

## Chapter 27 – Biomolecules: Lipids

### Chapter Outline

#### I. Esters (Sections 27.1 – 27.3).

##### A. Waxes, fats and oils (Section 27.1).

1. Waxes are esters of long-chain fatty acids with long-chain alcohols.
2. Fats and oils are triacylglycerols.
  - a. Hydrolysis of a fat yields glycerol and three fatty acids.
  - b. The fatty acids need not be the same.
3. Fatty acids.
  - a. Fatty acids are even-numbered, unbranched long-chain ( $C_{12}$ – $C_{20}$ ) carboxylic acids.
  - b. The most abundant saturated fatty acids are palmitic ( $C_{16}$ ) and stearic ( $C_{18}$ ) acids.
  - c. The most abundant unsaturated fatty acids are oleic and linoleic acids (both  $C_{18}$ ).  
Linoleic and arachidonic acids are polyunsaturated fatty acids.
  - d. Unsaturated fatty acids are lower-melting than saturated fatty acids because the double bonds keep molecules from packing closely.
  - e. The  $C=C$  bonds can be hydrogenated to produce higher-melting fats.  
Occasionally, cis–trans bond isomerization takes place.

##### B. Soap (Section 27.2).

1. Soap is a mixture of the sodium and potassium salts of fatty acids produced by hydrolysis of animal fat.
2. Soap acts as a cleanser because the two ends of a soap molecule are different.
  - a. The hydrophilic carboxylate end dissolves in water.
  - b. The hydrophobic hydrocarbon tails solubilize greasy dirt.
  - c. In water, the hydrocarbon tails aggregate into micelles, where greasy dirt can accumulate.
3. Soaps can form scum when they encounter  $Mg^{2+}$  and  $Ca^{2+}$  salts.  
This problem is circumvented by detergents, which don't form insoluble metal salts.

#### 3. Phospholipids (Section 27.3).

1. Glycerophospholipids.
  - a. Glycerophospholipids consist of glycerol, two fatty acids (at C1 and C2 of glycerol), and a phosphate group bonded to an amino alcohol at C3 of glycerol.
  - b. Glycerophospholipids comprise the major lipids in cell membranes.  
The phospholipid molecules are organized into a lipid bilayer, which has polar groups on the inside and outside, and nonpolar tails in the middle.
2. Sphingomyelins.
  - a. Sphingomyelins have sphingosine as their backbone.
  - b. They are abundant in brain and nerve tissue.

#### III. Prostaglandins and other eicosanoids (Section 27.4).

##### A. Prostaglandins.

1. Prostaglandins are  $C_{20}$  lipids that contain a  $C_5$  ring and two side chains.
2. Prostaglandins are present in small amounts in all body tissues and fluids.
3. Prostaglandins have many effects: they lower blood pressure, affect blood platelet aggregation, affect kidney function and stimulate uterine contractions.

**B. Eicosanoids.**

1. Prostaglandins and thromboxanes make up the eicosanoid class of compounds.
2. Eicosanoids are named by their ring system, substitution pattern and number of double bonds.
3. Eicosanoids are biosynthesized from arachidonic acid, which is synthesized from linoleic acid.
  - a. The transformation from arachidonic acid is catalyzed by the cyclooxygenase (COX) enzyme.
  - b. One form of the COX enzyme catalyzes the usual functions, and a second form produces additional prostaglandin as a result of inflammation.

**III. Terpenoids (Section 27.5).****A. Facts about terpenoids.**

1. Terpenoids occur as essential oils in lipid extractions of plants.
2. Terpenoids are small organic molecules with diverse structures.
3. All terpenoids are structurally related.
  - a. Terpenoids arise from head-to-tail bonding of isopentenyl diphosphate units.
  - b. Carbon 1 is the head, and carbon 4 is the tail.
4. Terpenoids are classified by the number of five-carbon multiples they contain.
  - a. Monoterpenoids are synthesized from two five-carbon units.
  - b. Sesquiterpenoids are synthesized from three five-carbon units.
  - c. Larger terpenoids occur in both animals and plants.

**B. Biosynthesis of terpenoids.**

1. Nature uses the isoprene equivalent isopentenyl diphosphate (IPP) to synthesize terpenoids.

IPP is biosynthesized by two routes that depend on the organism and the structure of the terpenoid.

  - i. The mevalonate pathway produces sesquiterpenoids and triterpenoids in most animals and plants.
  - ii. The 1-deoxyxylulose 5-phosphate pathway gives monoterpenoids, diterpenoids, and tetraterpenoids.
2. The mevalonate pathway.
  - a. Acetyl CoA undergoes Claisen condensation to form acetoacetyl CoA.
  - b. Another acetyl CoA undergoes an aldol-like addition to acetoacetyl CoA to give (3S)-3-hydroxy-3-methylglutaryl CoA (HMG-CoA).
  - c. HMG CoA is reduced by NADPH, yielding (*R*)-mevalonate.
  - d. Phosphorylation and decarboxylation convert (*R*)-mevalonate to IPP.
3. Conversion of IPP to terpenoids.
  - a. IPP is isomerized to dimethylallyl diphosphate (DMAPP) by a carbocation pathway.
  - b. The C=C bond of IPP displaces the PPO<sup>-</sup> group of dimethylallyl diphosphate, to form geranyl diphosphate, the precursor to all monoterpenoids.
  - c. Geranyl diphosphate reacts with IPP to yield farnesyl diphosphate, the precursor to sesquiterpenoids.
  - d. GPP is isomerized and cyclizes on the way to yielding many monoterpenoids.

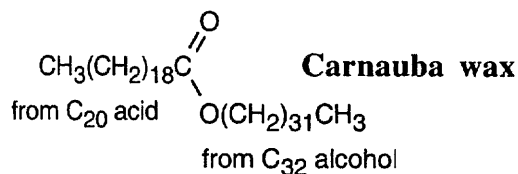
**IV. Steroids (Sections 27.6 – 27.7).****A. Stereochemistry of steroids (Section 27.6).**

1. Two cyclohexane rings can be joined either *cis* or *trans*.
  - a. In a *trans*-fused ring, the groups at the ring junction are *trans*.
  - b. In *cis*-fused rings, the groups at the ring junction are *cis*.
  - c. *Cis* ring fusions usually occur between rings A and B.
2. In both kinds of ring fusions, the angular methyl groups usually protrude above the rings.

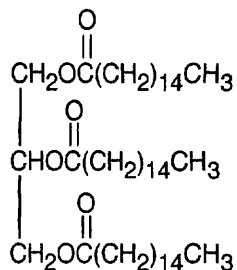
3. Steroids with A–B trans systems are more common.
  4. Substituents can be either axial or equatorial.  
Equatorial substituents are more favorable.
- B. Types of steroid hormones.
1. Sex hormones.
    - a. Androgens (testosterone, androsterone) are male sex hormones.
    - b. Estrogens (estrone, estradiol) and progestins are female sex hormones.
  2. Adrenocortical hormones.
    - a. Mineralocorticoids (aldosterone) regulate cellular  $\text{Na}^+$  and  $\text{K}^+$  balance.
    - b. Glucocorticoids (hydrocortisone) regulate glucose metabolism and control inflammation.
  3. Synthetic steroids.  
Oral contraceptives and anabolic steroids are examples of synthetic steroids.
- C. Biosynthesis of steroids (Section 27.7).
1. All steroids are biosynthesized from squalene.
  2. Squalene is first epoxidized to form 2,3-oxidosqualene.
  3. Nine additional steps are needed to form lanosterol.
    - a. The first several steps are cyclization reactions.
    - b. The last steps are hydride and methyl shifts.
  4. Other enzymes convert lanosterol to cholesterol.

### Solutions to Problems

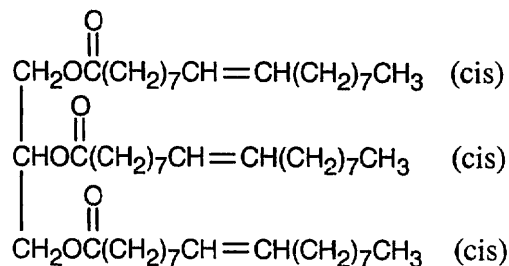
#### 27.1



#### 27.2



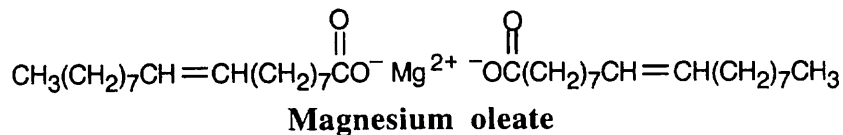
**Glyceryl tripalmitate**



**Glyceryl trioleate**

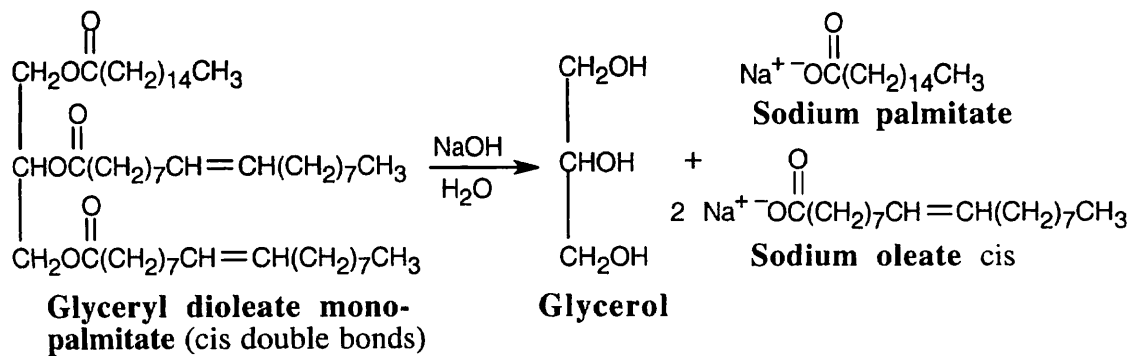
Glyceryl tripalmitate is higher melting because it is saturated.

27.3

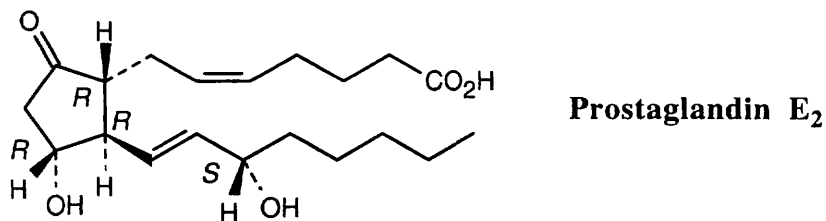


The double bonds are *cis*.

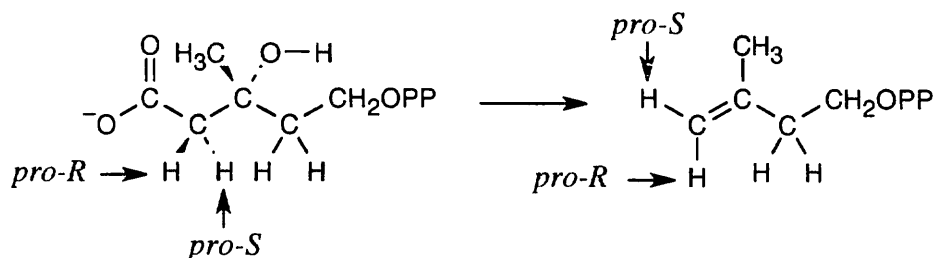
27.4



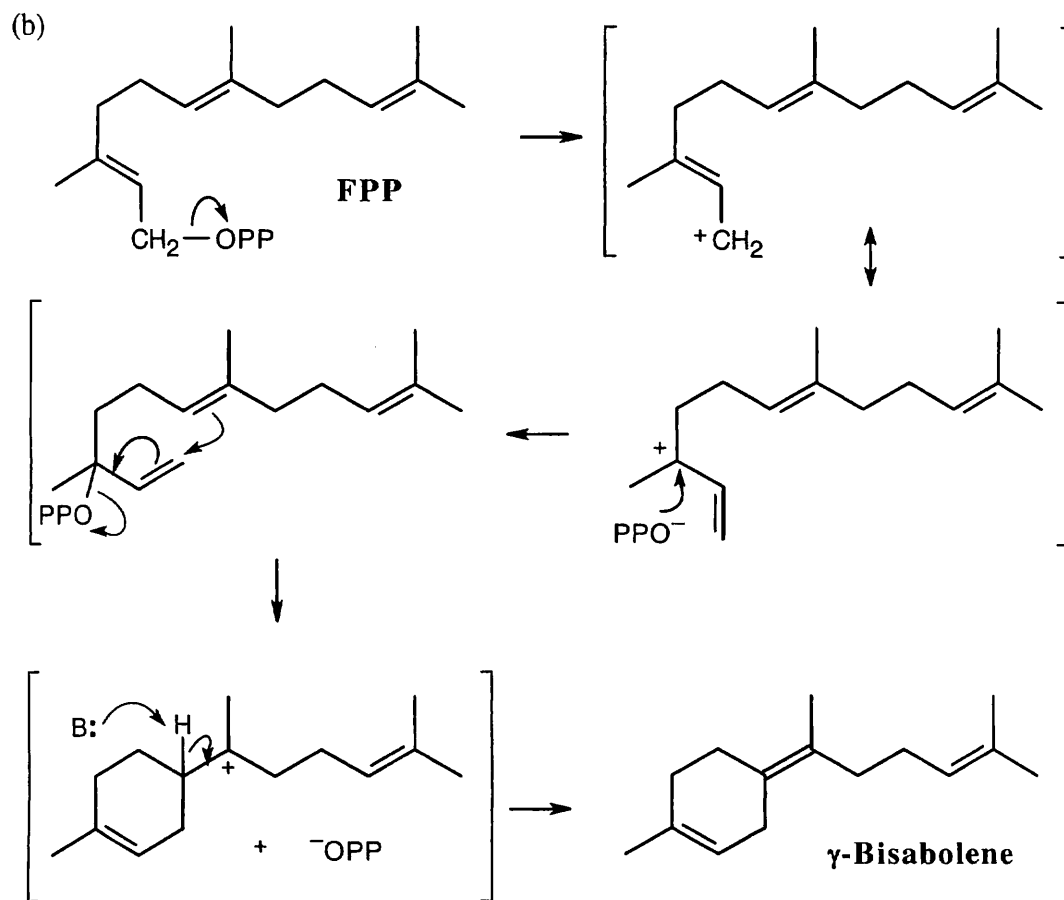
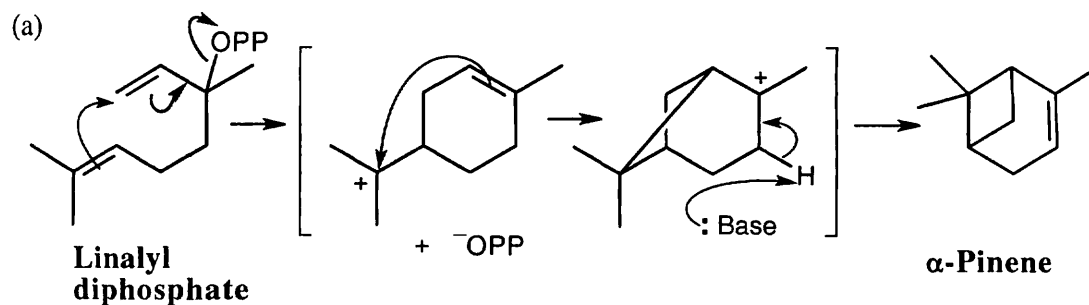
27.5



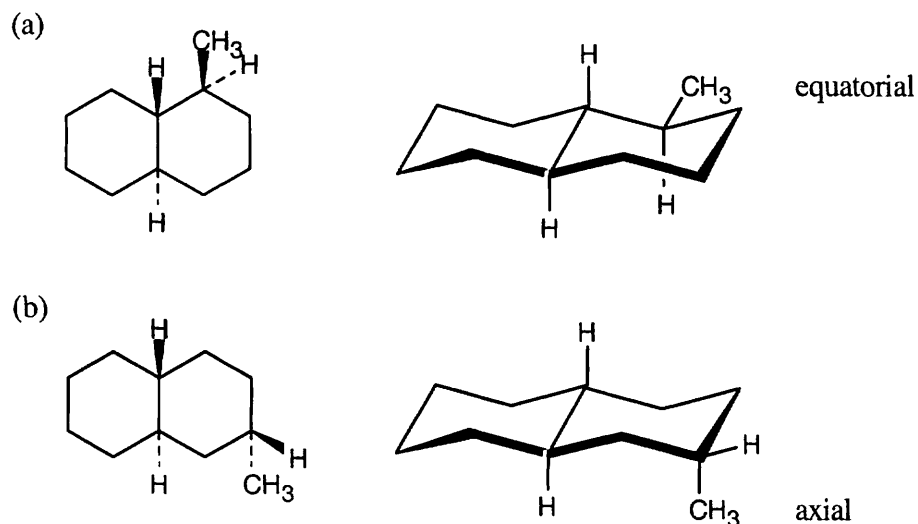
**27.6** The *pro-S* hydrogen (green) ends up *cis* to the methyl group, and the *pro-R* hydrogen (red) ends up *trans*.



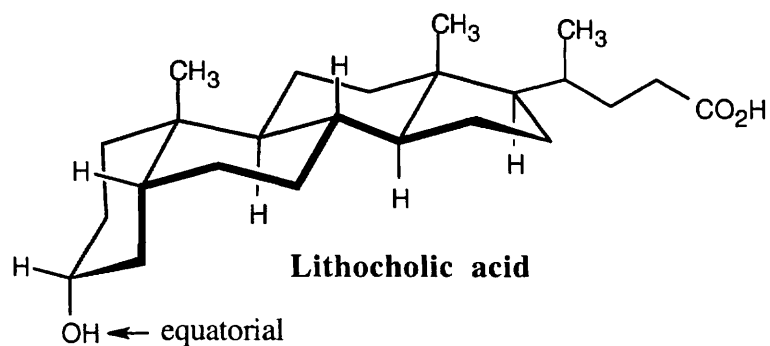
- 27.7 As described in Worked Example 27.1, draw the diphosphate precursor so that it resembles the product. Often, the precursor is linalyl diphosphate, which results from isomerization of geranyl diphosphate (the mechanism is shown in Figure 27.10). In (a), it's not easy to see the relationship, but once you've arrived at the product, rotate the structure.



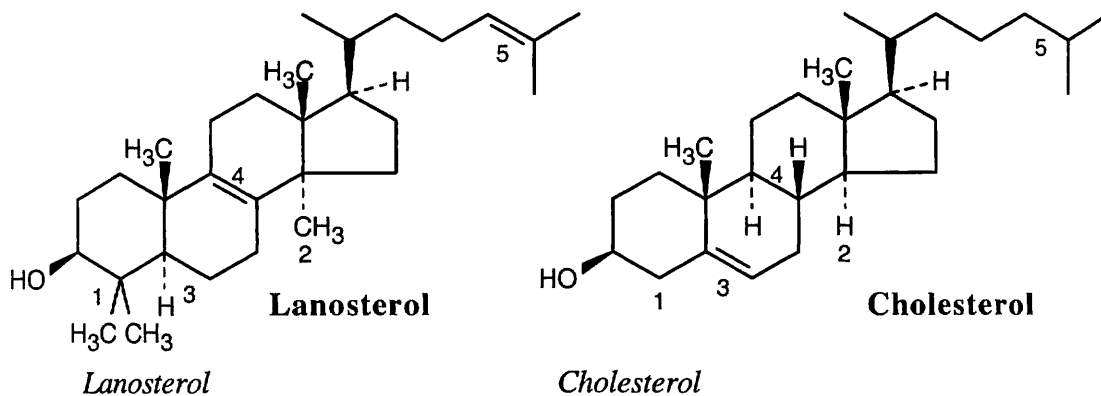
- 27.8** Both ring systems are trans-fused, and both hydrogens at the ring junctions are axial. Refer back to Chapter 4 if you have trouble remembering the relationships of substituents on a cyclohexane ring.



- 27.9** Draw the three-dimensional structure and note the relationship of the hydroxyl group to groups whose orientation is known.



## 27.10

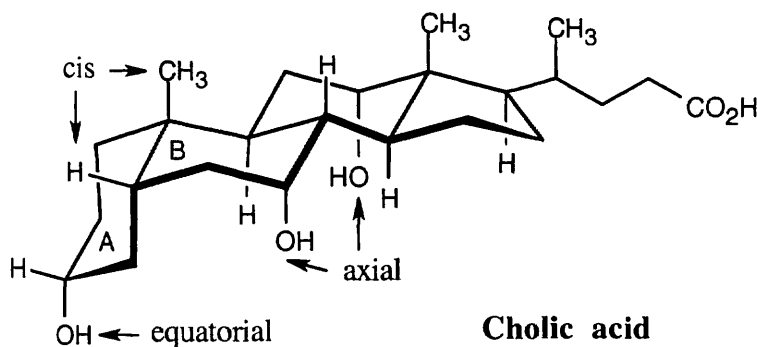


1. Two methyl groups at C4.
2. One methyl group at C14.
3. C5-C6 single bond.
4. C8-C9 double bond.
5. Double bond in side chain

1. Two hydrogens at C4.
2. One hydrogen at C14.
3. C5-C6 double bond
4. C8-C9 single bond.
5. Saturated side chain.

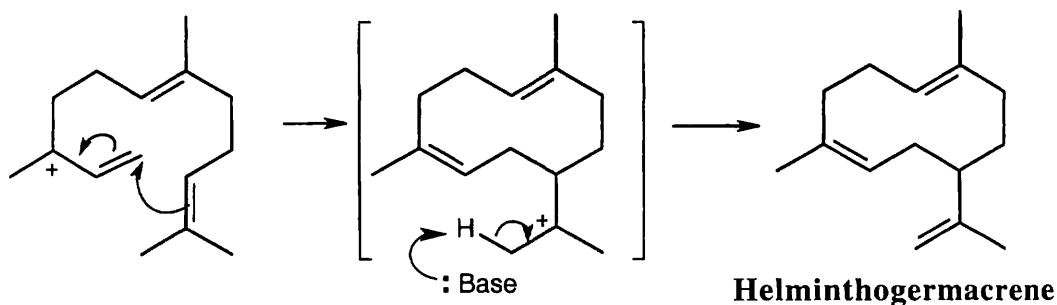
## Visualizing Chemistry

## 27.11



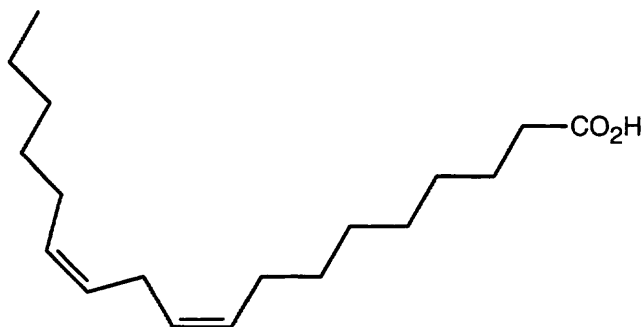
Cholic acid is an A-B cis steroid because the groups at the fusion of ring A and ring B have a cis relationship.

## 27.12



Draw farnesyl diphosphate in the configuration that resembles the product, then draw its allylic isomer (the mechanism for the formation of the isomer is shown in Problem 27.7). In this reaction, a cyclization, followed by loss of a proton to form the double bond, gives helminthogermacrene.

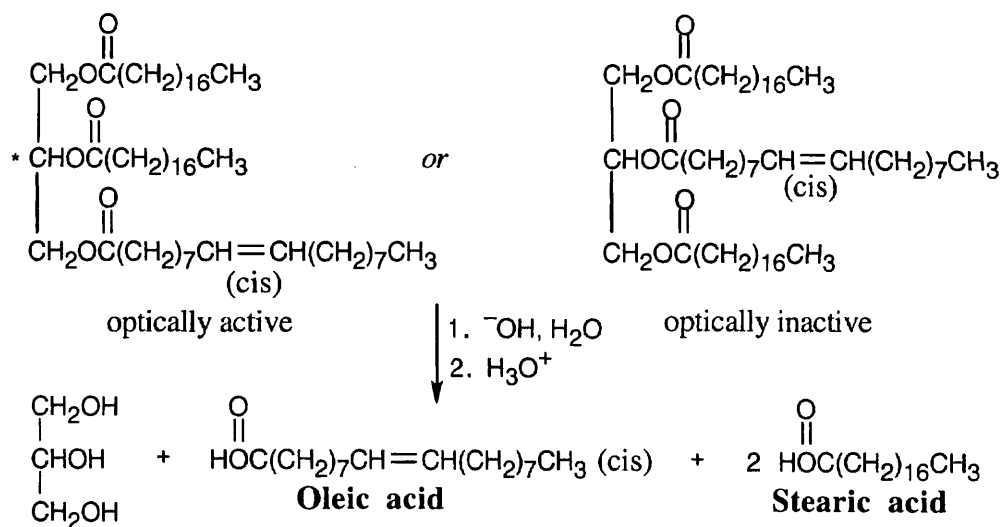
26.13

**Linoleic acid**

A polyunsaturated fat such as linoleic acid is more likely to be found in peanut oil.

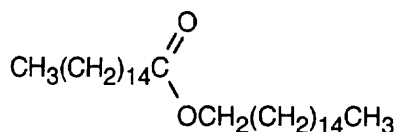
**Additional Problems**

27.14



Four different groups are bonded to the central glycerol carbon atom in the optically active fat.

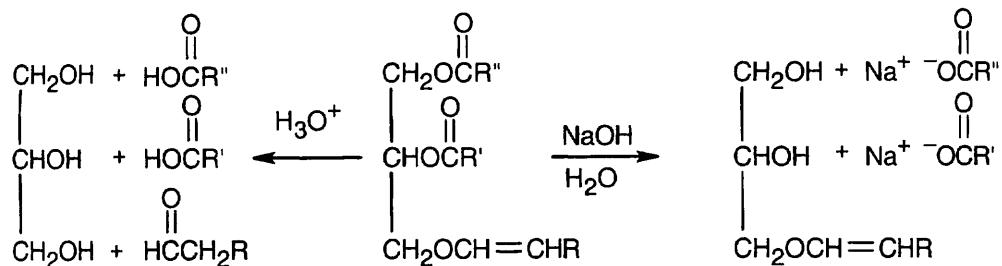
27.15

**Cetyl palmitate**

**27.16** Fats and plasmalogens are both esters of a glycerol molecule that has carboxylic acid ester groups at C1 and C2. The third group bonded to glycerol, however, differs with the type of lipid: a fat has a carboxylic acid ester at C3, and a plasmalogen has a vinyl ether in that location.

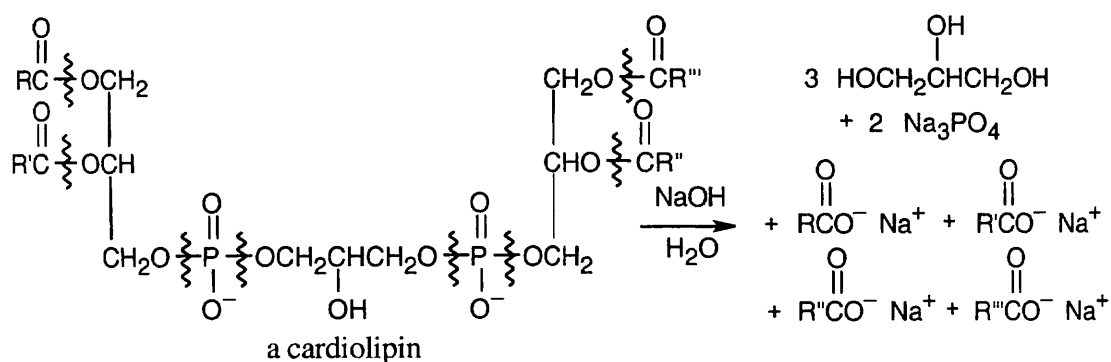


## 27.17



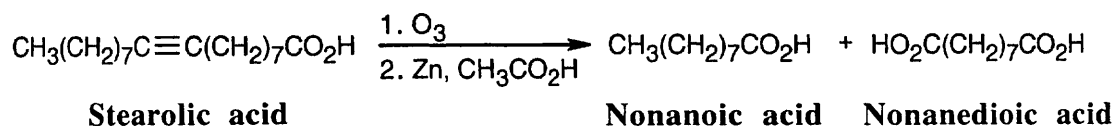
Basic hydrolysis cleaves the carboxylic acid ester bonds but doesn't affect the ether bond. Acidic hydrolysis cleaves all three groups bonded to glycerol and produces an aldehyde from the vinyl ether group.

## 27.18



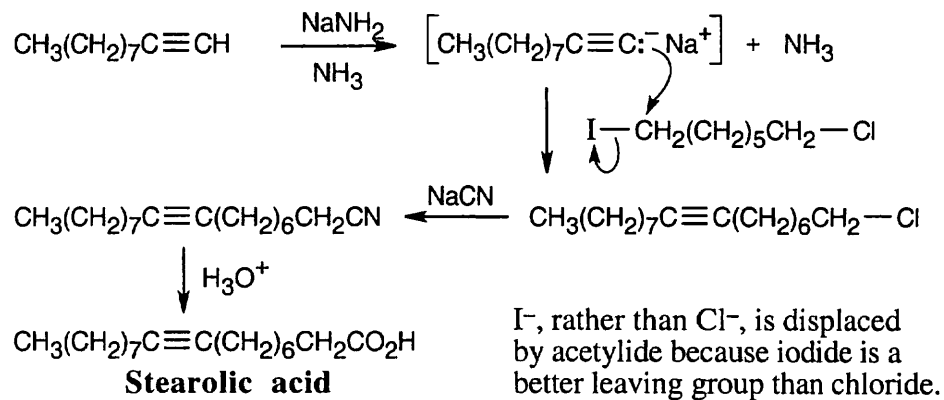
Saponification of a cardiolipin yields 4 different carboxylates, 3 equivalents of glycerol and two equivalents of phosphate.

## 27.19

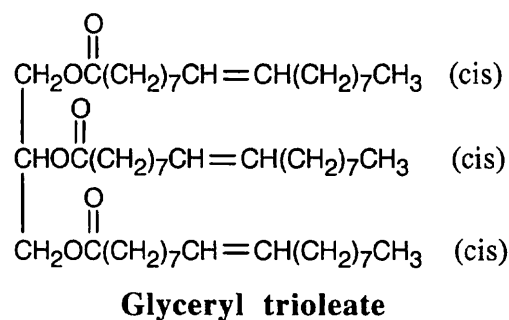


Stearolic acid contains a triple bond because the products of ozonolysis are carboxylic acids.

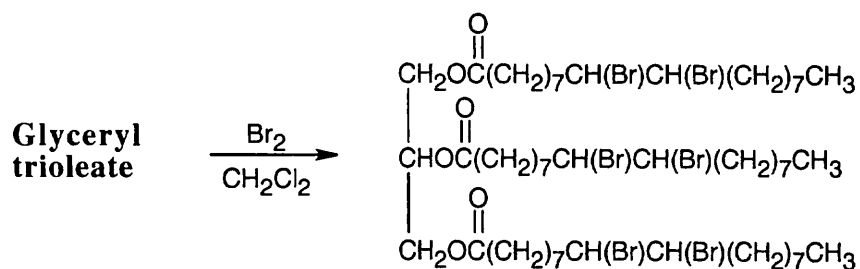
## 27.20



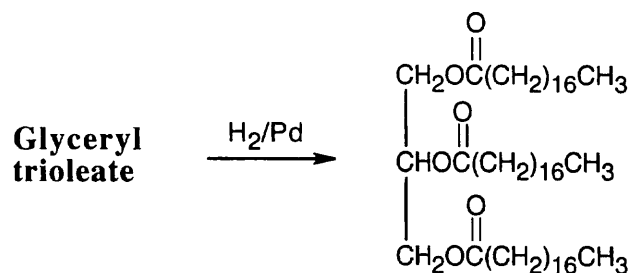
## 27.21

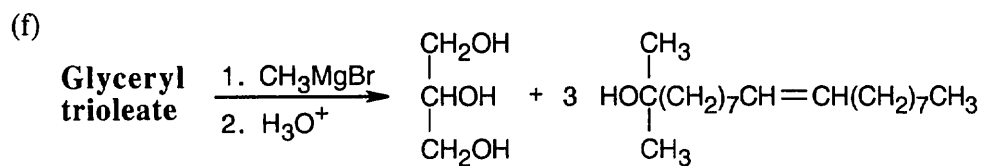
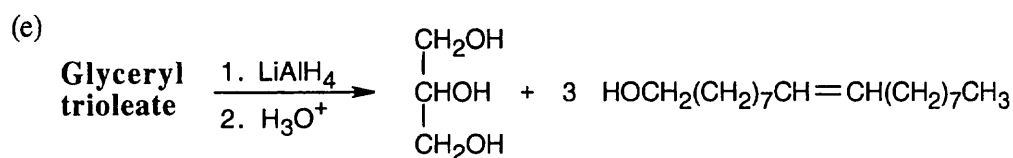
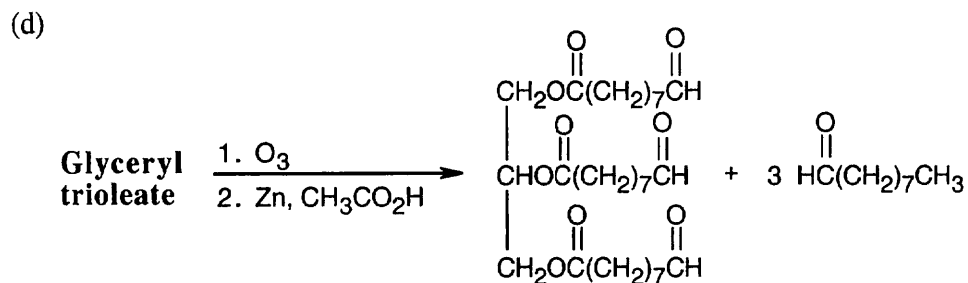
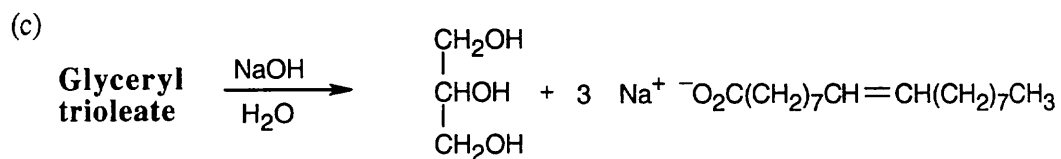


(a)

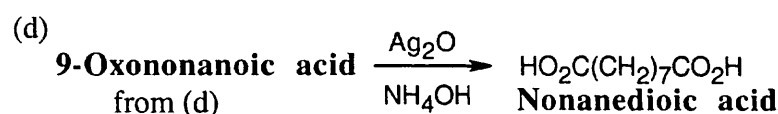
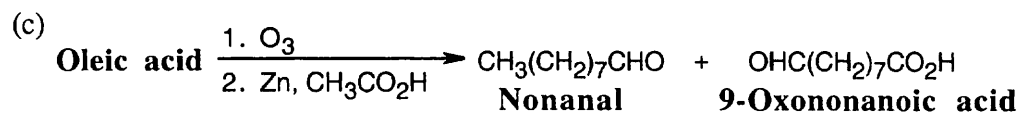
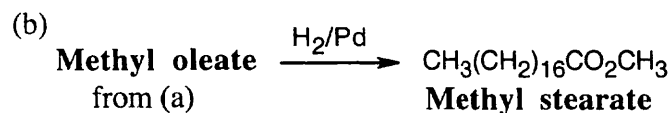
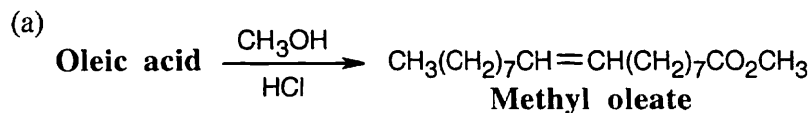
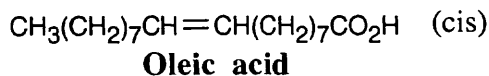


(b)

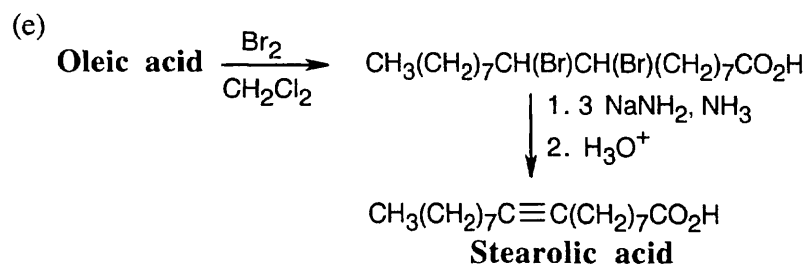




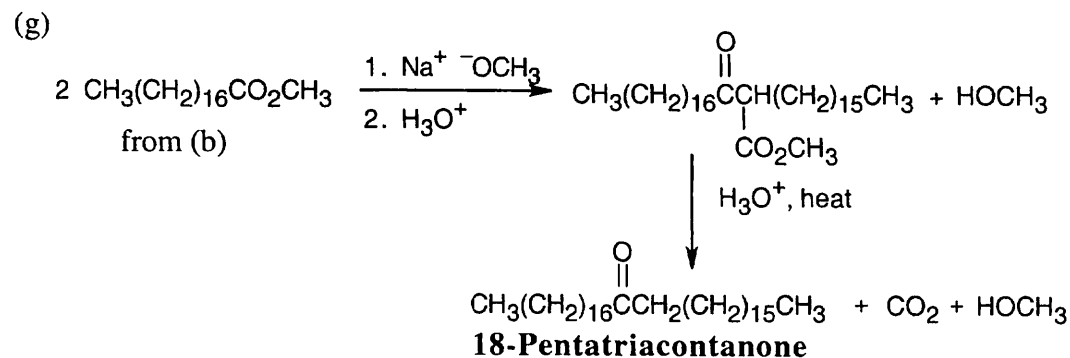
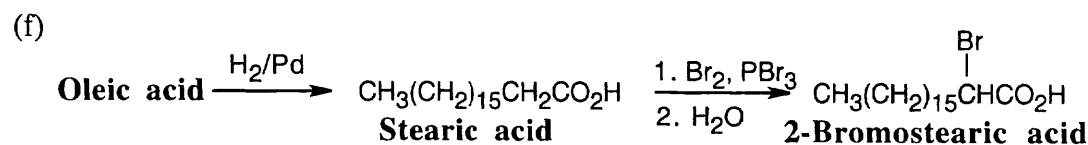
27.22



This is a Tollens oxidation.

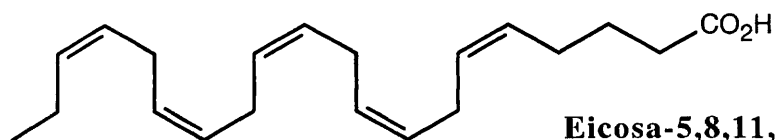


Three equivalents of the base are needed because one of them is neutralized by the carboxylic acid.



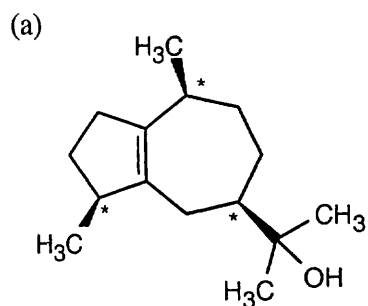
This synthesis uses a Claisen condensation, followed by a  $\beta$ -keto ester decarboxylation.

27.23

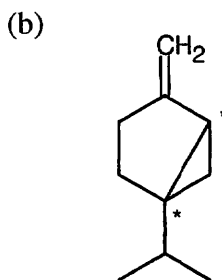
**Eicosa-5,8,11,14,17-pentaenoic acid**

27.24–27.26

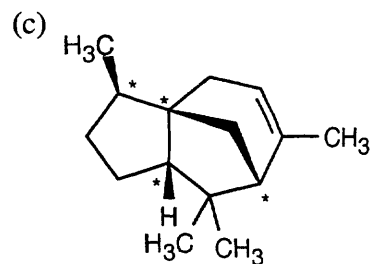
Remember that a compound with  $n$  chirality centers can have a maximum of  $2^n$  stereoisomers. Not all the possible stereoisomers of these compounds are found in nature or can be synthesized. Some stereoisomers have highly strained ring fusions; others contain 1,3-diaxial interactions.

**Guaiol**

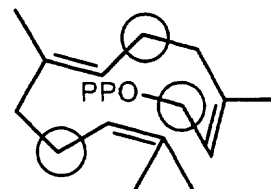
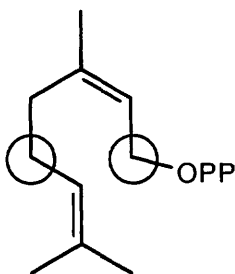
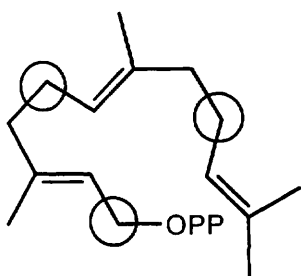
(8 possible stereoisomers)

**Sabinene**

(4 possible stereoisomers)

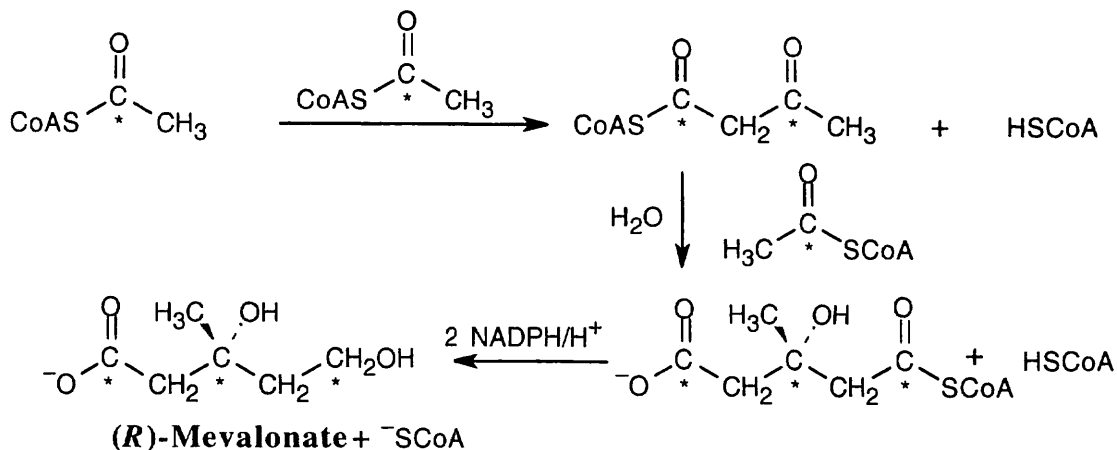
**Cedrene**

(16 possible stereoisomers)

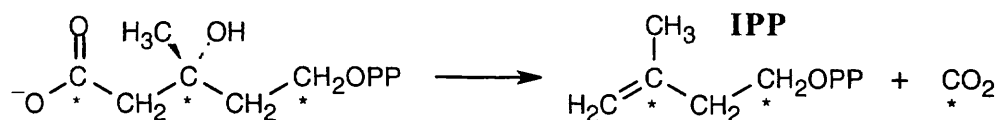


If carbon 1 of each diphosphate were isotopically labeled, the labels would appear at the circled positions of the terpenoids.

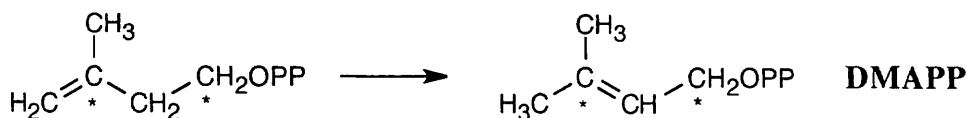
## 27.27



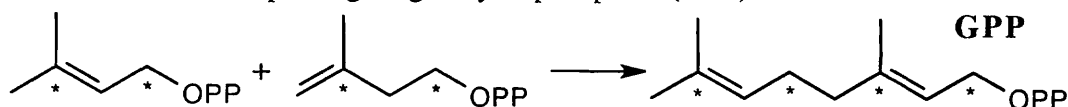
**27.28** First, mevalonate 5-diphosphate is converted to isopentenyl diphosphate (IPP) and dimethylallyl diphosphate (DMAPP).



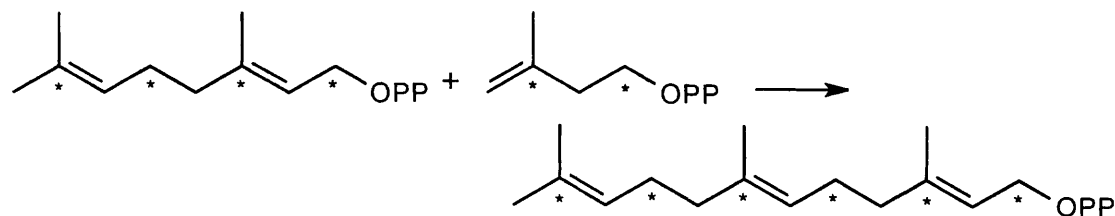
IPP is isomerized to DMAPP.



DMAPP and IPP couple to give geranyl diphosphate (GPP).

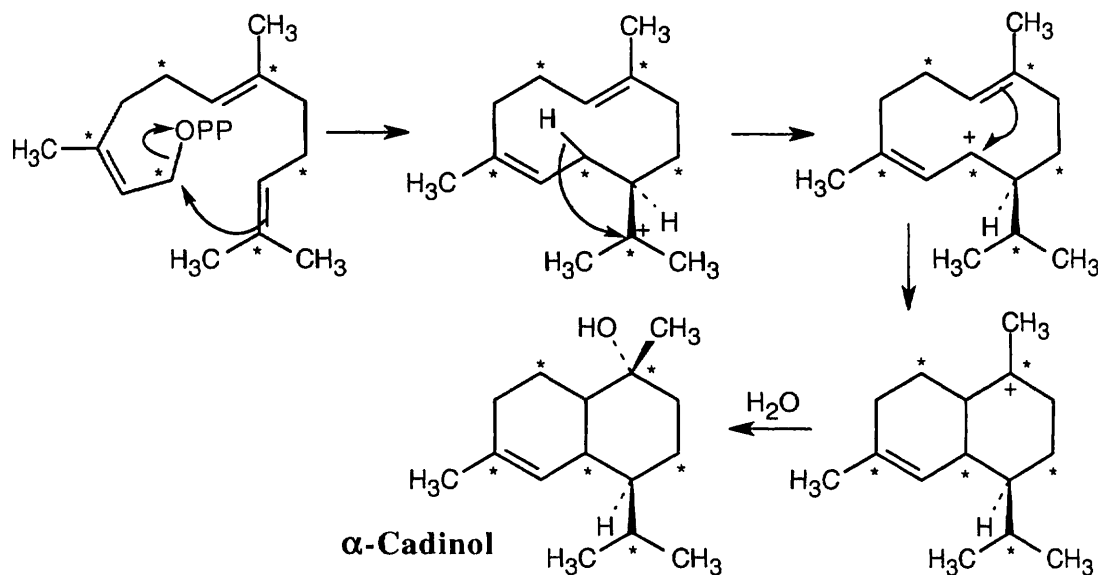


A second molecule of IPP adds to GPP to give farnesyl diphosphate, the precursor to  $\alpha$ -cadinene.

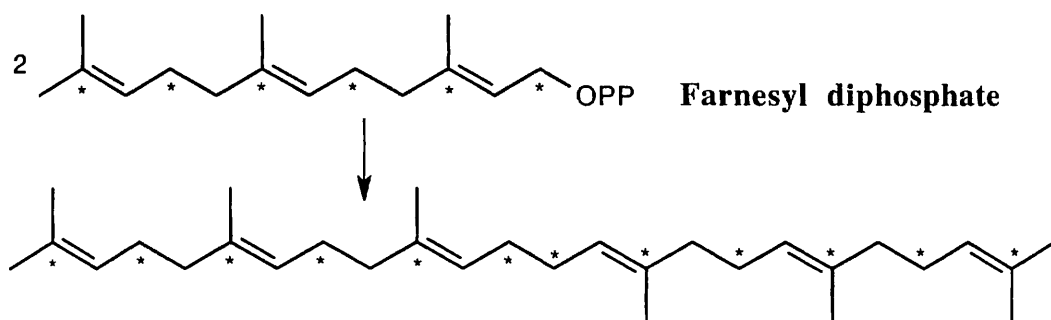


Notice that the  $^{14}\text{C}$  labels are located at two different positions: (1) at the carbon to which  $-\text{OPP}$  was bonded; (2) at the carbon bonded to the methyl group.

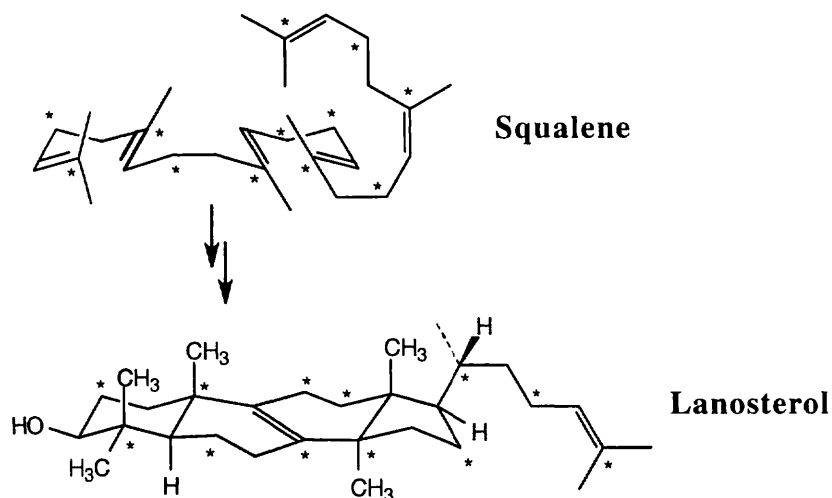
Now, arrange farnesyl diphosphate to resemble the skeleton of  $\alpha$ -cadinene. The first step in the reaction sequence is formation of the allylic isomer of FPP; the mechanism was shown in Problem 27.7.



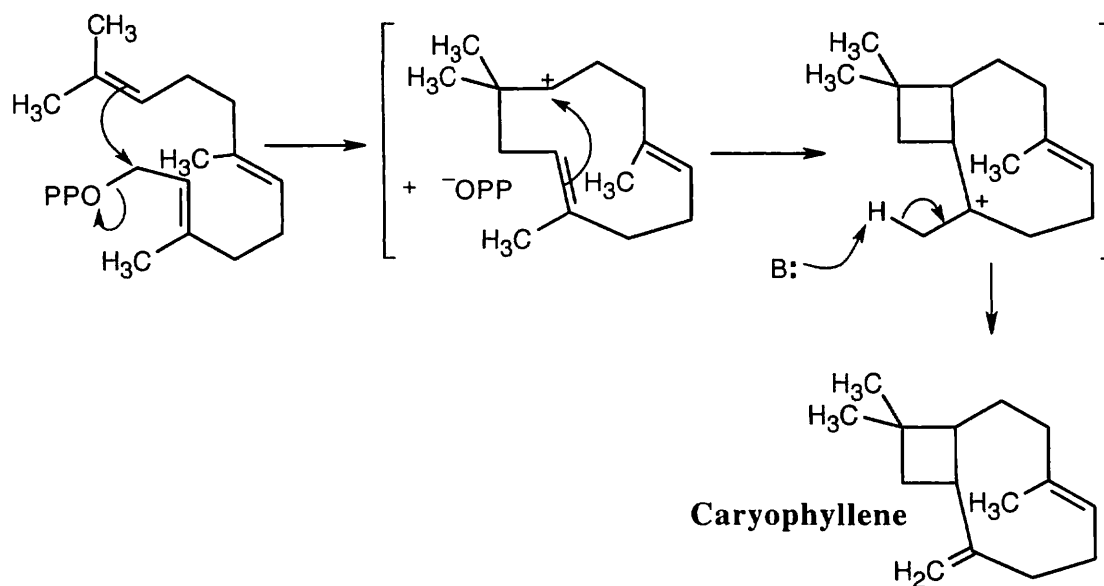
**27.29** Farnesyl diphosphate (from the previous problem) dimerizes to form squalene.



**27.30** Squalene is converted to lanosterol by the series of steps pictured in Figure 27.14.



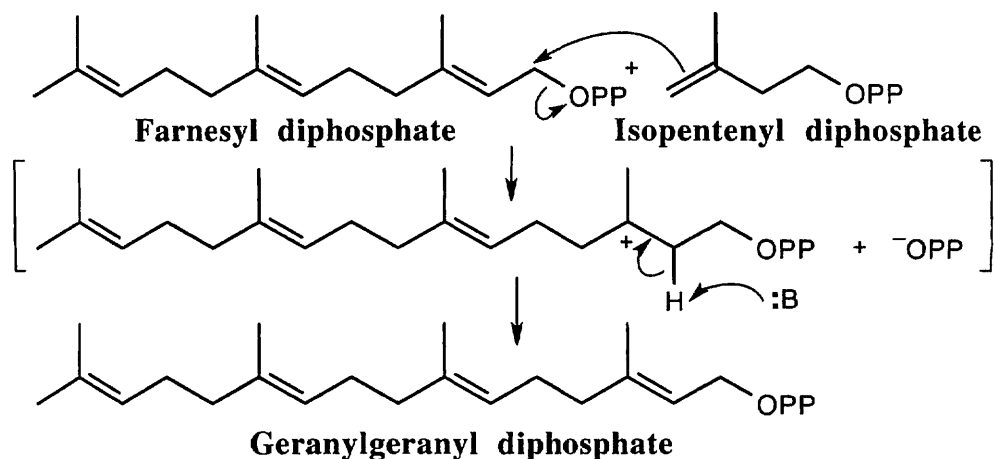
**27.31**



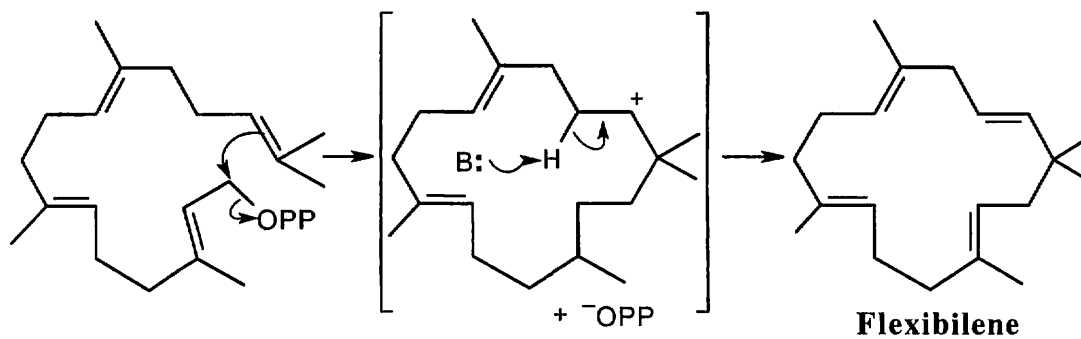
Draw farnesyl diphosphate in the correct orientation in order to make this problem much easier. Internal displacement of  $^-OPP$  by the electrons of one double bond is followed by attack of the electrons of the second double bond on the resulting carbocation. Loss of a proton from the carbon next to the resulting carbocation produces the double bond.



## 27.32

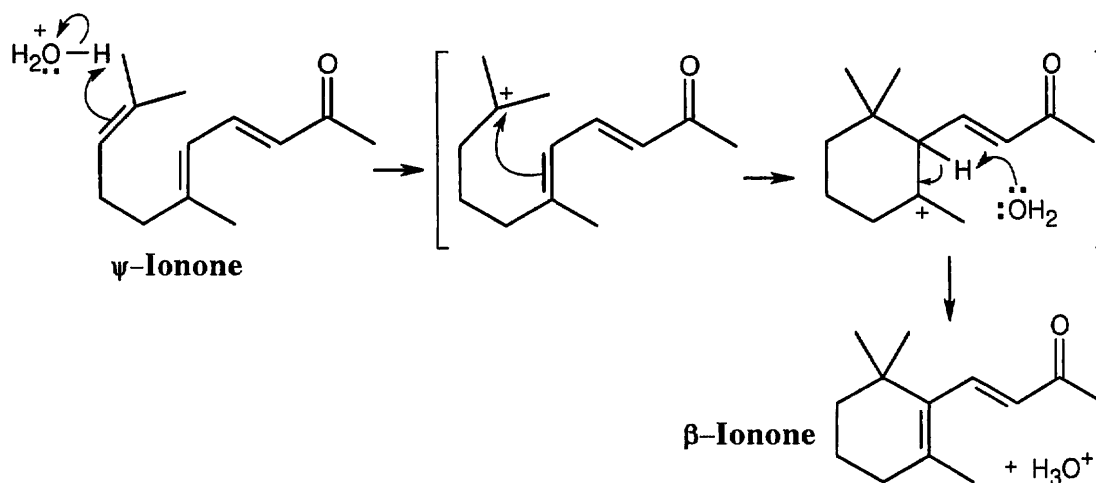


The precursor to flexibilene is formed from the reaction of farnesyl diphosphate and isopentenyl diphosphate.



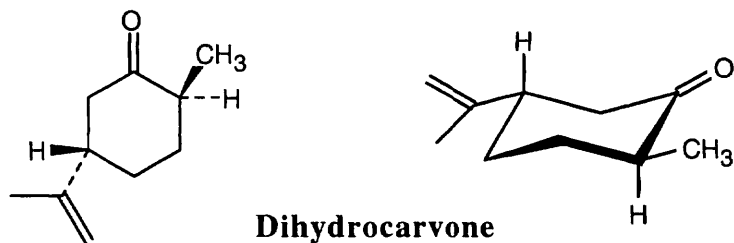
The precursor cyclizes by the now-familiar mechanism to produce flexibilene.

## 27.33



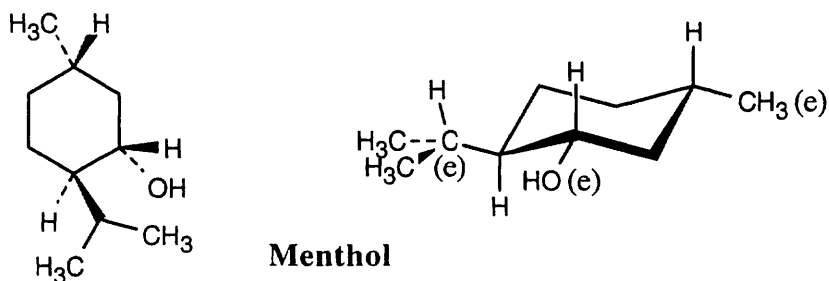
Acid protonates a double bond, and the electrons of a second double bond attack the carbocation. Deprotonation yields  $\beta$ -ionone.

27.34



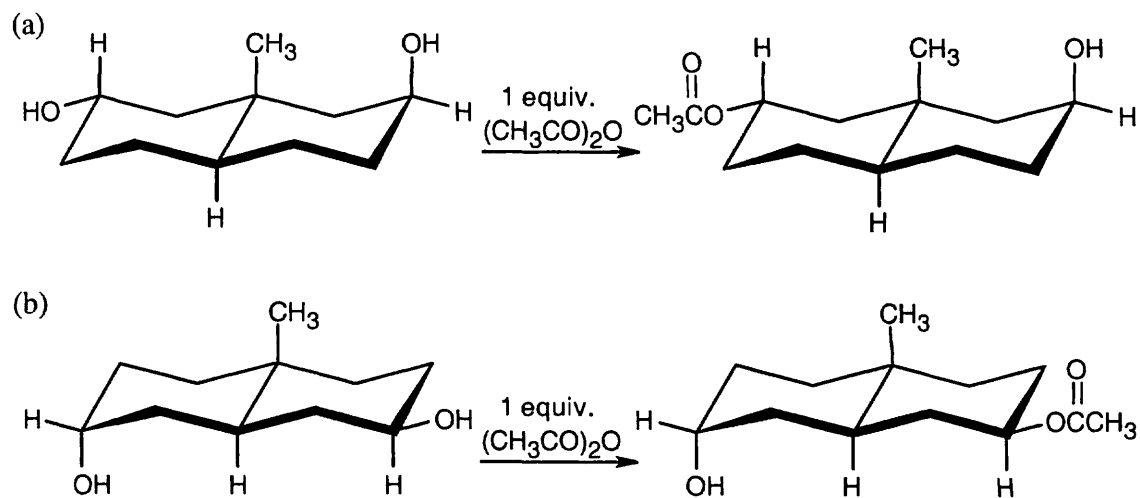
The two hydrocarbon substituents are equatorial in the most stable chair conformation.

27.35



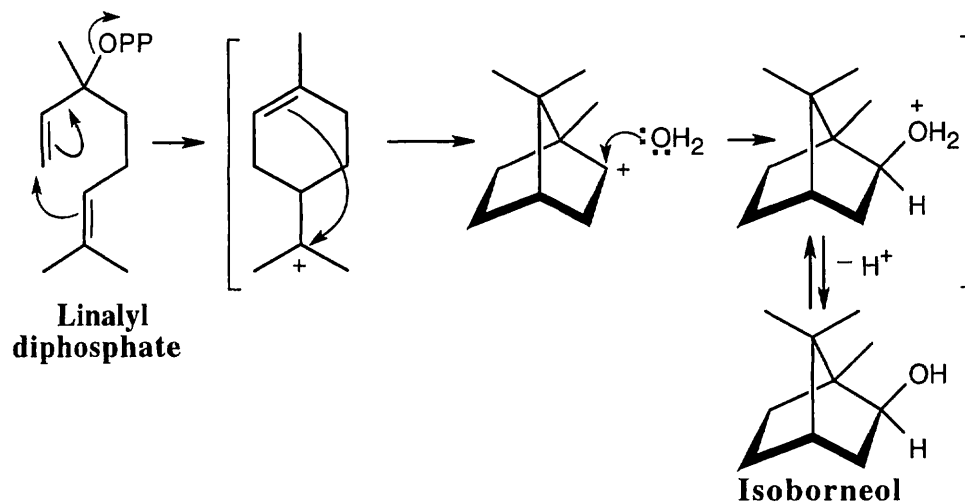
All ring substituents are equatorial in the most stable conformation of menthol.

27.36



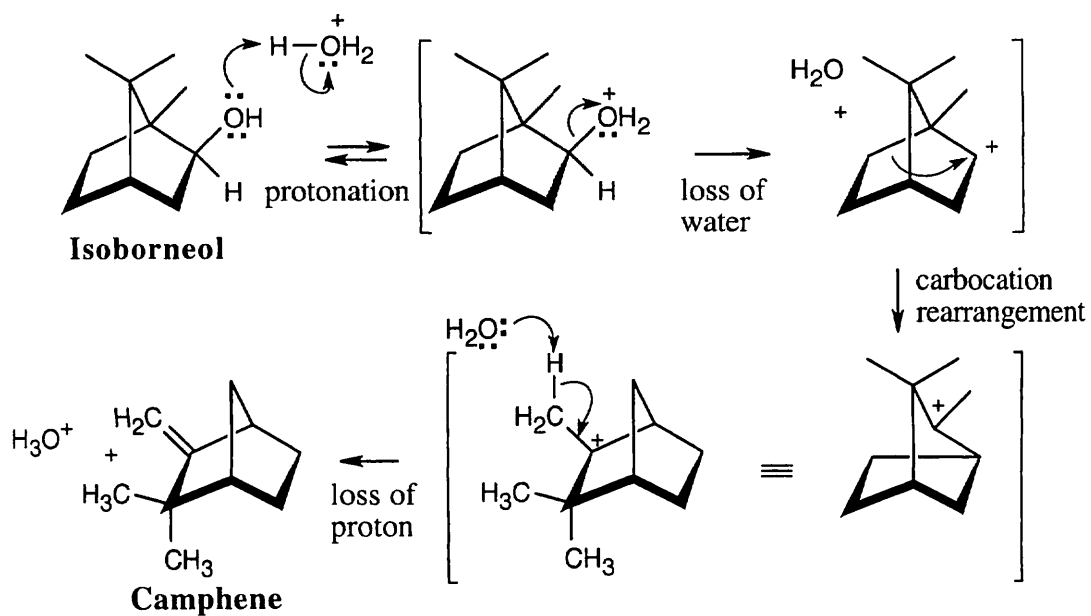
As always, use the stereochemistry of the groups at the ring junction to label the other substituents.

## 27.37



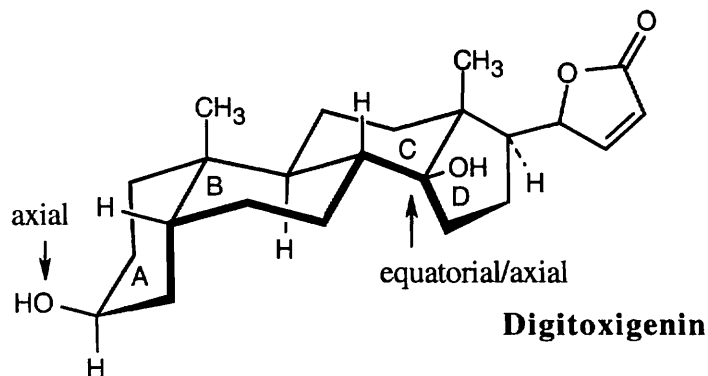
The cyclizations produce a secondary carbocation, which reacts with water to yield the secondary alcohol.

## 27.38



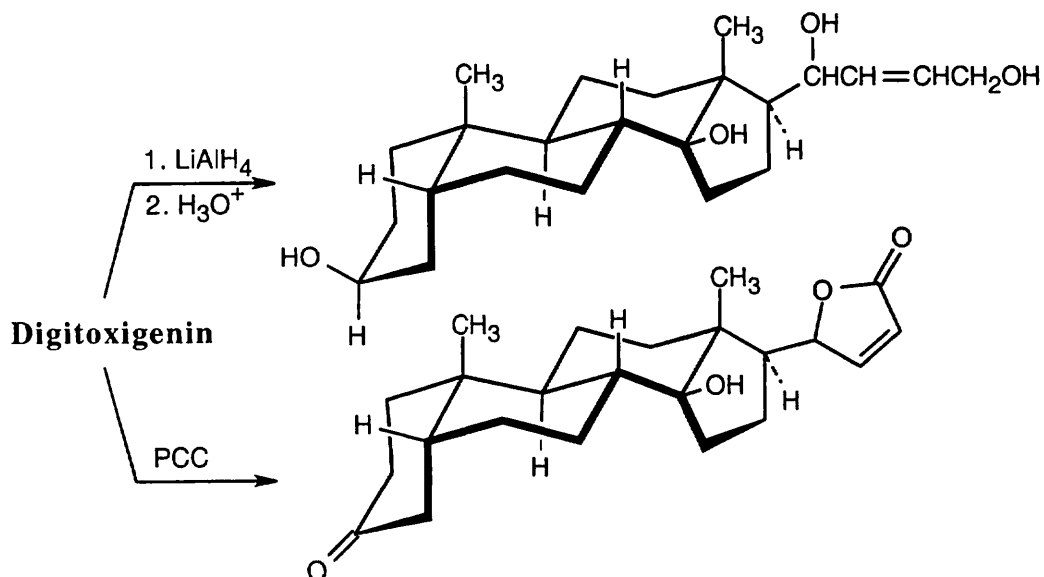
The key step is the carbocation rearrangement, which occurs by the migration of one of the ring bonds.

27.39



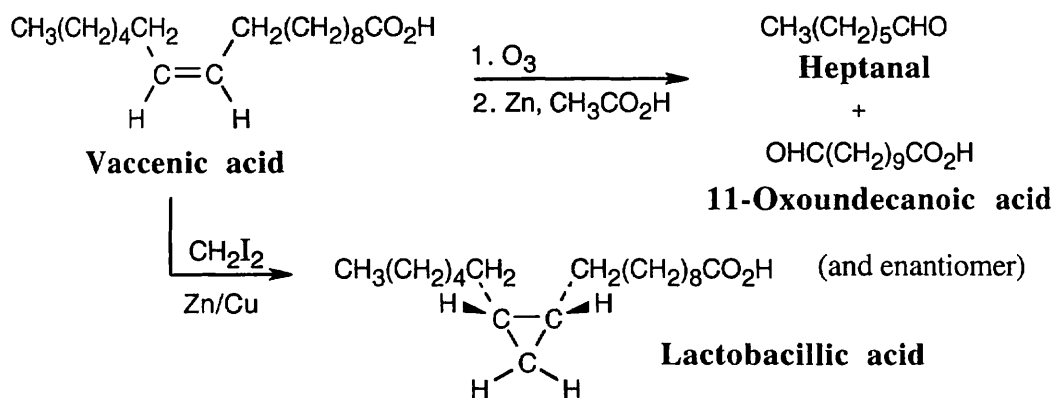
The hydroxyl group in ring A is axial, and the hydroxyl group at the ring C–D fusion is equatorial to ring C and axial to ring D. Notice that digitoxigenin has both an A–B cis ring fusion and a C–D cis ring fusion.

27.40

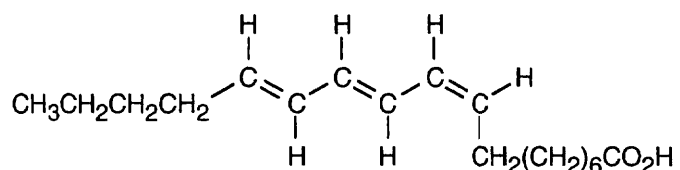


Lithium aluminum hydride reduces the lactone ring to a diol. PCC oxidizes only one hydroxyl group because the second group is tertiary.

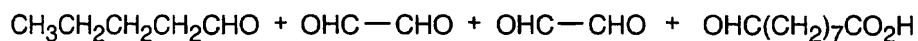
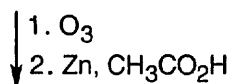
27.41



27.42

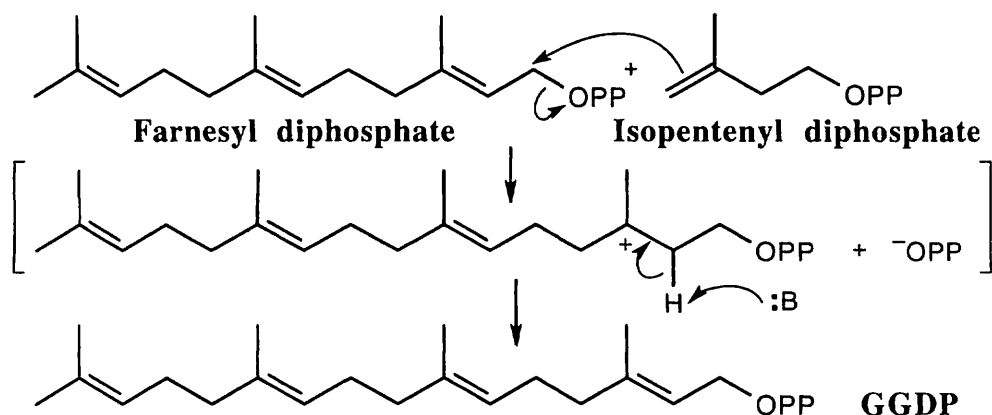


(9Z,11E,13E)-9,11,13-Octadecatrienoic acid  
(Eleostearic acid)

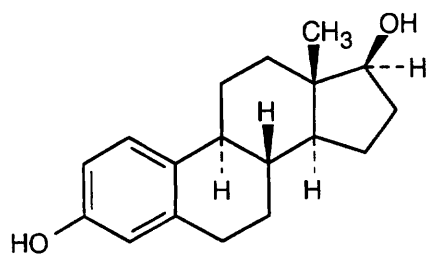
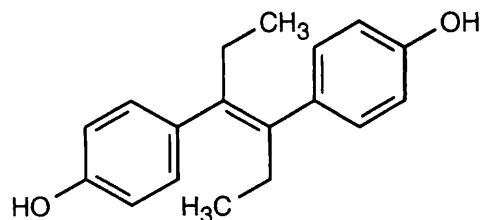


The stereochemistry of the double bonds can't be determined from the information given.

27.43 This mechanism also appears in Problem 27.32

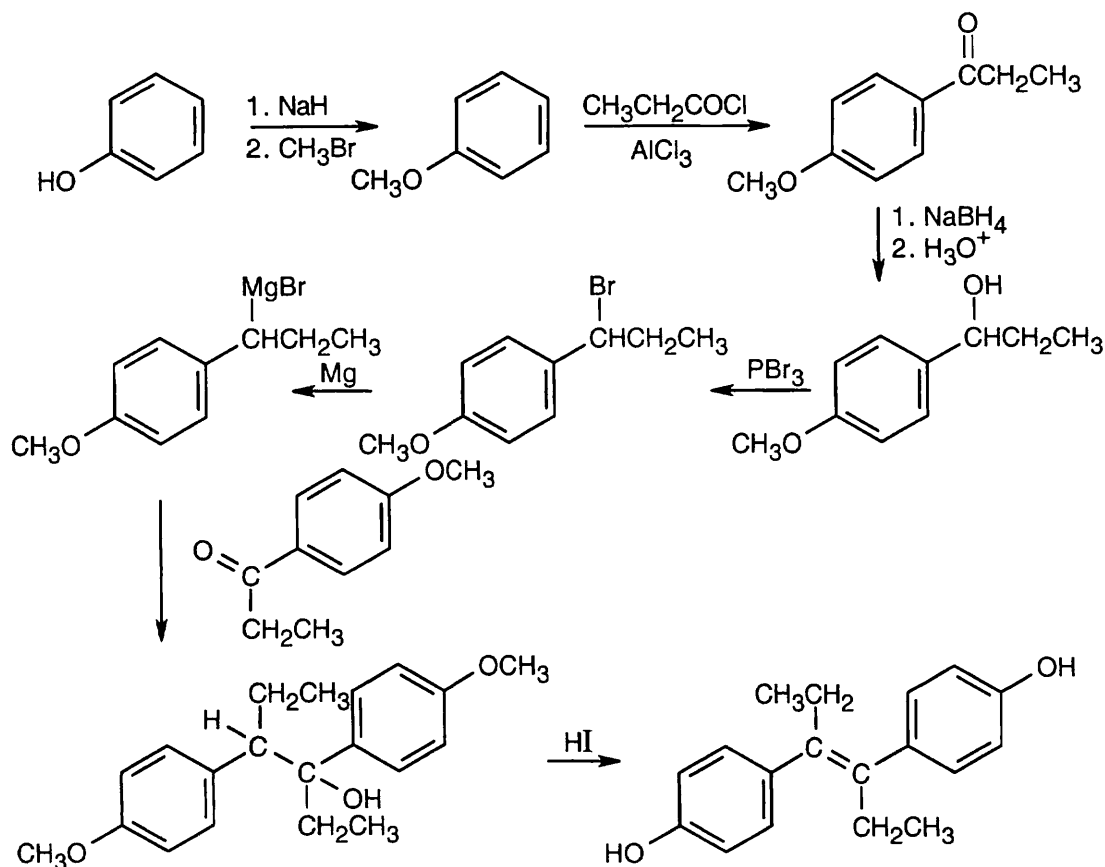


27.44

**Estradiol****Diethylstilbestrol**

Estradiol and diethylstilbestrol resemble each other in having similar carbon skeletons, in having a phenolic ring, and in being diols.

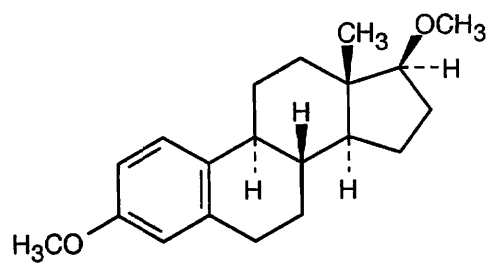
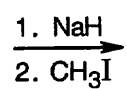
27.45

**Diethylstilbestrol**

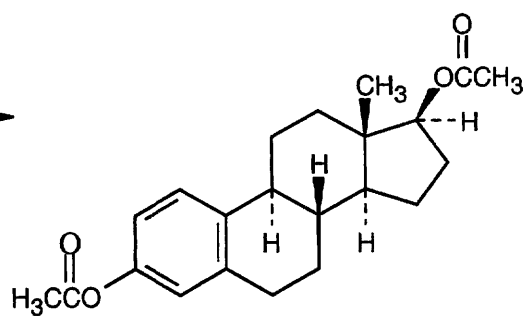
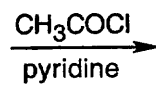
The key reaction is a Grignard reaction between two molecules that are both synthesized from phenol. Phenol is first converted to anisole, in order to avoid problems with acidic hydrogens interfering with the Grignard reaction. Next, anisole undergoes Friedel-Crafts acylation with propanoyl chloride. The resulting ketone is one of the Grignard components. The other component is prepared by reduction, bromination and treatment with magnesium of a quantity of the ketone. After the Grignard reaction, HI serves to both dehydrate the alcohol and cleave the methyl ether groups.

## 27.46

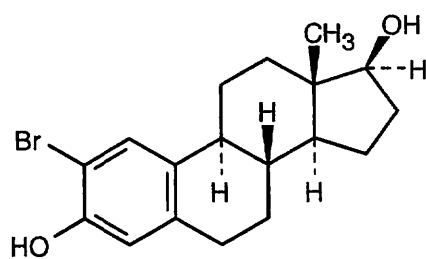
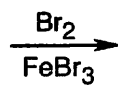
(a)

**Estradiol**

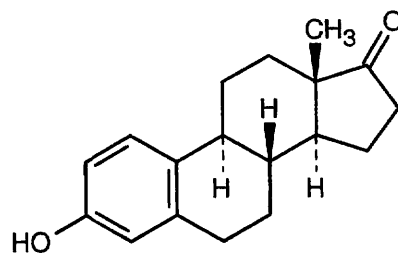
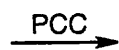
(b)

**Estradiol**

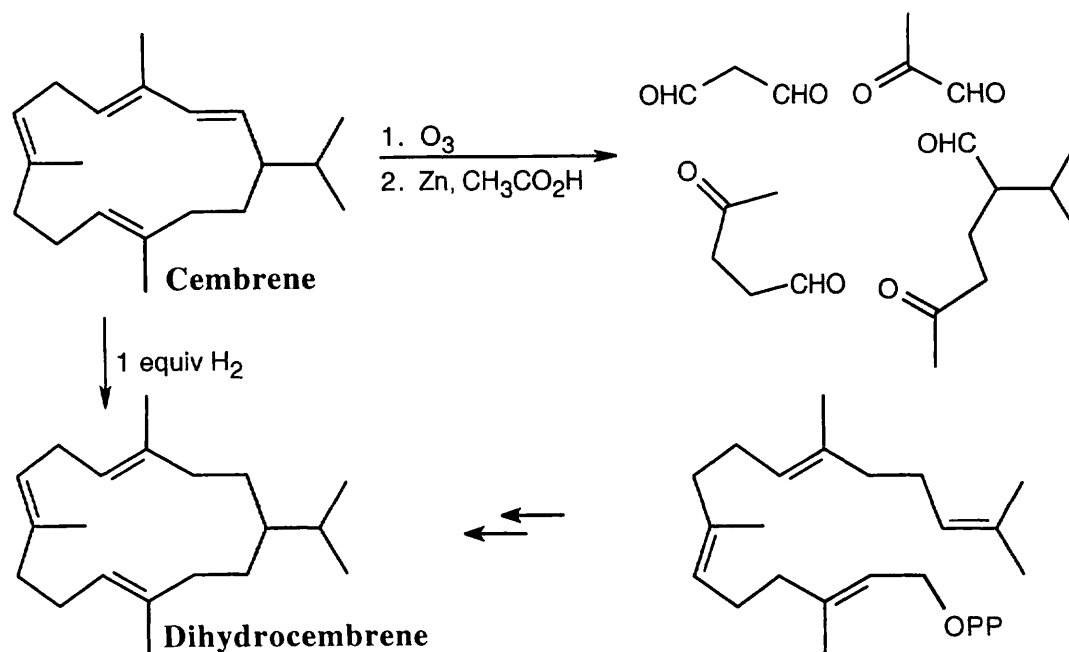
(c)

**Estradiol**

(d)

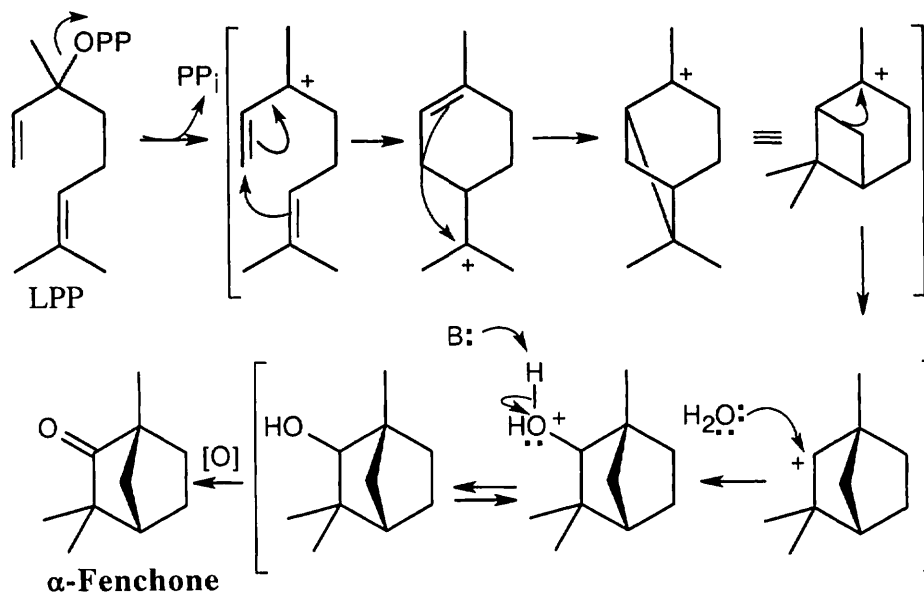
**Estradiol**

27.47



One equivalent of  $\text{H}_2$  hydrogenates the least substituted double bond. Dihydrocembrene has no ultraviolet absorption because it is not conjugated.

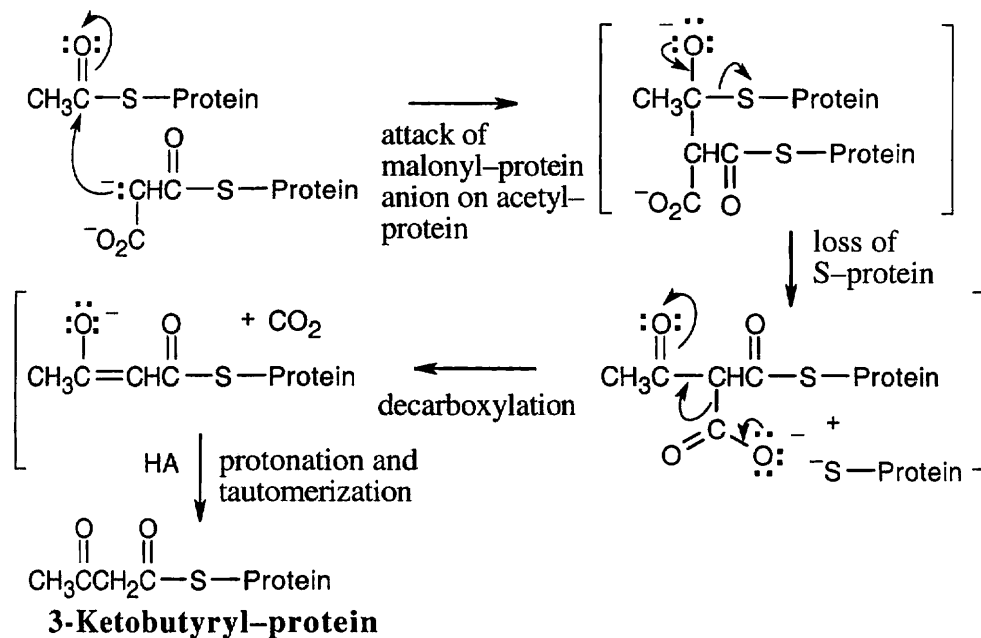
27.48



The mechanism follows the usual path: cyclization of linalyl diphosphate, followed by attack of the  $\pi$  electrons of the second double bond, produce an intermediate carbocation. A carbocation rearrangement occurs, and the resulting carbocation reacts with water to form an alcohol that is oxidized to give  $\alpha$ -fenchone.

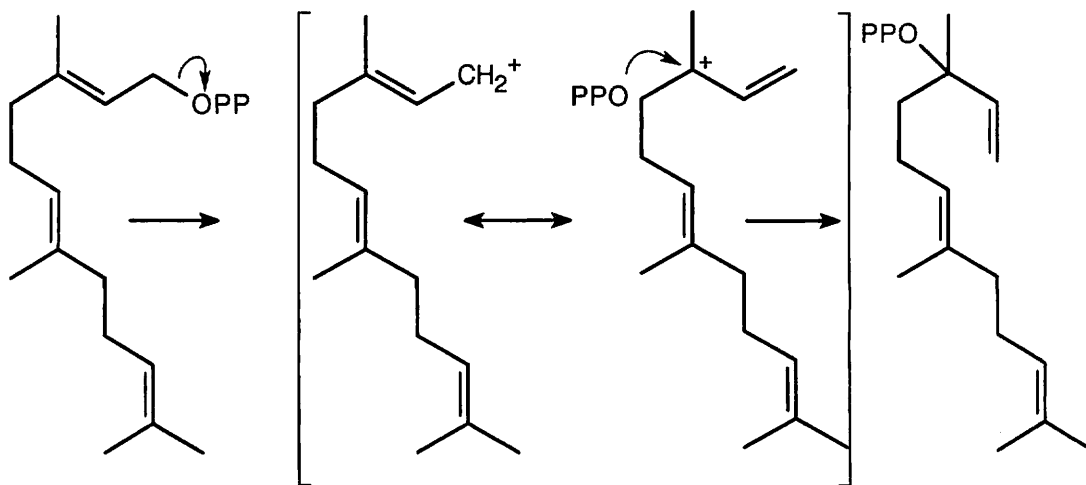


## 27.49

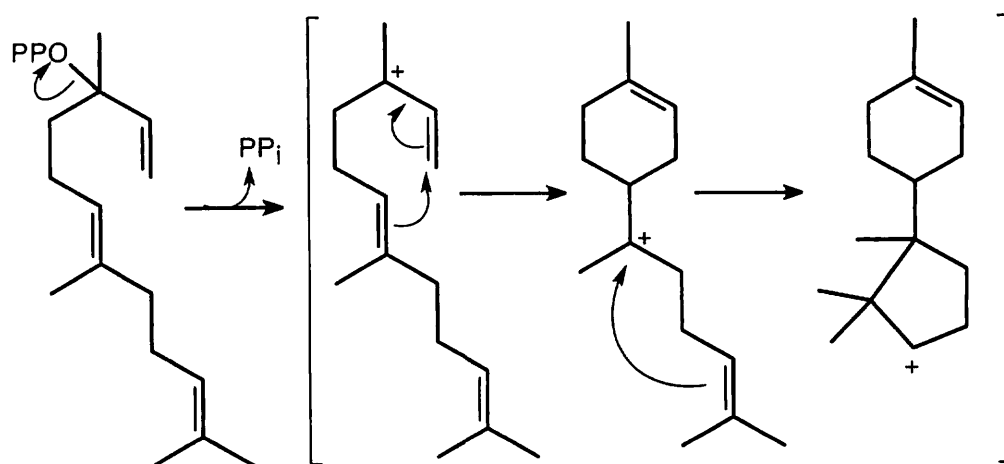


The first step of this sequence is a Claisen condensation.

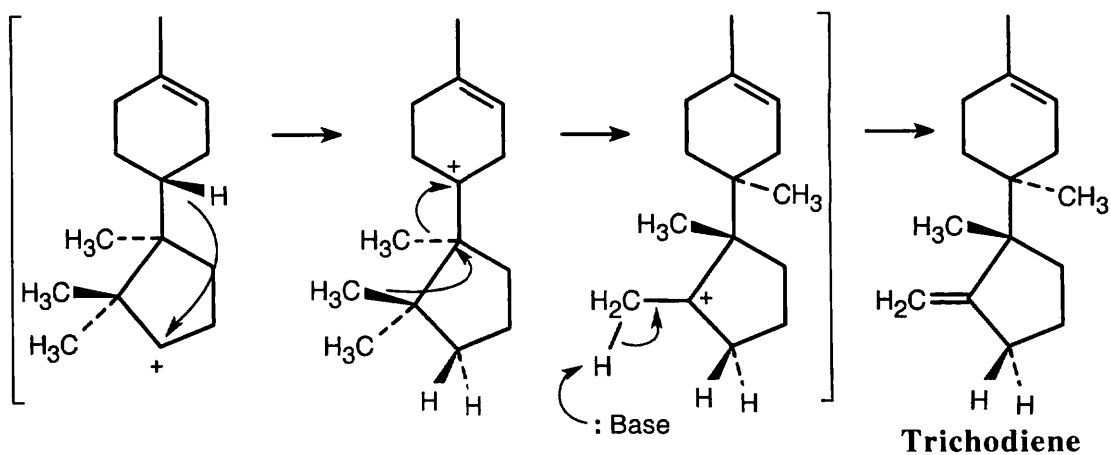
## 27.50



In this series of steps, dissociation of diphosphate ion allows bond isomerization to take place, making it possible for ring formation to occur. This mechanism is very similar to the mechanism shown in Figure 27.10.



Two cyclizations produce the trichodiene ring skeleton and a secondary carbocation.



A hydride shift, two methyl shifts, and loss of  $-H^+$  yield trichodiene.