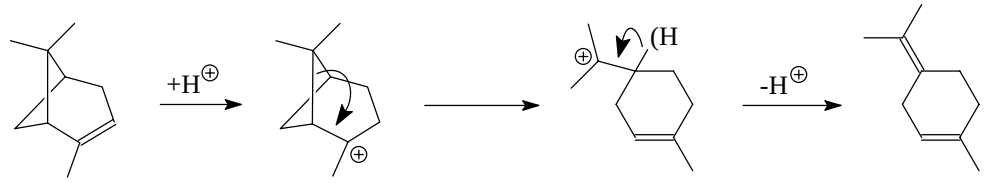
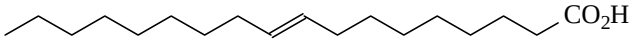


26.

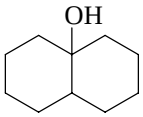


27.  => *trans*- DB

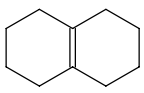


elaidic acid

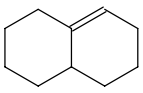
28. a.



A



B



C

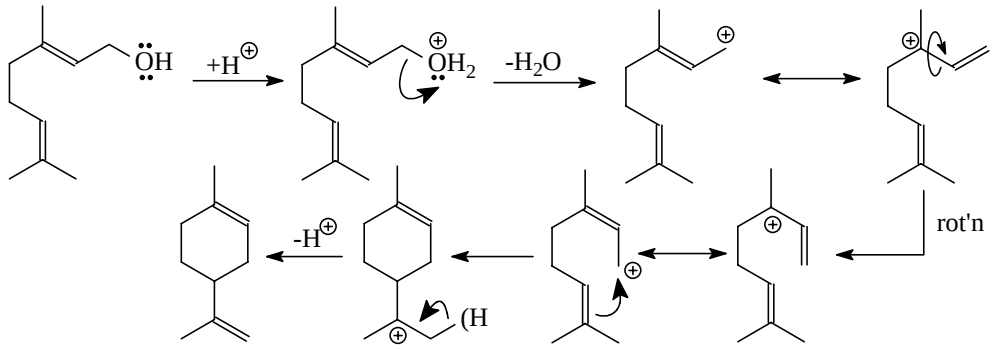
b.

A $\xrightarrow{Br_2}$ NR (deep red color of bromine persists); **B** or **C** $\xrightarrow{Br_2}$ color discharged

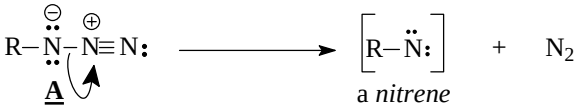
or Baeyer test:

A $\xrightarrow{KMnO_4}$ NR (purple color of $MnO_4^{\ominus}$ persists); **B** or **C** $\xrightarrow{KMnO_4}$ brown ppt (MnO_2) forms

29.

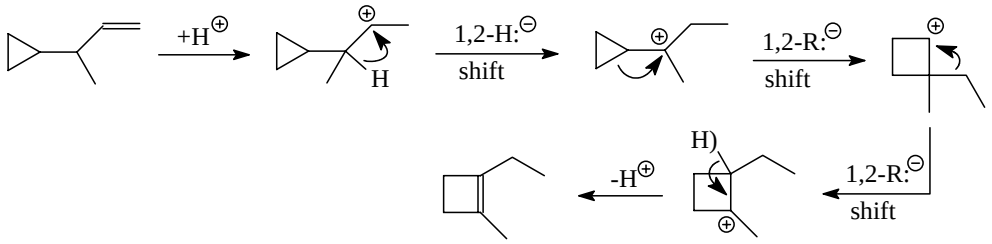


30. a., b.



c. *retention of configuration* suggests a concerted (or pericyclic) mechanism

31.



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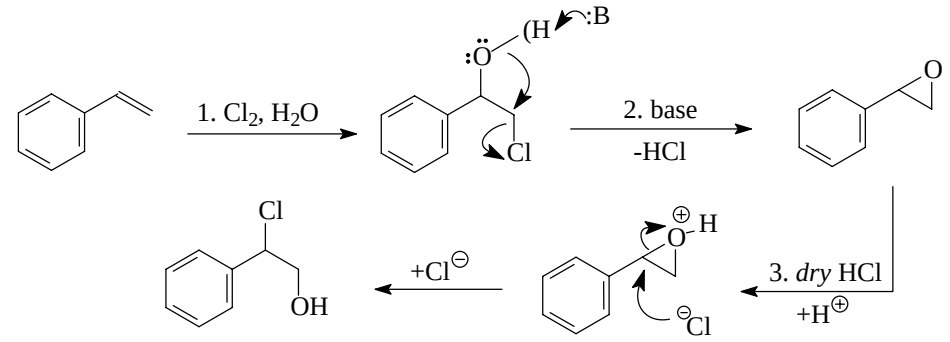
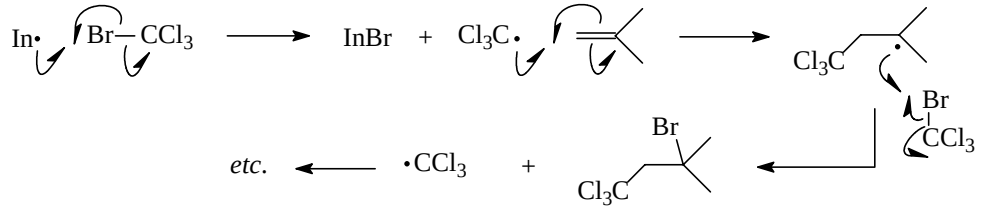


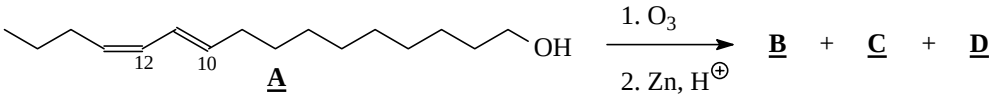
33.



(this mechanism is similar to the addition of HBr in the presence of peroxides)

34. a. no. deg. unsat: $C_{16}H_{34}$ - $C_{16}H_{30}$ = H_4 => $H_4/2$ = 2 deg.
hydrogenation: $C_{16}H_{34}O$ - $C_{16}H_{30}O$ = H_4 => $H_4/2$ = 2 DB

c. **E** => a *cis*- DB at C_{12}; **F** => a *trans*-DB at C_{10}



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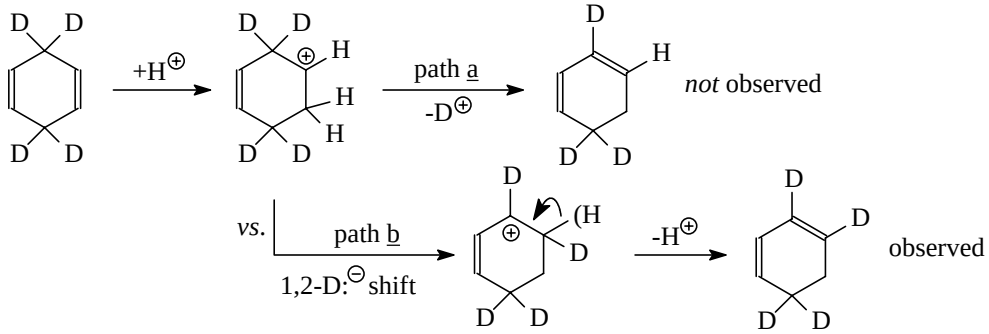
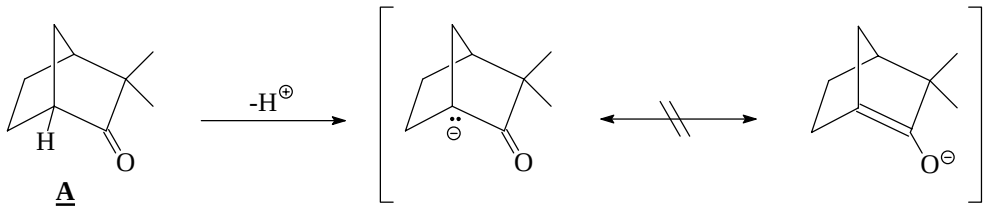


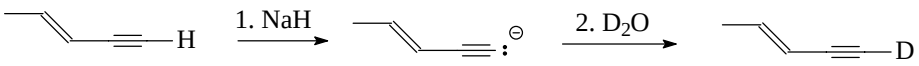
therefore, path b is favored

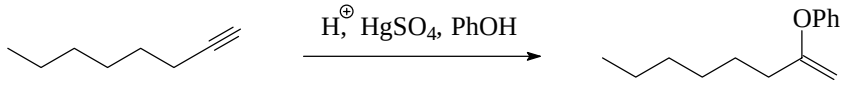
36. The rigidity of the bicyclic structure in the conjugate base of **A** prevents delocalization of the negative charge onto oxygen: such a contributing resonance structure would violate Bredt's rule (the olefinic region cannot be planar). Loss of this stabilization prevents the carbanion from forming (pK_a of **A** is raised relative to cyclohexanone), as required by the proposed mechanism, and therefore prevents hydrogen-deuterium exchange.

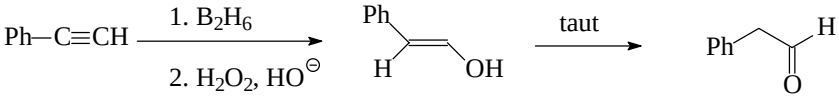


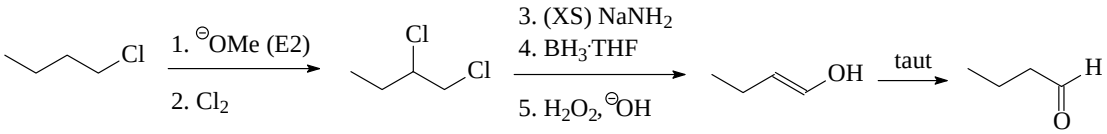
CHAPTER 6
ALKYNES

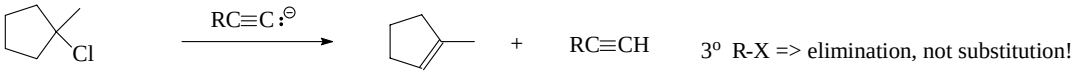
6.1 Reactions

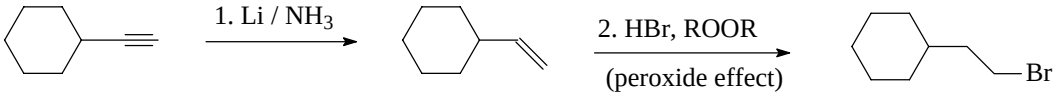
1. 

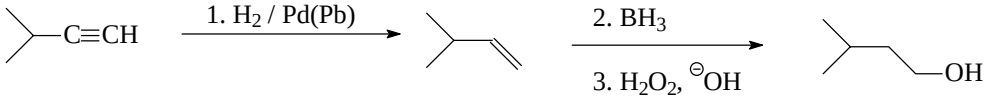
2. 

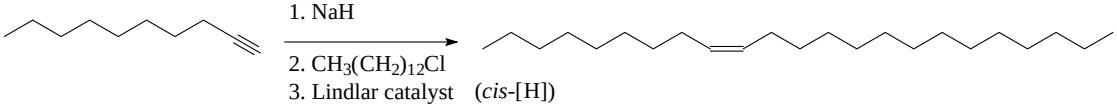
3. 

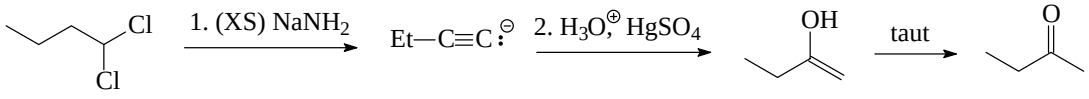
4. 

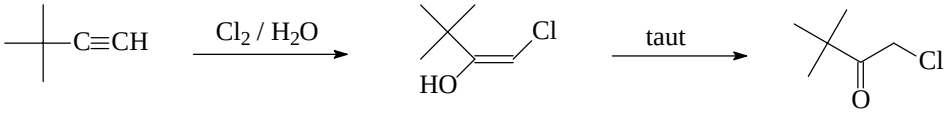
5. 

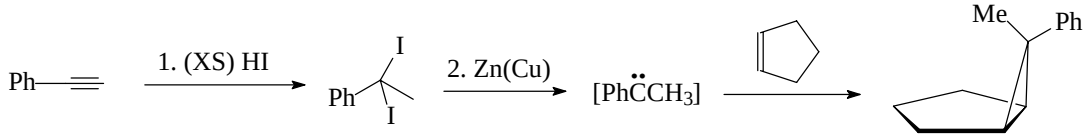
6. 

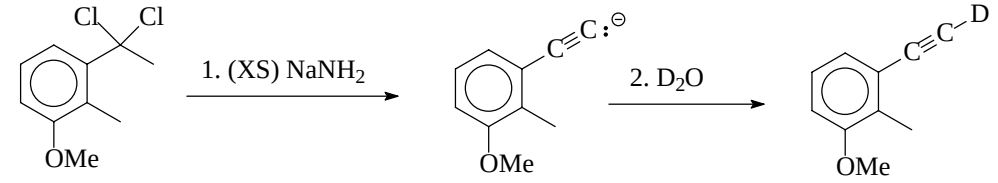
7. 

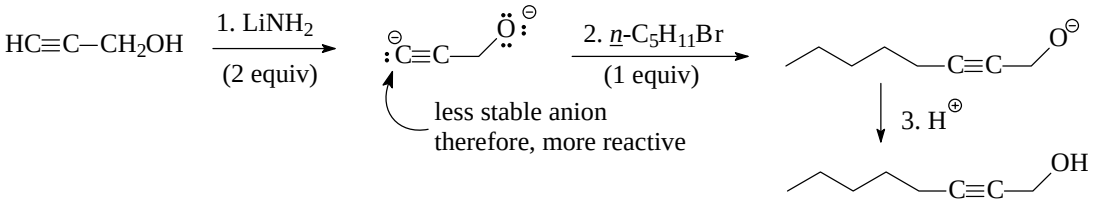
8. 

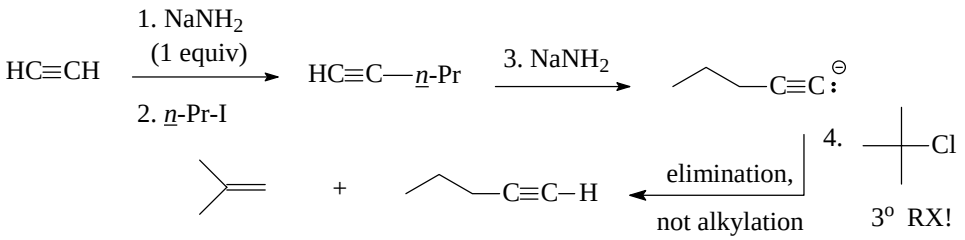
9. 

10. 

11. 

12. 

13. 

14. 

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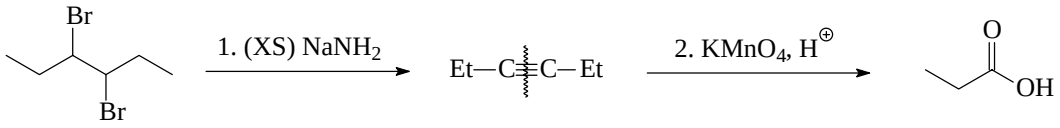
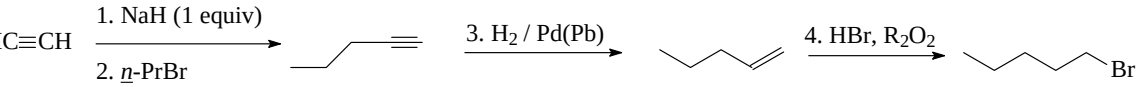
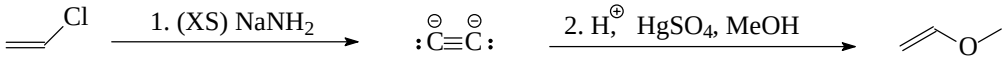
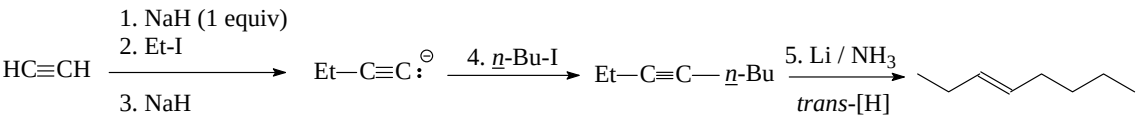
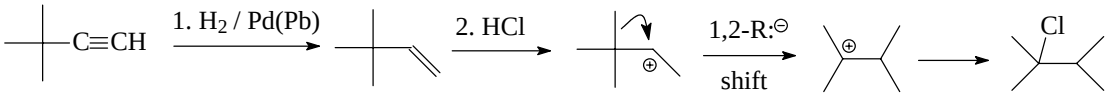
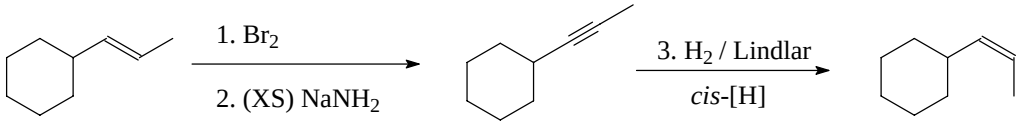
1. 

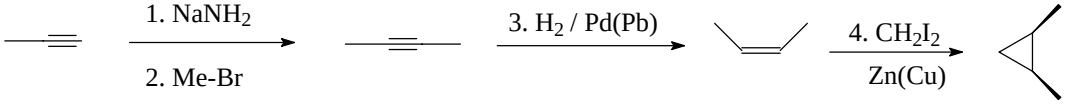
2. 

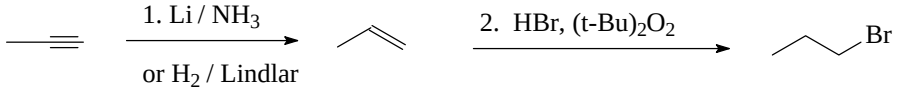
3. 

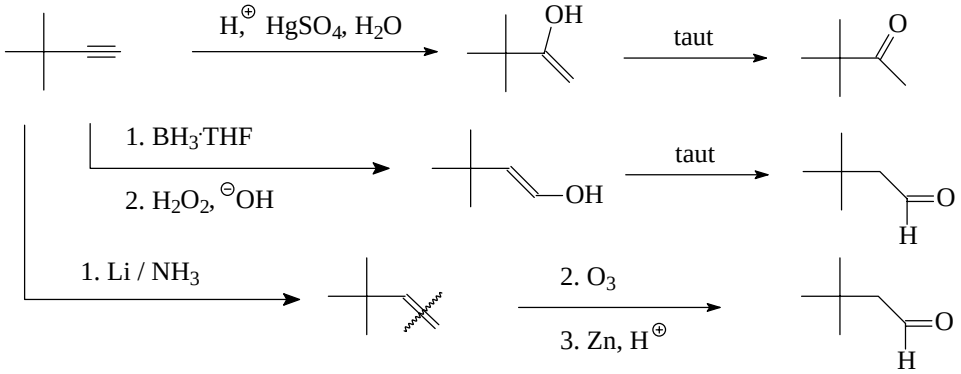
4. 

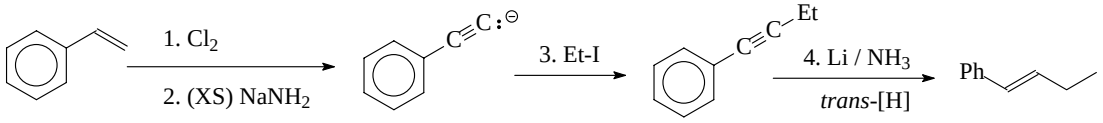
5. 

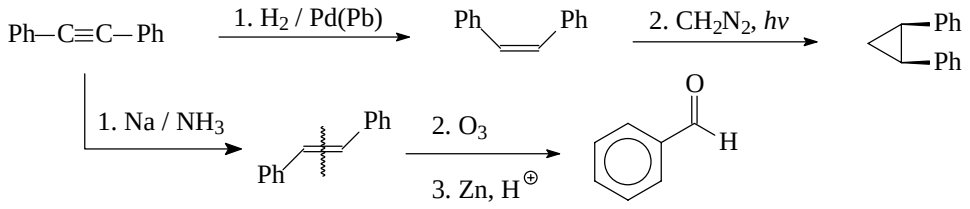
6. 

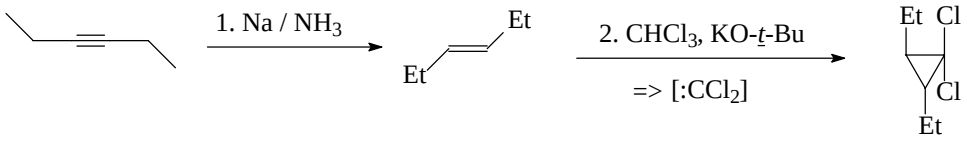
7. 

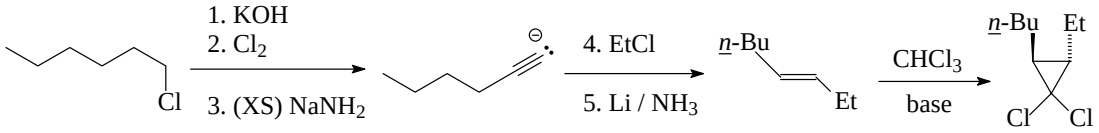
8. 

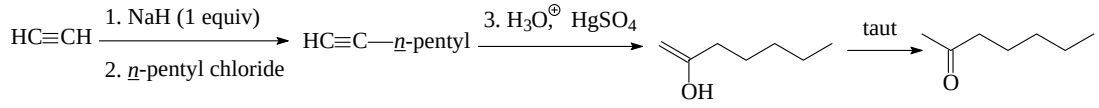
9. 

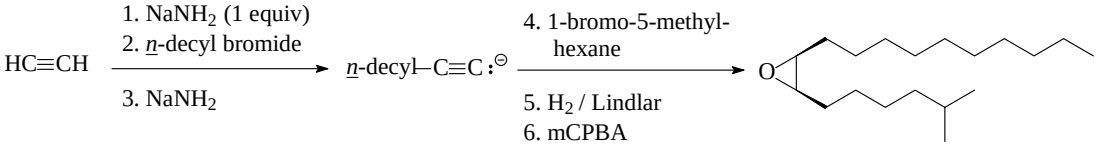
10. 

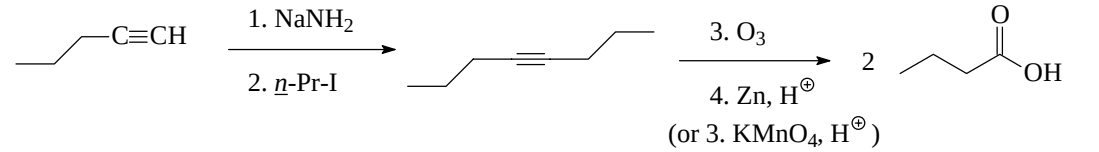
11. 

12. 

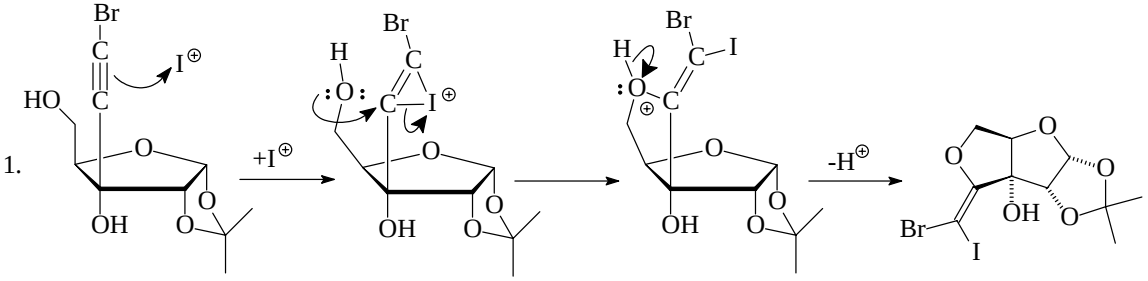
13. 

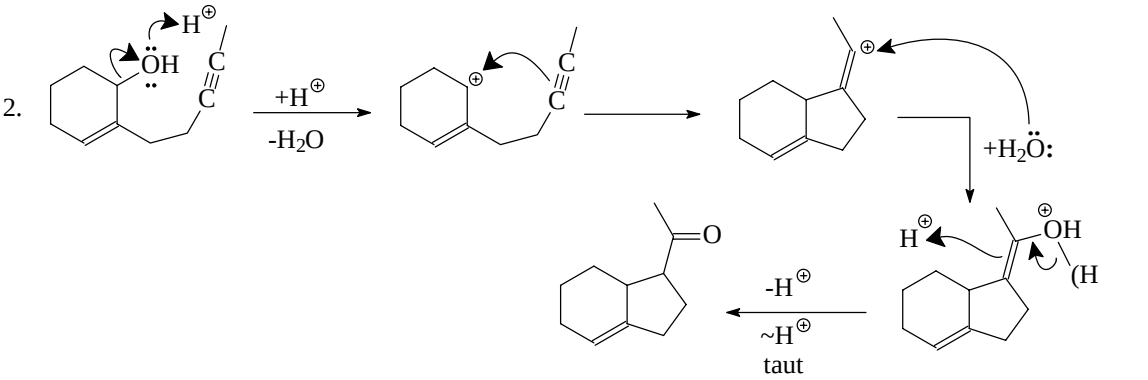
14. 

15. 

16. 

6.3 Mechanisms

1. 

2. 

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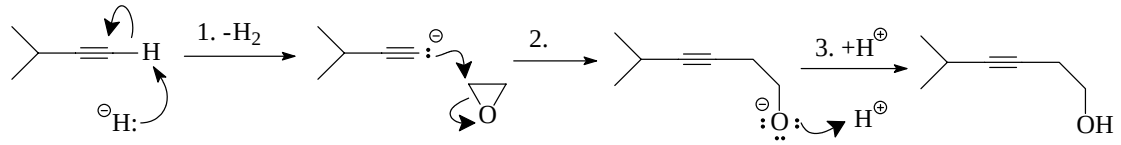
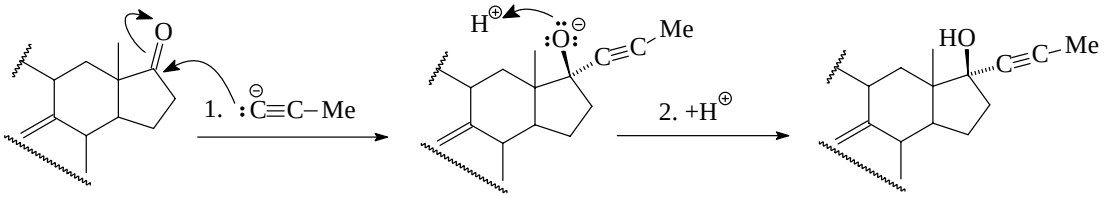
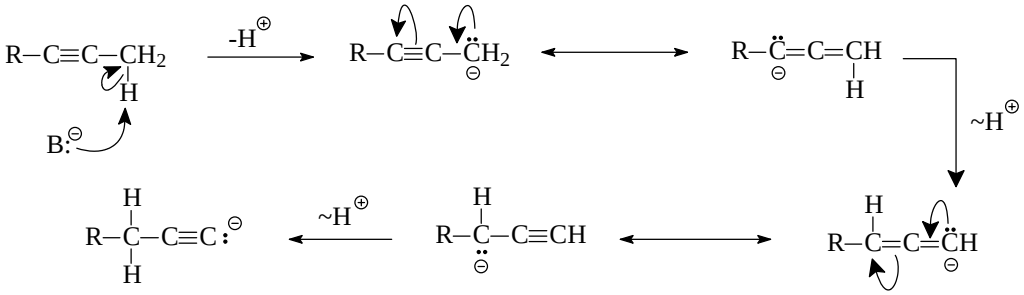

1. -H2
2.
3. +H
H
H:
O
OH

4.


O
1.
C≡C–Me
H
Me
HO
2. +H

5.


R–C≡C–CH2
H
B:
-H
R–C≡C–CH2
R–C=C=CH
H
~H
R–C–C≡C
H
~H
R–C–C≡CH
H
R–C=C=CH
H

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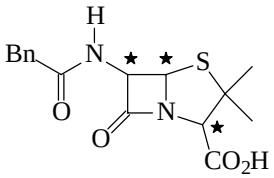
CHAPTER 7
STEREOCHEMISTRY

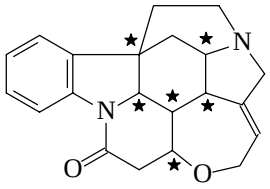
7.1 General

1. chiral molecules: a, b, f, h, and l.

2. a. 3.



b. 6.



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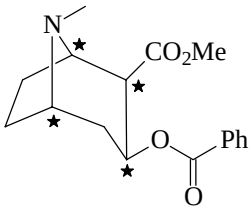
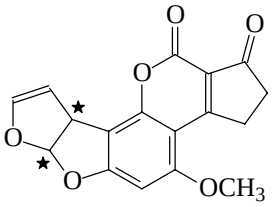


d. 2.



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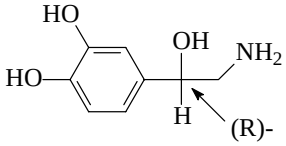
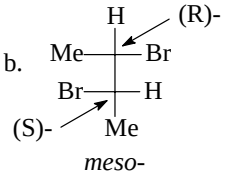
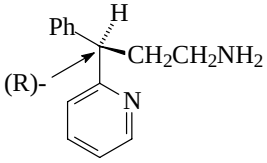


b.



meso-

c.



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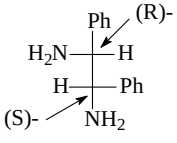
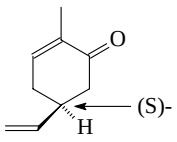
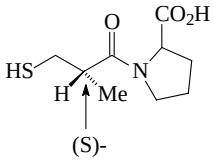


meso-

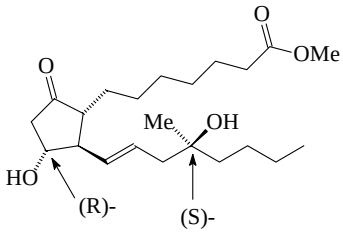
e.



f.



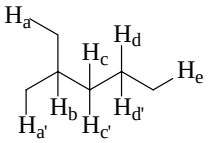
g.



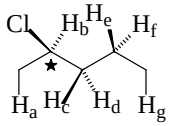
4. a. enantiomers b. enantiomers c. diastereomers d. enantiomers

e. identical f. diastereomers g. enantiomers h. diastereomers

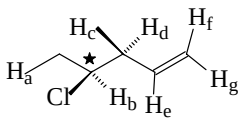
i. enantiomers j. enantiomers

5. a. 8. 

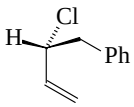
a, a'; c, c'; d, d' are enantiomeric

b. 7. 

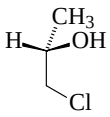
c, d; e, f are diastereomeric

c. 7. 

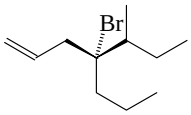
c, d; f, g are diastereomeric

6. a. 

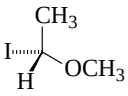
(R)-3-chloro-4-phenyl-1-butene

b. 

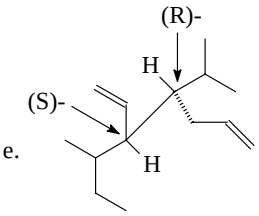
(S)-1-chloro-2-propanol

c. 

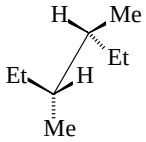
(R)-4-bromo-5-methyl-4-*n*-propyl-1-heptene

d. 

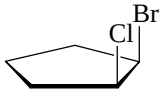
(R)-1-iodoethyl methyl ether

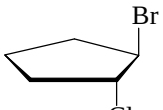
e. 

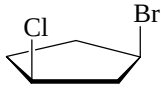
(3S, 4R)-3-*s*-butyl-4-isopropyl-1,6-heptadiene

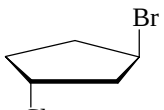
f. 

meso-3,4-dimethylhexane

7. a. 4 pairs. 

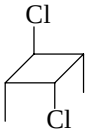
(±) 

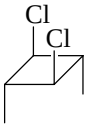
(±) 

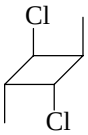
(±) 

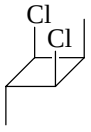
(±)

b. 5. 







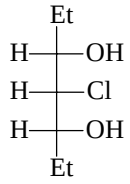


c. 2 pairs. 

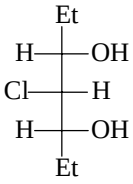
(±) 

(±)

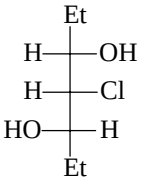
d. 2 *meso*-isomers, 1 pair of enantiomers.



meso-

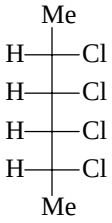


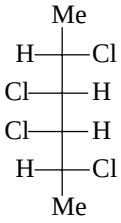
meso'-



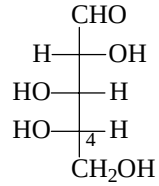
(±)

e. 2 *meso*-isomers.



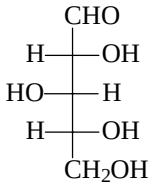


8. a.



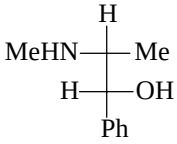
enantiomer of **A**

epimerize at C_4

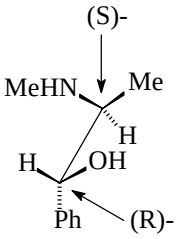


D-xylose

b. i.



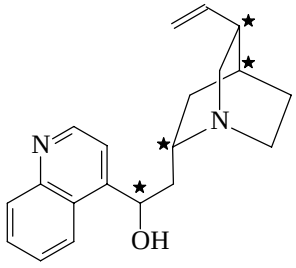
=



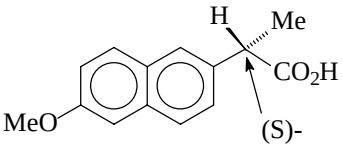
ii. ee = +10° / +40° = 25% (+), 75% (±)
therefore, % (+) = 25% + (75% / 2) = 63%

9. ee = +68° / +170° = 40% (+), 60% (±)
therefore, % (-) = 60% / 2 = 30%

no. chiral carbons: 4.

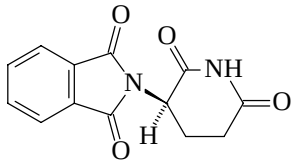


10.

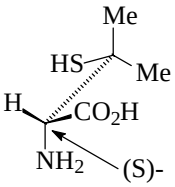


11. a. ED b. D c. ED d. ED e. D f. D

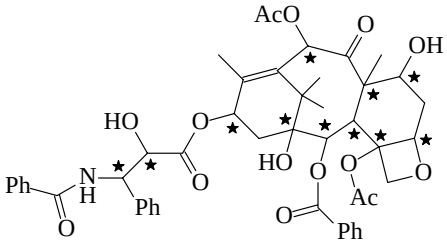
g. E h. ED

12. 

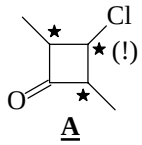
(R)-thalidomide

13. 

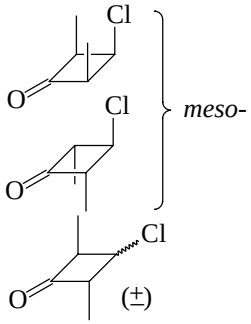
14. a. 11.



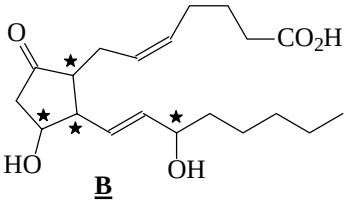
b. ee = +24° / +120° = 20% (+), 80% (±)
therefore, % (+) = 20% + (80% / 2) = 60%

15. 

A



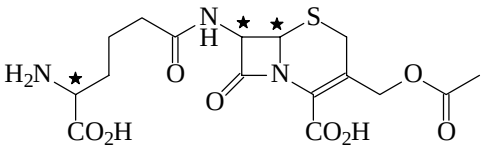
3 chiral carbons, 2 *meso* stereoisomers, 1 pair of enantiomers



B

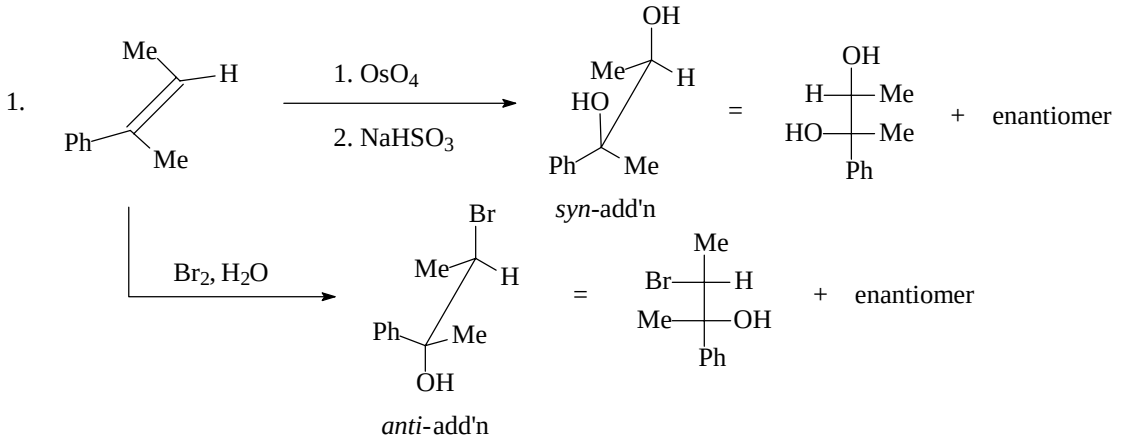
no. stereoisomers: $2^n = 2^4 = 16$.

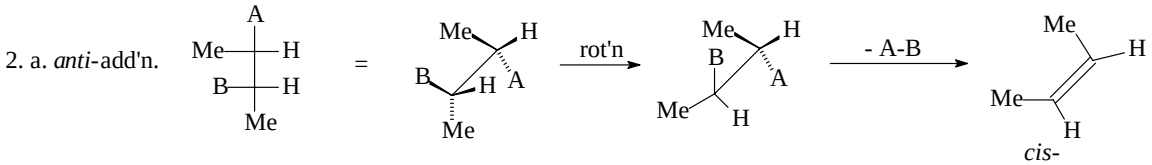
16. a. no. stereoisomers: $2^3 = 8$.

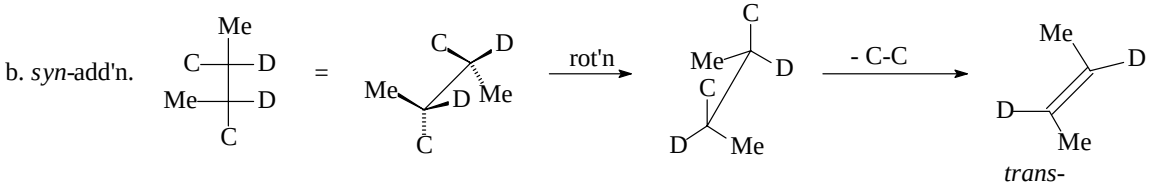


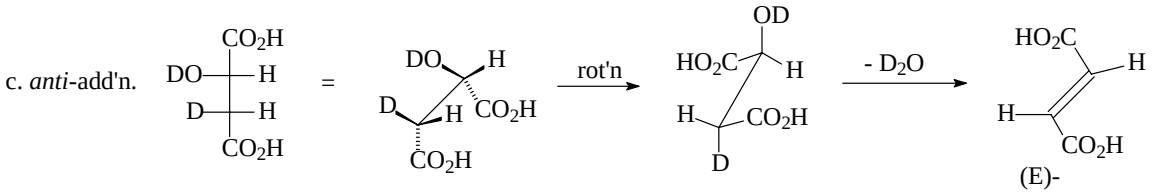
b. ee = +82° / +103° = 80% (+), 20% (±); therefore, % (-) = 20% / 2 = 10%

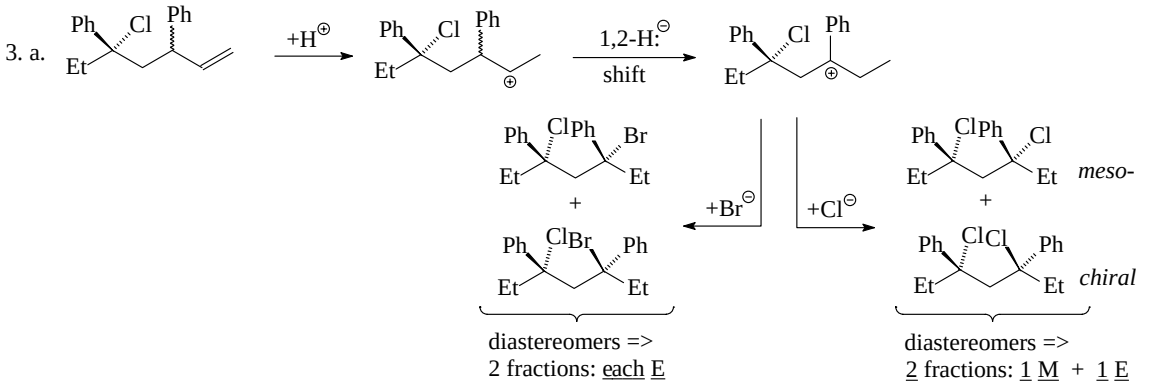
7.2 Reactions and stereochemistry

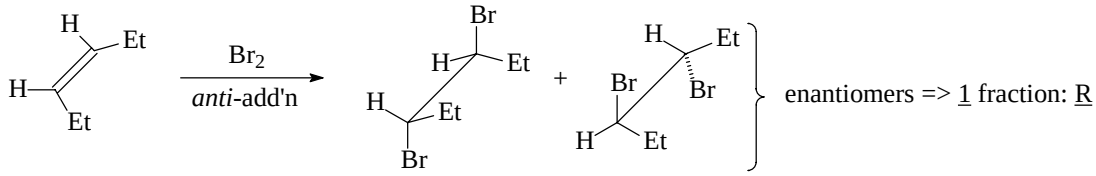




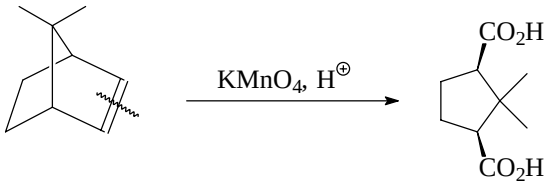




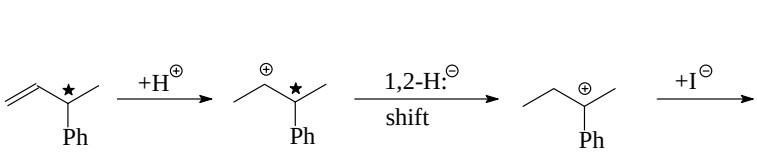


b. 

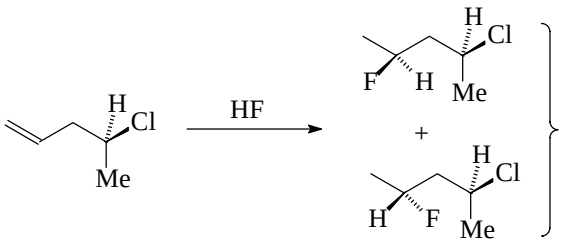
enantiomers => 1 fraction: R

c. 

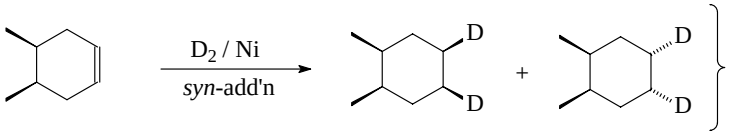
=> 1 fraction: M

d. 

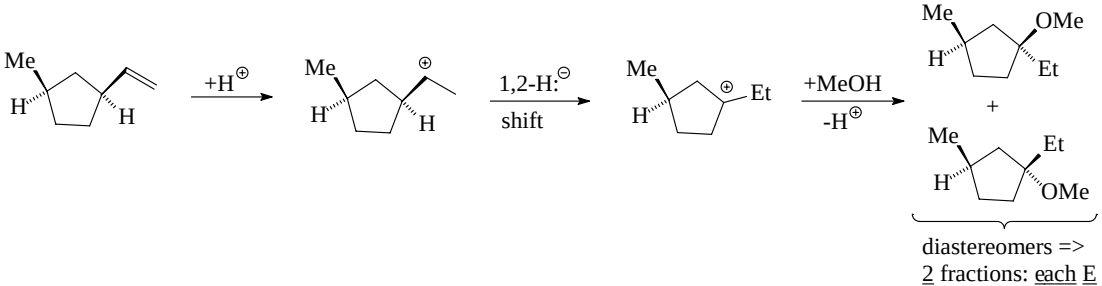
enantiomers => 1 fraction: R

e. 

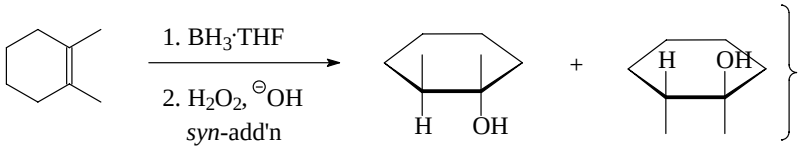
diastereomers => 2 fractions: each E

f. 

diastereomers => 2 fractions: each M

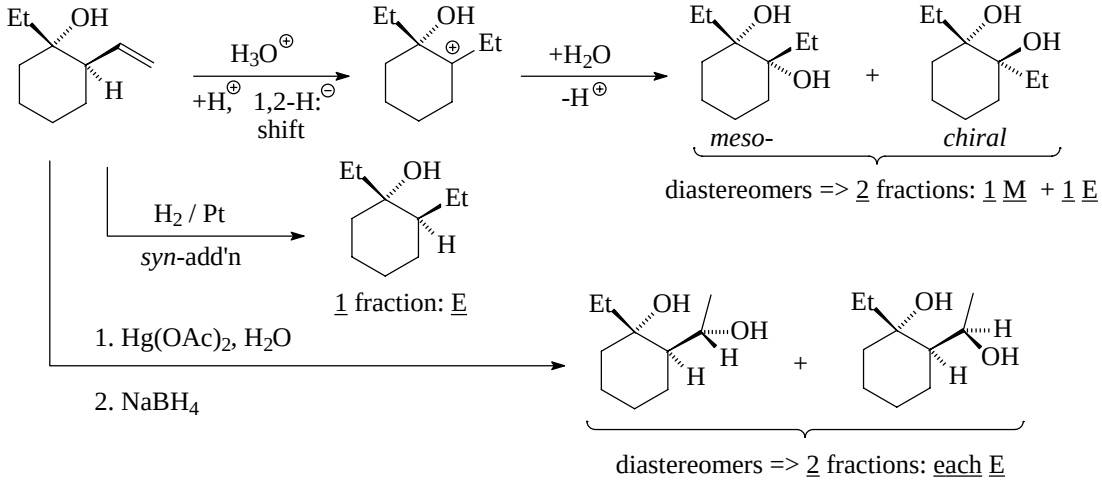
g. 

diastereomers => 2 fractions: each E

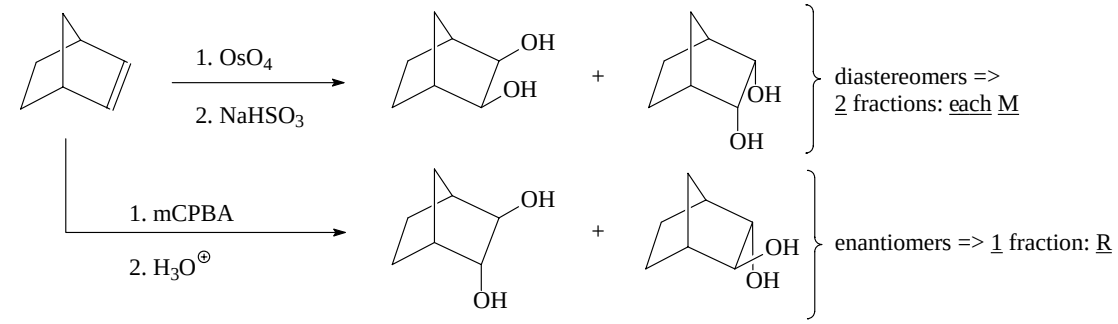
h. 

enantiomers => 1 fraction: R

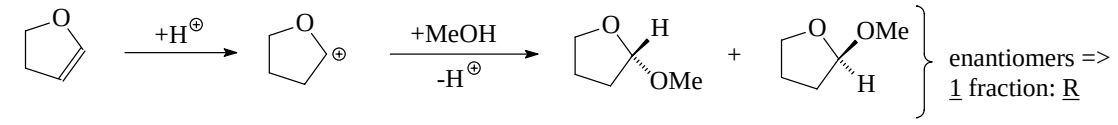
i.



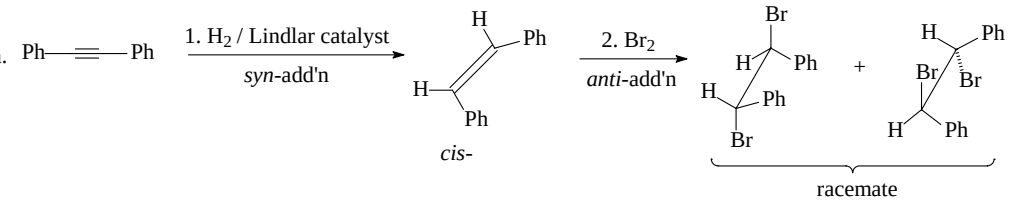
j.



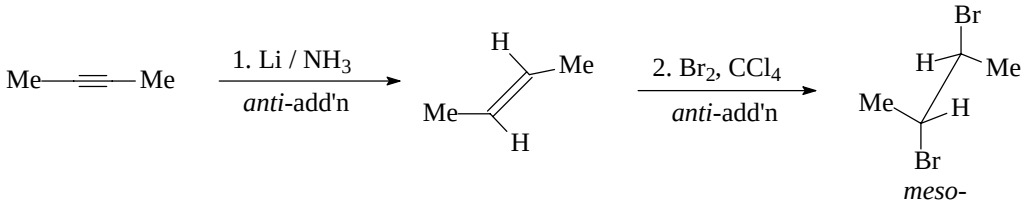
k.

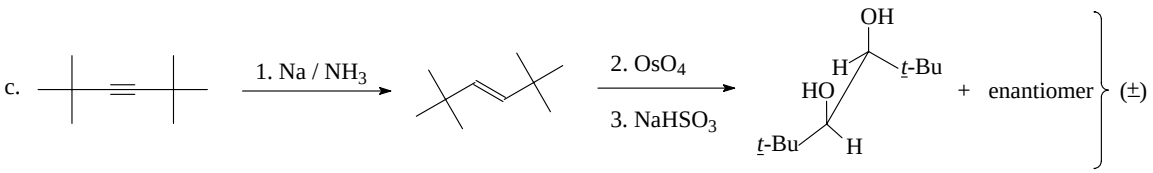


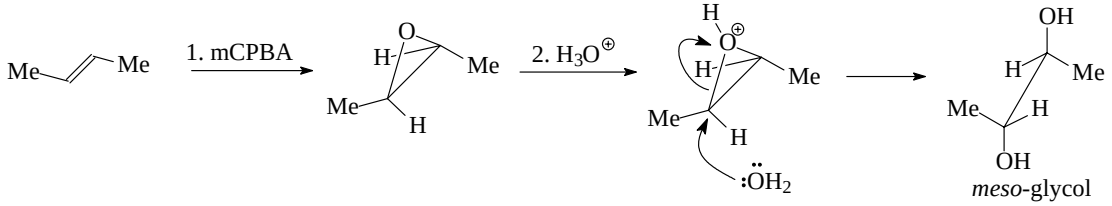
4. a.



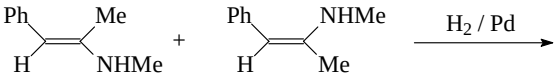
note: reduction of the alkyne to a *trans*-olefin, followed by Br_2 addition, would yield the *meso*-dibromide (*see next problem*)

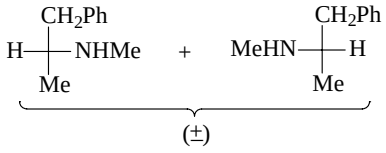
b. 

c. 

d. 

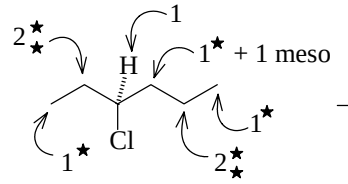
5. a. $2^2 = \underline{4}$. b. diastereomers c. cannot predict (actual $[\alpha]_D = +62^o$)

d. i. <u>2</u>. 

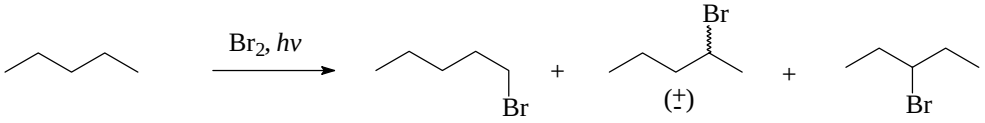
ii. <u>2</u>. 

CHAPTER 8
ALKYL HALIDES AND RADICALS

8.1 Reactions

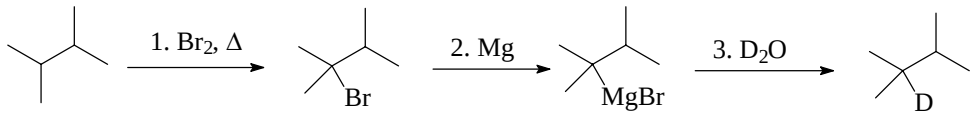
1. 

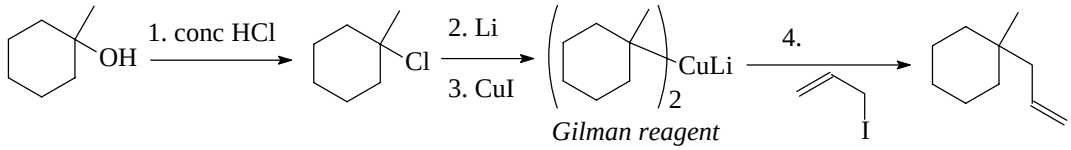
Cl_2, *hv* → 9 fractions { 7★ are optically active; 2 are optically inactive }

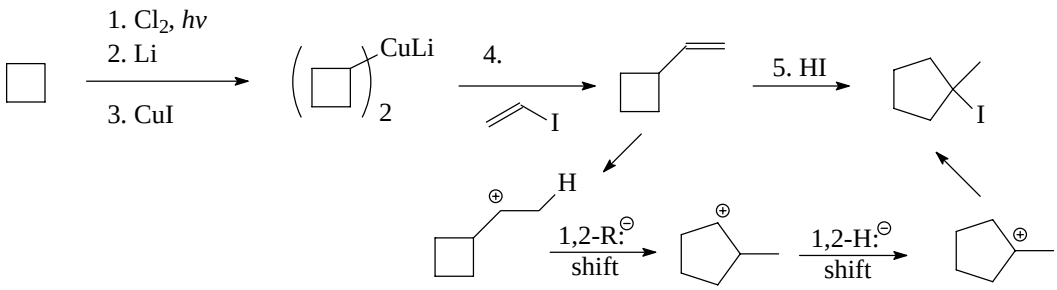
2. 

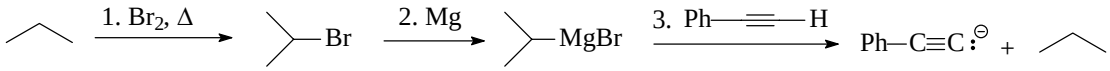
(no. H) x (reactivity) = 6 x 1.0 = 6.0 4 x 82 = 328 2 x 82 = 164

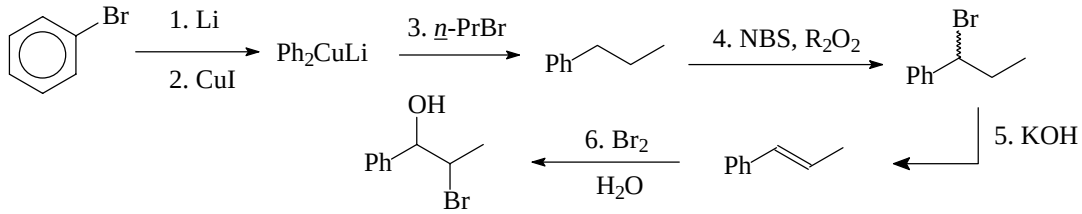
% *racemic* 2-bromopentane = 328/(6 + 328 + 164)*100 = 66%; therefore, % (R)- = 33%

3. 

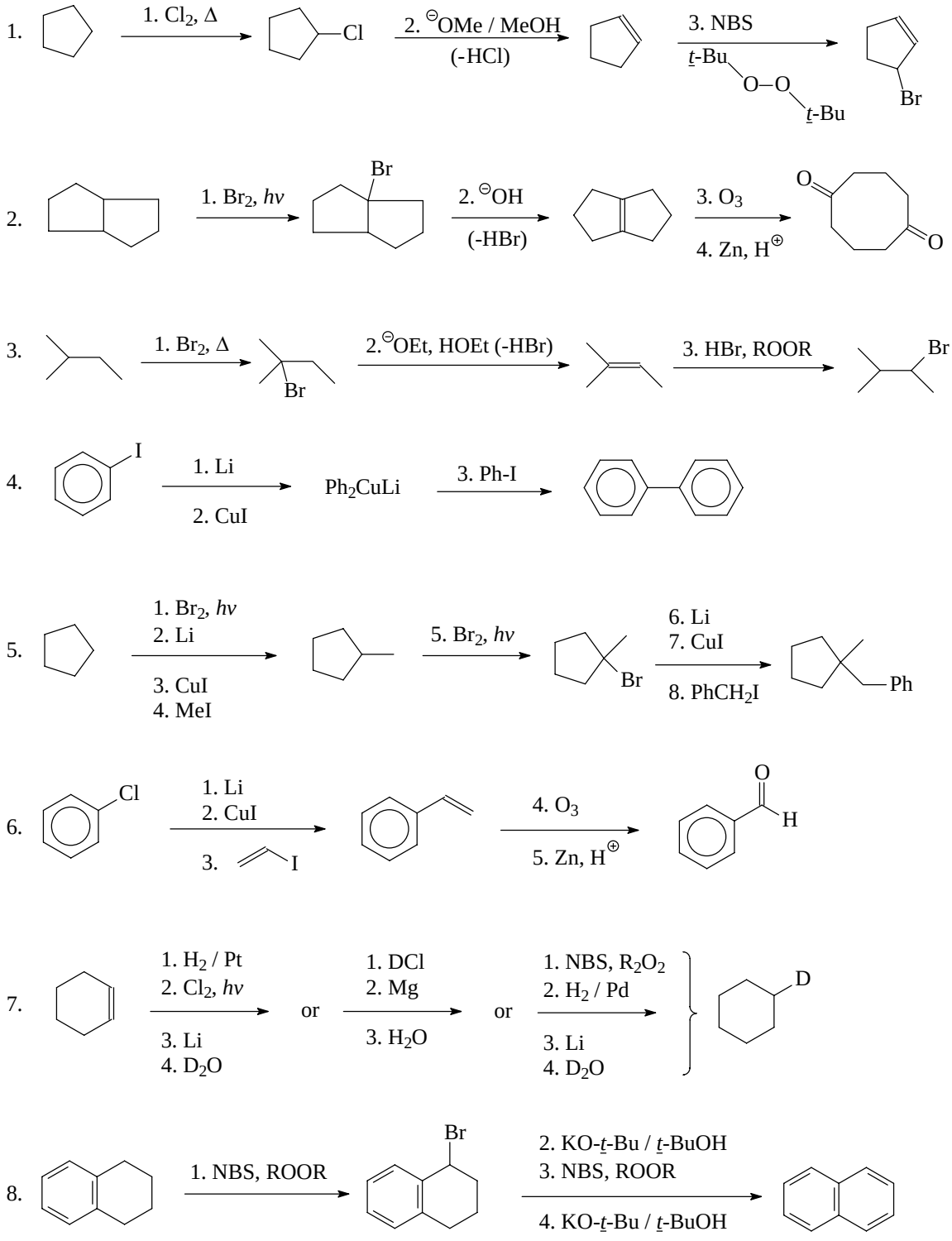
4. 

5. 

6. 

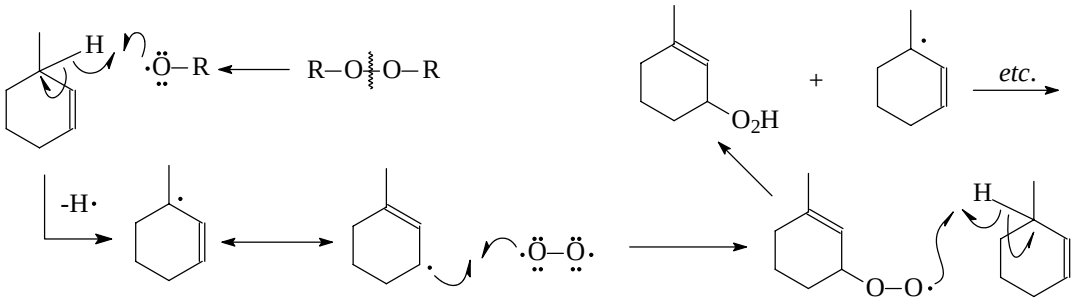
7. 

8.2 Syntheses



8.3 Mechanisms

1.



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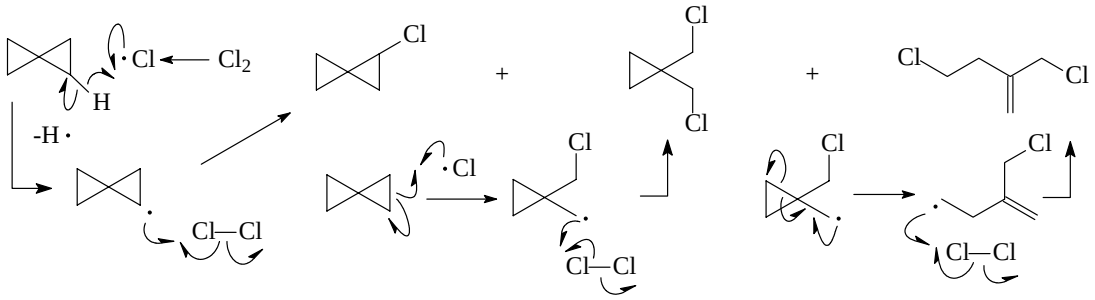

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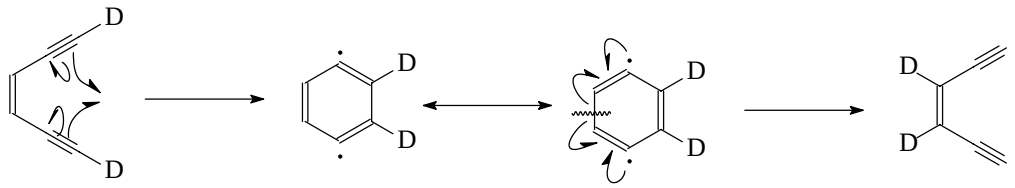

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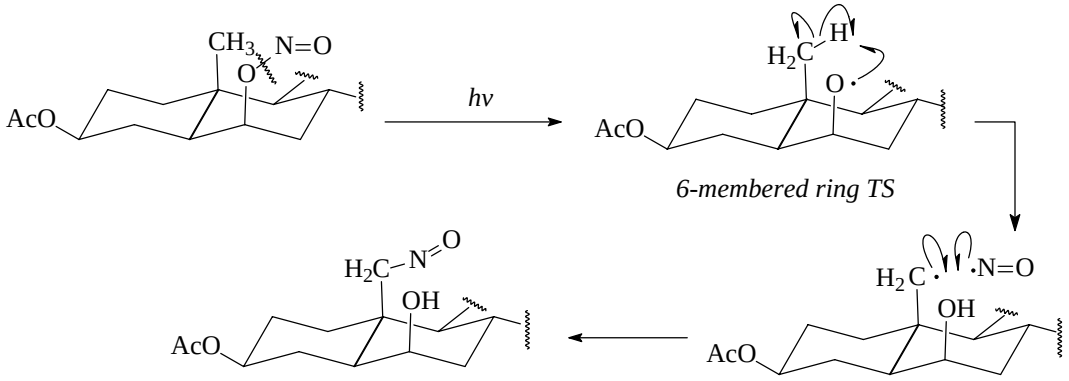
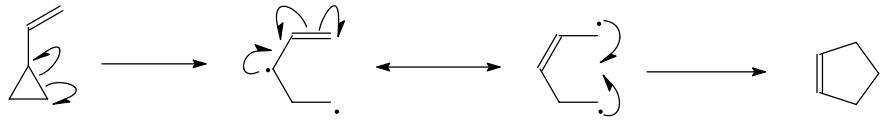
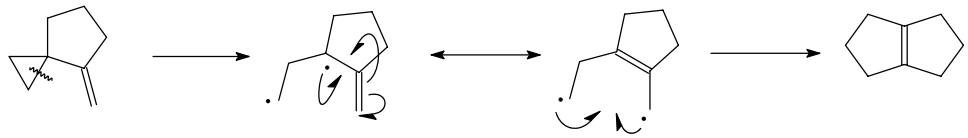


5. a.



b.



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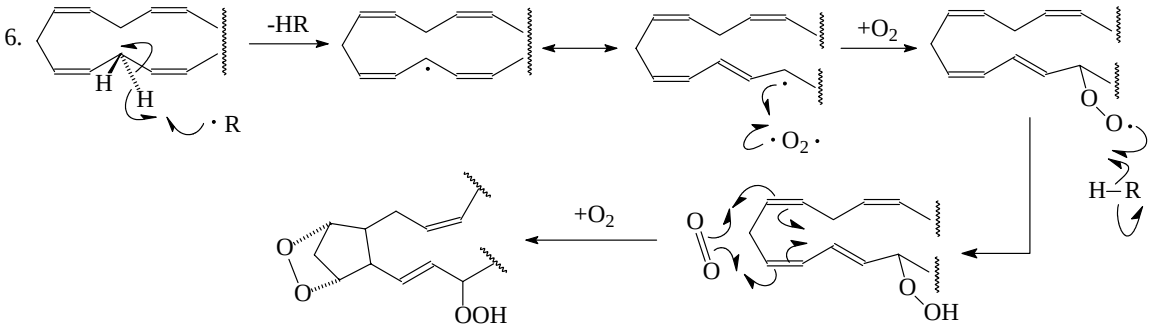
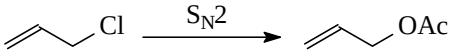


CHAPTER 9

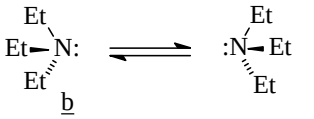
S_N1, S_N2, E1, AND E2 REACTIONS

9.1 General

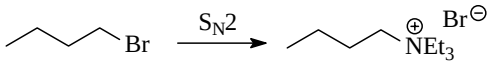
1. faster reaction: b. $AcO^{\ominus}$ + 

solvent effect: acetate in HMPA (polar aprotic) is more nucleophilic than in ethanol (polar protic); the later H-bonds to acetate, thereby dampening its nucleophilicity

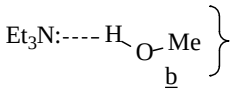
2. poorest leaving group: b. 'leavability' parallels the acidity of the CA of the leaving group; $:NH_3$ is the weakest CA (of the choices, c has the best leaving group)

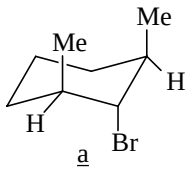
3. stronger nucleophile: a. 
rapid pyramidal inversion lowers nucleophilicity; such "flipping" is impossible with a

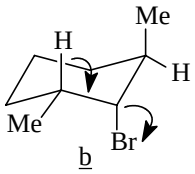
4. most reactive by an S_N2 pathway: c. least sterically crowded target carbon; note that even though a is primary, it is neopentyl-like, which generally never undergoes an S_N2 reaction

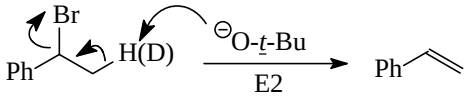
5. solvent that will maximize the rate of reaction: a. $Et_3N:$ + 

polar solvents (a or b) stabilize the developing charge in the TS; the amine is more nucleophilic in DMSO (polar aprotic) than methanol (polar protic):


H-bonding stabilizes the amine, thereby increasing $\Delta G^{\ddagger}$

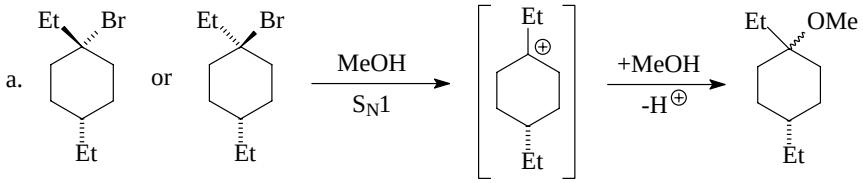
6. more reactive by an E2 pathway: b. 
no *trans*-diaxial hydrogen available

vs. 
anti-periplanar TS possible

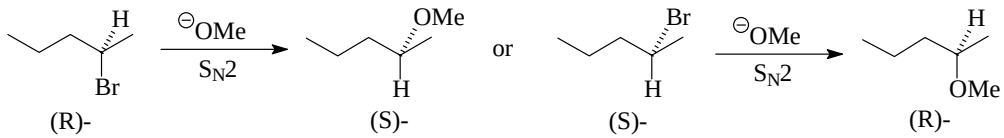
7. approximate k_H / k_D: c. 

a carbon-hydrogen (deuterium) bond is broken in the rate-determining-step; therefore, a primary hydrogen kinetic isotope effect (~7) is observed

8. reaction to yield the more stereochemically pure product: b.

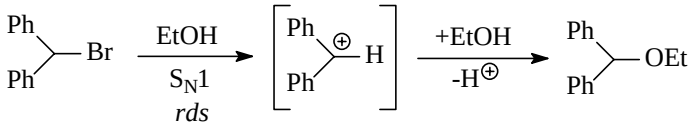
a. 

either diastereomer would give the same ratio of diastereomeric ethers because of a common intermediate

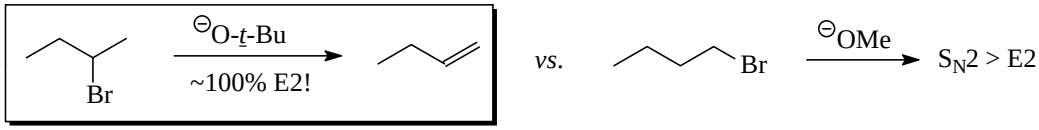
b. 

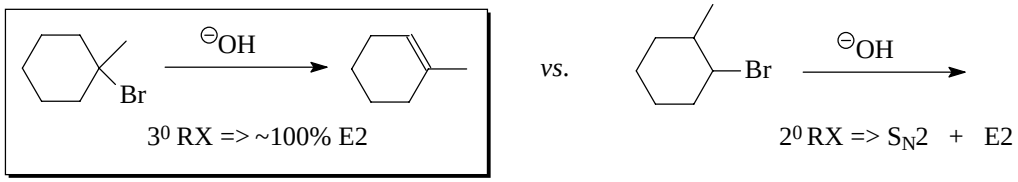
(R)- (S)- (S)- (R)-

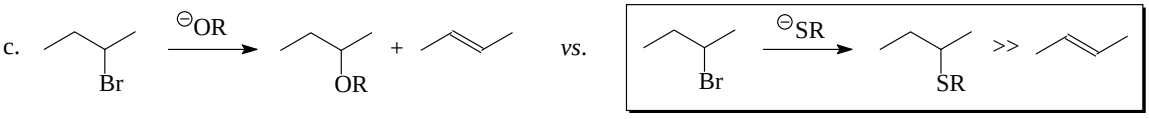
stereospecific: either enantiomer gives an optically pure, but different, ether

9. change in rate of reaction: b. 

rate = k[RX] ; changing the concentration of EtOH has no effect on the rate

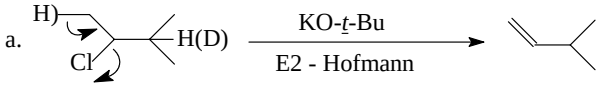
10. a. 

b. 

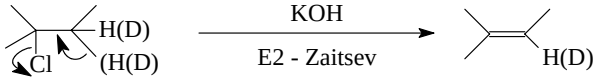
c. 

$RS^{\ominus}$ is a better nucleophile, and weaker base, than $RO^{\ominus}$; therefore, S_N2 / E2 ratio is larger for $RS^{\ominus}$

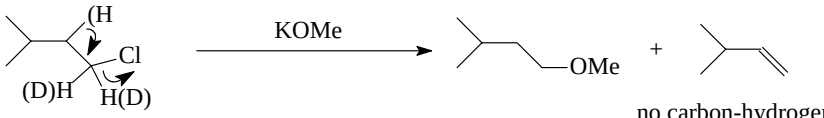
11. expected primary hydrogen kinetic isotope effect: b.

a. 

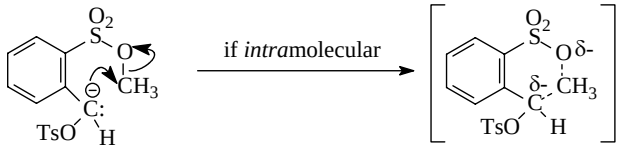
no carbon-hydrogen (deuterium) bond is broken in rds; therefore, $k_H / k_D \sim 1$

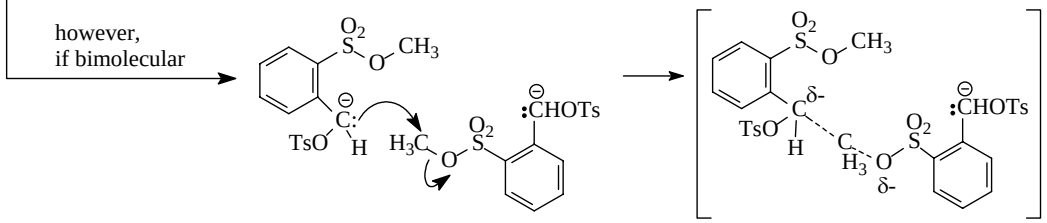
b. 

a carbon-hydrogen (deuterium) bond is broken in rds; therefore, $k_H / k_D \sim 7$

c. 

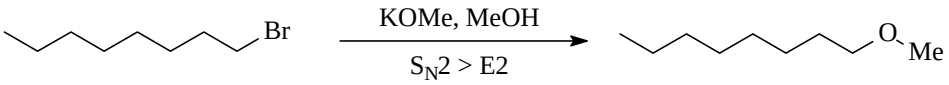
no carbon-hydrogen (deuterium) bond is broken in rds

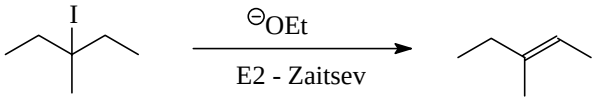
12. 

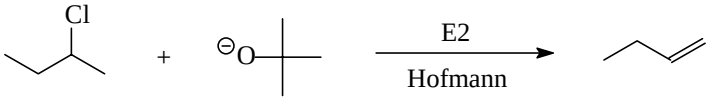


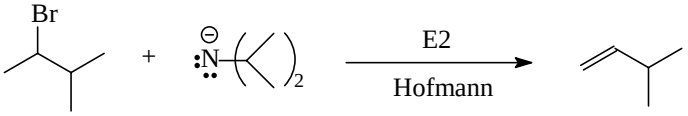
a linear TS is possible => $< \Delta G^{\ddagger}$; therefore, an *inter*molecular reaction is kinetically favored

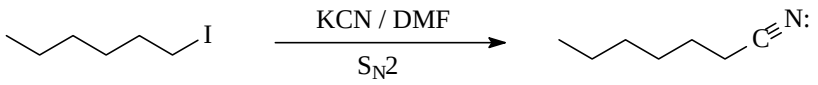
9.2 Reactions

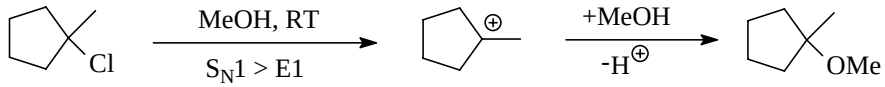
1. 

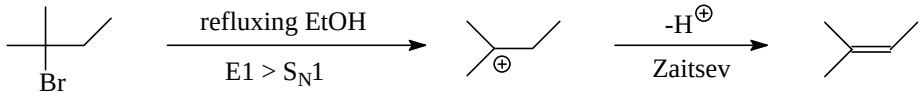
2. 

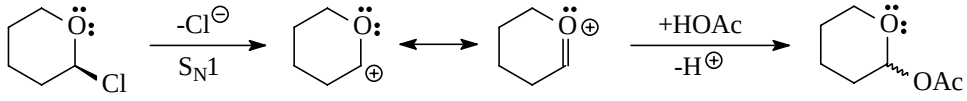
3. 

4. 

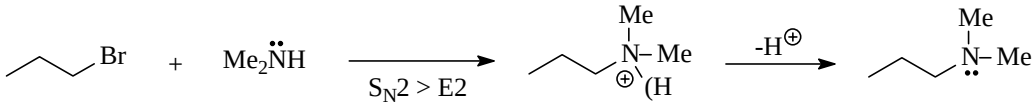
5. 

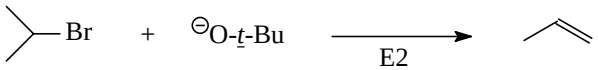
6. 

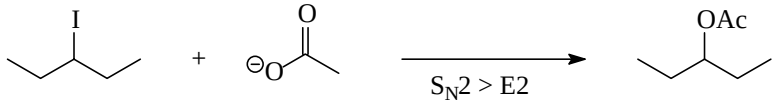
7. 

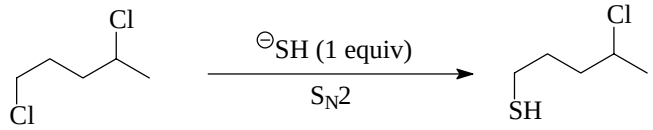
8. 

racemate

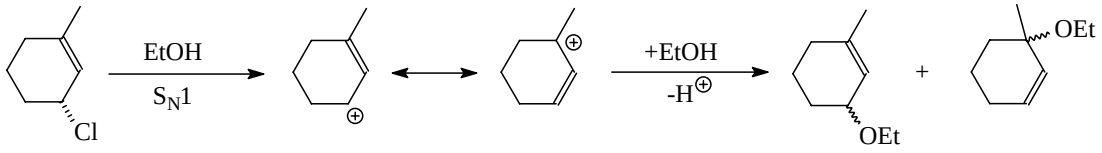
9. 

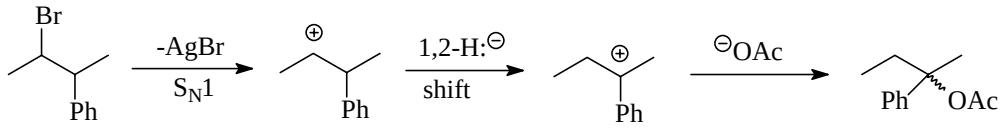
10. 

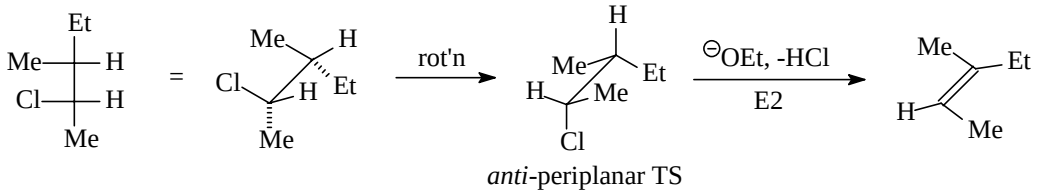
11. 

12. 

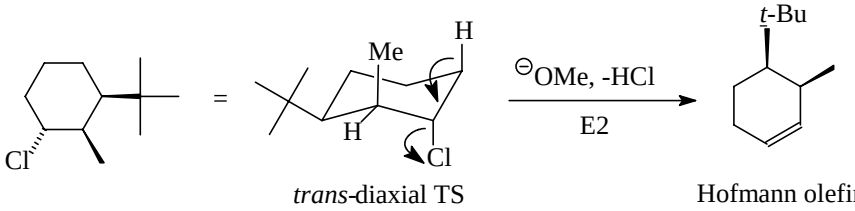
reactivity: $1^0 > 2^0$

13. 

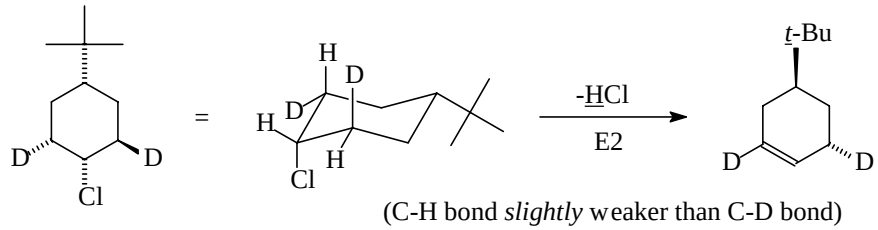
14. 

15. 

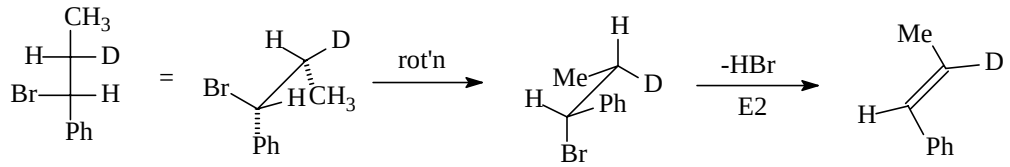
anti-periplanar TS

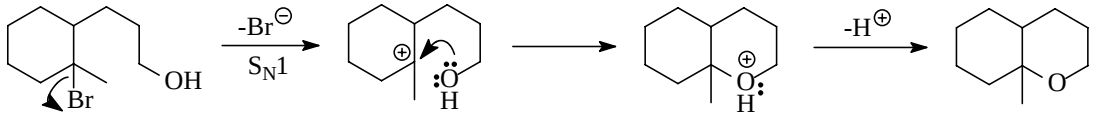
16. 

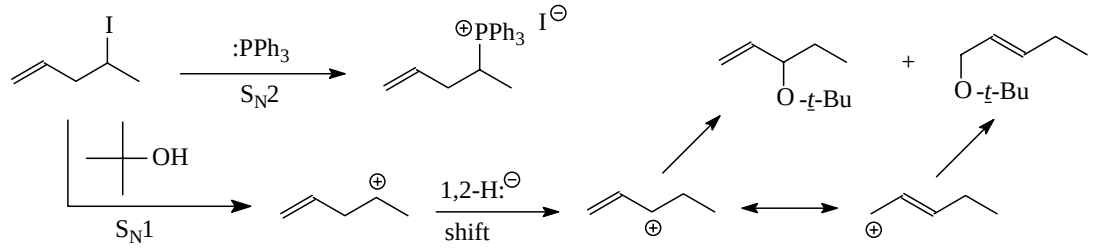
trans-diaxial TS Hofmann olefin

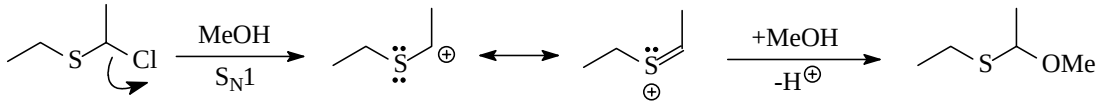
17. 

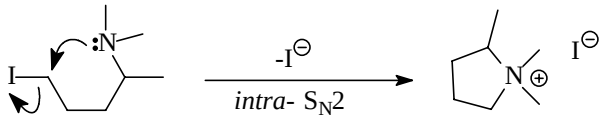
(C-H bond *slightly* weaker than C-D bond)

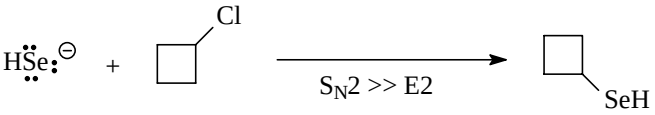
18. 

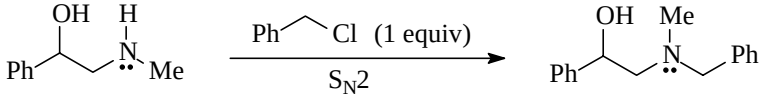
19. 

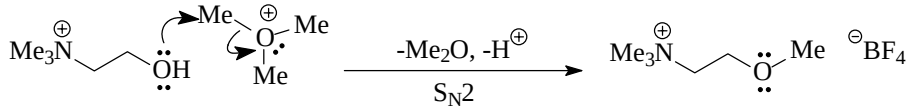
20. 

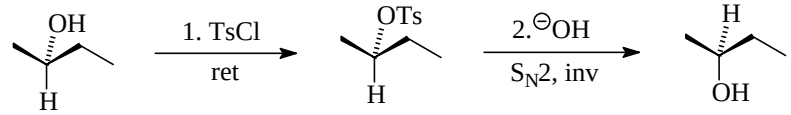
21. 

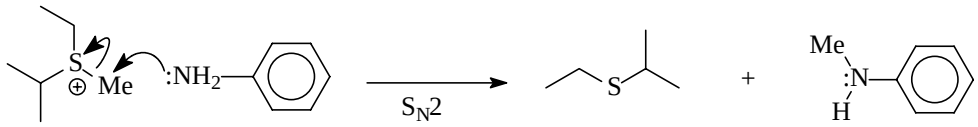
22. 

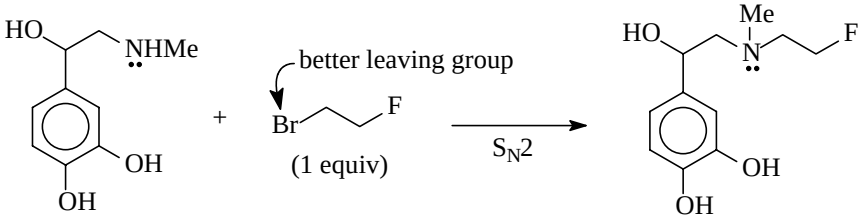
23. 

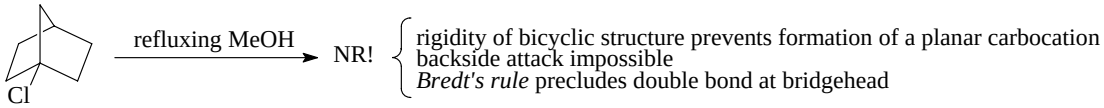
24. 

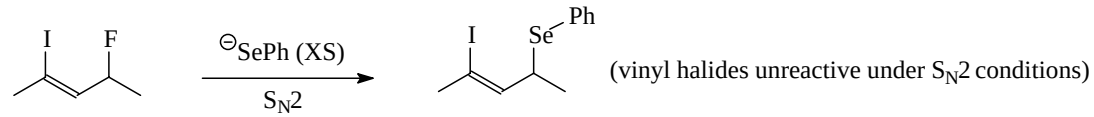
25. 

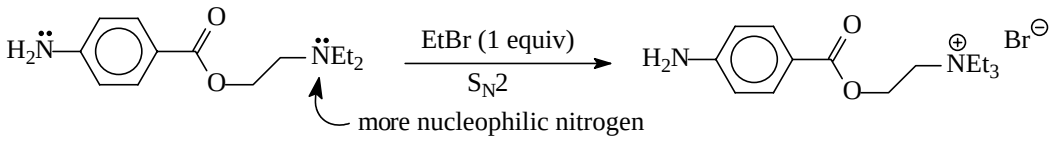
26. 

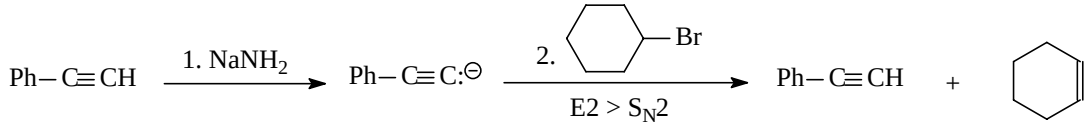
27. 

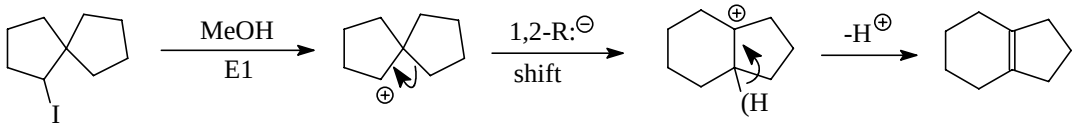
28. 

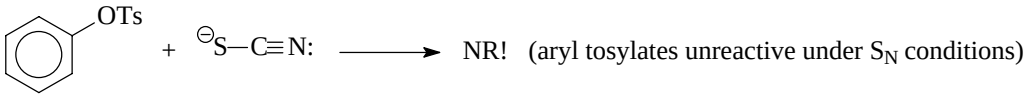
29. 

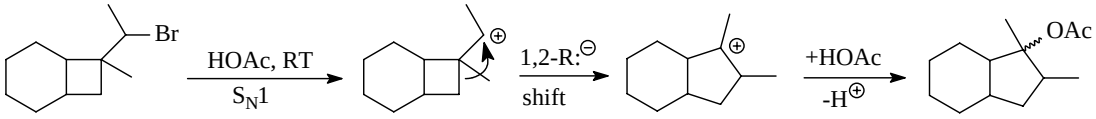
30. 

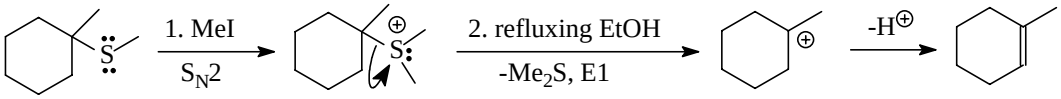
31. 

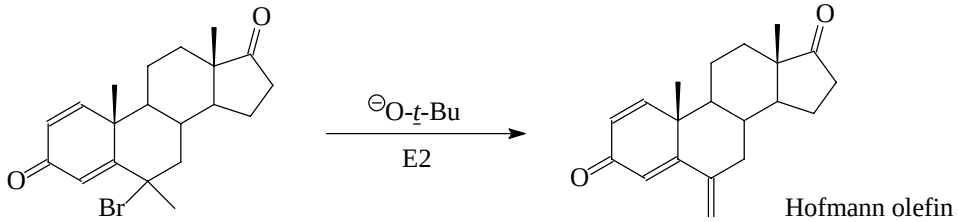
32. 

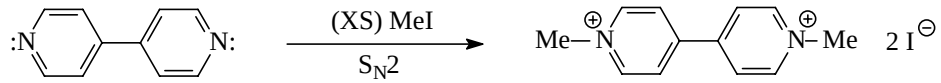
33. 

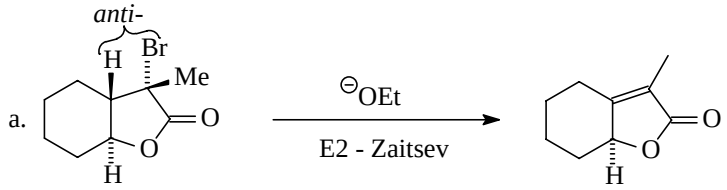
34. 

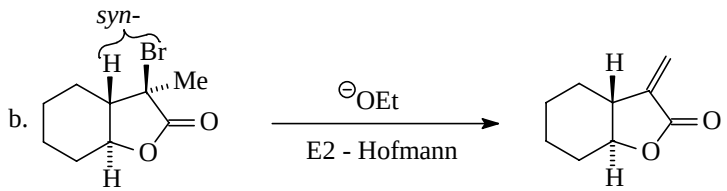
35. 

36. 

37. 

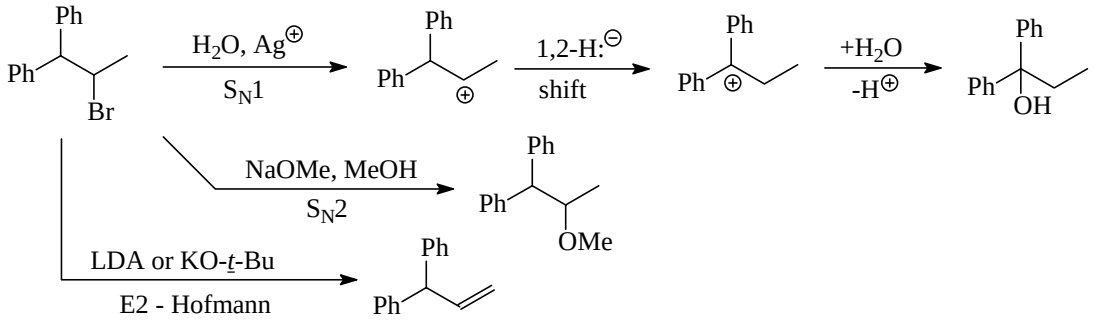
38. 

39. a. 

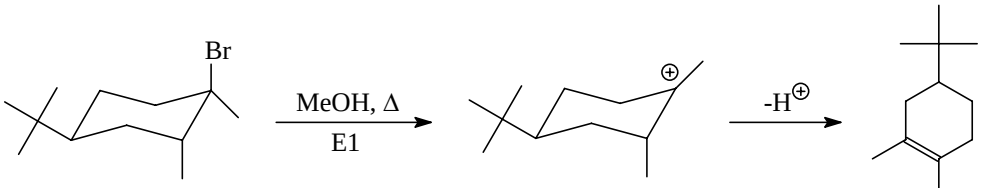
b. 

9.3 Syntheses

1.

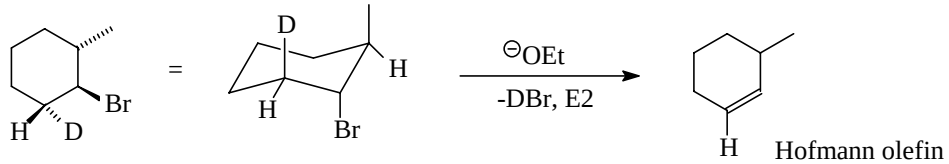


2.



(not $^{\ominus}$OMe! => E2 - Hofmann olefin)

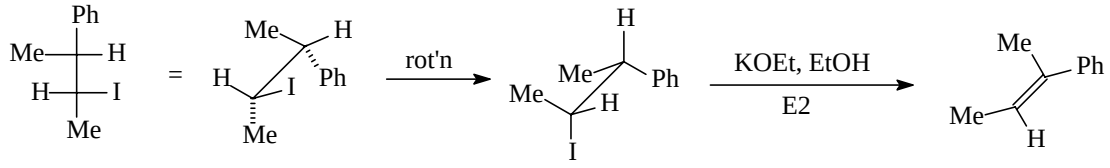
3.



Hofmann olefin

(not HOEt, Δ! => E1 - Zaitsev olefin)

4.



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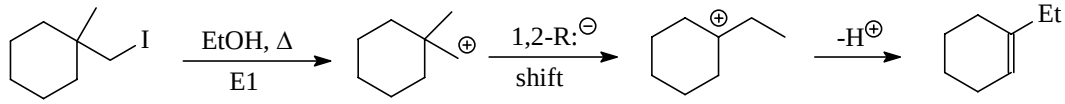

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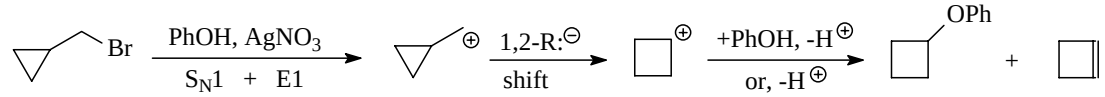

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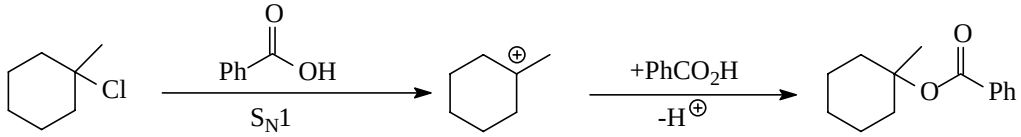
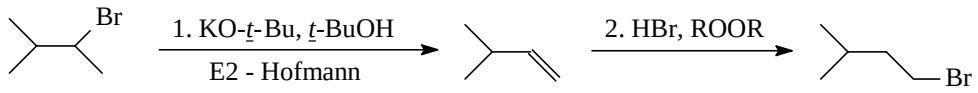
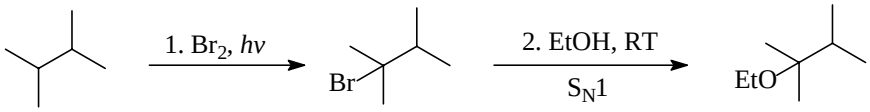
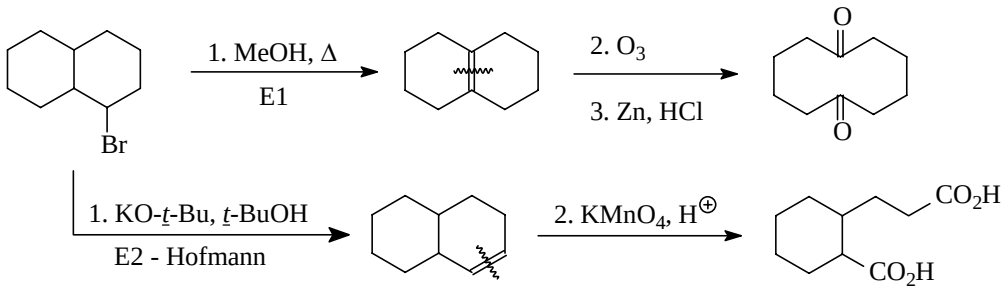
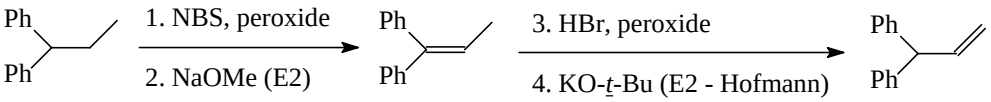


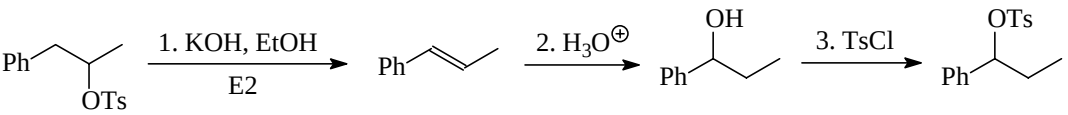
8. 

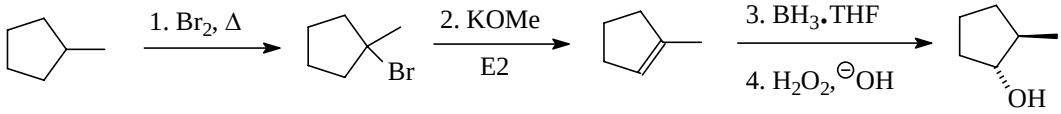
9. 

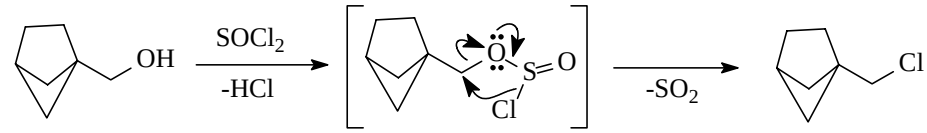
(not $^{\ominus}$OEt! => 100% E2)

10. 

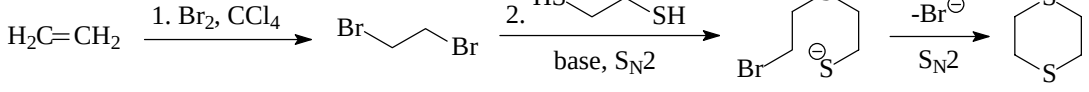
11. 

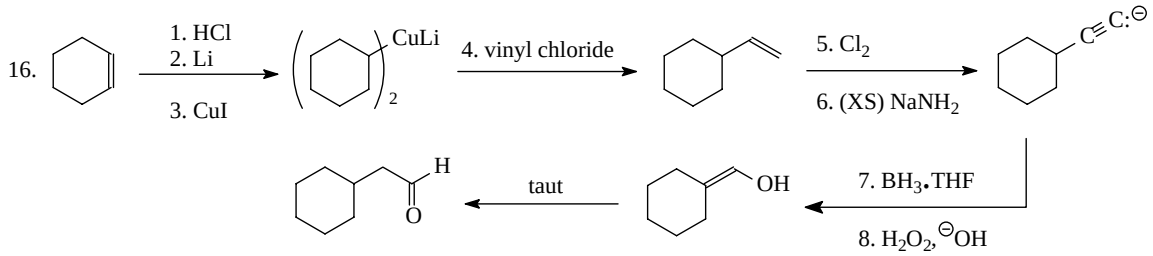
12. 

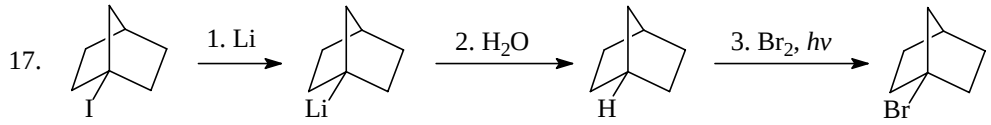
13. 

14. 

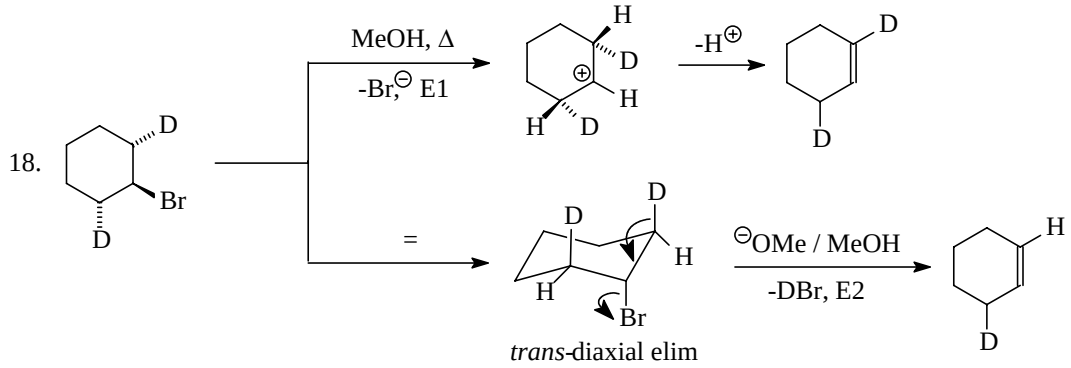
[S_N2 reactivity slow (neopentyl-like); avoid S_N1 (rearrangement)]

15. 

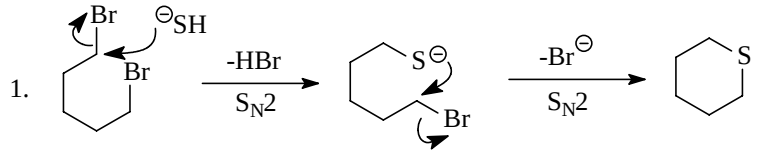
16. 

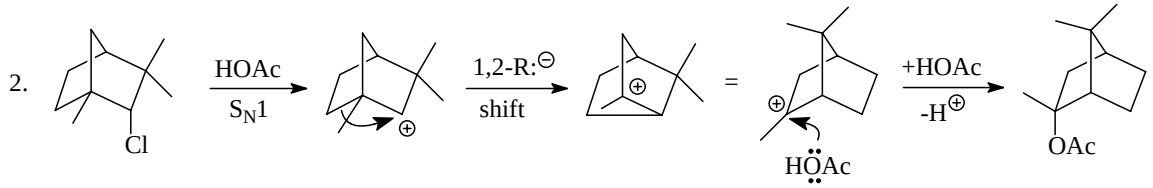
17. 

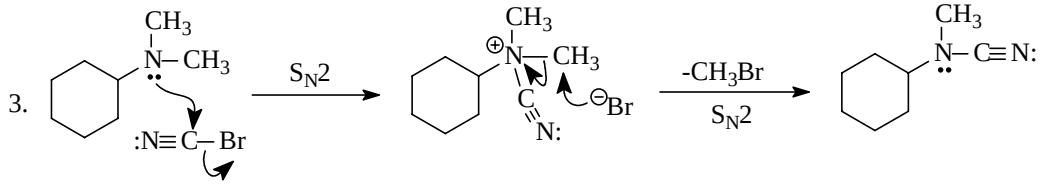
(S_N or E not possible)

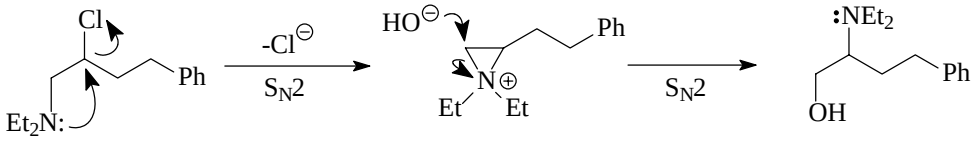
18. 

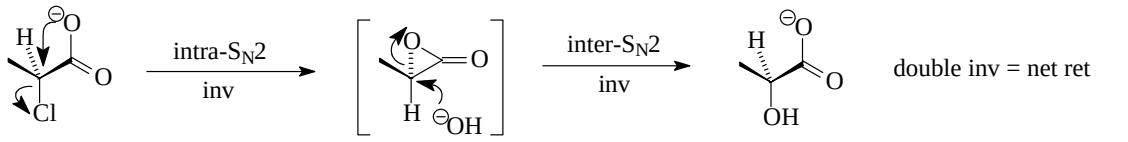
9.4 Mechanisms

1. 

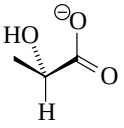
2. 

3. 

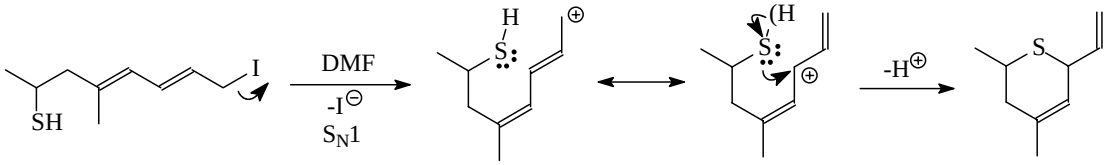
4. 

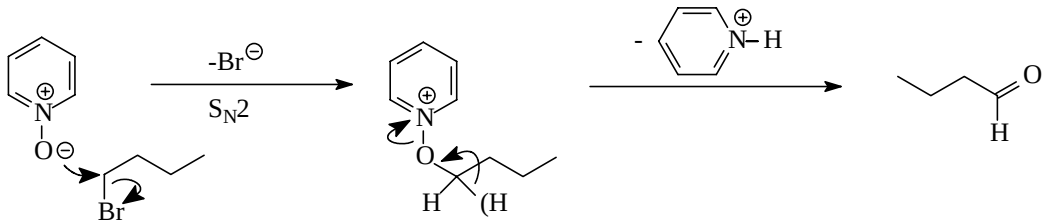
5. 

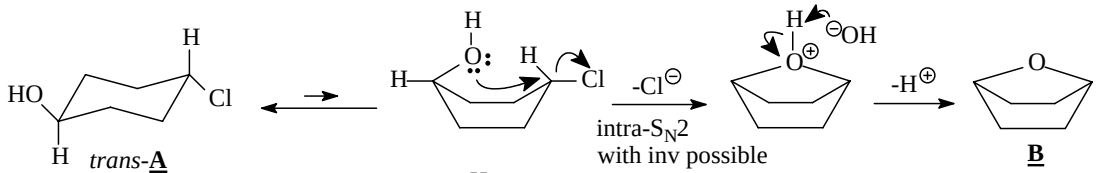
double inv = net ret

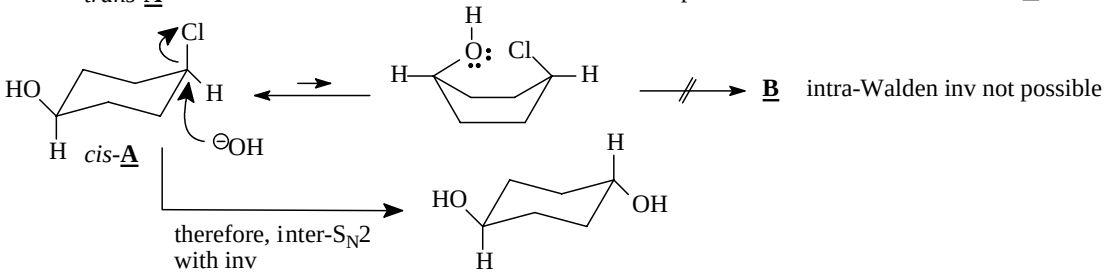
(in conc ⊖OH, product is 

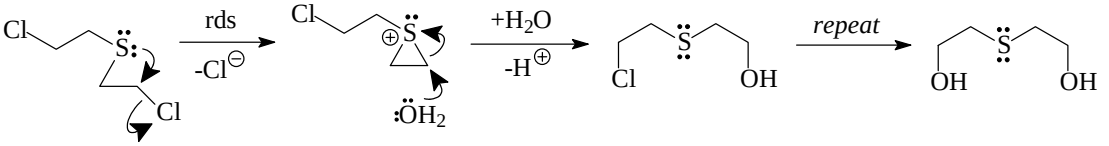
, formed by initial inter-S_N2)

6. 

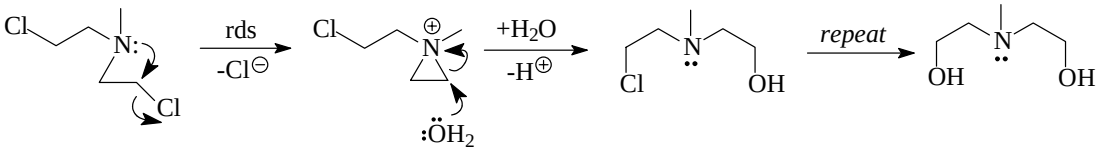
7. 

8. 



9. 

9. (*cont.*) similarly,



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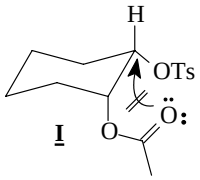
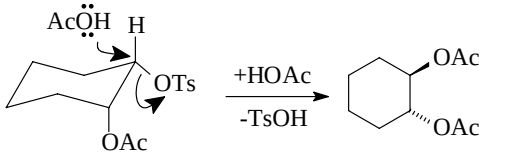


I

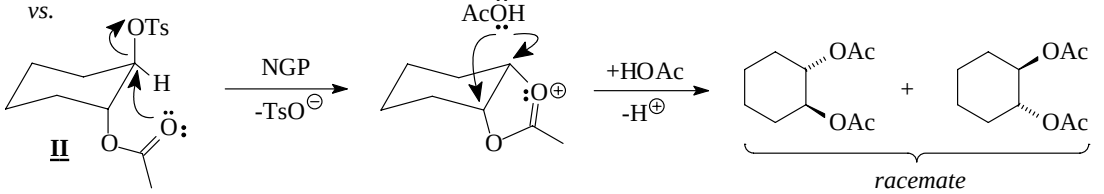
intra-S_N2 (NGP) not possible

therefore, inter-S_N2:



trans-enantiomer only

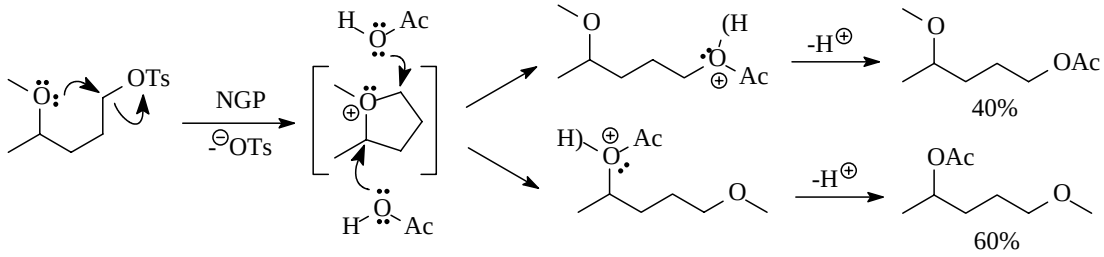
vs.



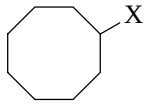
II

racemate

11.



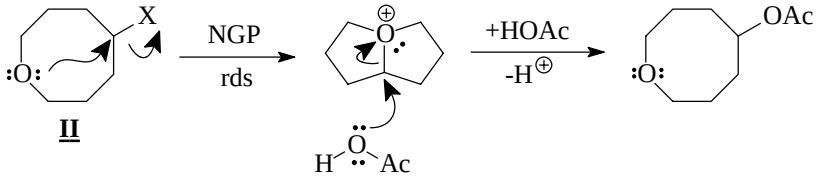
12.



I

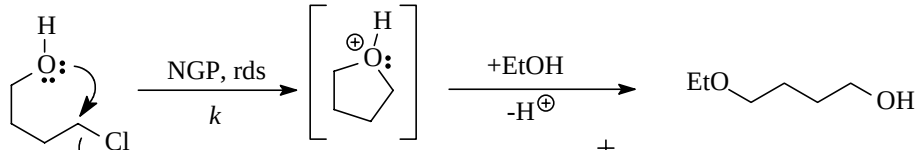
NGP not possible - therefore, no kinetic enhancement

vs.



II

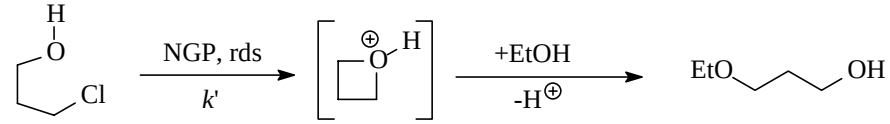
13.

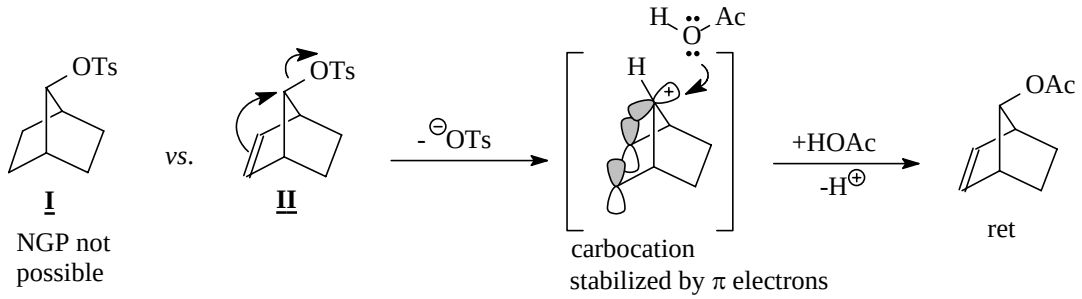


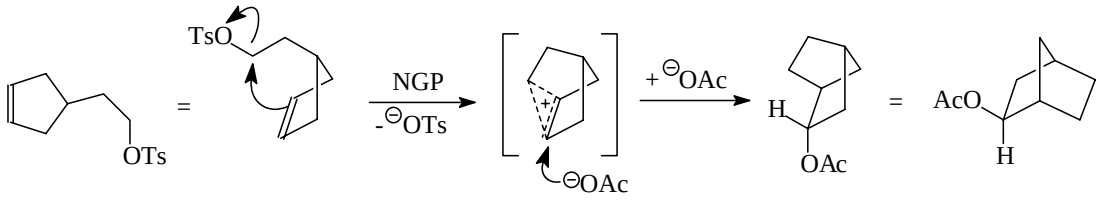
vs.

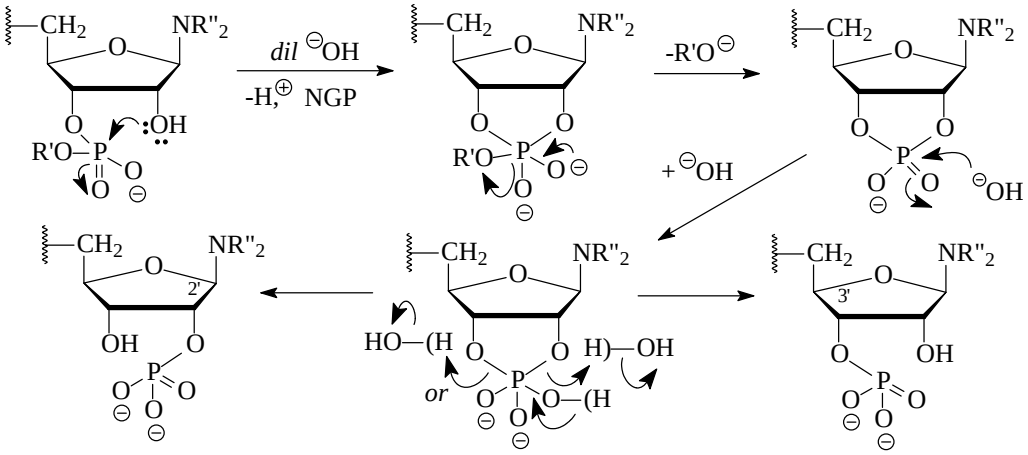
less strained intermediate => < $\Delta G^{\ddagger}$

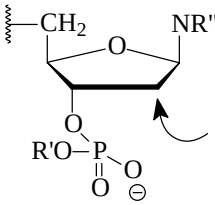
therefore, $k >> k'$

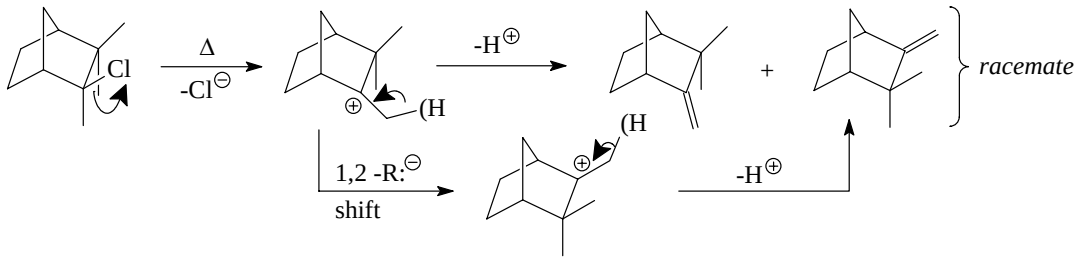


14. 

15. 

16. RNA: 

DNA: 

17. 

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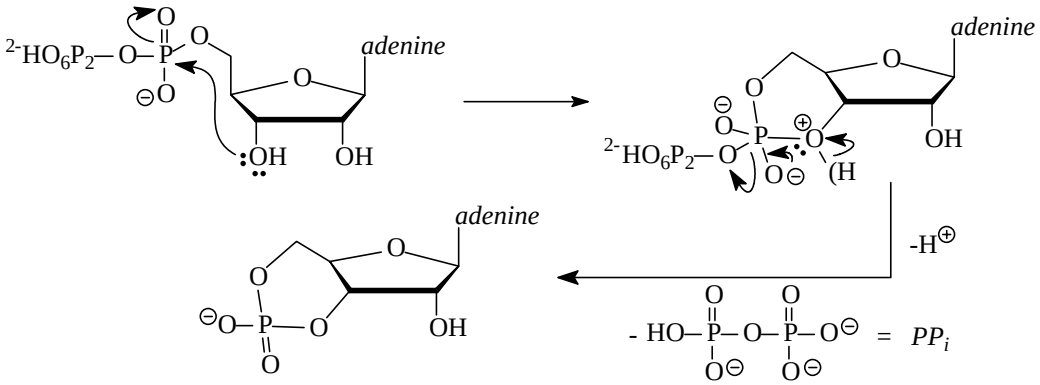

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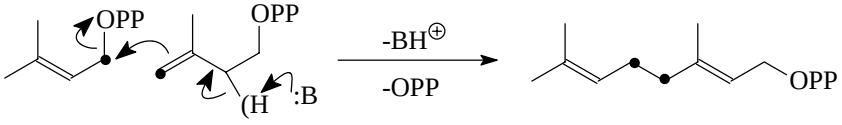

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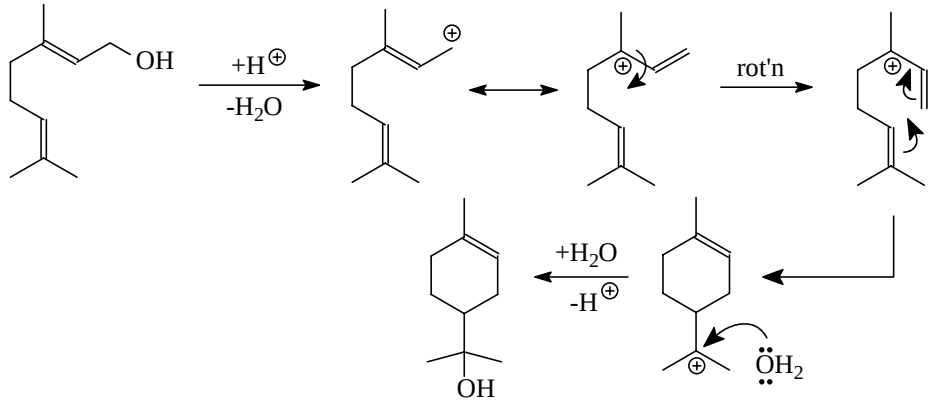

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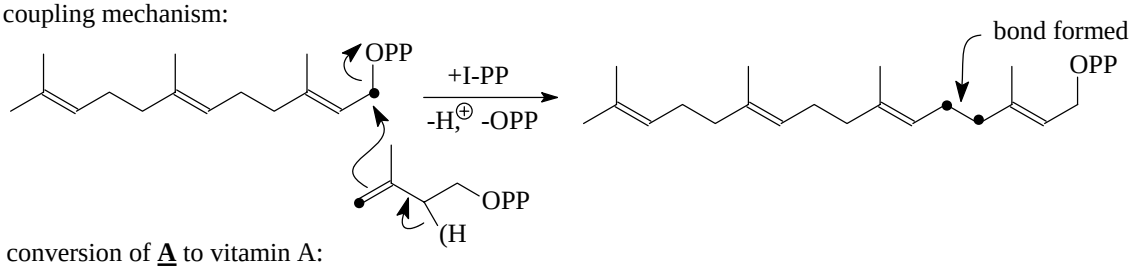
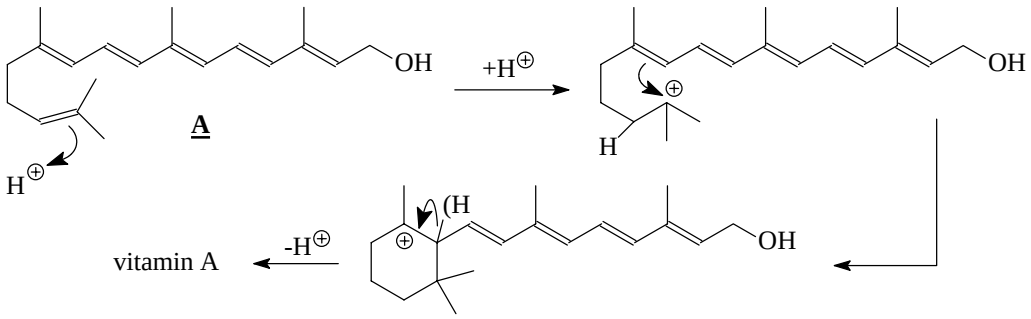


conversion of **A** to vitamin A:



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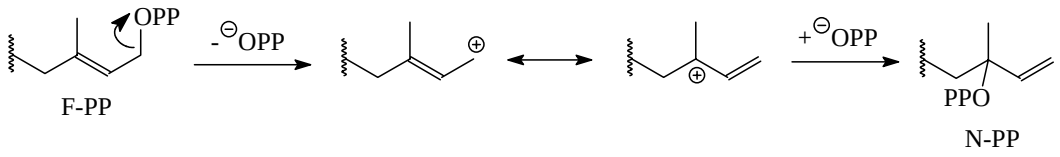

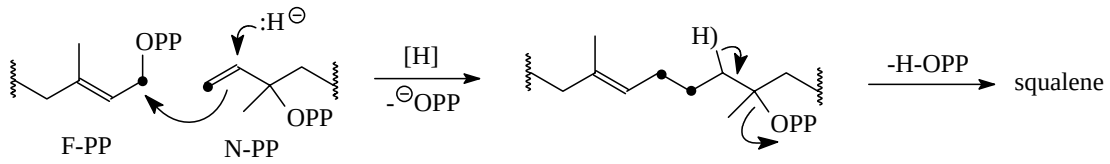

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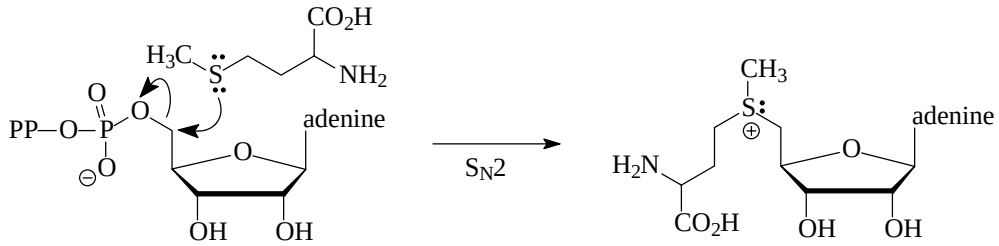
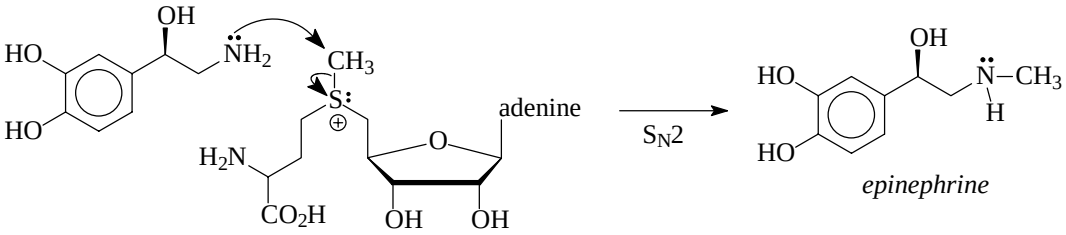


SAM



epinephrine

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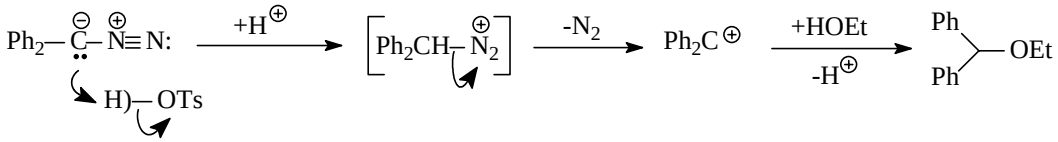

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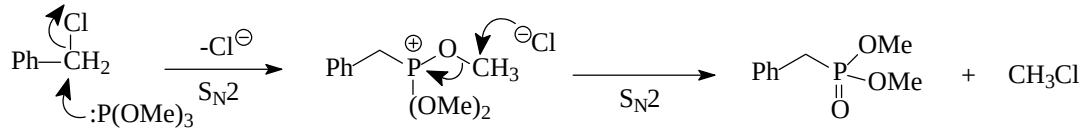

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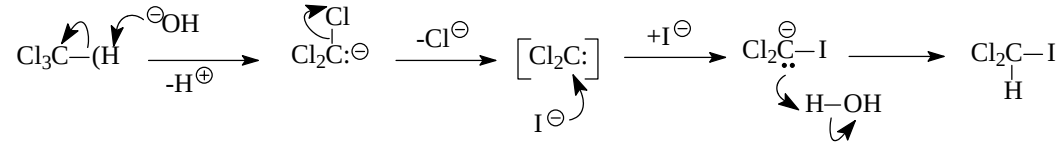

note: $HCCl_3 + I^{\ominus} \not\longrightarrow HCCl_2I$ *via* S_N2

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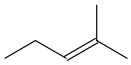
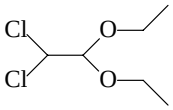
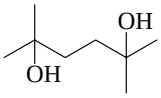
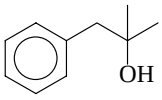
CHAPTER 10

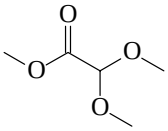
NMR

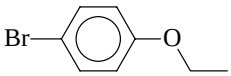
1. 

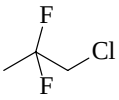
2. 

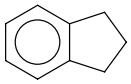
3. 

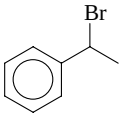
4. 

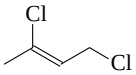
5. 

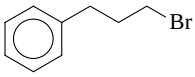
6. 

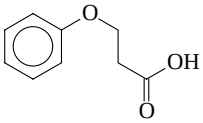
7. 

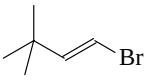
8. 

9. 

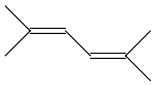
10. 

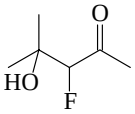
11. 

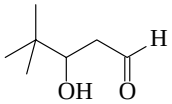
12. 

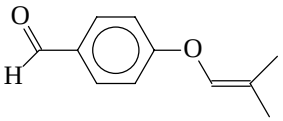
13. 

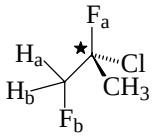
J => *trans-*

14. 

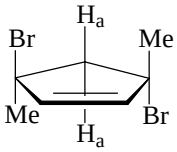
15. 

16. 

17. 

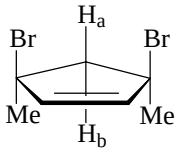
18. 

H_a and H_b are diastereomeric protons; ^{19}F (I = 1/2)
therefore, max multiplicity for $H_{a\ or\ b}$ = doublet x doublet x doublet = <u>8 lines</u>

19. 

A

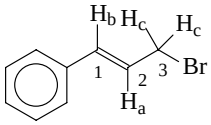
vs.

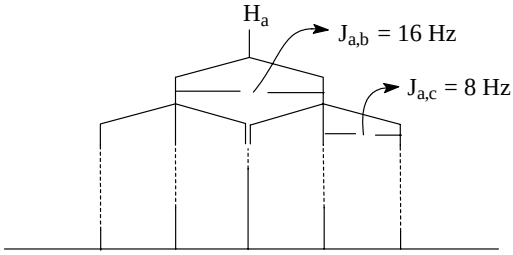


B

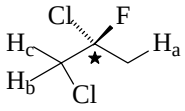
methylene protons are identical
=> singlet

H_a => doublet; H_b => doublet
(appears as a multiplet)

20. 

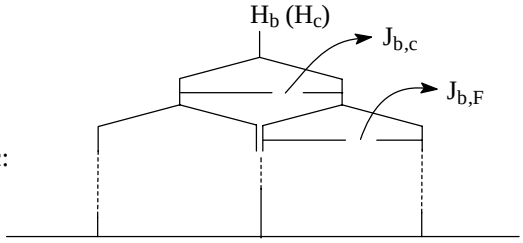


multiplicity: 5 lines (pentuplet)

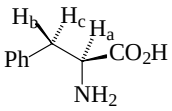
21. a. 

highest field proton is H_a
$J_{a,F}$ => doublet

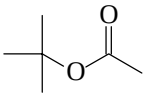
b. H_b and H_c are diastereomeric:



$J_{b,c} \approx J_{b,F}$ => triplet

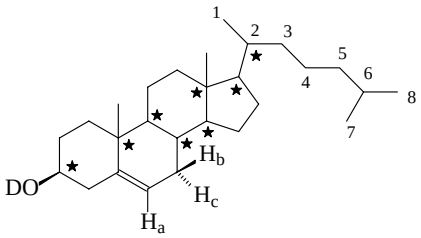
22. 

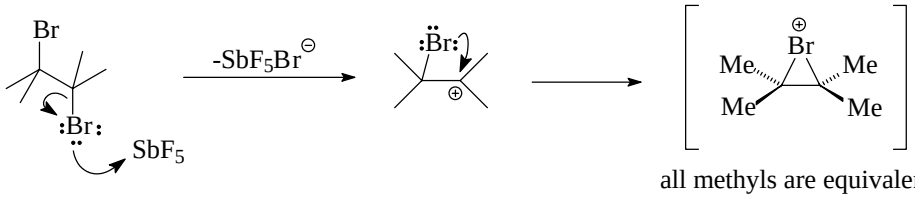
H_b and H_c are diastereomeric and independently couple with H_a; if $J_{a,b} \neq J_{a,c}$, H_a would appear as a doublet x doublet = 4 lines (assuming no coupling through nitrogen)

23. 

24. a. H_a (lowest field proton): doublet x doublet => 4 lines

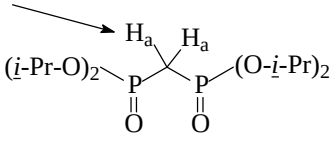
b. C_7 and C_8 are diastereomeric carbons; therefore, 8 chemical shifts



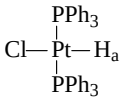
25. 

all methyls are equivalent
therefore, appear as a singlet

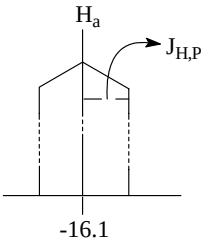
26. ^{31}P (I = 1/2), $n_P = 2$; therefore, 2nI + 1 = 3 (triplet)



27. a. *amplitude*: signal at δ -16.1 is highest amplitude because most molecules (66%) contain Pt with I = 0 (no further spin-spin coupling with H_a is observed, *i.e.*, $J_{H,Pt} = 0$)

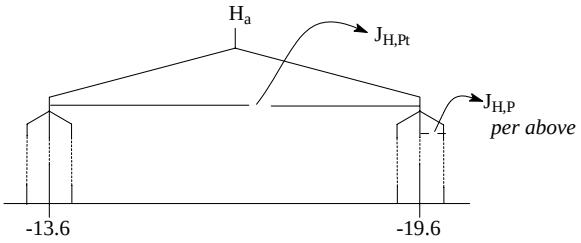


multiplicity: ^{31}P (I = 1/2), so $J_{H,?} = J_{H,P} > 0$, $n_P = 2$
therefore, 2nI + 1 = triplet

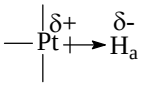


b. *amplitude*: signals at δ -13.6 and -19.6 arise from fewer (34%) molecules containing ^{195}Pt (I = 1/2)

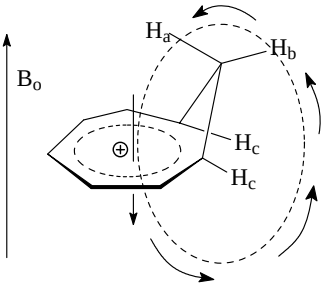
multiplicity: H_a now undergoes spin-spin coupling with both P *and* Pt to give a doublet of triplets ($J_{H,Pt} >> J_{H,P}$)



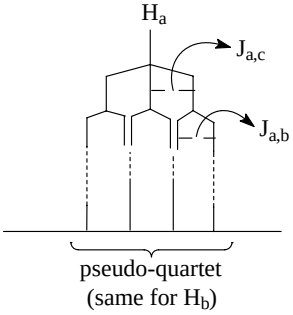
c. H_a is very *highly shielded,* essentially a hydride, because of the polarization of the Pt-H bond (much higher electron density around H_a than typically encountered in C-H bonds)

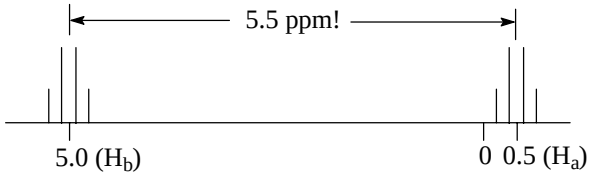


28.

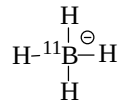


Because of magnetic anisotropy of the aromatic ring current, H_a experiences diamagnetic (and H_b paramagnetic) lines of force relative to applied field B_o. Therefore, H_a is more shielded (and H_b deshielded) than normally observed in hydrocarbon protons on sp^3 carbons.

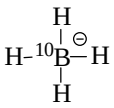




29. *multiplicities*:



vs.



^{11}B (I = 3/2)
therefore, 2nI + 1 = quartet
(higher amplitude)

^{10}B (I = 3)
therefore, 2nI + 1 = septet
(lower amplitude)

relative *amplitudes* of quartet/septet reflect the natural abundance of $^{11}B/^{10}B$ = 80%/20%

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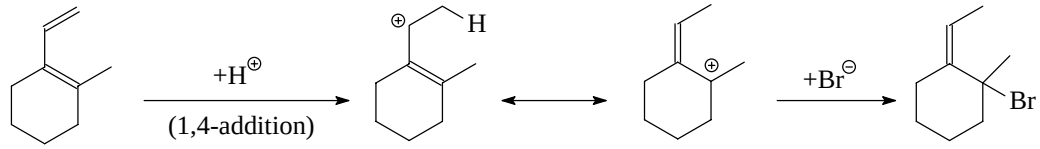
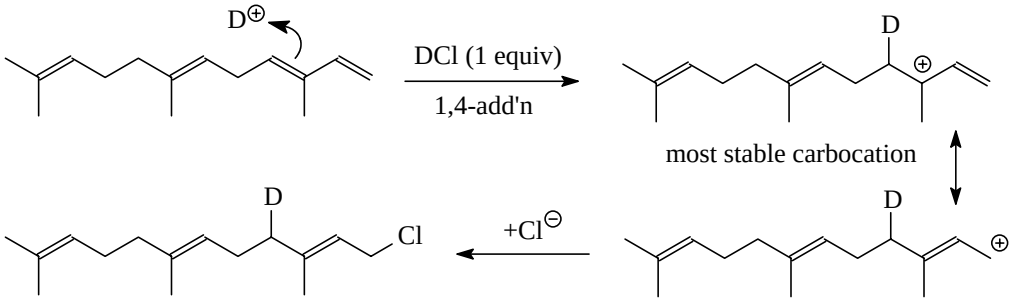
CHAPTER 11
CONJUGATED SYSTEMS

11.1 Reactions

1.



2.



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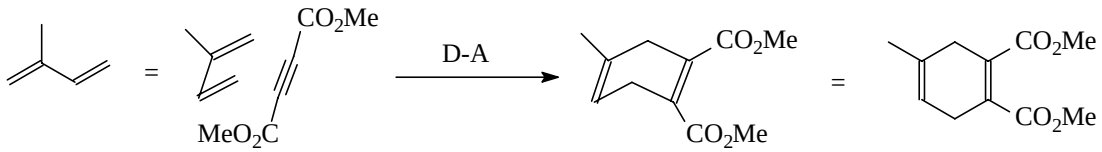

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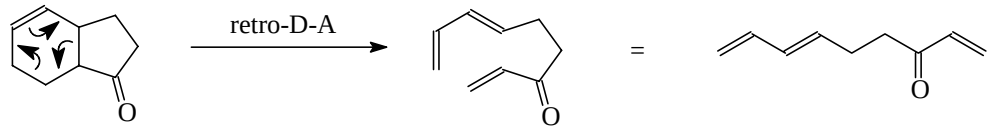
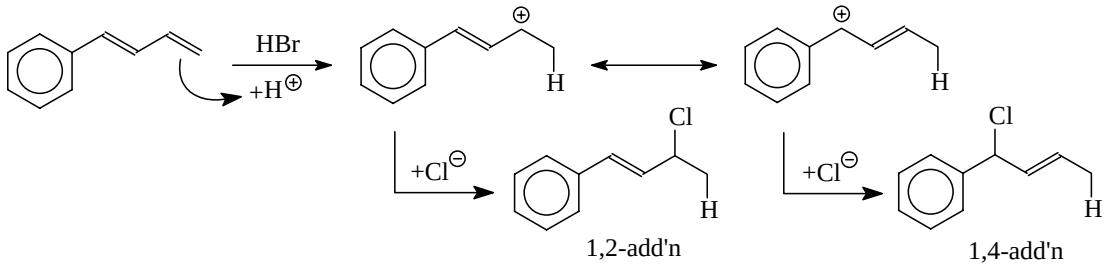
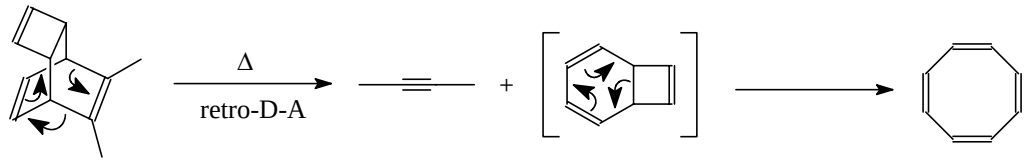
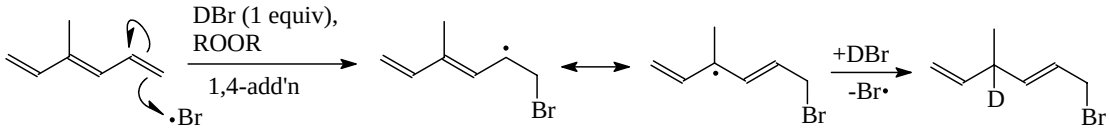


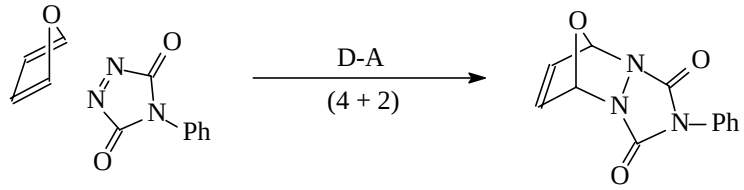
5.

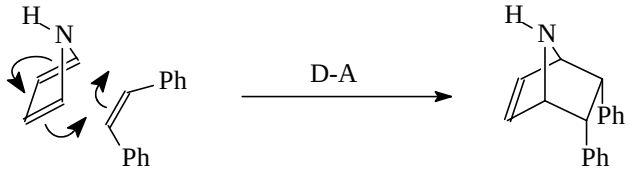


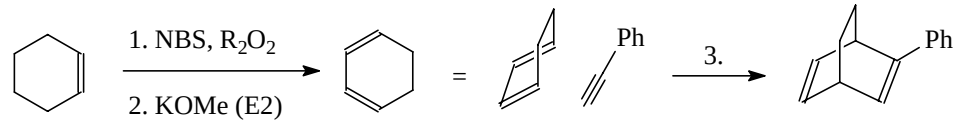
*product of thermodynamic contro*l -
more conjugated system than 1,4-adduct,
therefore, more stable

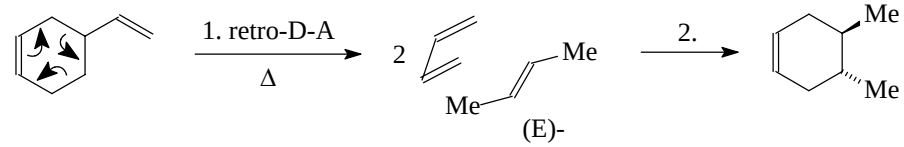
6. 
Δ
retro-D-A
+

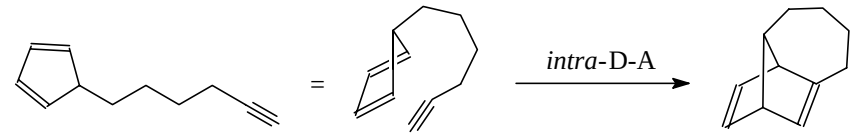
7. 
DBr (1 equiv),
ROOR
1,4-add'n
•Br
Br
Br
+DBr
-Br•
D
Br

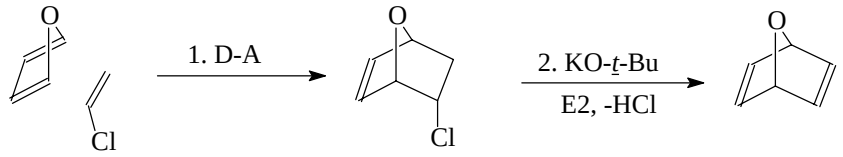
8. 
O
N
N
O
N
Ph
O
D-A
(4 + 2)
O
N
N
O
N
Ph
O

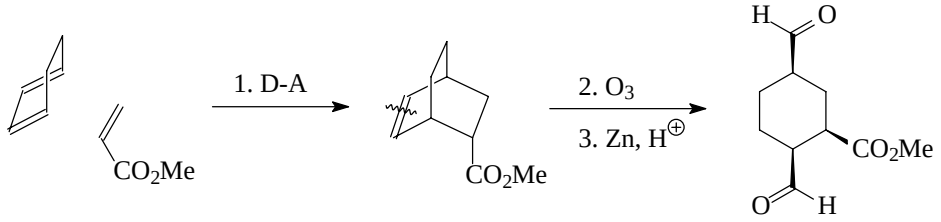
9. 
H
N
Ph
Ph
D-A
H
N
Ph
Ph

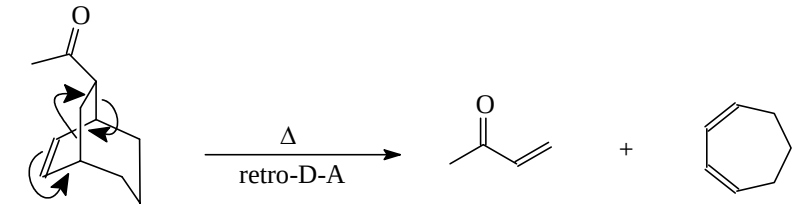
10. 
1. NBS, R2O2
2. KOMe (E2)
=
Ph
3.
Ph

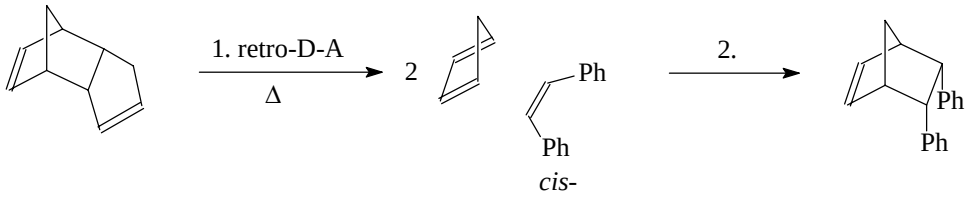
11. 
1. retro-D-A
Δ
2
Me
Me
(E)-
2.
Me
Me

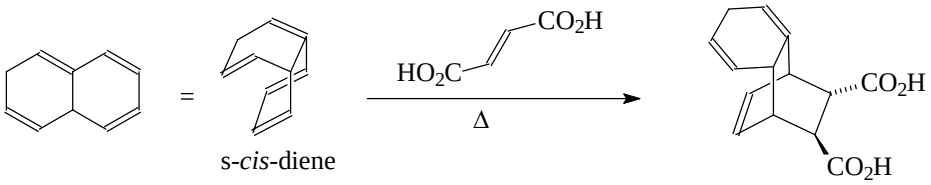
12. 
=
intra-D-A

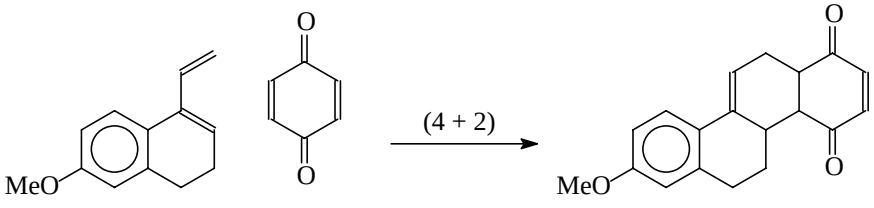
13. 

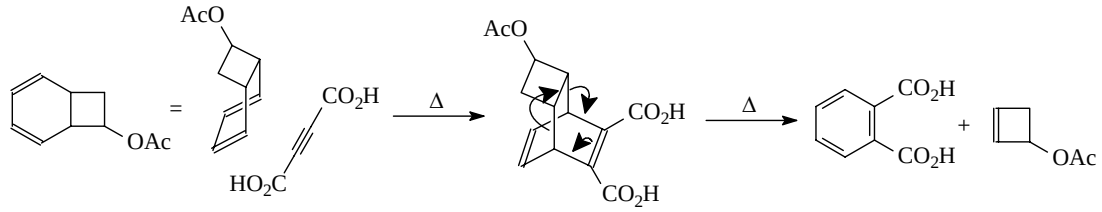
14. 

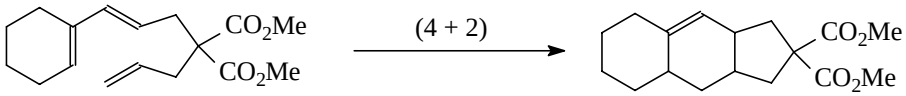
15. 

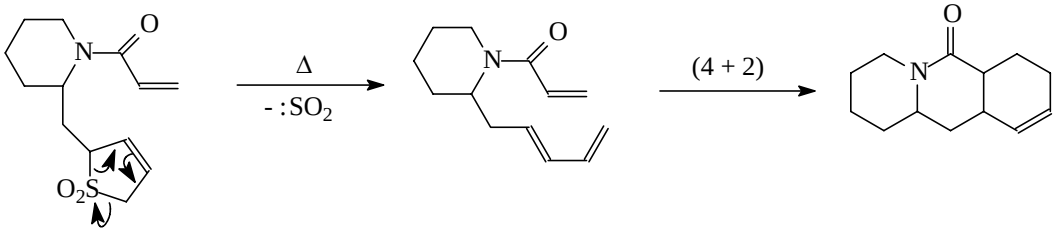
16. 

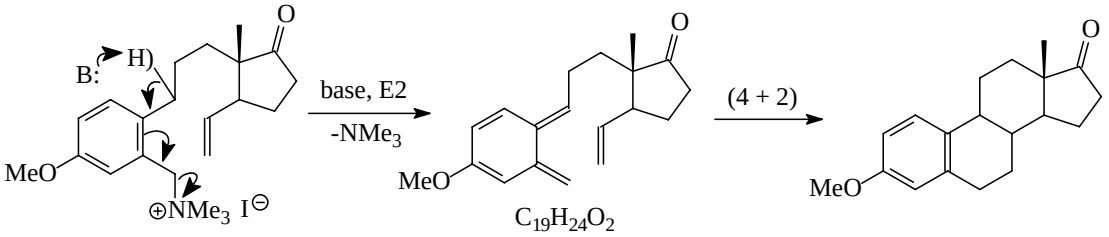
17. 

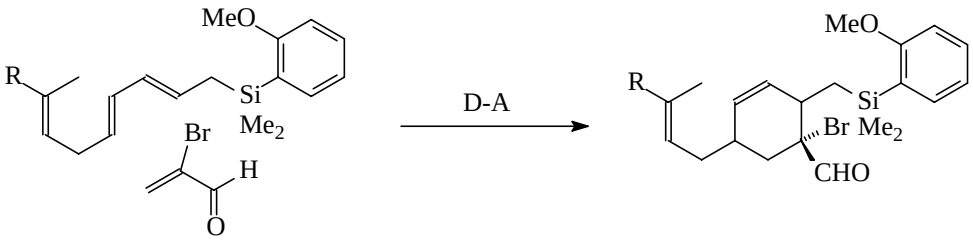
18. 

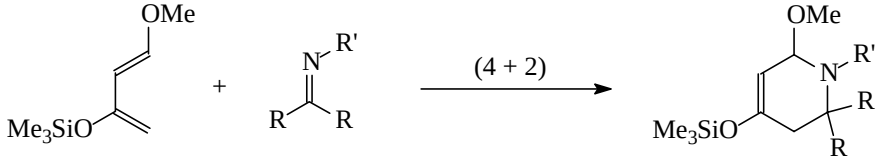
19. 

20. 

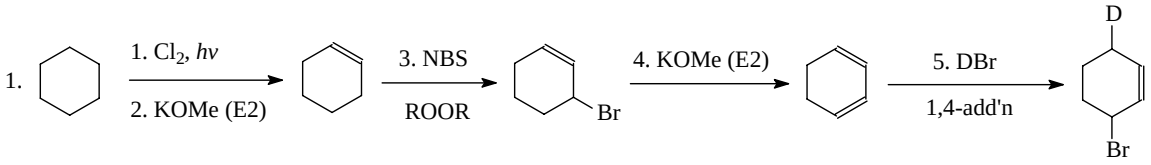
21. 

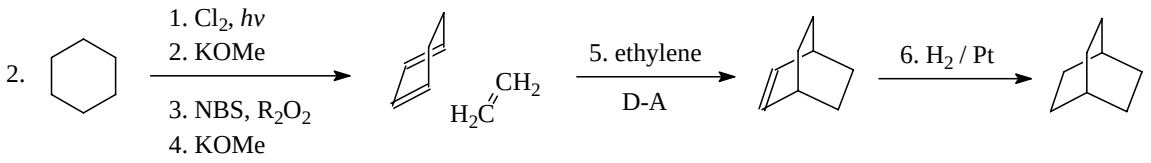
22. 

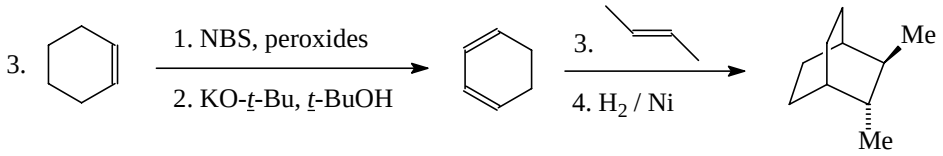
23. 

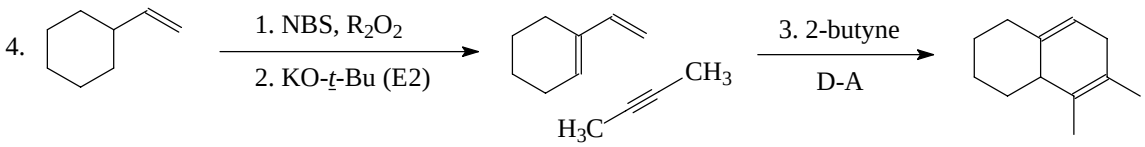
24. 

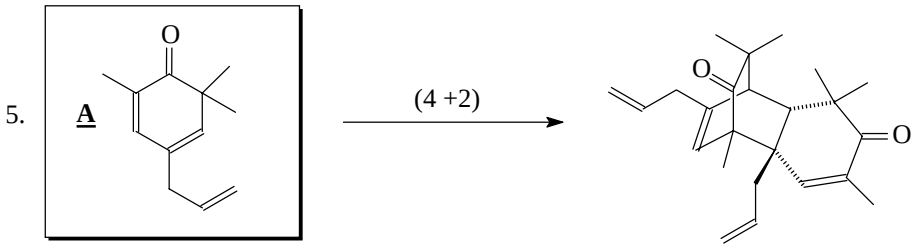
11.2 Syntheses

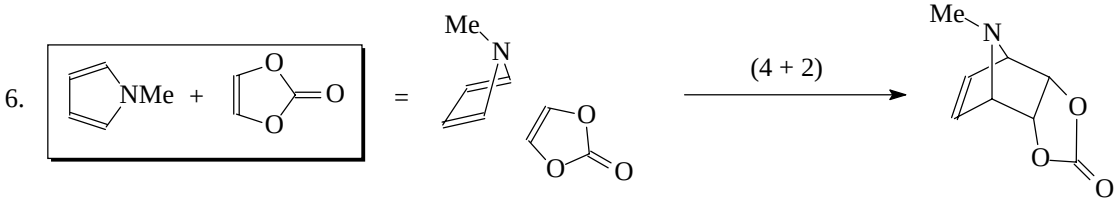
1. 

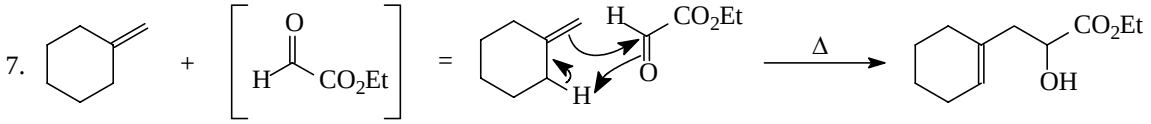
2. 

3. 

4. 

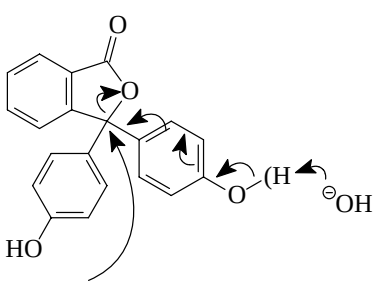
5. 

6. 

7. 

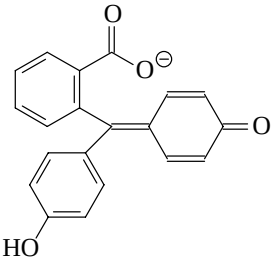
11.3 Mechanisms

1.



> pH 8.5

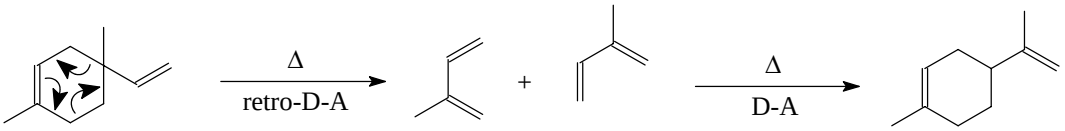
$-H^{\oplus}$



- sp^3 carbon prevents conjugation from one ring to the other two; therefore, absorption occurs at shorter wavelengths (UV in this case)

- > conjugation results in a 'red shift;' absorption occurs at a longer wavelength, moving into the VIS, and the molecule, therefore, is "colored"

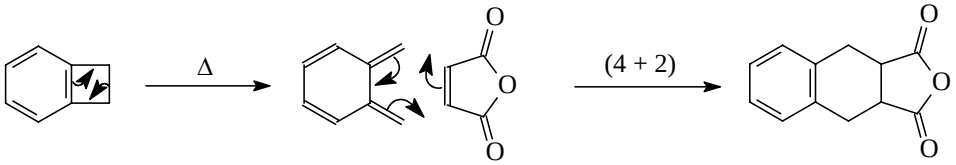
2.



Δ retro-D-A

Δ D-A

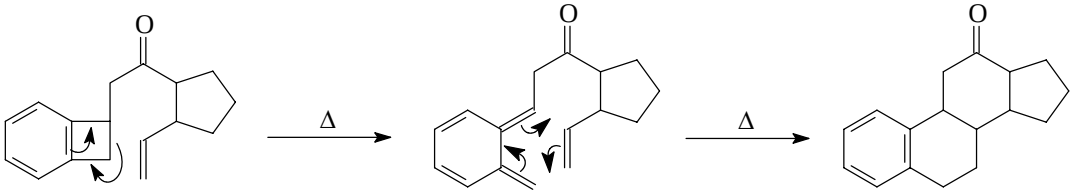
3. a.



Δ

(4 + 2)

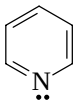
3. b.



Δ

Δ

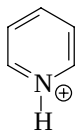
4. a.



longest λ_{max}: n ⟶ π*

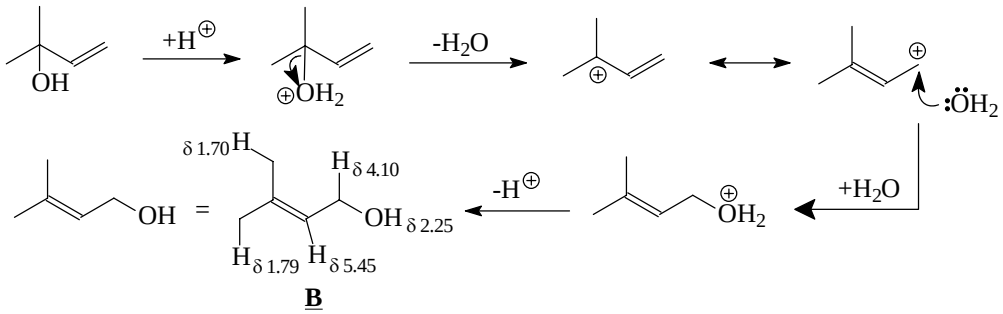
b. *low* probability $A = \varepsilon \cdot c \cdot d$ ε (molar absorptivity) only ~ 10 - 100 for $n \longrightarrow \pi^*$ transitions (*vs.* > 10,000 for $\pi \longrightarrow \pi^*$ transitions)

c.



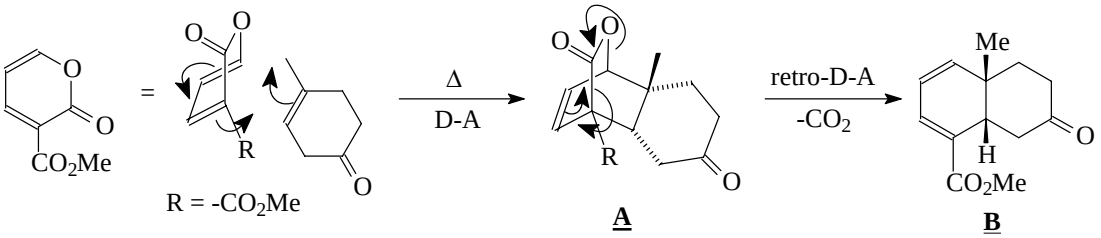
no non-bonding electrons in the CA of pyridine; therefore, no $n \longrightarrow \pi^*$ transition

5.


+H⊕
-H2O
OH
⊕OH2
:ÖH2
+H2O
-H⊕
δ 1.70 H
H δ 4.10
OH δ 2.25
H δ 1.79
H δ 5.45

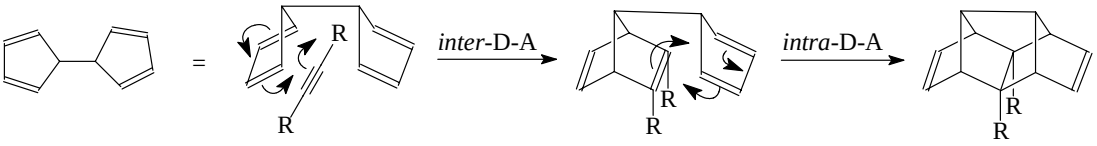
B

6.

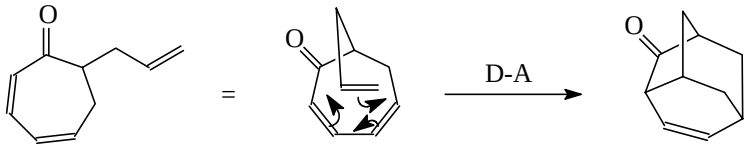

O
O
CO2Me
=
R = -CO2Me
Δ
D-A
retro-D-A
-CO2
Me
H
CO2Me

A **B**

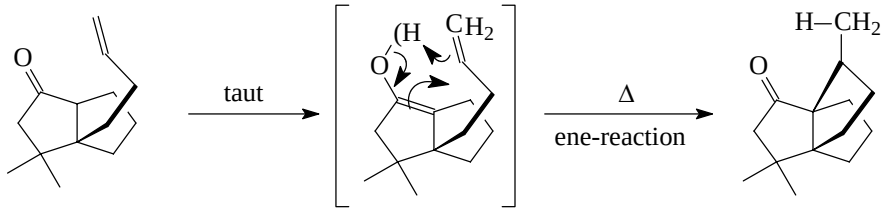
7.


=
R
R
inter-D-A
intra-D-A

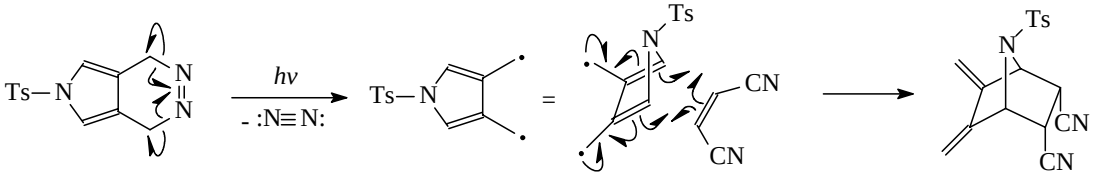
8.


O
=
D-A

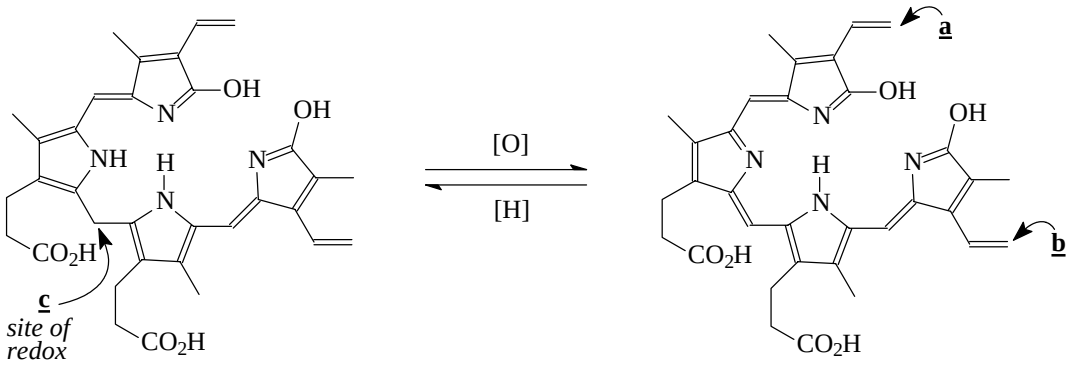
9.


O
taut
(H
CH2
O
Δ
ene-reaction
H—CH2
O

10.


Ts—N
N
N
hv
- :N≡N:
Ts—N
=
Ts
N
CN
CN
Ts
N
CN
CN

11.

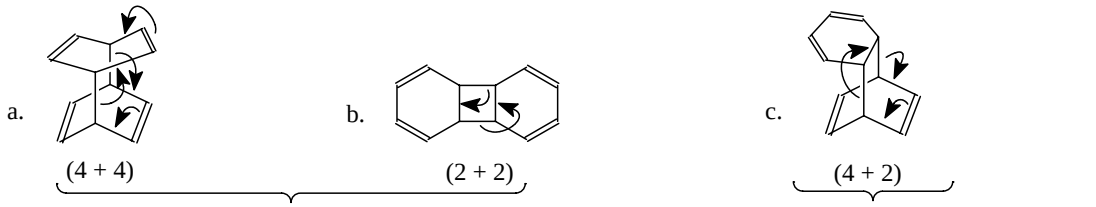


bilirubin (red) biliverdin (green)

Increased conjugation promotes a 'red shift' in λ_{max}, causing the color of pigments to move toward the green-blue end of the VIS spectrum:

- biliverdin is conjugated from C_a to C_b, whereas bilirubin's conjugation is disrupted (as a consequence of reduction) at C_c
- biliverdin, therefore, absorbs at longer wavelengths (red) than bilirubin; alternatively, biliverdin is transparent to shorter wavelengths (green).

12.



thermally forbidden

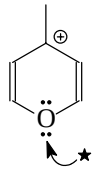
thermally allowed
therefore, most likely to occur

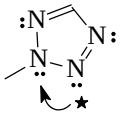
CHAPTER 12
AROMATICS

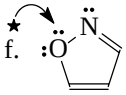
12.1 General

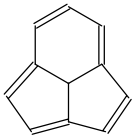
1. The following compounds obey the Hückel (4n +2) rule and would be expected to have aromatic character:

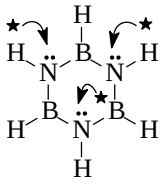
 = lone pairs of electrons are in a p orbital (other lone pairs are in sp^2 orbitals)

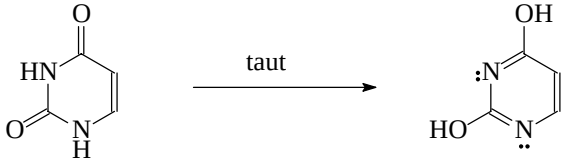
b. 

d. 

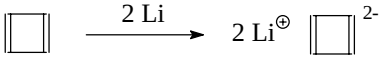
f. 

i. 

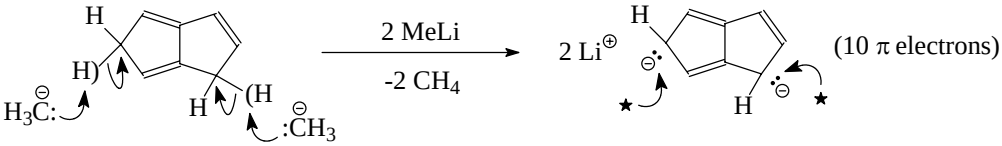
j. 

k. 

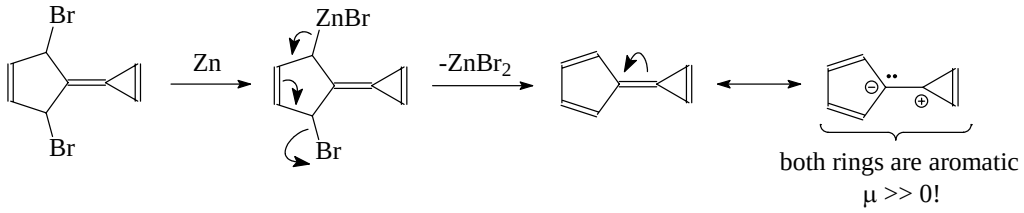
(6 π electrons)

m. product: 

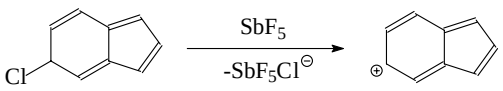
(6 π electrons)

n. product: 

(10 π electrons)

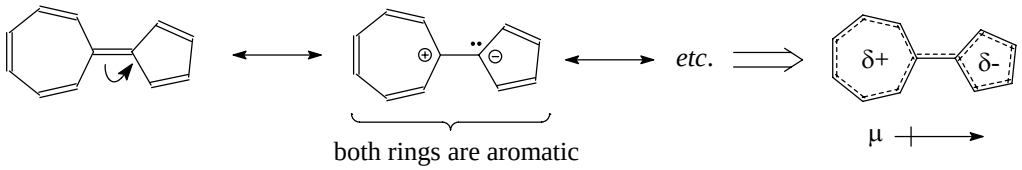
o. product: 

both rings are aromatic
μ >> 0!

Note: l. carbocation from the reaction of 

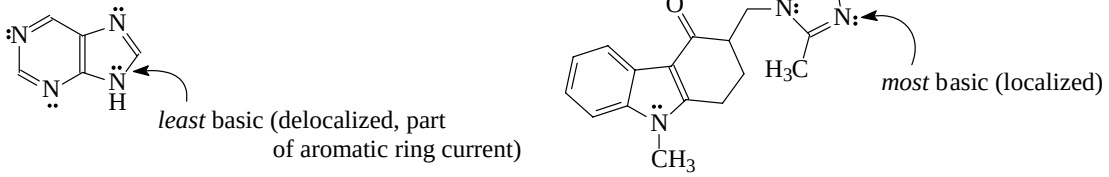
(8 π electrons ≠ 4n+ 2)

2. largest μ: a.

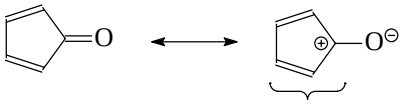


note: flow of electrons in either direction in b or c would result in one ring being aromatic and the other anti-aromatic, thereby lessening the benefit of charge separation and lowering μ.

3.

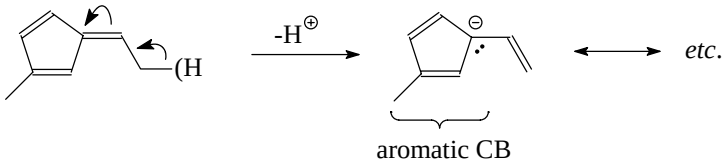


4. least stable: b.



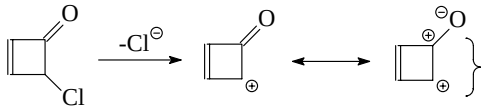
a and c have corresponding aromatic, and therefore stabilizing, contributing resonance structures

5. most acidic: d.

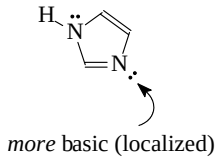


loss of a proton from a, b, or c would produce a resonance-stabilized, *but not aromatic*, CB

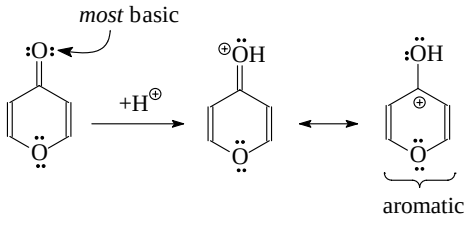
6. most likely to undergo an S_N1 reaction: a.



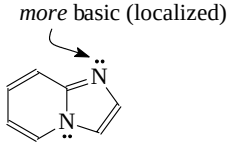
7. a.

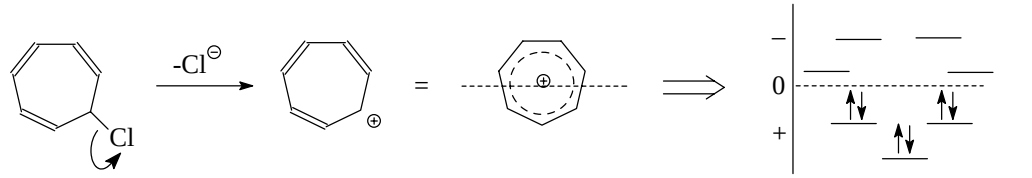


b.

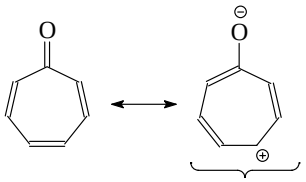


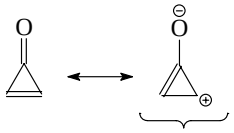
c.



8. 

aromatic - all protons are equivalent ⟸ all bonding MOs are filled

9. largest molecular dipole moment: b. 

vs. d. 

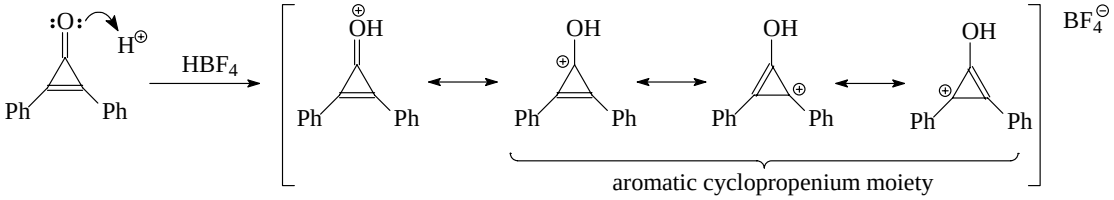
aromatic contributor with longer charge separation (>*d*)

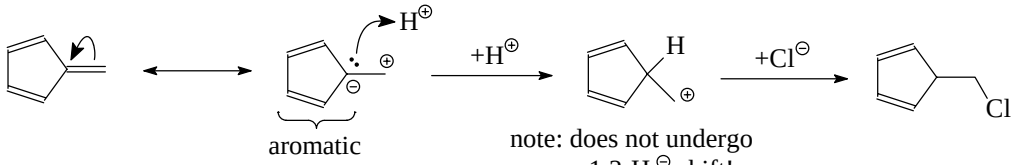
aromatic contributor with shorter charge separation

$\mu = \varepsilon \cdot d$

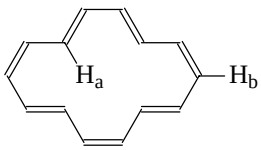
-aromaticity promotes charge separation in b and d (but not a or c), thereby increasing ε

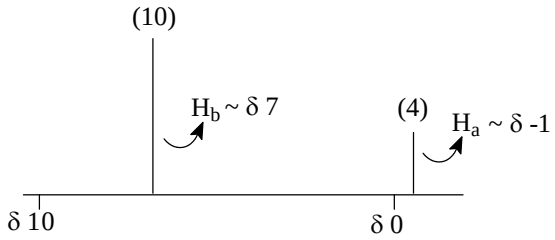
-charge separation distance (*d*) is greater in b than d

10. 

11. 

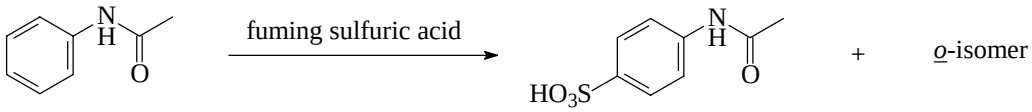
note: does not undergo a 1,2-H:⊖ shift!

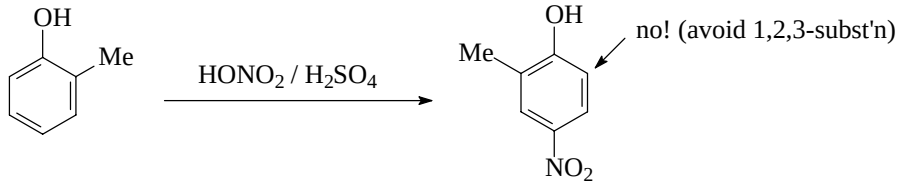
12. 

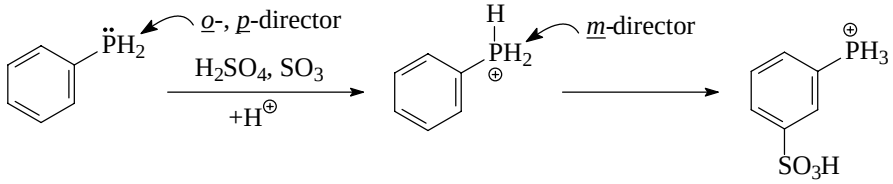
^{1}H NMR: 

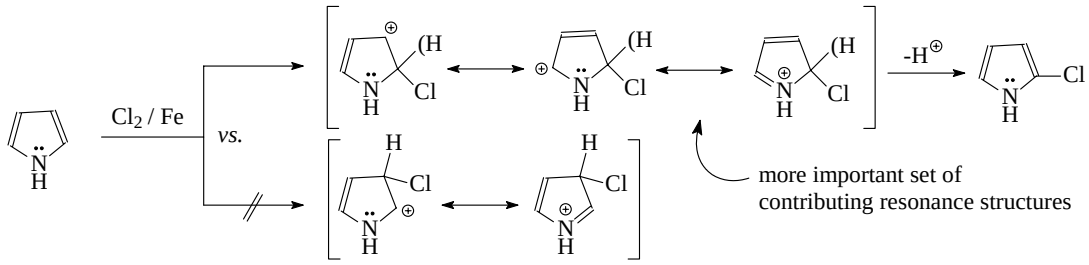
magnetic anisotropy causes the four H_a protons to be highly shielded (above TMS) and the ten H_b protons to be deshielded (into the aromatic region)

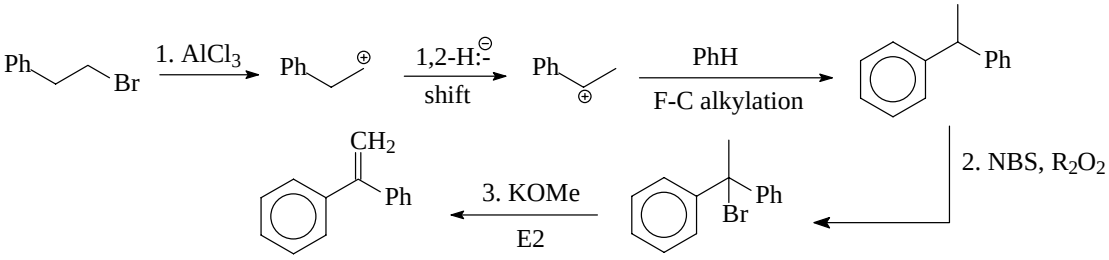
12.2 Reactions

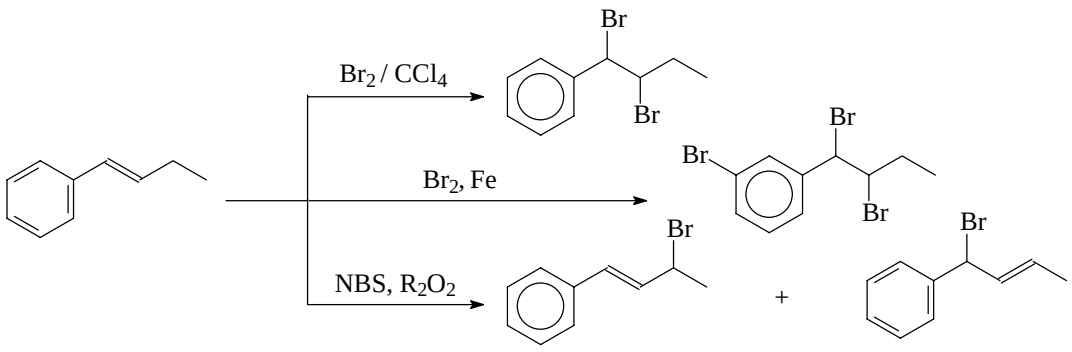
1. 

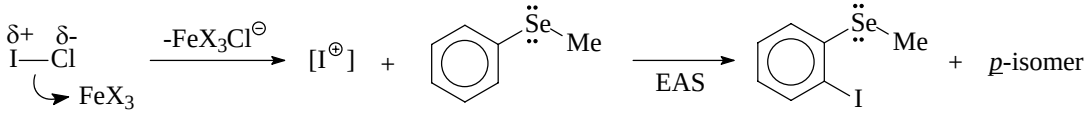
2. 

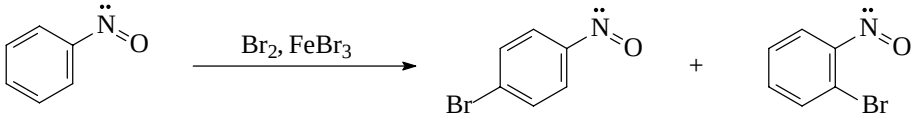
3. 

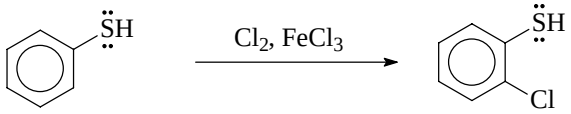
4. 

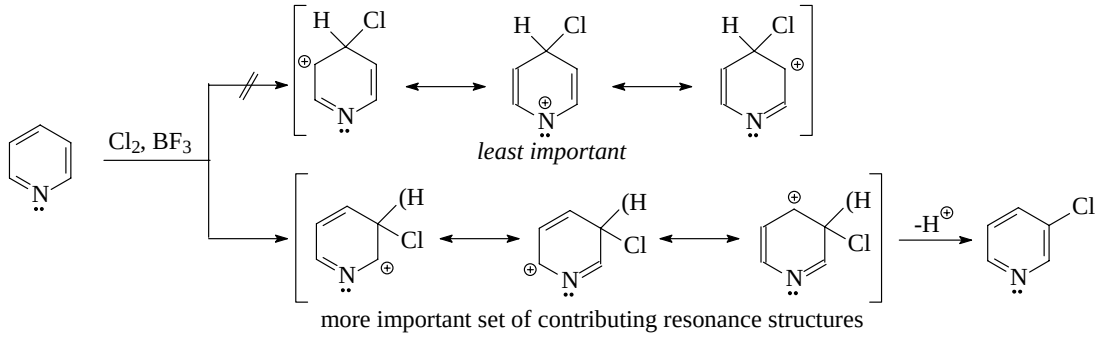
5. 

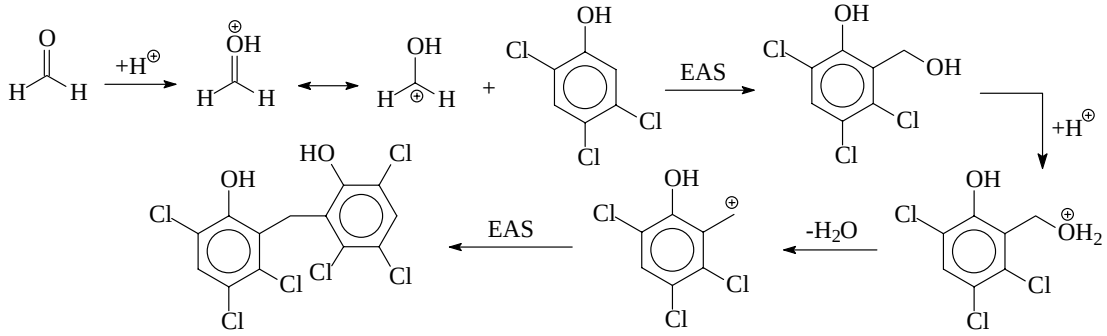
6. 

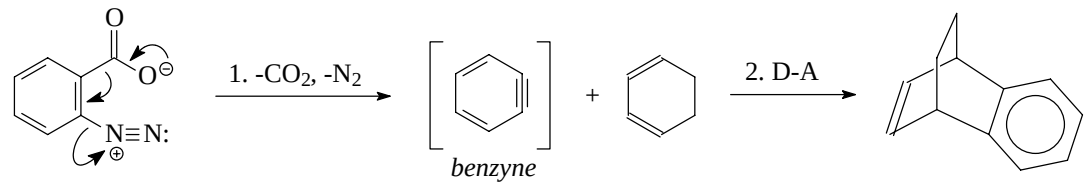
7. 
δ+ δ-
I—Cl
FeX3
-FeX3Cl⊖
[I⊕]
+
Se
Me
EAS
Se
Me
I
+ p-isomer

8. 
N
O
Br2, FeBr3
Br
+
N
O
Br

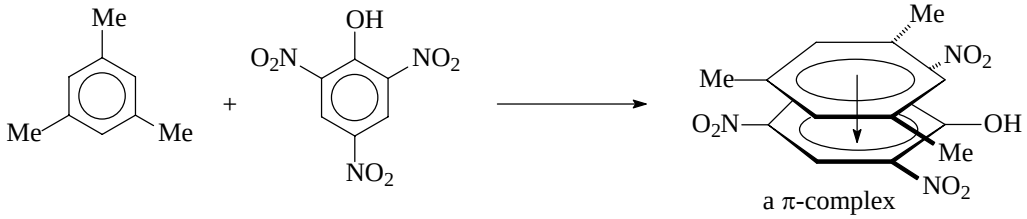
9. 
SH
Cl2, FeCl3
SH
Cl
+ p-isomer

10. 
Cl2, BF3
least important
more important set of contributing resonance structures
-H⊕
Cl

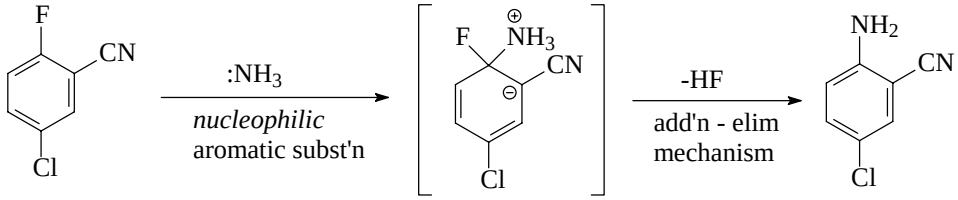
11. 
+H⊕
EAS
-H2O
EAS
+H⊕

12. 
1. -CO2, -N2
benzyne
+
2. D-A

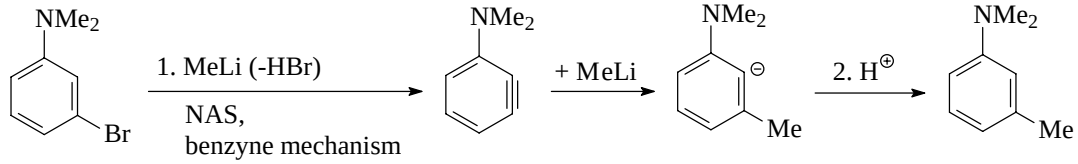
13.



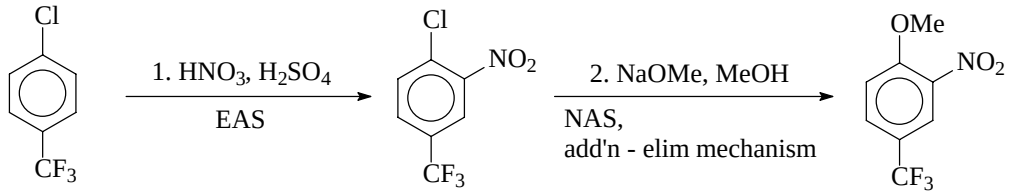
14.



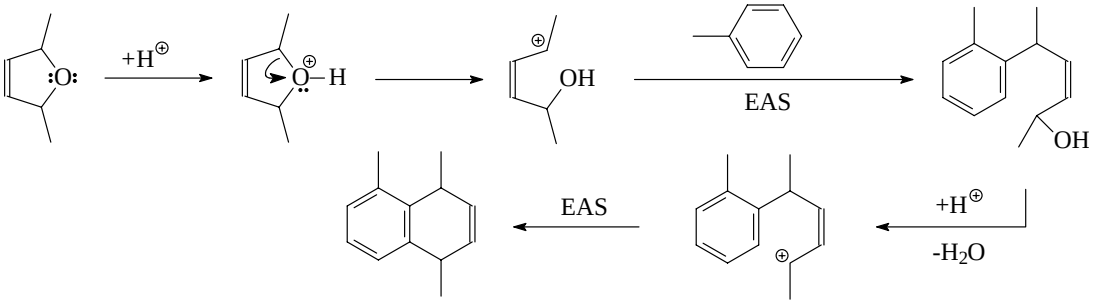
15.



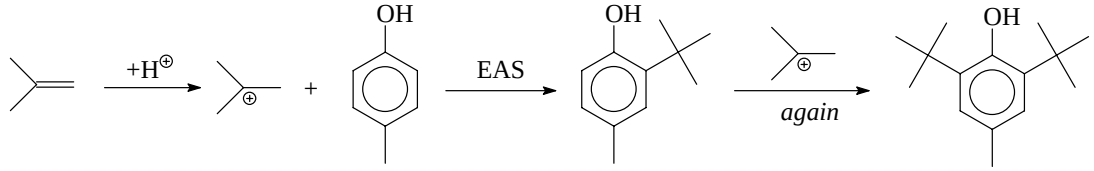
16.



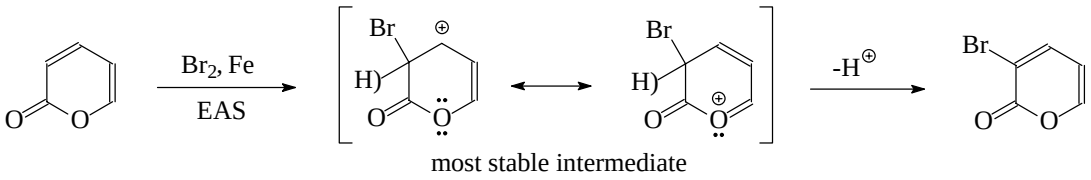
17.



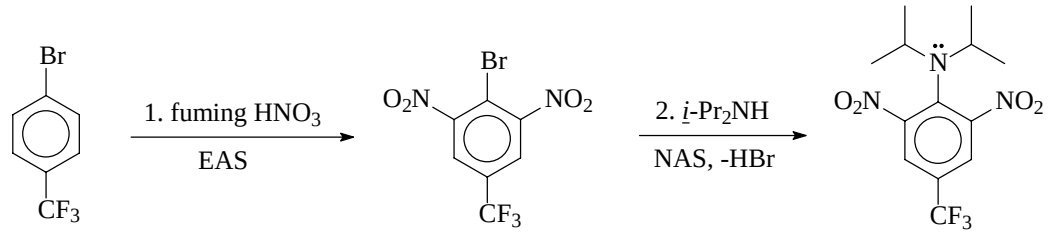
18.



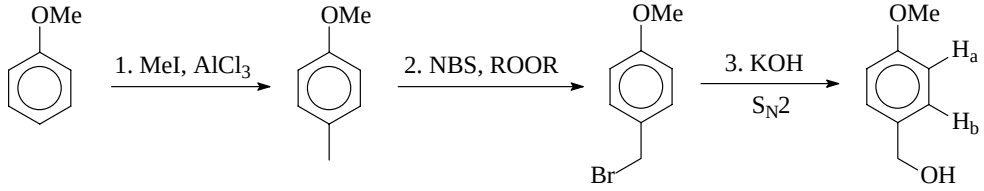
19.



20.

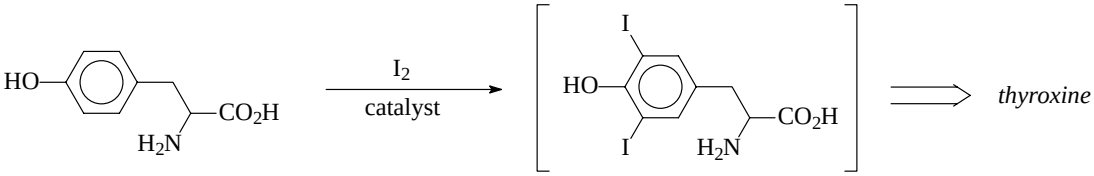


21.

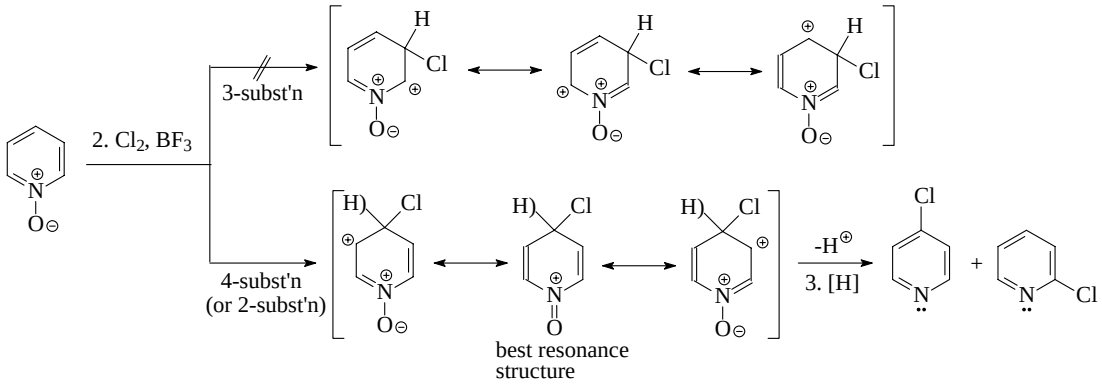


^{1}H NMR: aromatic a-b quartet suggests *p*-subst'n

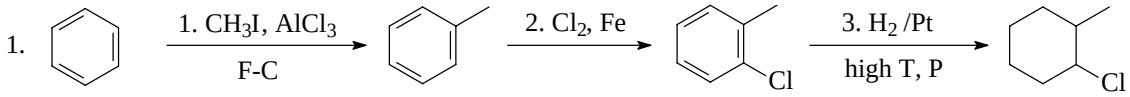
22.

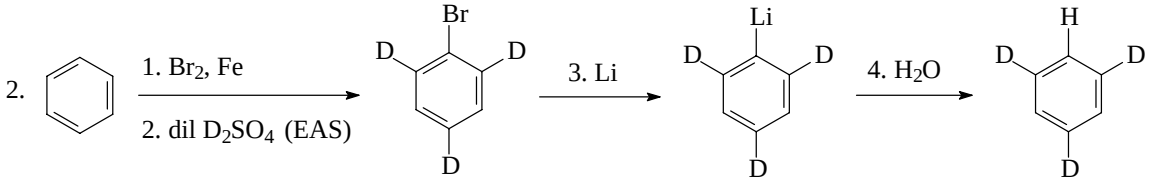


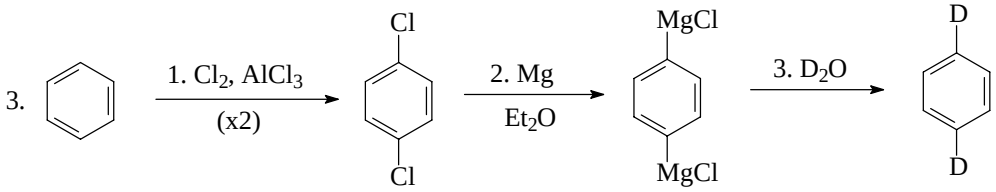
23.

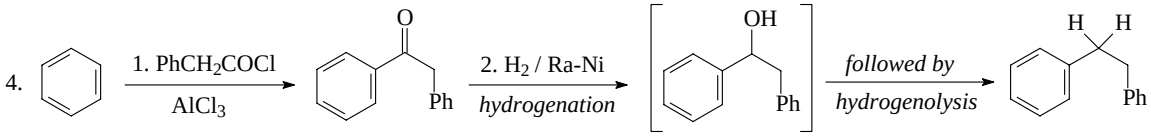


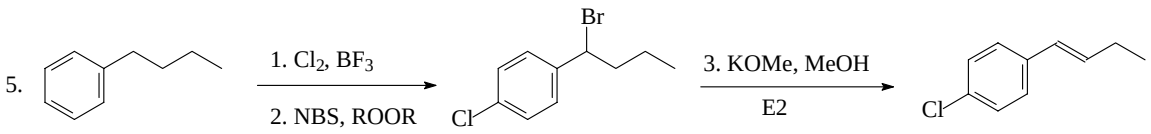
12.3 Syntheses

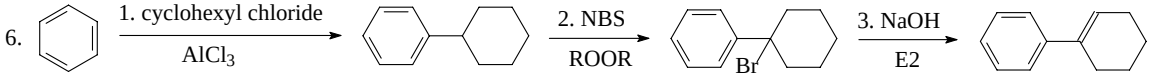
1. 

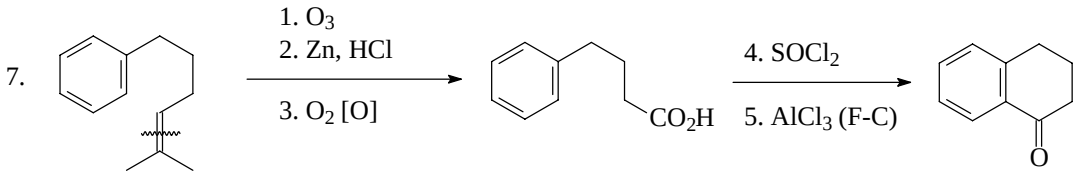
2. 

3. 

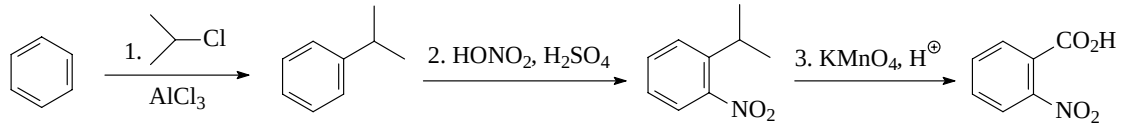
4. 

5. 

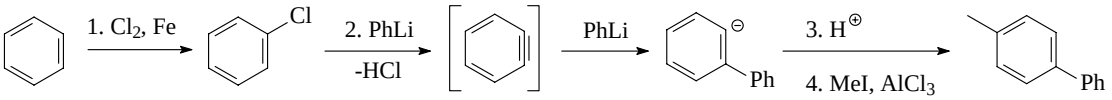
6. 

7. 

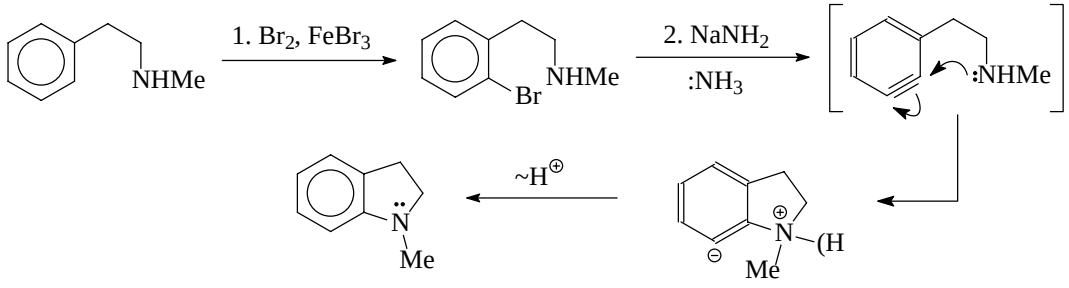
8.


1.
Cl
AlCl3
2. HONO2, H2SO4
NO2
3. KMnO4, H⊕
CO2H
NO2

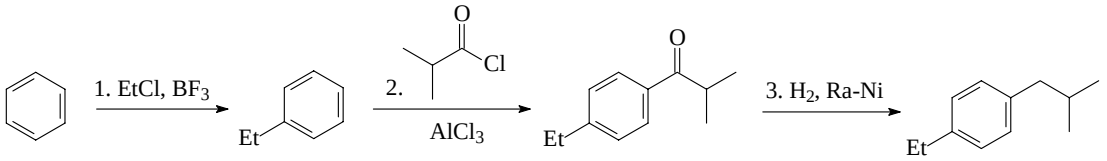
9.


1. Cl2, Fe
Cl
2. PhLi
-HCl
PhLi
Ph
3. H⊕
4. MeI, AlCl3
Ph

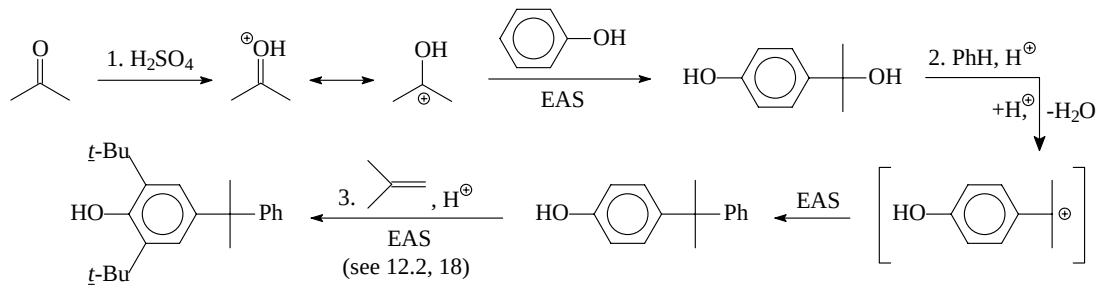
10.


NHMe
1. Br2, FeBr3
Br
NHMe
2. NaNH2
:NH3
:NHMe
~H⊕
N
Me
N
(H
Me

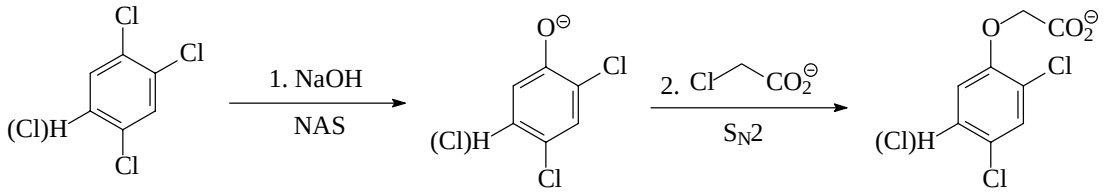
11.

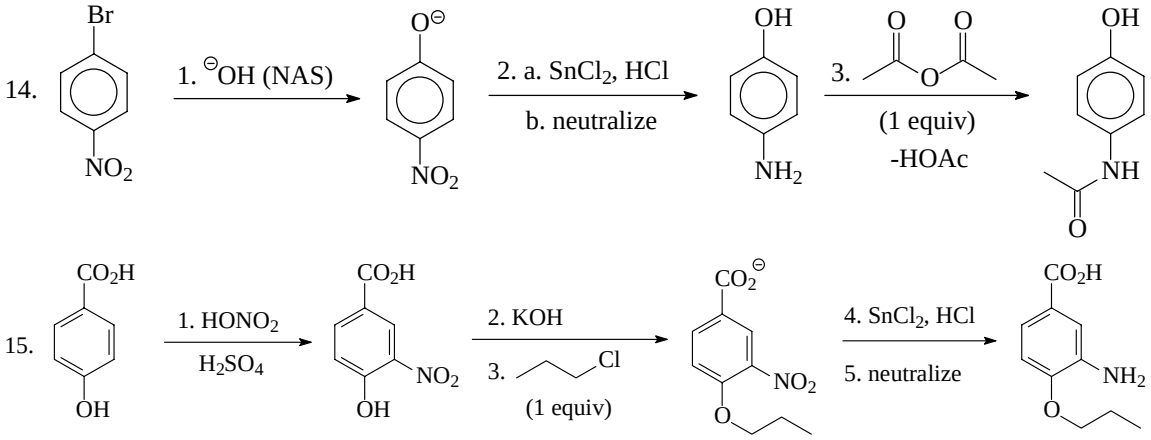

1. EtCl, BF3
Et
2.
O
Cl
AlCl3
Et
O
3. H2, Ra-Ni
Et

12.

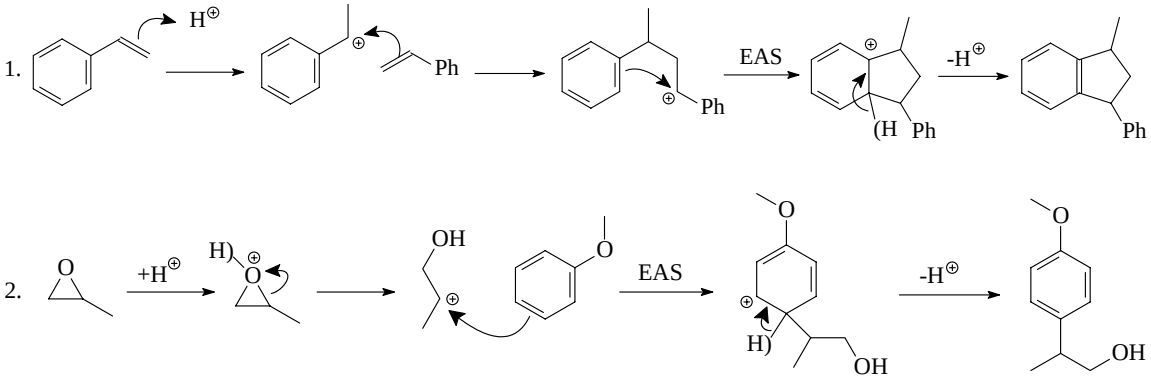

O
1. H2SO4
⊕OH
OH
OH
EAS
HO
OH
2. PhH, H⊕
+H⊕
-H2O
t-Bu
HO
Ph
t-Bu
3.
, H⊕
EAS
(see 12.2, 18)
HO
Ph
EAS
HO

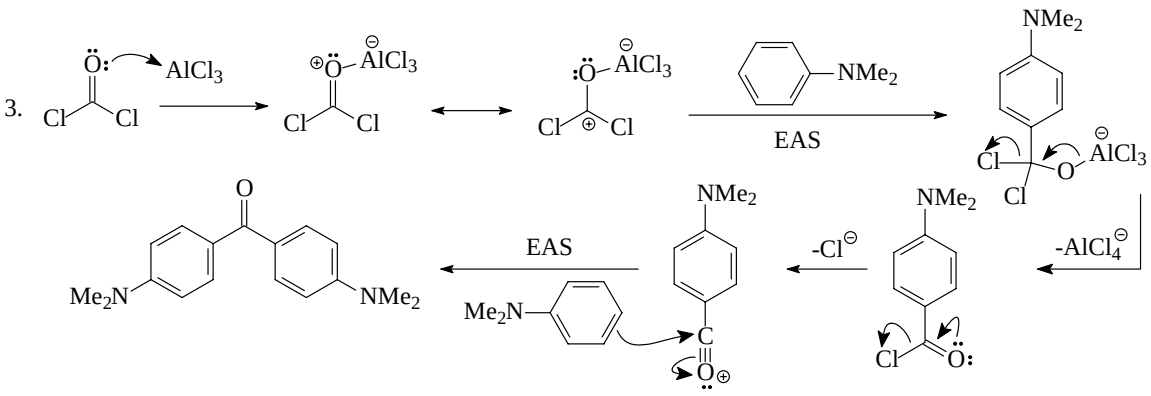
13.

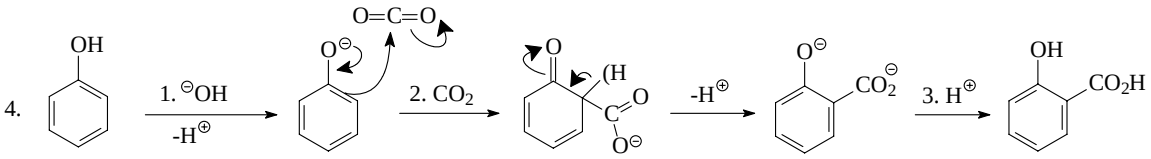

Cl
Cl
(Cl)H
Cl
1. NaOH
NAS
O⊖
Cl
(Cl)H
Cl
2. Cl
CO2⊖
SN2
O
CO2⊖
Cl
(Cl)H
Cl



12.4 Mechanisms







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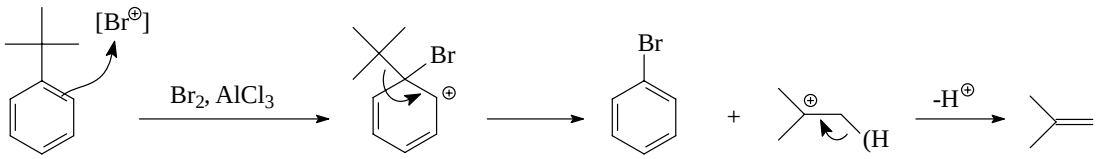
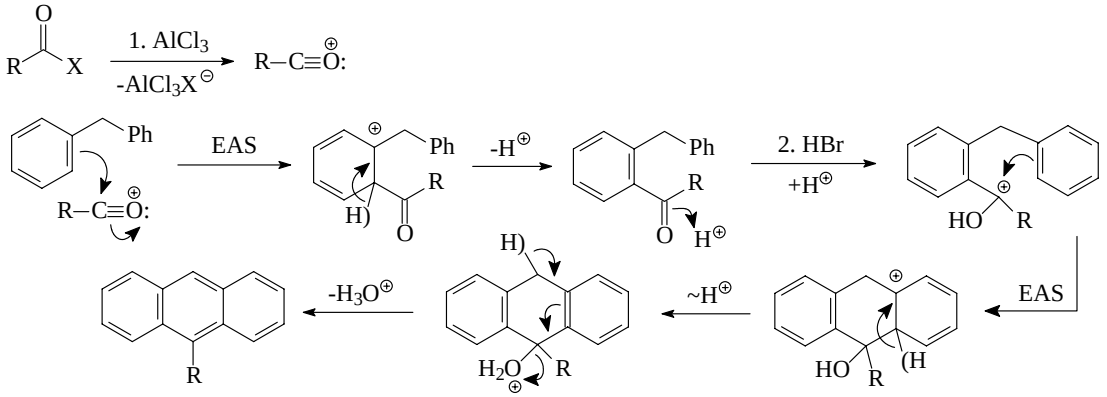
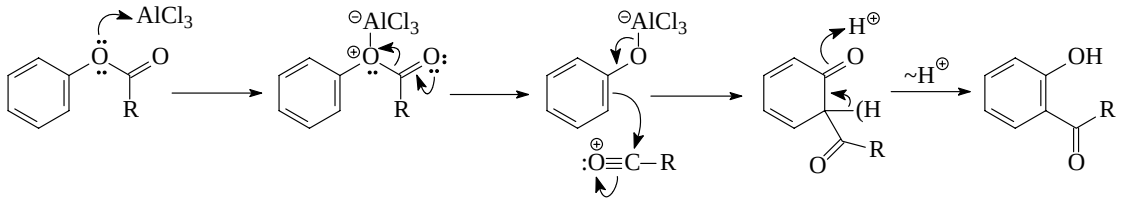

[Br⊕]
Br2, AlCl3
Br
+
(H
-H⊕

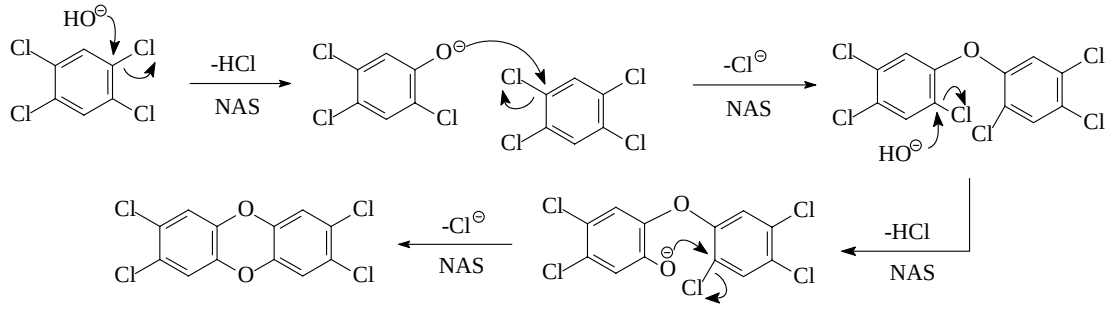
6.


1. AlCl3
-AlCl3X⊖
R–C≡O:
Ph
EAS
-H⊕
2. HBr
+H⊕
HO
R
-H3O⊕
~H⊕
H2O
(H
H)

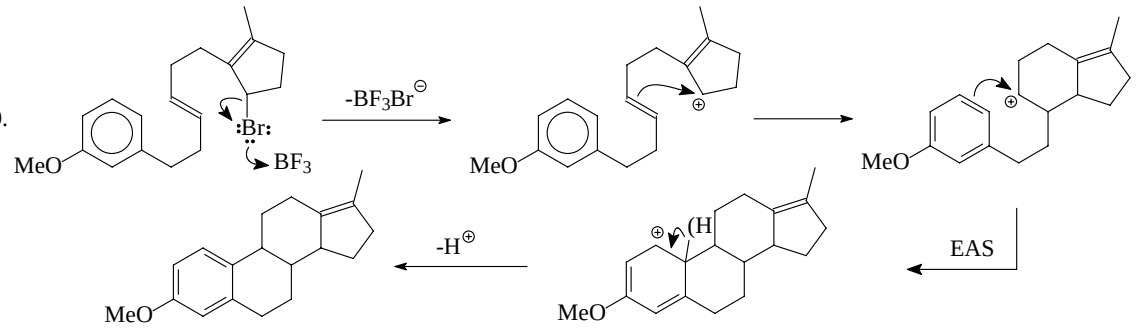
7.


AlCl3
:O≡C–R
~H⊕
OH

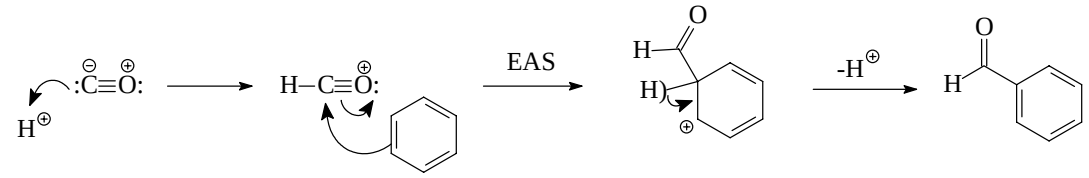
8.


HO⊖
-HCl
NAS
-Cl⊖
-Cl⊖
-HCl

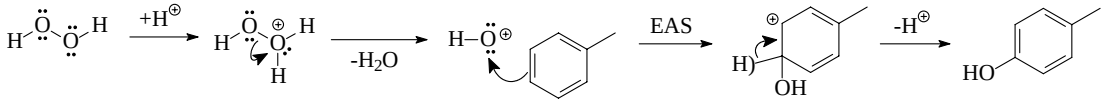
9.


-BF3Br⊖
MeO
BF3
-H⊕
EAS
(H

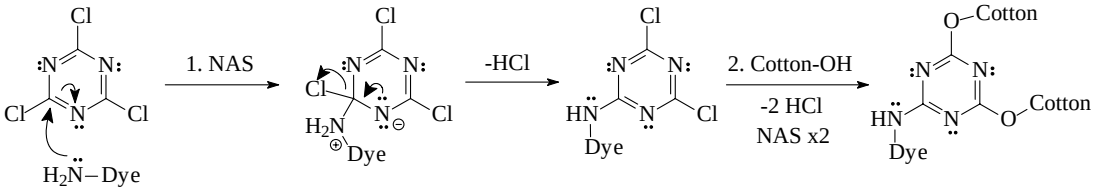
10.


EAS
-H⊕

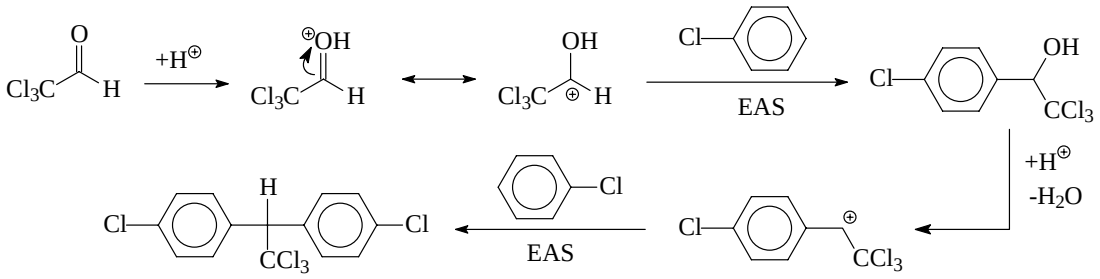
11.


+H⊕
-H2O
EAS
-H⊕

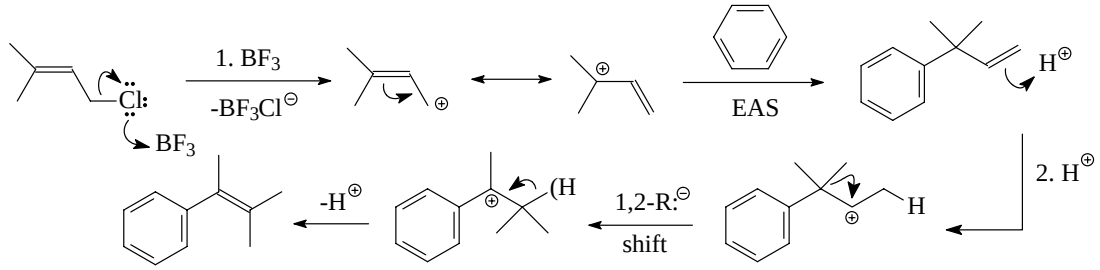
12.


1. NAS
-HCl
2. Cotton-OH
-2 HCl
NAS x2
H2N–Dye
Dye
Cotton

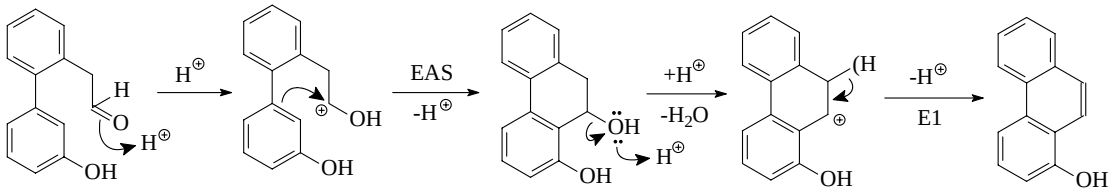
13.


+H⊕
EAS
+H⊕
-H2O
EAS

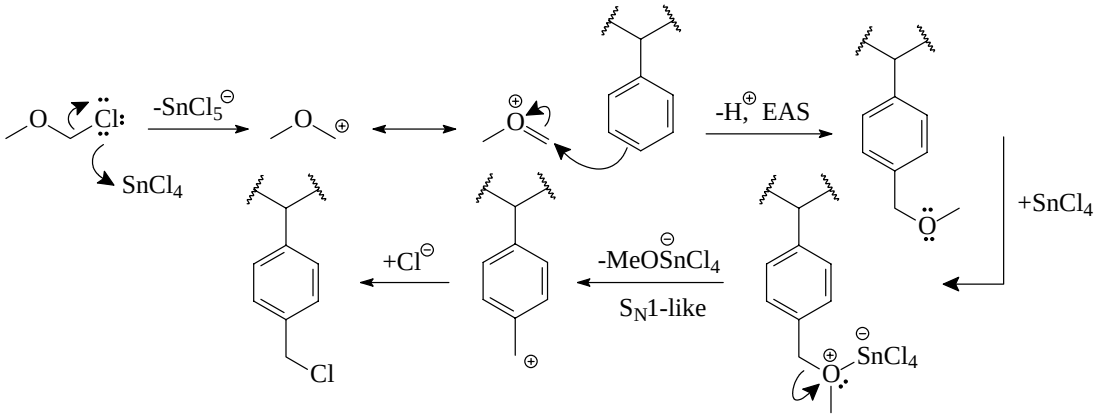
14.


1. BF3
-BF3Cl⊖
EAS
2. H⊕
1,2-R:⊖
shift
-H⊕

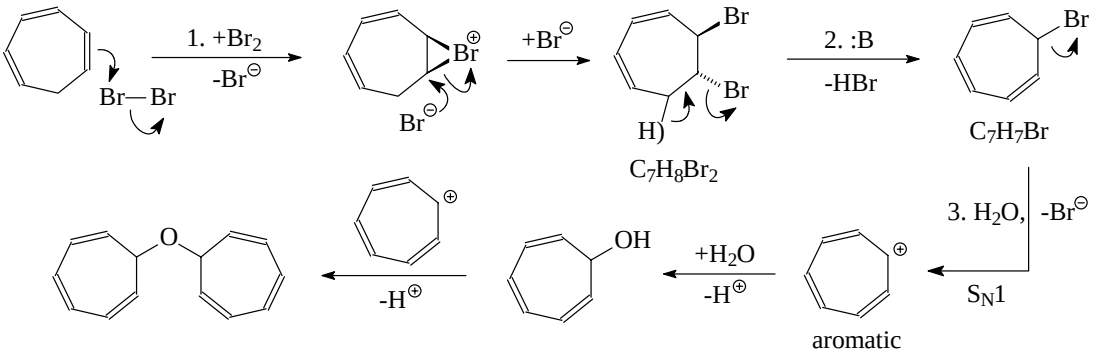
15.


H⊕
EAS
-H⊕
+H⊕
-H2O
-H⊕
E1
OH

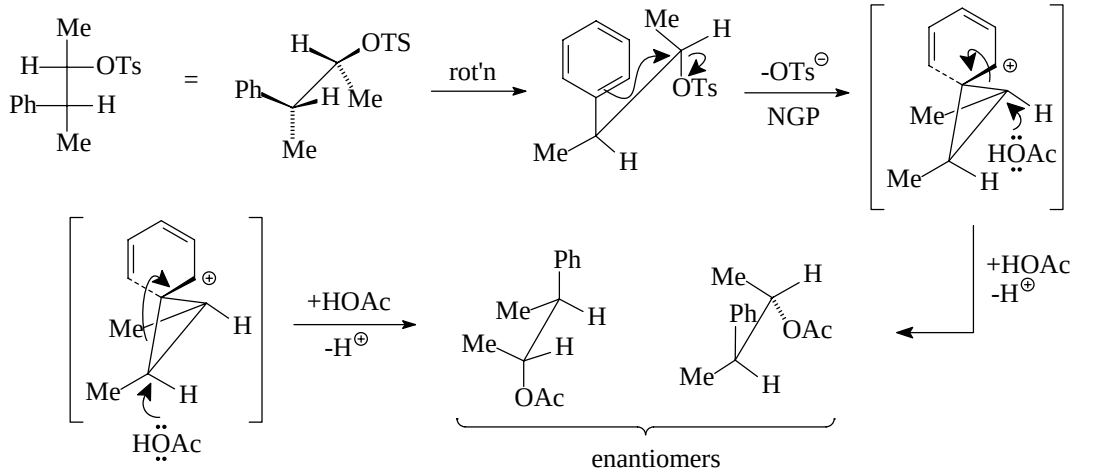
16.


-SnCl5⊖
SnCl4
-H⊕, EAS
+SnCl4
+Cl⊖
-MeOSnCl4⊖
SN1-like
SnCl4⊖
Cl

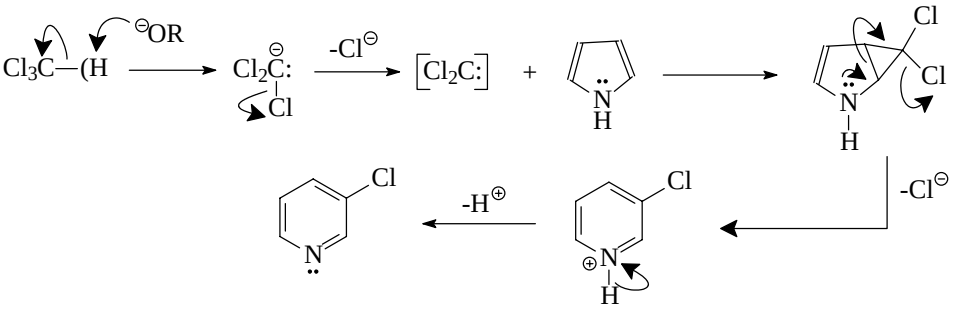
17.


1. +Br2
-Br⊖
+Br⊖
2. :B
-HBr
C7H8Br2
C7H7Br
3. H2O, -Br⊖
SN1
aromatic
+H2O
-H⊕
-H⊕

18.


=
rot'n
-OTs⊖
NGP
+HOAc
-H⊕
+HOAc
-H⊕
enantiomers

19.



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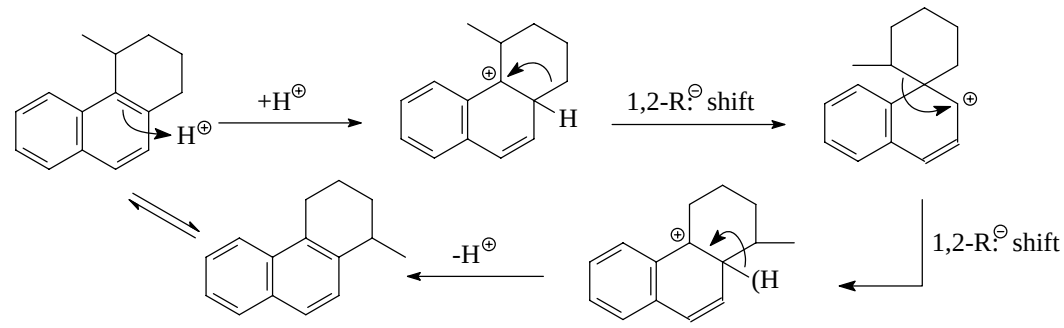

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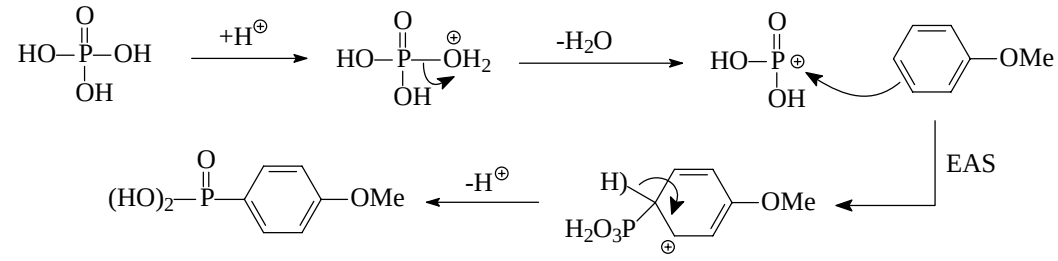

CHAPTER 13
ALCOHOLS

13.1 Reactions

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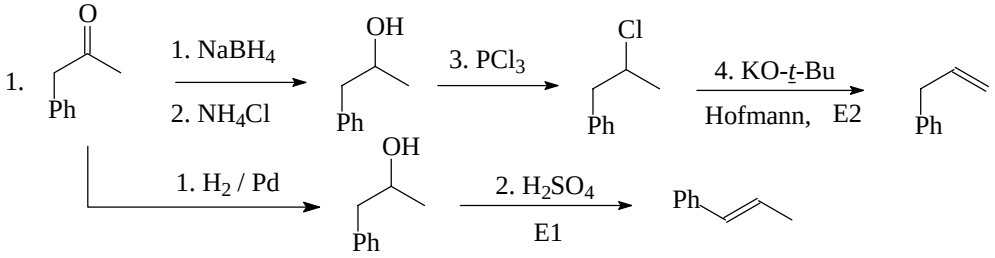

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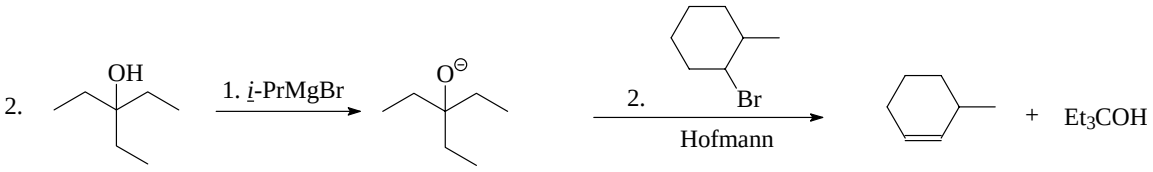

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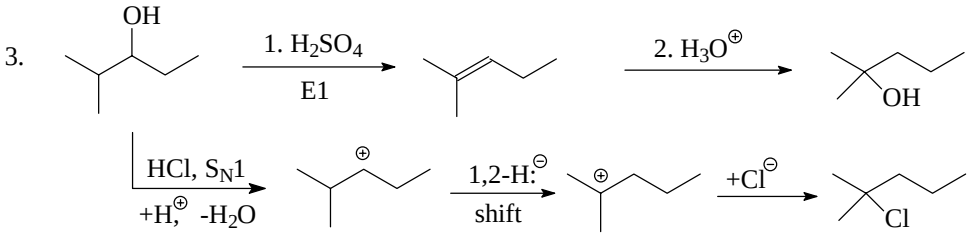

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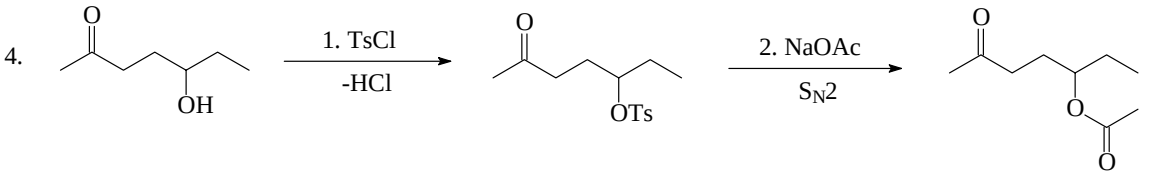

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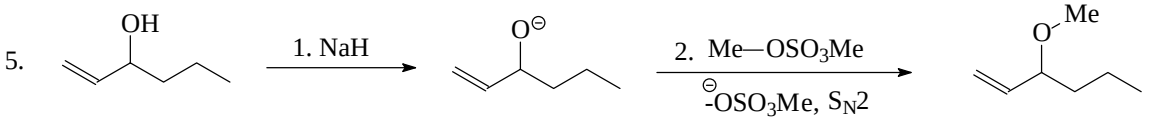

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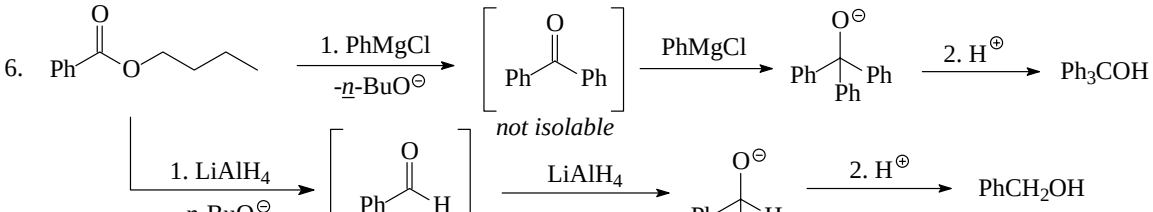

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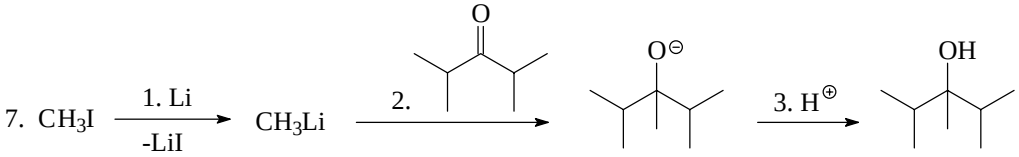
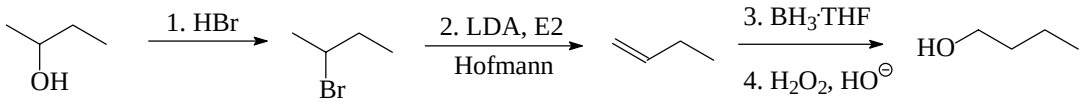
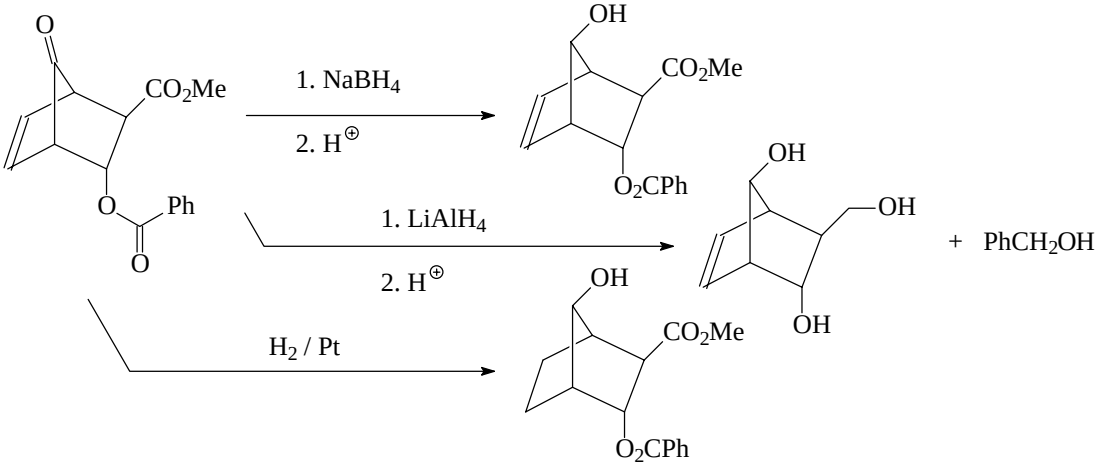
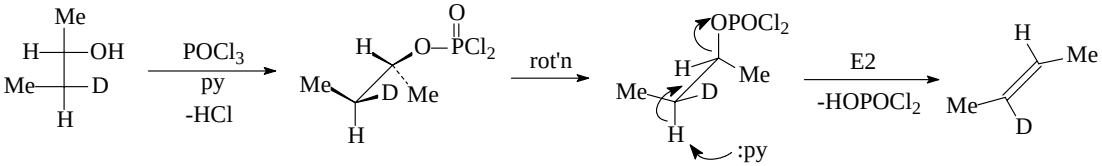
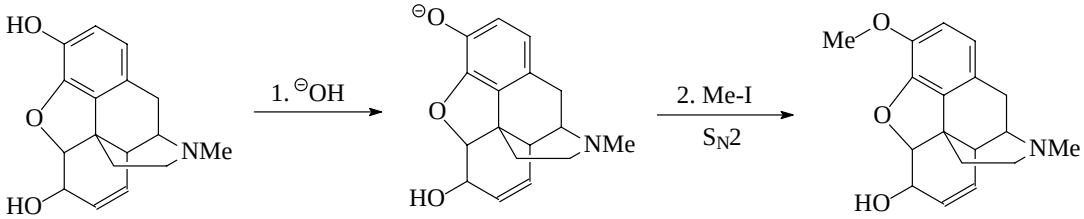
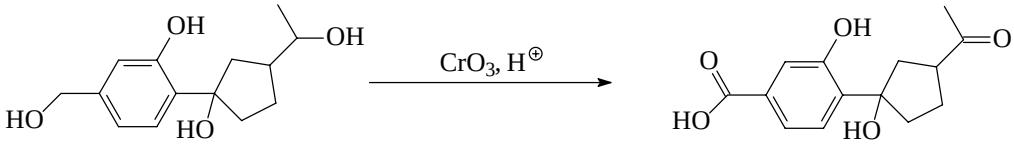


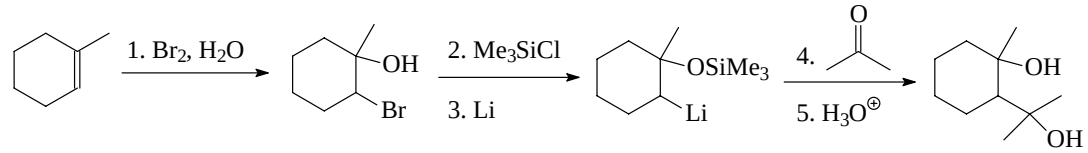
8. 

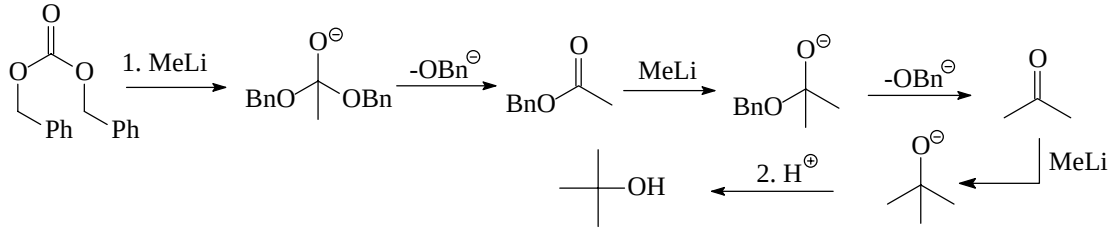
9. 

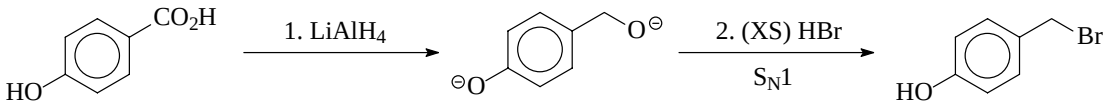
10. 

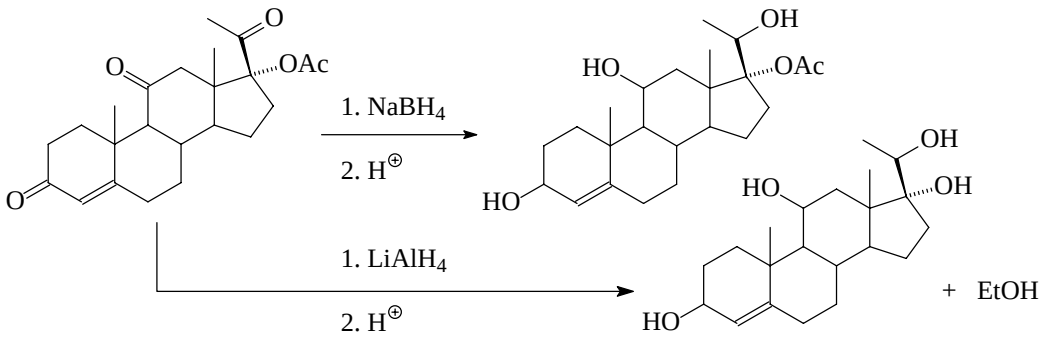
11. 

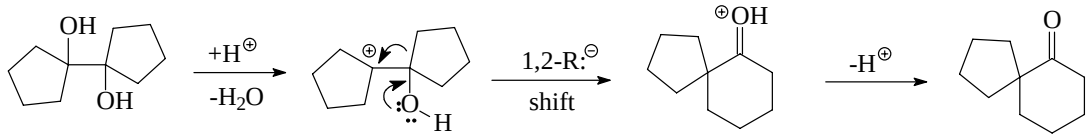
12. 

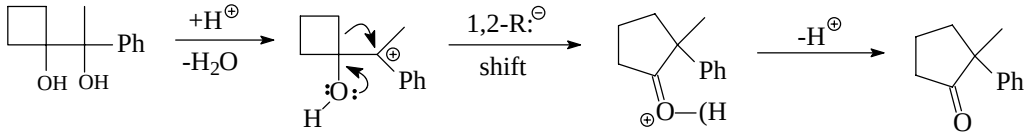
13. 

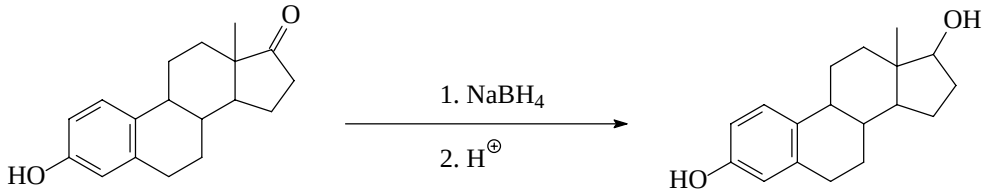
14. 

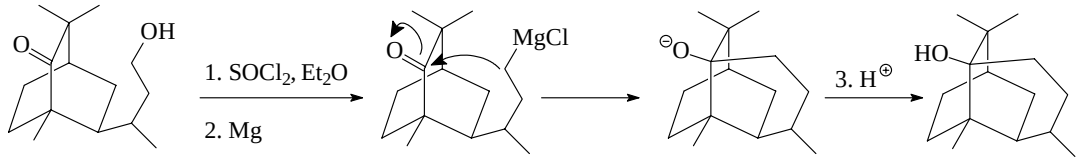
15. 

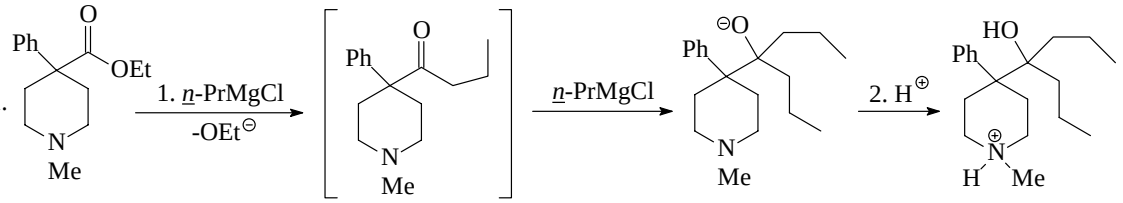
16. 

17. 

18. 

19. 

20. 

21. 

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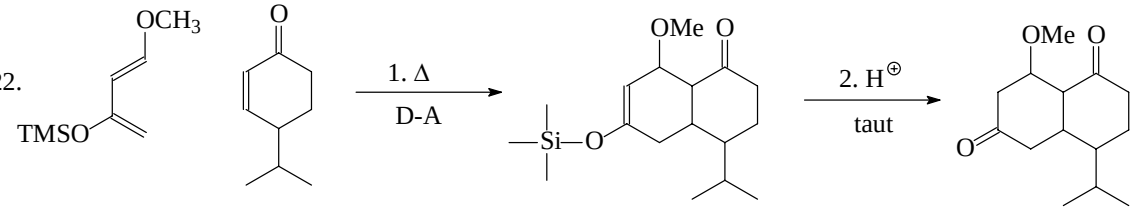

13.2 Syntheses

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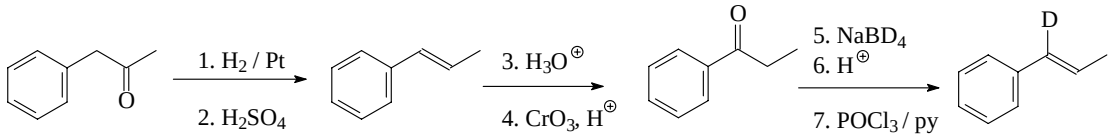

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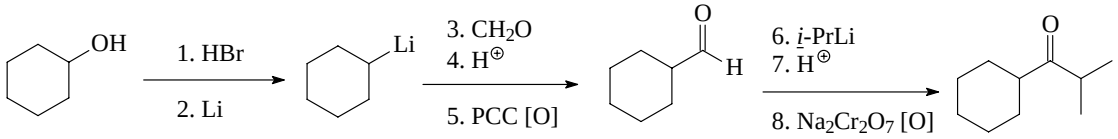

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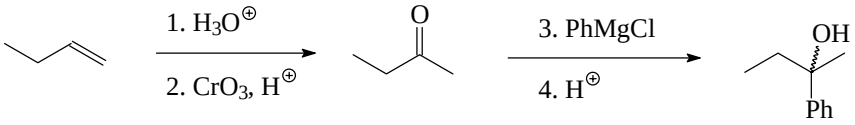

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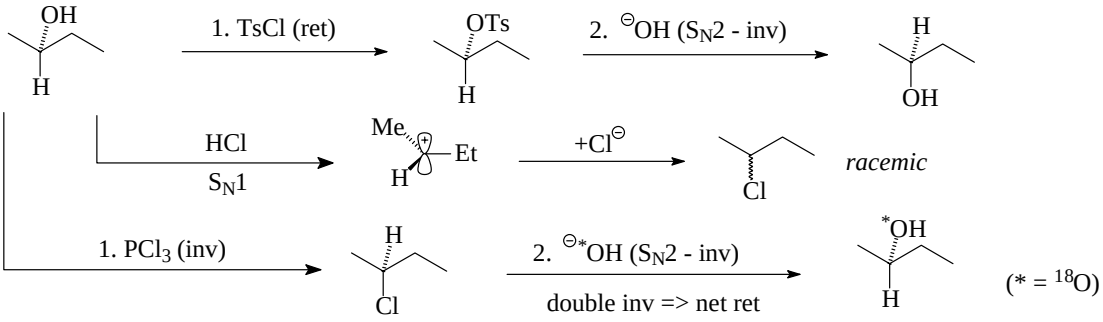

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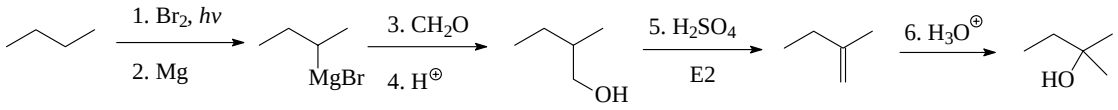

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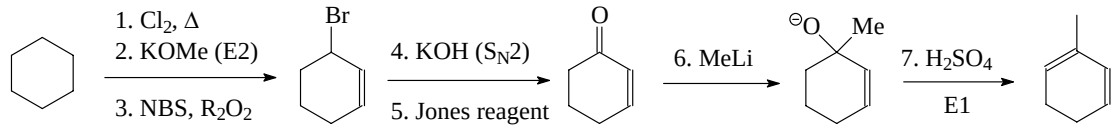
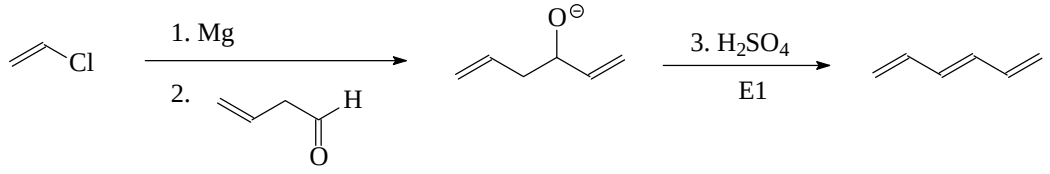
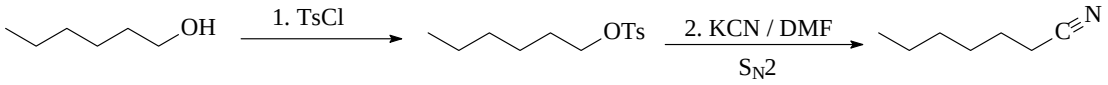
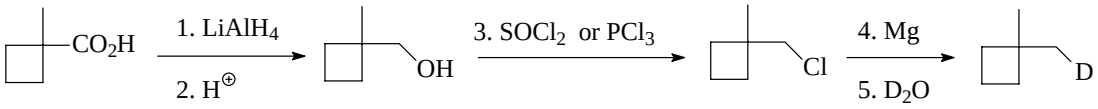
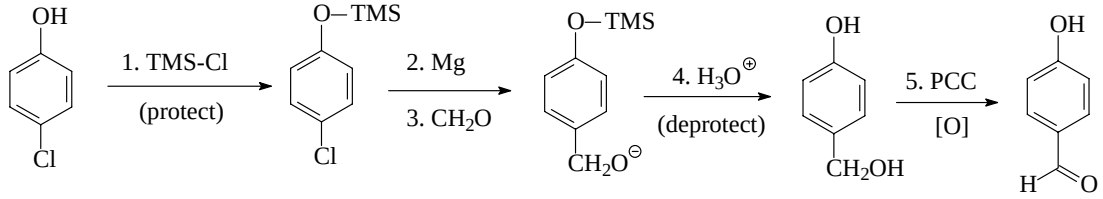
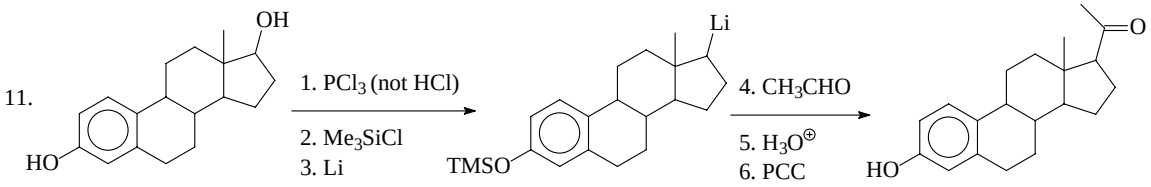


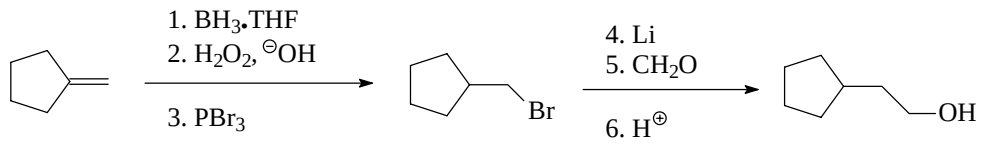
7. 

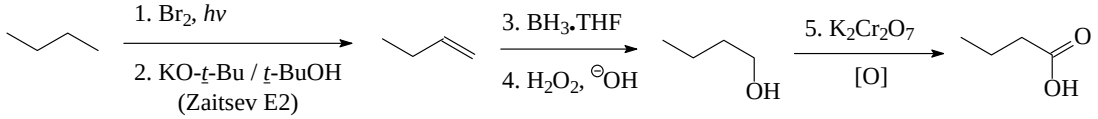
8. 

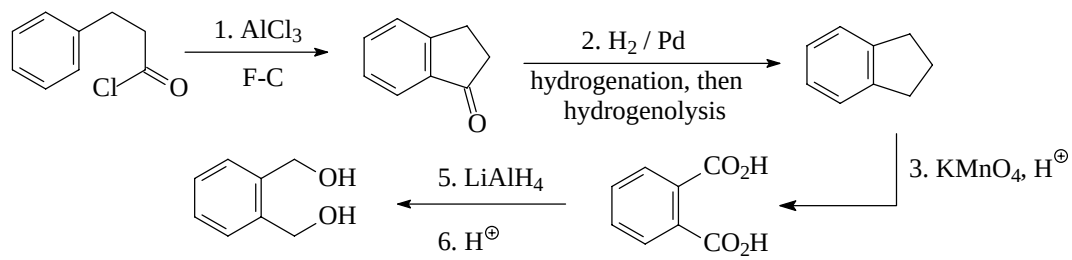
9. 

10. 

11. 

12. 

13. 

14. 

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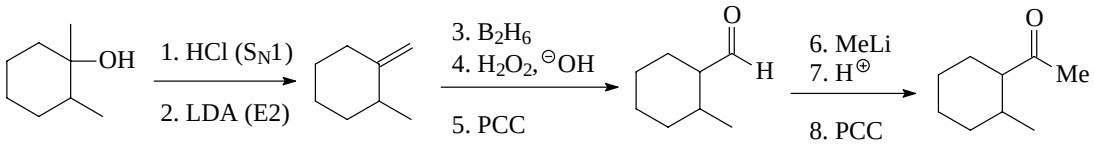

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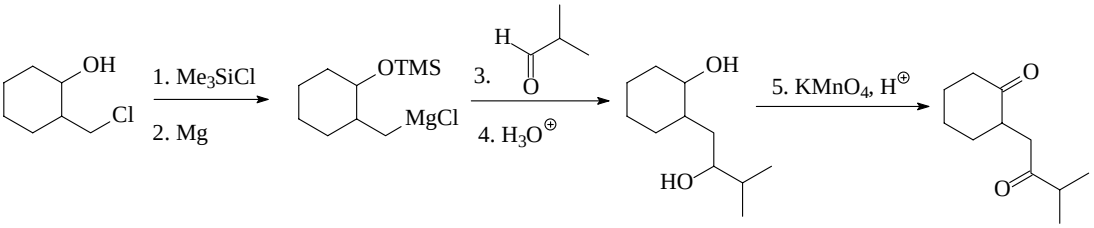

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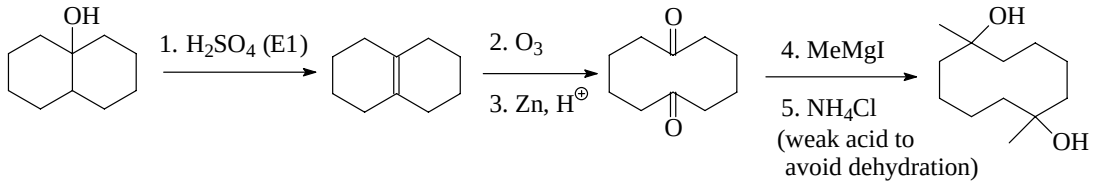

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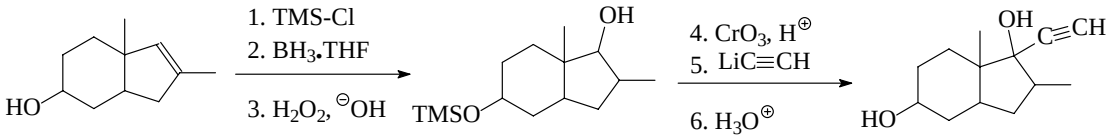

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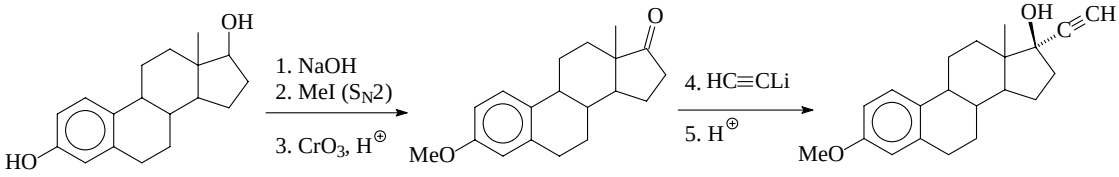

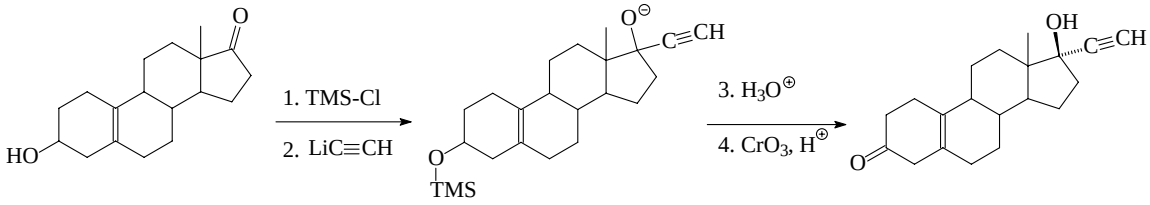

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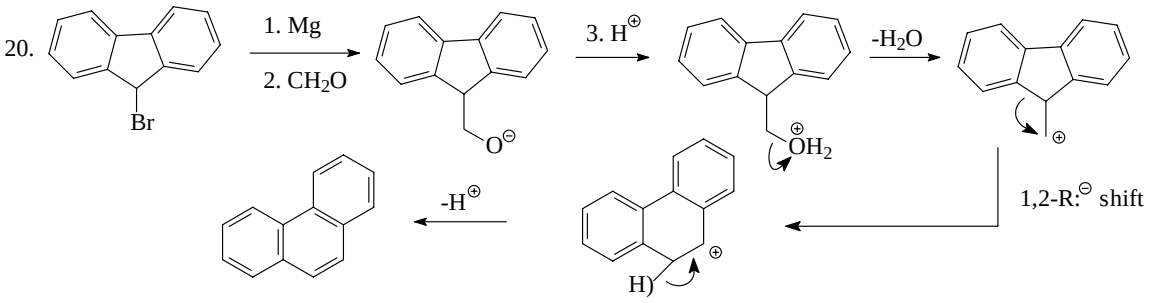
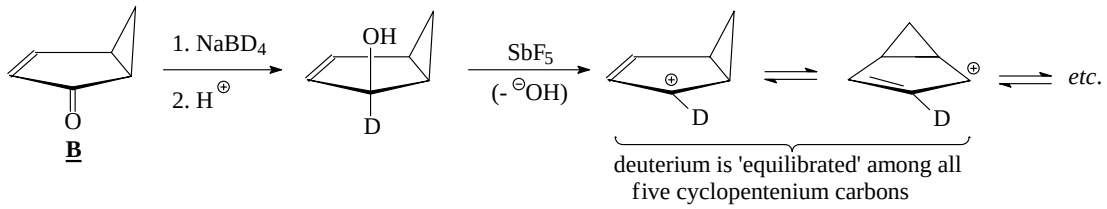
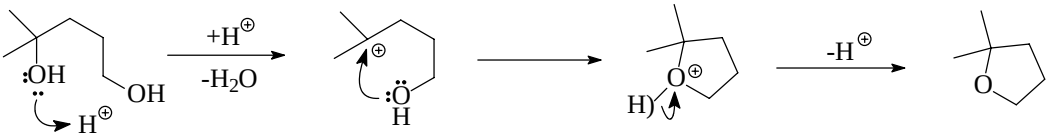
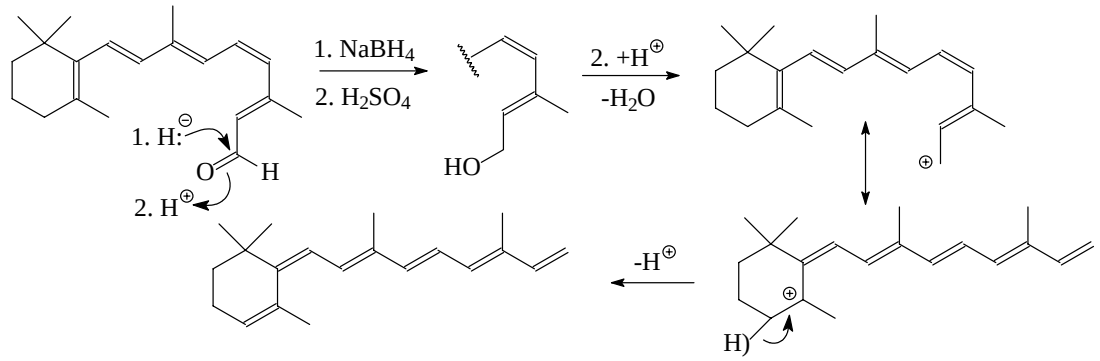


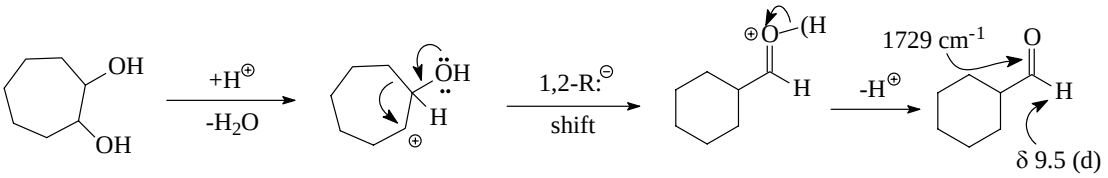
21. 

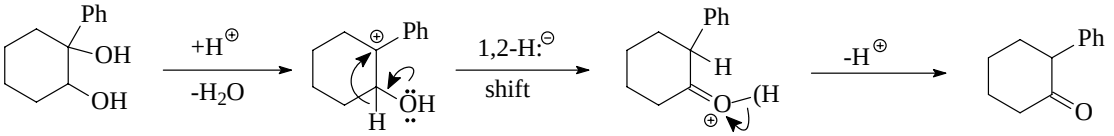
B

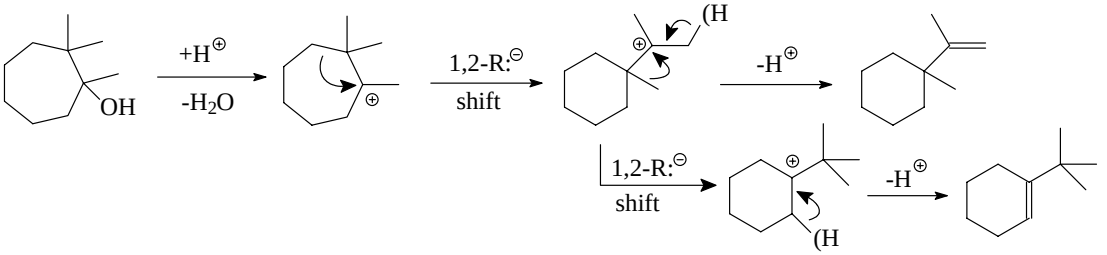
13.3 Mechanisms

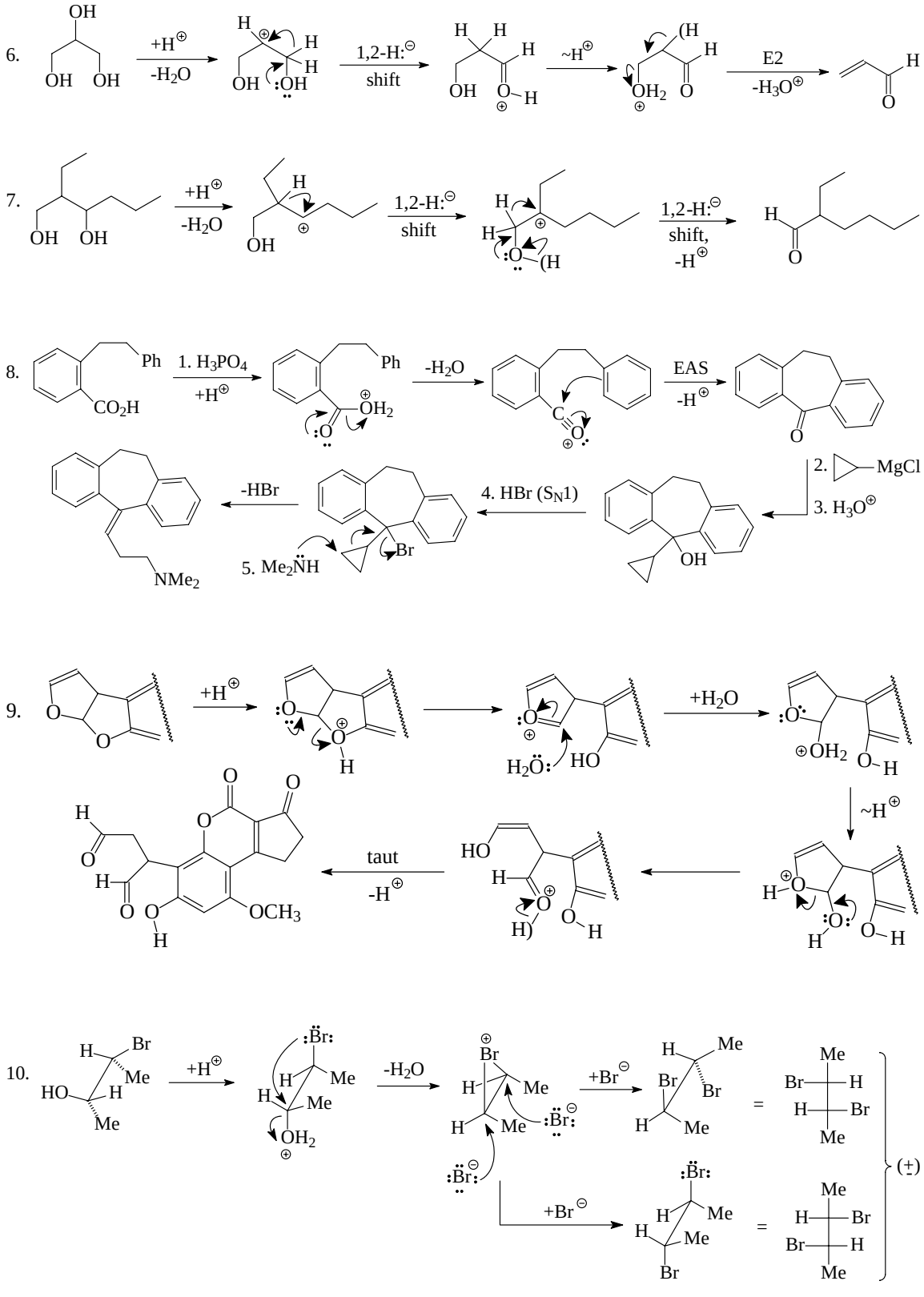
1. 

2. 

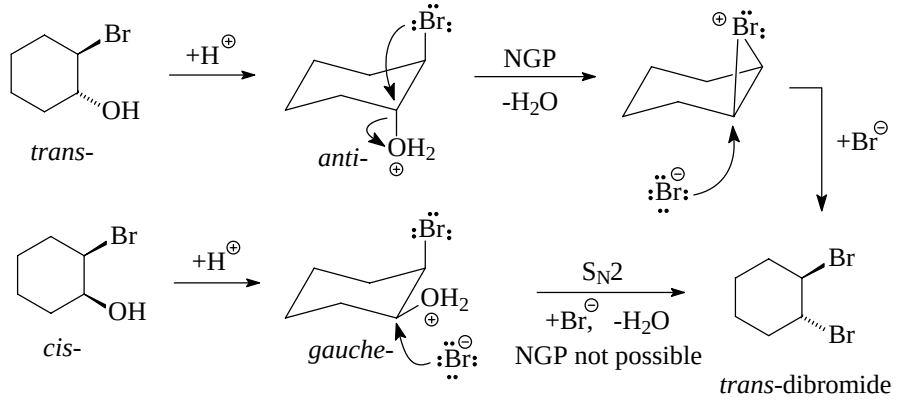
3. 

4. 

5. 


6.
+H⊕
-H2O
1,2-H:⊖
shift
~H⊕
E2
-H3O⊕
7.
+H⊕
-H2O
1,2-H:⊖
shift
1,2-H:⊖
shift,
-H⊕
8.
1. H3PO4
+H⊕
-H2O
EAS
-H⊕
2.
MgCl
3. H3O⊕
4. HBr (SN1)
5. Me2NH
-HBr
9.
+H⊕
+H2O
~H⊕
taut
-H⊕
10.
+H⊕
-H2O
+Br⊖
+Br⊖
(±)

11.



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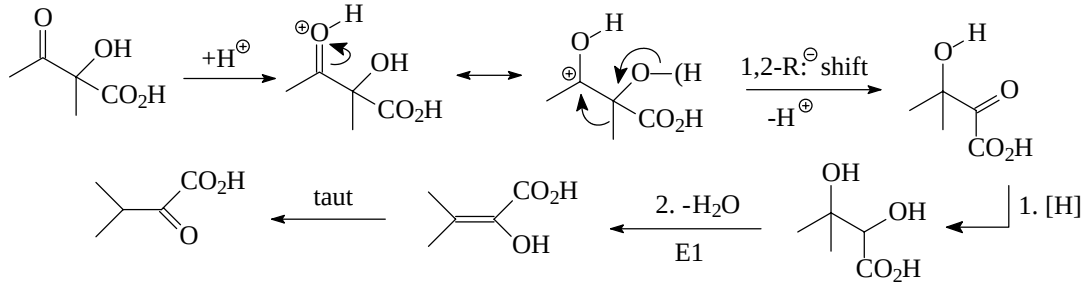

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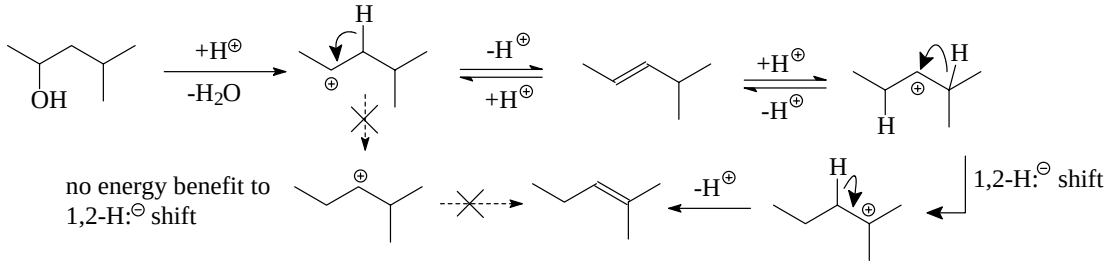

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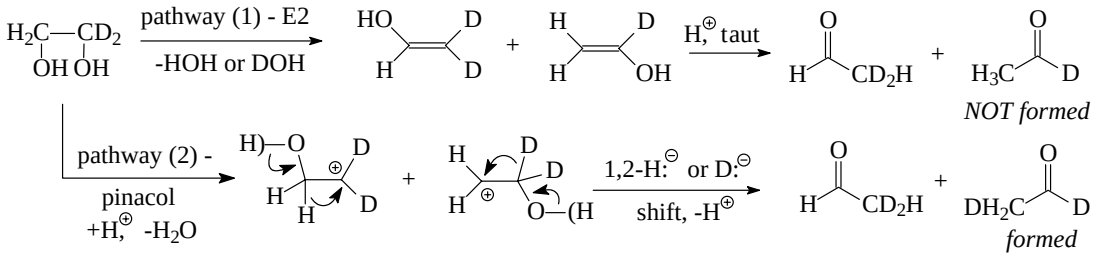
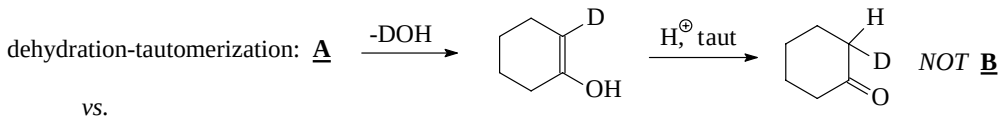


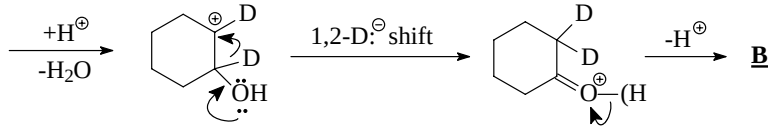
-- therefore, pathway (2) is favored

15. a. dehydration-tautomerization: **A**

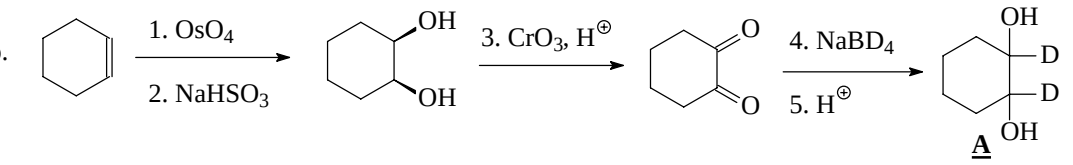


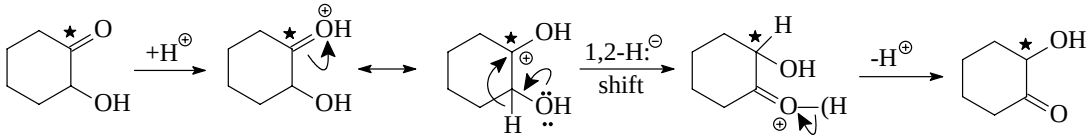
vs.

pinacol-like: **A**

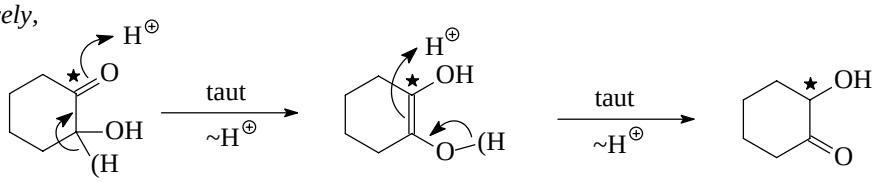


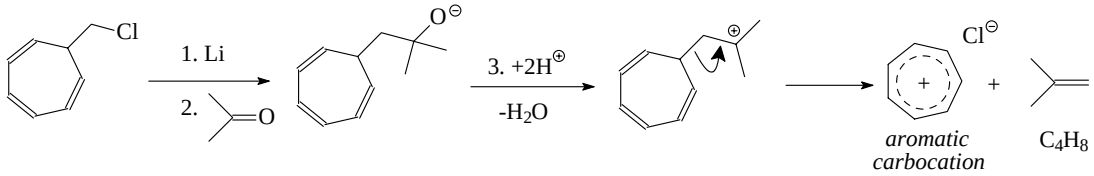
-- therefore, the pinacol-like pathway is favored

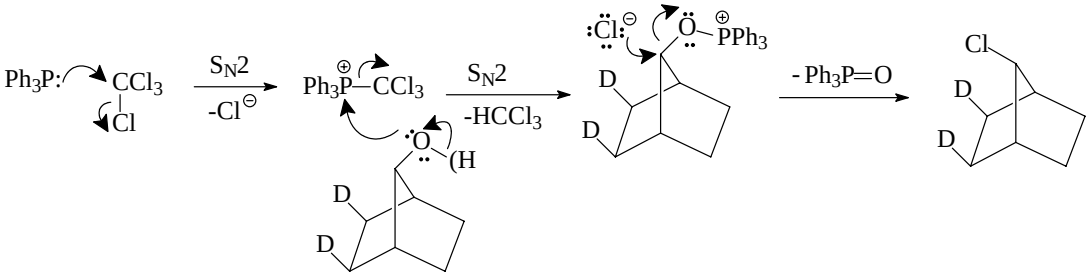
15. b. 

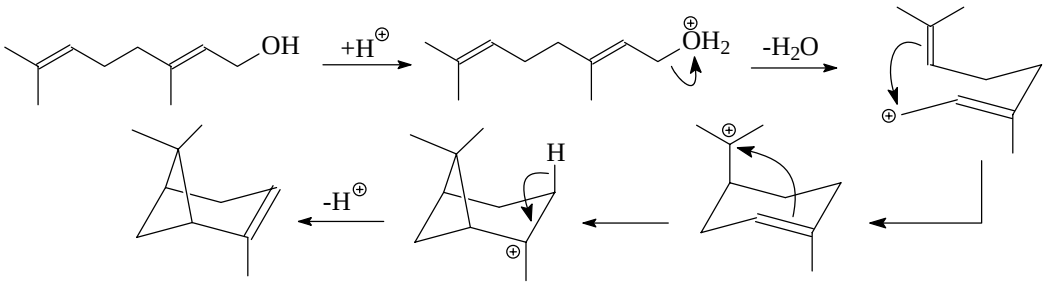
16. 

alternatively,



17. 

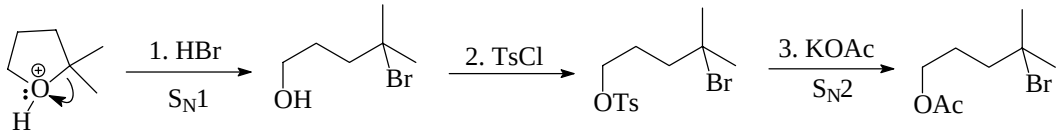
18. 

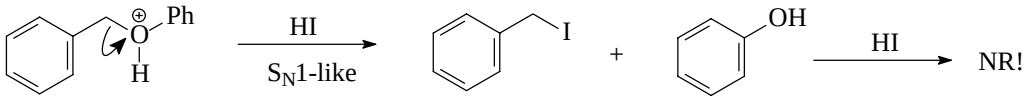
19. 

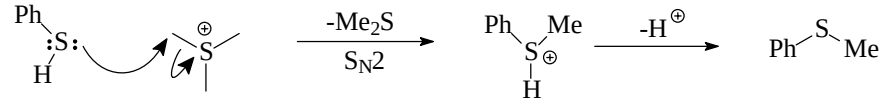
CHAPTER 14

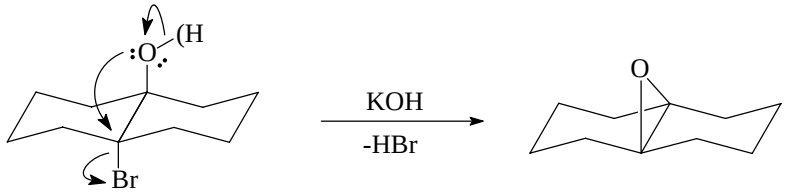
ETHERS

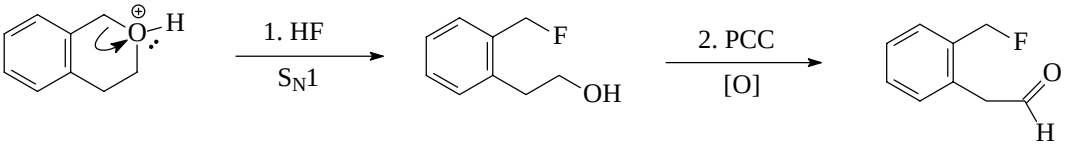
14.1 Reactions

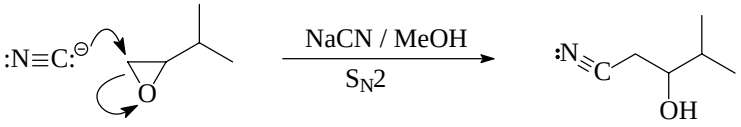
1. 

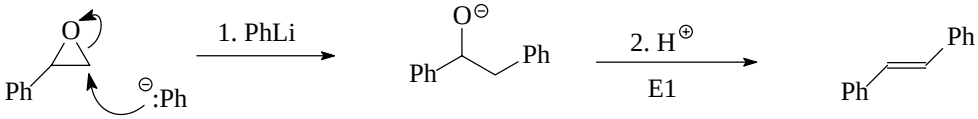
2. 

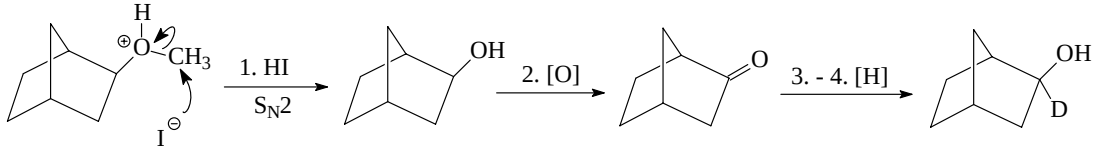
3. 

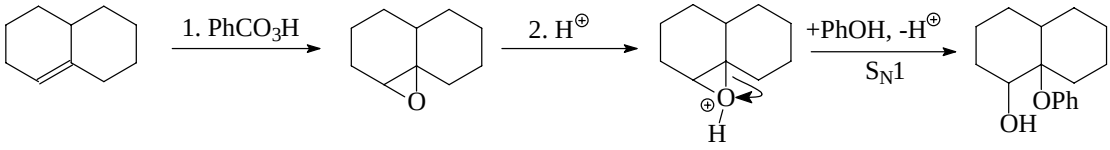
4. 

5. 

6. 

7. 

8. 

9. 

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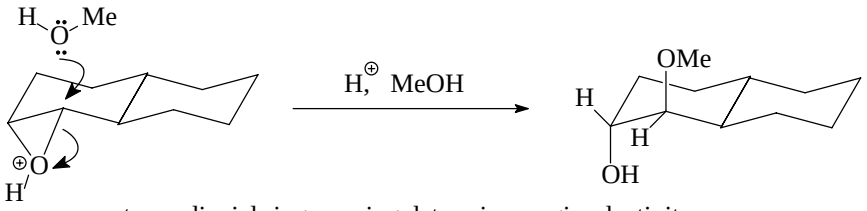
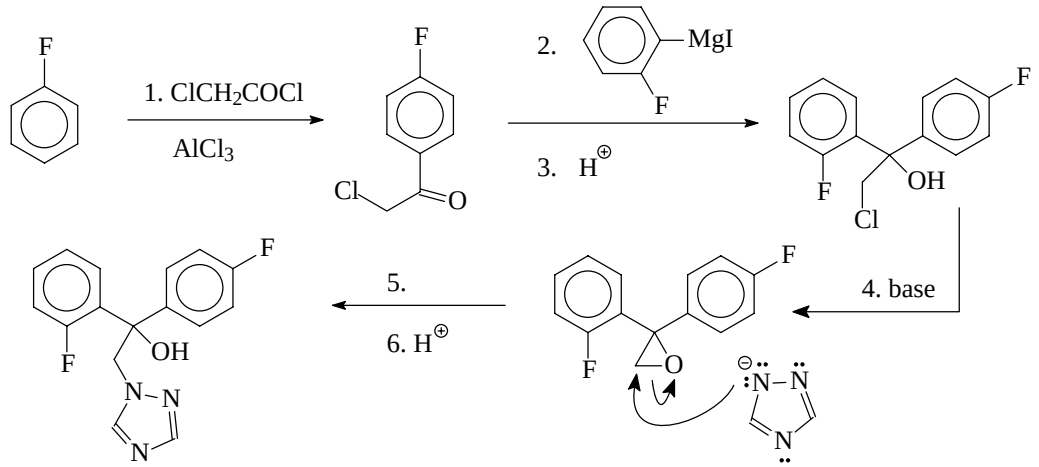


trans-diaxial ring opening determines regioselectivity

11.



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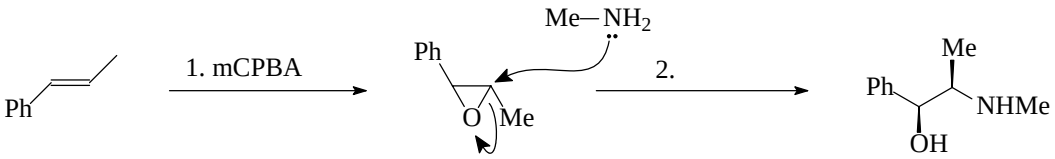

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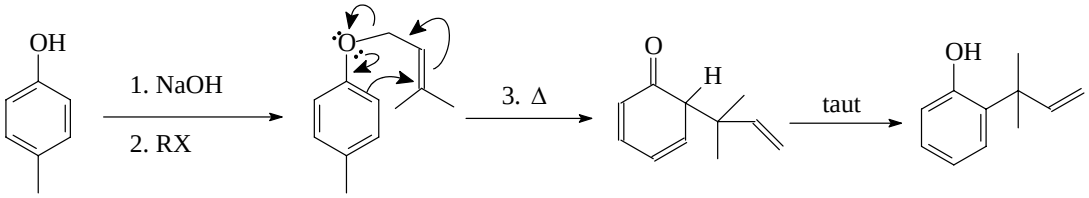

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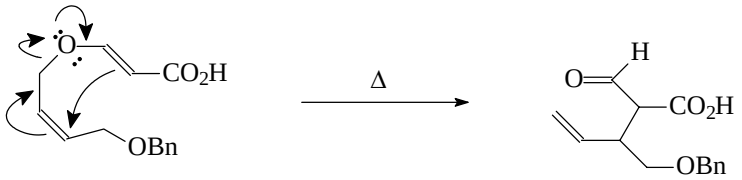

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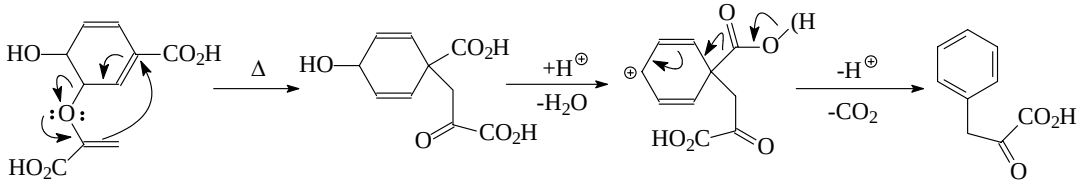
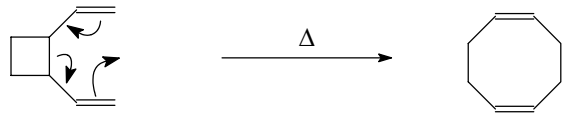
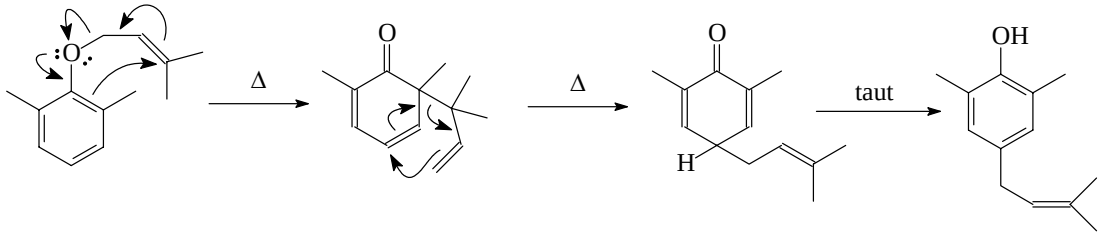
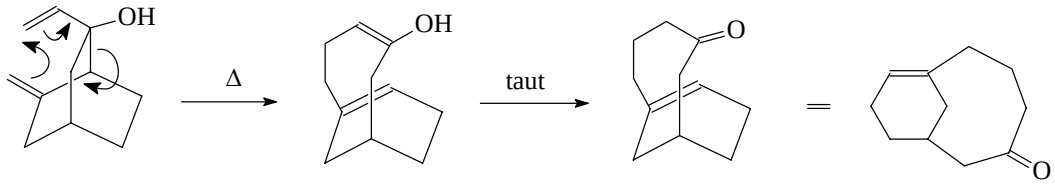
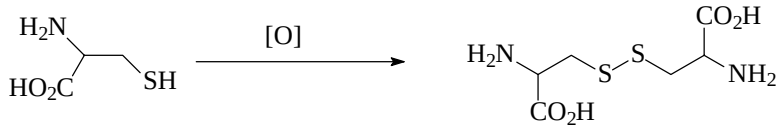
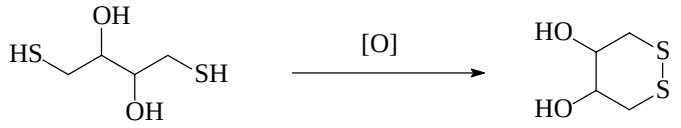


15. 

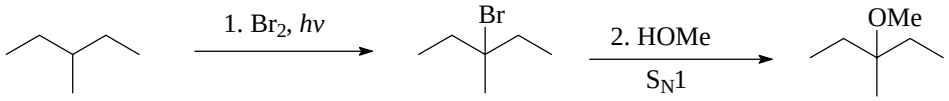
16. 

17. 

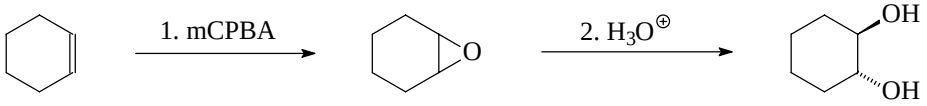
18. 

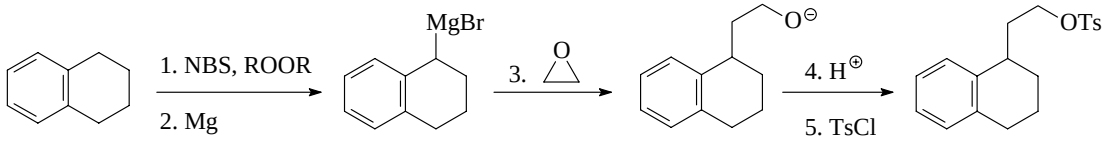
19. 

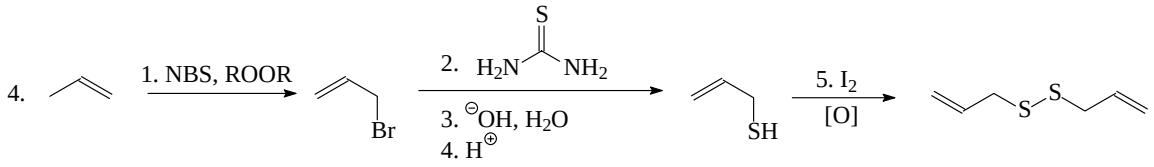
14.2 Syntheses

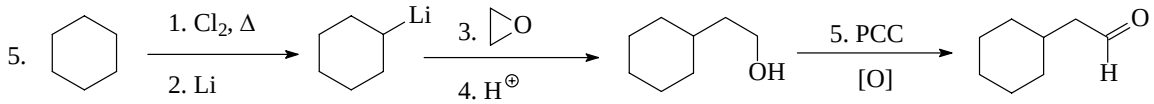
1. 

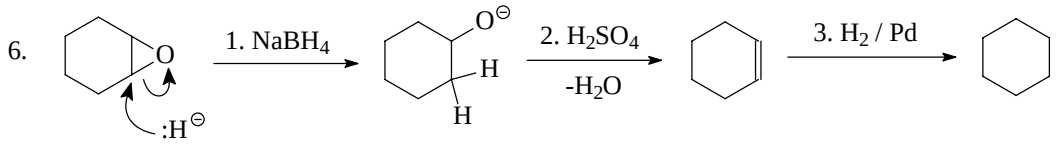
not $^{\ominus}$OMe (=> 100% E2!)

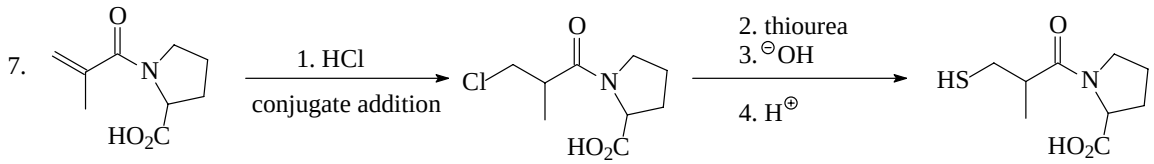
2. 

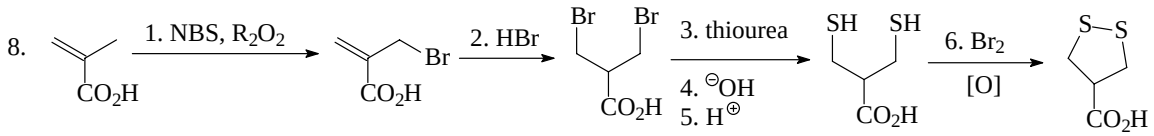
3. 



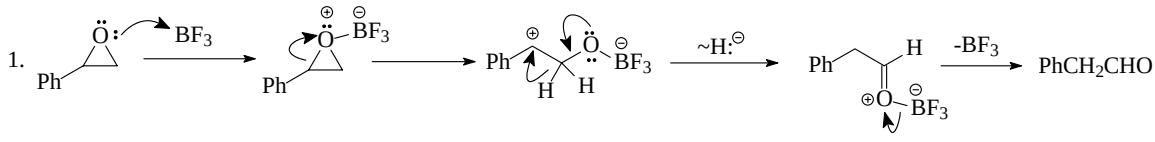


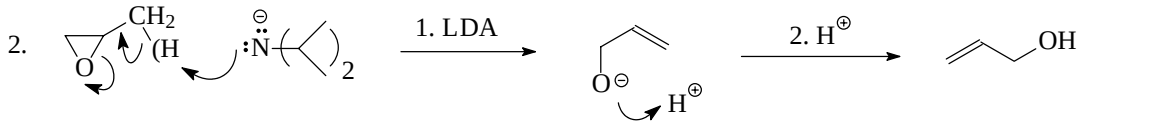


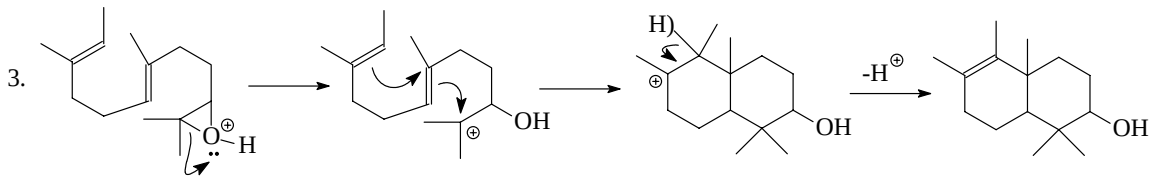




14.3 Mechanisms

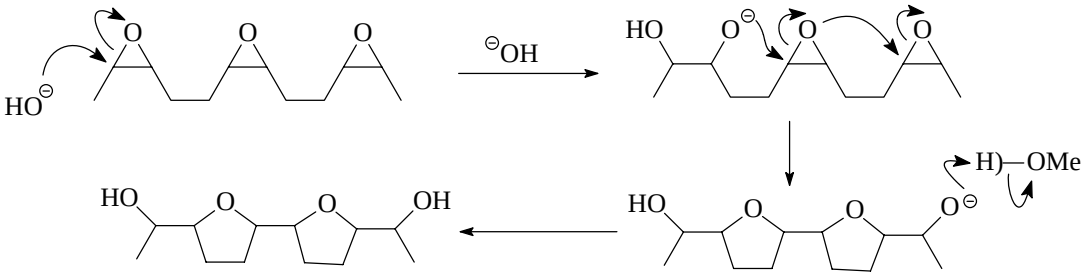




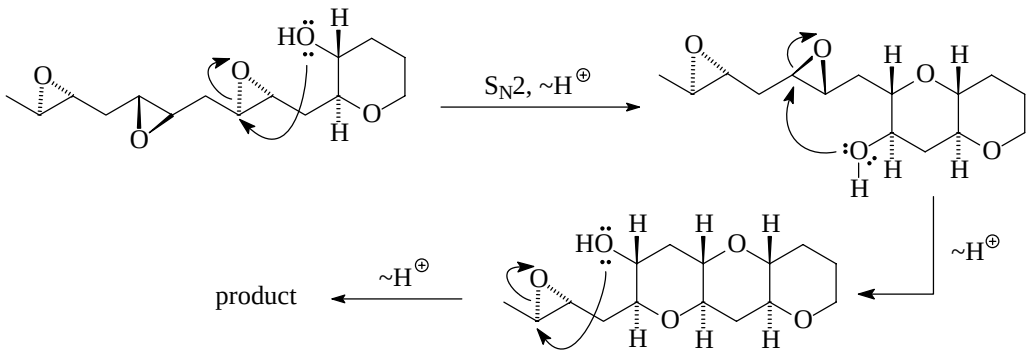


-- see 14.3, 6 for an even more impressive polycyclization!

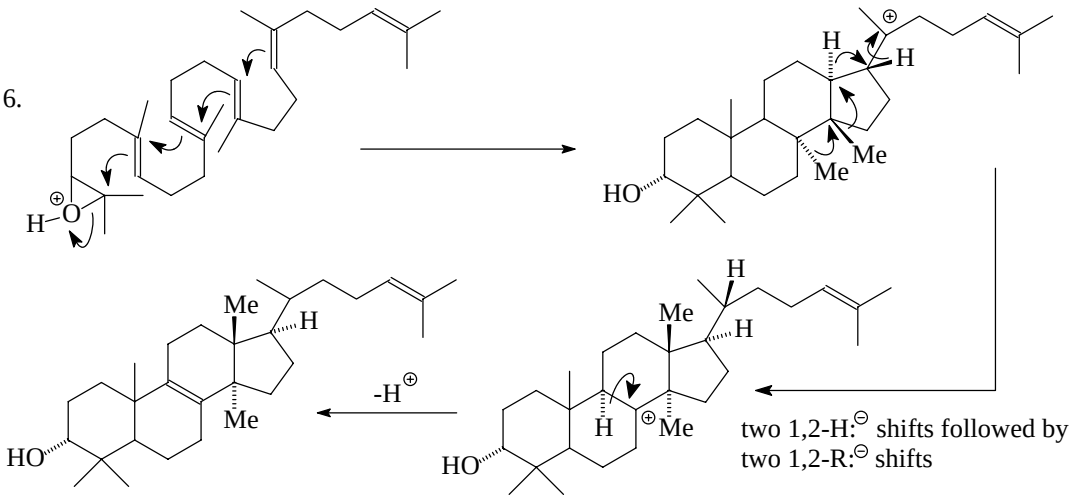
4.


HO
⊖OH
HO
H)—OMe
HO
OH

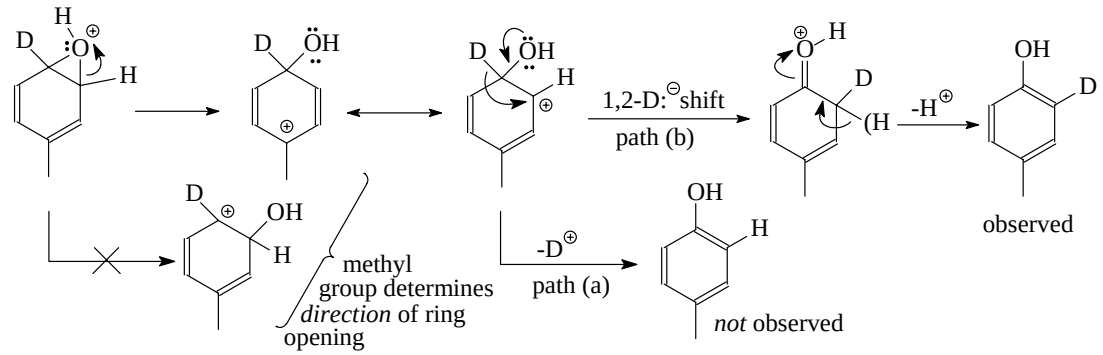
5.


HO
SN2, ~H⊕
~H⊕
~H⊕
product

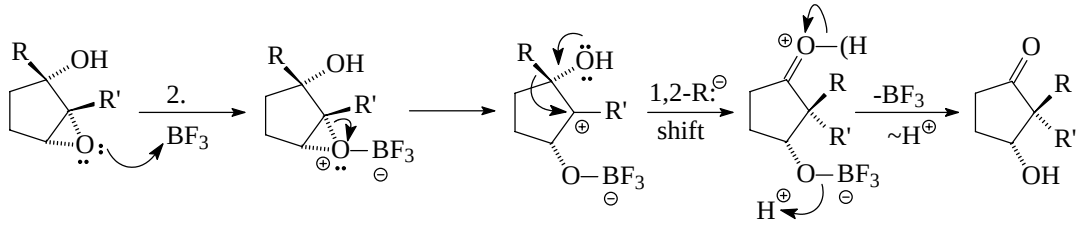
6.


H⊕
HO
-H⊕
HO
two 1,2-H:⊖ shifts followed by
two 1,2-R:⊖ shifts

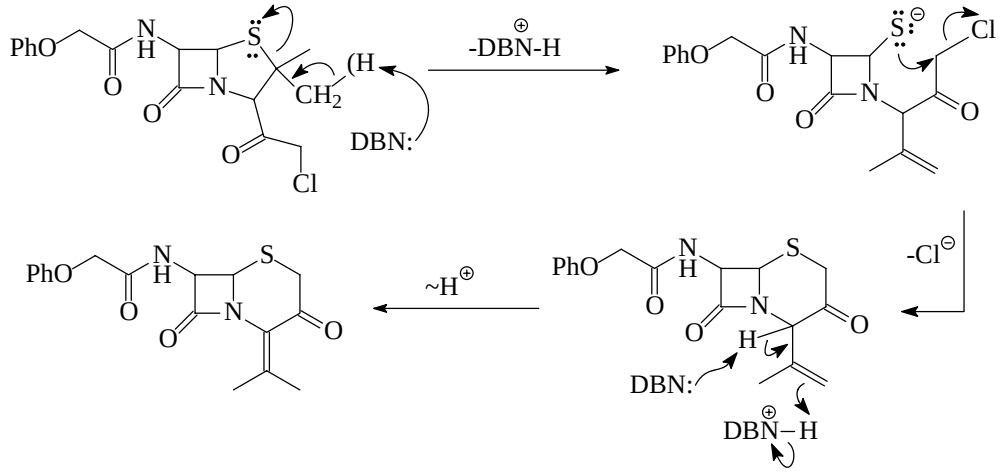
7.


1,2-D:⊖shift
path (b)
-H⊕
observed
methyl
group determines
direction of ring
opening
-D⊕
path (a)
not observed

8.

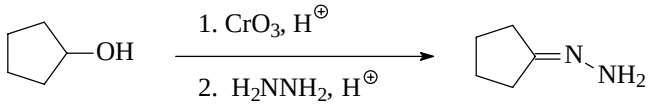

R
OH
R'
2.
BF3
O—BF3
1,2-R:
shift
-BF3
~H
O
OH

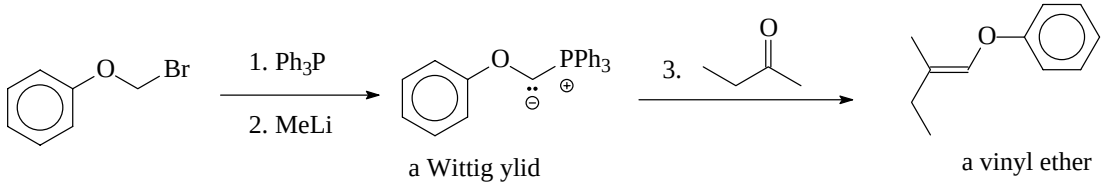
9.

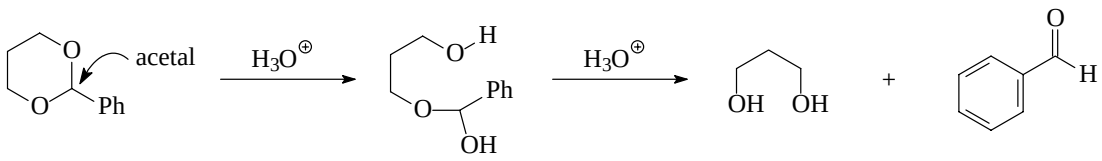

PhO
N
H
S
O
CH2
DBN:
-DBN-H
Cl
-Cl
~H
DBN—H

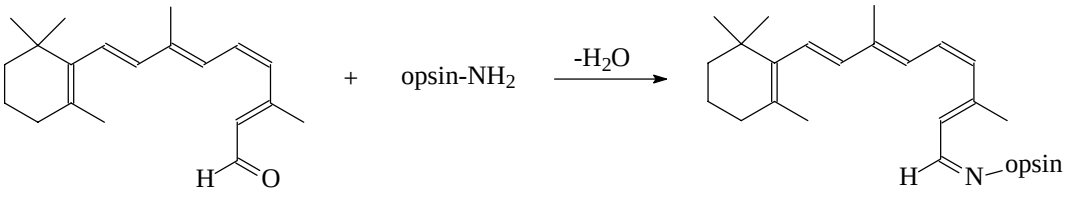
CHAPTER 15
ALDEHYDES AND KETONES

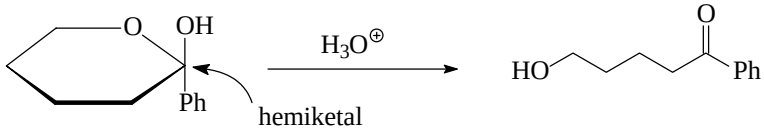
15.1 Reactions

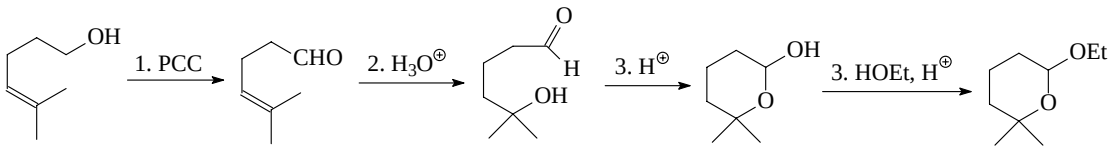
1. 

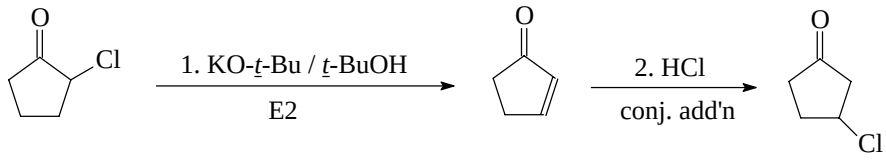
2. 

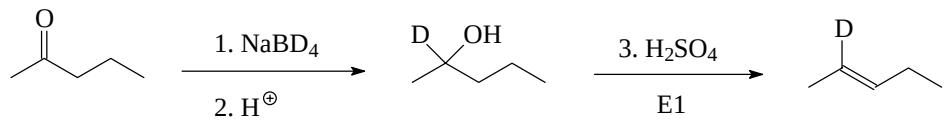
3. 

4. 

5. 

6. 

7. 

8. 

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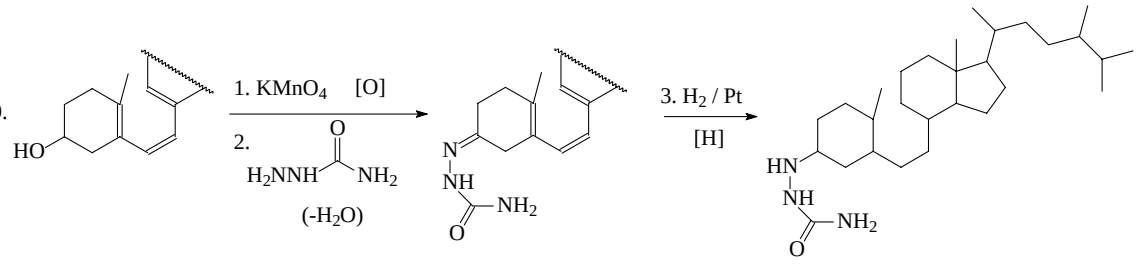

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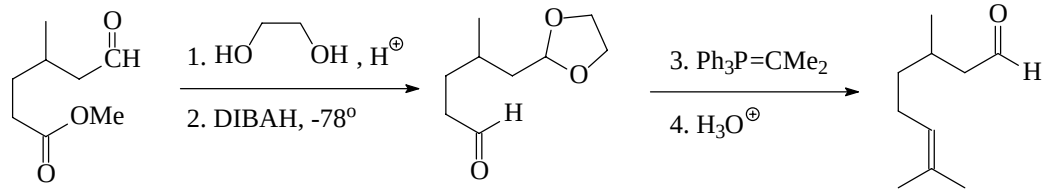

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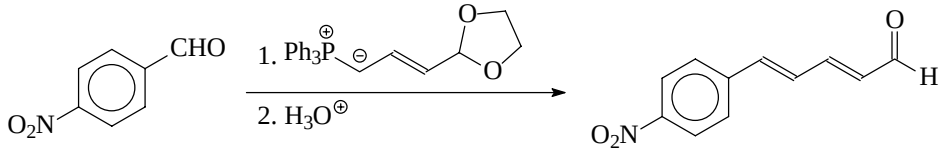

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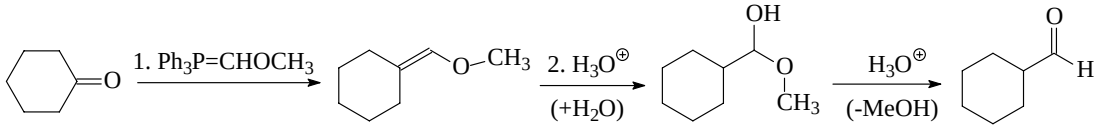

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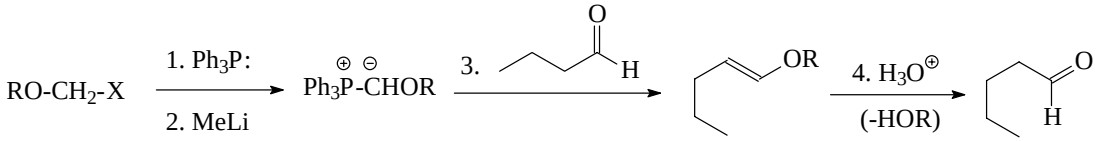

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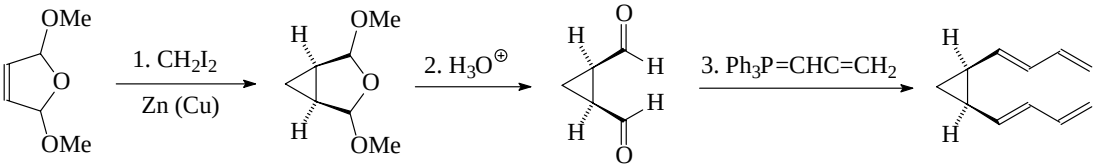

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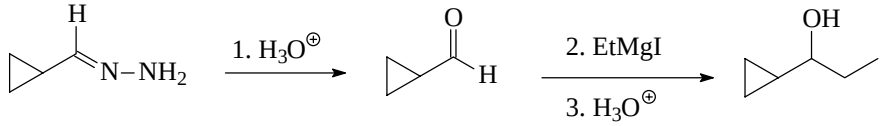

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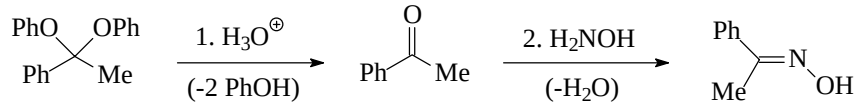
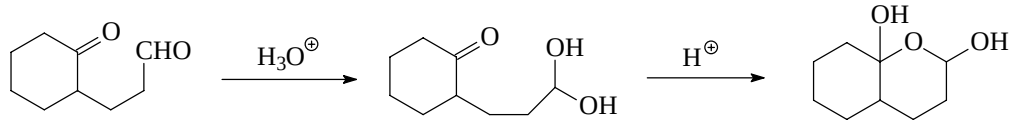
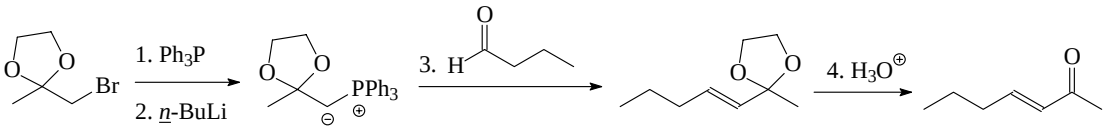
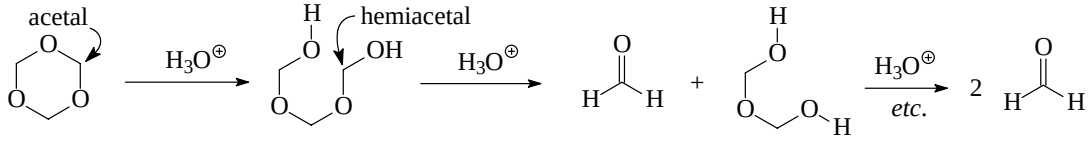
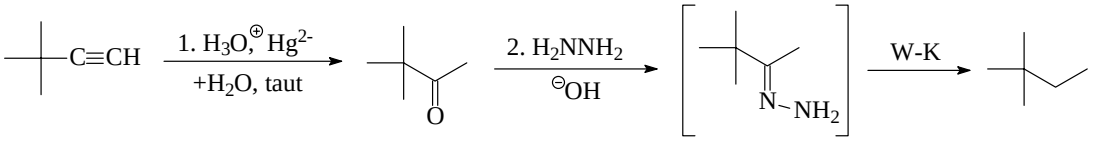
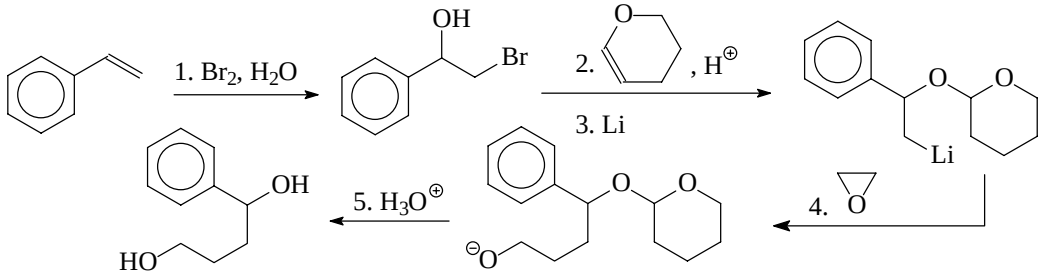


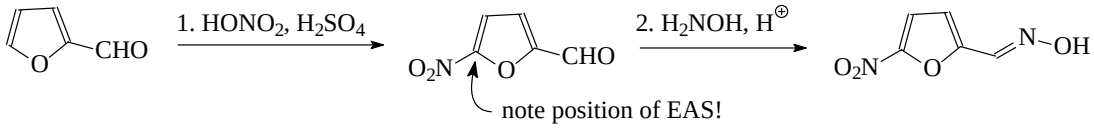
17. 

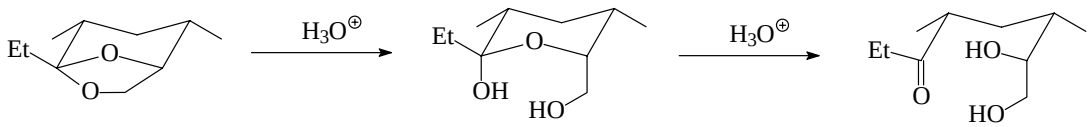
18. 

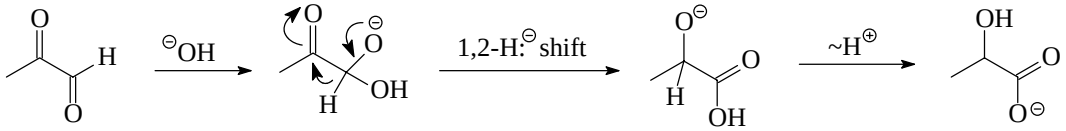
19. 

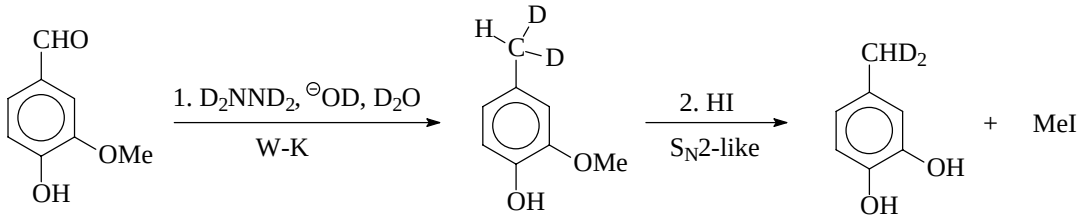
20. 

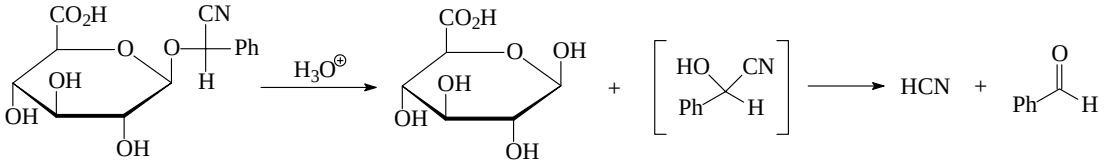
21. 

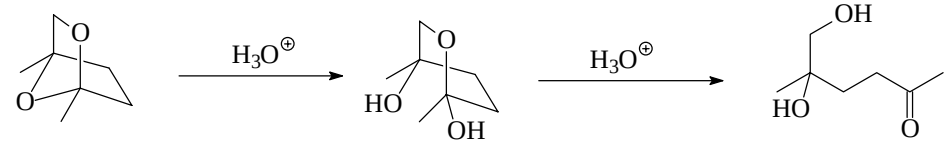
22. 

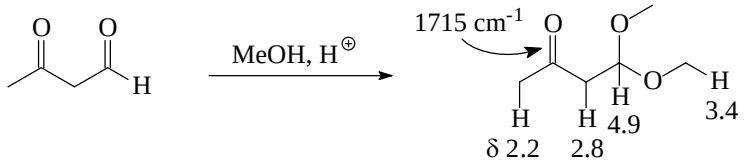
23. 

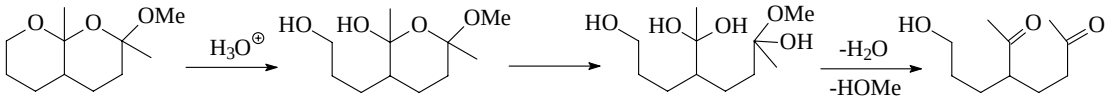
24. 

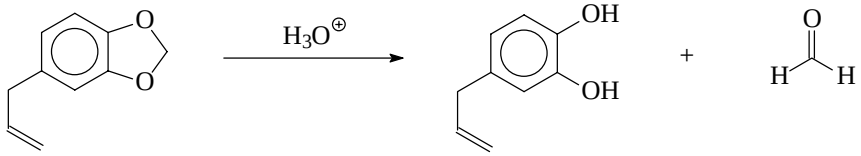
25. 

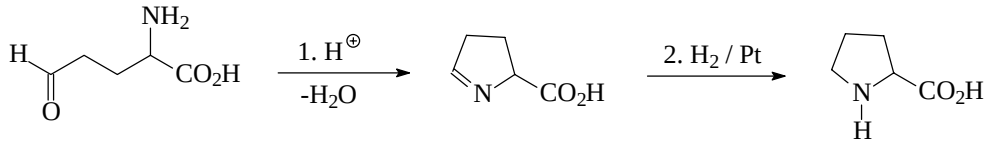
26. 

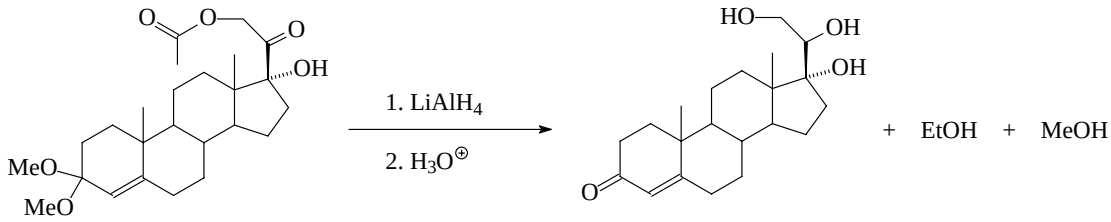
27. 

28. 

29. 

30. 

31. 

32. 

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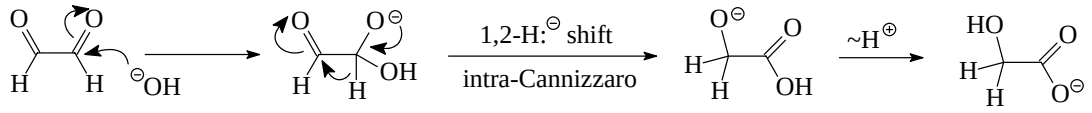

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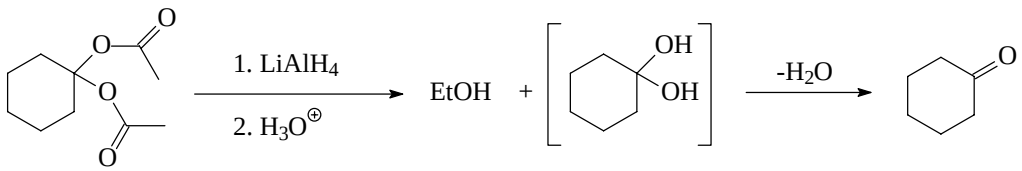

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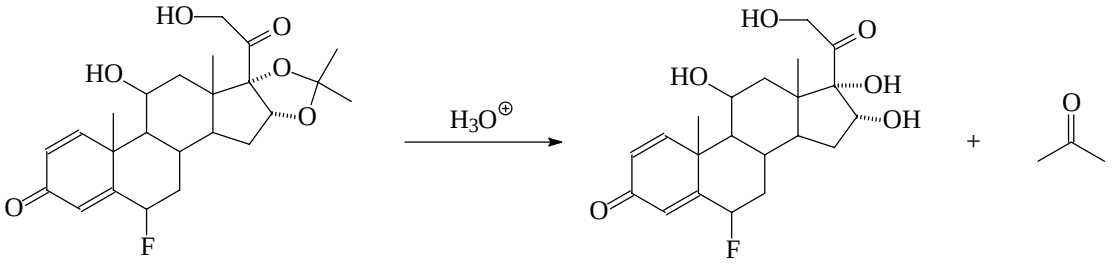

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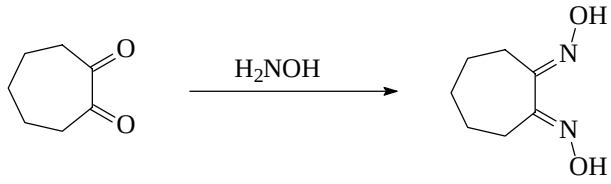

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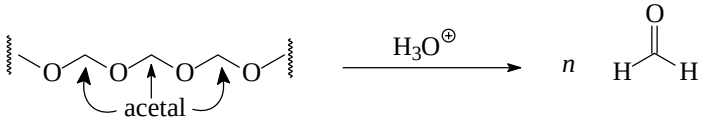

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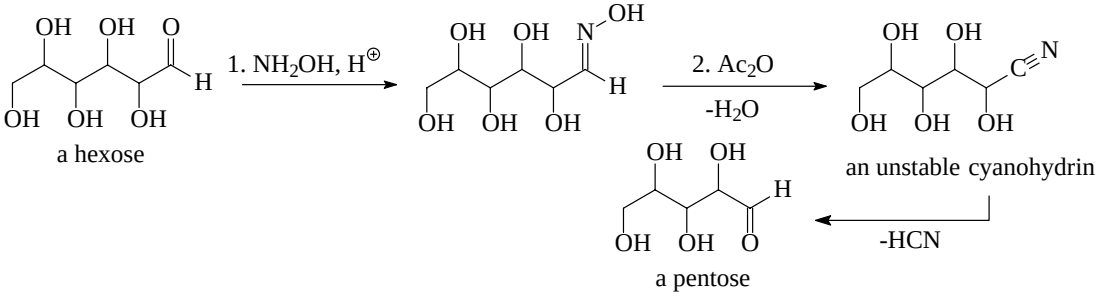

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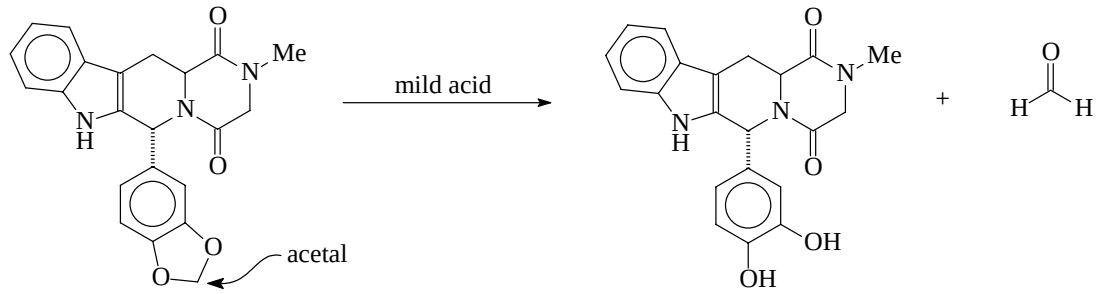

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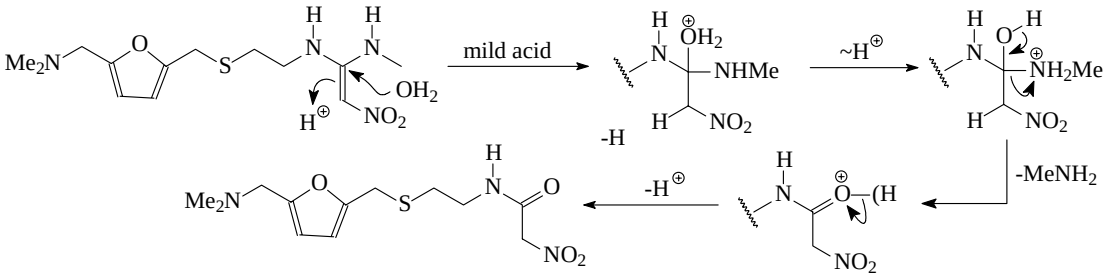

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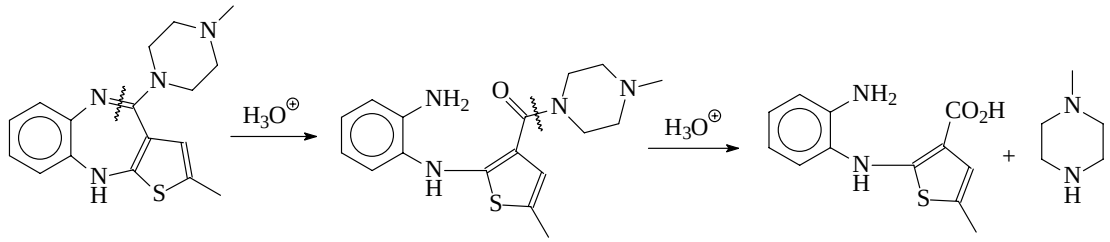

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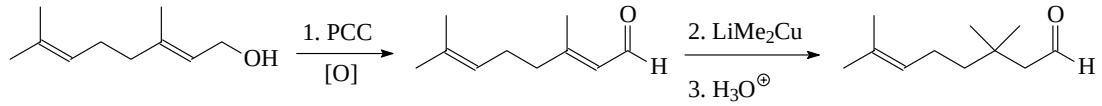

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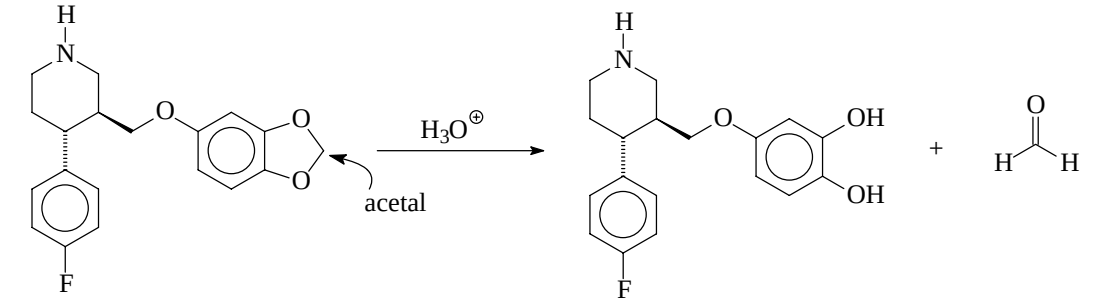

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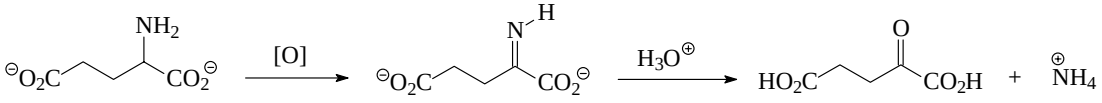

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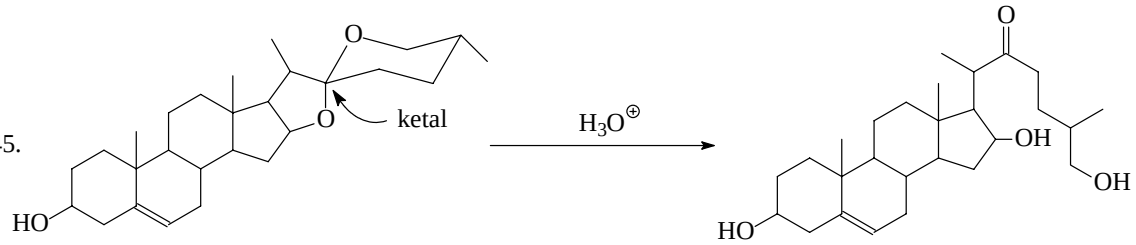

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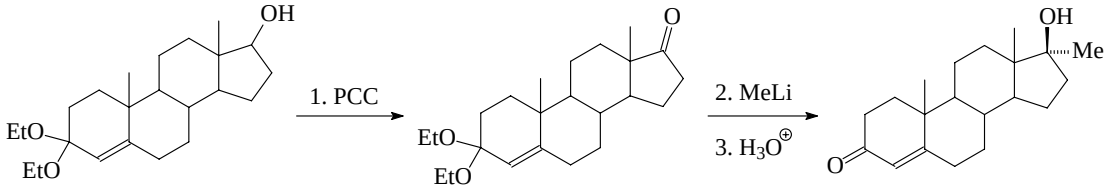
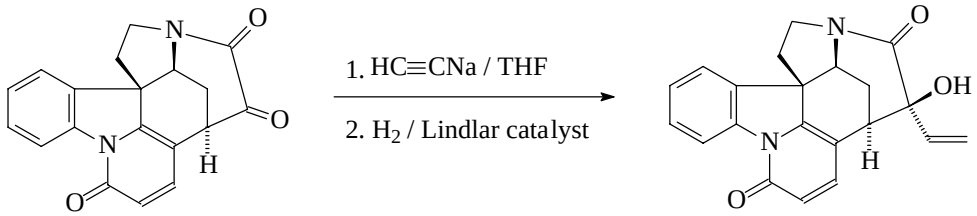
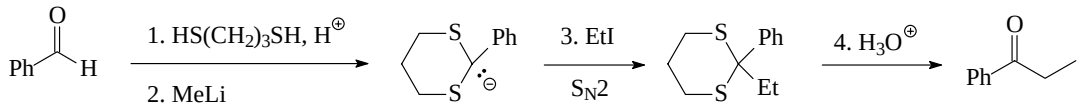


47.

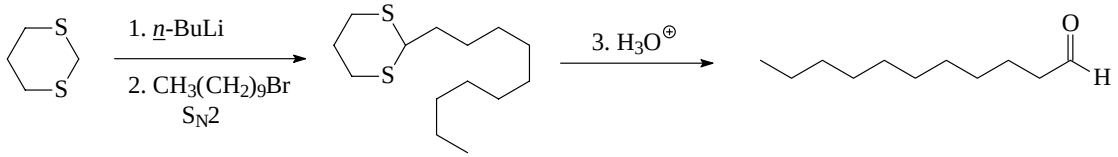


note: addition to ketone, not amide carbonyls

48. a.



b.



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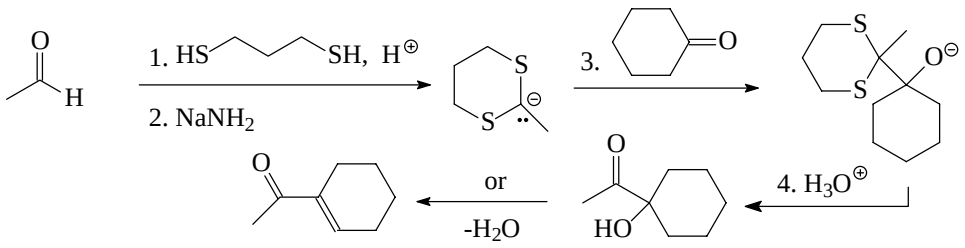

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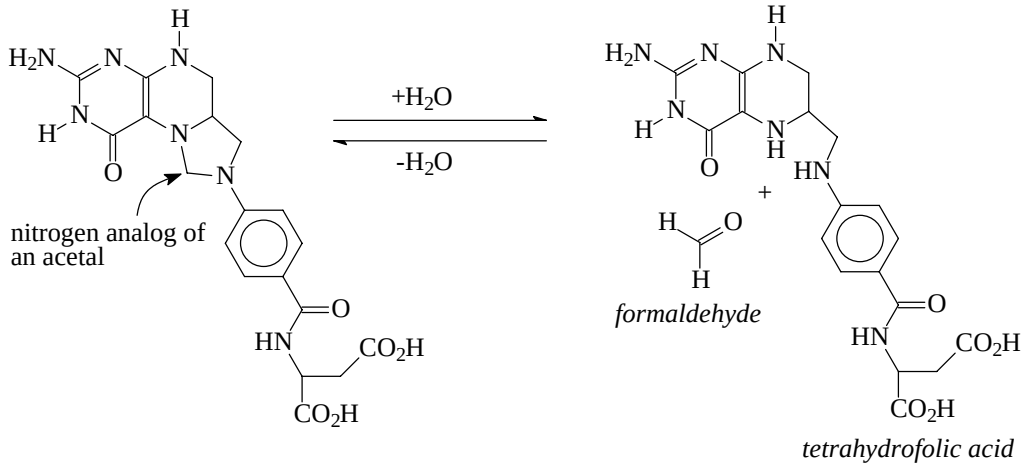

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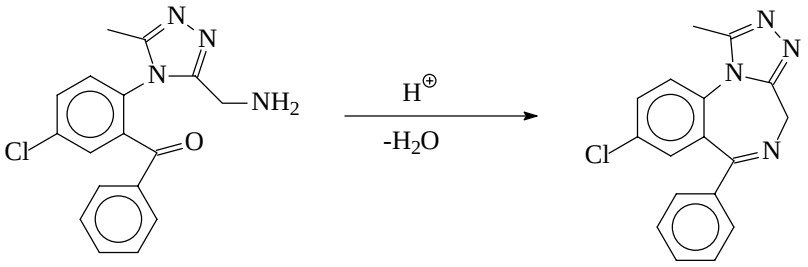
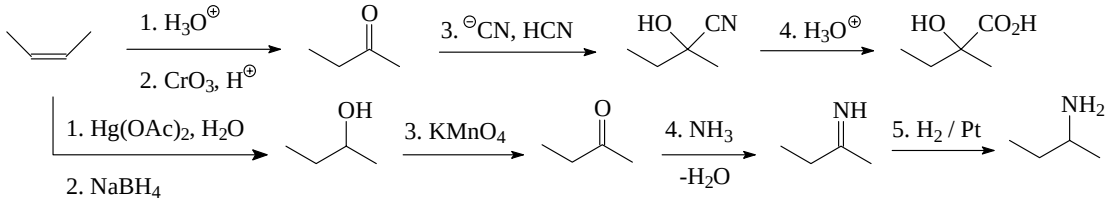


Xanax™ - (anxiolytic)

15.2 Syntheses

1.



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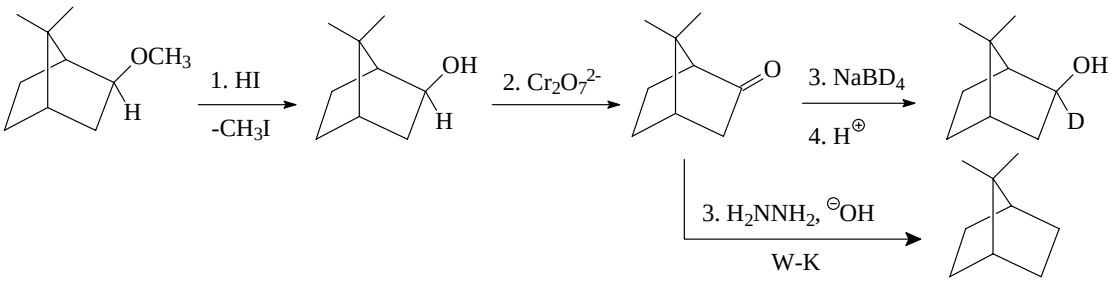
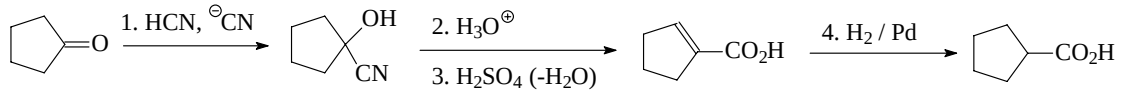
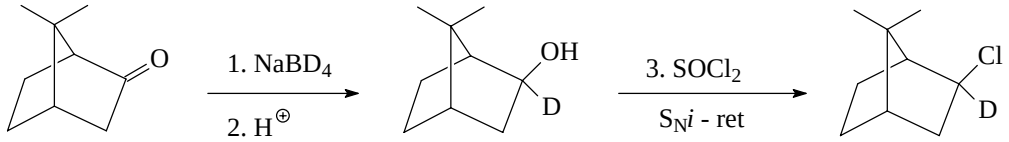
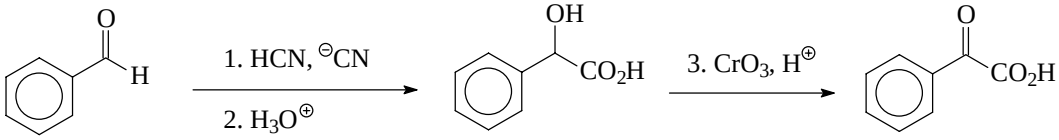
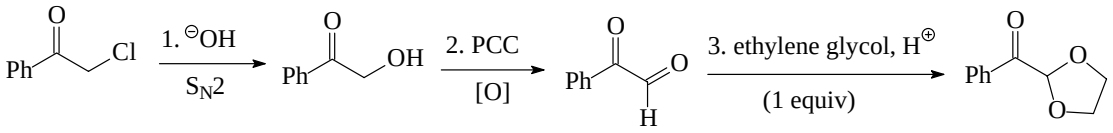


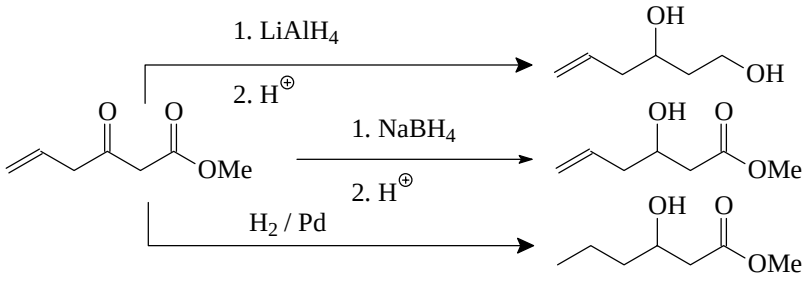
3. 

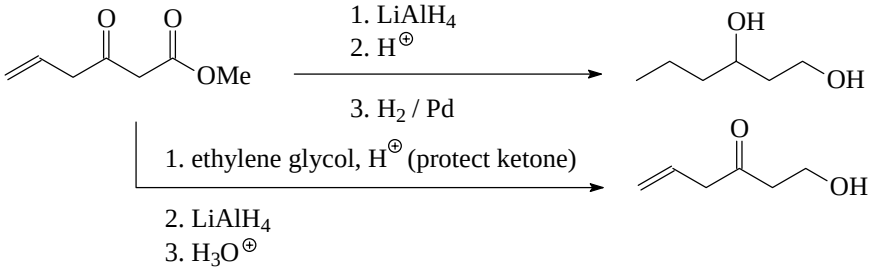
4. 

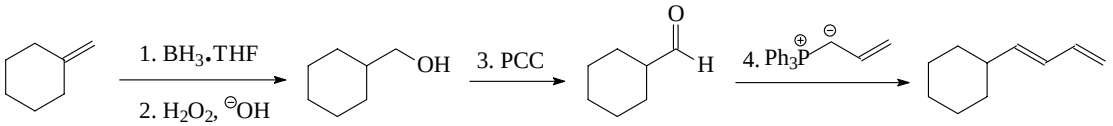
5. 

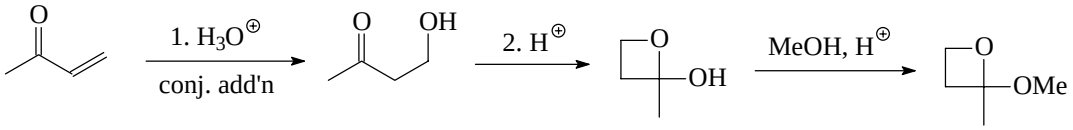
6. 

(*aldehyde more reactive than ketone*)

7. 

7. (*cont.*) 

8. 

9. 

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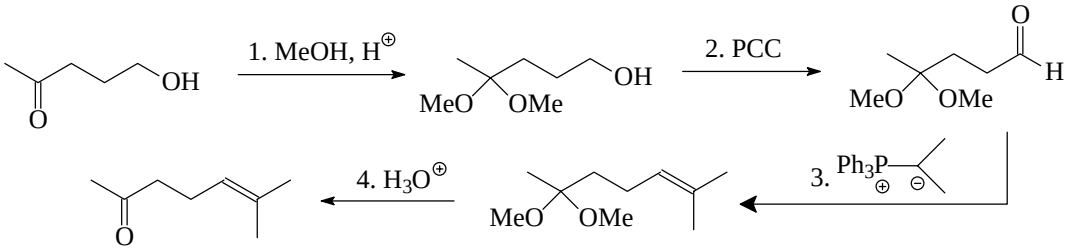

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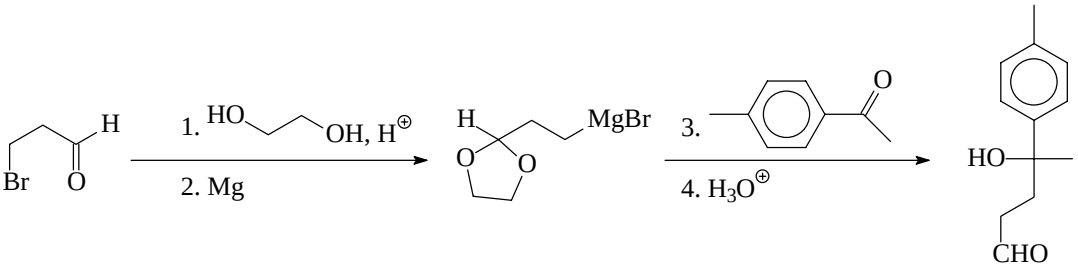

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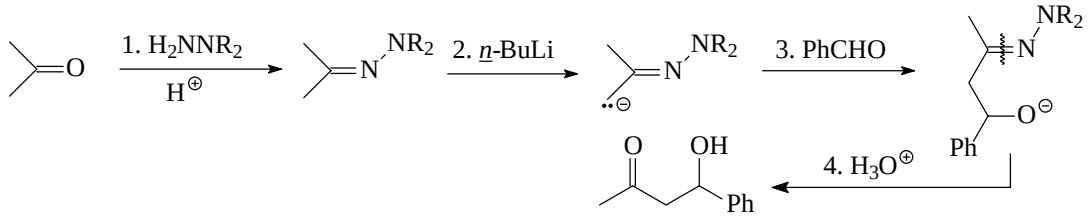

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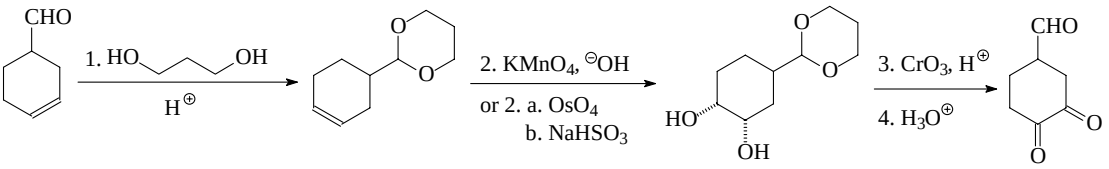

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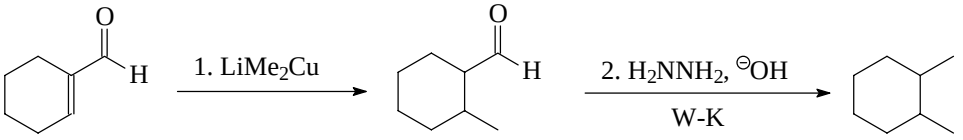

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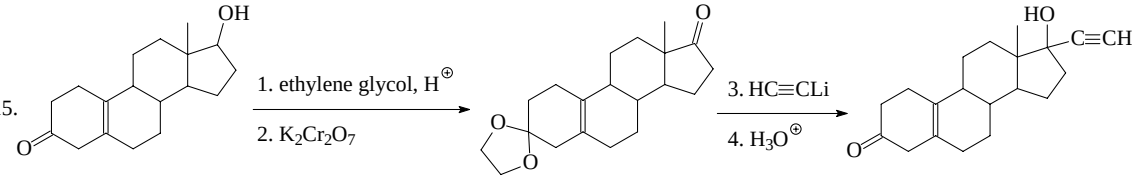
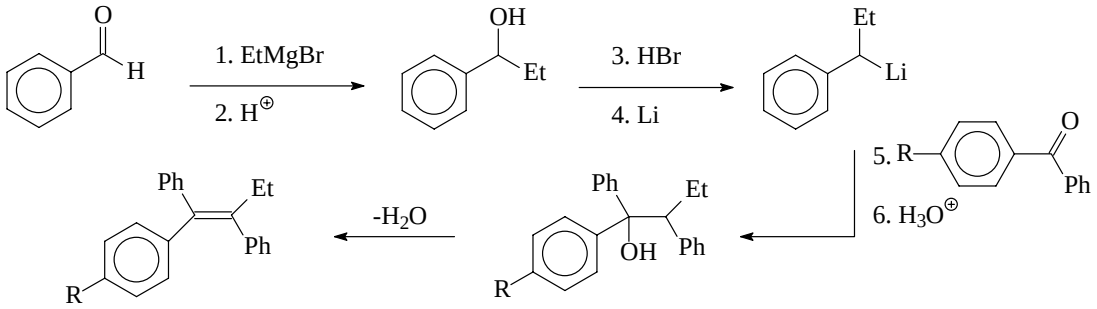
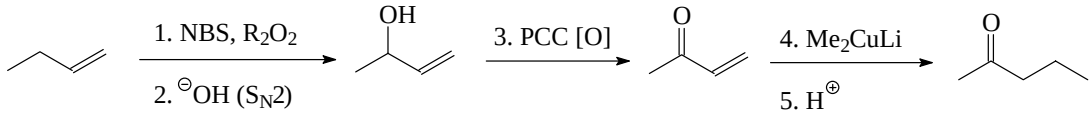
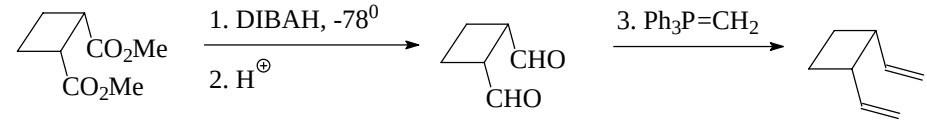
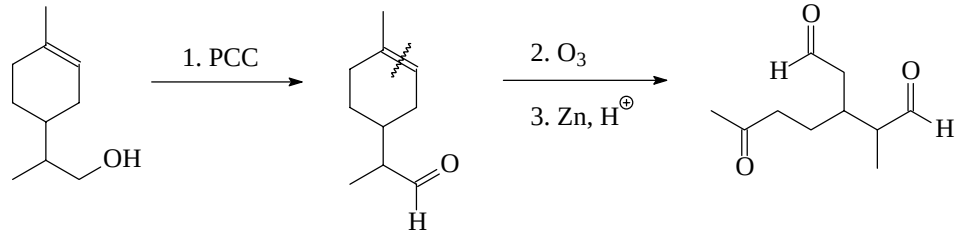
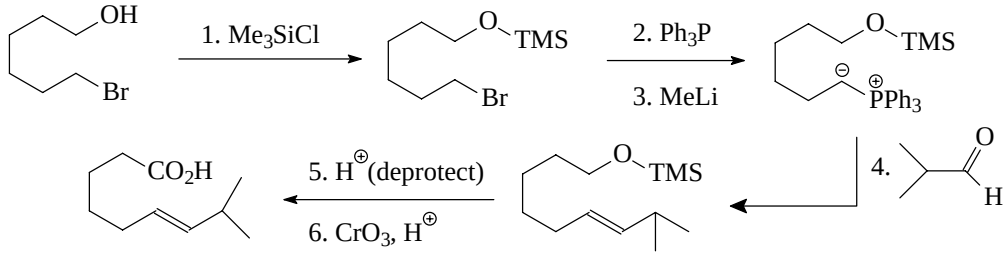


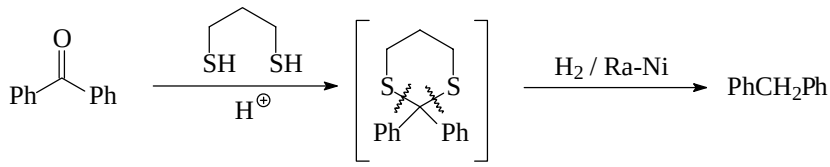
16. 

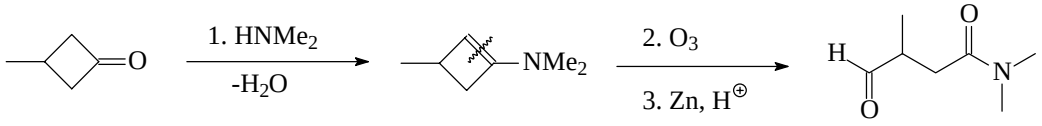
17. 

18. 

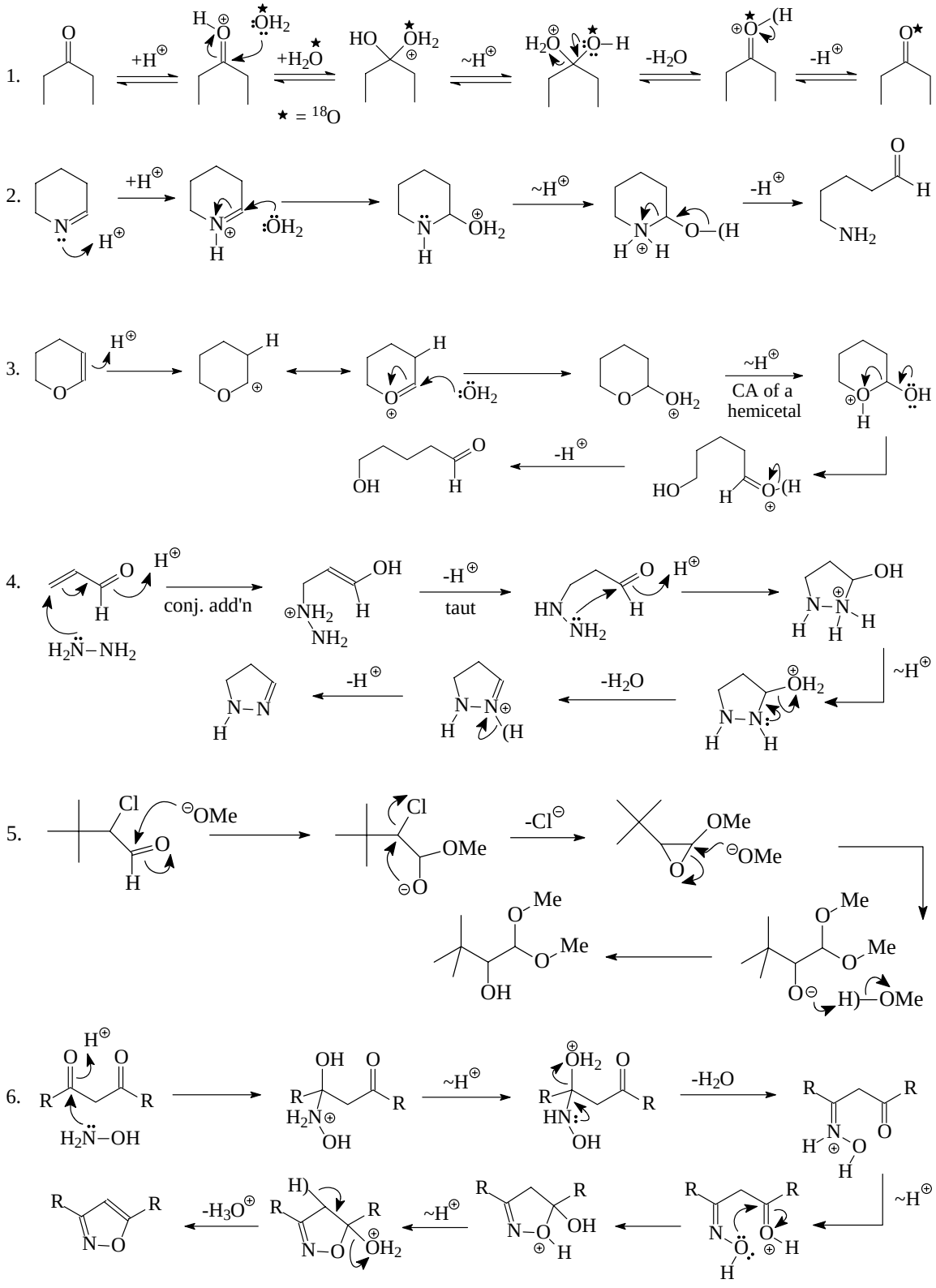
19. 

20. 

21. 

22. 

15.3 Mechanisms



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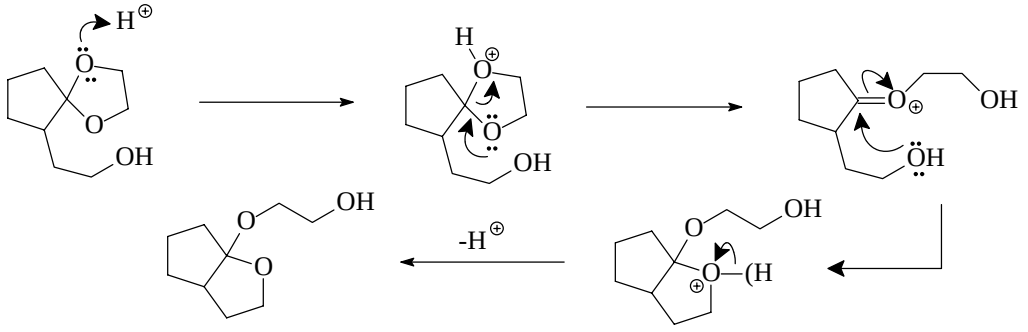

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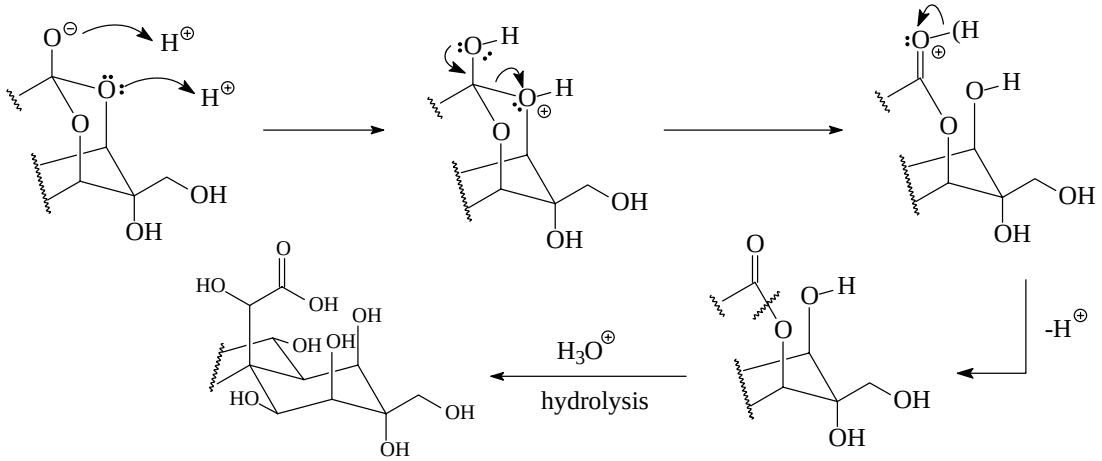

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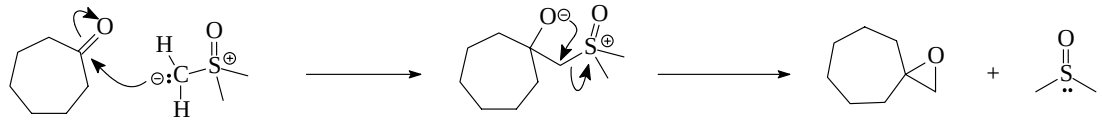

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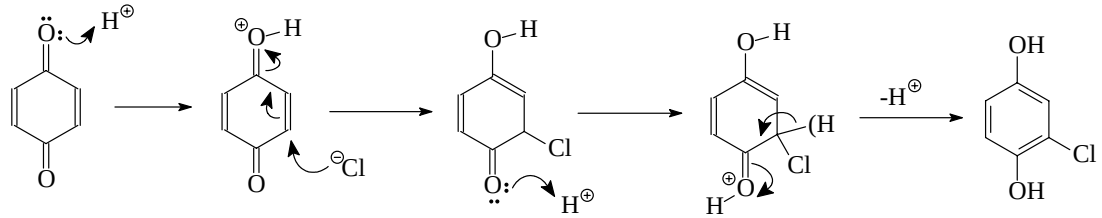

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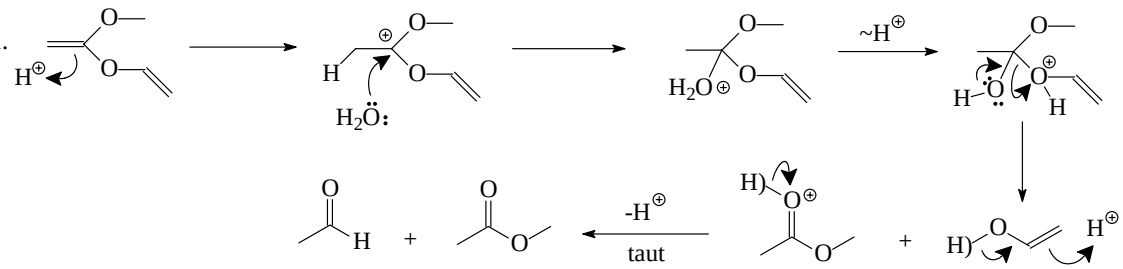
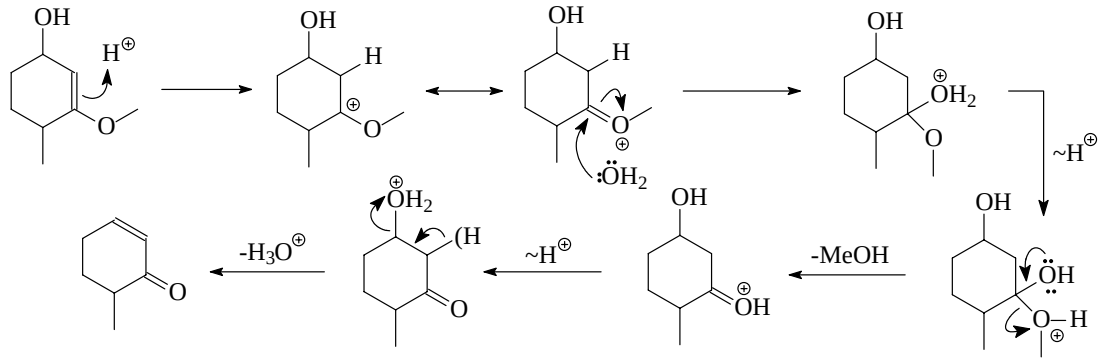
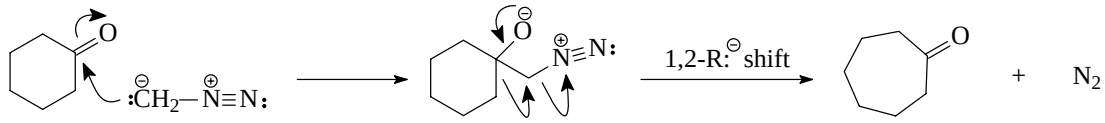


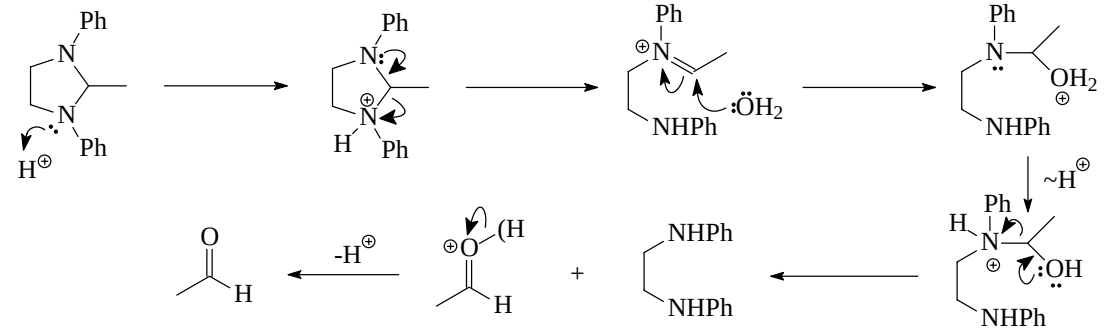
12.


OH
H⊕
O
H
:ÖH2
OH2
~H⊕
-MeOH
-H3O⊕
~H⊕
(H
:OH
O–H

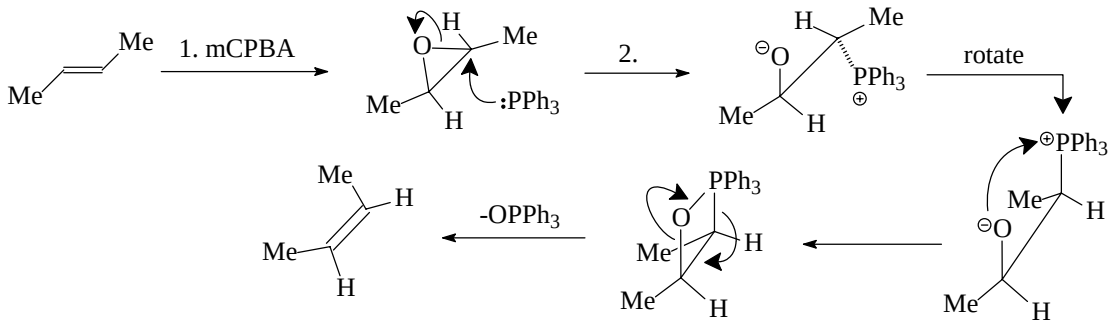
13.


O
:CH2—N≡N:
N≡N:
1,2-R:⊖ shift
+ N2

14.


Ph
N
H⊕
:ÖH2
NHPh
OH2
~H⊕
-H⊕
(H
+
:OH

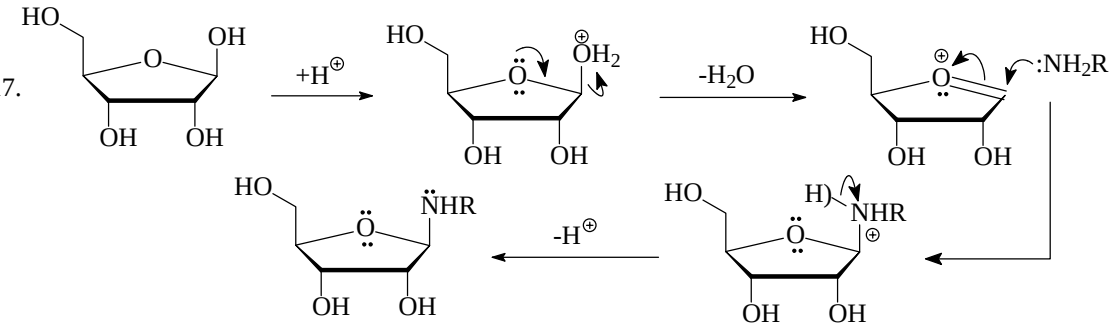
15.


Me
1. mCPBA
H
O
:PPh3
2.
PPh3
rotate
-OPPh3

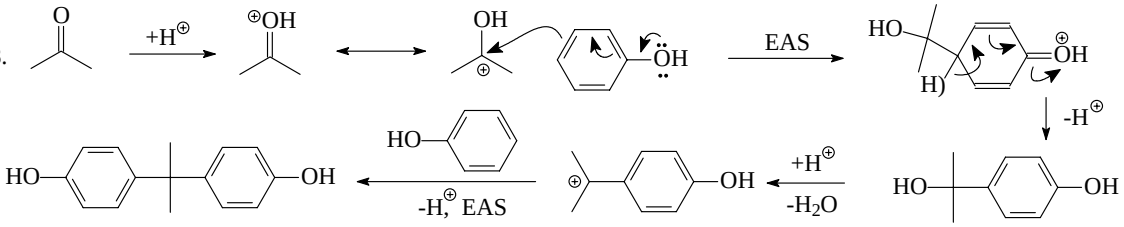
16.


O
:P(OMe)3
P(OMe)3
-OP(OMe)3

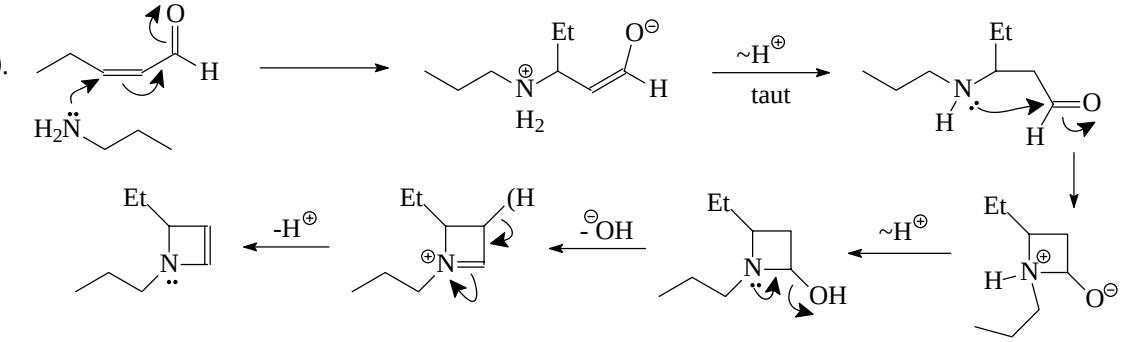
17.


HO
OH
O
OH
OH
+H⊕
HO
OH2
-H2O
:NH2R
NHR
-H⊕
H)

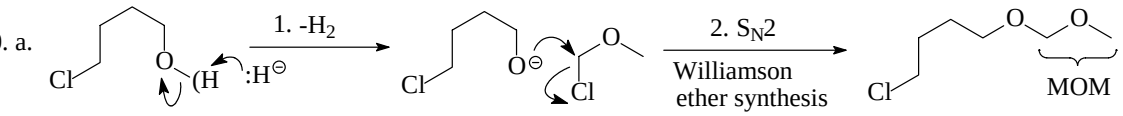
18.


O
+H⊕
OH
EAS
HO
H)
-H⊕
HO
OH
-H⊕, EAS
+H⊕
-H2O

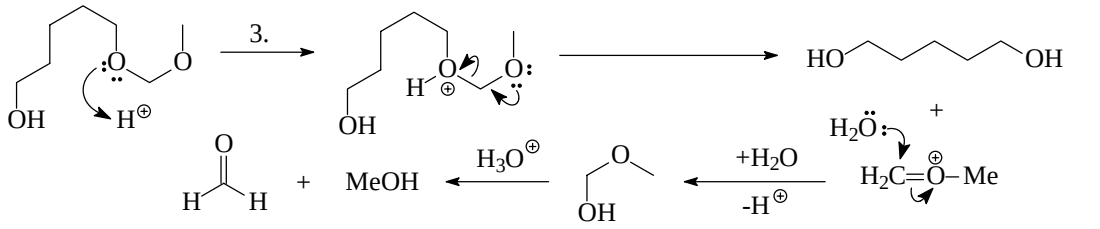
19.


O
H
H2N
Et
O⊖
N⊕
H2
~H⊕
taut
H
-H⊕
-⊖OH
~H⊕

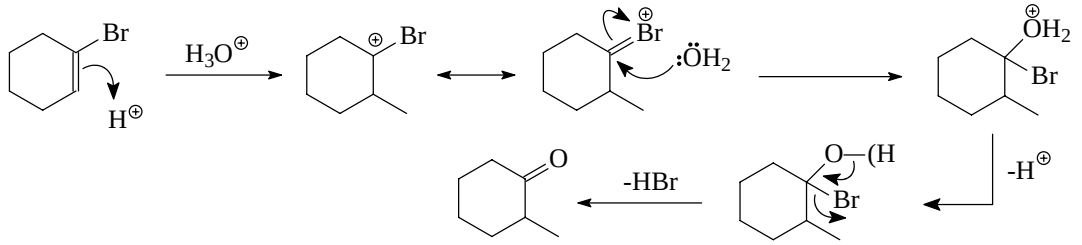
20. a.


Cl
O
(H
:H⊖
1. -H2
2. SN2
Williamson
ether synthesis
MOM

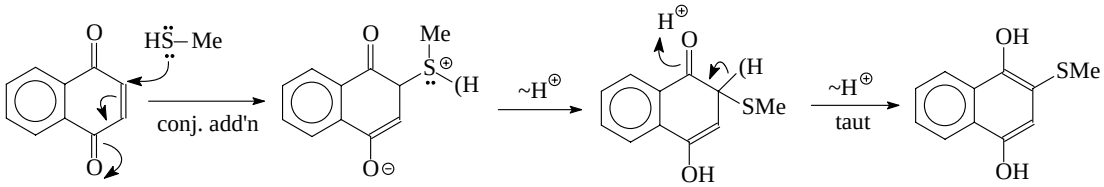
b.


OH
H⊕
3.
HO
OH
H2O
+
H2C=O−Me
+H2O
-H⊕
H3O⊕
MeOH

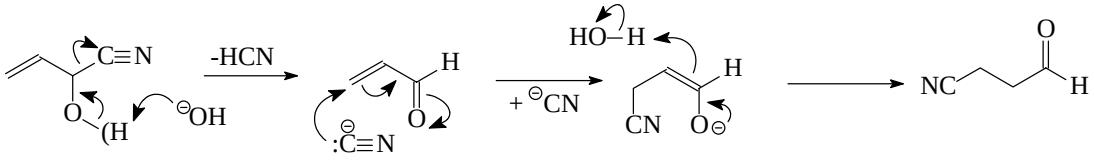
21.



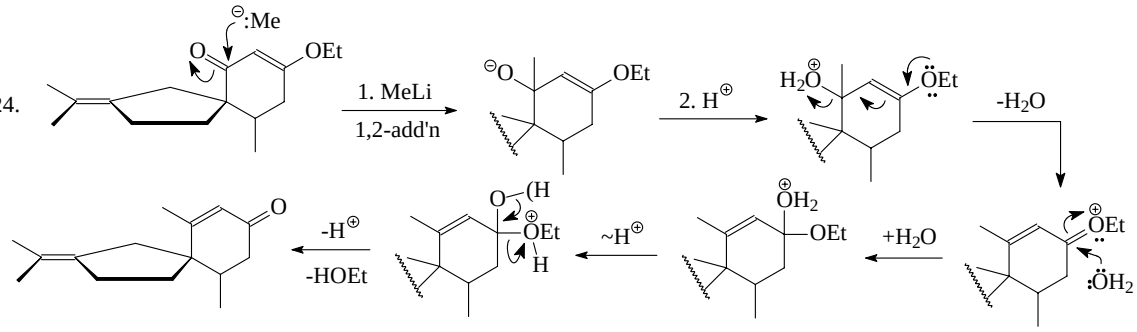
22.



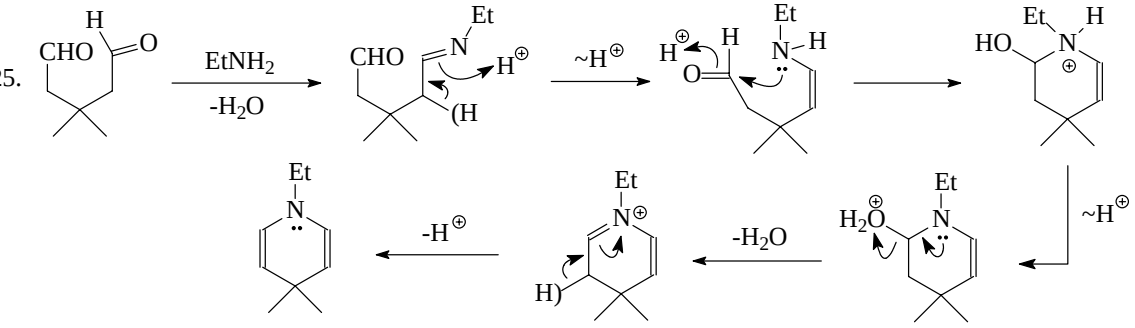
23.



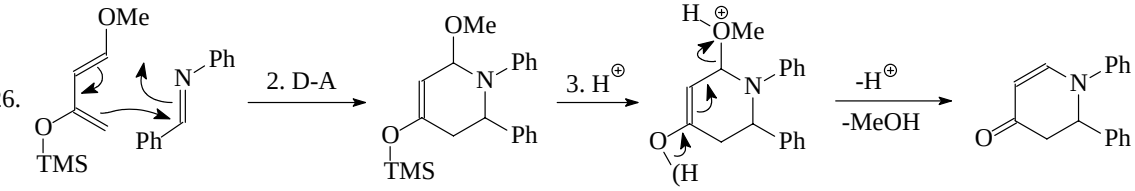
24.



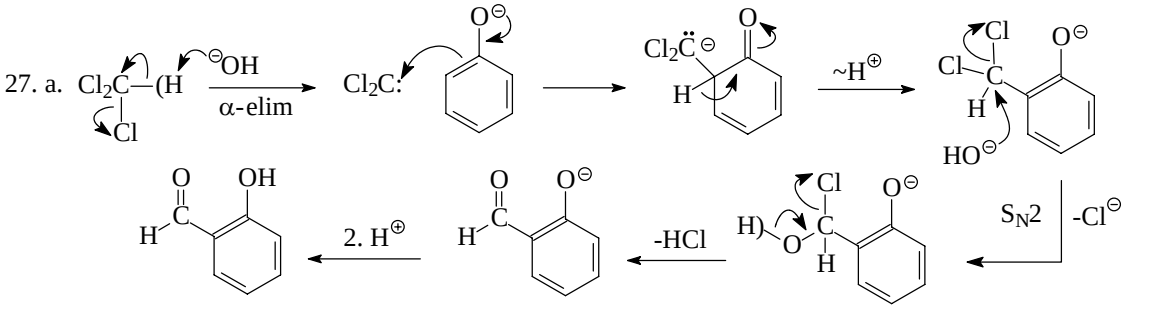
25.



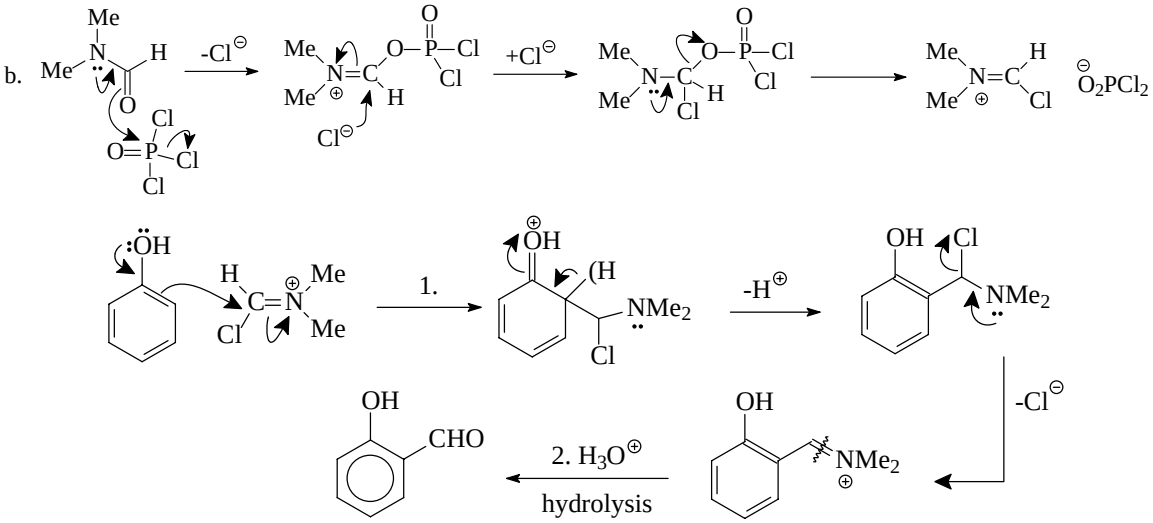
26.



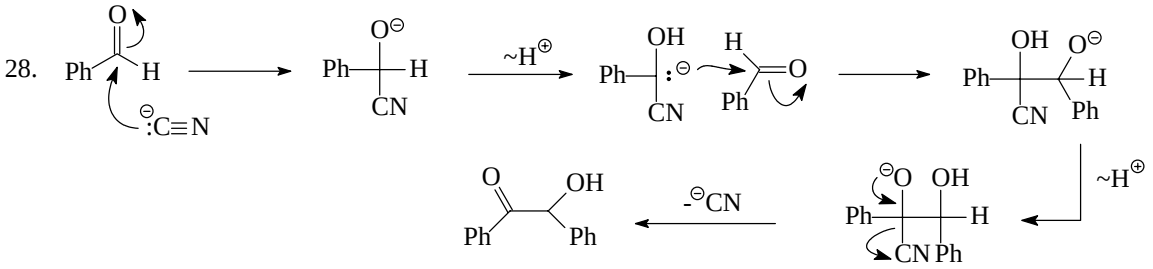
27. a.


α-elim
~H⊕
S_N2
-Cl⊖
-HCl
2. H⊕

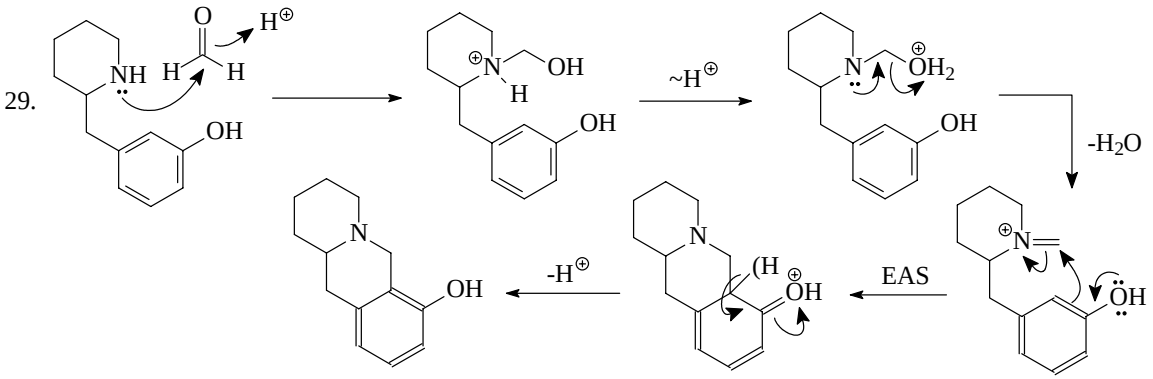
b.


-Cl⊖
+Cl⊖
O2PCl2
1.
-H⊕
-Cl⊖
2. H3O⊕
hydrolysis

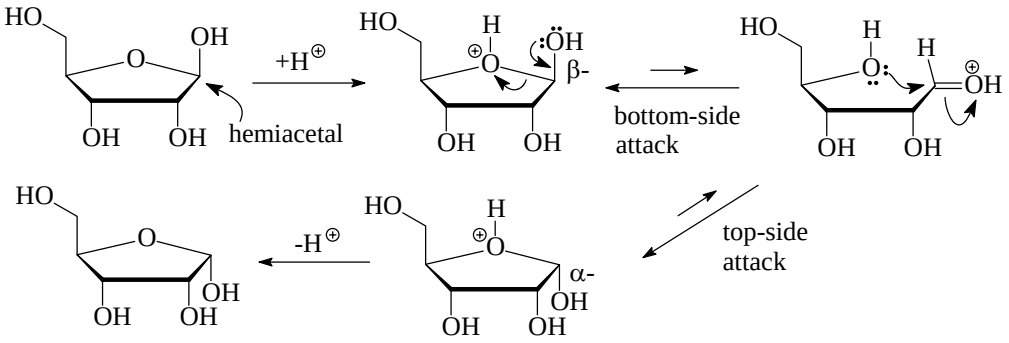
28.


~H⊕
-⊖CN
~H⊕

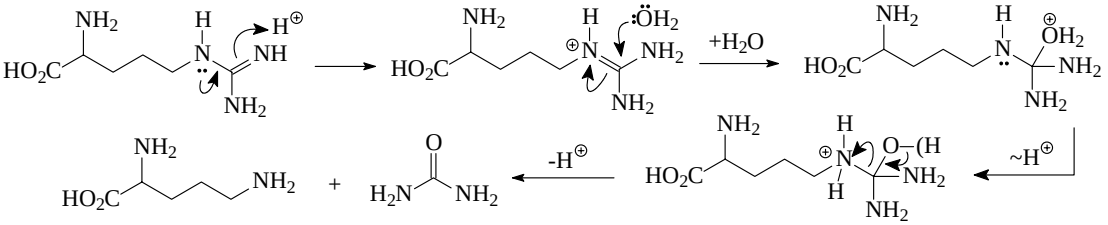
29.


~H⊕
-H2O
EAS
-H⊕

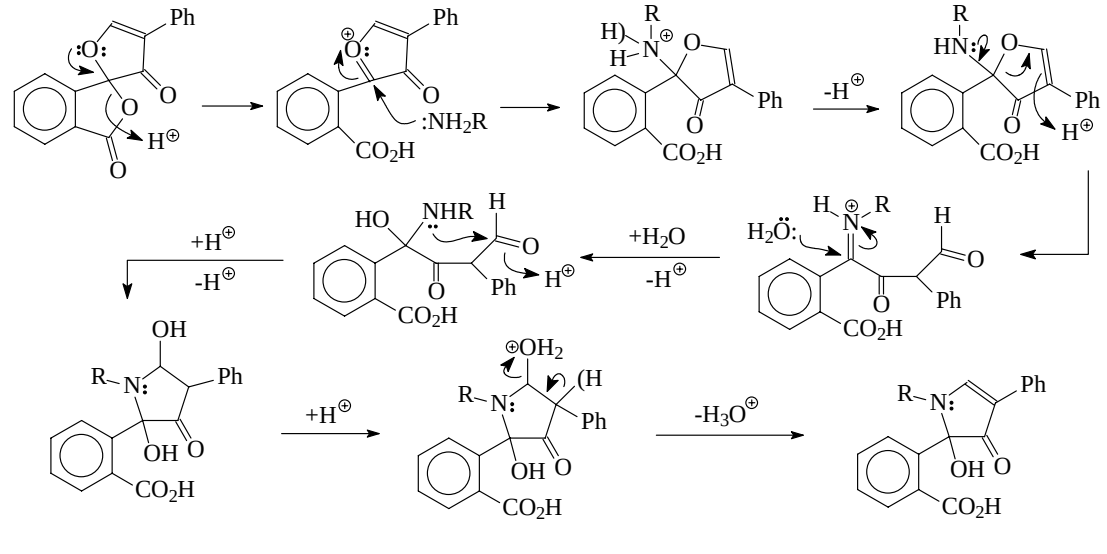
30.


HO
OH
O
OH
OH
hemiacetal
+H⊕
β-
bottom-side
attack
top-side
attack
α-
-H⊕

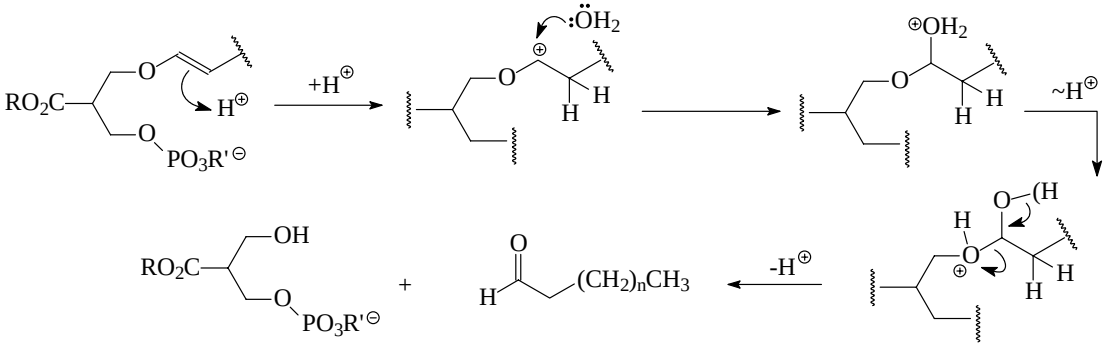
31.


NH2
HO2C
NH
+H2O
~H⊕
-H⊕
H2N
NH2

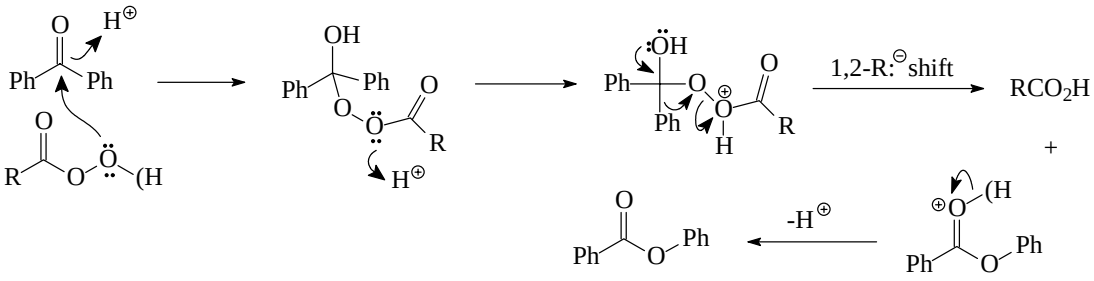
32.


Ph
CO2H
:NH2R
-H⊕
~H⊕
+H⊕
-H⊕
+H2O
-H⊕
NHR
Ph
CO2H

33.


RO2C
PO3R'⊖
+H⊕
~H⊕
-H⊕
(CH2)nCH3

34.



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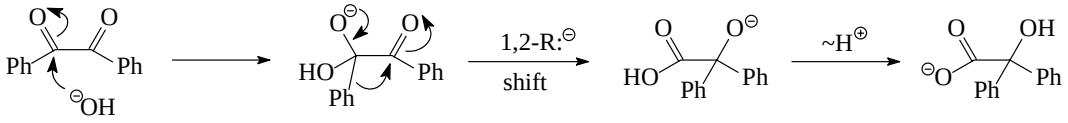
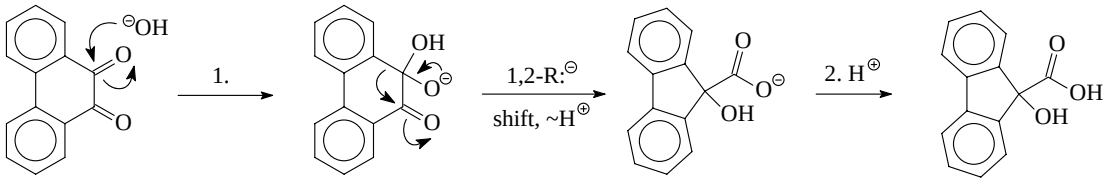
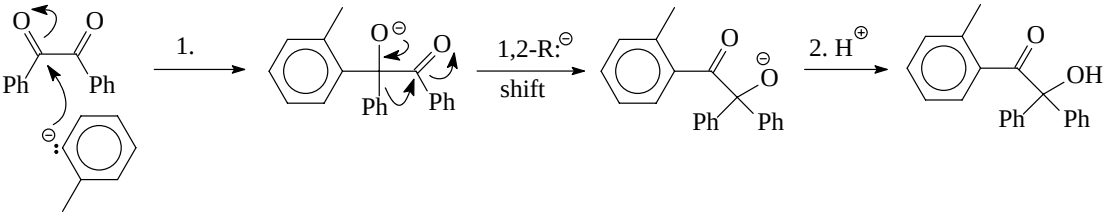


b.



c.



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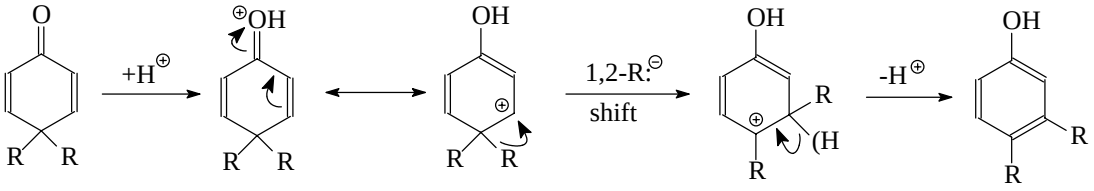

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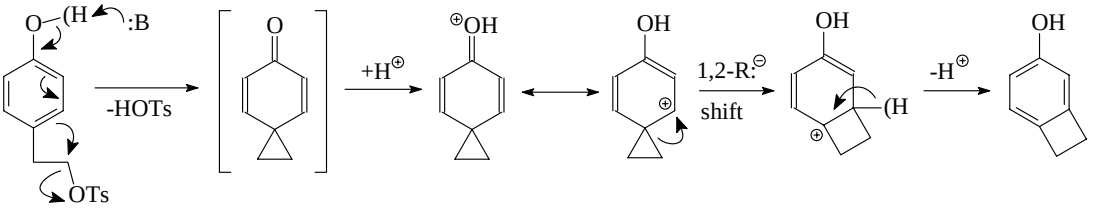

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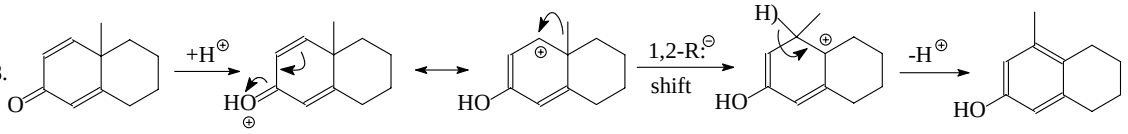

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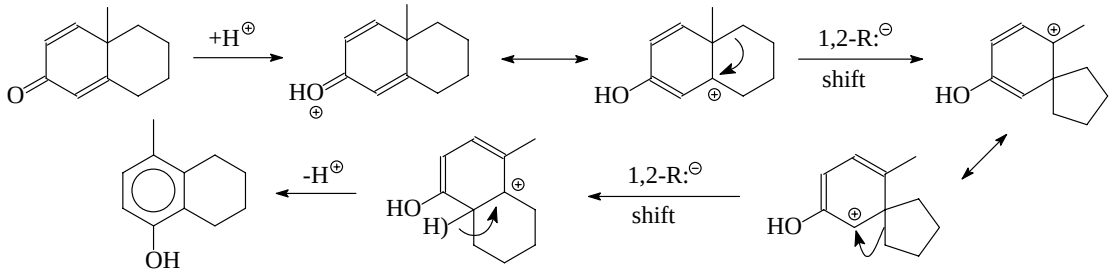

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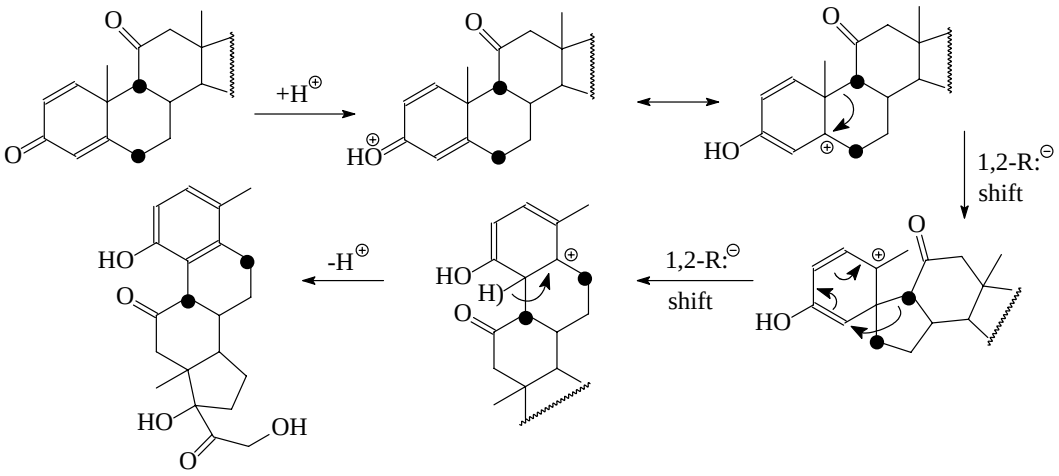

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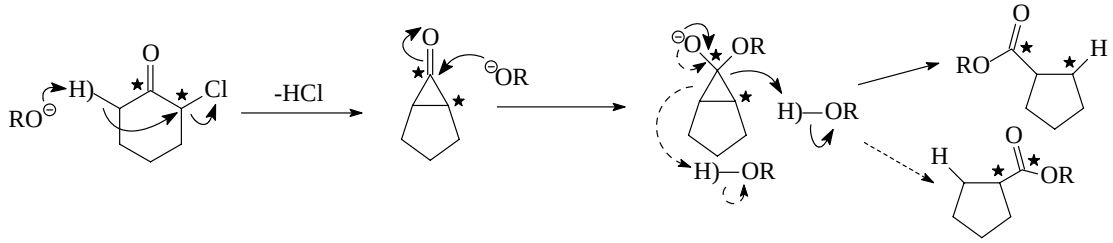

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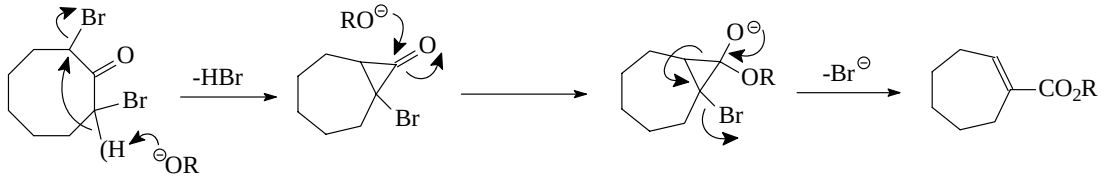

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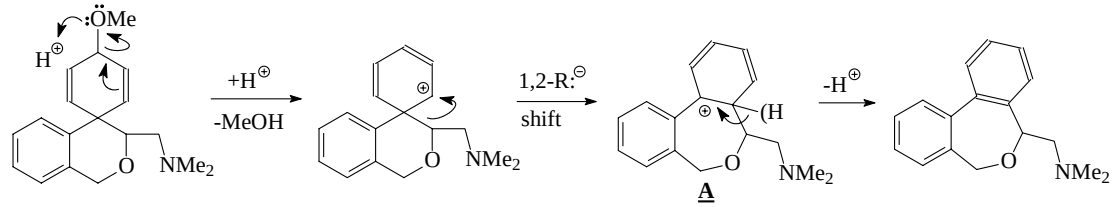
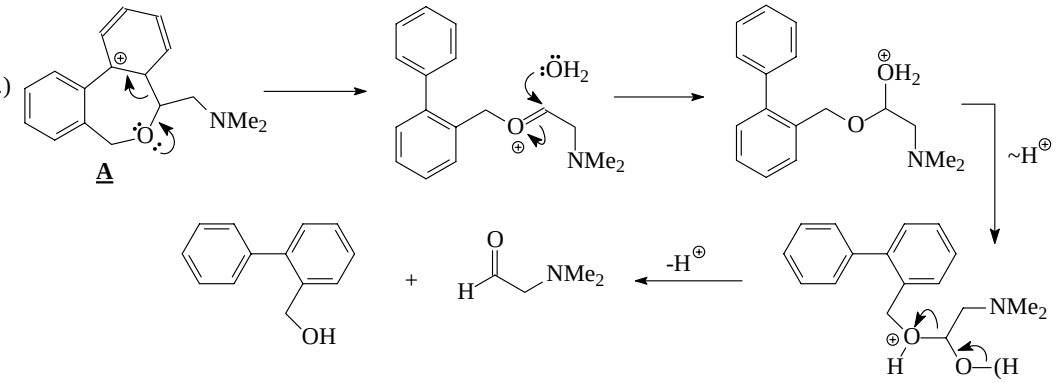


A

43. (*cont.*)



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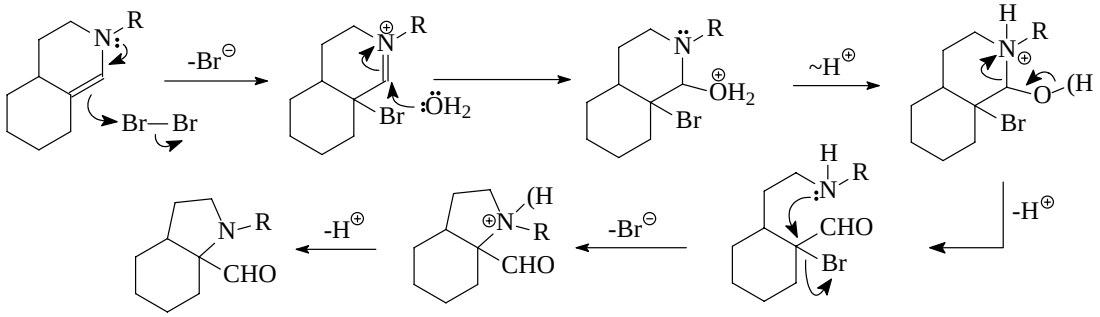

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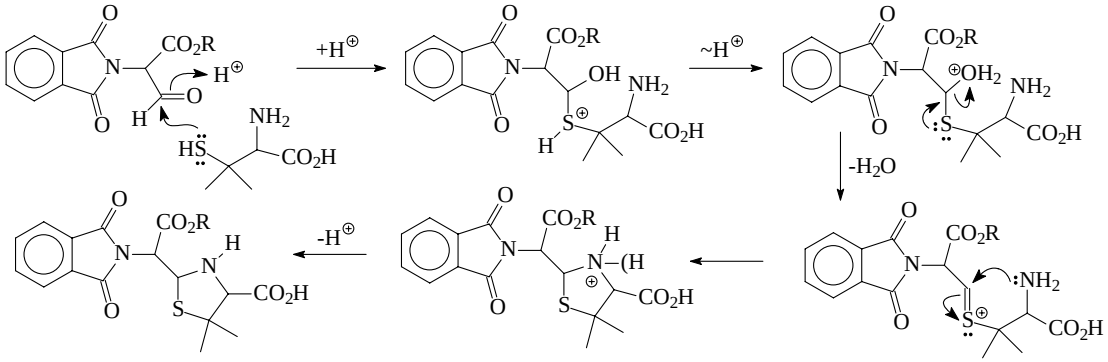

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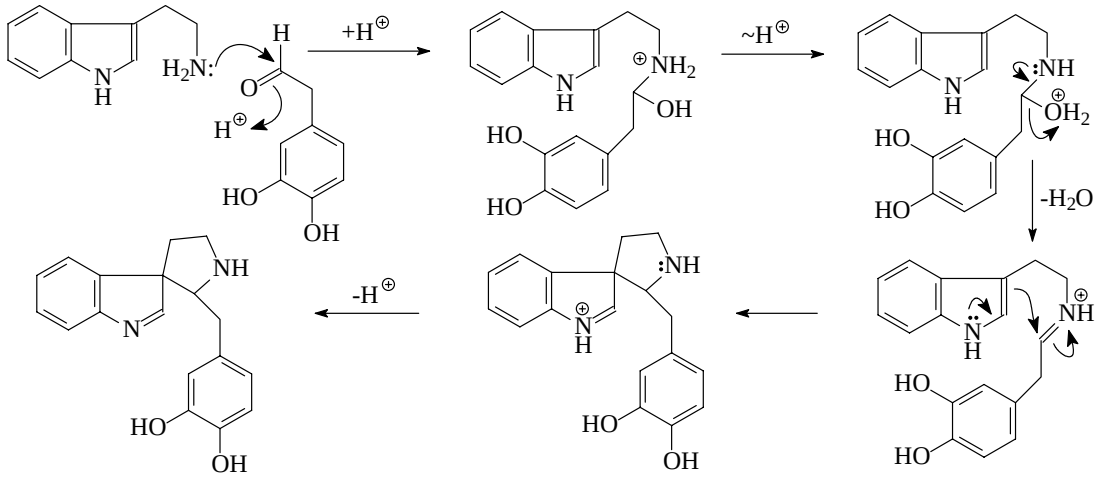

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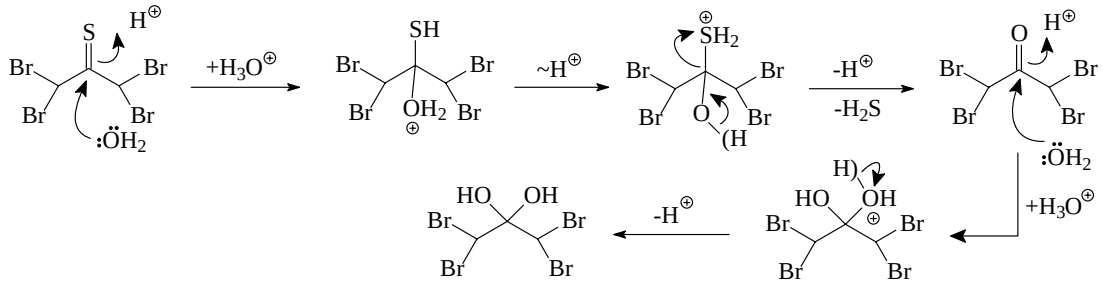
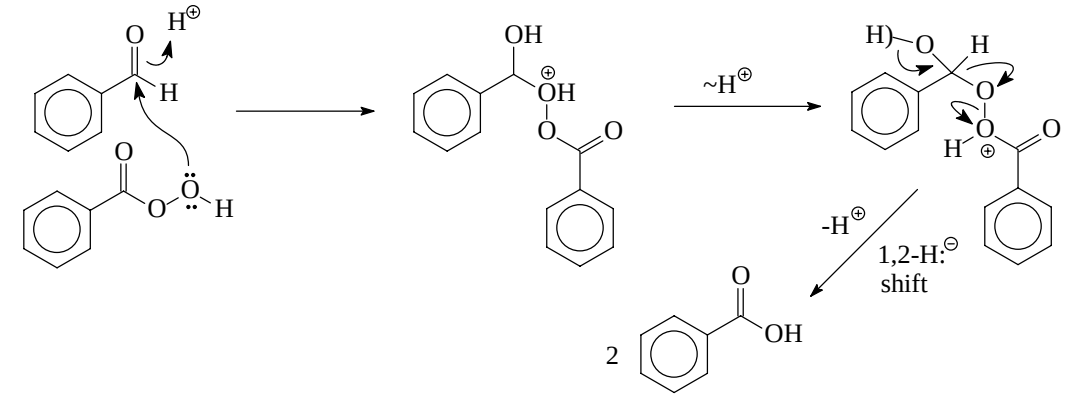
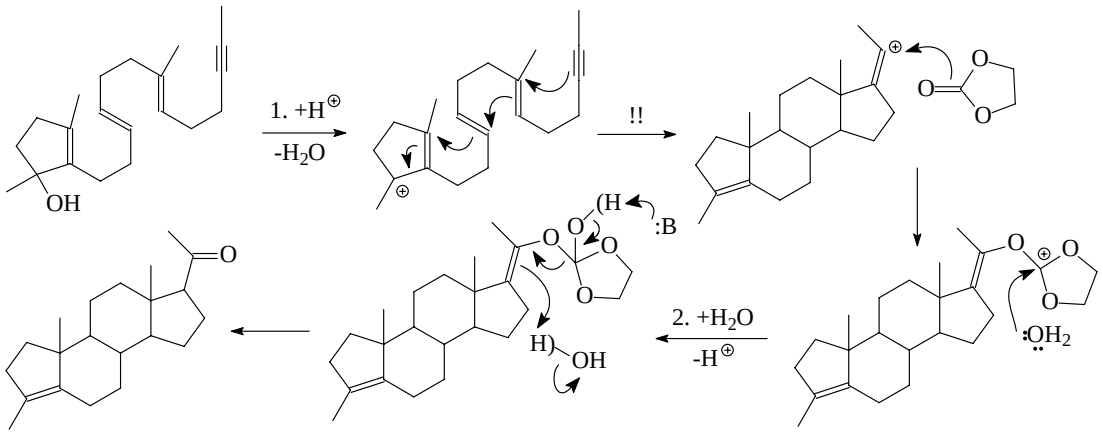

S
H⊕
Br
Br
Br
Br
:ÖH2
+H3O⊕
SH
OH2
~H⊕
SH2
O
(H
-H⊕
-H2S
H)
HO
OH
+H3O⊕
-H⊕

48.

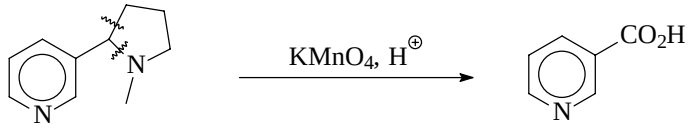

O
H⊕
H
O
O
H
OH
O
O
~H⊕
H)
O
H
O
H
-H⊕
1,2-H:⊖
shift
2
O
OH

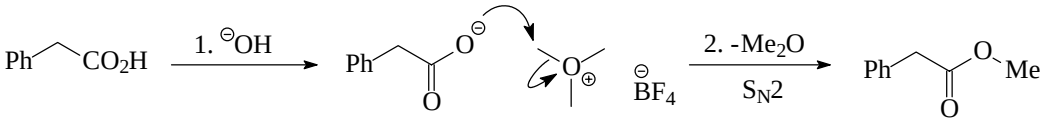
49.

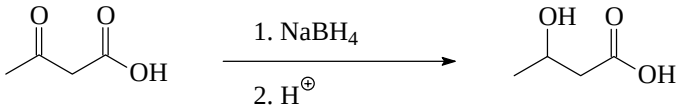

OH
1. +H⊕
-H2O
!!
O
O
O
(H
:B
O
O
O
O
H)
OH
2. +H2O
-H⊕
O
O
O
:ÖH2
O

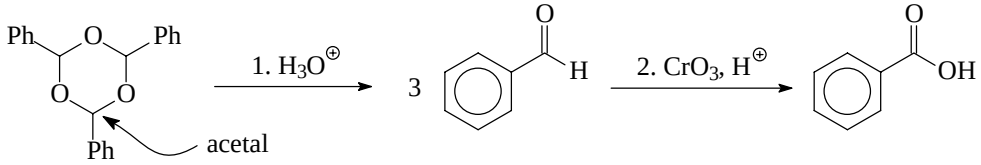
CHAPTER 16
CARBOXYLIC ACIDS

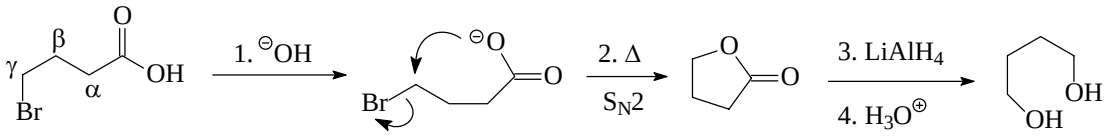
16.1 Reactions

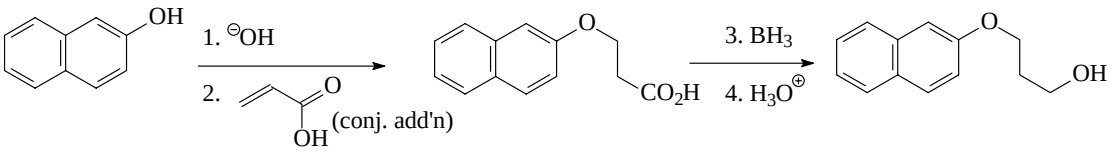
1. 

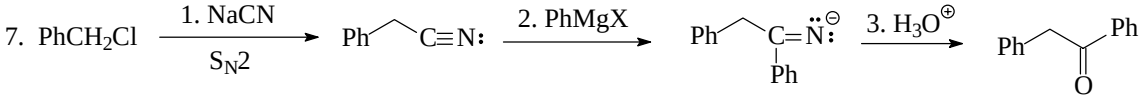
2. 

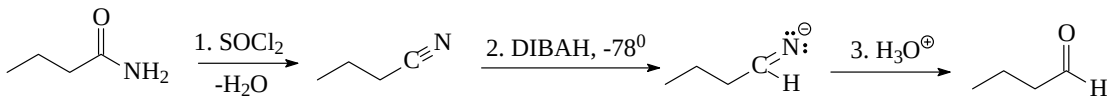
3. 

4. 

5. 

6. 

7. 

8. 

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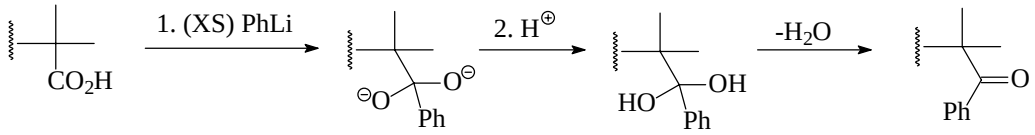

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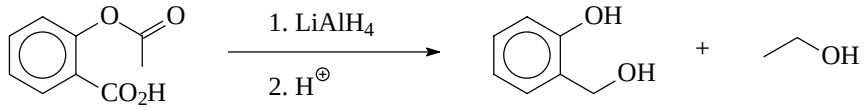

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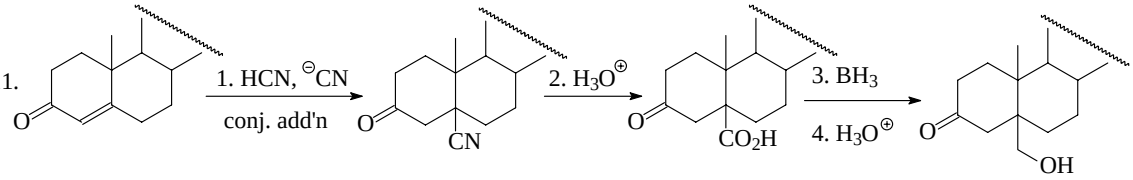

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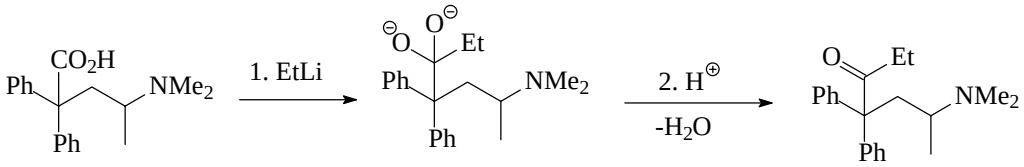

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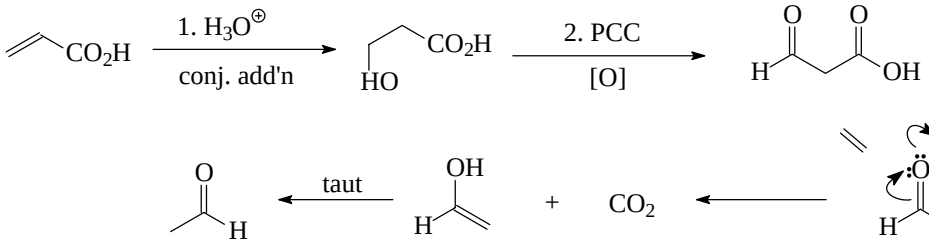

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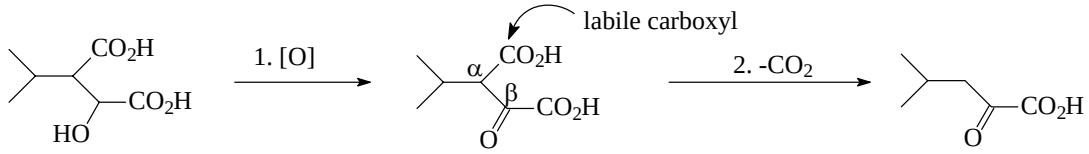

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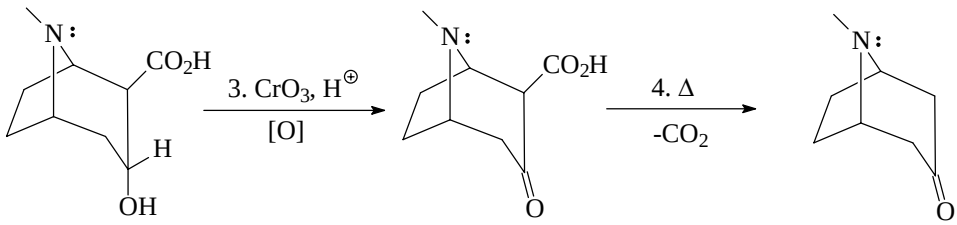
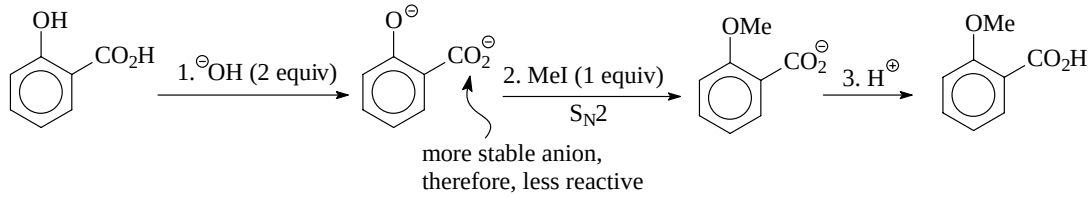
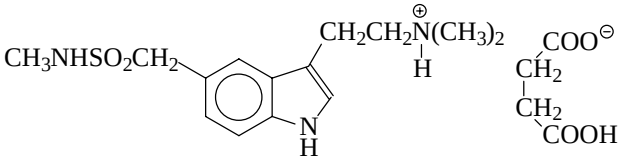
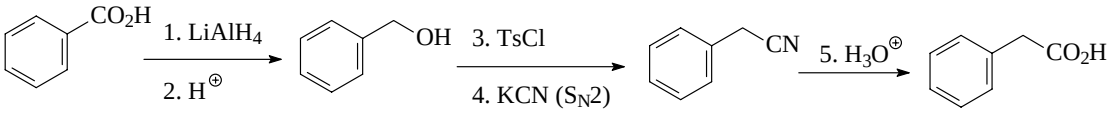


16. 

17. 

a salt!

16.2 Syntheses

1. 

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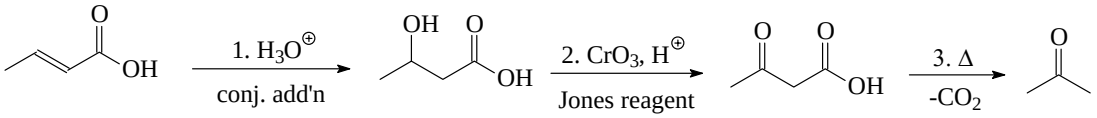
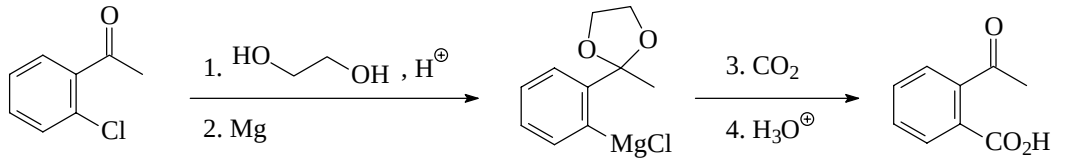
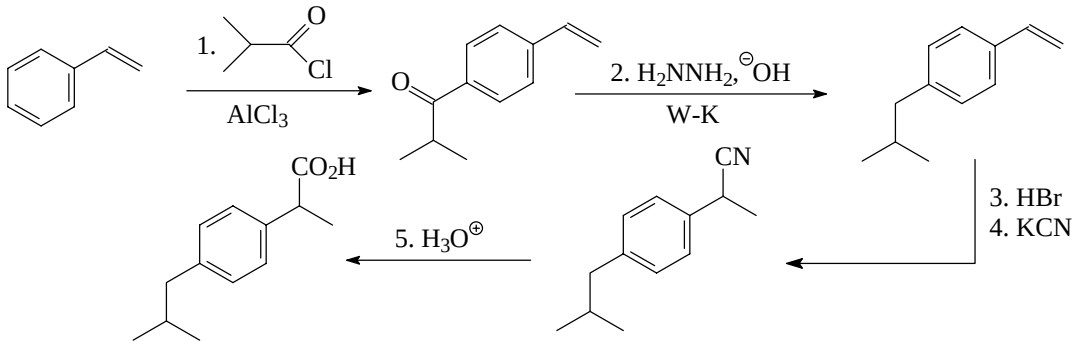
3. 

4. 

5. 

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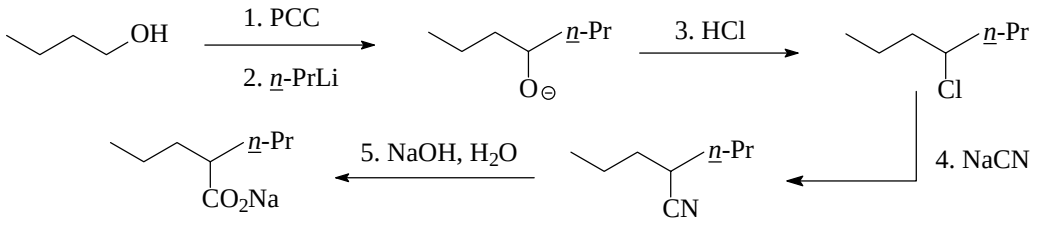

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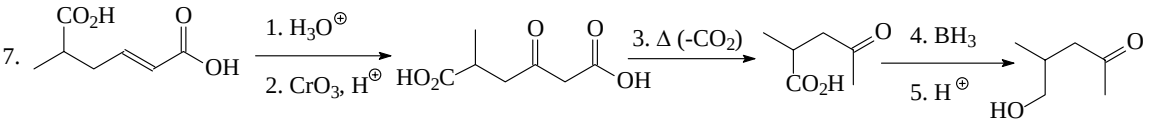

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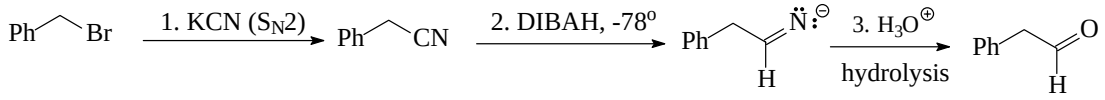

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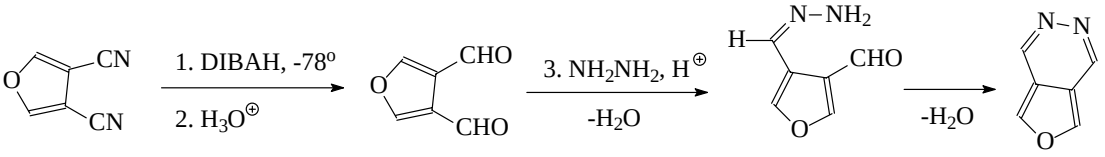

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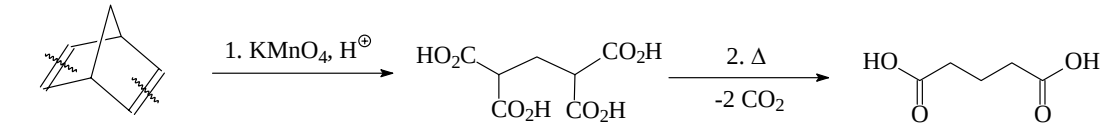

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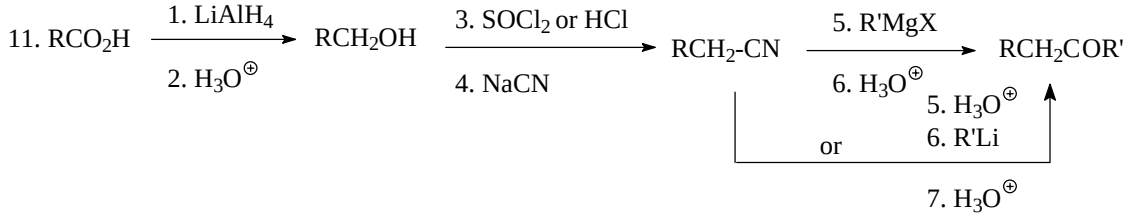

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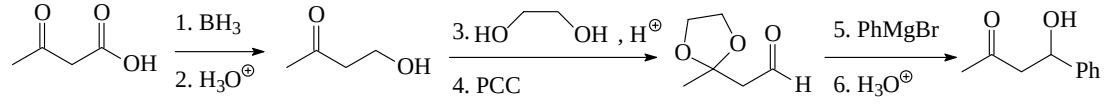

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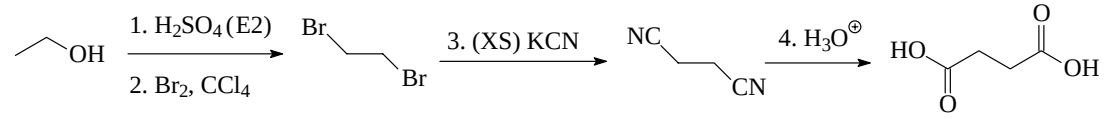
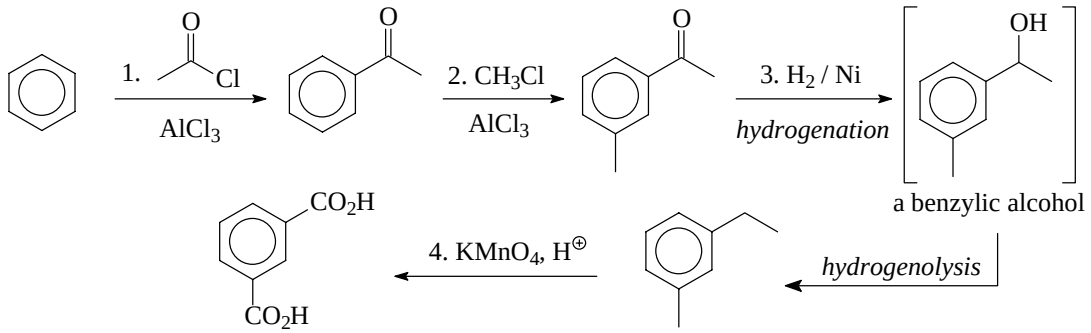
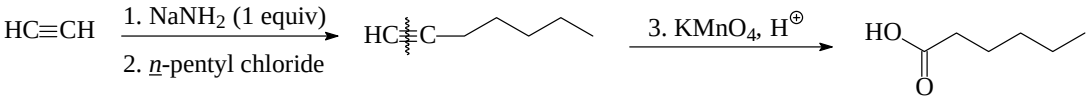
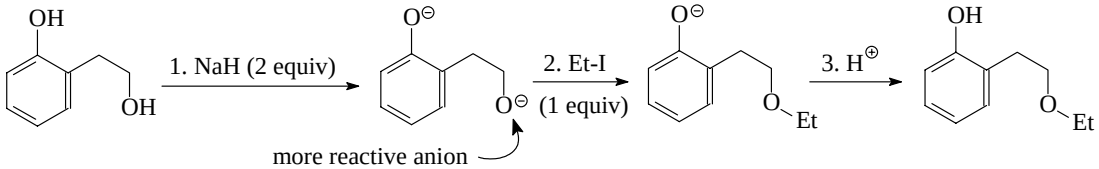
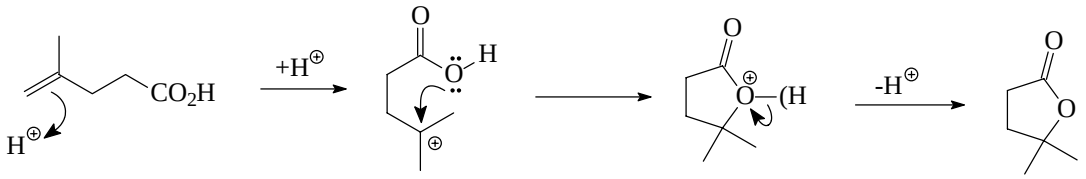


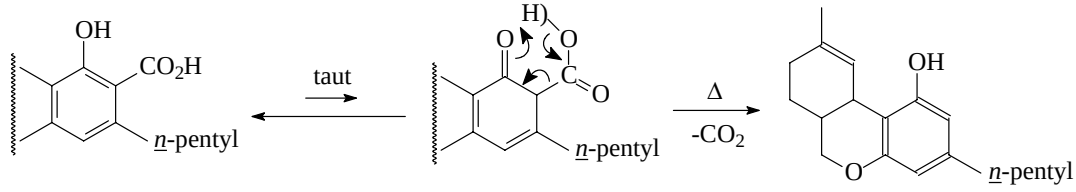
14. 

15. 

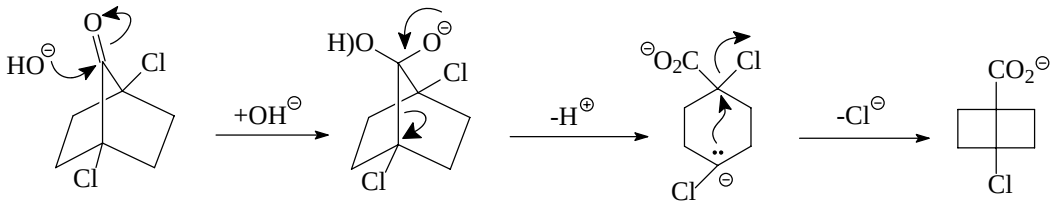
16. 

16.3 Mechanisms

1. 

2. 

tautomerization to β-ketocarboxylic acid facilitates decarboxylation

3. 

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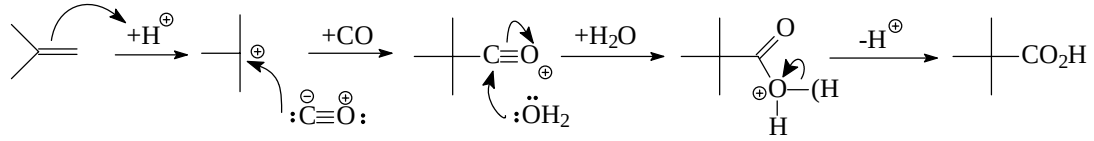

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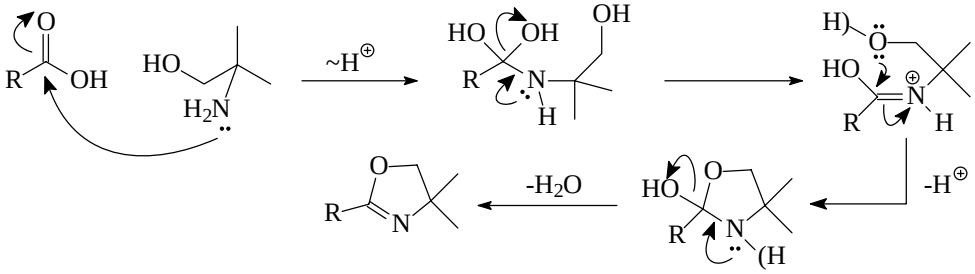

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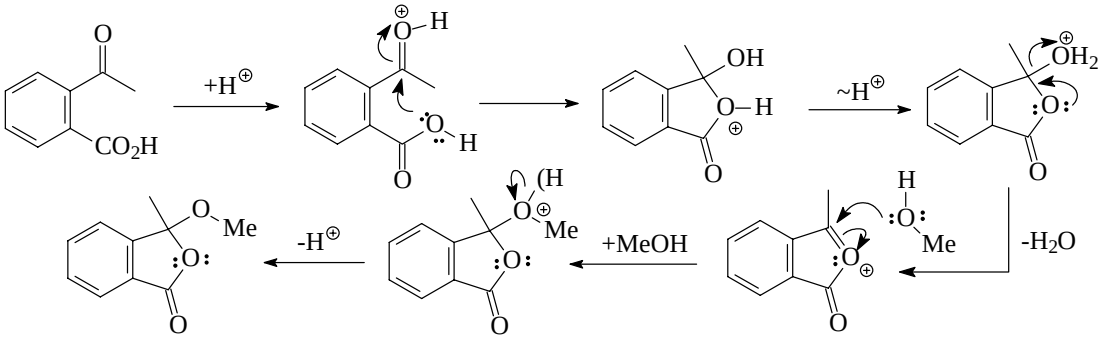

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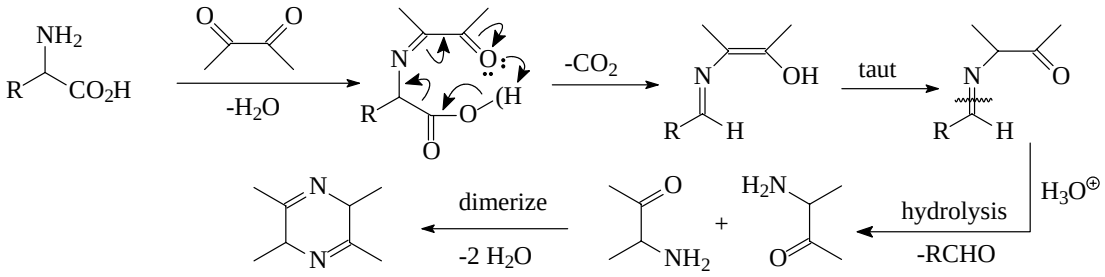

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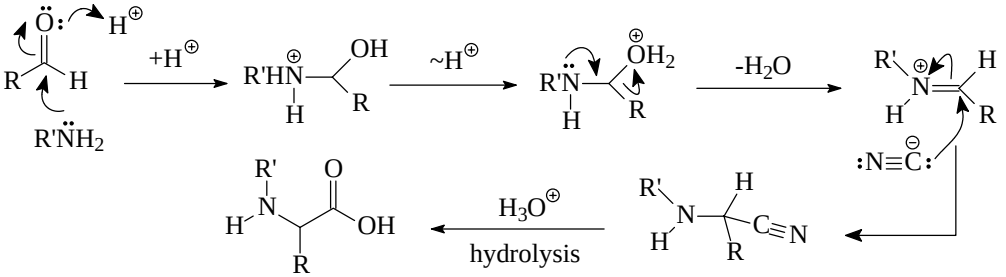

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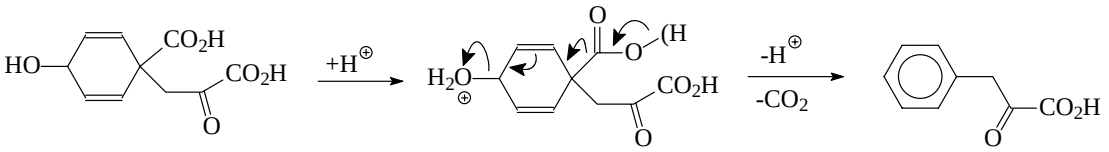

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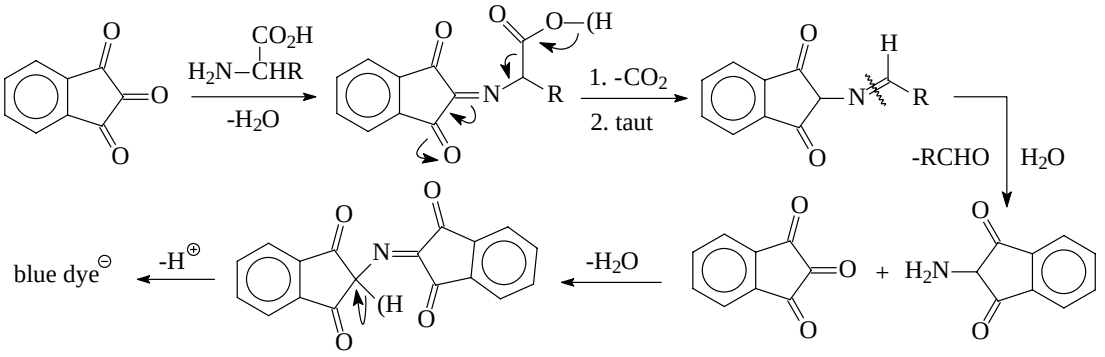

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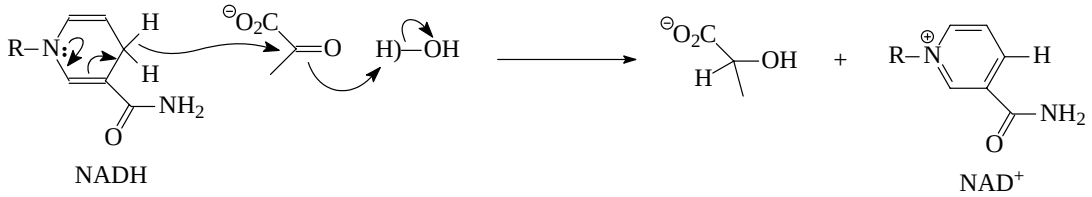

NADH NAD$^+$

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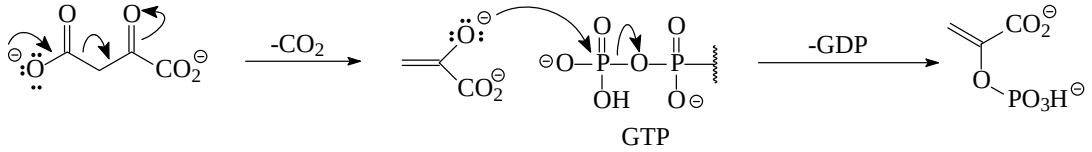
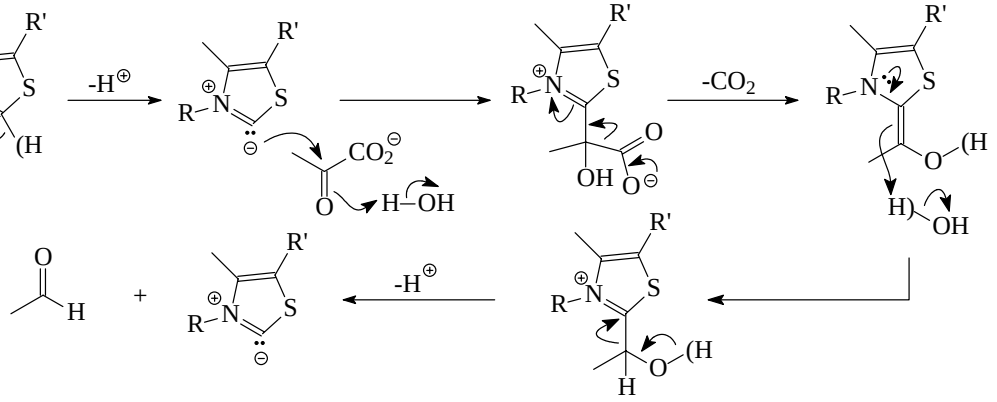


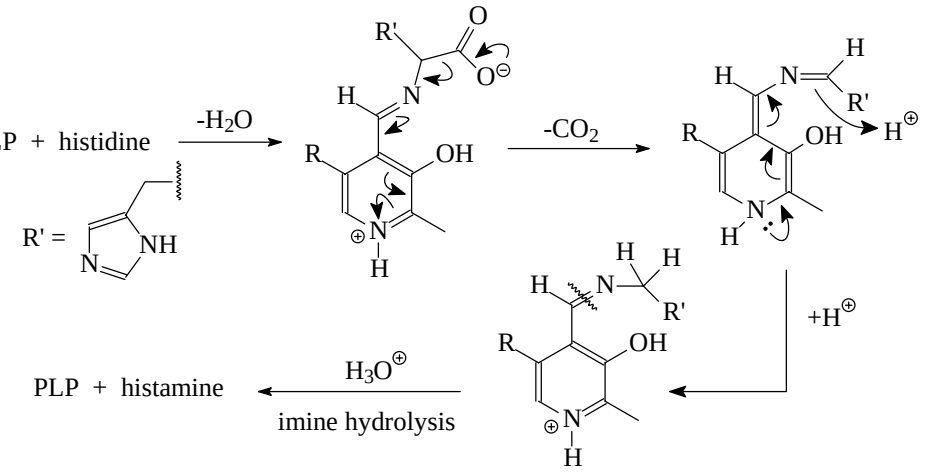
GTP

13.



16.3 Mechanisms

14. PLP + histidine



15. 2

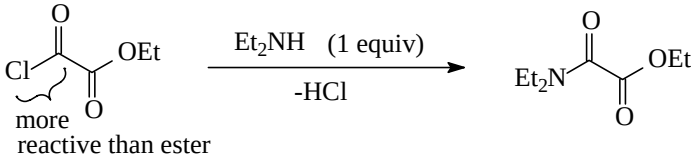
MW = 60

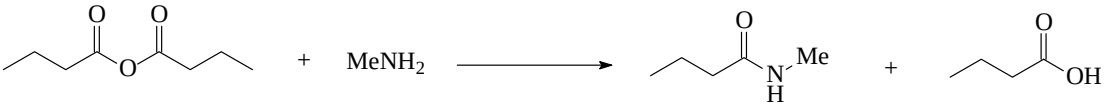
MW = 120

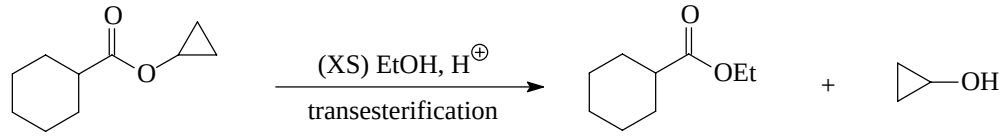
intermolecular hydrogen bonding forms a tight dimeric complex in nonpolar solvents

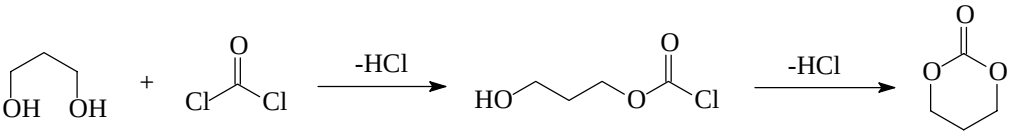
CHAPTER 17
CARBOXYLIC ACID DERIVATIVES

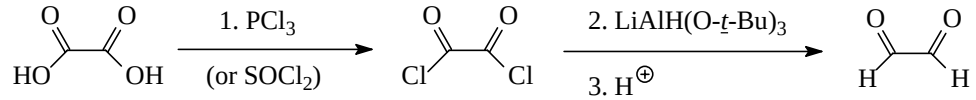
17.1 Reactions

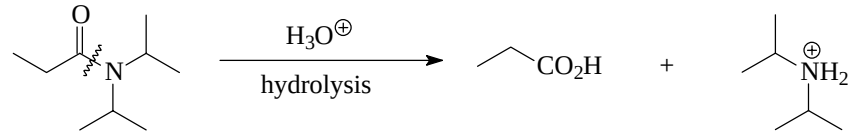
1. 

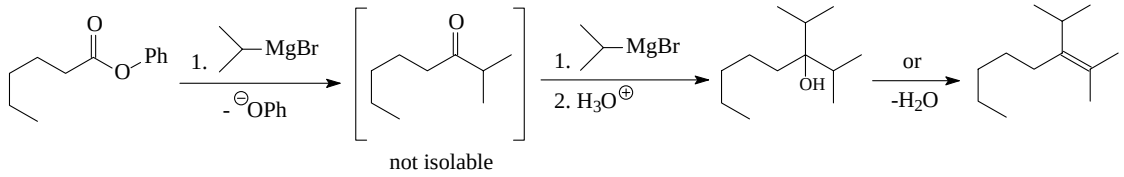
2. 

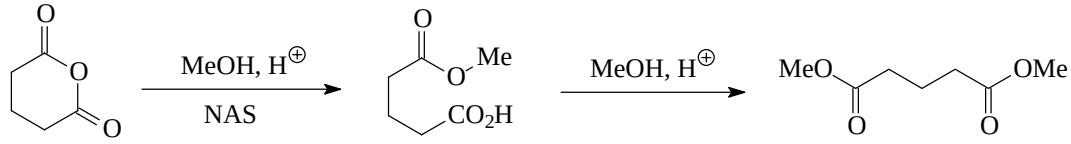
3. 

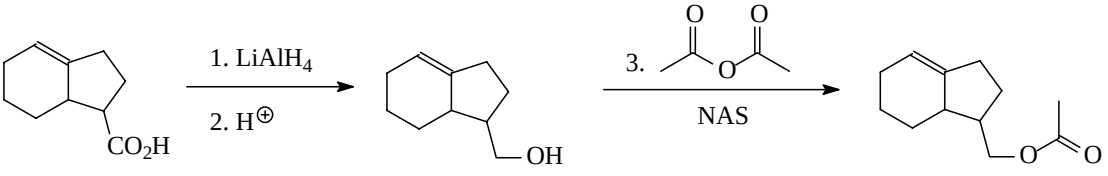
4. 

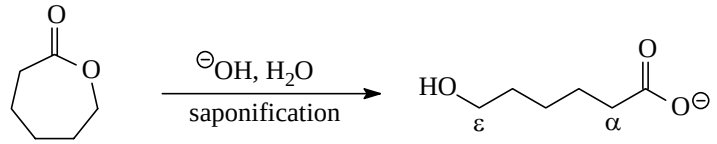
5. 

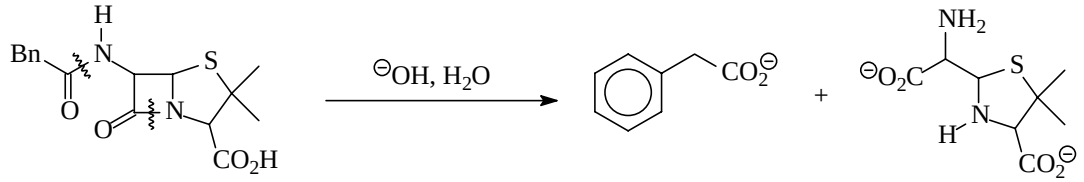
6. 

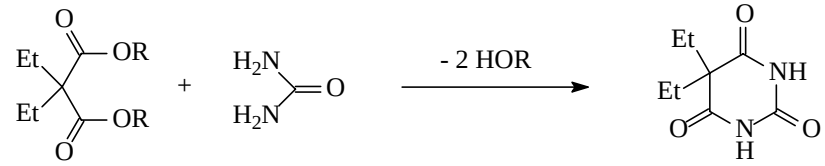
7. 

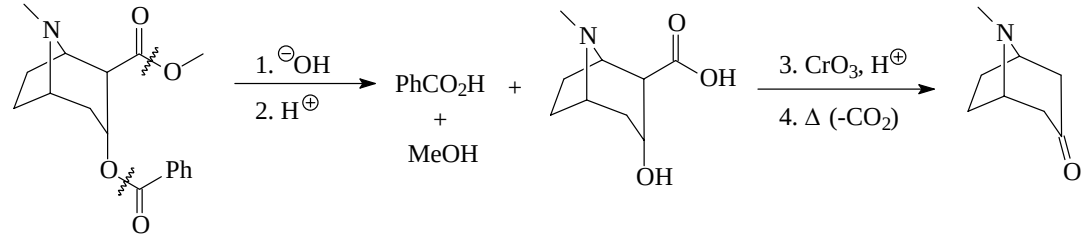
8. 

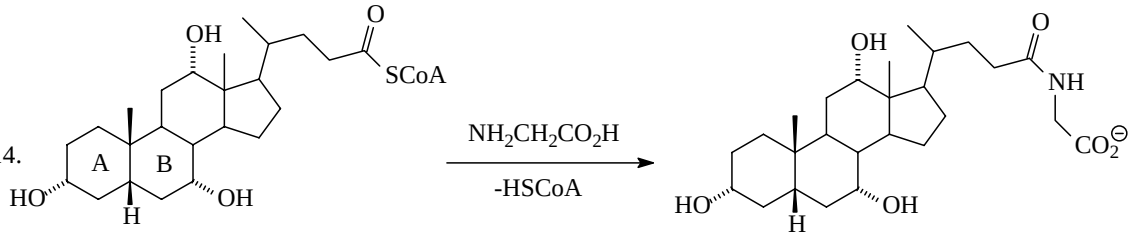
9. 

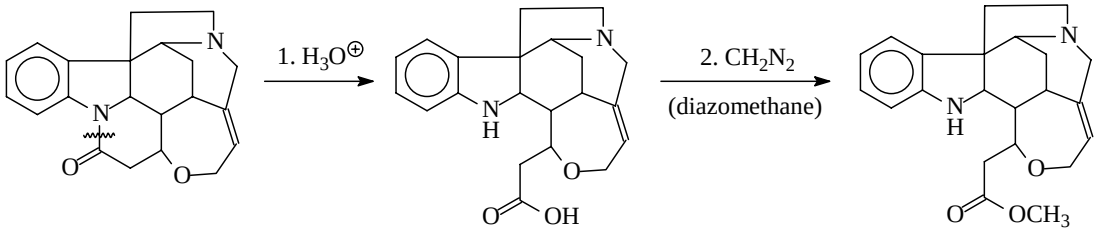
10. 

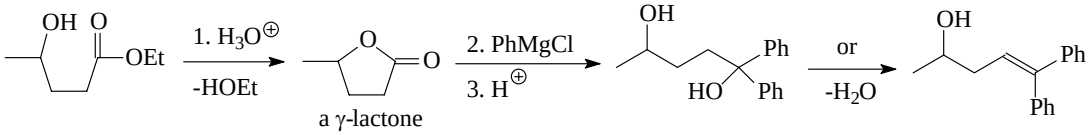
11. 

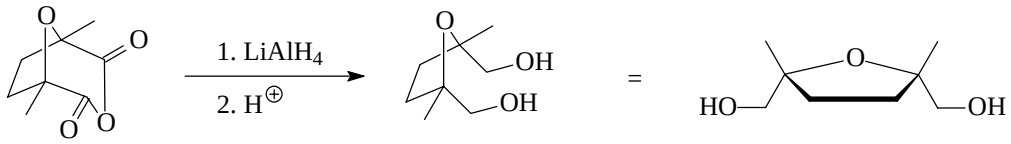
12. 

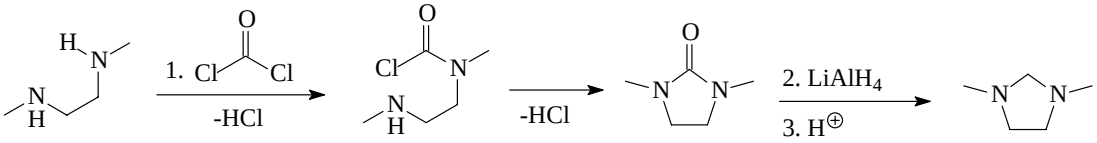
13. 

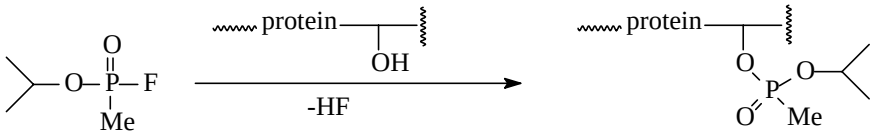
14. 

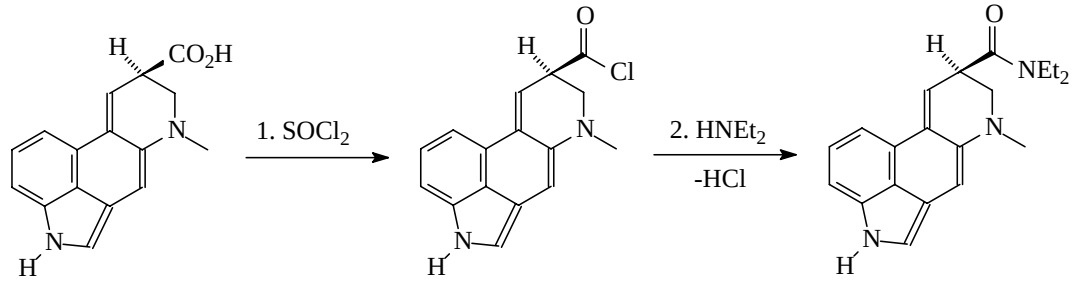
15. 

16. 

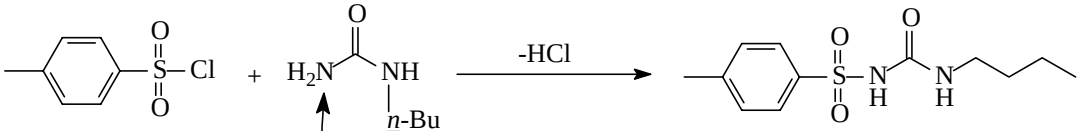
17. 

18. 

19. 

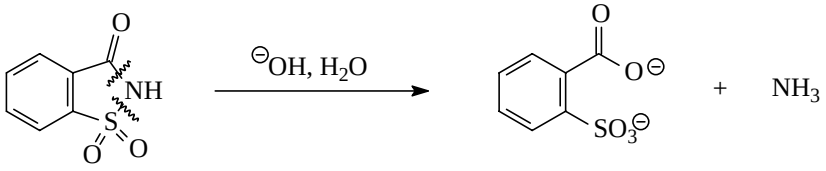
20. 

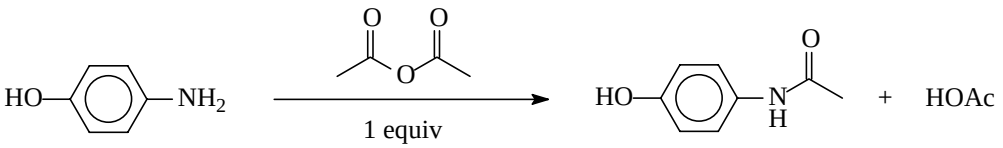
*lys*ergic acid *di*ethylamide

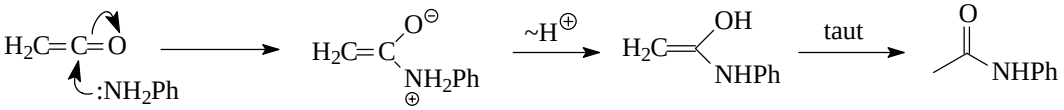
21. 

tosyl chloride

more nucleophilic nitrogen

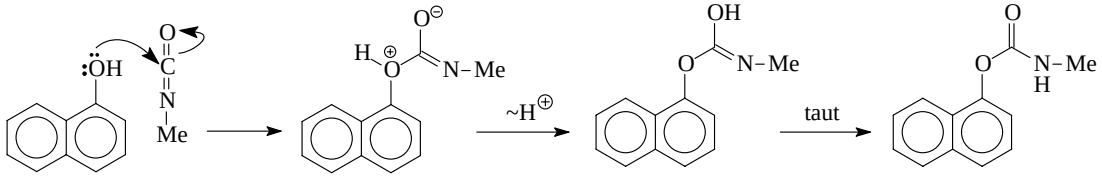
22. 

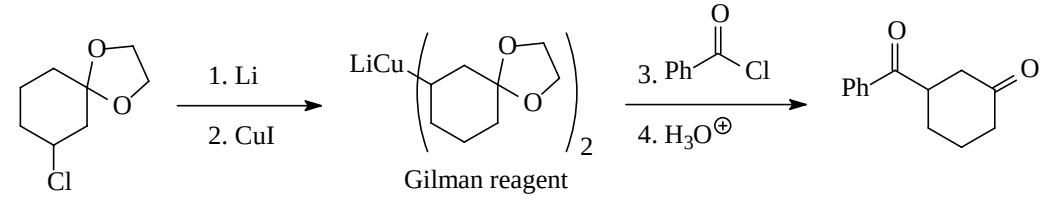
23. 

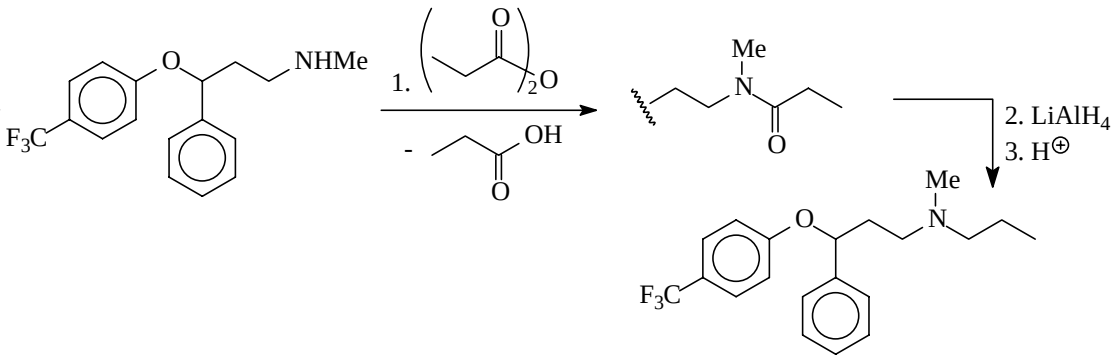
24. 

25. dimethyl phthalate + HO–CH$_2$–CH$_2$–OH, $H^{\oplus}$, transesterification → a polyester

26. HO–C$_6$H$_4$–C(CH$_3$)$_2$–C$_6$H$_4$–OH + ClCOCl → - *n* HCl

27. 

28. 

29. 

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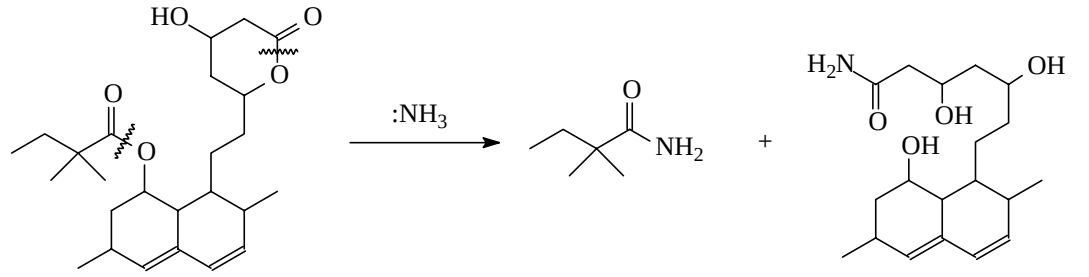

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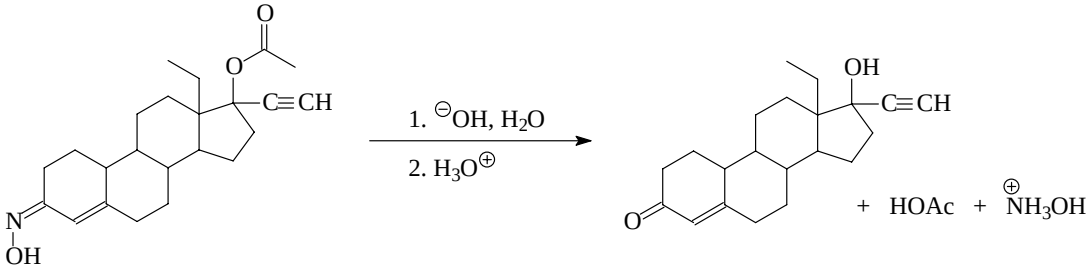

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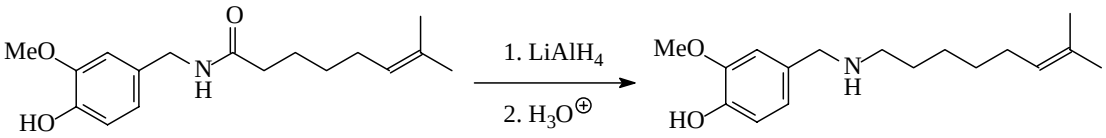

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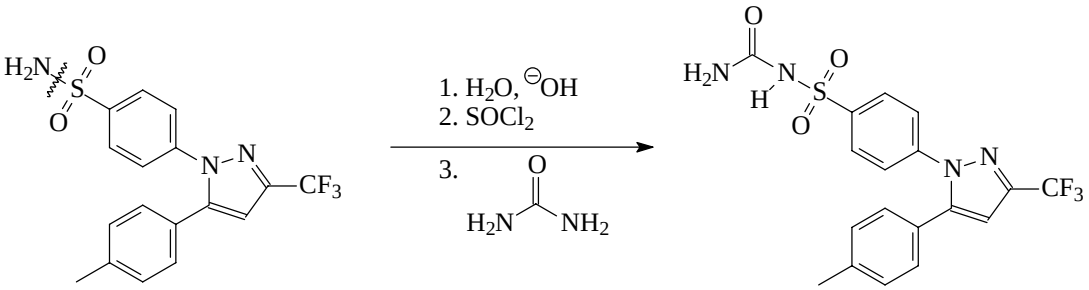

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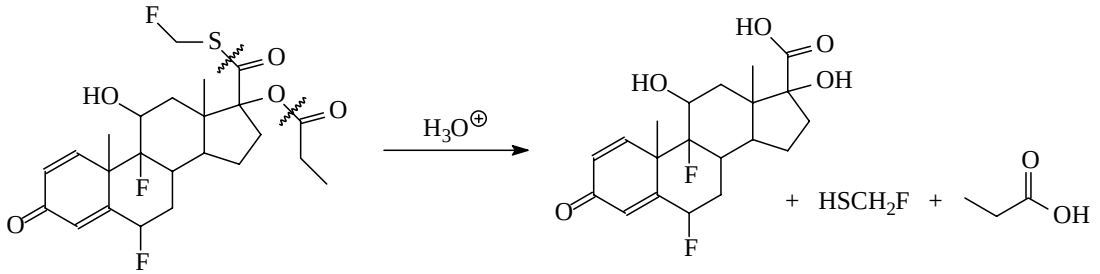

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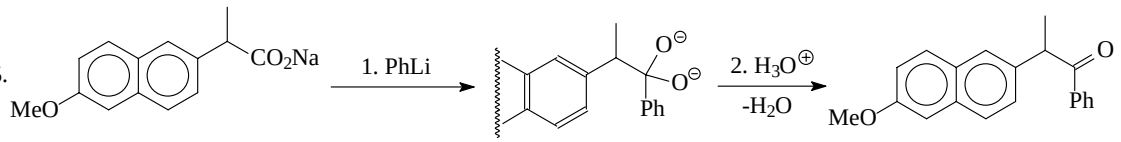

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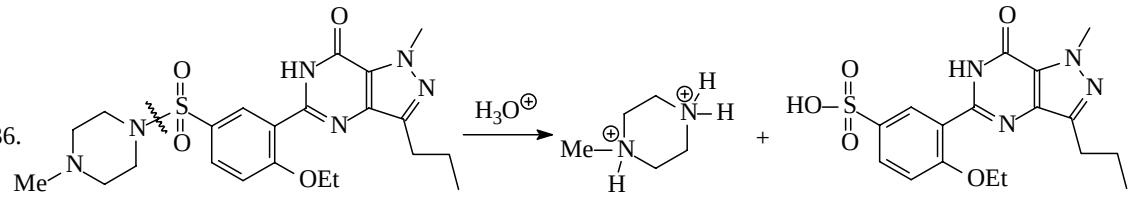

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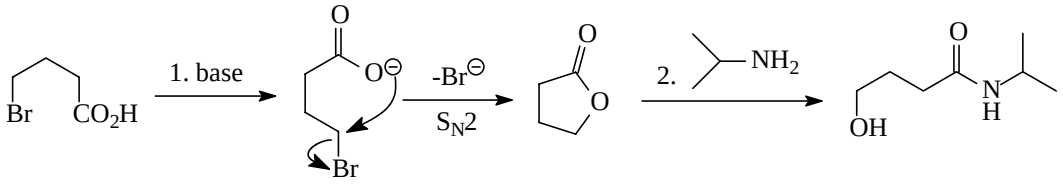

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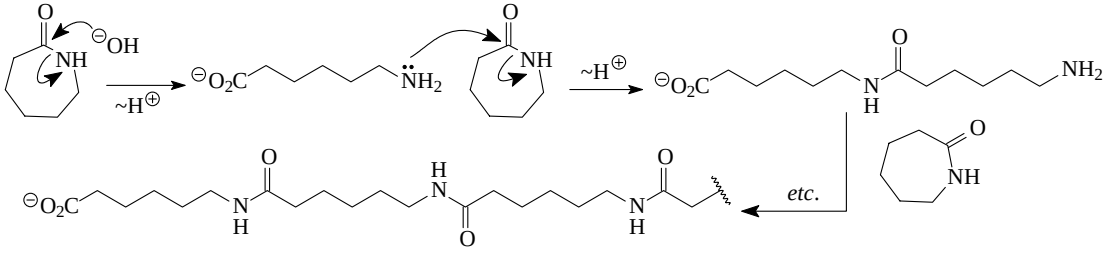

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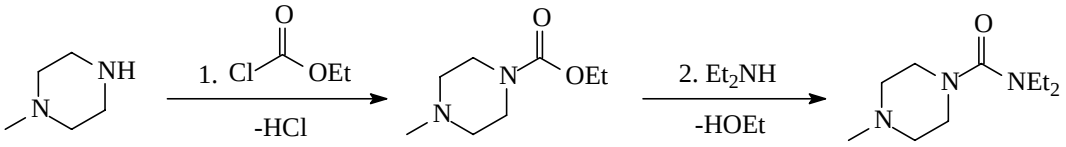

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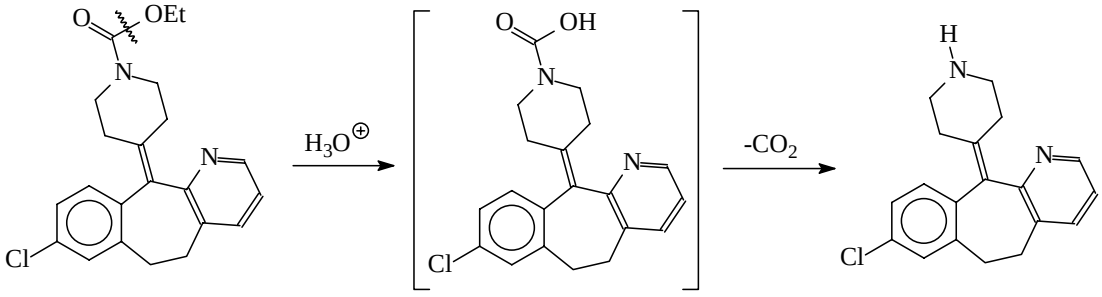

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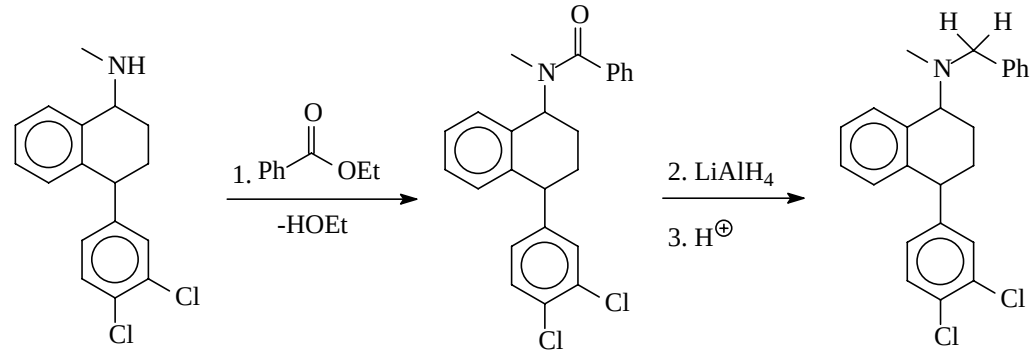
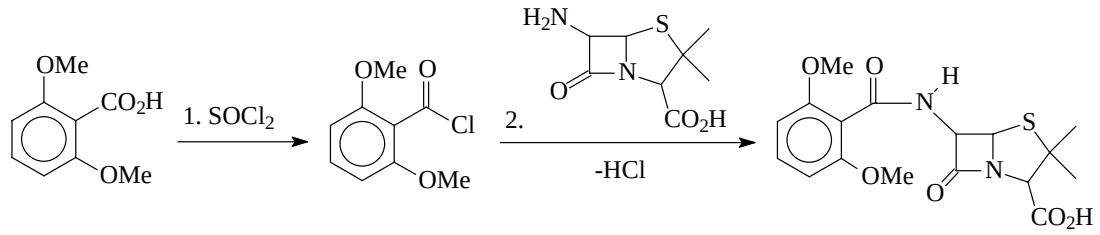
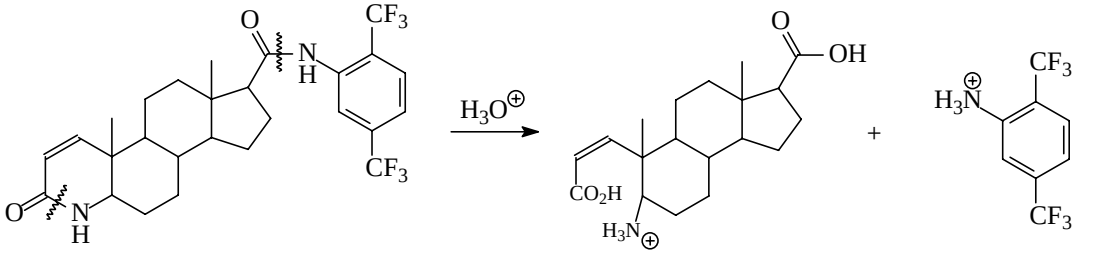
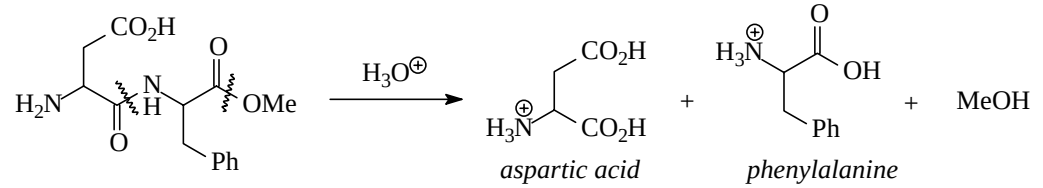
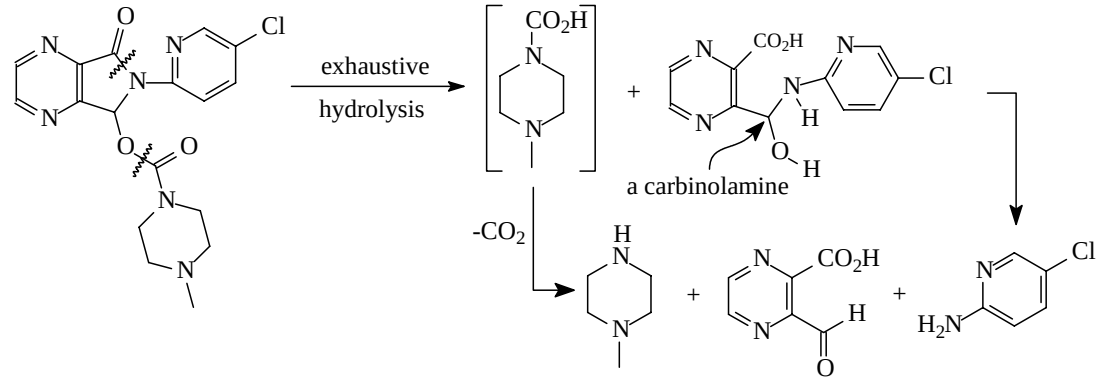
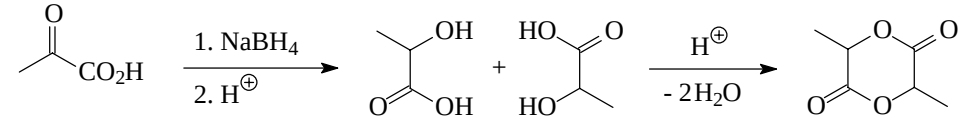


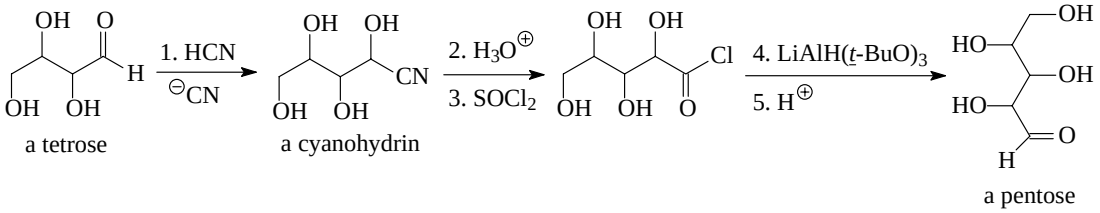
42. 

43. 

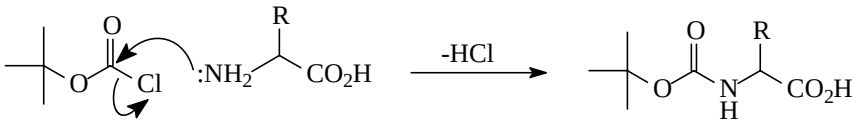
44. 

45. 

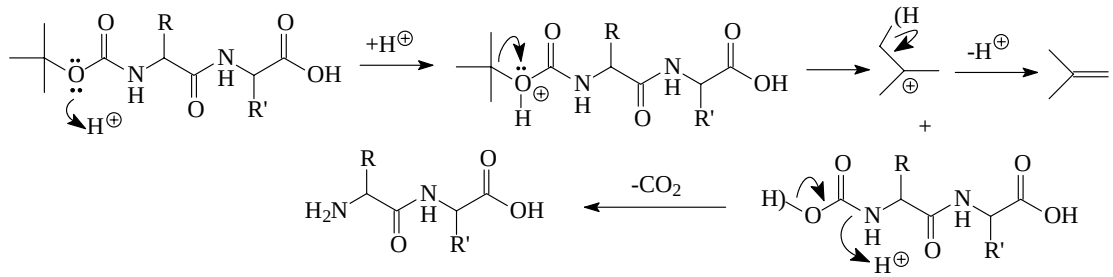
46. 

47. 

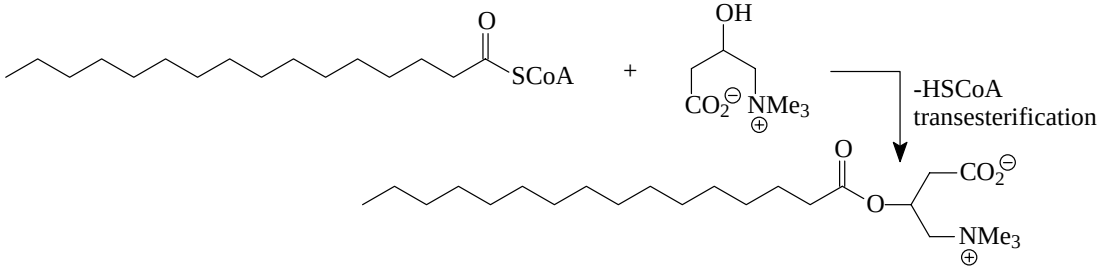
48. a.



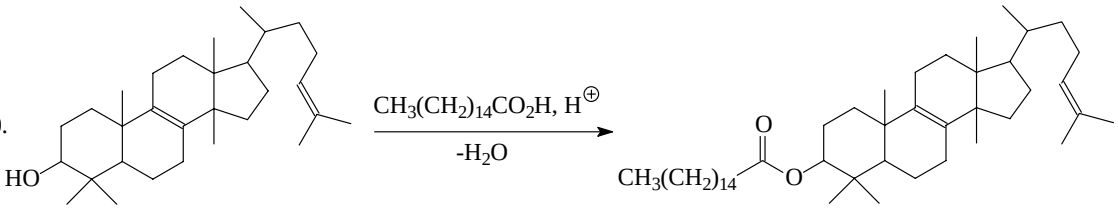
b.



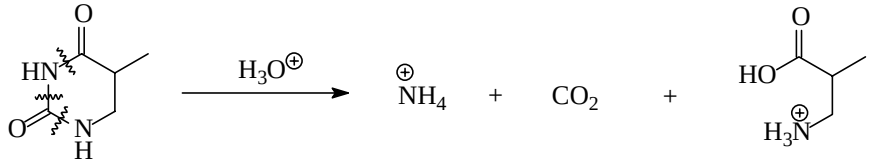
49.



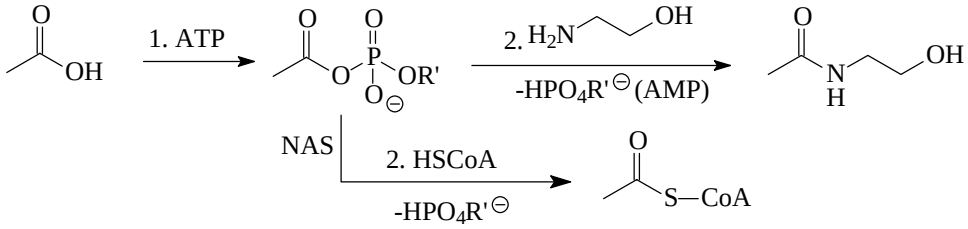
50.

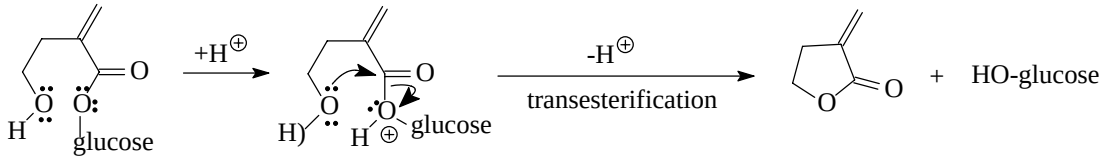


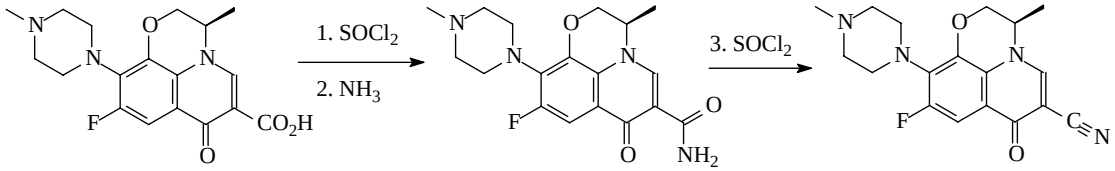
51.

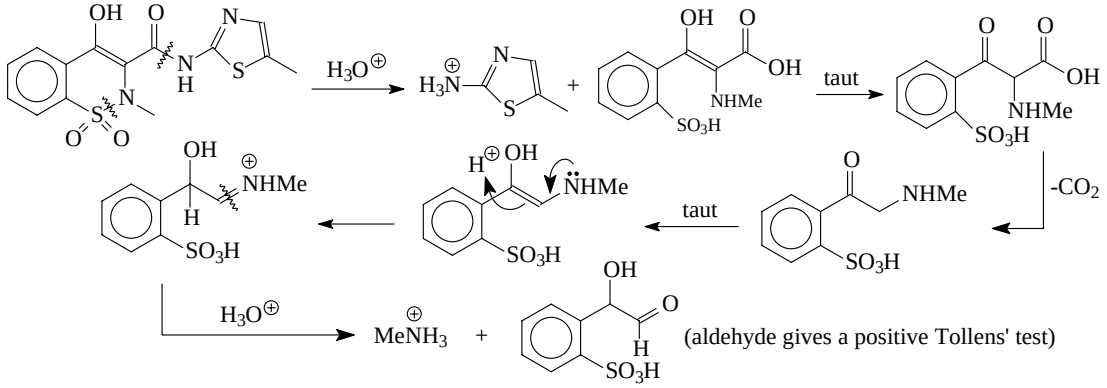


52.

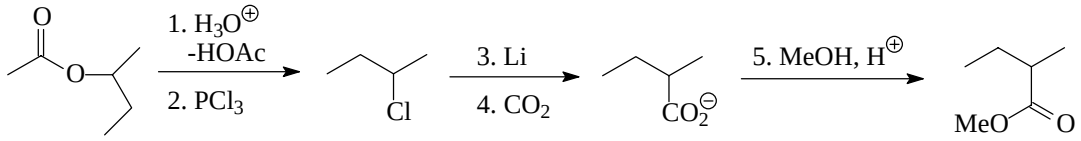


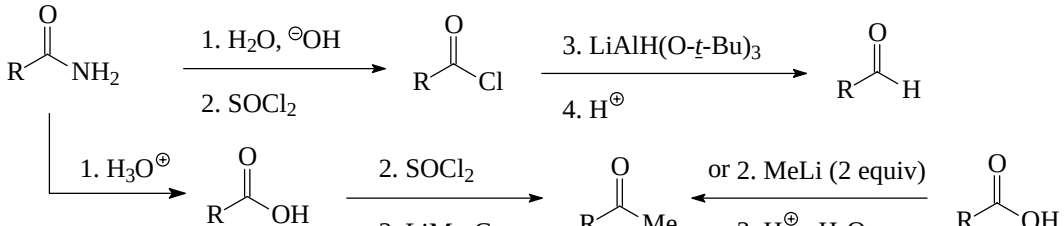
53. 

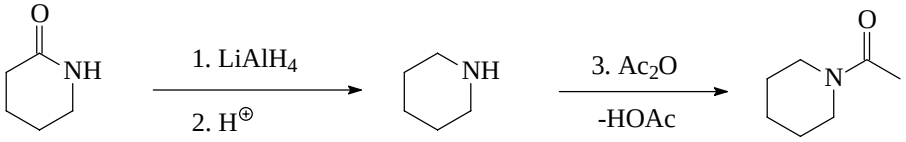
54. 

55. 

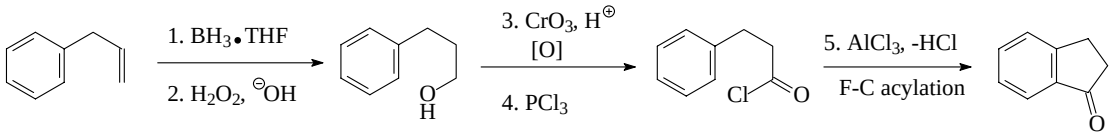
17.2 Syntheses

1. 

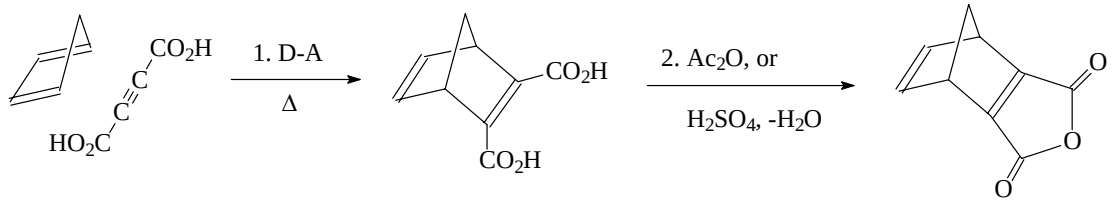
2. 

3. 

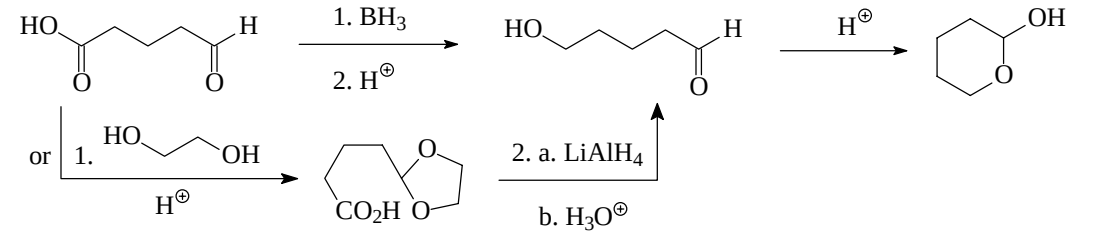
4.


1. BH3•THF
2. H2O2, ⊖OH
3. CrO3, H⊕
[O]
4. PCl3
5. AlCl3, -HCl
F-C acylation

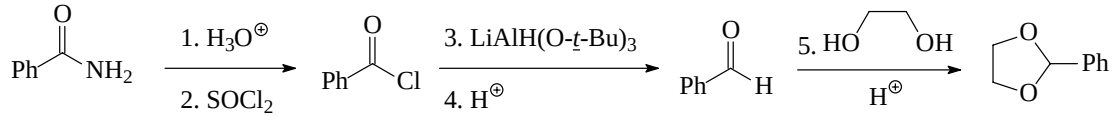
5.


CO2H
HO2C
1. D-A
Δ
CO2H
CO2H
2. Ac2O, or
H2SO4, -H2O

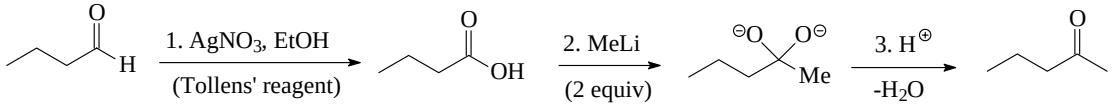
6.


1. BH3
2. H⊕
H⊕
or
1.
H⊕
2. a. LiAlH4
b. H3O⊕

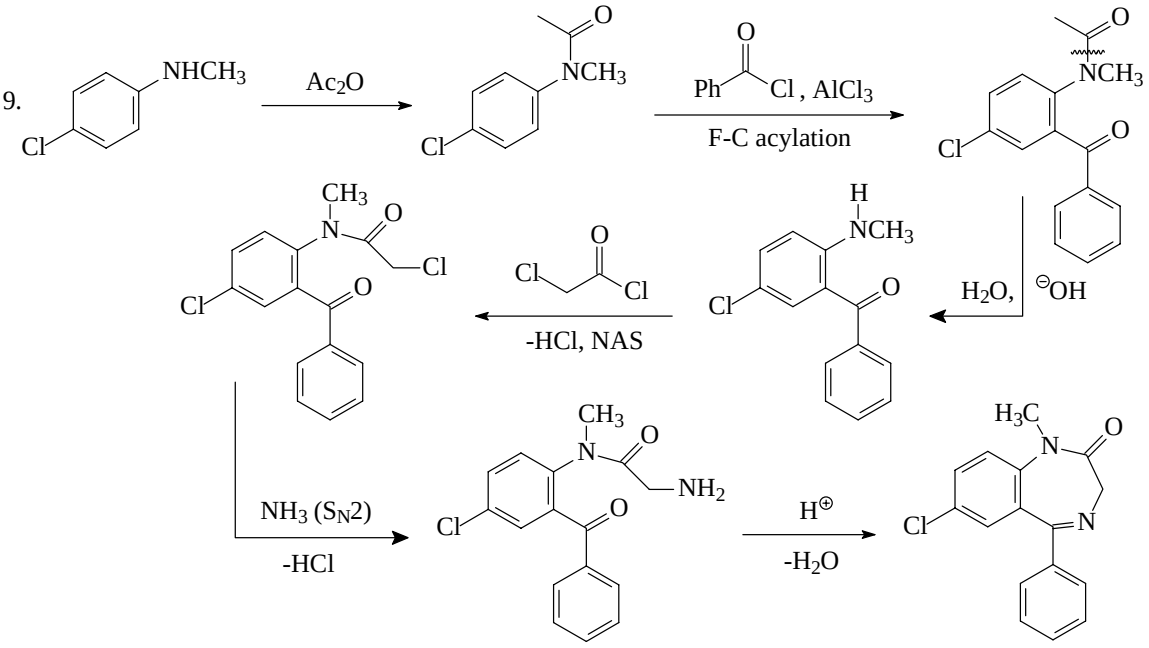
7.


1. H3O⊕
2. SOCl2
3. LiAlH(O-t-Bu)3
4. H⊕
5.
H⊕

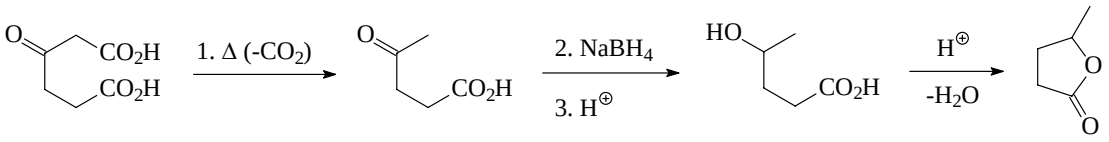
8.


1. AgNO3, EtOH
(Tollens' reagent)
2. MeLi
(2 equiv)
3. H⊕
-H2O

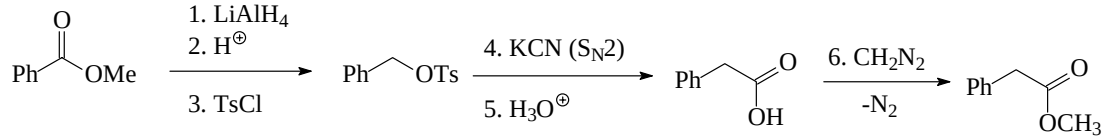
9.


Ac2O
F-C acylation
H2O, ⊖OH
-HCl, NAS
NH3 (SN2)
-HCl
H⊕
-H2O

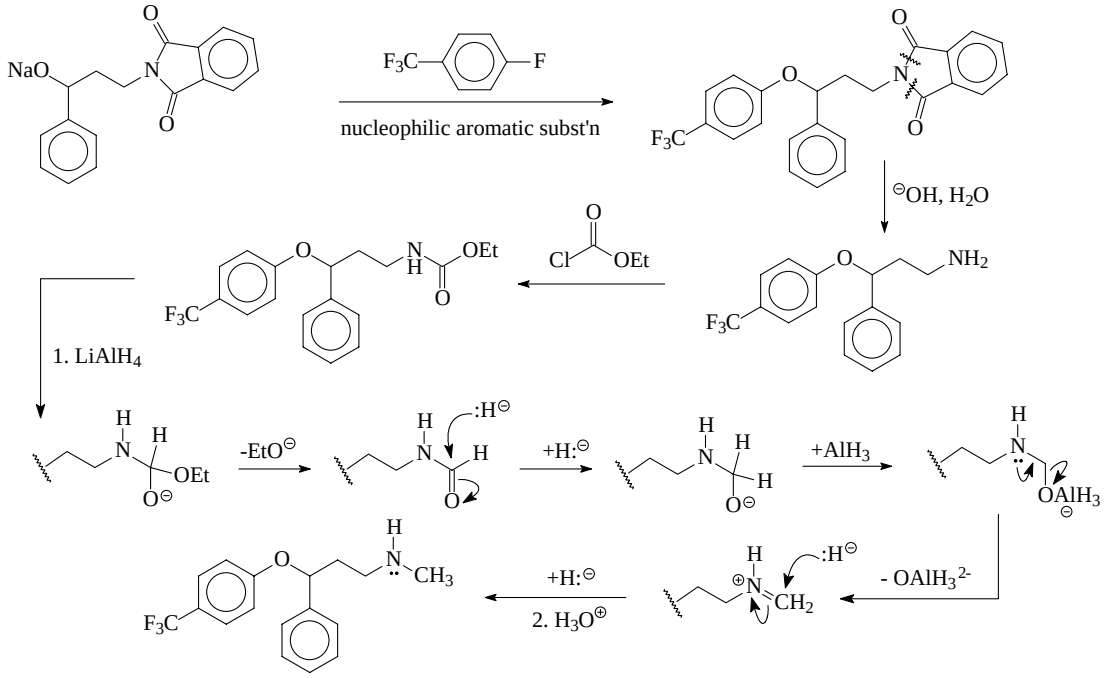
10.



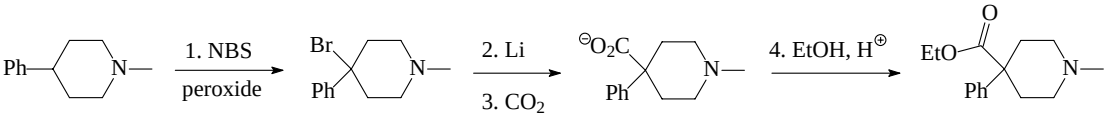
11.



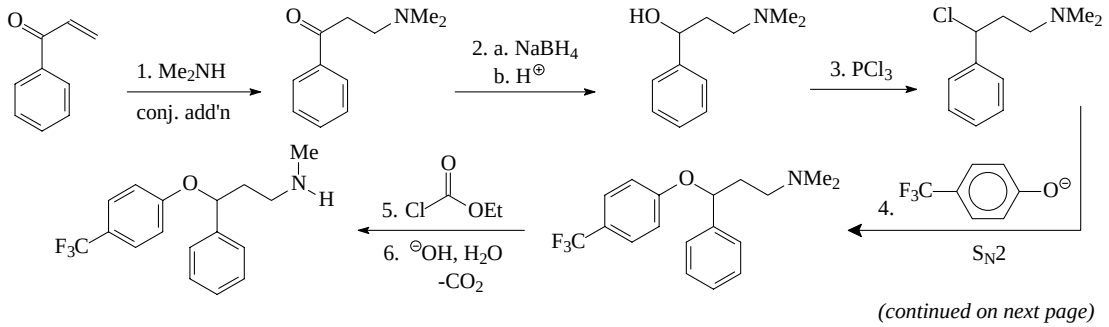
12.



13.

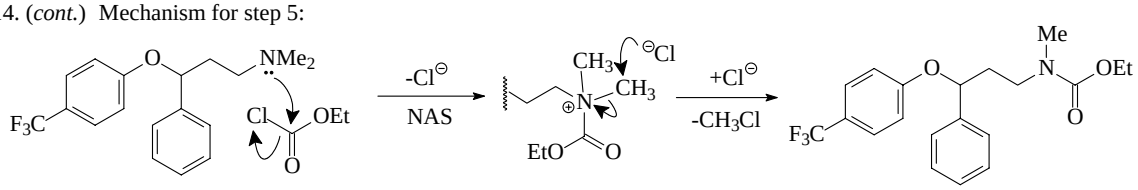


14.

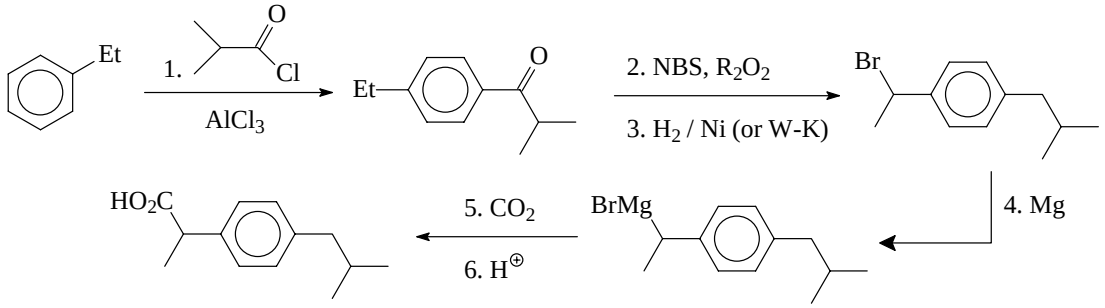


(continued on next page)

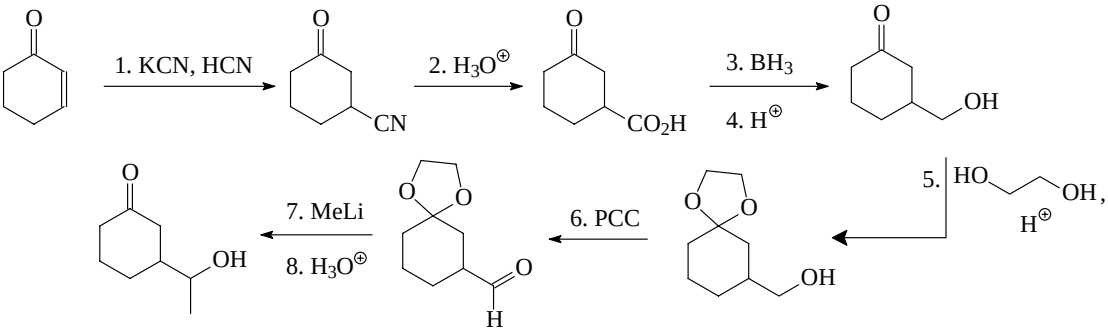
14. (*cont.*) Mechanism for step 5:



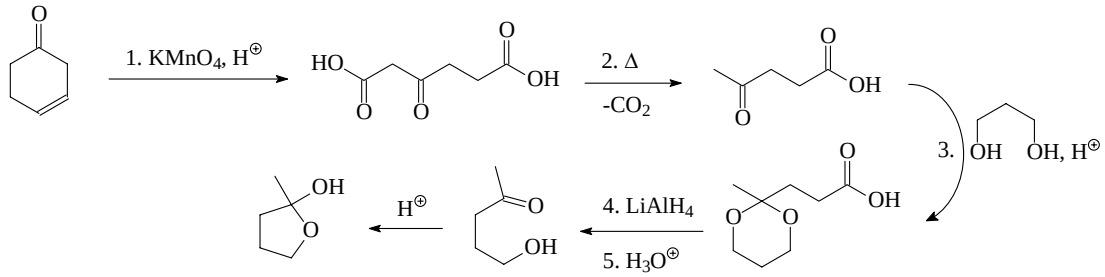
15.



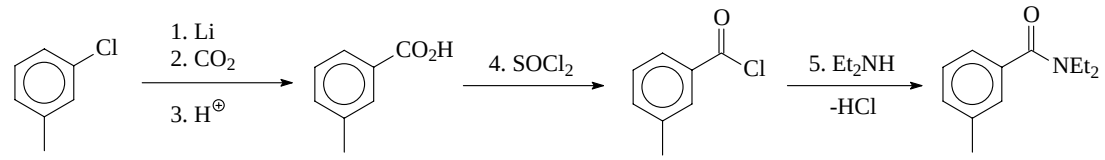
16.



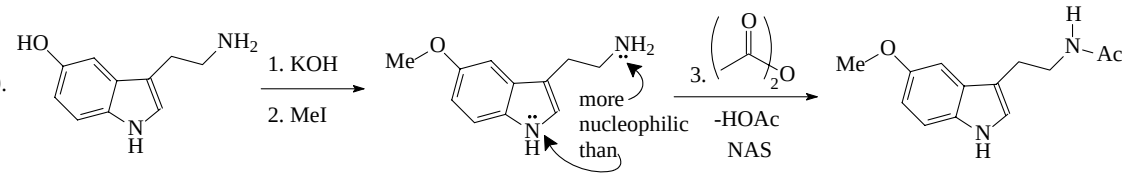
17.



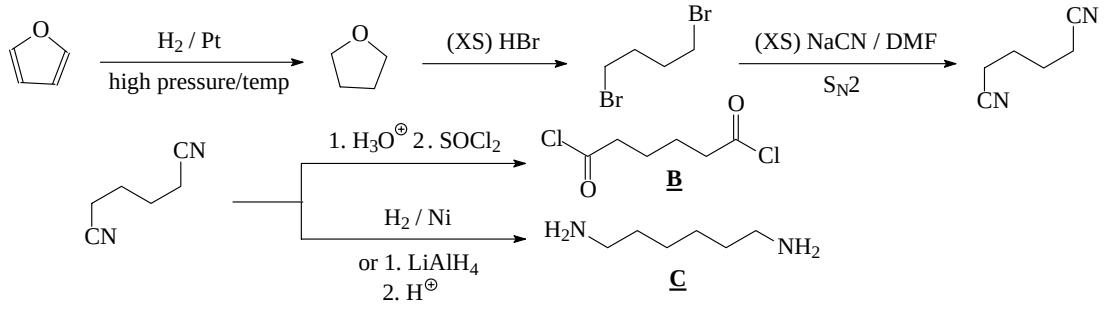
18.



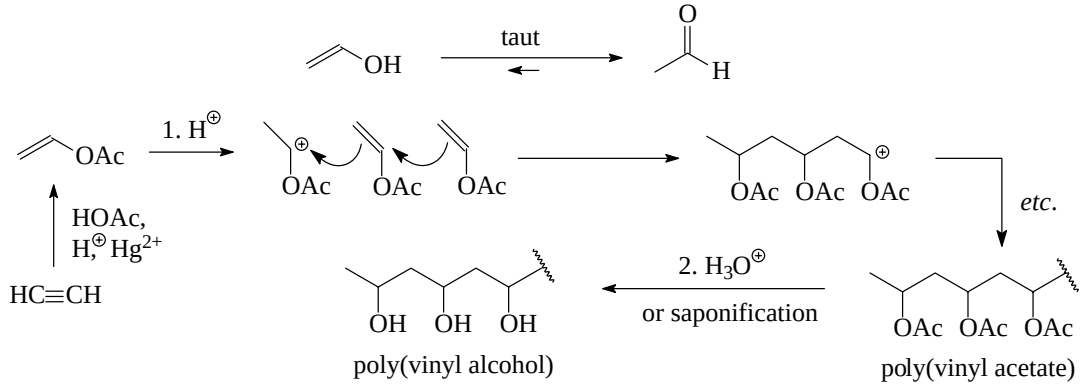
19.



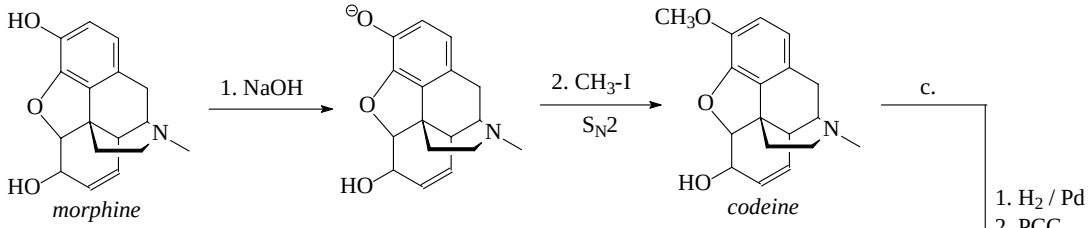
20.



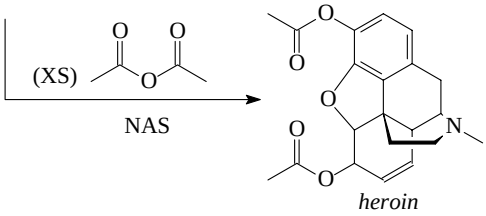
21. Poly(vinyl alcohol). Vinyl alcohol is unstable and rapidly tautomerizes to acetaldehyde:



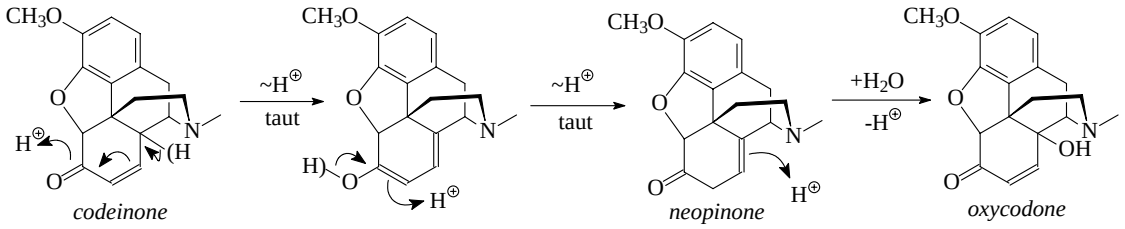
22. a.



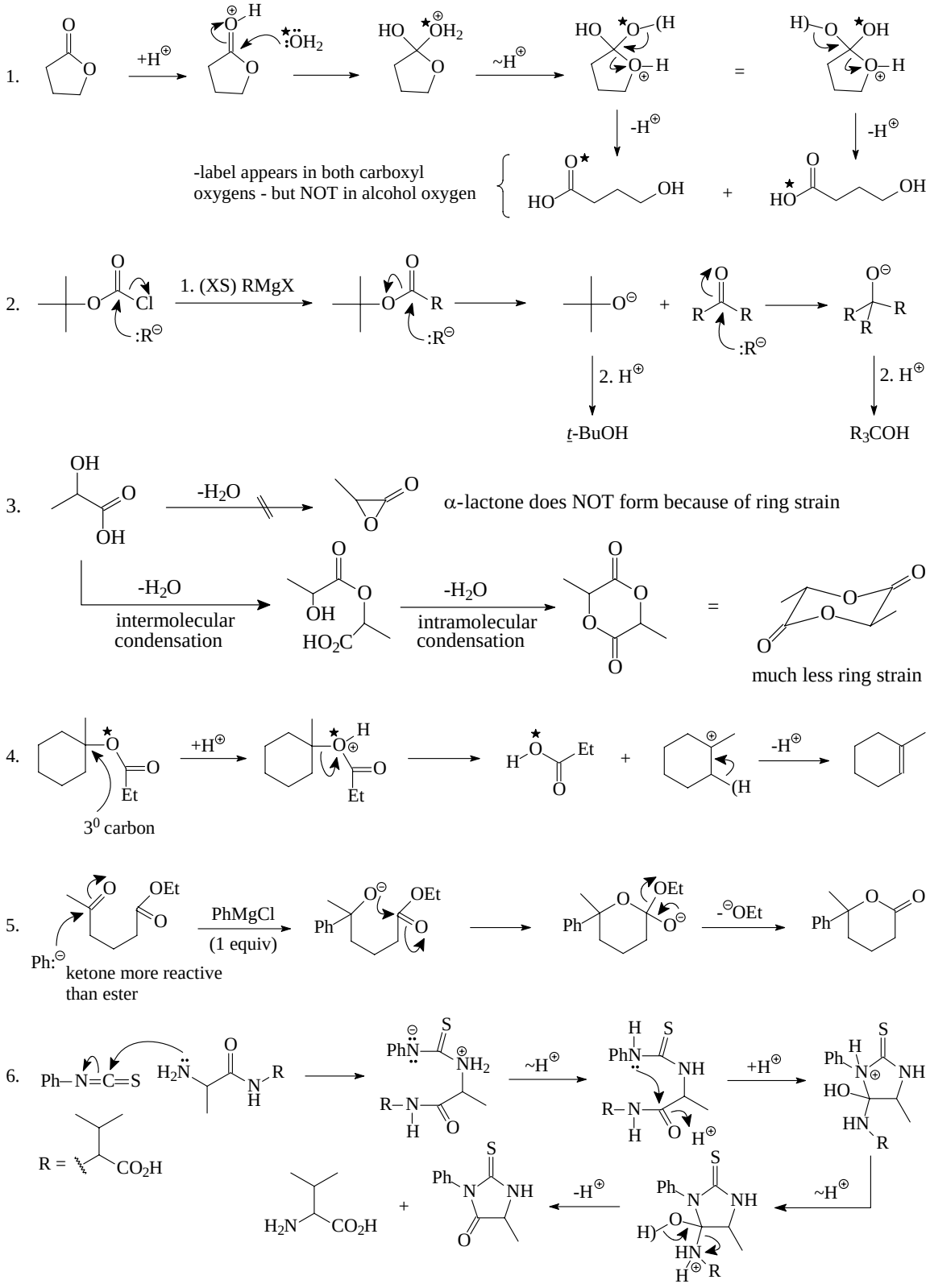
b.



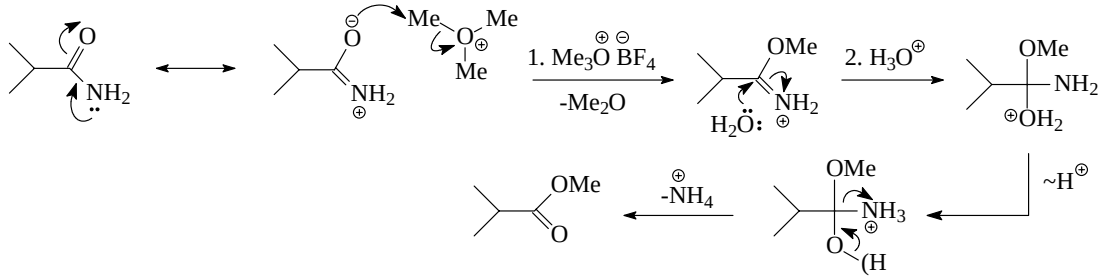
d.



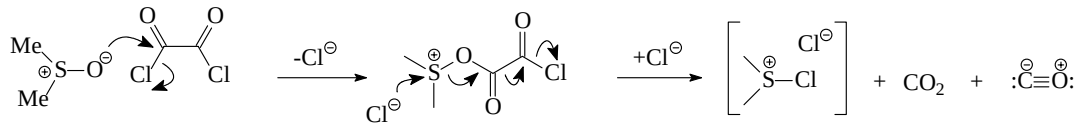
17.3 Mechanisms



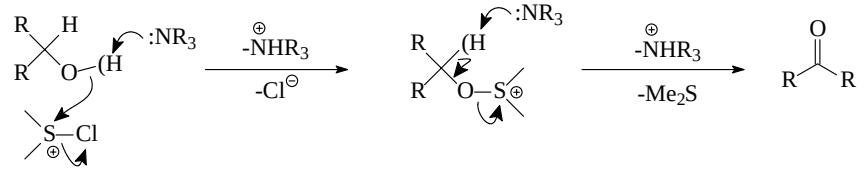
7.


1. $Me_3O^{\oplus}\ BF_4^{\ominus}$
-Me_2O
2. $H_3O^{\oplus}$
-$NH_4^{\oplus}$
~$H^{\oplus}$

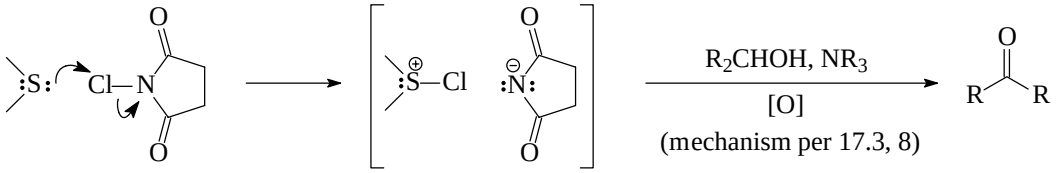
8. a.


-$Cl^{\ominus}$
+$Cl^{\ominus}$
+ CO_2 +

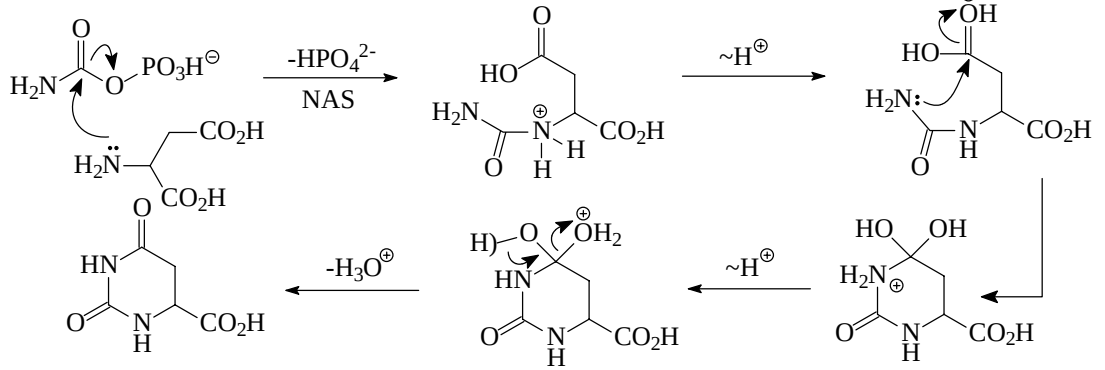
b.


-$NHR_3^{\oplus}$
-$Cl^{\ominus}$
-$NHR_3^{\oplus}$
-Me_2S

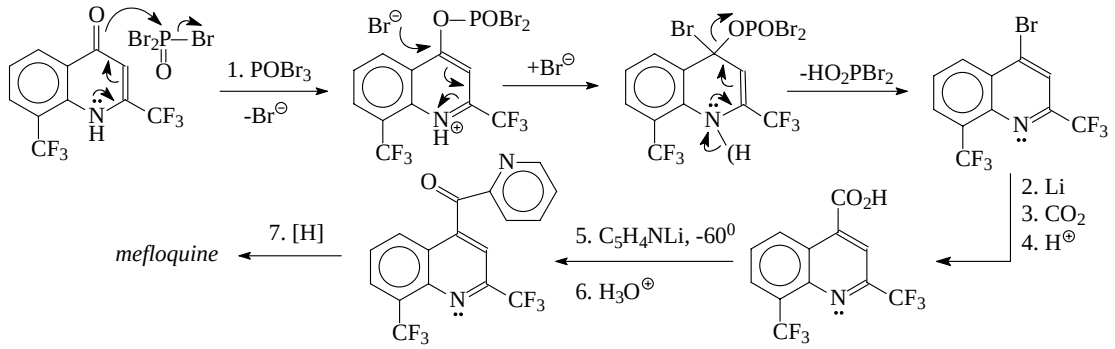
9.


R_2CHOH, NR_3
[O]
(mechanism per 17.3, 8)

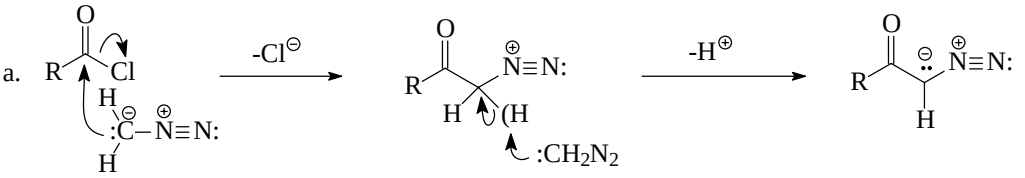
10.


-HPO_4^{2-}
NAS
~$H^{\oplus}$
~$H^{\oplus}$
-$H_3O^{\oplus}$

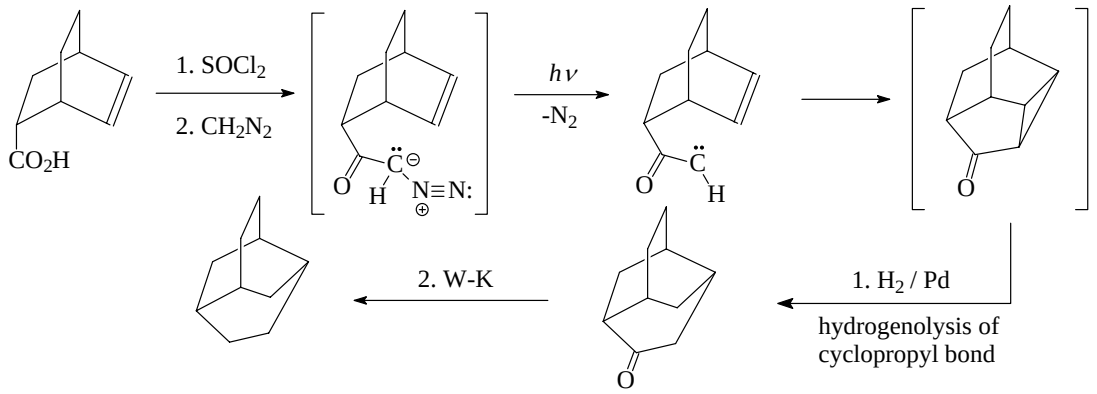
11.


1. $POBr_3$
-$Br^{\ominus}$
+$Br^{\ominus}$
-HO_2PBr_2
2. Li
3. CO_2
4. $H^{\oplus}$
5. C_5H_4NLi, -60^0
6. $H_3O^{\oplus}$
7. [H]
mefloquine

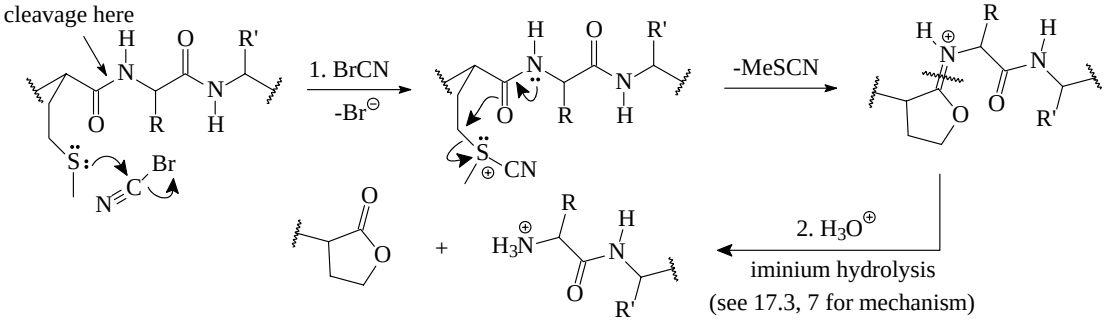
12. a.


-Cl⊖
-H⊕
:CH2N2

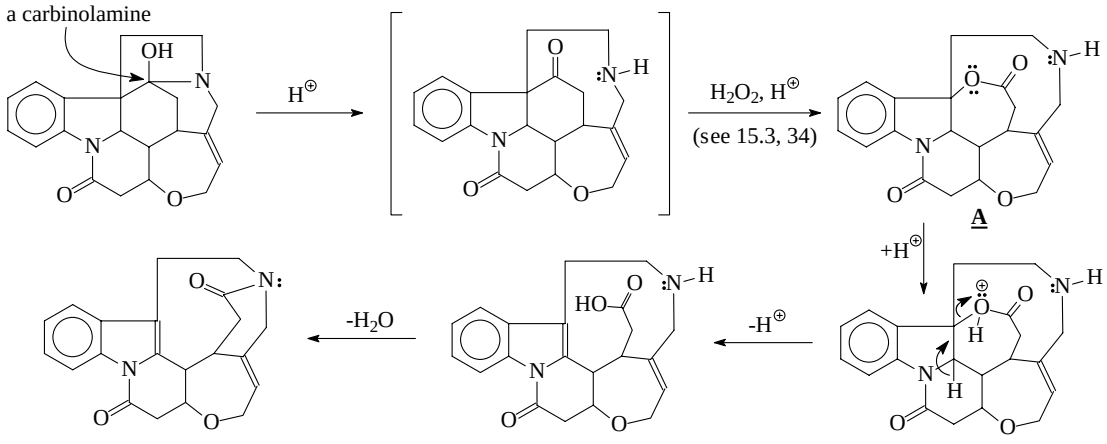
b.


1. SOCl2
2. CH2N2
hν
-N2
1. H2 / Pd
hydrogenolysis of
cyclopropyl bond
2. W-K

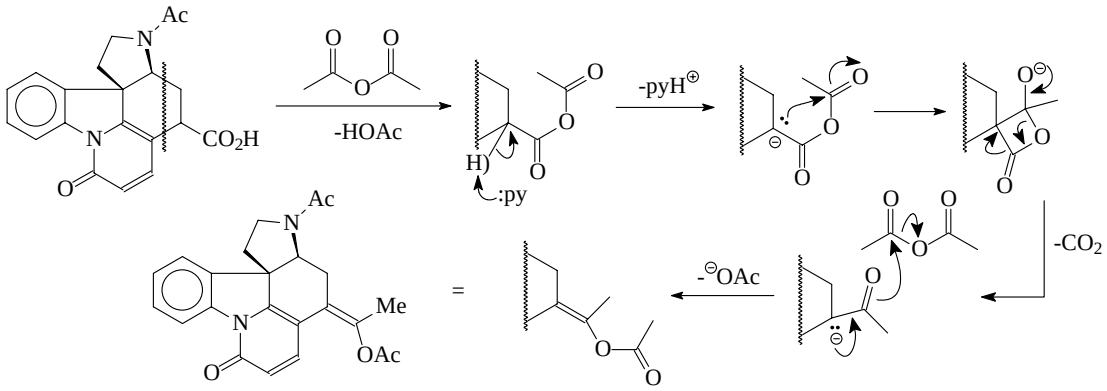
13.


cleavage here
1. BrCN
-Br⊖
-MeSCN
2. H3O⊕
iminium hydrolysis
(see 17.3, 7 for mechanism)

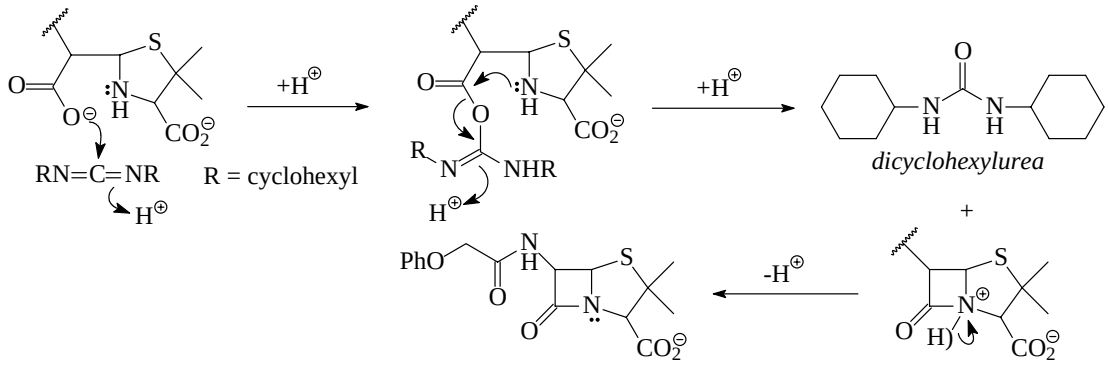
14.


a carbinolamine
H⊕
H2O2, H⊕
(see 15.3, 34)
A
+H⊕
-H⊕
-H2O

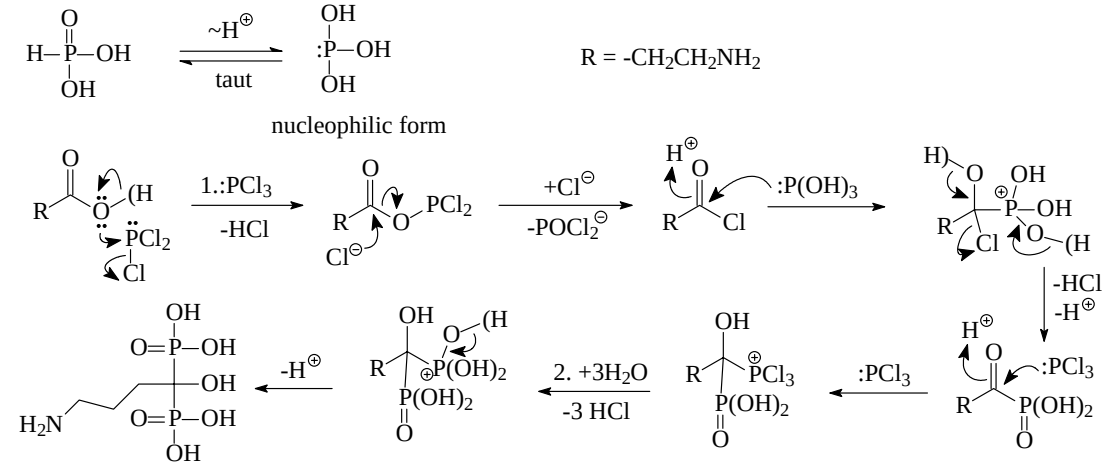
15.


Ac
N
CO2H
O
-HOAc
-pyH⊕
H
:py
-CO2
-⊖OAc
Me
OAc
=

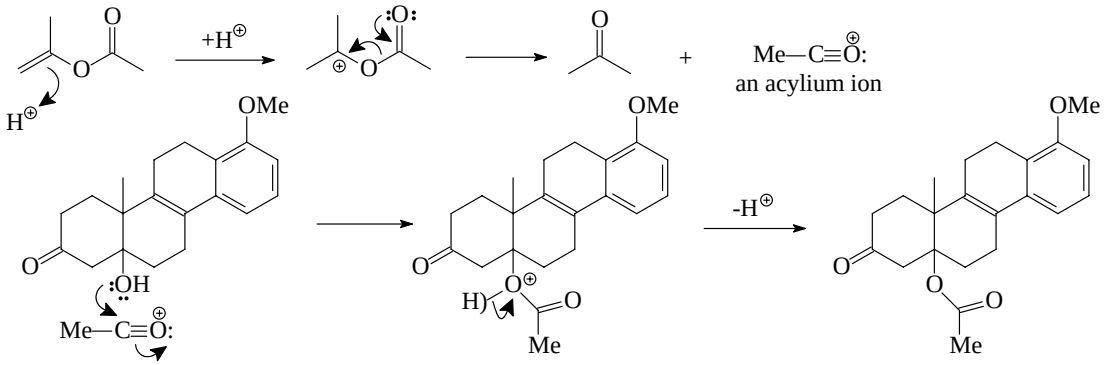
16.


+H⊕
RN=C=NR
R = cyclohexyl
NHR
dicyclohexylurea
+
PhO
-H⊕

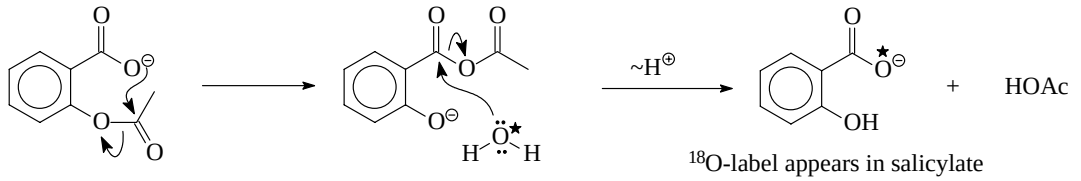
17.


~H⊕
taut
nucleophilic form
R = -CH2CH2NH2
1.:PCl3
-HCl
+Cl⊖
-POCl2⊖
:P(OH)3
-HCl
-H⊕
:PCl3
2. +3H2O
-3 HCl
-H⊕

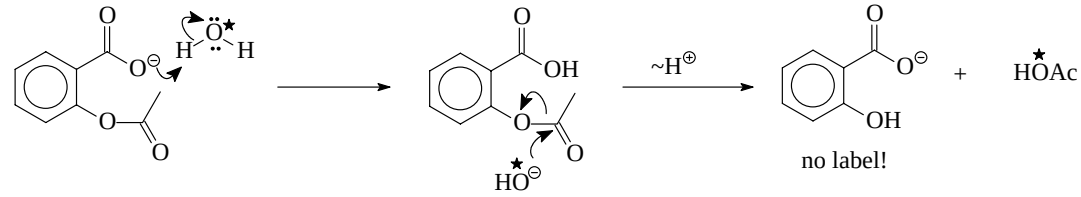
18.


+H⊕
Me—C≡O:
an acylium ion
OMe
-H⊕

19. a. Carboxylate as a *nucleophile*:

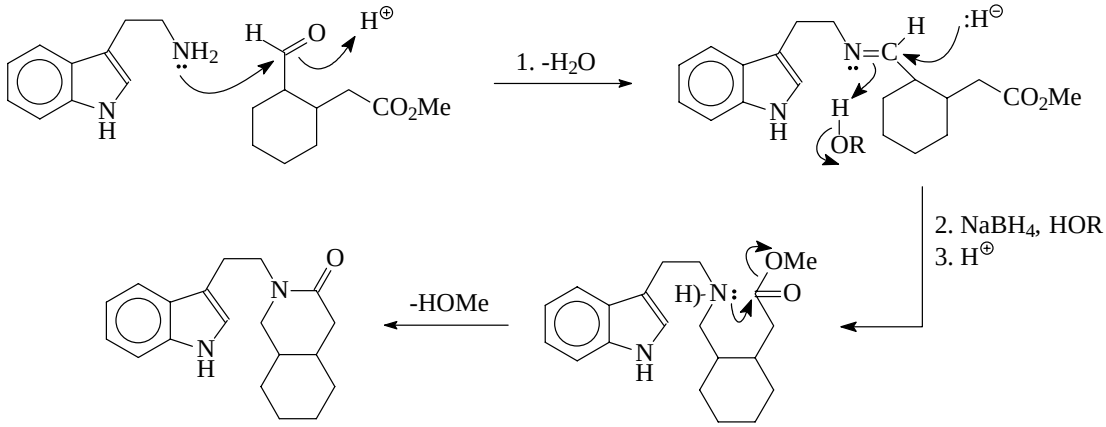


b. Carboxylate as a *base*:



c. Therefore, *pathway b* is preferred.

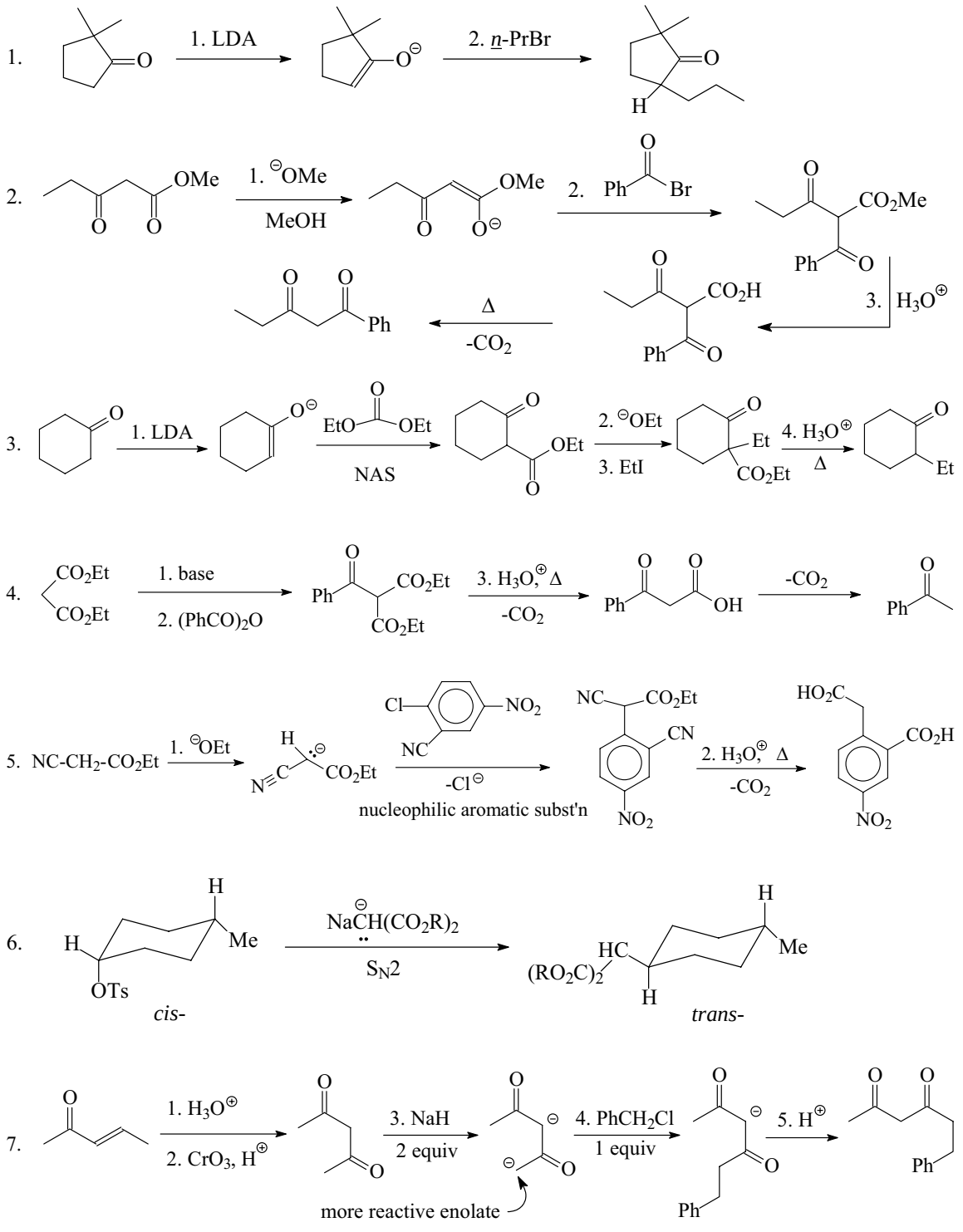
20.

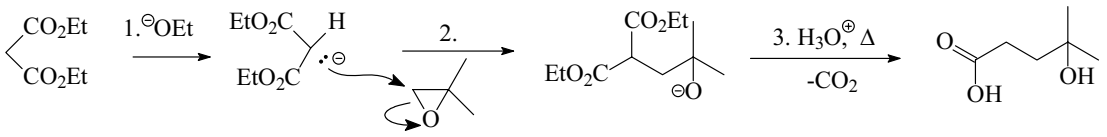


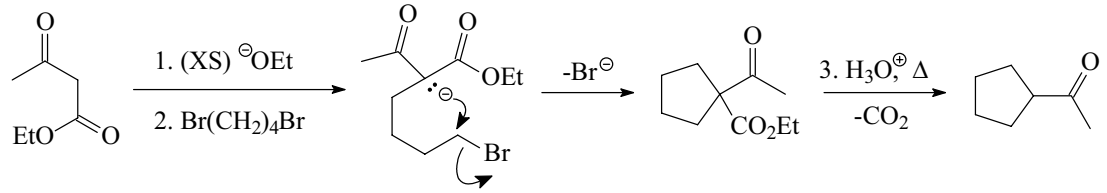
CHAPTER 18

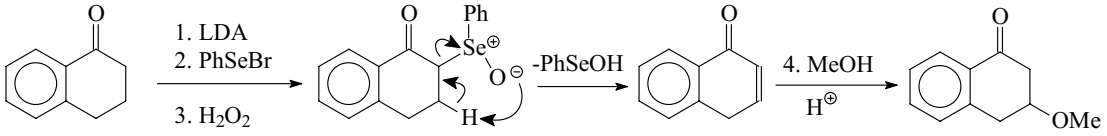
CARBONYL α-SUBSTITUTION REACTION AND ENOLATES

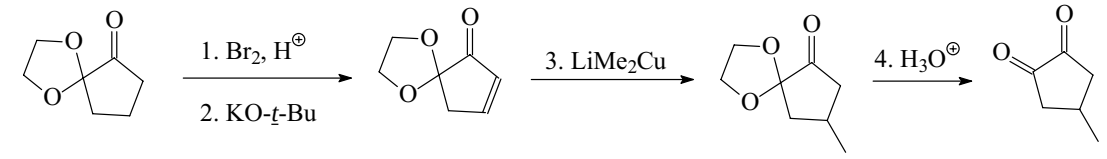
18.1 Reactions

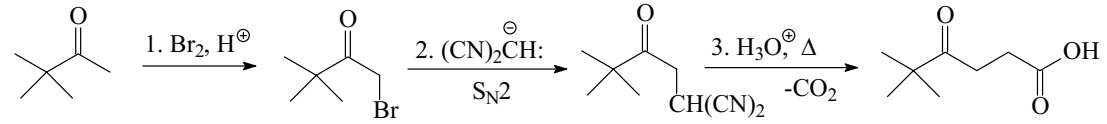


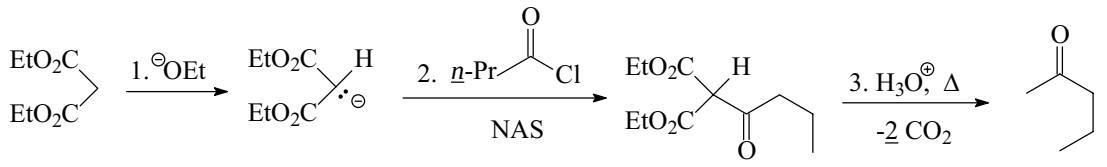
8. 

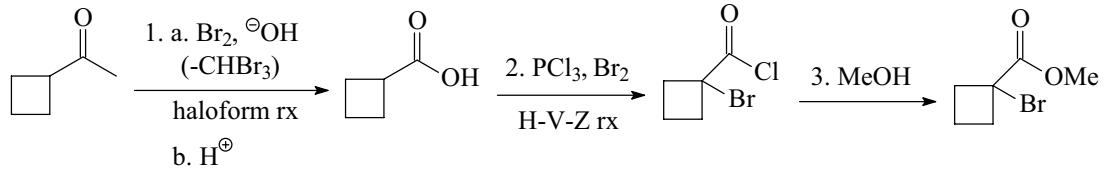
9. 

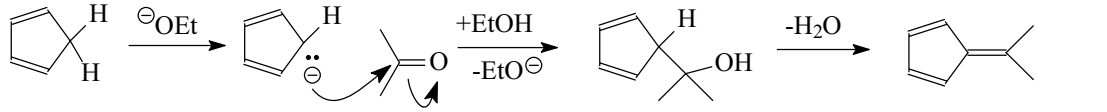
10. 

11. 

12. 

13. 

14. 

15. 

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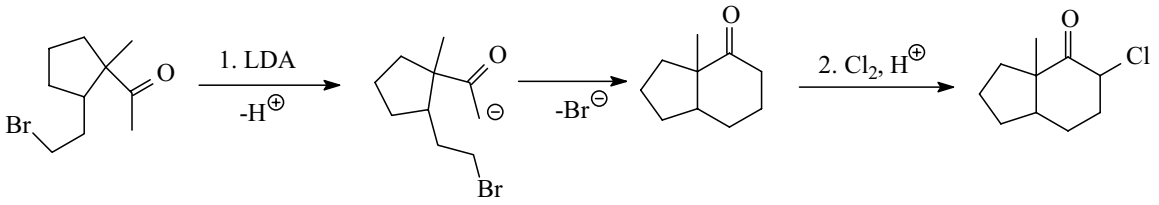

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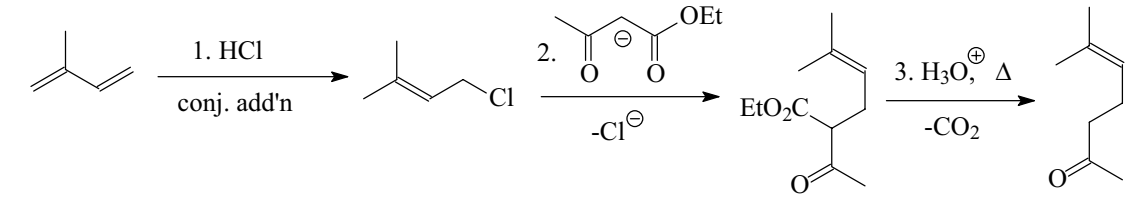

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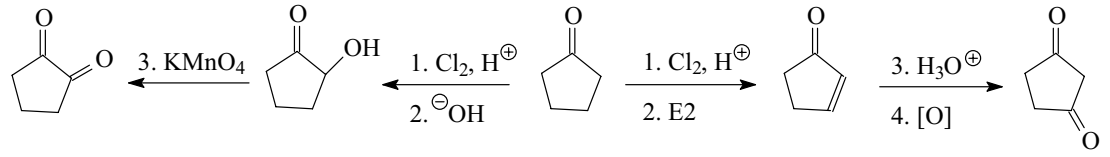

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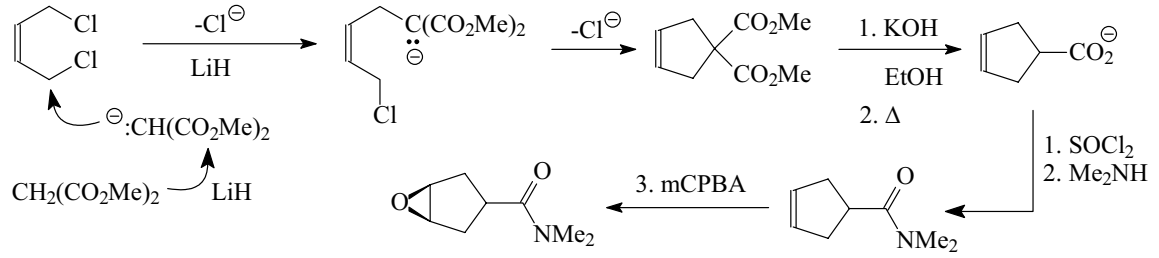

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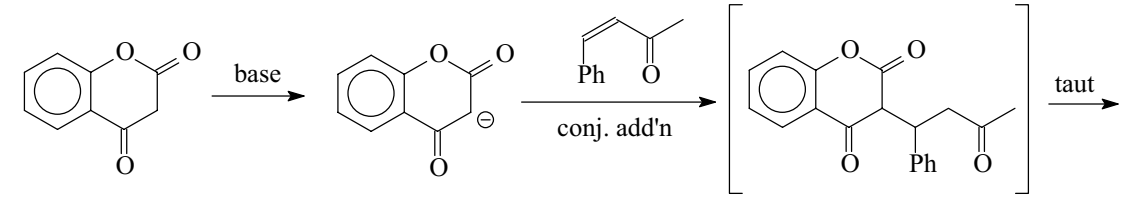
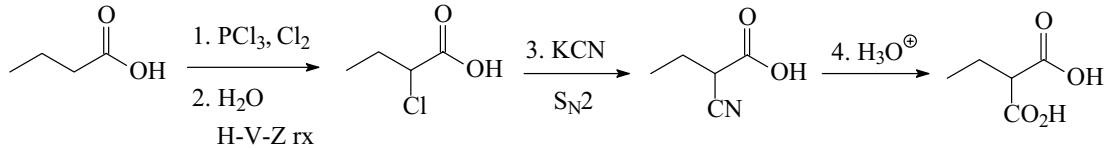


18.2 Syntheses

1.



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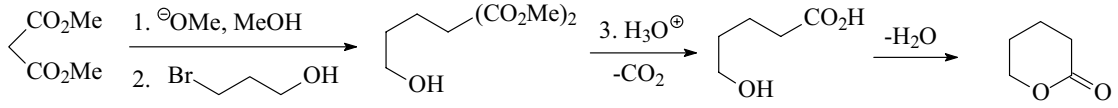
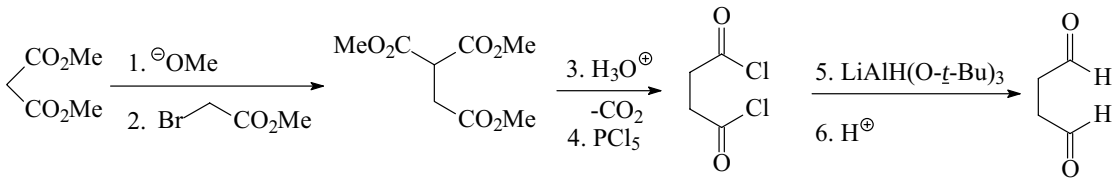
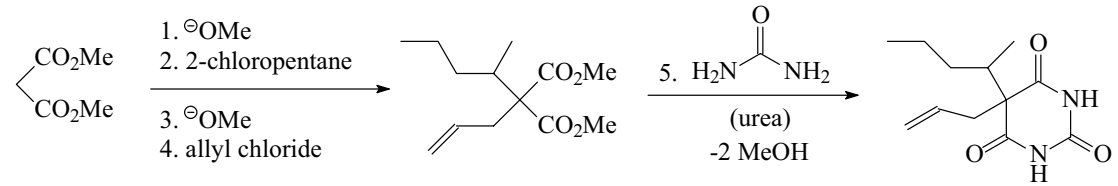

CO2Me
CO2Me
1. ⊖OMe, MeOH
2. Br OH
(CO2Me)2
OH
3. H3O⊕
-CO2
CO2H
OH
-H2O
O
O

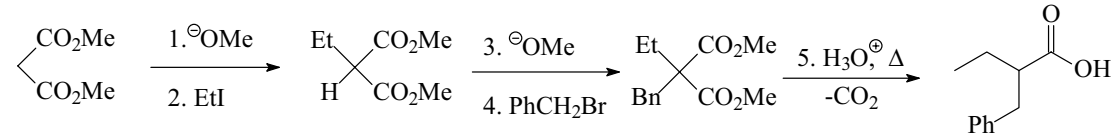
3.


CO2Me
CO2Me
1. ⊖OMe
2. Br CO2Me
MeO2C
CO2Me
CO2Me
3. H3O⊕
-CO2
4. PCl5
O
Cl
Cl
O
5. LiAlH(O-t-Bu)3
6. H⊕
O
H
H
O

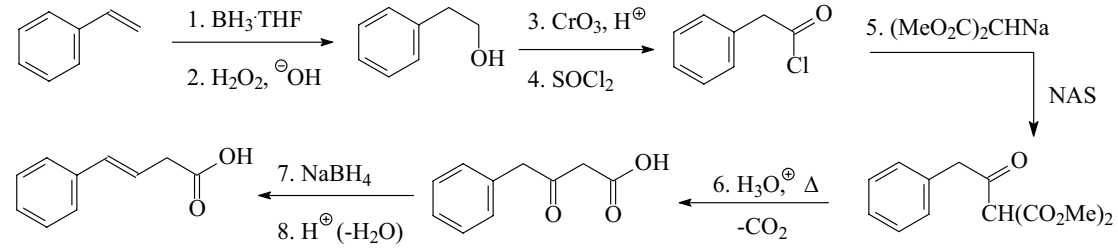
4.


CO2Me
CO2Me
1. ⊖OMe
2. 2-chloropentane
3. ⊖OMe
4. allyl chloride
CO2Me
CO2Me
5. H2N NH2
O
(urea)
-2 MeOH
O
NH
O
N
H
O

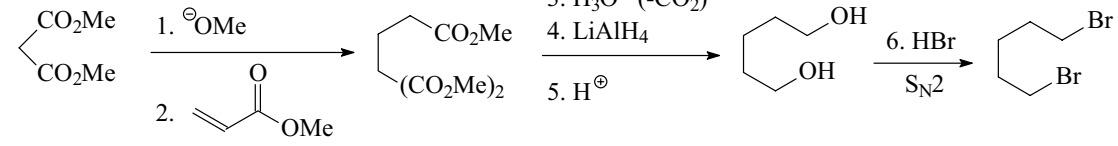
5.


CO2Me
CO2Me
1.⊖OMe
2. EtI
Et
CO2Me
H
CO2Me
3. ⊖OMe
4. PhCH2Br
Et
CO2Me
Bn
CO2Me
5. H3O,⊕ Δ
-CO2
O
OH
Ph

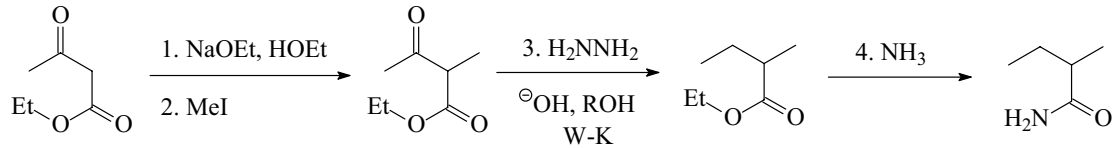
6.

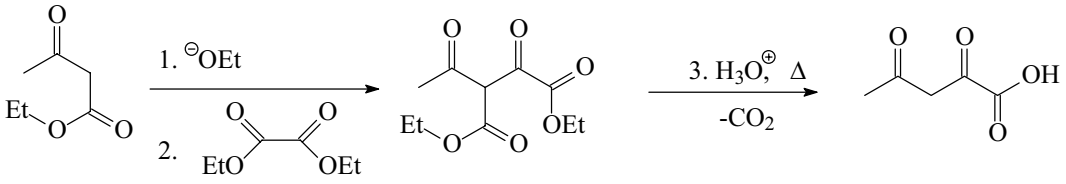

1. BH3·THF
2. H2O2, ⊖OH
OH
3. CrO3, H⊕
4. SOCl2
O
Cl
5. (MeO2C)2CHNa
NAS
O
CH(CO2Me)2
6. H3O,⊕ Δ
-CO2
OH
O
O
7. NaBH4
8. H⊕ (-H2O)
OH
O

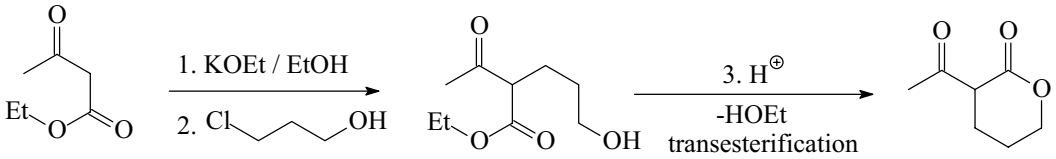
7.

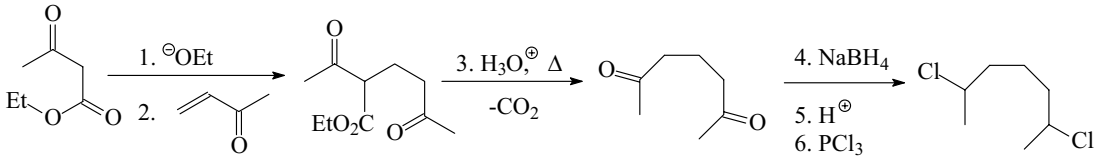

CO2Me
CO2Me
1. ⊖OMe
2.
O
OMe
CO2Me
(CO2Me)2
3. H3O⊕ (-CO2)
4. LiAlH4
5. H⊕
OH
OH
6. HBr
SN2
Br
Br

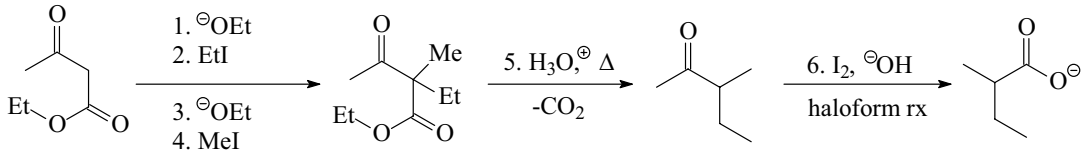
8.


O
Et
O
O
1. NaOEt, HOEt
2. MeI
O
Et
O
O
3. H2NNH2
⊖OH, ROH
W-K
Et
O
O
4. NH3
H2N
O

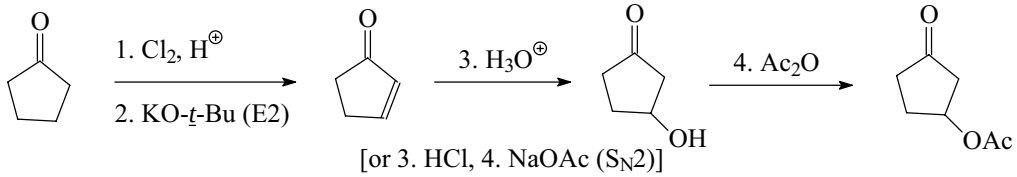
9. 

10. 

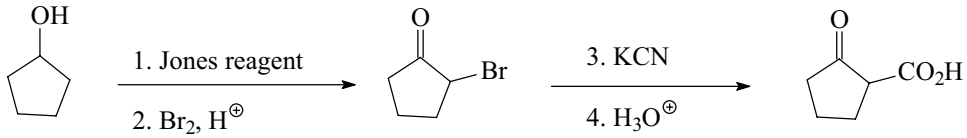
11. 

12. 

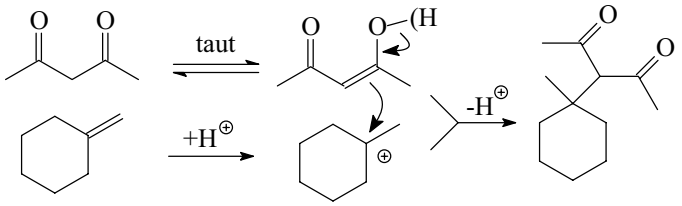
+ HCI_3

13. 

[or 3. HCl, 4. NaOAc (S_N2)]

14. 

[or 3. ethylene glycol, H,⊕ 4. Mg, 5. CO_2, 6. H⊕]

15. 

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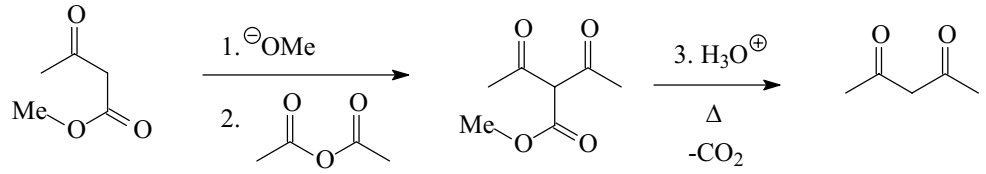

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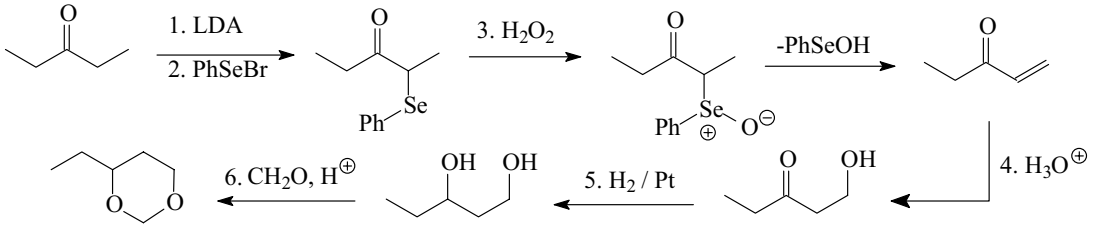

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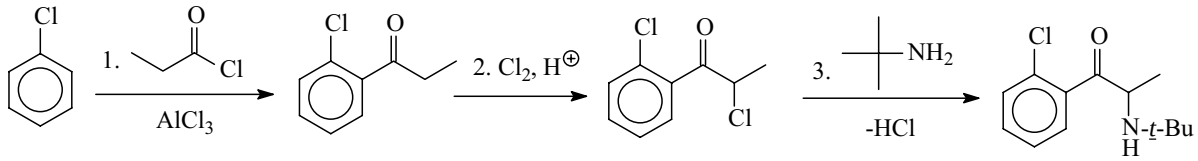

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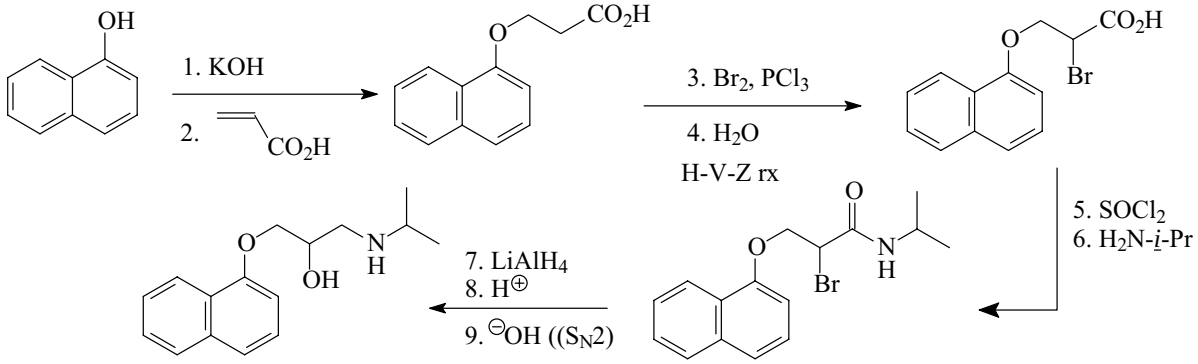

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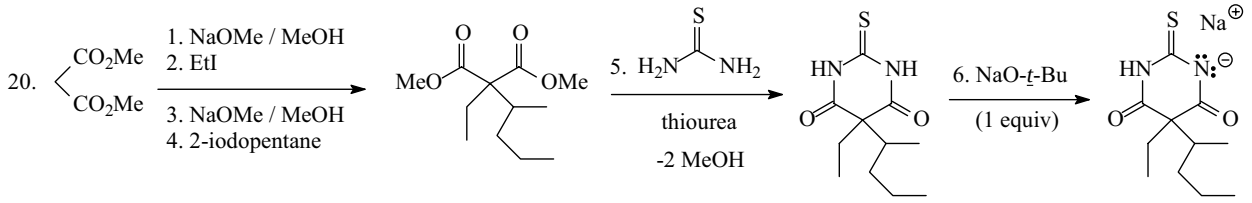

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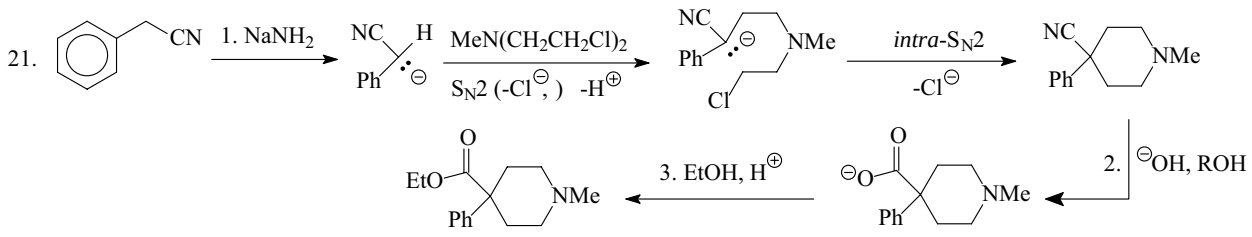
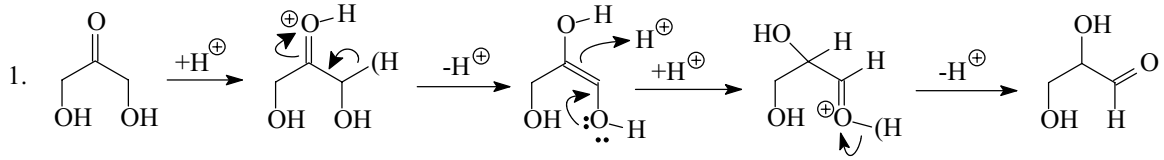
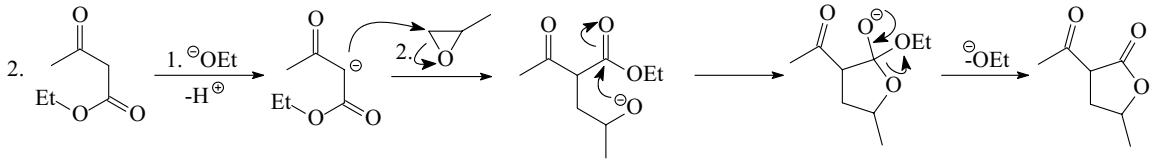
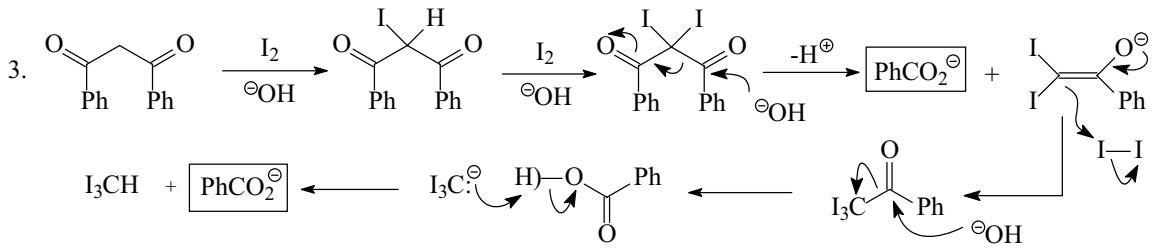
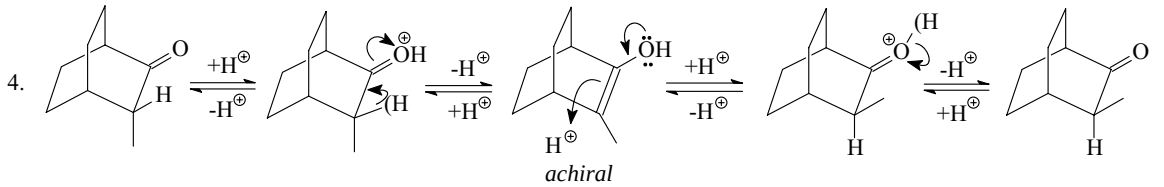


18.3 Mechanisms

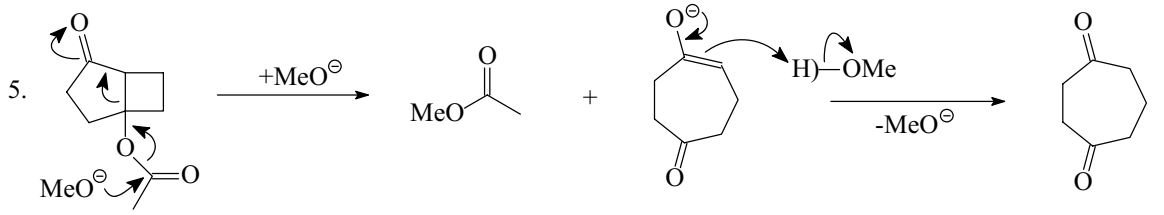


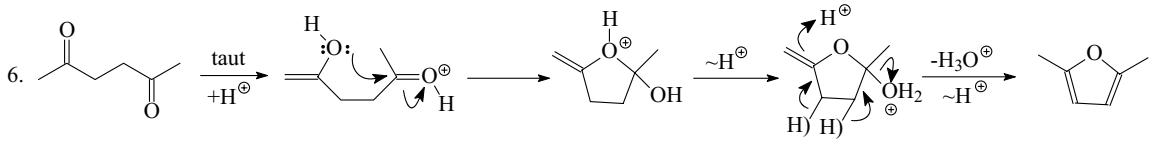


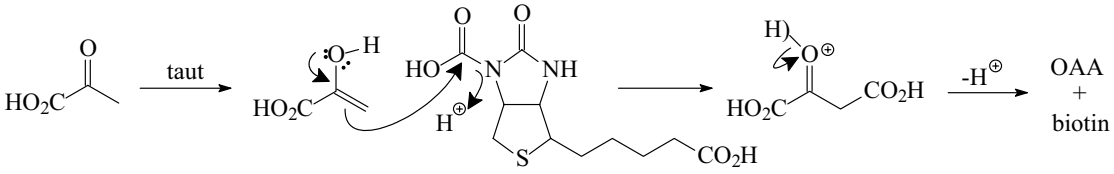


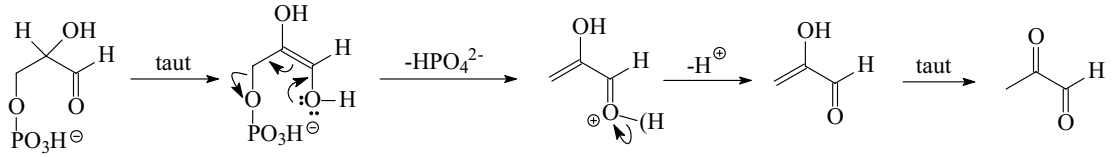


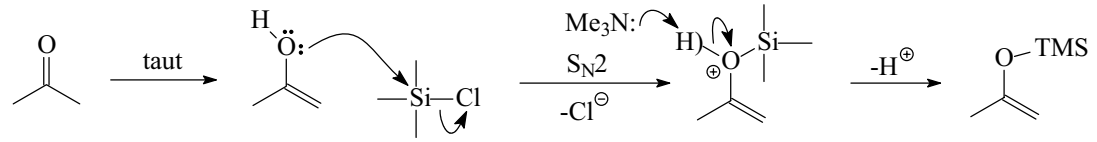
achiral





7. 

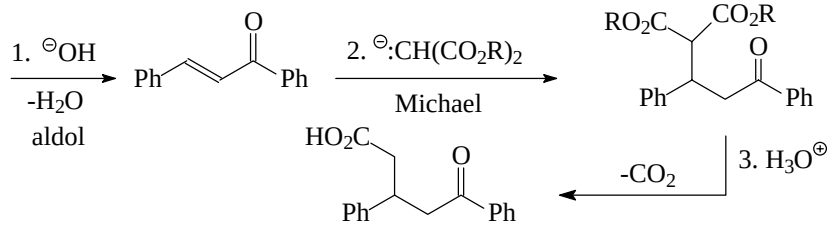
8. 

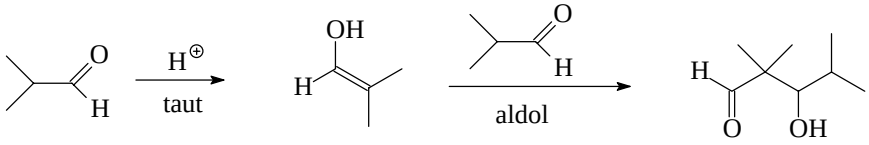
9. 

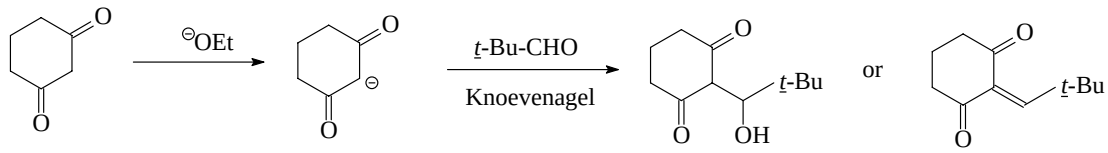
CHAPTER 19

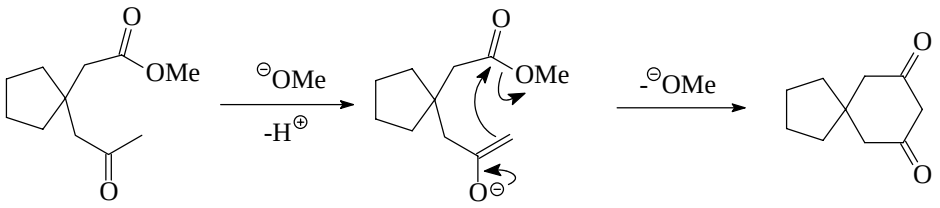
CARBONYL CONDENSATION REACTIONS

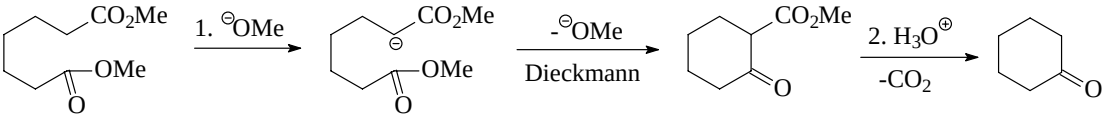
19.1 Reactions

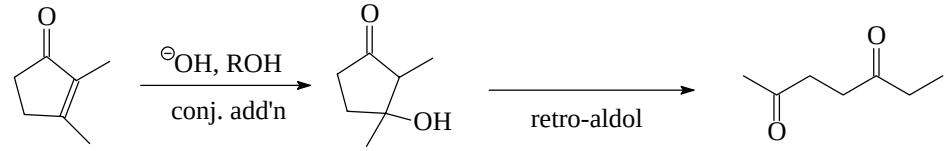
1. PhCHO + $PhCOCH_3$ 

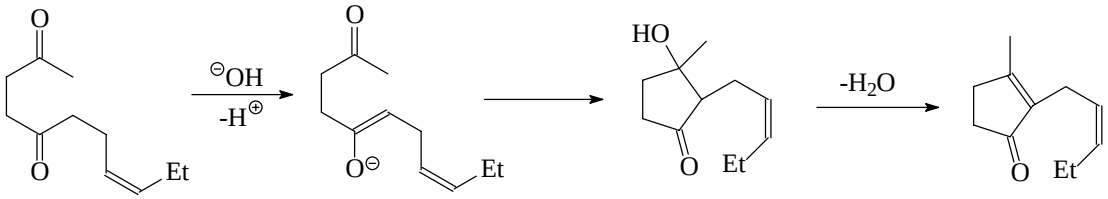
2. 

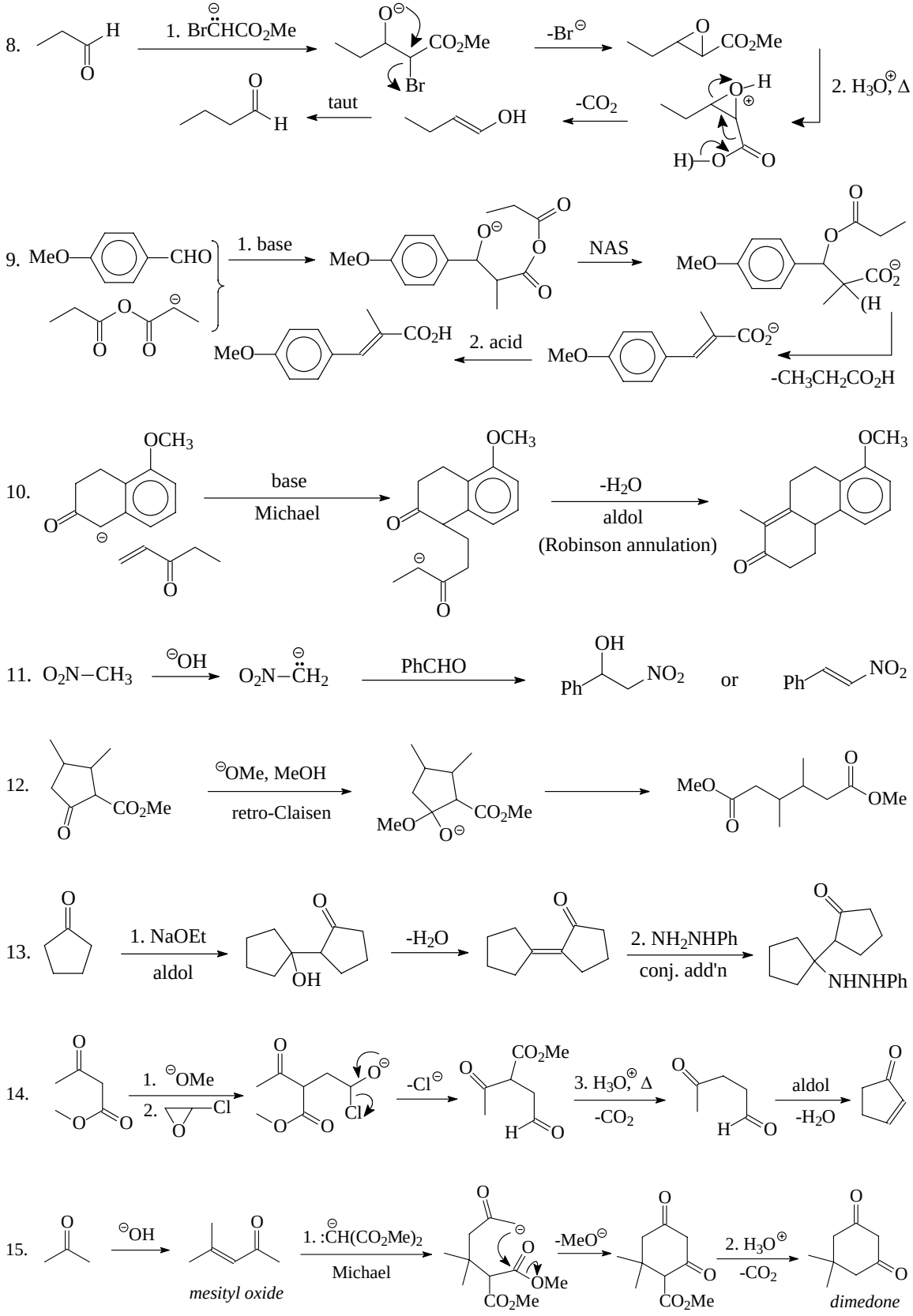
3. 

4. 

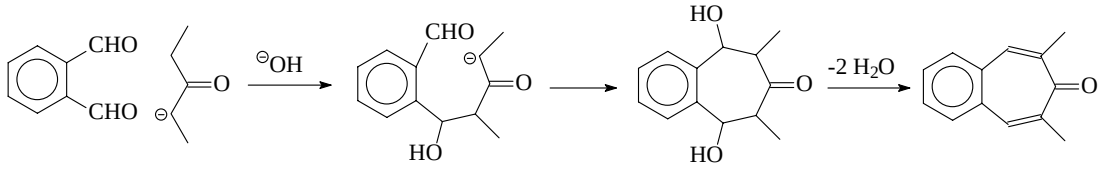
5. 

6. 

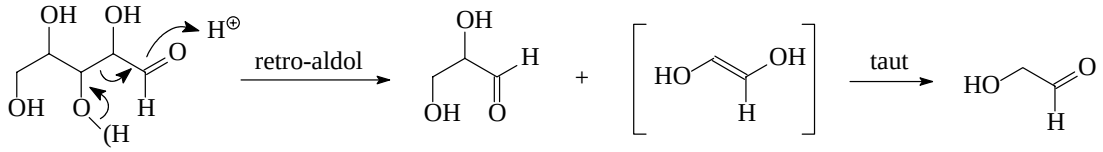
7. 


8.
1. BrCHCO2Me
CO2Me
-Br
2. H3O, Δ
-CO2
taut
OH
9.
MeO
CHO
1. base
NAS
2. acid
CO2H
CO2
-CH3CH2CO2H
10.
OCH3
base
Michael
-H2O
aldol
(Robinson annulation)
11.
O2N−CH3
OH
O2N−CH2
PhCHO
Ph
NO2
or
12.
CO2Me
OMe, MeOH
retro-Claisen
MeO
OMe
13.
1. NaOEt
aldol
-H2O
2. NH2NHPh
conj. add'n
NHNHPh
14.
1. OMe
2.
Cl
-Cl
3. H3O, Δ
-CO2
aldol
-H2O
15.
OH
1. :CH(CO2Me)2
Michael
-MeO
2. H3O
-CO2
OMe
CO2Me
mesityl oxide
dimedone

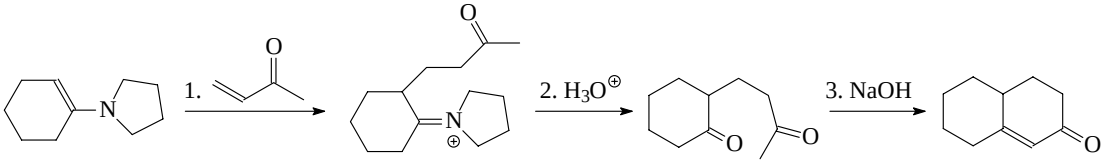
16.



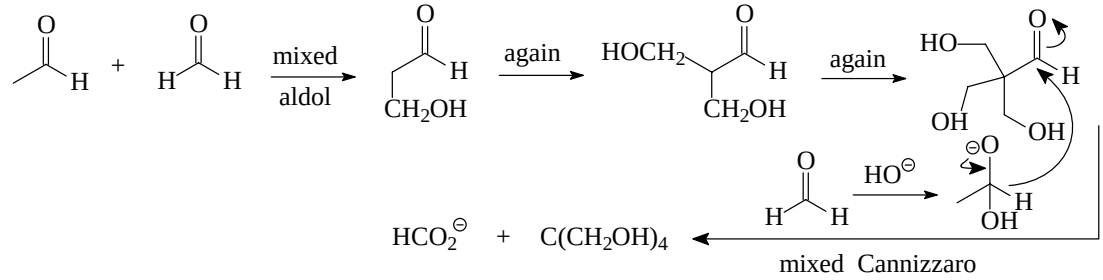
17.



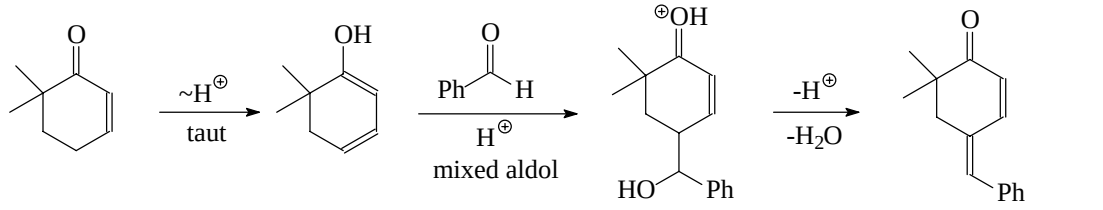
18.



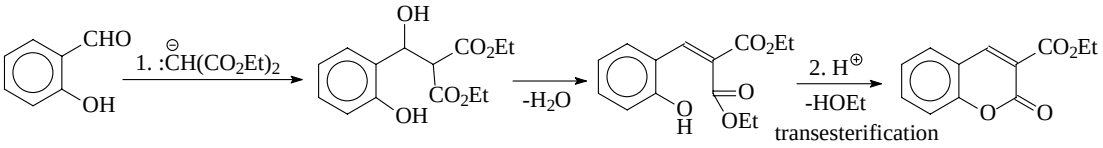
19.



20.



21.



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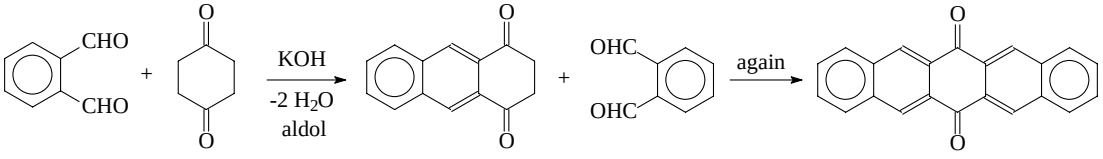

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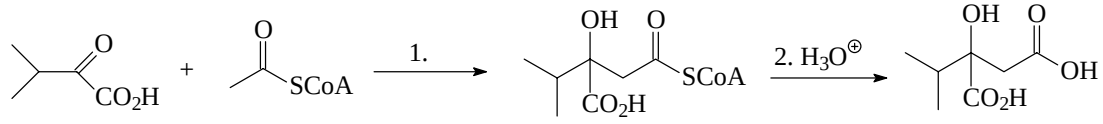
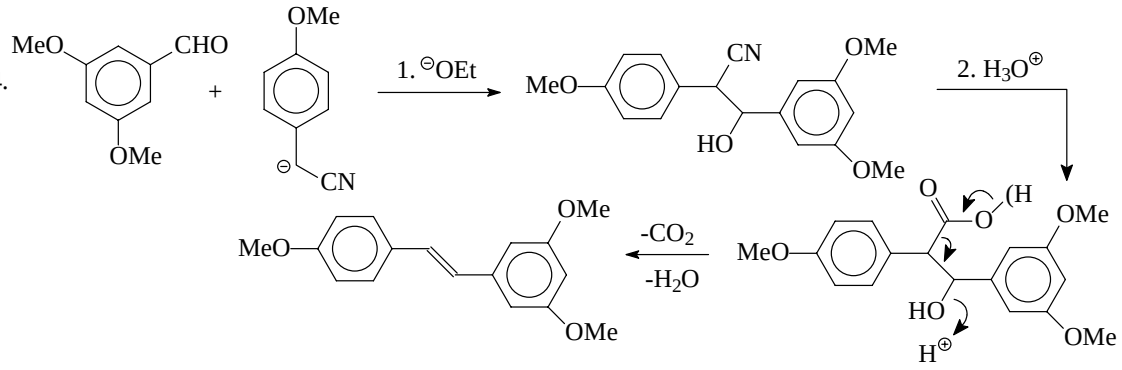
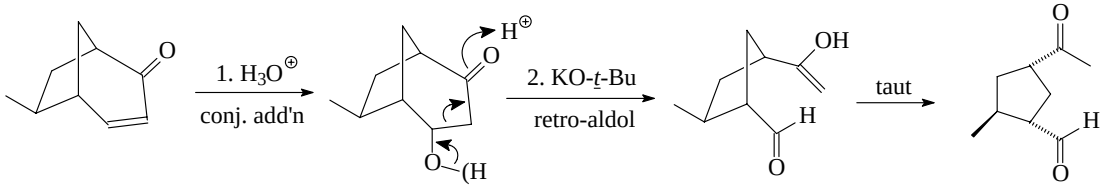


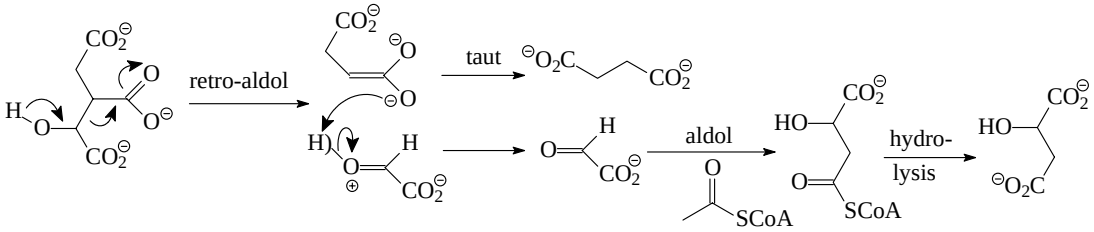
24.


MeO
CHO
OMe
+
OMe
CN
1. ⊖OEt
MeO
CN
OMe
HO
OMe
2. H3O⊕
O
(H
OMe
MeO
HO
H⊕
OMe
-CO2
-H2O
MeO
OMe
OMe

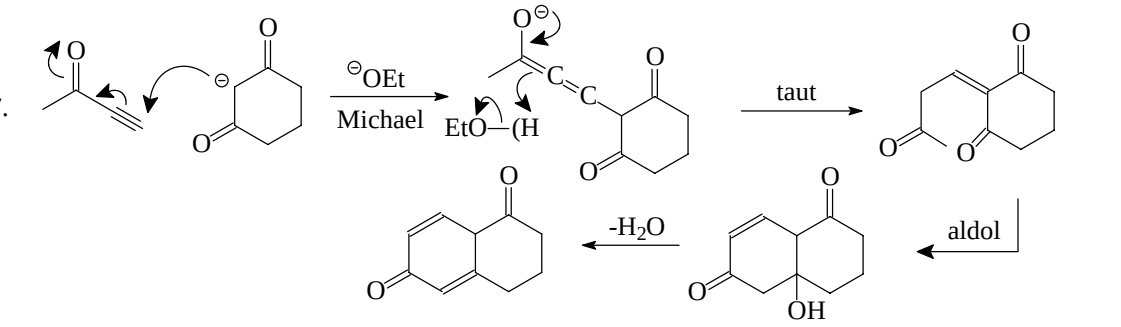
25.


O
1. H3O⊕
conj. add'n
H⊕
O
O
(H
2. KO-t-Bu
retro-aldol
OH
H
O
taut
O
H
O

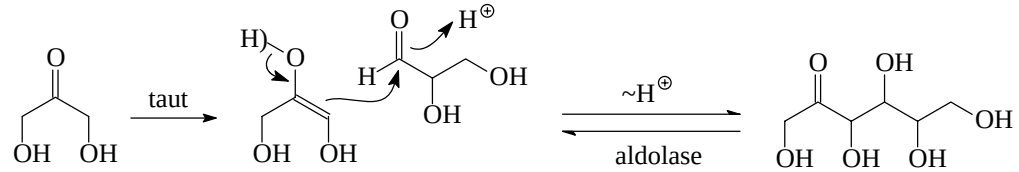
26.


CO2⊖
O
H
O
O⊖
CO2⊖
retro-aldol
CO2⊖
O
⊖O
H)
O
H
CO2⊖
taut
⊖O2C
CO2⊖
O
H
CO2⊖
aldol
HO
CO2⊖
O
O
SCoA
SCoA
hydro-
lysis
HO
CO2⊖
⊖O2C

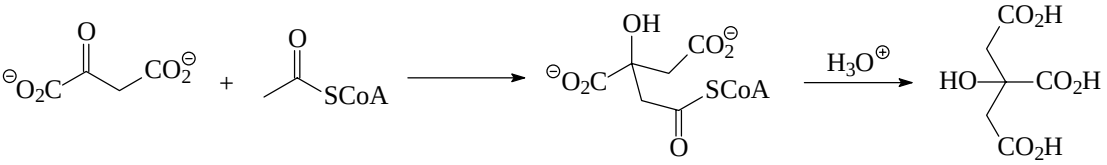
27.


O
O
⊖
O
⊖OEt
Michael
O⊖
C
C
EtO—(H
O
O
taut
O
O
aldol
O
O
OH
-H2O
O
O

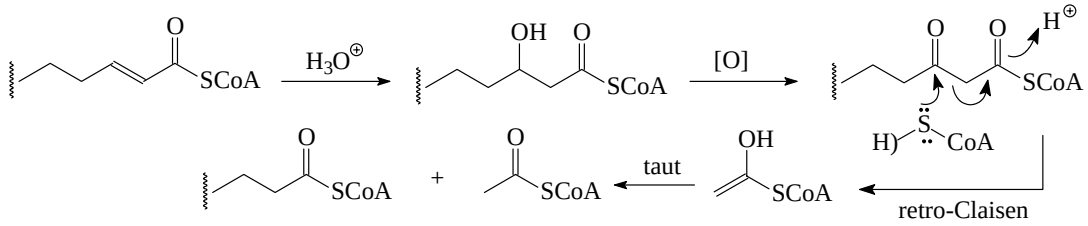
28.


O
OH
OH
taut
H)
O
O
H⊕
H
OH
OH
OH
OH
~H⊕
aldolase
O
OH
OH
OH
OH
OH

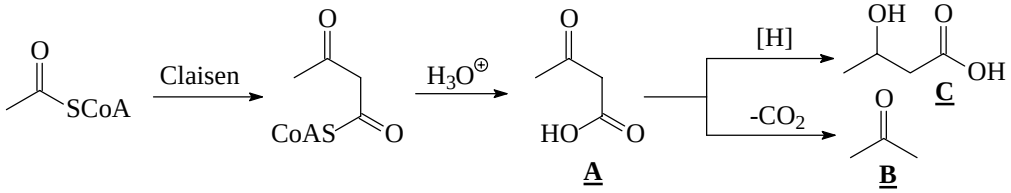
29.



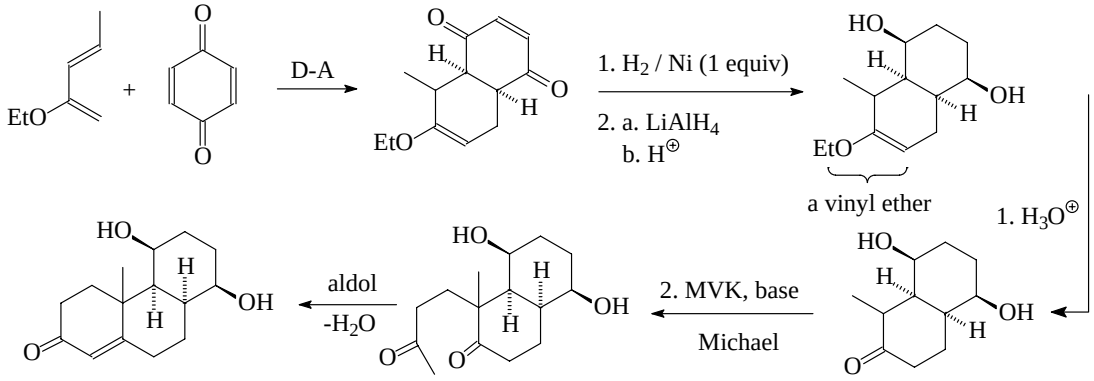
30.



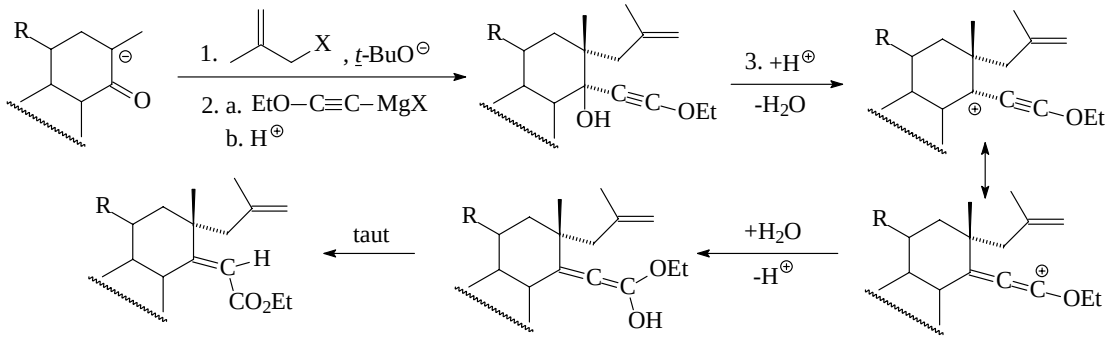
31.



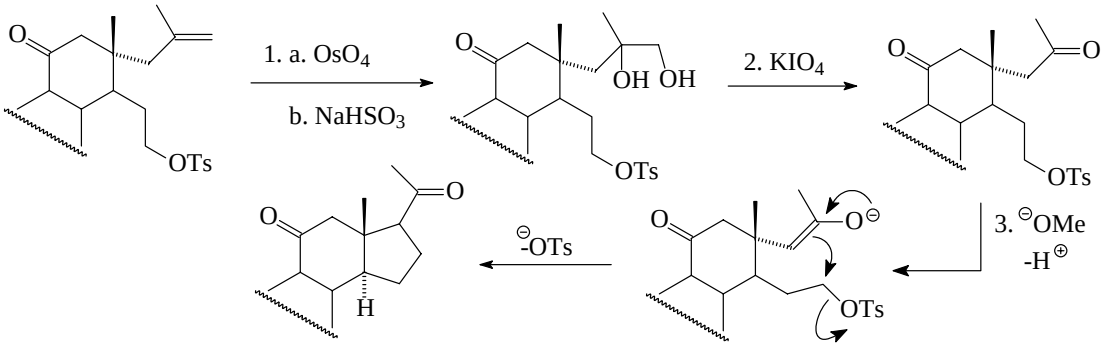
32. a.



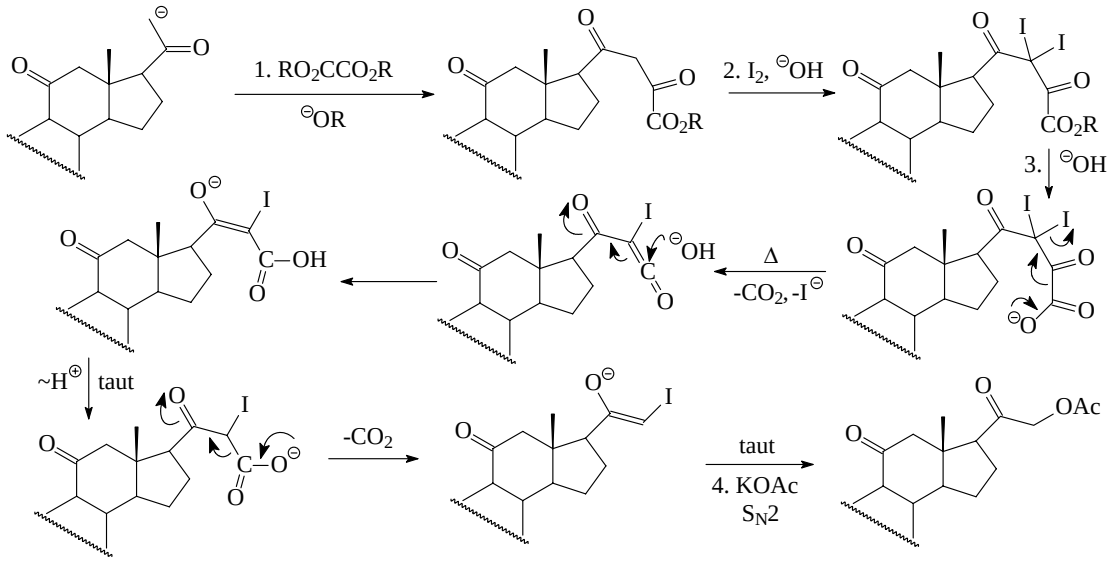
b.



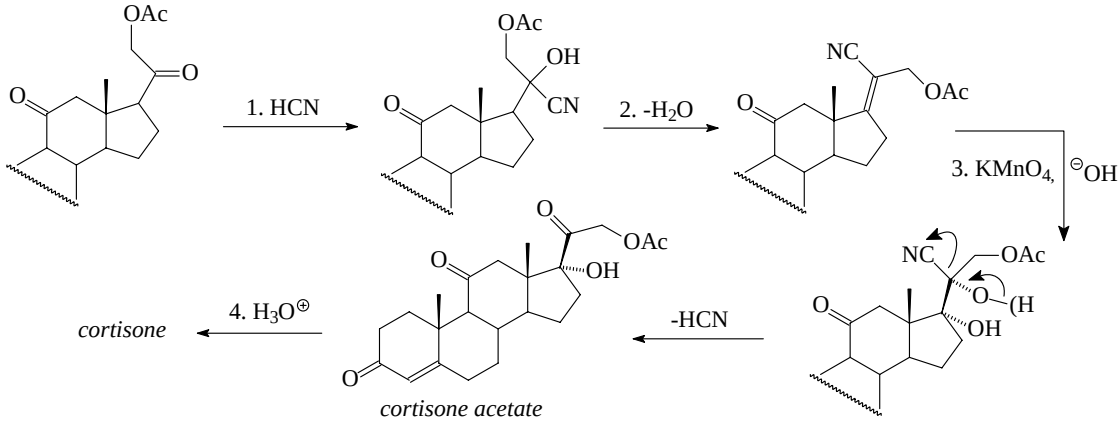
c.


1. a. OsO4
b. NaHSO3
2. KIO4
3. ⊖OMe
-H⊕
⊖-OTs
OTs
OH OH

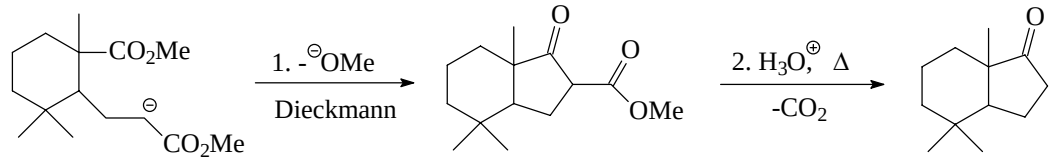
d.


1. RO2CCO2R
⊖OR
2. I2, ⊖OH
3. ⊖OH
Δ
-CO2, -I⊖
~H⊕
taut
-CO2
taut
4. KOAc
SN2
CO2R
C–OH

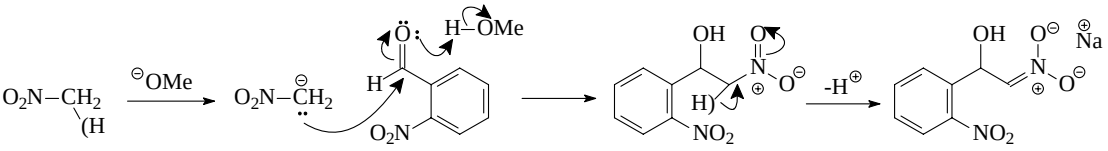
e.


1. HCN
2. -H2O
3. KMnO4, ⊖OH
4. H3O⊕
-HCN
cortisone
cortisone acetate
OAc
OH
CN
NC

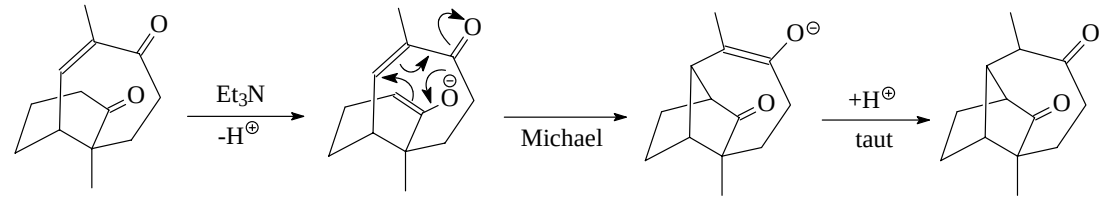
33.


CO2Me
CO2Me
1. -⊖OMe
Dieckmann
OMe
2. H3O⊕, Δ
-CO2

34.

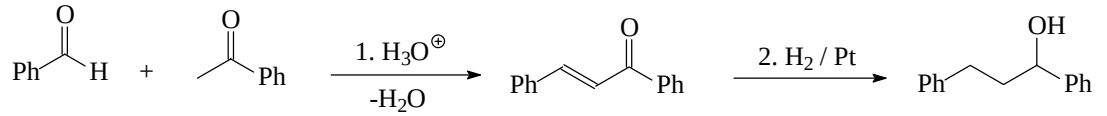


35.

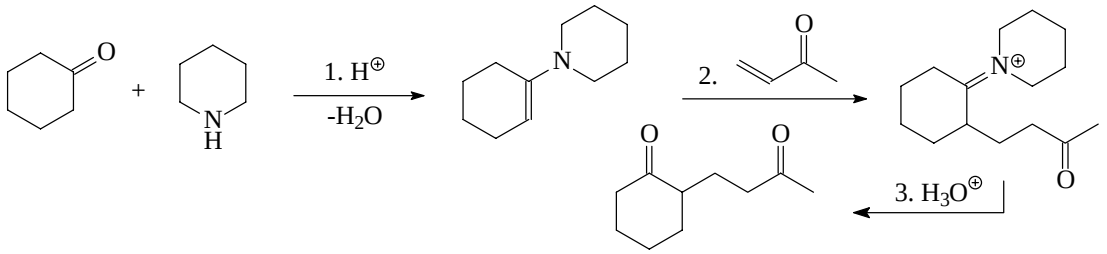


19.2 Syntheses

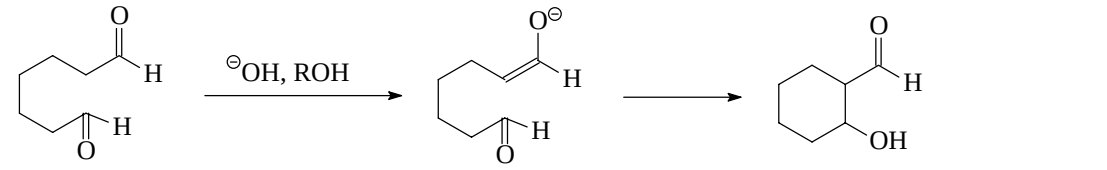
1.



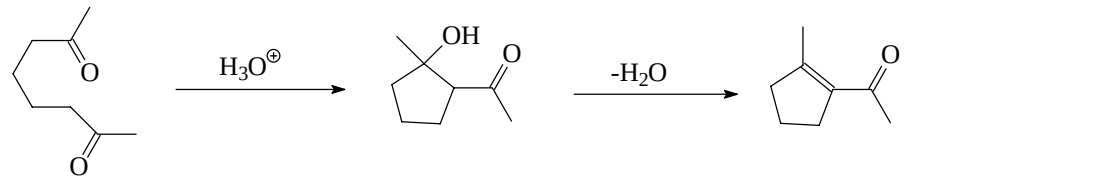
2.



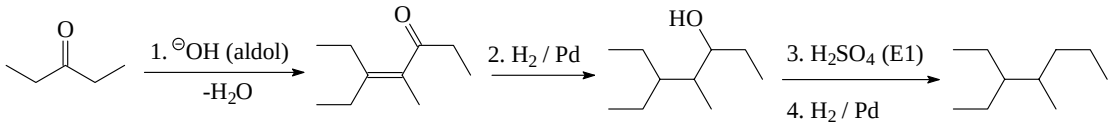
3.



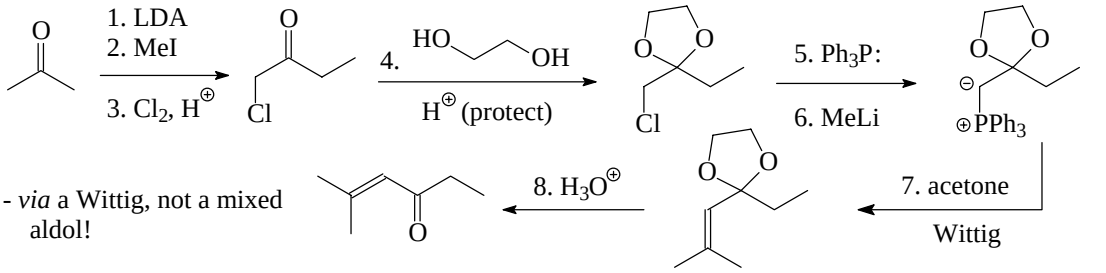
4.



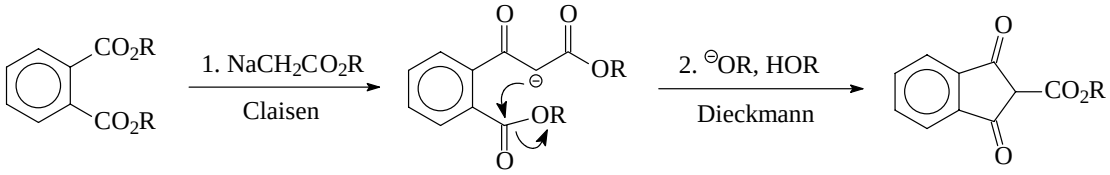
5.



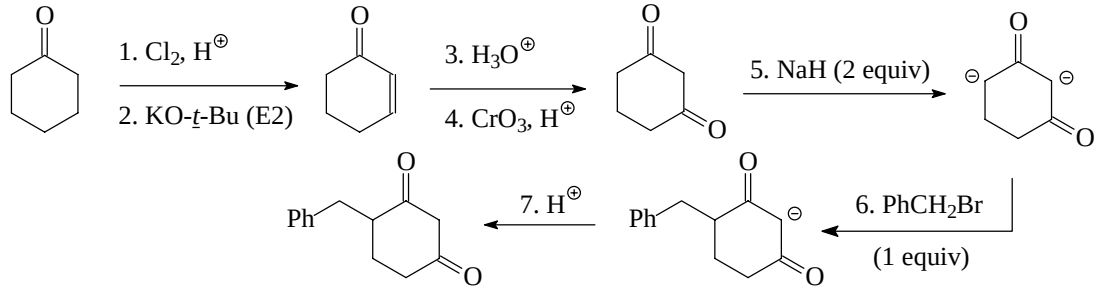
6.


1. LDA
2. MeI
3. Cl2, H⊕
4.
HO
OH
H⊕ (protect)
5. Ph3P:
6. MeLi
⊕PPh3
7. acetone
Wittig
8. H3O⊕
- via a Wittig, not a mixed aldol!

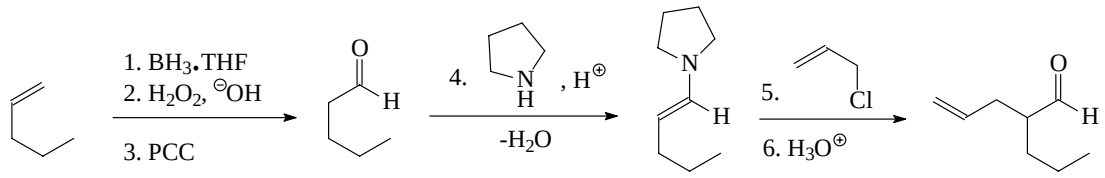
7.


CO2R
CO2R
1. NaCH2CO2R
Claisen
OR
2. ⊖OR, HOR
Dieckmann

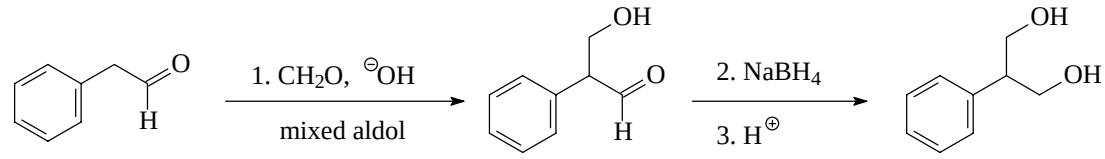
8.


1. Cl2, H⊕
2. KO-t-Bu (E2)
3. H3O⊕
4. CrO3, H⊕
5. NaH (2 equiv)
6. PhCH2Br
(1 equiv)
7. H⊕
Ph

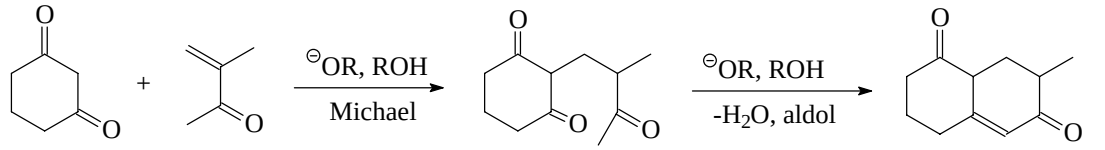
9.


1. BH3.THF
2. H2O2, ⊖OH
3. PCC
4.
N
H
, H⊕
-H2O
5.
Cl
6. H3O⊕

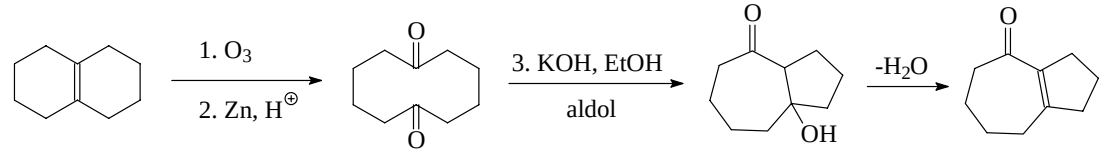
10.

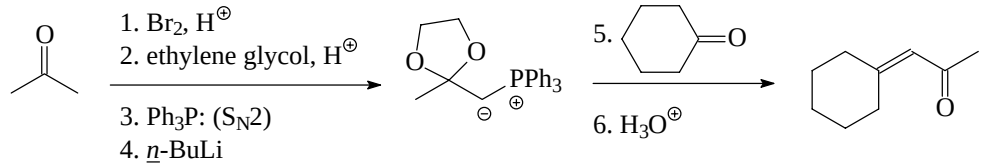

1. CH2O, ⊖OH
mixed aldol
OH
2. NaBH4
3. H⊕

11.

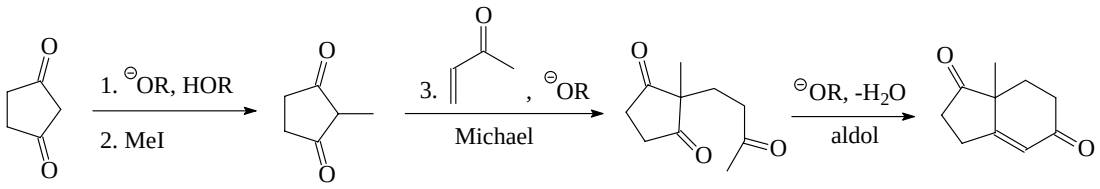

⊖OR, ROH
Michael
⊖OR, ROH
-H2O, aldol

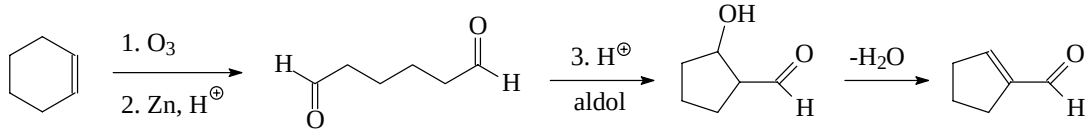
12.

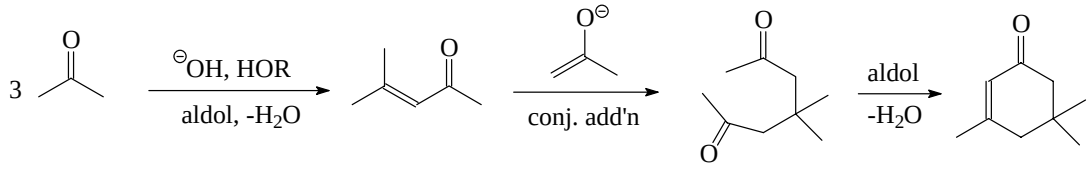

1. O3
2. Zn, H⊕
3. KOH, EtOH
aldol
-H2O
OH

13. 

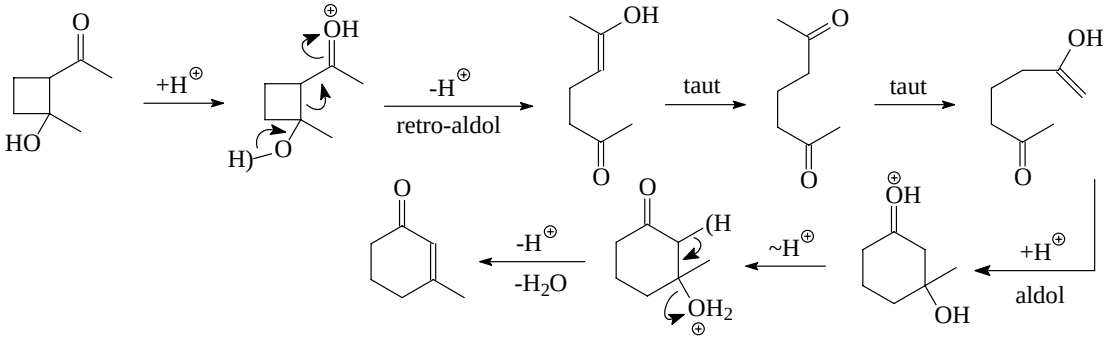
- the reaction of cyclohexanone with acetone *via* an aldol would yield four possible products!

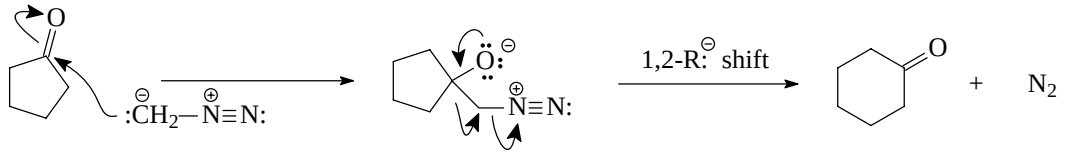
14. 

15. 

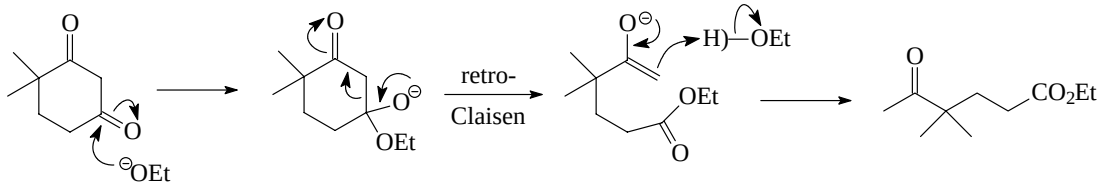
16. 

19.3 Mechanisms

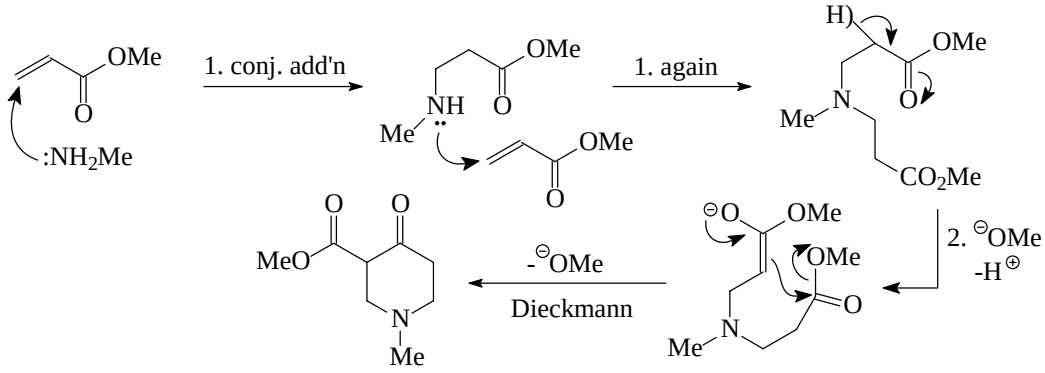
1. 

2. 

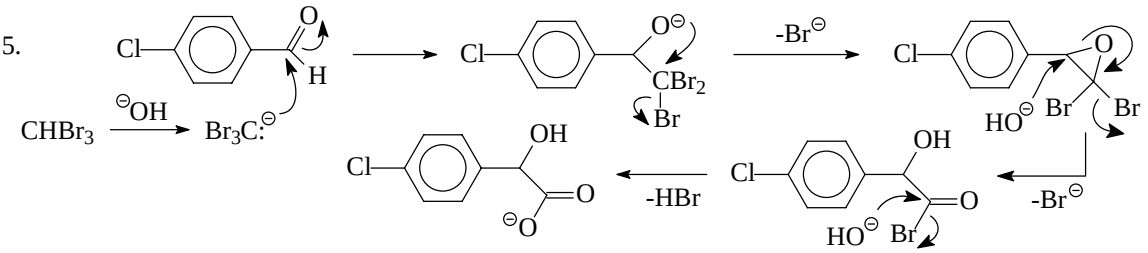
3.


retro-
Claisen
OEt
CO2Et

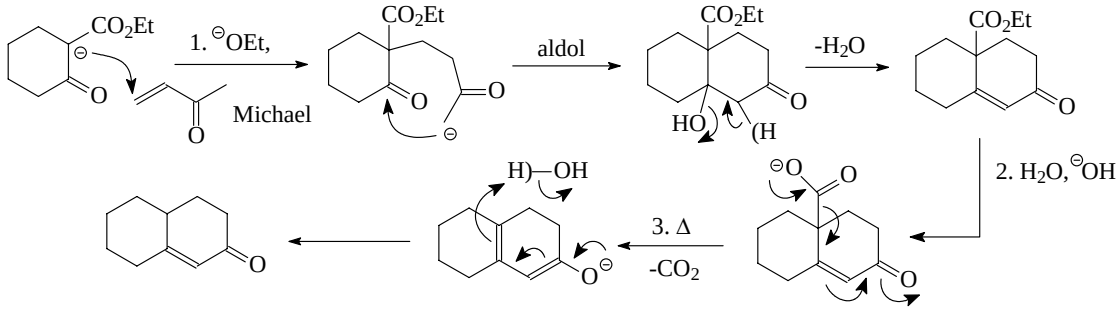
4.


1. conj. add'n
1. again
:NH2Me
2. OMe
-H
-OMe
Dieckmann

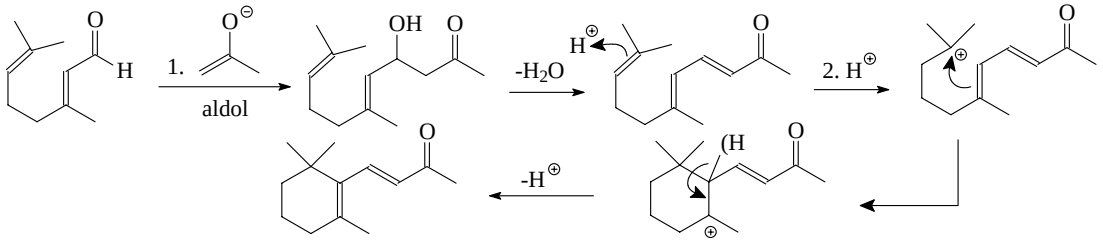
5.


CHBr3
Br3C:
-Br
-HBr

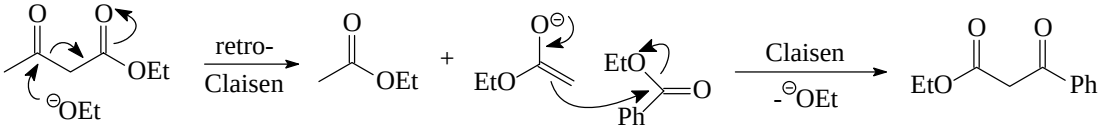
6.


1. OEt,
Michael
aldol
-H2O
2. H2O, OH
3. Δ
-CO2

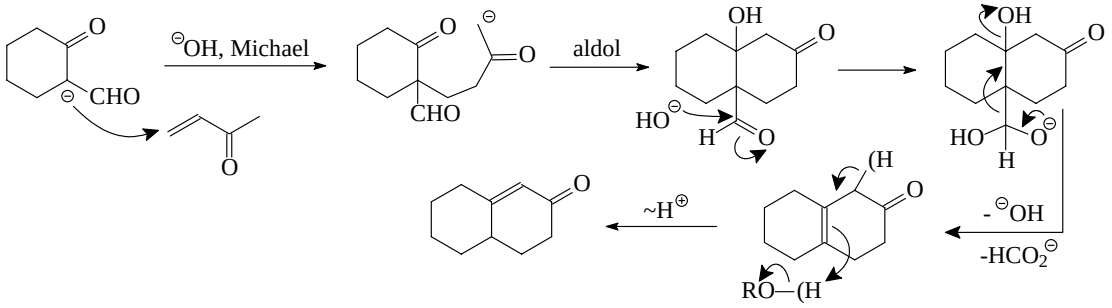
7.


1.
aldol
-H2O
2. H
-H

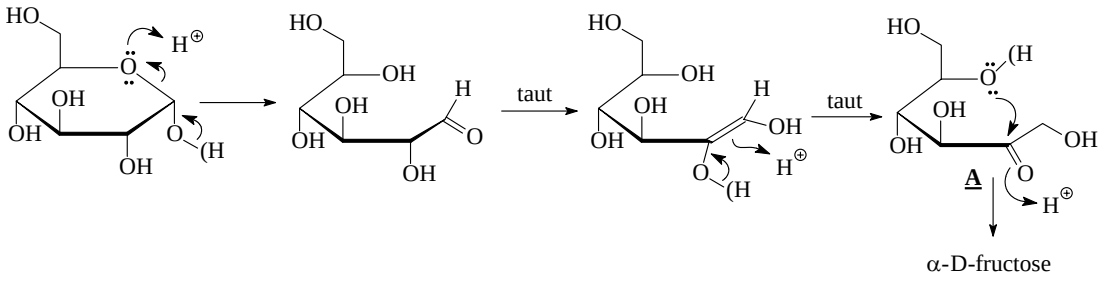
8.

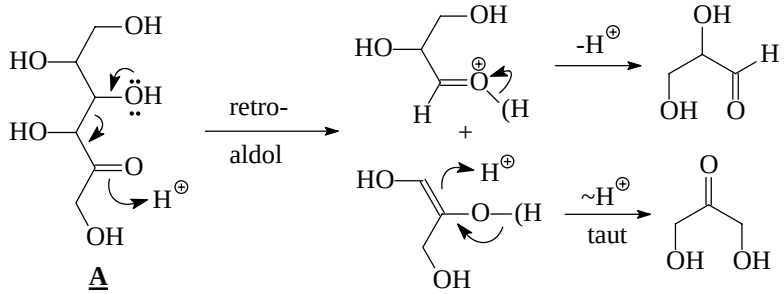

retro-
Claisen
Claisen
-OEt

9.

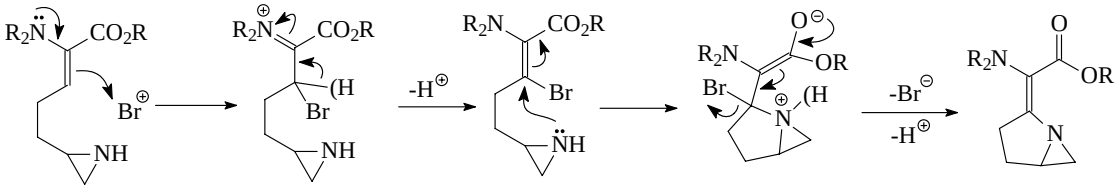

⊖OH, Michael
aldol
~H⊕
- ⊖OH
-HCO2⊖

10.

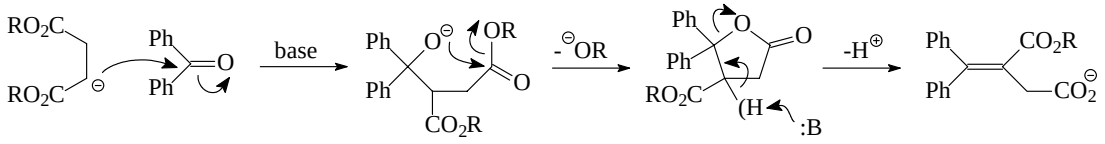

taut
taut
A
α-D-fructose


retro-
aldol
-H⊕
~H⊕
taut
A

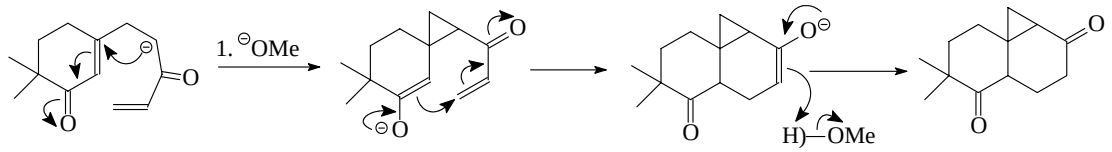
11.


-H⊕
-Br⊖
-H⊕

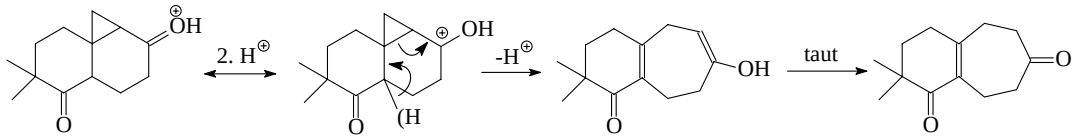
12.


base
- ⊖OR
-H⊕
:B

13.


1. ⊖OMe

13. (*cont.*)



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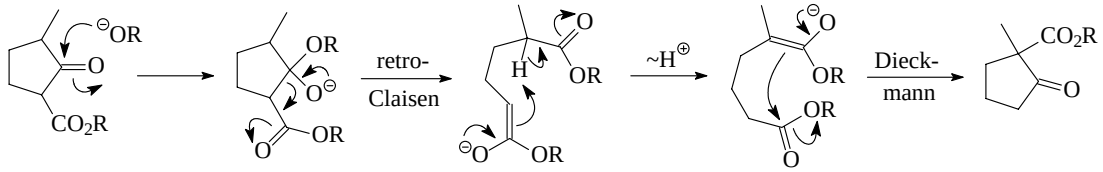

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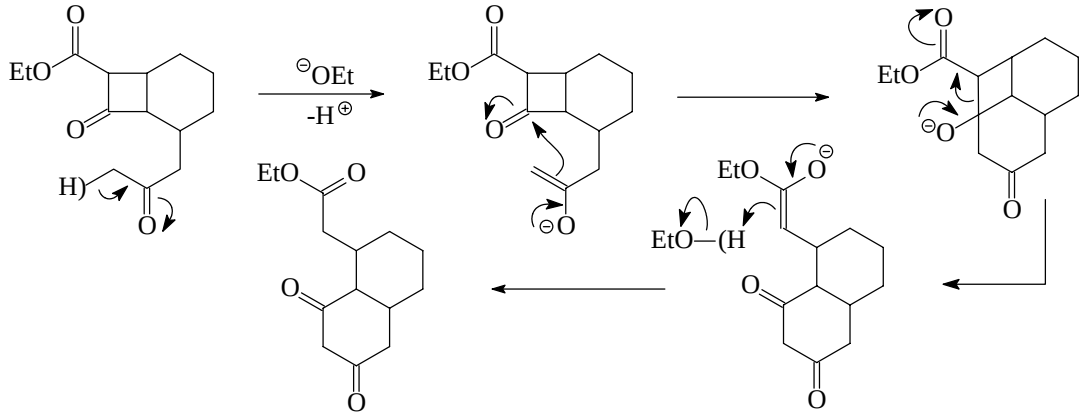

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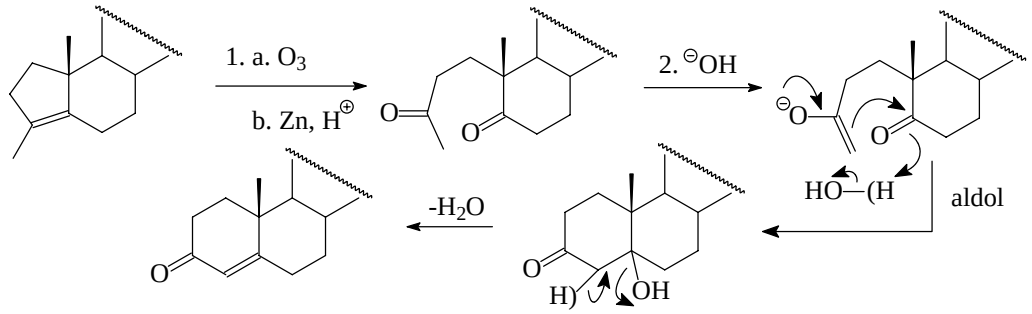

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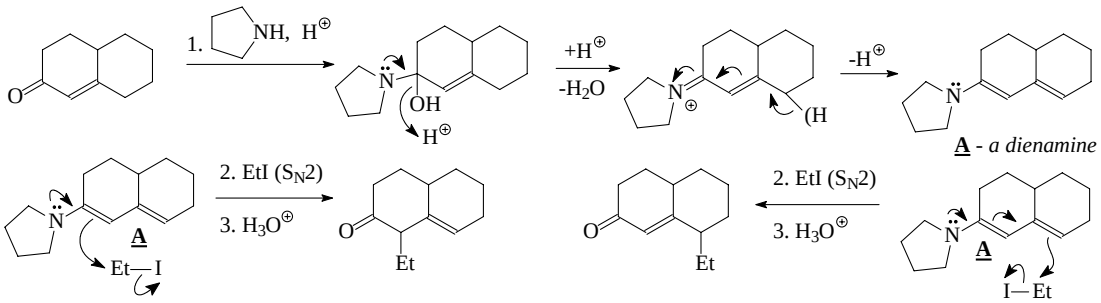

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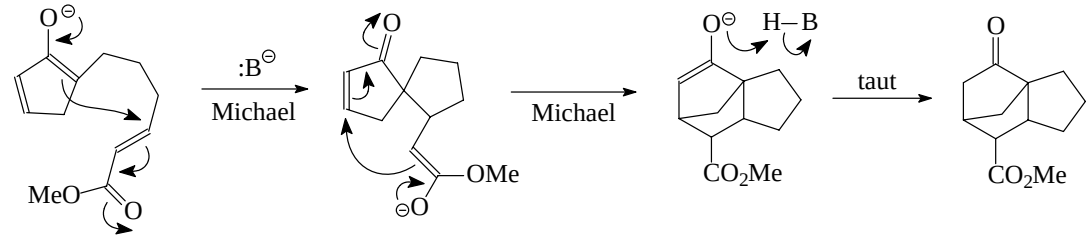

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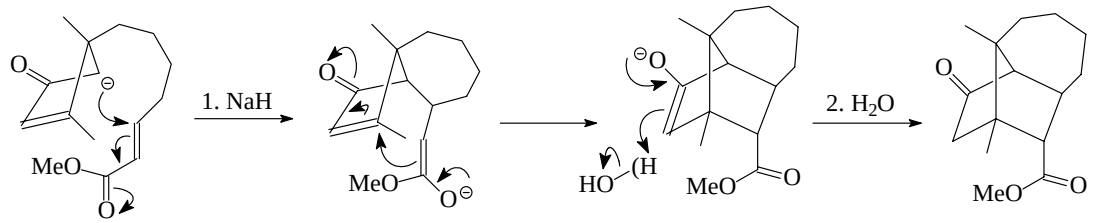

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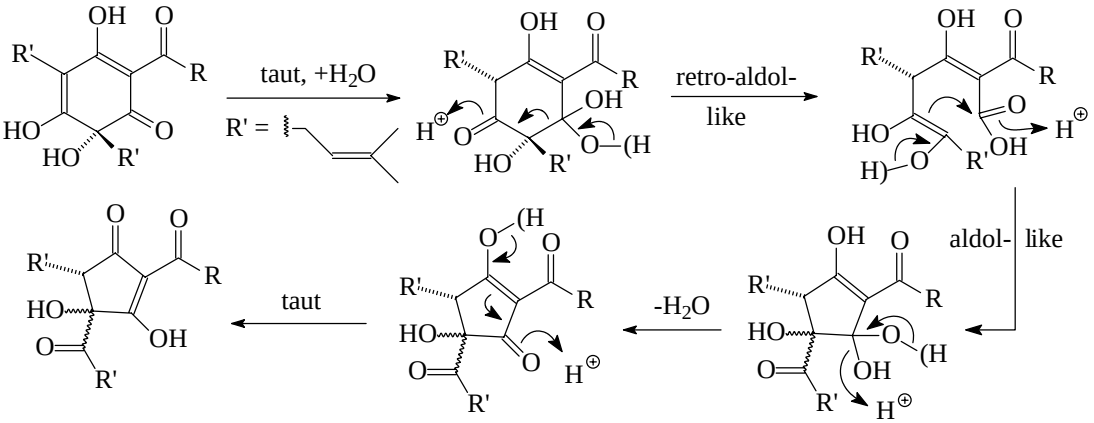
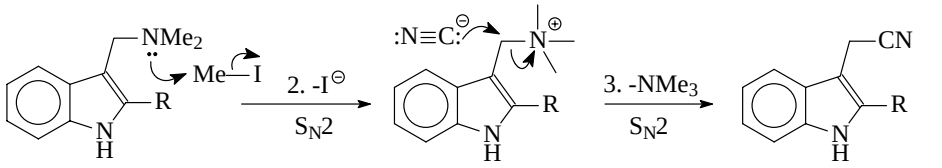
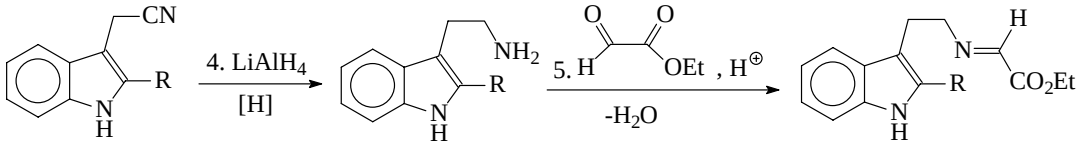


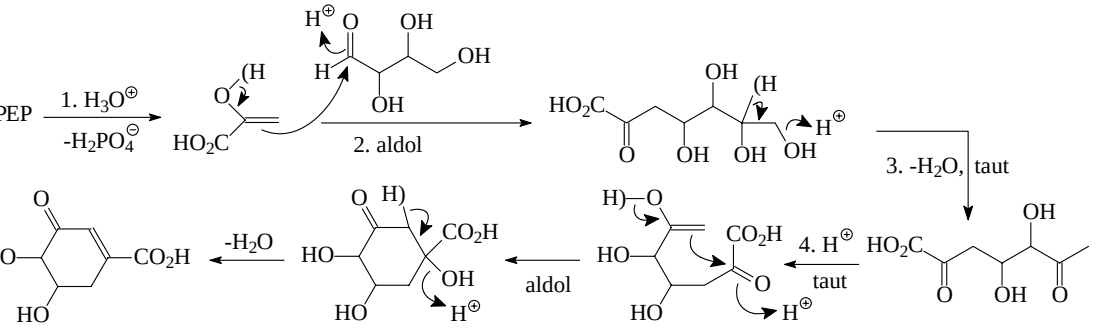
21. a. Mannich b.



c.



22. PEP



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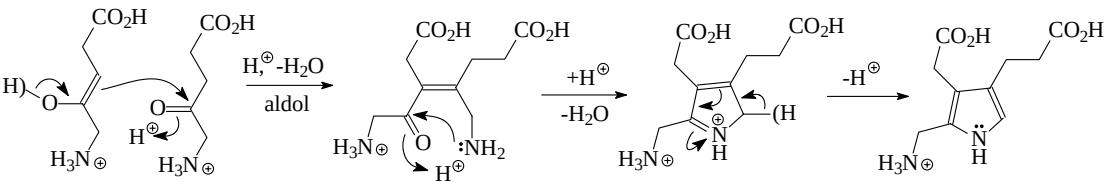

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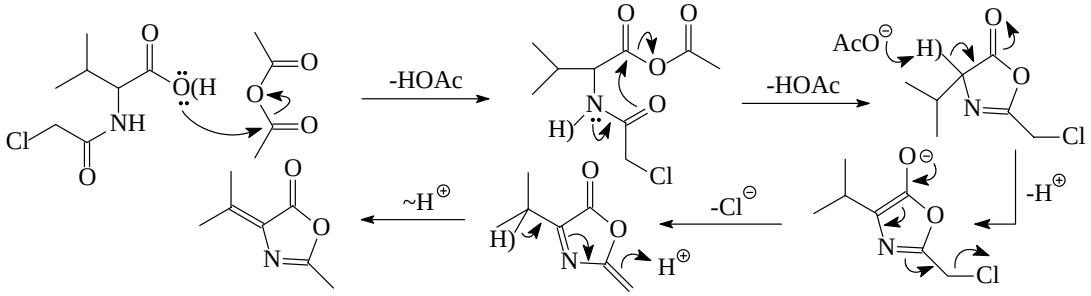
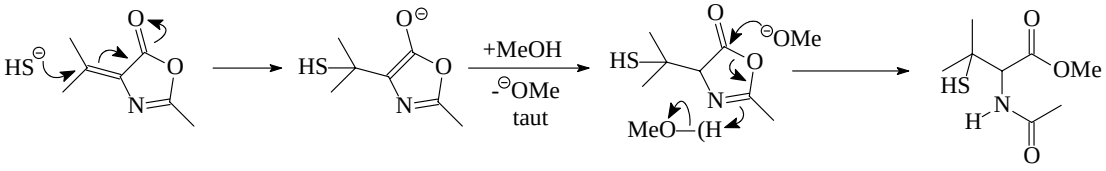


b.



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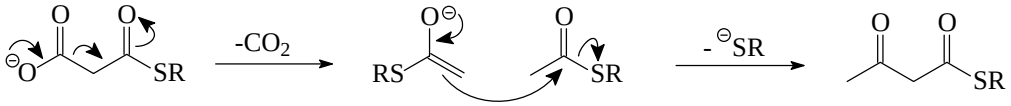

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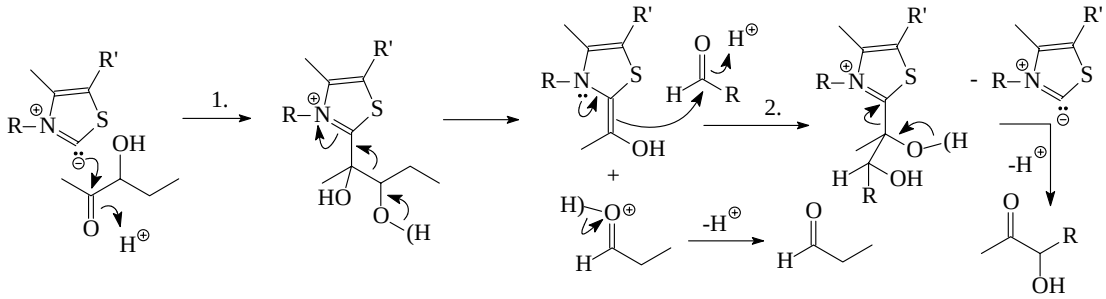

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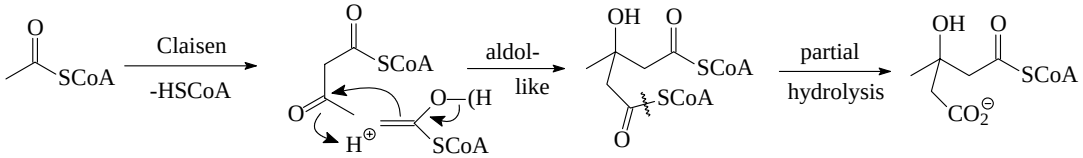

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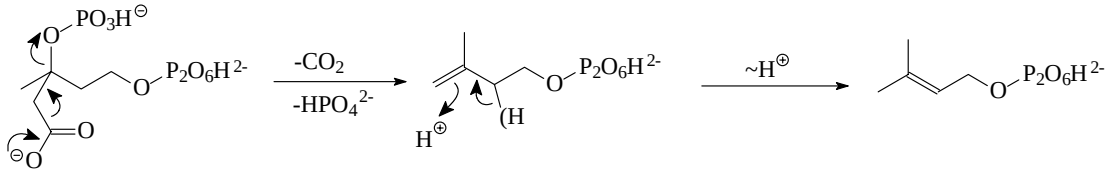
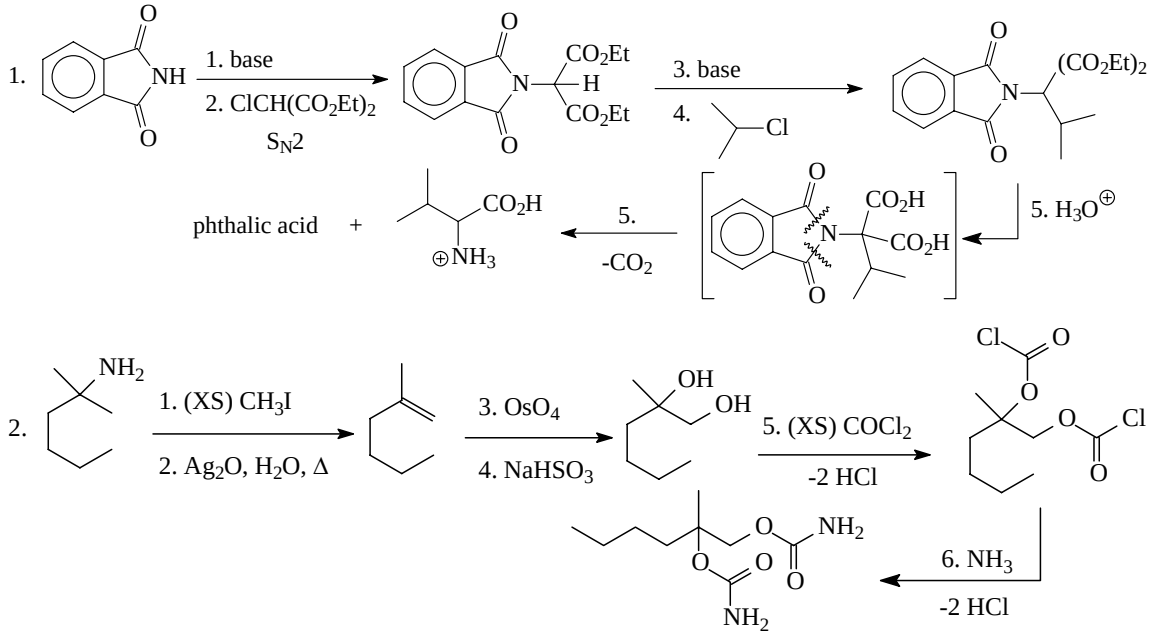


CHAPTER 20

AMINES

20.1 Reactions



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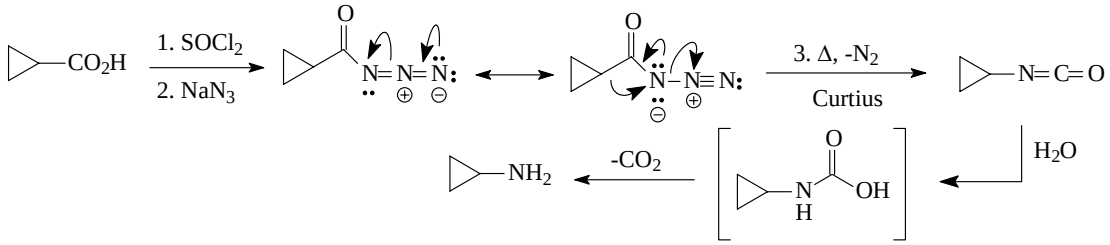

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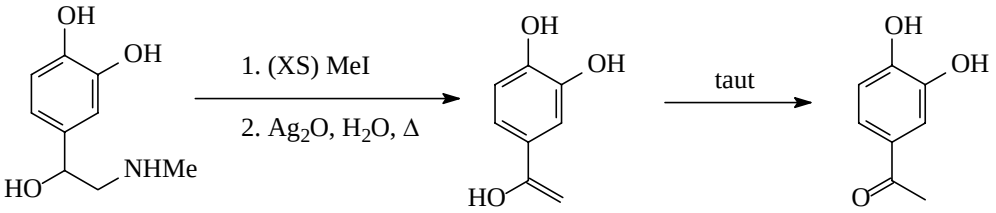

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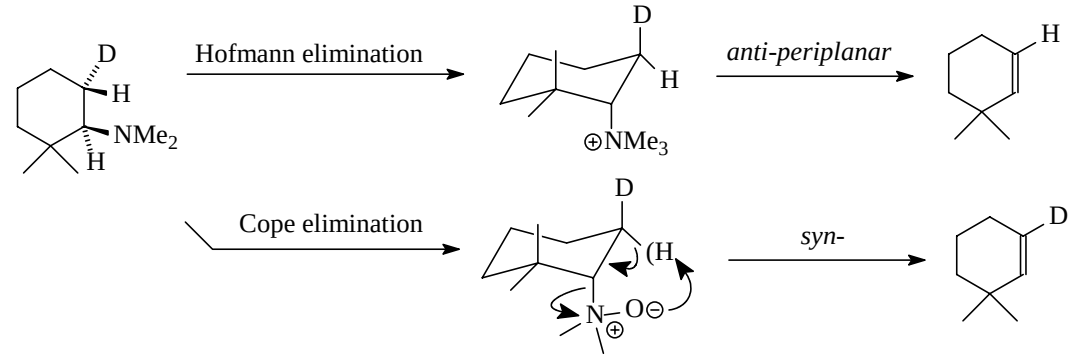

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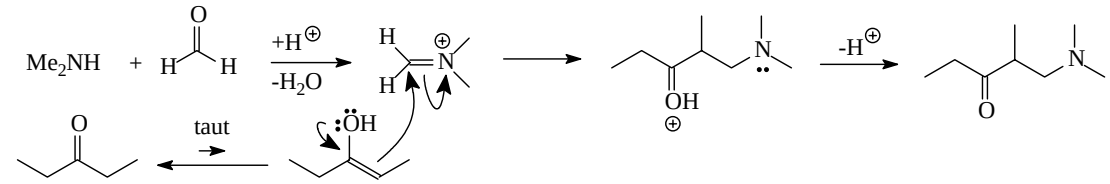

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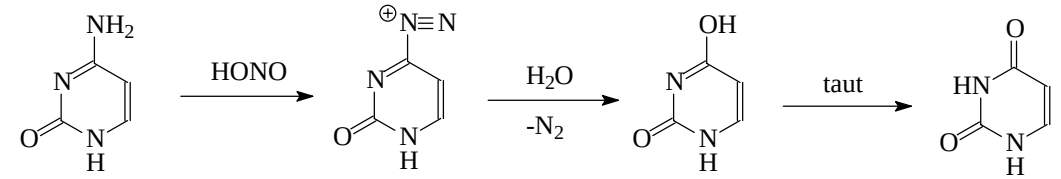

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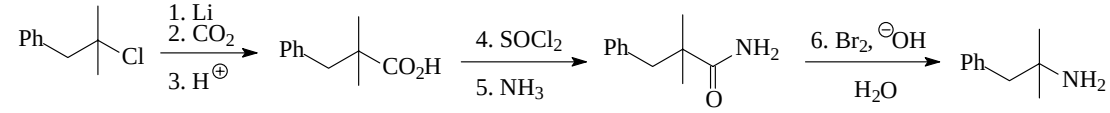

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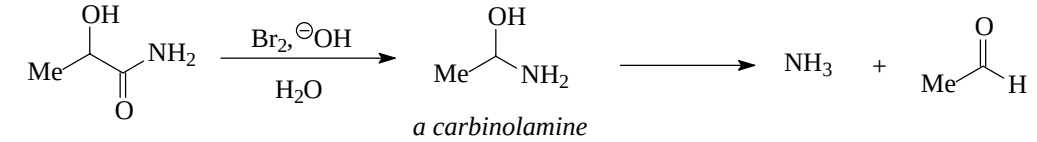
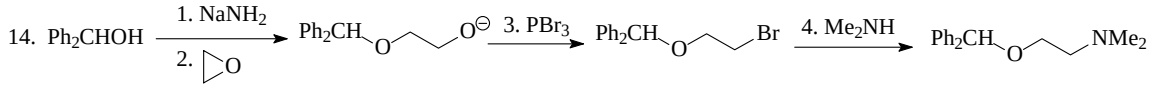
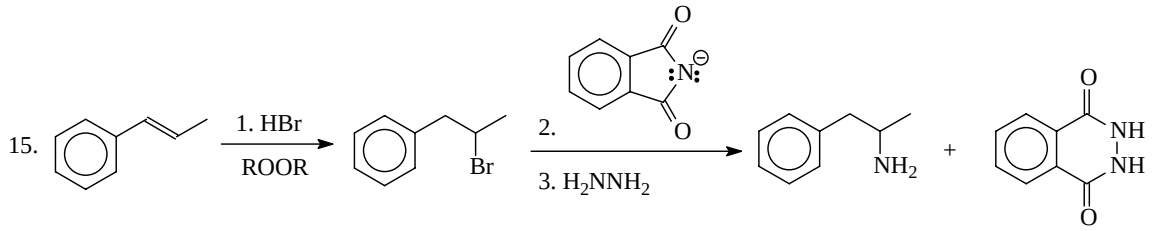
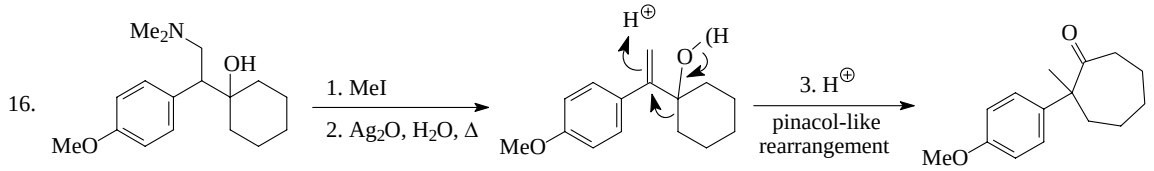
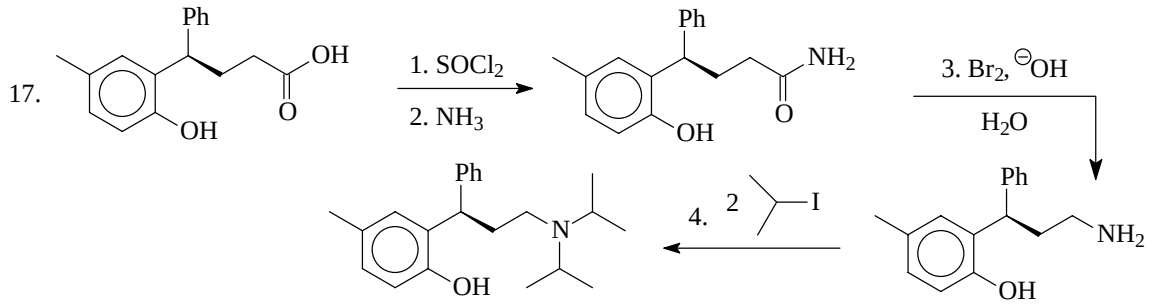


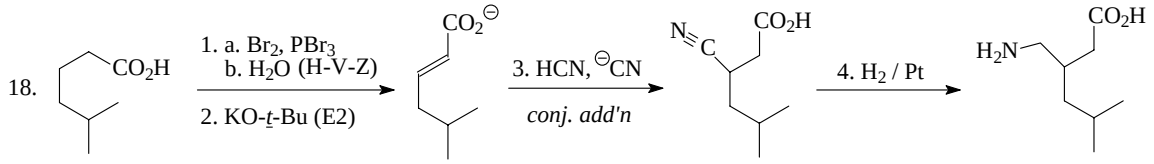
a carbinolamine

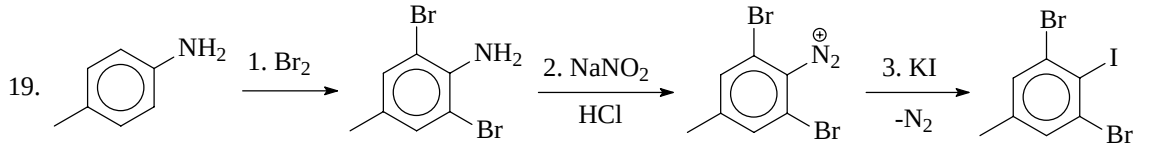
14. 

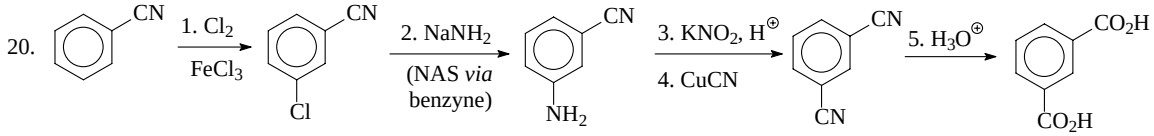
15. 

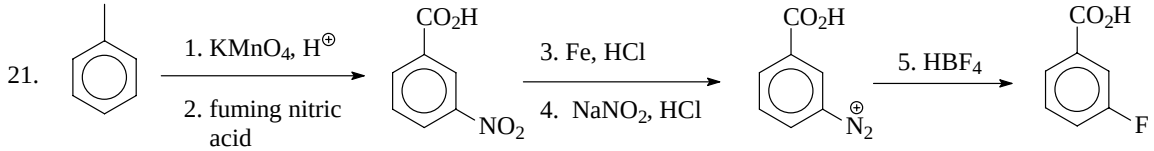
16. 

17. 

18. 

19. 

20. 

21. 

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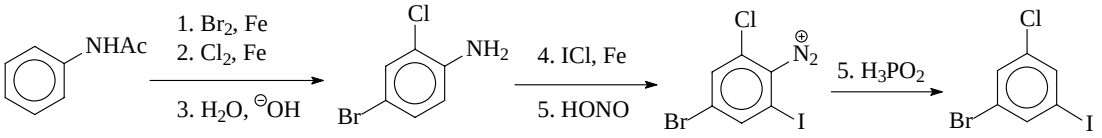

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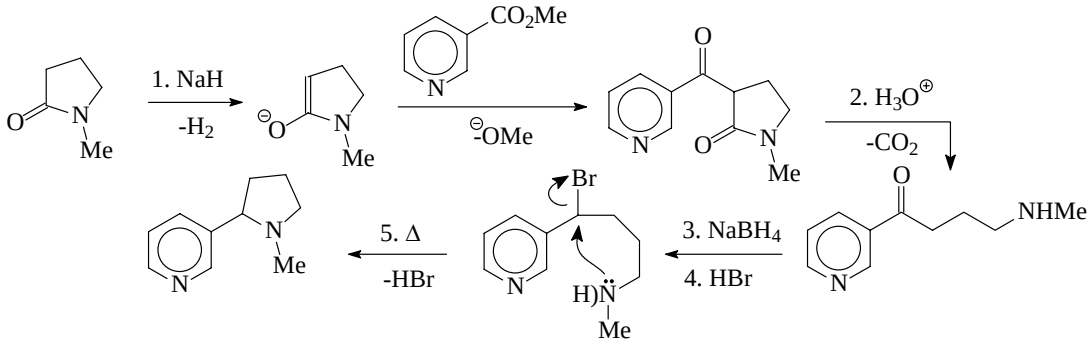

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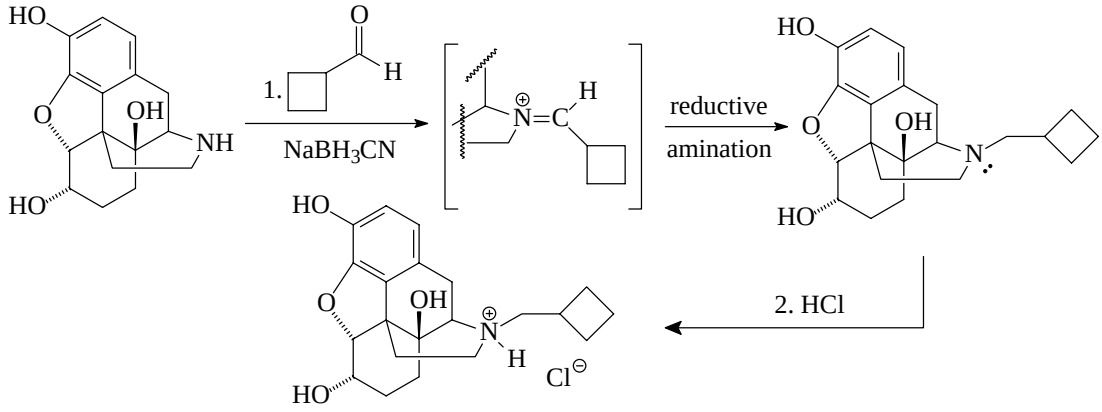
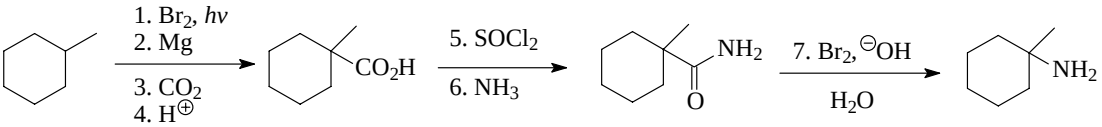


20.2 Syntheses

1.



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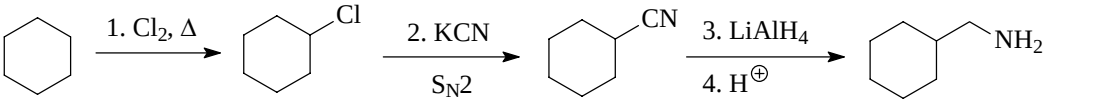

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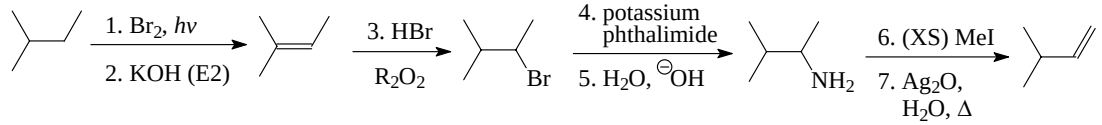
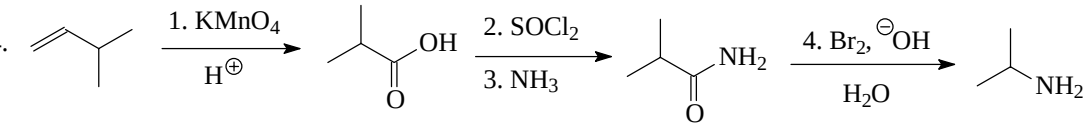
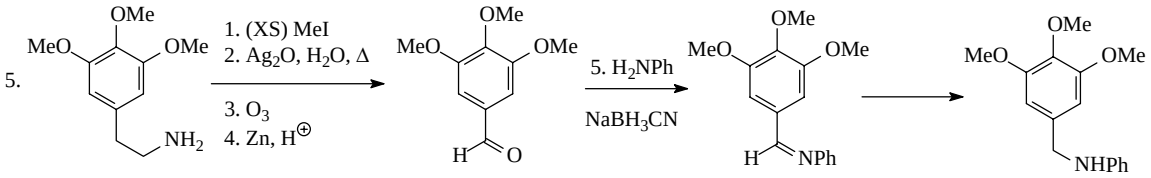
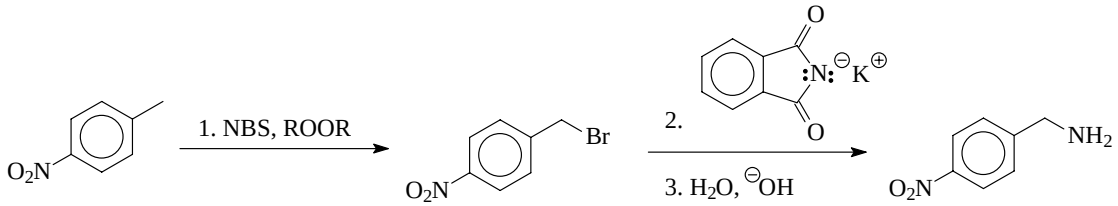
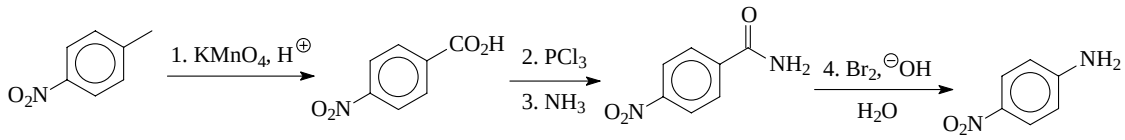
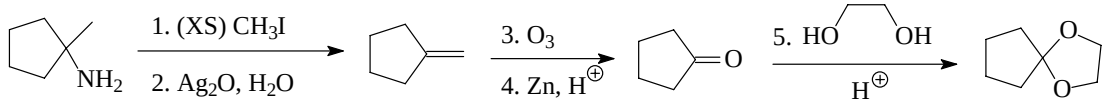


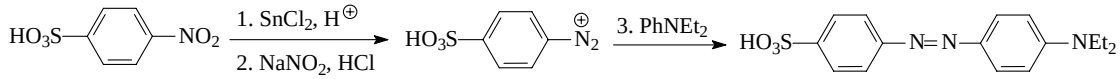
4. 
1. KMnO4
H⊕
OH
O
2. SOCl2
3. NH3
NH2
O
4. Br2, ⊖OH
H2O
NH2

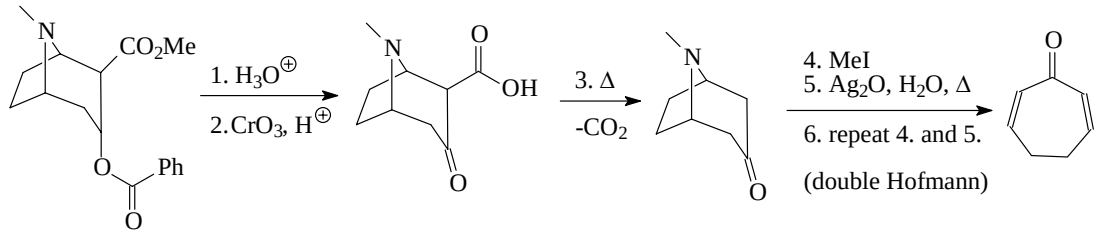
5. 
OMe
MeO
OMe
NH2
1. (XS) MeI
2. Ag2O, H2O, Δ
3. O3
4. Zn, H⊕
H
O
5. H2NPh
NaBH3CN
NPh
NHPh

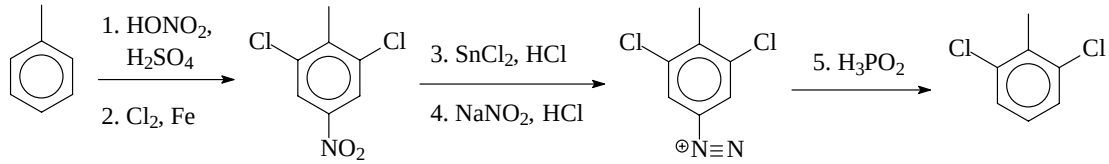
6. 
O2N
1. NBS, ROOR
Br
O
N: ⊖ K⊕
2.
3. H2O, ⊖OH
NH2

7. 
O2N
1. KMnO4, H⊕
CO2H
2. PCl3
3. NH3
NH2
O
4. Br2, ⊖OH
H2O

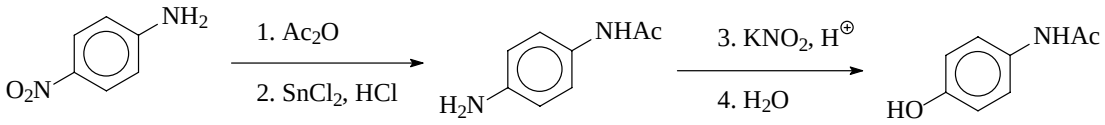
8. 
NH2
1. (XS) CH3I
2. Ag2O, H2O
3. O3
4. Zn, H⊕
O
5. HO OH
H⊕
O

9. 
HO3S
NO2
1. SnCl2, H⊕
2. NaNO2, HCl
N2
3. PhNEt2
N= N
NEt2

10. 
N
CO2Me
O
Ph
O
1. H3O⊕
2.CrO3, H⊕
OH
3. Δ
-CO2
4. MeI
5. Ag2O, H2O, Δ
6. repeat 4. and 5.
(double Hofmann)

11. 
1. HONO2,
H2SO4
2. Cl2, Fe
Cl
NO2
3. SnCl2, HCl
4. NaNO2, HCl
⊕N≡N
5. H3PO2

12.



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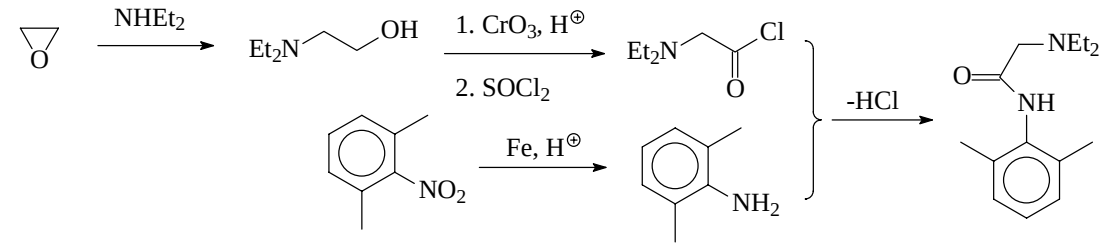
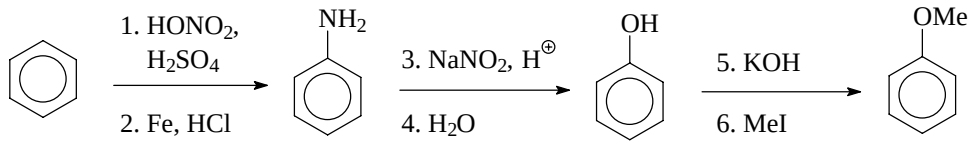


14.



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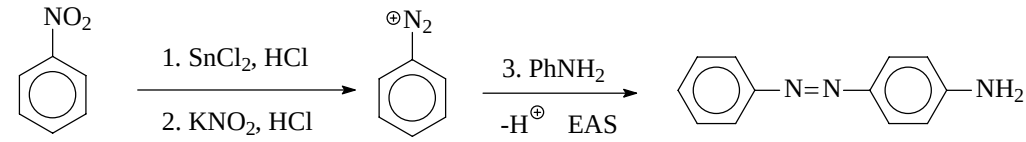

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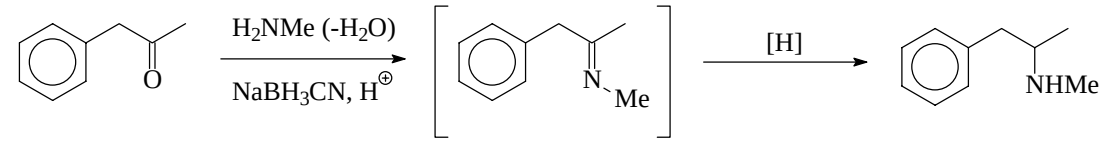

(alternatively, 1. H_2NMe, 2. H_2 / Pd)

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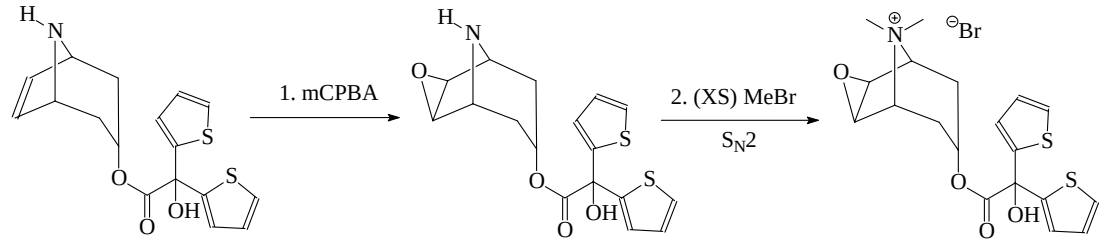

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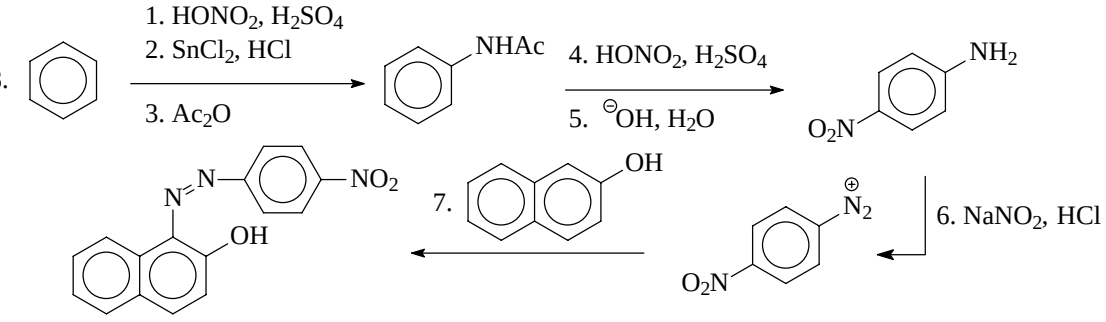

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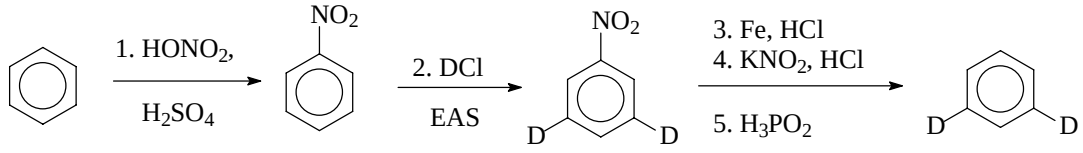

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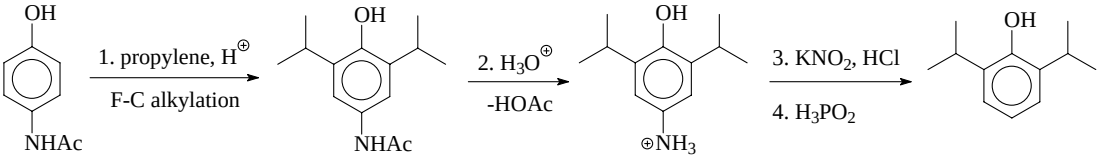
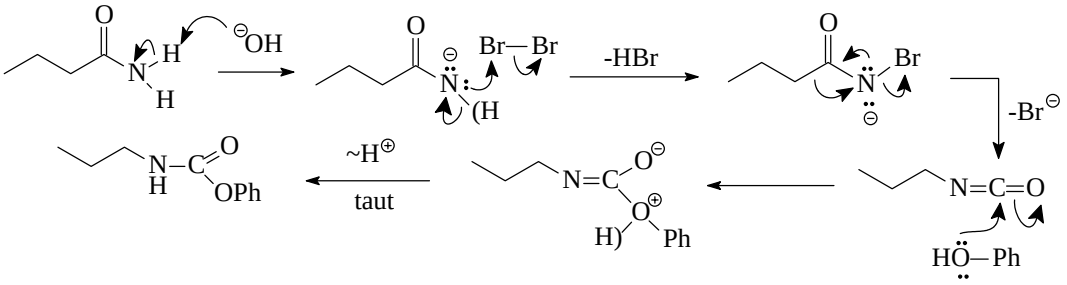


20.3 Mechanisms

1.



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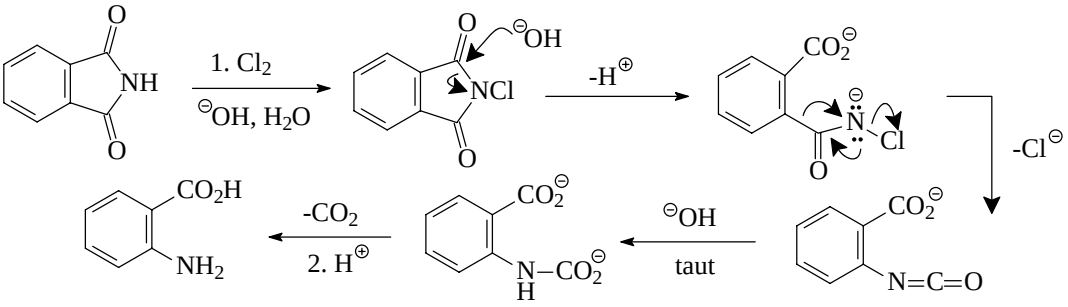

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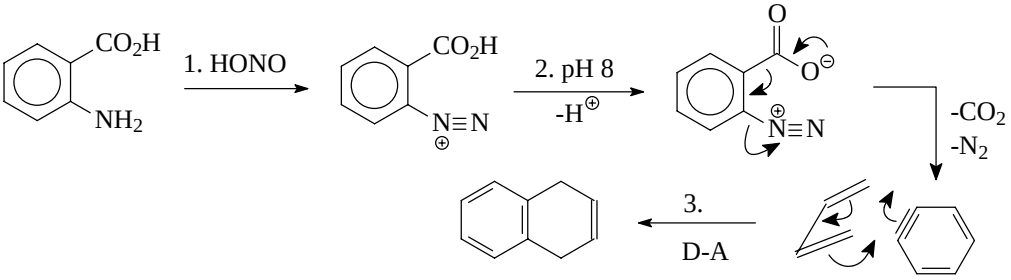

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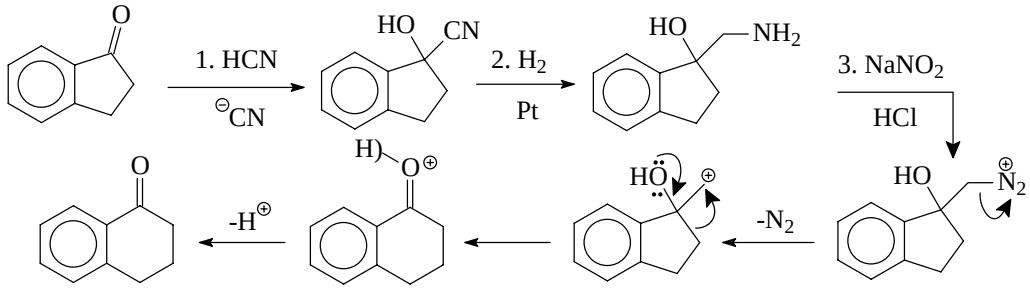

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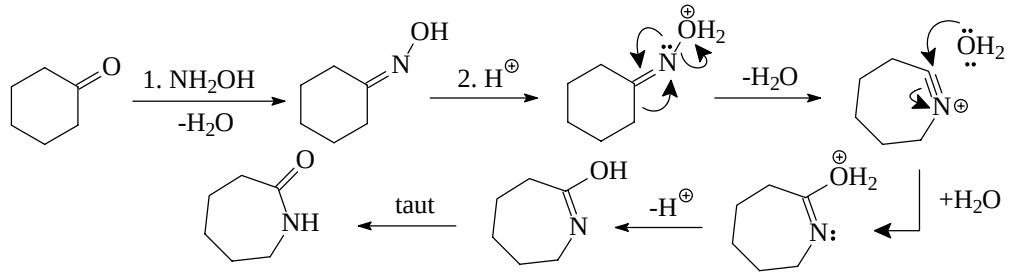

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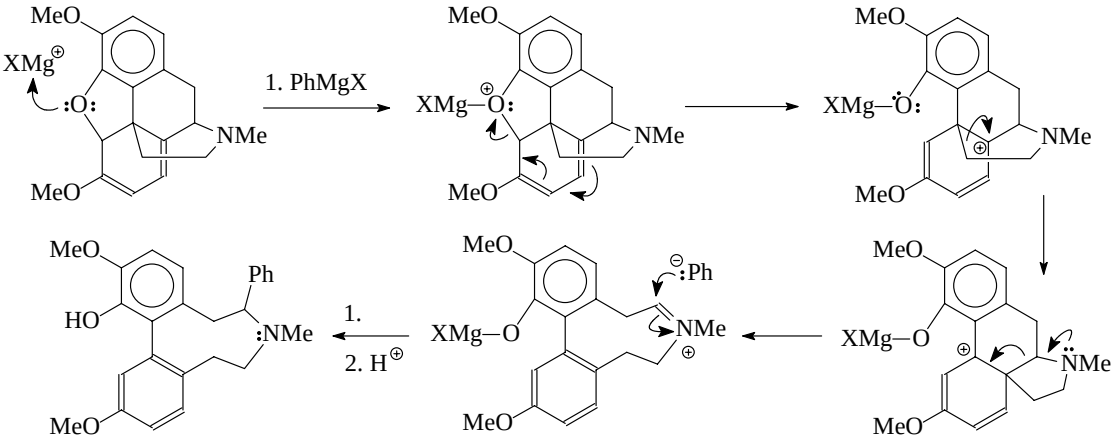
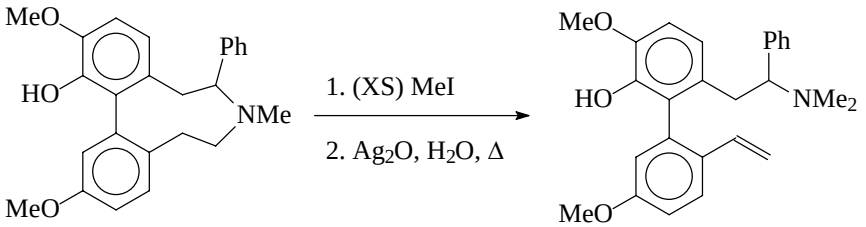


Hofmann:



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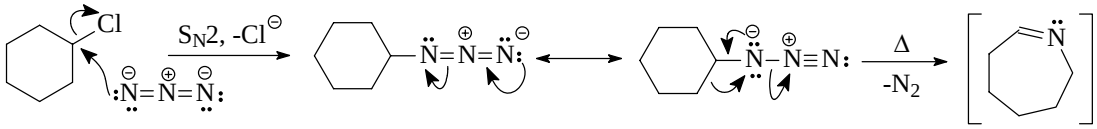

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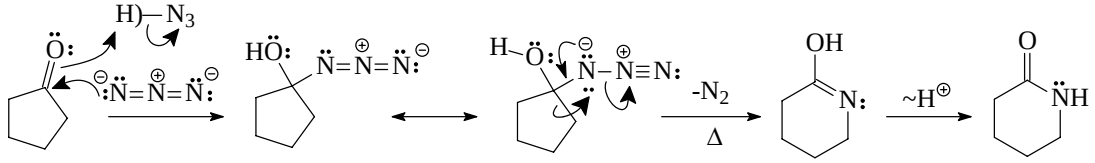

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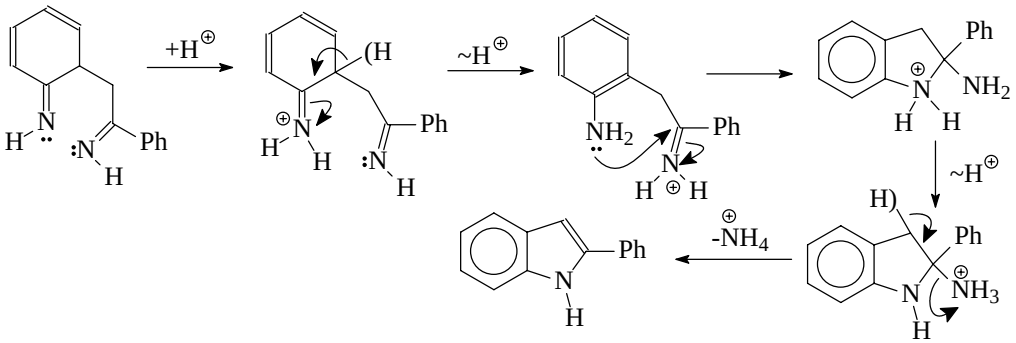

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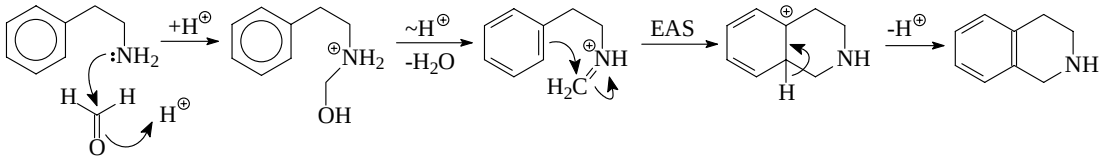

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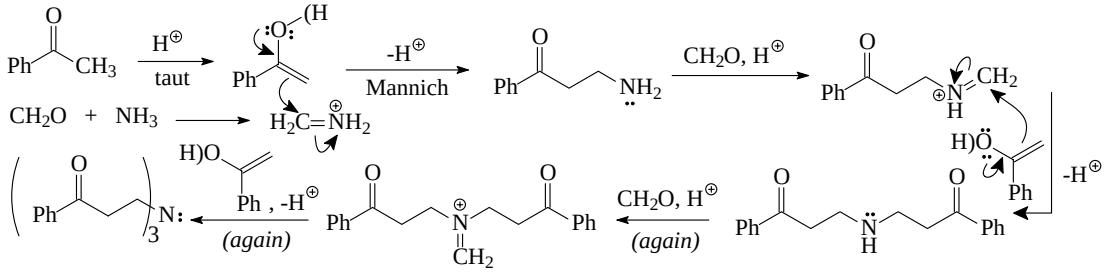

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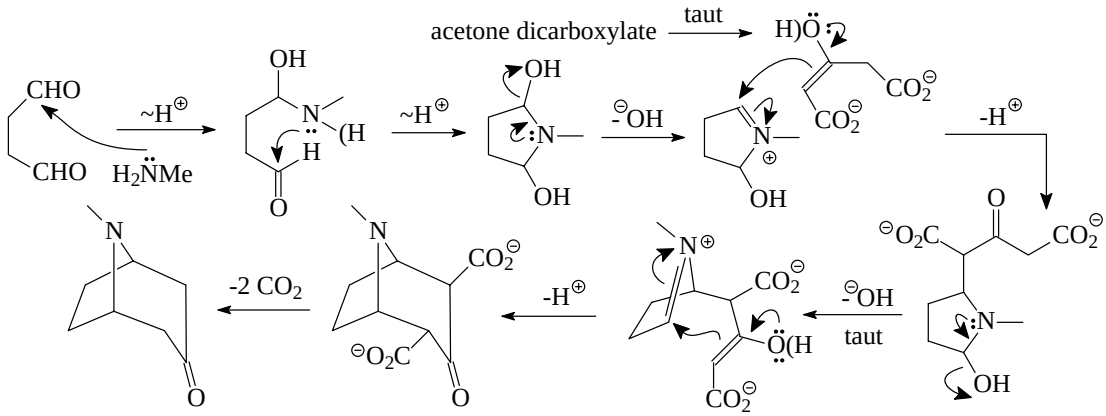
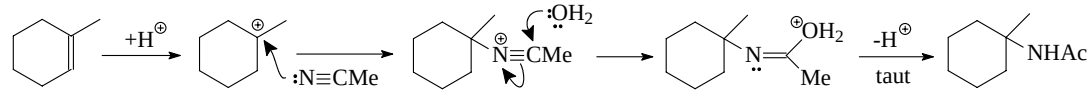


13. a.



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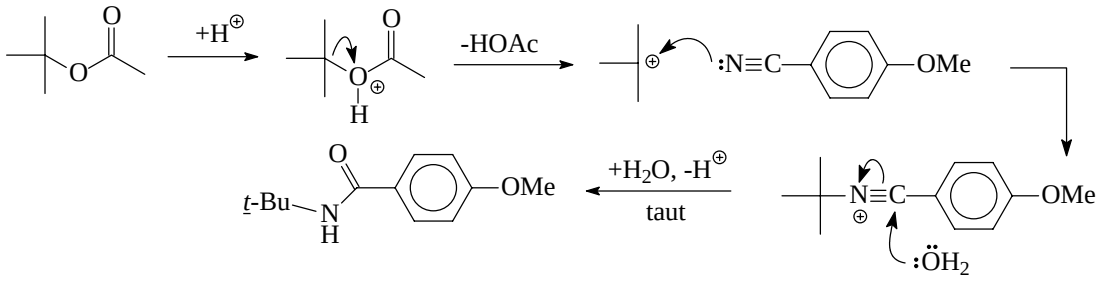

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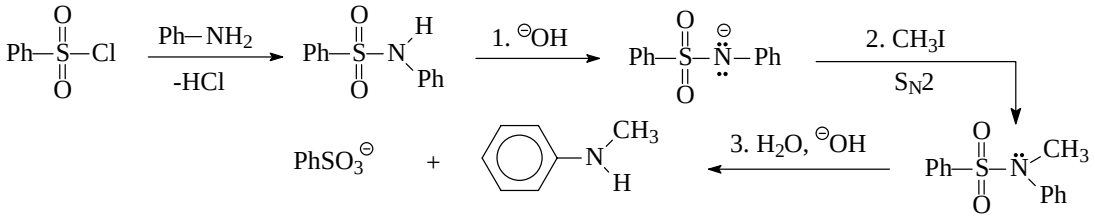

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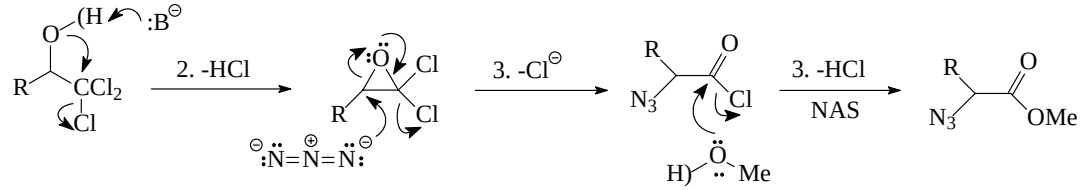

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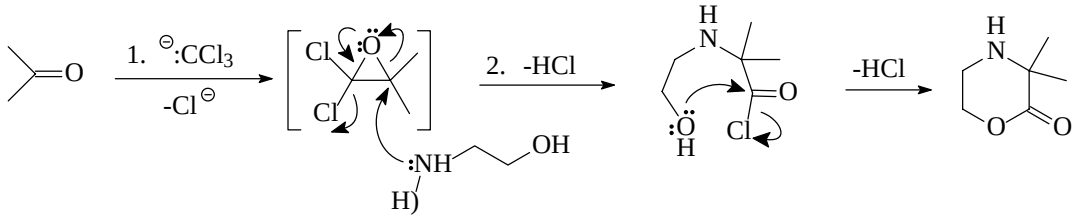

16.