27 Biomolecules: Lipids

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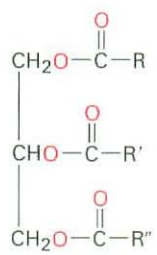
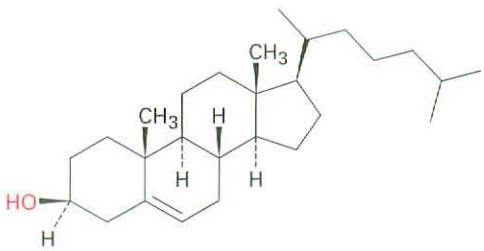
Lipids are naturally occurring organic molecules that have limited solubility in water and can be isolated from organisms by extraction with nonpolar organic solvents. Fats, oils, waxes, many vitamins and hormones, and most nonprotein cell-membrane components are examples. Note that this definition differs from the sort used for carbohydrates and proteins in that lipids are defined by a physical property (solubility) rather than by structure. Of the many kinds of lipids, we'll be concerned in this chapter only with a few: triacylglycerols, eicosanoids, terpenoids, and steroids.

Lipids are classified into two broad types: those like fats and waxes, which contain ester linkages and can be hydrolyzed, and those like cholesterol and other steroids, which don't have ester linkages and can't be hydrolyzed.



Animal fat—a triester (R, R′, R″ = C_{11}–C_{19} chains)



Cholesterol

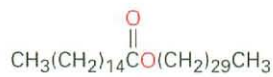
WHY THIS CHAPTER?

We've now covered two of the four major classes of biomolecules—proteins and carbohydrates—and have two remaining. We'll cover lipids, the largest and most diverse class of biomolecules, in this chapter, looking both at their structure and function and at their metabolism.

Sean Duggan

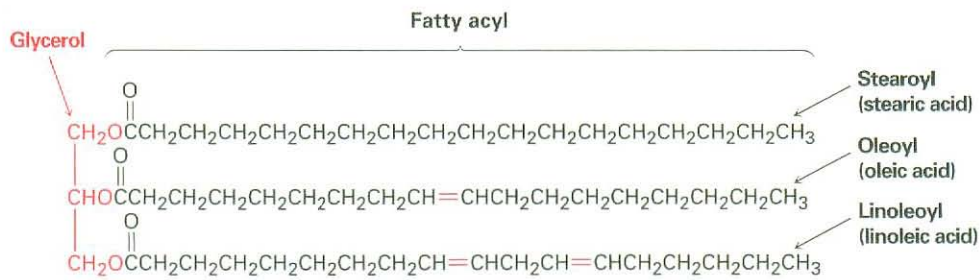
27.1 Waxes, Fats, and Oils

Waxes are mixtures of esters of long-chain carboxylic acids with long-chain alcohols. The carboxylic acid usually has an even number of carbons from 16 through 36, while the alcohol has an even number of carbons from 24 through 36. One of the major components of beeswax, for instance, is triacontyl hexadecanoate, the ester of the C_{30} alcohol triacontanol and the C_{16} acid hexadecanoic acid. The waxy protective coatings on most fruits, berries, leaves, and animal furs have similar structures.



Triacontyl hexadecanoate (from beeswax)

Animal **fats** and vegetable **oils** are the most widely occurring lipids. Although they appear different—animal fats like butter and lard are solids, whereas vegetable oils like corn and peanut oil are liquid—their structures are closely related. Chemically, fats and oils are *triglycerides*, or **triacylglycerols**—triesters of glycerol with three long-chain carboxylic acids called **fatty acids**. Animals use fats for long-term energy storage because they are much less highly oxidized than carbohydrates and provide about six times as much energy as an equal weight of stored, hydrated glycogen.



A triacylglycerol

Hydrolysis of a fat or oil with aqueous NaOH yields glycerol and three fatty acids. The fatty acids are generally unbranched and contain an even number of carbon atoms between 12 and 20. If double bonds are present, they have largely, although not entirely, *Z*, or cis, geometry. The three fatty acids of a specific triacylglycerol molecule need not be the same, and the fat or oil from a given source is likely to be a complex mixture of many different triacylglycerols. Table 27.1 lists some of the commonly occurring fatty acids, and Table 27.2 lists the approximate composition of fats and oils from different sources.

More than 100 different fatty acids are known, and about 40 occur widely. Palmitic acid (C_{16}) and stearic acid (C_{18}) are the most abundant saturated fatty acids; oleic and linoleic acids (both C_{18}) are the most abundant unsaturated ones. Oleic acid is *monounsaturated* since it has only one double bond, whereas linoleic, linolenic, and arachidonic acids are **polyunsaturated fatty acids** because they have more than one double bond. Linoleic and linolenic

Table 27.1 Structures of Some Common Fatty Acids

Name	No. of carbons	Melting point (°C)	Structure
Saturated			
Lauric	12	43.2	$CH_3(CH_2)_{10}CO_2H$
Myristic	14	53.9	$CH_3(CH_2)_{12}CO_2H$
Palmitic	16	63.1	$CH_3(CH_2)_{14}CO_2H$
Stearic	18	68.8	$CH_3(CH_2)_{16}CO_2H$
Arachidic	20	76.5	$CH_3(CH_2)_{18}CO_2H$
Unsaturated			
Palmitoleic	16	−0.1	(*Z*)-$CH_3(CH_2)_5CH{=}CH(CH_2)_7CO_2H$
Oleic	18	13.4	(*Z*)-$CH_3(CH_2)_7CH{=}CH(CH_2)_7CO_2H$
Linoleic	18	−12	(*Z,Z*)-$CH_3(CH_2)_4(CH{=}CHCH_2)_2(CH_2)_6CO_2H$
Linolenic	18	−11	(all *Z*)-$CH_3CH_2(CH{=}CHCH_2)_3(CH_2)_6CO_2H$
Arachidonic	20	−49.5	(all *Z*)-$CH_3(CH_2)_4(CH{=}CHCH_2)_4CH_2CH_2CO_2H$

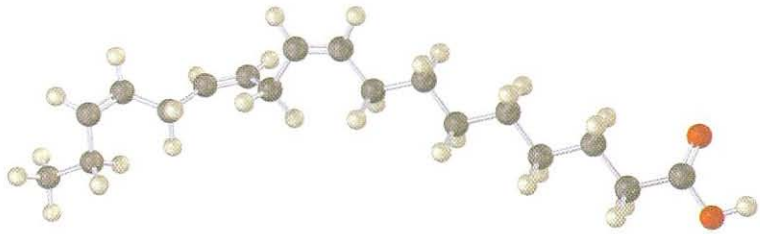
Table 27.2 Approximate Composition of Some Fats and Oils

	Saturated fatty acids (%)				Unsaturated fatty acids (%)	
Source	C_{12} lauric	C_{14} myristic	C_{16} palmitic	C_{18} stearic	C_{18} oleic	C_{18} linoleic
Animal fat						
Lard	—	1	25	15	50	6
Butter	2	10	25	10	25	5
Human fat	1	3	25	8	46	10
Whale blubber	—	8	12	3	35	10
Vegetable oil						
Coconut	50	18	8	2	6	1
Corn	—	1	10	4	35	45
Olive	—	1	5	5	80	7
Peanut	—	—	7	5	60	20

acids occur in cream and are essential in the human diet; infants grow poorly and develop skin lesions if fed a diet of nonfat milk for prolonged periods.

$CH_3CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2\overset{O}{\overset{\|}{C}}OH$

Stearic acid

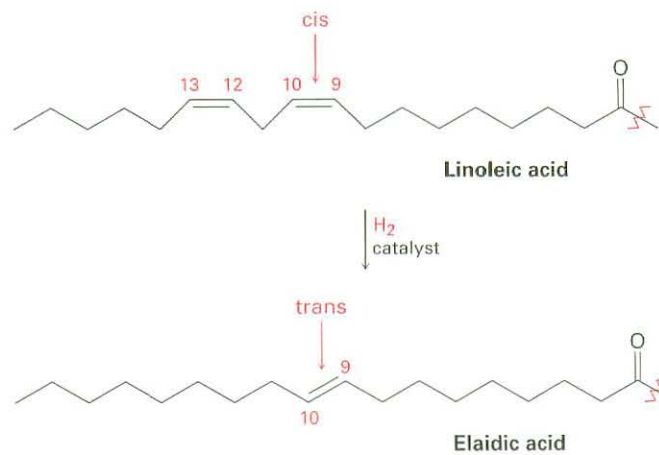


$$CH_3CH_2CH{=}CHCH_2CH{=}CHCH_2CH{=}CHCH_2CH_2CH_2CH_2CH_2CH_2C(=O)OH$$

Linolenic acid, a polyunsaturated fatty acid

The data in Table 27.1 show that unsaturated fatty acids generally have lower melting points than their saturated counterparts, a trend that is also true for triacylglycerols. Since vegetable oils generally have a higher proportion of unsaturated to saturated fatty acids than animal fats (Table 27.2), they have lower melting points. The difference is a consequence of structure. Saturated fats have a uniform shape that allows them to pack together efficiently in a crystal lattice. In unsaturated vegetable oils, however, the C=C bonds introduce bends and kinks into the hydrocarbon chains, making crystal formation more difficult. The more double bonds there are, the harder it is for the molecules to crystallize and the lower the melting point of the oil.

The C=C bonds in vegetable oils can be reduced by catalytic hydrogenation, typically carried out at high temperature using a nickel catalyst, to produce saturated solid or semisolid fats. Margarine and shortening are produced by hydrogenating soybean, peanut, or cottonseed oil until the proper consistency is obtained. Unfortunately, the hydrogenation reaction is accompanied by some cis–trans isomerization of the double bonds that remain, producing fats with about 10% to 15% trans unsaturated fatty acids. Dietary intake of trans fatty acids increases cholesterol levels in the blood, thereby increasing the risk of heart problems. The conversion of linoleic acid into elaidic acid is an example.

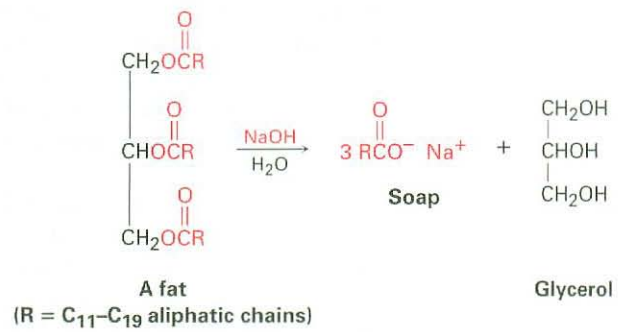


Problem 27.1 Carnauba wax, used in floor and furniture polishes, contains an ester of a C_{32} straight-chain alcohol with a C_{20} straight-chain carboxylic acid. Draw its structure.

Problem 27.2 Draw structures of glyceryl tripalmitate and glyceryl trioleate. Which would you expect to have a higher melting point?

27.2 Soap

Soap has been known since at least 600 BC, when the Phoenicians prepared a curdy material by boiling goat fat with extracts of wood ash. The cleansing properties of soap weren't generally recognized, however, and the use of soap did not become widespread until the 18th century. Chemically, soap is a mixture of the sodium or potassium salts of the long-chain fatty acids produced by hydrolysis *(saponification)* of animal fat with alkali. Wood ash was used as a source of alkali until the early 1800s, when the development of the LeBlanc process for making Na_2CO_3 by heating sodium sulfate with limestone became available.



Crude soap curds contain glycerol and excess alkali as well as soap but can be purified by boiling with water and adding NaCl or KCl to precipitate the pure carboxylate salts. The smooth soap that precipitates is dried, perfumed, and pressed into bars for household use. Dyes are added to make colored soaps, antiseptics are added for medicated soaps, pumice is added for scouring soaps, and air is blown in for soaps that float. Regardless of these extra treatments and regardless of price, though, all soaps are basically the same.

Soaps act as cleansers because the two ends of a soap molecule are so different. The carboxylate end of the long-chain molecule is ionic and therefore hydrophilic (Section 2.13), or attracted to water. The long hydrocarbon portion of the molecule, however, is nonpolar and hydrophobic, avoiding water and therefore more soluble in oils. The net effect of these two opposing tendencies is that soaps are attracted to both oils and water and are therefore useful as cleansers.

When soaps are dispersed in water, the long hydrocarbon tails cluster together on the inside of a tangled, hydrophobic ball, while the ionic heads on the surface of the cluster stick out into the water layer. These spherical clusters, called **micelles**, are shown schematically in Figure 27.1. Grease and oil droplets

are solubilized in water when they are coated by the nonpolar tails of soap molecules in the center of micelles. Once solubilized, the grease and dirt can be rinsed away.

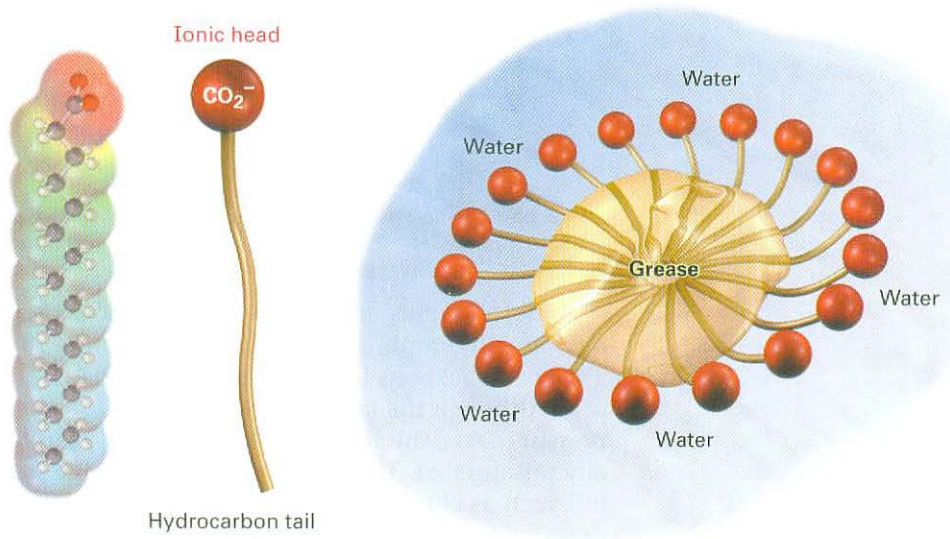
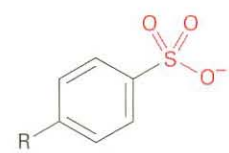


Figure 27.1 A soap micelle solubilizing a grease particle in water. An electrostatic potential map of a fatty acid carboxylate shows how the negative charge is located in the head group.

As useful as they are, soaps also have some drawbacks. In hard water, which contains metal ions, soluble sodium carboxylates are converted into insoluble magnesium and calcium salts, leaving the familiar ring of scum around bathtubs and the gray tinge on white clothes. Chemists have circumvented these problems by synthesizing a class of synthetic detergents based on salts of long-chain alkylbenzenesulfonic acids. The principle of synthetic detergents is the same as that of soaps: the alkylbenzene end of the molecule is attracted to grease, while the anionic sulfonate end is attracted to water. Unlike soaps, though, sulfonate detergents don't form insoluble metal salts in hard water and don't leave an unpleasant scum.



A synthetic detergent
(R = a mixture of C_{12} chains)

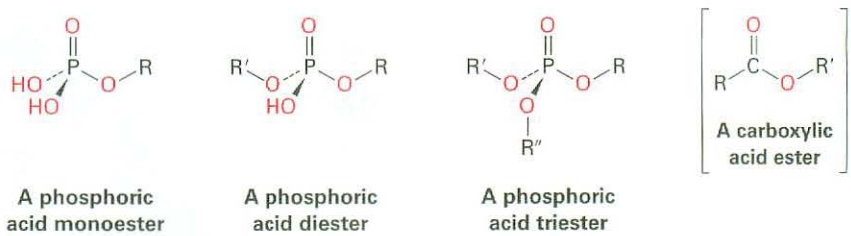
Problem 27.3 Draw the structure of magnesium oleate, a component of bathtub scum.

Problem 27.4 Write the saponification reaction of glyceryl dioleate monopalmitate with aqueous NaOH.

27.3 Phospholipids

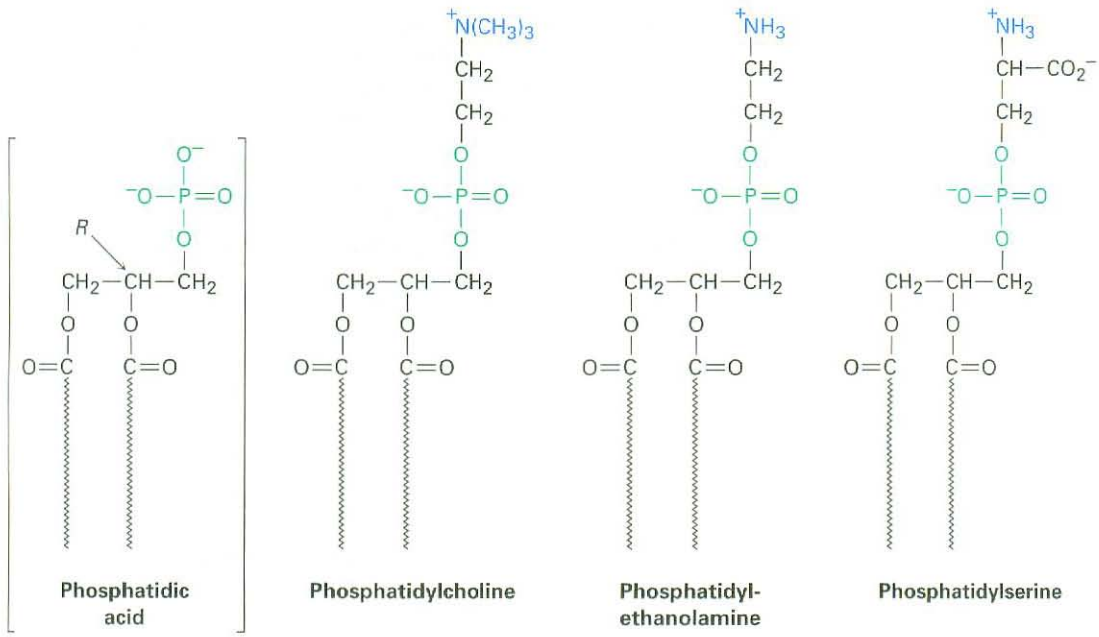
ThomsonNOW Click *Organic Interactive* to **learn to identify common phospholipids by their charge and type.**

Just as waxes, fats, and oils are esters of carboxylic acids, **phospholipids** are diesters of phosphoric acid, H_3PO_4.

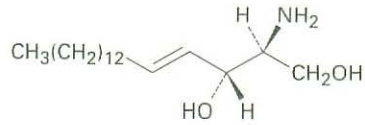


A phosphoric acid monoester **A phosphoric acid diester** **A phosphoric acid triester**

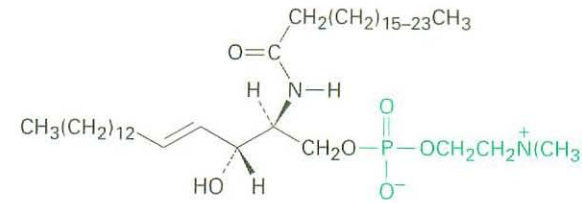
Phospholipids are of two general kinds: *glycerophospholipids* and *sphingomyelins*. Glycerophospholipids are based on phosphatidic acid, which contains a glycerol backbone linked by ester bonds to two fatty acids and one phosphoric acid. Although the fatty-acid residues can be any of the C_{12}–C_{20} units typically present in fats, the acyl group at C1 is usually saturated and the one at C2 is usually unsaturated. The phosphate group at C3 is also bonded to an amino alcohol such as choline $[HOCH_2CH_2N(CH_3)_3]^+$, ethanolamine $(HOCH_2CH_2NH_2)$, or serine $[HOCH_2CH(NH_2)CO_2H]$. The compounds are chiral and have an L, or *R*, configuration at C2.



Sphingomyelins are the second major group of phospholipids. These compounds have sphingosine or a related dihydroxyamine as their backbone and are particularly abundant in brain and nerve tissue, where they are a major constituent of the coating around nerve fibers.



Sphingosine



A sphingomyelin

Phospholipids are found widely in both plant and animal tissues and make up approximately 50% to 60% of cell membranes. Because they are like soaps in having a long, nonpolar hydrocarbon tail bound to a polar ionic head, phospholipids in the cell membrane organize into a **lipid bilayer** about 5.0 nm (50 Å) thick. As shown in Figure 27.2, the nonpolar tails aggregate in the center of the bilayer in much the same way that soap tails aggregate in the center of a micelle. This bilayer serves as an effective barrier to the passage of water, ions, and other components into and out of cells.

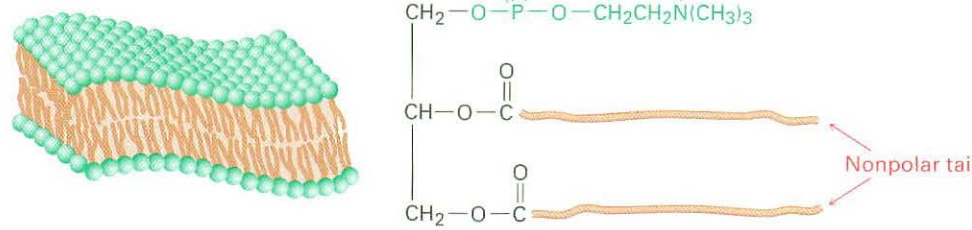


Figure 27.2 Aggregation of glycerophospholipids into the lipid bilayer that composes cell membranes.

27.4 Prostaglandins and Other Eicosanoids

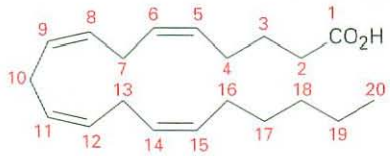
The **prostaglandins** are a group of C_{20} lipids that contain a five-membered ring with two long side chains. First isolated in the 1930s by Ulf von Euler at the Karolinska Institute in Sweden, much of the structural and chemical work on the prostaglandins was carried out by Sune Bergström and Bengt Samuelsson. The name *prostaglandin* derives from the fact that the compounds were first isolated from sheep prostate glands, but they have subsequently been shown to be present in small amounts in all body tissues and fluids.

The several dozen known prostaglandins have an extraordinarily wide range of biological effects. Among their many properties, they can lower blood pressure, affect blood-platelet aggregation during clotting, lower gastric secretions, control inflammation, affect kidney function, affect reproductive systems, and stimulate uterine contractions during childbirth.

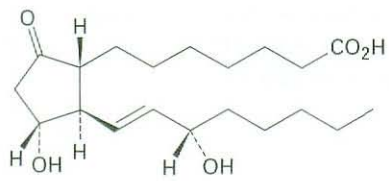
Prostaglandins, together with related compounds called thromboxanes and leukotrienes, make up a class of compounds called **eicosanoids** because they are derived biologically from 5,8,11,14-eicosatetraenoic acid, or arachidonic

acid (Figure 27.3). Prostaglandins (PG) have a cyclopentane ring with two long side chains; thromboxanes (TX) have a six-membered, oxygen-containing ring; and leukotrienes (LT) are acyclic.

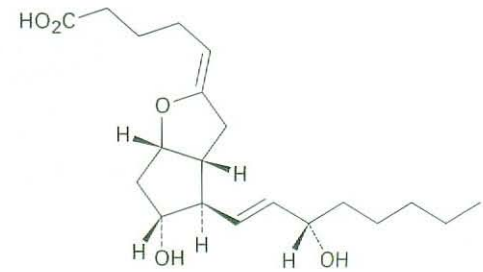
Figure 27.3 Structures of some representative eicosanoids. All are derived biologically from arachidonic acid.



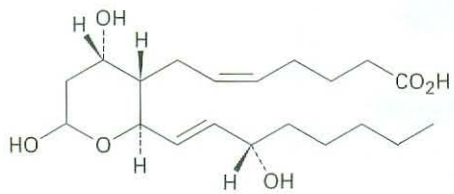
Arachidonic acid



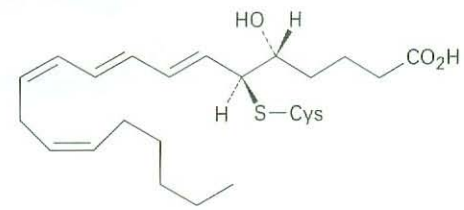
Prostaglandin E_1 (PGE_1)



Prostaglandin I_2 (PGI_2) (prostacyclin)



Thromboxane B_2 (TXB_2)



Leukotriene E_4 (LTE_4)

Ulf Svante von Euler	Sune K. Bergström	Bengt Samuelsson
Ulf Svante von Euler (1905–1983) was born in Stockholm, Sweden, to a distinguished academic family. His father, Hans von Euler-Chelpin, received the 1929 Nobel Prize in chemistry; his godfather, Svante Arrhenius, received the 1903 Nobel Prize in chemistry; and his mother had a Ph.D. in botany. Von Euler received an M.D. from the Karolinska Institute in 1930, and then remained there his entire career (1930–1971). He received the 1970 Nobel Prize in medicine for his work on the chemical transmission of nerve impulses.	**Sune K. Bergström** (1916–2004) was born in Stockholm, Sweden, and received an M.D. from the Karolinska Institute in 1944. He was professor at the University of Lund (1947–1958) before moving back to the Karolinska Institute in 1958. He shared the 1982 Nobel Prize in medicine for his work on identifying and studying the prostaglandins.	**Bengt Samuelsson** (1934–) was born in Halmstad, Sweden, and received both Ph.D. (1960) and M.D. (1961) degrees from the Karolinska Institute, where he worked with Sune Bergström. He remained at the Karolinska Institute as professor and shared the 1982 Nobel Prize in medicine with Bergström and John R. Vane.

Eicosanoids are named based on their ring system (PG, TX, or LT), substitution pattern, and number of double bonds. The various substitution patterns on the ring are indicated by letter as in Figure 27.4, and the number of double bonds is indicated by a subscript. Thus, PGE_1 is a prostaglandin with the "E" substitution pattern and one double bond. The numbering of the atoms in the various eicosanoids is the same as in arachidonic acid, starting with the $-CO_2H$ carbon as C1, continuing around the ring, and ending with the $-CH_3$ carbon at the other end of the chain as C20.

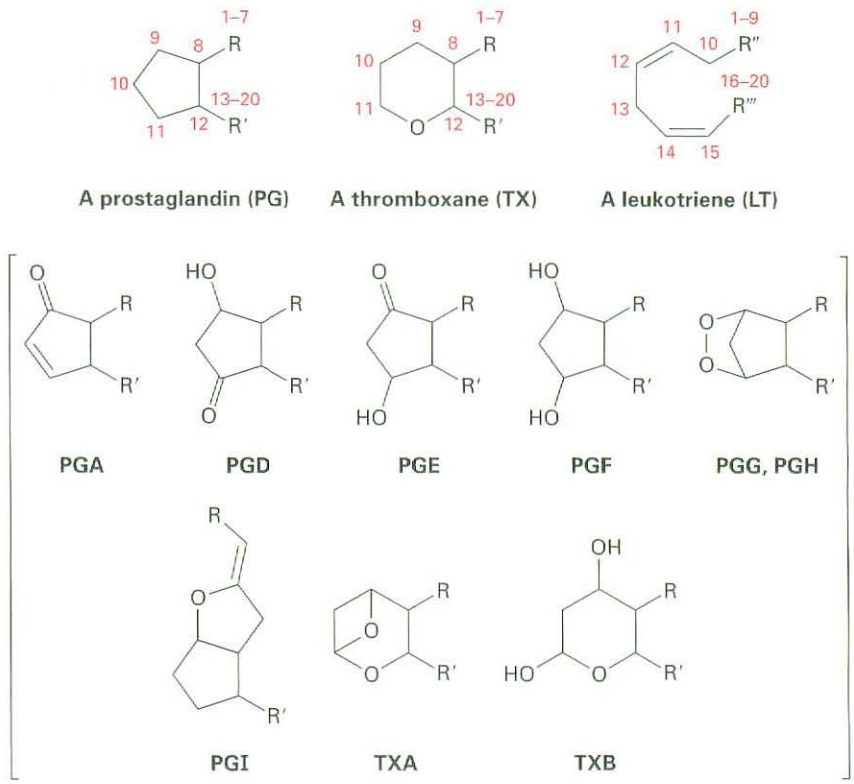
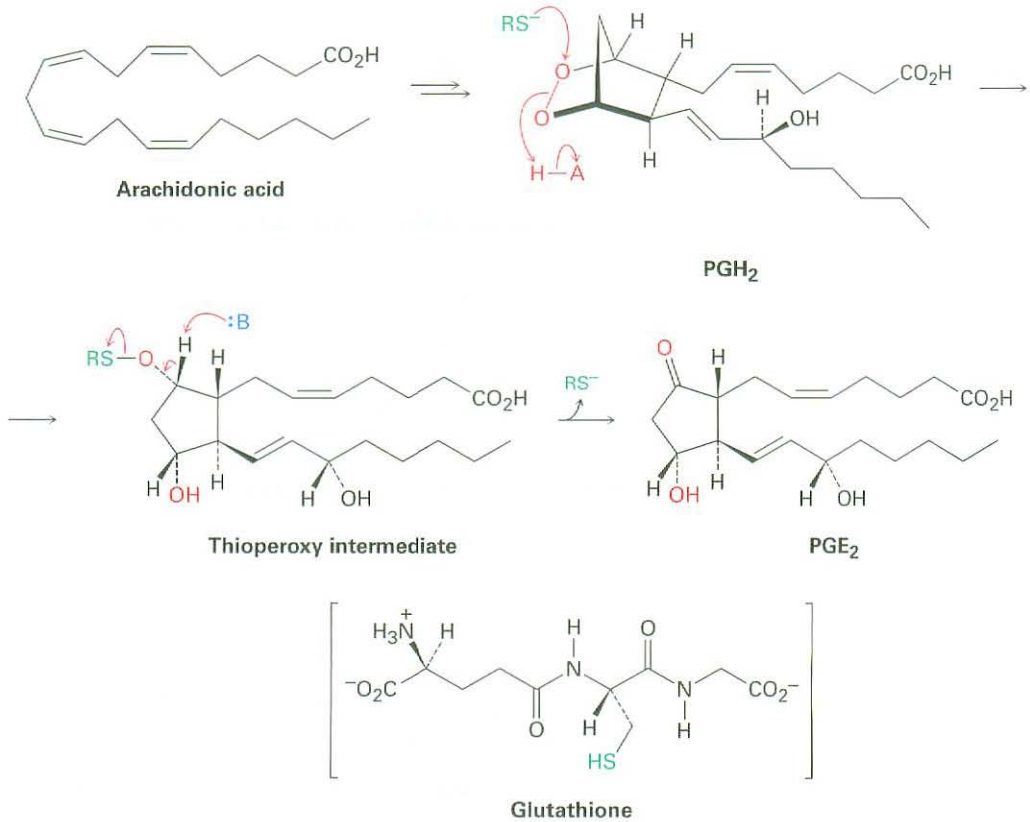


Figure 27.4 The nomenclature system for eicosanoids.

Eicosanoid biosynthesis begins with the conversion of arachidonic acid to PGH_2, catalyzed by the multifunctional PGH synthase (PGHS), also called cyclooxygenase (COX). There are two distinct enzymes, PGHS-1 and PGHS-2 (or COX-1 and COX-2), both of which accomplish the same reaction but appear to function independently. COX-1 carries out the normal physiological production of prostaglandins, and COX-2 produces additional prostaglandin in response to arthritis or other inflammatory conditions. Vioxx, Celebrex, Bextra, and several other drugs selectively inhibit the COX-2 enzyme but also appear to cause potentially serious heart problems in weakened patients. (See the Chapter 15 *Focus On*.)

PGHS accomplishes two transformations, an initial reaction of arachidonic acid with O_2 to yield PGG_2 and a subsequent reduction of the hydroperoxide group ($-OOH$) to the alcohol PGH_2. The sequence of steps involved in these transformations was shown in Figure 7.9, page 244.

Further processing of PGH_2 then leads to other eicosanoids. PGE_2, for instance, arises by an isomerization of PGH_2 catalyzed by PGE synthase (PGES). The coenzyme glutathione is needed for enzyme activity, although it is not chemically changed during the isomerization and its role is not fully understood. One possibility is that the glutathione thiolate anion breaks the O–O bond in PGH_2 by an S_N2-like attack on one of the oxygen atoms, giving a thioperoxy intermediate (R—S—O—R′) that eliminates glutathione to give the ketone (Figure 27.5).



Glutathione

Figure 27.5 Mechanism of the conversion of PGH_2 into PGE_2.

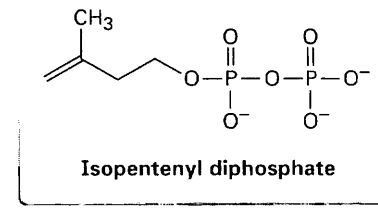
Problem 27.5 Assign *R* or *S* configuration to each chirality center in prostaglandin E_2 (Figure 27.5), the most abundant and biologically potent of mammalian prostaglandins.

27.5 Terpenoids

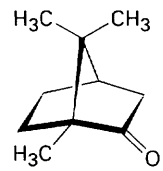
In the Chapter 6 *Focus On*, "Terpenes: Naturally Occurring Alkenes," we looked briefly at **terpenoids**, a vast and diverse group of lipids found in all living organisms. Despite their apparent structural differences, all terpenoids are related. All contain a multiple of five carbons and are derived biosynthetically from the five-carbon precursor isopentenyl diphosphate (Figure 27.6). Note that formally, a

terpenoid contains oxygen, while a *terpene* is a hydrocarbon. For simplicity, we'll use the term *terpenoid* to refer to both.

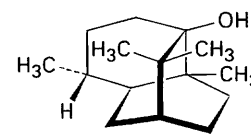
Figure 27.6 Structures of some representative terpenoids.



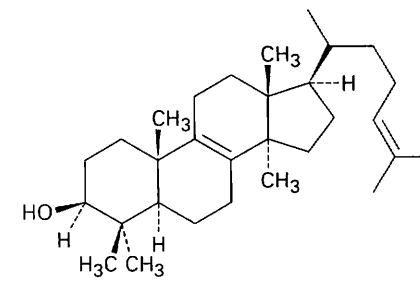
Isopentenyl diphosphate



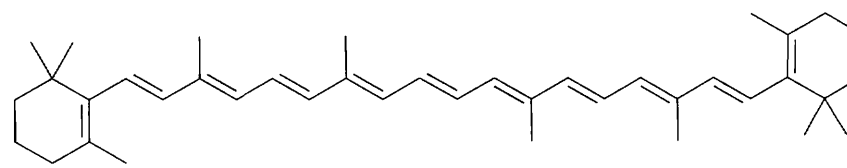
Camphor
(a monoterpenoid—C_{10})



Patchouli alcohol
(a sesquiterpenoid—C_{15})



Lanosterol
(a triterpenoid—C_{30})

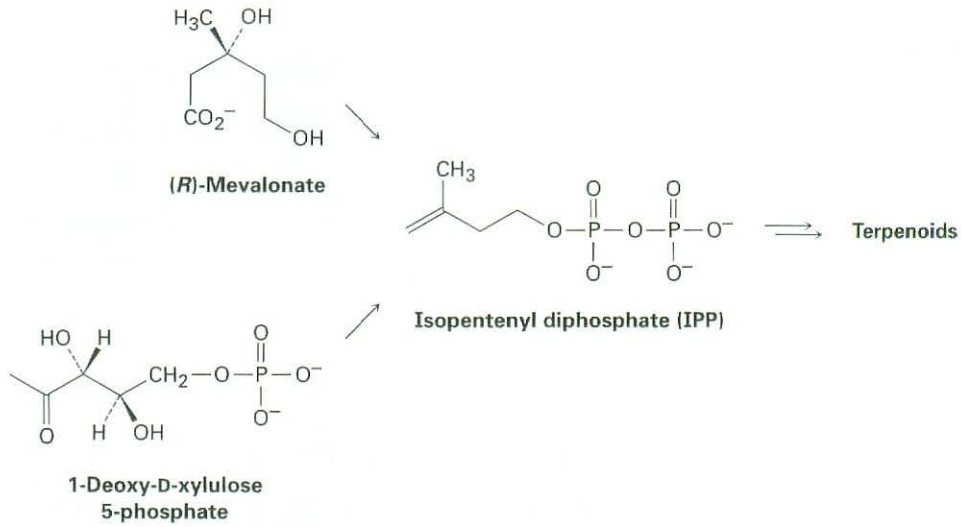


β-Carotene
(a tetraterpenoid—C_{40})

Terpenoids are classified according to the number of five-carbon multiples they contain. *Monoterpenoids* contain 10 carbons and are derived from two isopentenyl diphosphates, *sesquiterpenoids* contain 15 carbons and are derived from three isopentenyl diphosphates, *diterpenoids* contain 20 carbons and are derived from four isopentenyl diphosphates, and so on, up to triterpenoids (C_{30}) and tetraterpenoids (C_{40}). Monoterpenoids and sesquiterpenoids are found primarily in plants, bacteria, and fungi, but the higher terpenoids occur in both plants and animals. The triterpenoid lanosterol, for example, is the precursor from which steroid hormones are made, and the tetraterpenoid β-carotene is a dietary source of vitamin A (Figure 27.6).

The terpenoid precursor isopentenyl diphosphate, formerly called isopentenyl pyrophosphate and abbreviated IPP, is biosynthesized by two different pathways depending on the organism and the structure of the final product. In animals and higher plants, sesquiterpenoids and triterpenoids arise primarily from the *mevalonate* pathway, whereas monoterpenoids, diterpenoids, and tetraterpenoids are biosynthesized by the *1-deoxyxylulose 5-phosphate (DXP)* pathway. In bacteria,

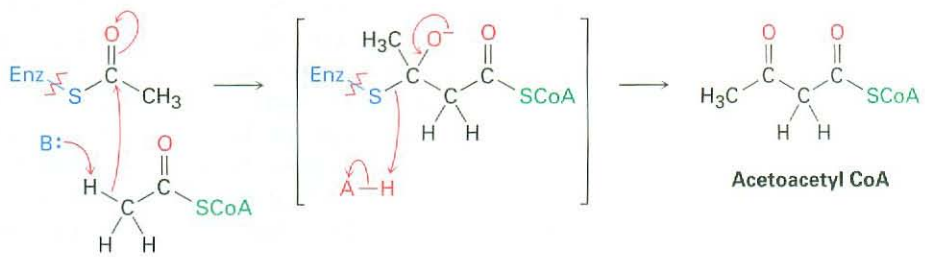
both pathways are used. We'll look only at the mevalonate pathway, which is more common and better understood at present.



The Mevalonate Pathway to Isopentenyl Diphosphate

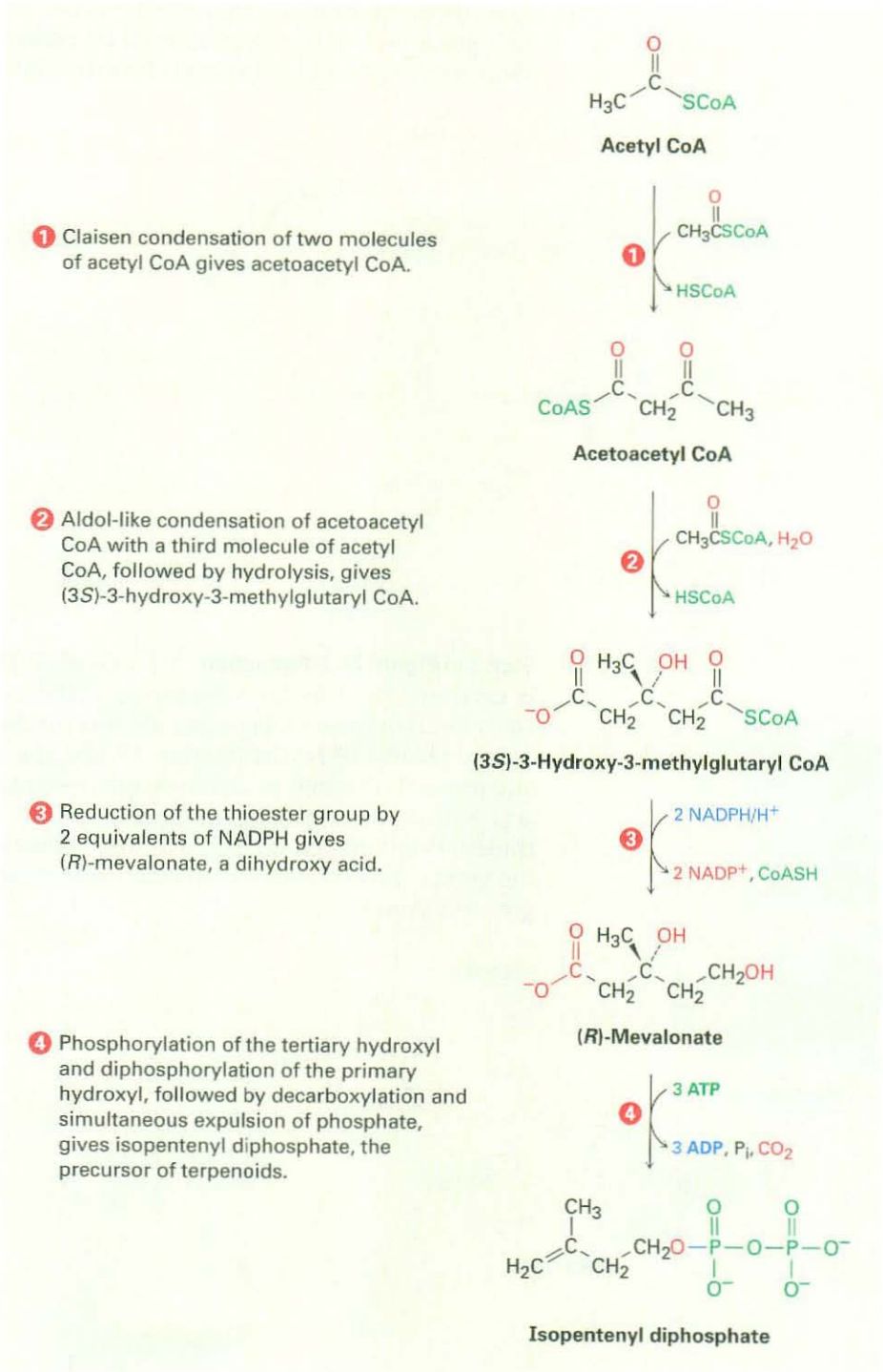
As summarized in Figure 27.7, the mevalonate pathway begins with the conversion of acetate to acetyl CoA, followed by Claisen condensation to yield acetoacetyl CoA. A second carbonyl condensation reaction with a third molecule of acetyl CoA, this one an aldol-like process, then yields the six-carbon compound 3-hydroxy-3-methylglutaryl CoA, which is reduced to give mevalonate. Phosphorylation, followed by loss of CO_2 and phosphate ion, completes the process.

Step 1 of Figure 27.7: Claisen Condensation The first step in mevalonate biosynthesis is a Claisen condensation (Section 23.7) to yield acetoacetyl CoA, a reaction catalyzed by acetoacetyl-CoA acetyltransferase. An acetyl group is first bound to the enzyme by a nucleophilic acyl substitution reaction with a cysteine –SH group. Formation of an enolate ion from a second molecule of acetyl CoA, followed by Claisen condensation, then yields the product.

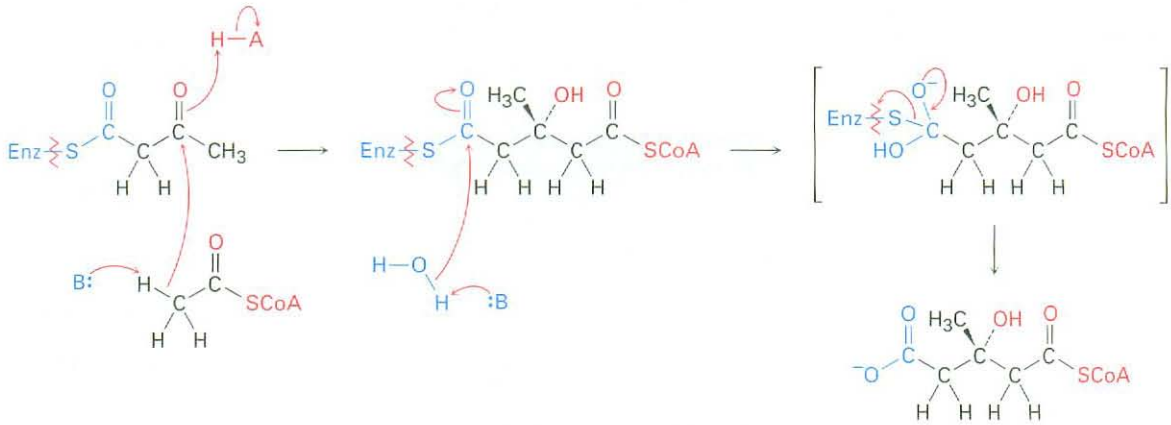


Step 2 of Figure 27.7: Aldol Condensation Acetoacetyl CoA next undergoes an aldol-like addition (Section 23.1) of an acetyl CoA enolate ion in a reaction catalyzed by 3-hydroxy-3-methylglutaryl-CoA synthase. The reaction again occurs

Figure 27.7 MECHANISM: *The mevalonate pathway for the biosynthesis of isopentenyl diphosphate from three molecules of acetyl CoA. Individual steps are explained in the text.*

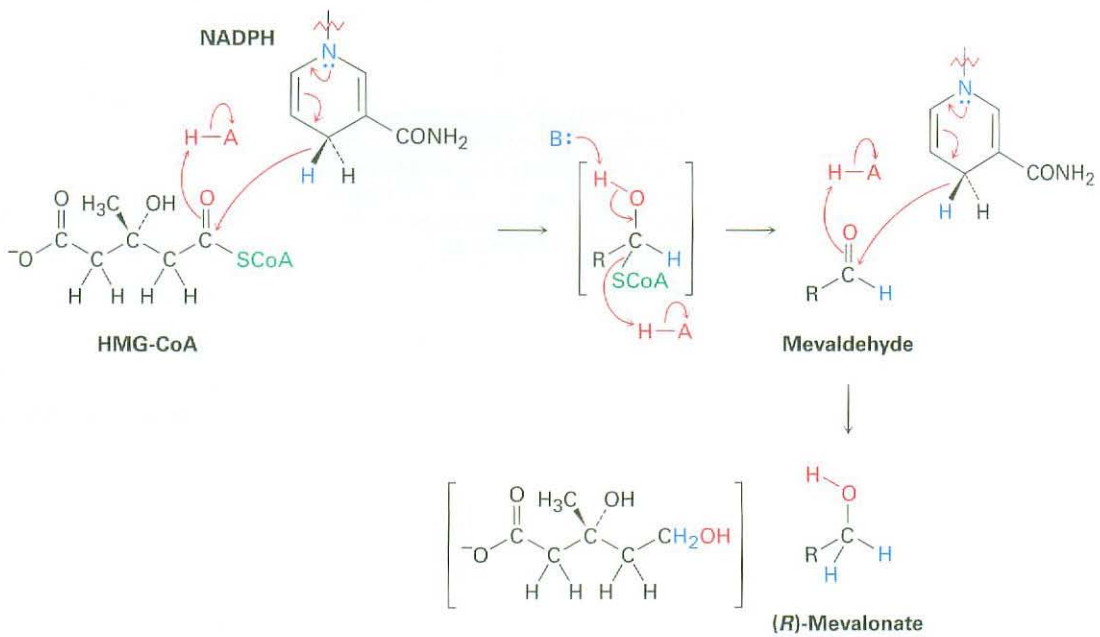


by initial formation of a thioester bond between the substrate and a cysteine –SH group in the enzyme, followed by enolate-ion addition and subsequent hydrolysis to give (3*S*)-3-hydroxy-3-methylglutaryl CoA (HMG-CoA).



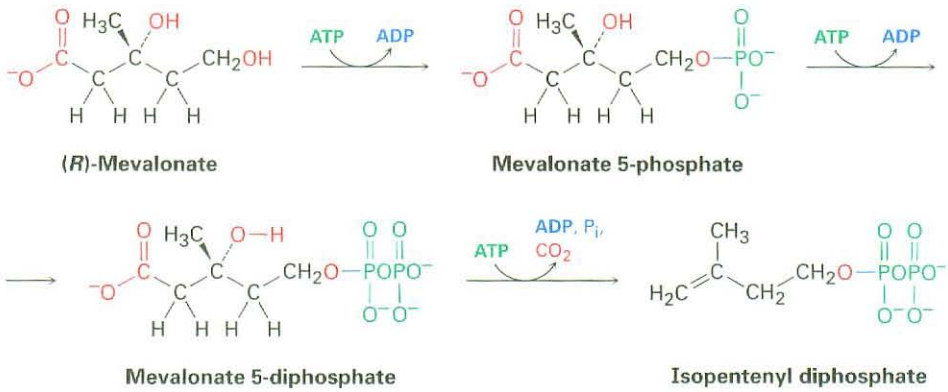
(3*S*)-3-Hydroxy-3-methylglutaryl CoA (HMG-CoA)

Step 3 of Figure 27.7: Reduction Reduction of HMG-CoA to give (*R*)-mevalonate is catalyzed by 3-hydroxy-3-methylglutaryl-CoA reductase and requires two equivalents of reduced nicotinamide adenine dinucleotide phosphate (NADPH), a close relative of NADH (Section 19.12). The reaction occurs in several steps and proceeds through an aldehyde intermediate. The first step is a nucleophilic acyl substitution reaction involving hydride transfer from NADPH to the thioester carbonyl group of HMG-CoA. Following expulsion of HSCoA as leaving group, the aldehyde intermediate undergoes a second hydride addition to give mevalonate.



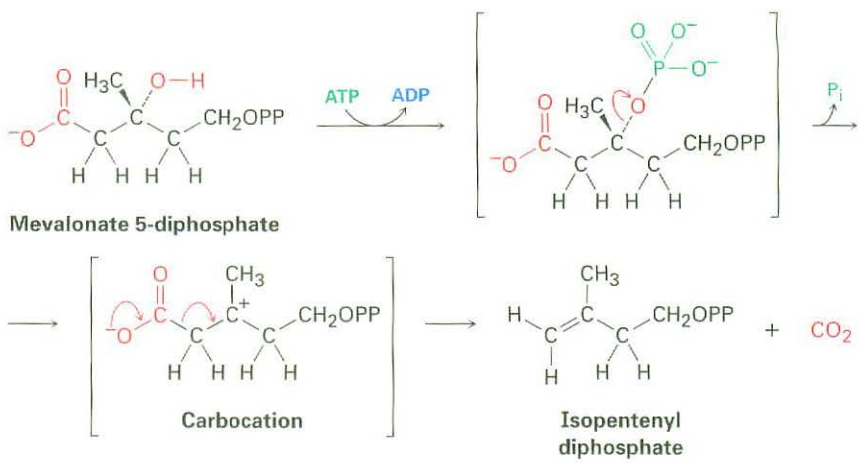
HMG-CoA **Mevaldehyde** **(*R*)-Mevalonate**

Step 4 of Figure 27.7: Phosphorylation and Decarboxylation Three additional reactions are needed to convert mevalonate to isopentenyl diphosphate. The first two are straightforward phosphorylations that occur by nucleophilic substitution reactions on the terminal phosphorus of ATP. Mevalonate is first converted to mevalonate 5-phosphate (phosphomevalonate) by reaction with ATP in a process catalyzed by mevalonate kinase. Mevalonate 5-phosphate then reacts with a second ATP to give mevalonate 5-diphosphate (diphosphomevalonate). The third reaction results in phosphorylation of the tertiary hydroxyl group, followed by decarboxylation and loss of phosphate ion.



The final decarboxylation of mevalonate 5-diphosphate appears unusual because decarboxylations of acids do not typically occur except in β-keto acids and malonic acids, in which the carboxylate group is two atoms away from an additional carbonyl group (Section 22.7). The function of this second carbonyl group is to act as an electron acceptor and stabilize the charge resulting from loss of CO_2. In fact, though, the decarboxylation of a β-keto acid and the decarboxylation of mevalonate 5-diphosphate are closely related.

Catalyzed by mevalonate-5-diphosphate decarboxylase, the substrate is first phosphorylated on the free —OH group by reaction with ATP to give a tertiary phosphate, which undergoes spontaneous dissociation to give a tertiary carbocation. The positive charge then acts as an electron acceptor to facilitate decarboxylation in exactly the same way a β carbonyl group does, giving isopentenyl diphosphate. (In the following structures, the diphosphate group is abbreviated OPP.)



Problem 27.6 Studies of the conversion of mevalonate 5-phosphate to isopentenyl diphosphate have shown the following result. Which hydrogen, *pro-R* or *pro-S*, ends up cis to the methyl group, and which ends up trans?

Mevalonate 5-diphosphate → **Isopentenyl diphosphate**

Conversion of Isopentenyl Diphosphate to Terpenoids

The conversion of isopentenyl diphosphate (IPP) to terpenoids begins with its isomerization to dimethylallyl diphosphate, abbreviated DMAPP and formerly called dimethylallyl pyrophosphate. These two C_5 building blocks then combine to give the C_{10} unit geranyl diphosphate (GPP). The corresponding alcohol, geraniol, is itself a fragrant terpenoid that occurs in rose oil.

Further combination of GPP with another IPP gives the C_{15} unit farnesyl diphosphate (FPP), and so on, up to C_{25}. Terpenoids with more than 25 carbons—that is, triterpenoids (C_{30}) and tetraterpenoids (C_{40})—are synthesized by dimerization of C_{15} and C_{20} units, respectively (Figure 27.8). Triterpenoids and

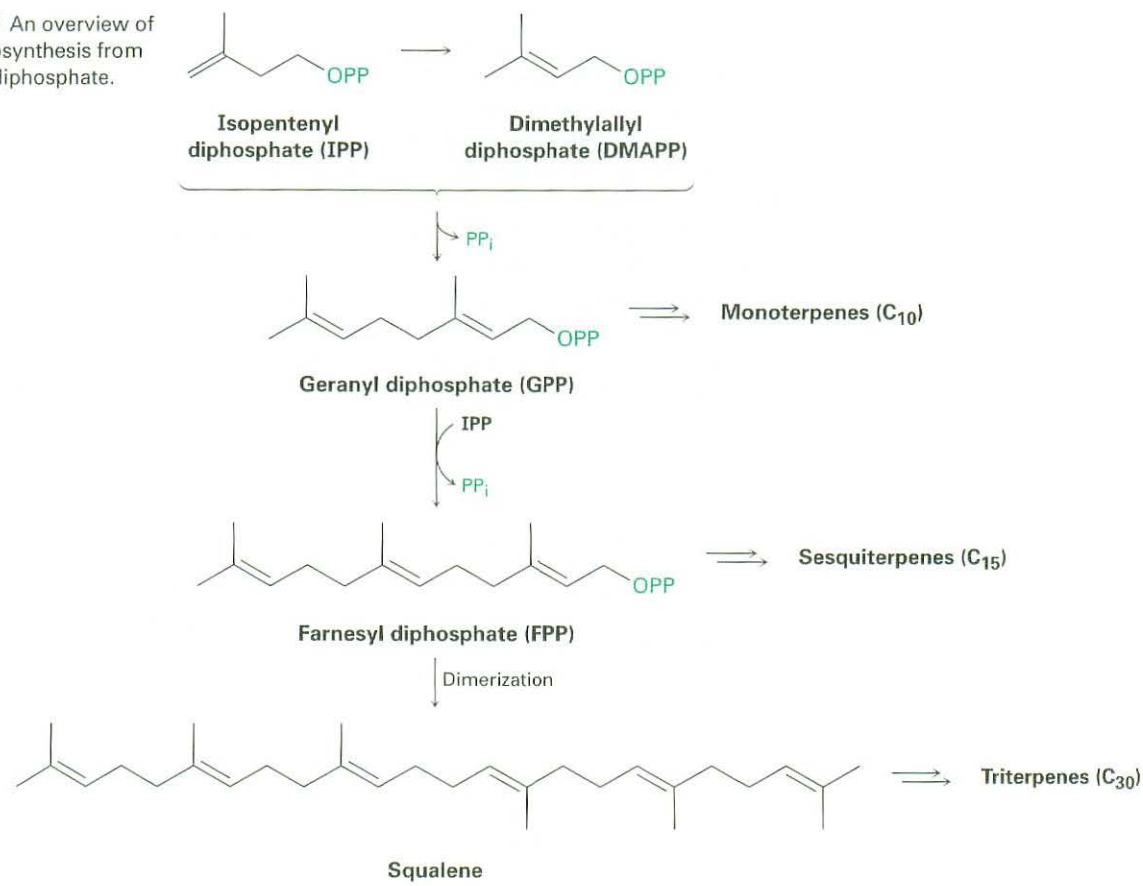
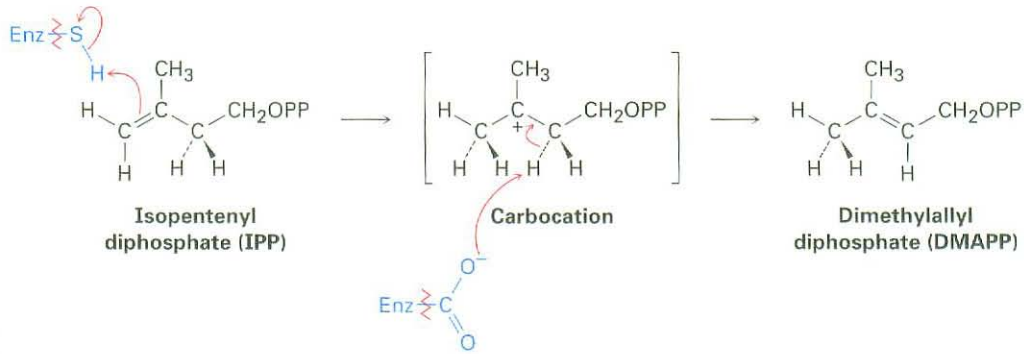


Figure 27.8 An overview of terpenoid biosynthesis from isopentenyl diphosphate.

steroids, in particular, arise from reductive dimerization of farnesyl diphosphate to give squalene.

The isomerization of isopentenyl diphosphate to dimethylallyl diphosphate is catalyzed by IPP isomerase and occurs through a carbocation pathway. Protonation of the IPP double bond by a hydrogen-bonded cysteine residue in the enzyme gives a tertiary carbocation intermediate, which is deprotonated by a glutamate residue as base to yield DMAPP. X-ray structural studies on the enzyme show that it holds the substrate in an unusually deep, well-protected pocket to shield the highly reactive carbocation from reaction with solvent or other external substances.



Both the initial coupling of DMAPP with IPP to give geranyl diphosphate and the subsequent coupling of GPP with a second molecule of IPP to give farnesyl diphosphate are catalyzed by farnesyl diphosphate synthase. The process requires Mg^{2+} ion, and the key step is a nucleophilic substitution reaction in which the double bond of IPP behaves as a nucleophile in displacing diphosphate ion leaving group (PP_i). The exact mechanism of the nucleophilic substitution step—whether S_N1 or S_N2—is difficult to establish conclusively. Available evidence suggests, however, that the substrate develops considerable cationic character and that spontaneous dissociation of the allylic diphosphate ion in an S_N1-like pathway probably occurs (Figure 27.9).

The further conversion of geranyl diphosphate into monoterpenoids typically involves carbocation intermediates and multistep reaction pathways that are catalyzed by terpene cyclases. Monoterpene cyclases function by first isomerizing geranyl diphosphate to its allylic isomer linalyl diphosphate (LPP), a process that occurs by spontaneous S_N1-like dissociation to an allylic carbocation, followed by recombination. The effect of this isomerization is to convert the C2–C3 double bond of GPP into a single bond, thereby making cyclization possible and allowing *E/Z* isomerization of the double bond. Further dissociation and cyclization by electrophilic addition of the cationic carbon to the terminal double bond then gives a cyclic cation, which might either rearrange, undergo a hydride shift, be captured by a nucleophile, or be deprotonated to give any of the several hundred known monoterpenoids. As just one example, limonene, a monoterpene found in many citrus oils, arises by the biosynthetic pathway shown in Figure 27.10.

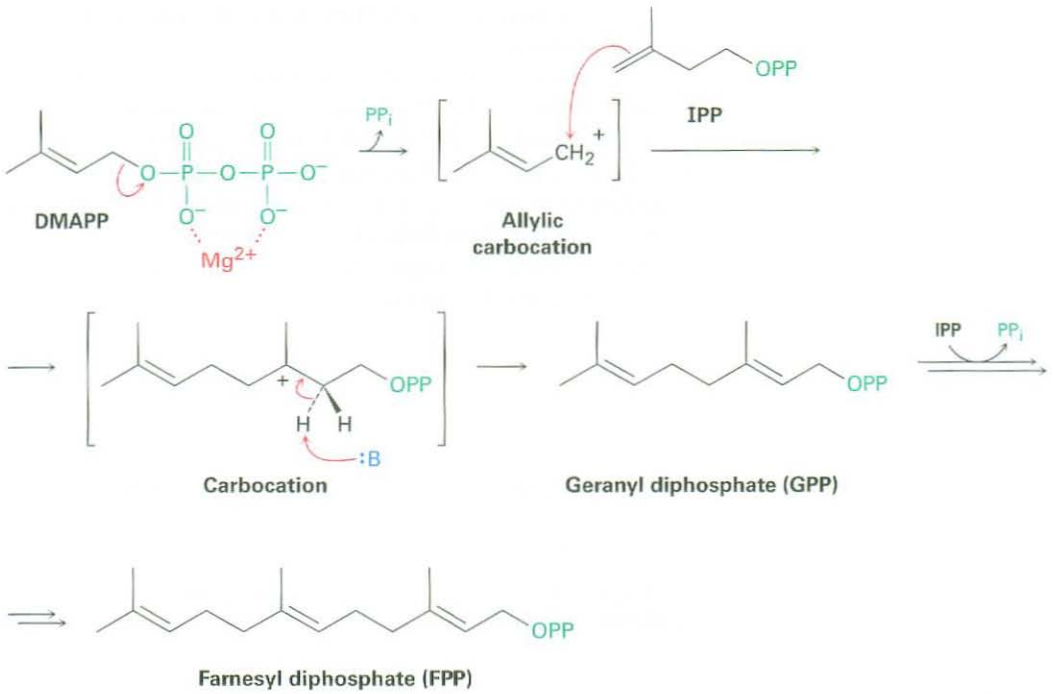


Figure 27.9 Mechanism of the coupling reaction of dimethylallyl diphosphate (DMAPP) and isopentenyl diphosphate (IPP), to give geranyl diphosphate (GPP).

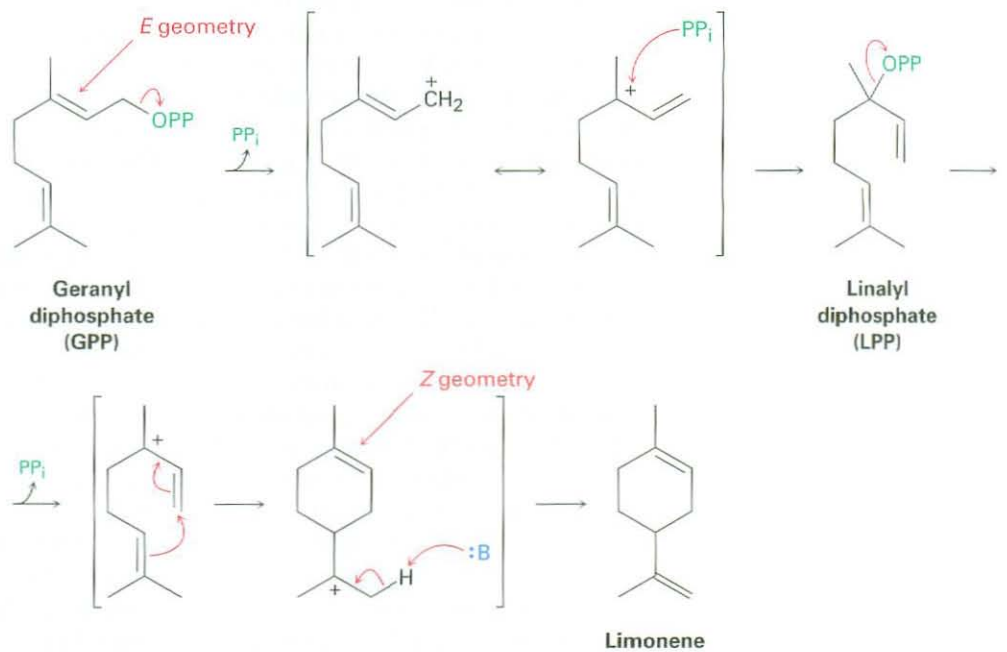
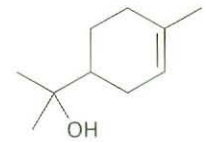


Figure 27.10 Mechanism of the formation of the monoterpene limonene from geranyl diphosphate.

WORKED EXAMPLE 27.1 ***Proposing a Terpenoid Biosynthesis Pathway***

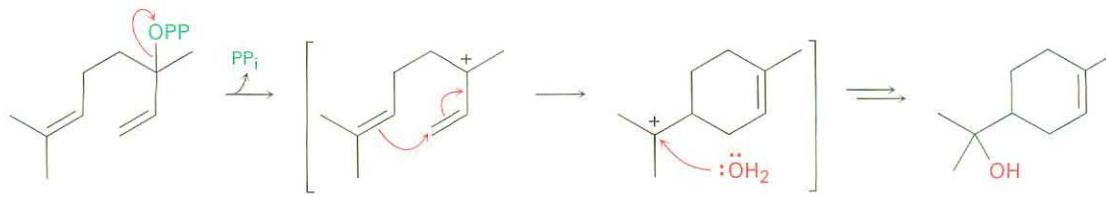
Propose a mechanistic pathway for the biosynthesis of α-terpineol from geranyl diphosphate.



α-Terpineol

Strategy α-Terpineol, a monoterpenoid, must be derived biologically from geranyl diphosphate through its isomer linalyl diphosphate. Draw the precursor in a conformation that approximates the structure of the target molecule, and then carry out a cationic cyclization, using the appropriate double bond to displace the diphosphate leaving group. Since the target is an alcohol, the carbocation resulting from cyclization must react with water.

Solution

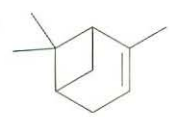


Linalyl diphosphate

α-Terpineol

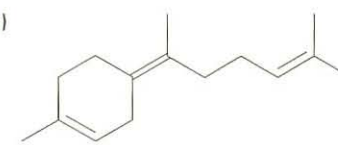
Problem 27.7 Propose mechanistic pathways for the biosynthetic formation of the following terpenes:

(a)



α-Pinene

(b)



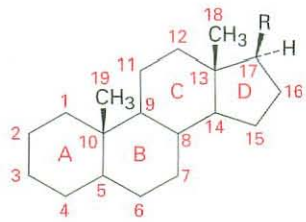
γ-Bisabolene

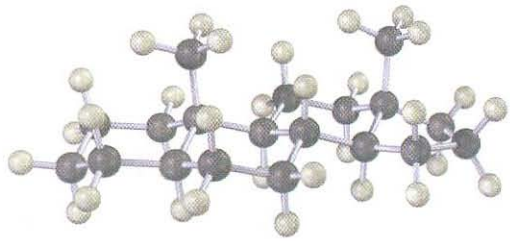
27.6 Steroids

ThomsonNOW Click *Organic Interactive* to **use a web-based palette to assign *R,S* designations to chiral centers in steroids.**

In addition to fats, phospholipids, eicosanoids, and terpenoids, the lipid extracts of plants and animals also contain **steroids**, molecules that are derived from the triterpene lanosterol (Figure 27.6) and whose structures are based on a tetracyclic ring system. The four rings are designated A, B, C, and D, beginning at the lower left, and the carbon atoms are numbered beginning in the A ring. The three six-membered rings (A, B, and C) adopt chair conformations but are

prevented by their rigid geometry from undergoing the usual cyclohexane ring-flips (Section 4.6).

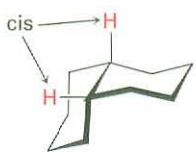




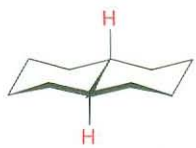
A steroid
(R = various side chains)

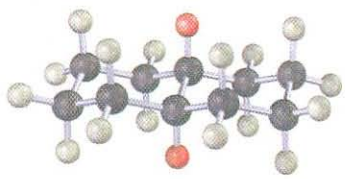
Two cyclohexane rings can be joined in either a cis or a trans manner. With cis fusion to give *cis*-decalin, both groups at the ring-junction positions (the *angular* groups) are on the same side of the two rings. With trans fusion to give *trans*-decalin, the groups at the ring junctions are on opposite sides.

***cis*-Decalin**



***trans*-Decalin**

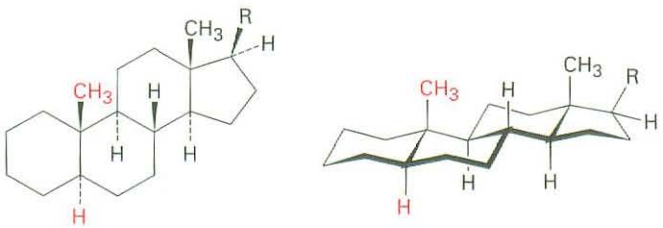




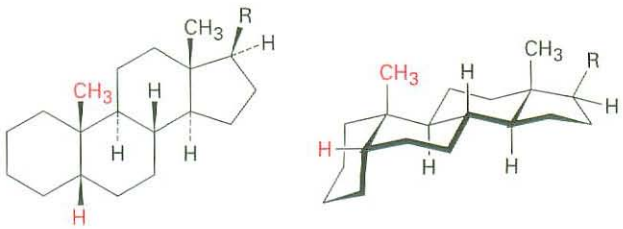
As shown in Figure 27.11, steroids can have either a cis or a trans fusion of the A and B rings, but the other ring fusions (B–C and C–D) are usually trans. An A–B trans steroid has the C19 angular methyl group up, denoted β, and the hydrogen atom at C5 down, denoted α, on opposite sides of the molecule. An A–B cis steroid, by contrast, has both the C19 angular methyl group and the C5 hydrogen atom on the same side (β) of the molecule. Both kinds of steroids are relatively long, flat molecules that have their two methyl groups (C18 and C19) protruding axially above the ring system. The A–B trans steroids are the more common, although A–B cis steroids are found in liver bile.

Figure 27.11 Steroid conformations. The three six-membered rings have chair conformations but are unable to undergo ring-flips. The A and B rings can be either cis-fused or trans-fused.

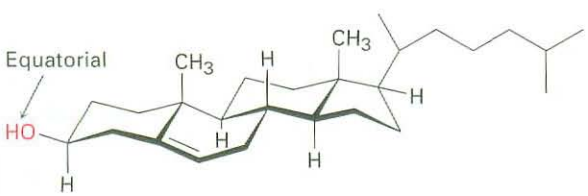
An A–B trans steroid

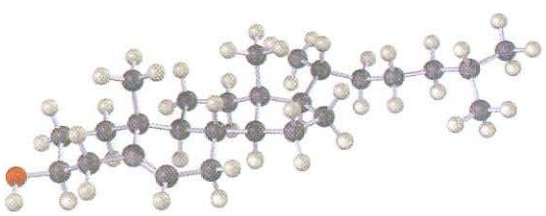


An A–B cis steroid



Substituent groups on the steroid ring system can be either axial or equatorial. As with simple cyclohexanes (Section 4.7), equatorial substitution is generally more favorable than axial substitution for steric reasons. The hydroxyl group at C3 of cholesterol, for example, has the more stable equatorial orientation. Unlike what happens with simple cyclohexanes, however, steroids are rigid molecules whose geometry prevents cyclohexane ring-flips.

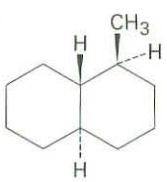




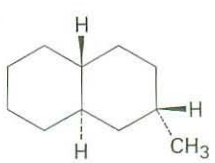
Cholesterol

Problem 27.8 Draw the following molecules in chair conformations, and tell whether the ring substituents are axial or equatorial:

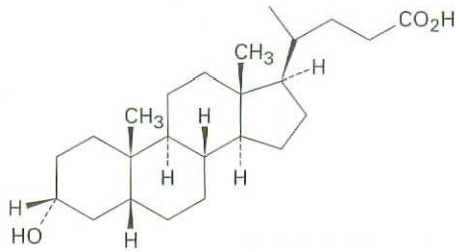
(a)



(b)



Problem 27.9 Lithocholic acid is an A–B cis steroid found in human bile. Draw lithocholic acid showing chair conformations as in Figure 27.11, and tell whether the hydroxyl group at C3 is axial or equatorial.

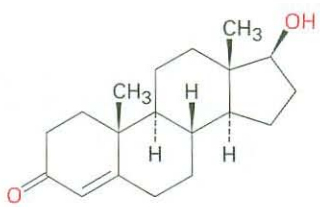


Lithocholic acid

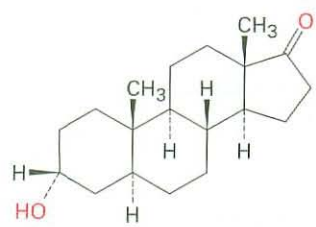
Steroid Hormones

In humans, most steroids function as **hormones**, chemical messengers that are secreted by endocrine glands and carried through the bloodstream to target tissues. There are two main classes of steroid hormones: the *sex hormones*, which control maturation, tissue growth, and reproduction, and the *adrenocortical hormones*, which regulate a variety of metabolic processes.

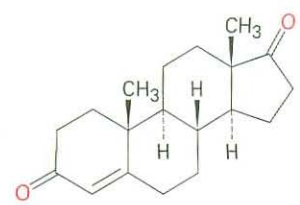
Sex Hormones Testosterone and androsterone are the two most important male sex hormones, or *androgens*. Androgens are responsible for the development of male secondary sex characteristics during puberty and for promoting tissue and muscle growth. Both are synthesized in the testes from cholesterol. Androstenedione is another minor hormone that has received particular attention because of its use by prominent athletes.



Testosterone



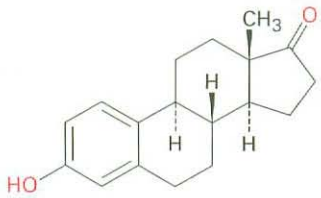
Androsterone



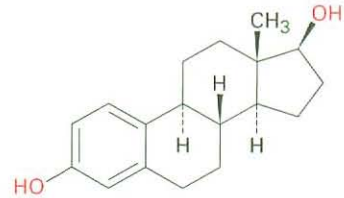
Androstenedione

(Androgens)

Estrone and estradiol are the two most important female sex hormones, or *estrogens*. Synthesized in the ovaries from testosterone, estrogenic hormones are responsible for the development of female secondary sex characteristics and for regulation of the menstrual cycle. Note that both have a benzene-like aromatic A ring. In addition, another kind of sex hormone called a *progestin* is essential for preparing the uterus for implantation of a fertilized ovum during pregnancy. Progesterone is the most important progestin.

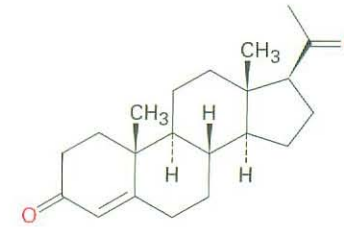


Estrone



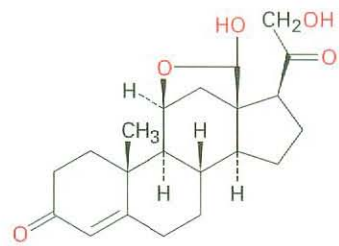
Estradiol

(Estrogens)

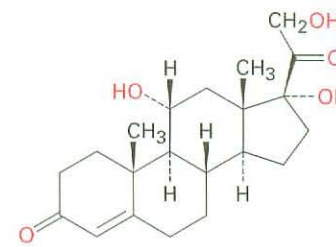


Progesterone
(a progestin)

Adrenocortical Hormones Adrenocortical steroids are secreted by the adrenal glands, small organs located near the upper end of each kidney. There are two types of adrenocortical steroids, called *mineralocorticoids* and *glucocorticoids*. Mineralocorticoids, such as aldosterone, control tissue swelling by regulating cellular salt balance between Na^+ and K^+. Glucocorticoids, such as hydrocortisone, are involved in the regulation of glucose metabolism and in the control of inflammation. Glucocorticoid ointments are widely used to bring down the swelling from exposure to poison oak or poison ivy.

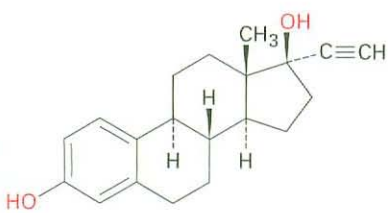


Aldosterone
(a mineralocorticoid)

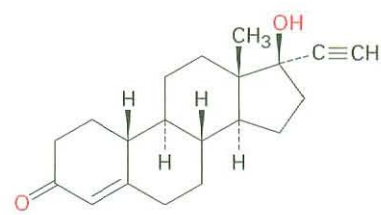


Hydrocortisone
(a glucocorticoid)

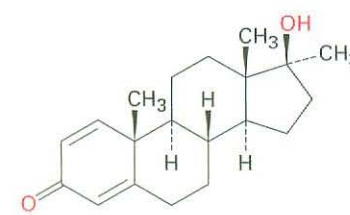
Synthetic Steroids In addition to the many hundreds of steroids isolated from plants and animals, thousands more have been synthesized in pharmaceutical laboratories in a search for new drugs. Among the best-known synthetic steroids are the oral contraceptives and anabolic agents. Most birth-control pills are a mixture of two compounds, a synthetic estrogen, such as ethynylestradiol, and a synthetic progestin, such as norethindrone. Anabolic steroids, such as methandrostenolone (Dianabol), are synthetic androgens that mimic the tissue-building effects of natural testosterone.



Ethynylestradiol
(a synthetic estrogen)



Norethindrone
(a synthetic progestin)



Methandrostenolone
(Dianabol)

27.7 Biosynthesis of Steroids

Steroids are heavily modified triterpenoids that are biosynthesized in living organisms from farnesyl diphosphate (C_{15}) by a reductive dimerization to the acyclic hydrocarbon squalene (C_{30}), which is converted into lanosterol (Figure 27.12). Further rearrangements and degradations then take place to yield various steroids. The conversion of squalene to lanosterol is among the most intensively studied of all biosynthetic transformations, with notable contributions by Konrad Bloch and J. W. Cornforth, who received Nobel Prizes for their work. Starting from an achiral, open-chain polyene, the entire process requires only two enzymes and results in the formation of six carbon–carbon bonds, four rings, and seven chirality centers.

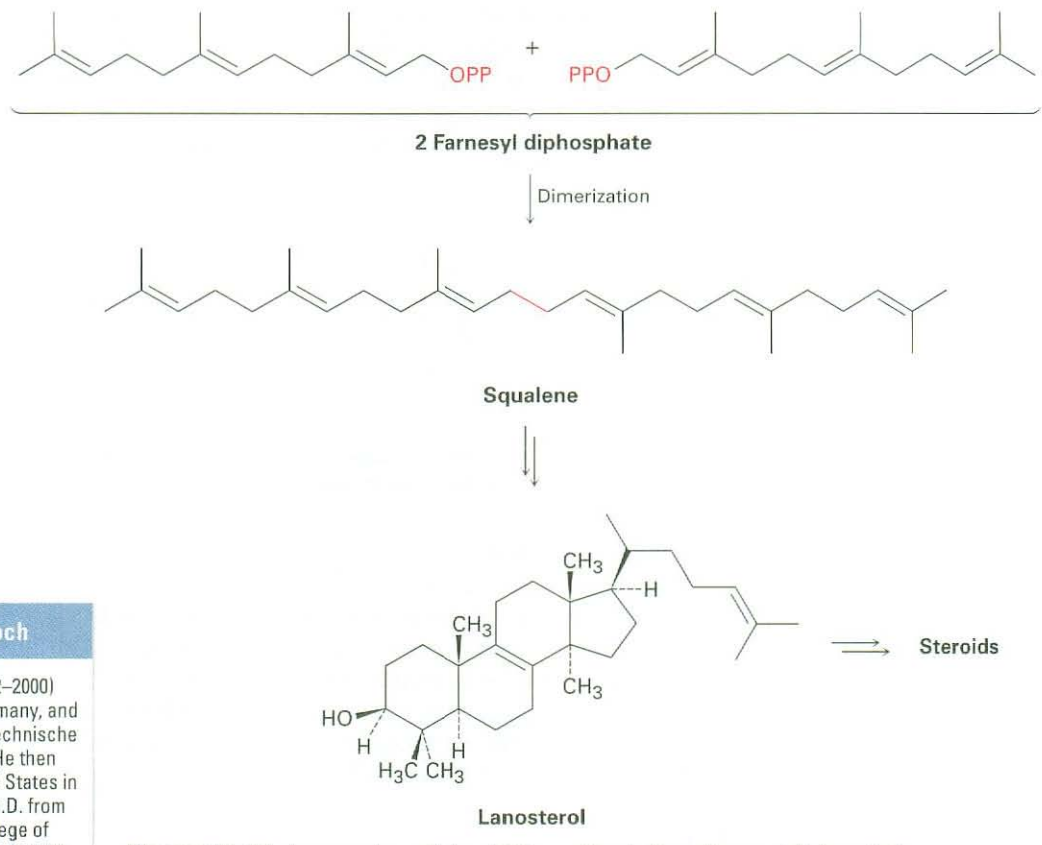


Figure 27.12 An overview of steroid biosynthesis from farnesyl diphosphate.

Konrad Emil Bloch

Konrad Emil Bloch (1912–2000) was born in Neisse, Germany, and began his study at the Technische Hochschule in Munich. He then immigrated to the United States in 1936 and obtained his Ph.D. from Columbia University College of Physicians and Surgeons in 1938. After first serving as professor at the University of Chicago, he moved to Harvard University in 1954. He is best known for his work on cholesterol biosynthesis, for which he shared the 1964 Nobel Prize in medicine.

Lanosterol biosynthesis begins with the selective conversion of squalene to its epoxide, (3*S*)-2,3-oxidosqualene, catalyzed by squalene epoxidase. Molecular O_2 provides the source of the epoxide oxygen atom, and NADPH is required, along with a flavin coenzyme. The proposed mechanism involves

Sir John Warcup Cornforth

Sir John Warcup Cornforth (1917–2004) was born in Sydney, Australia, and earned his Ph.D. from Oxford University in 1941 working with Sir Robert Robinson. He was on the staff of the National Institute for Medical Research in London from 1946 to 1962, at Shell Research Ltd. (1962–1975), and ultimately at Sussex University (1975–1982). Profoundly deaf since his teens, he worked in constant collaboration with his wife, Rita Harradence. He received the 1975 Nobel Prize in chemistry.

reaction of $FADH_2$ with O_2 to produce a flavin hydroperoxide intermediate (ROOH), which transfers an oxygen to squalene in a pathway initiated by nucleophilic attack of the squalene double bond on the terminal hydroperoxide oxygen (Figure 27.13). The flavin alcohol formed as a by-product loses H_2O to give FAD, which is reduced back to $FADH_2$ by NADPH. As noted in Section 7.8, such an epoxidation mechanism is closely analogous to that by which peroxyacids (RCO_3H) react with alkenes to give epoxides in the laboratory.

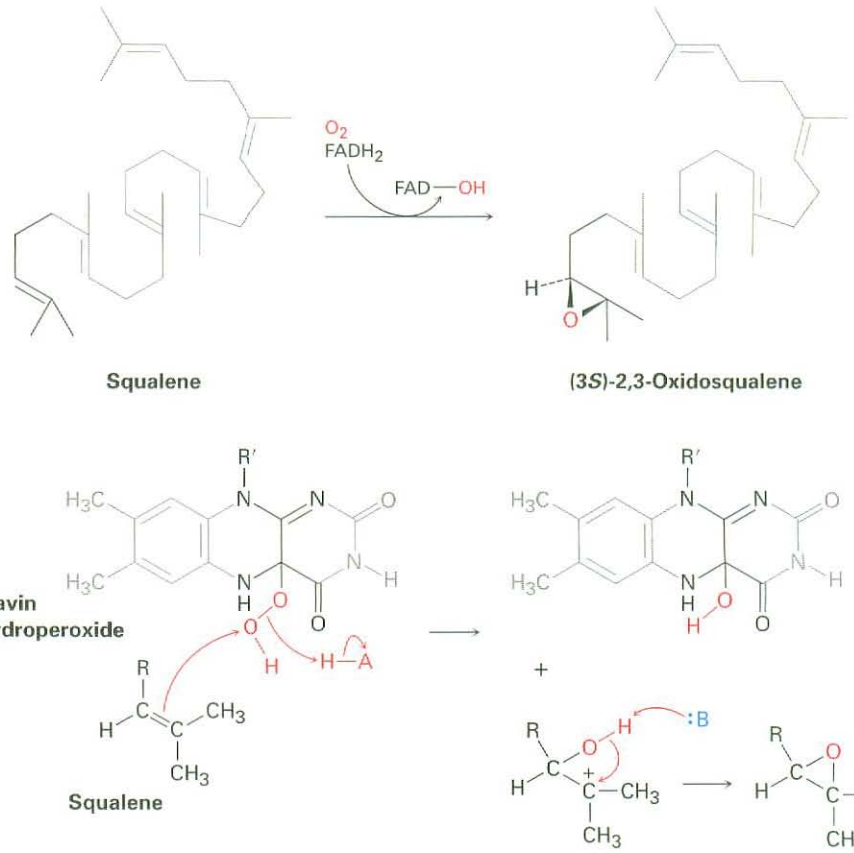


Figure 27.13 Proposed mechanism of the oxidation of squalene by flavin hydroperoxide.

The second part of lanosterol biosynthesis is catalyzed by oxidosqualene: lanosterol cyclase and occurs as shown in Figure 27.14. Squalene is folded by the enzyme into a conformation that aligns the various double bonds for undergoing a cascade of successive intramolecular electrophilic additions, followed by a series of hydride and methyl migrations. Except for the initial epoxide protonation/cyclization, the process is probably stepwise and appears to involve discrete carbocation intermediates that are stabilized by electrostatic interactions with electron-rich aromatic amino acids in the enzyme.

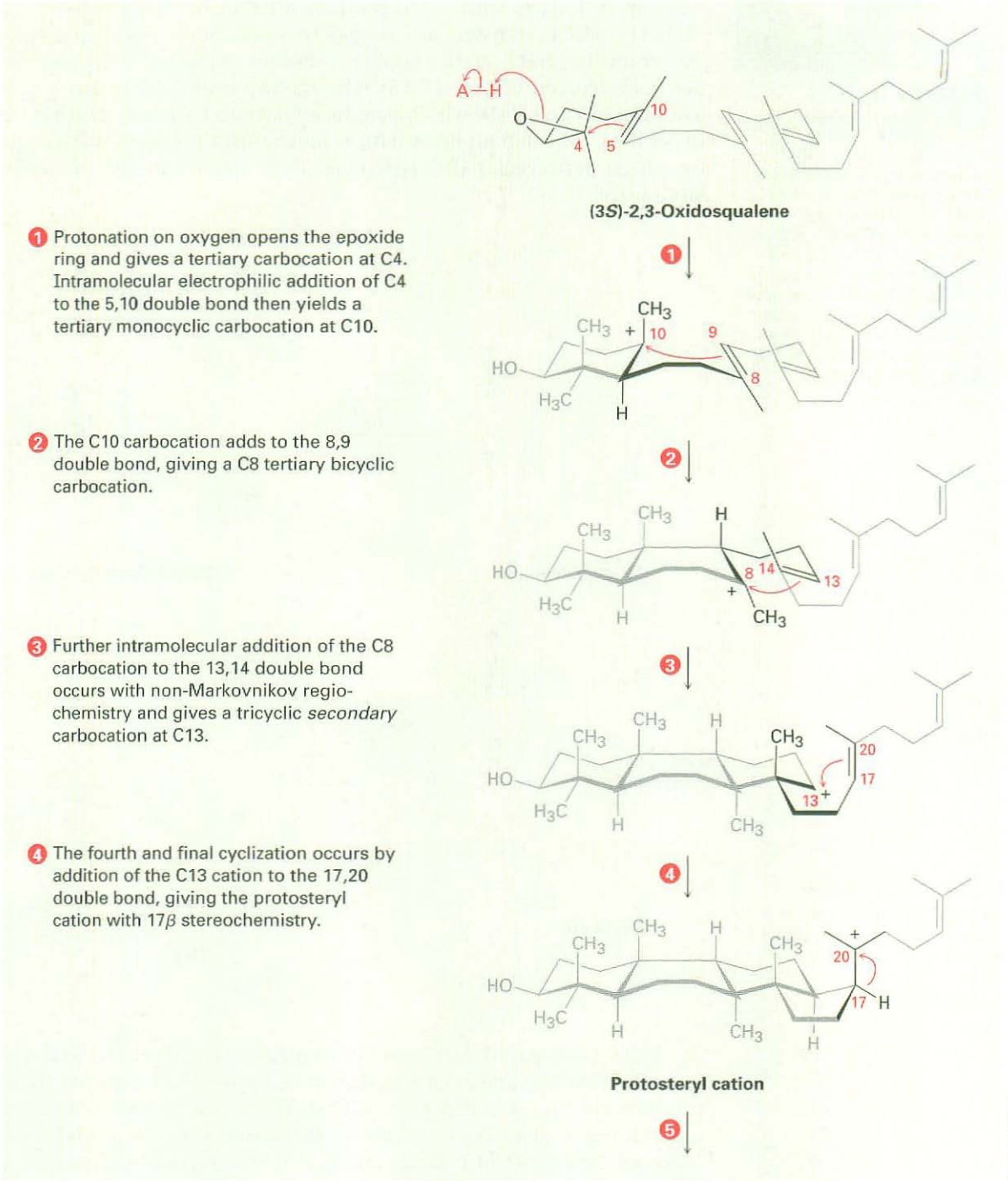
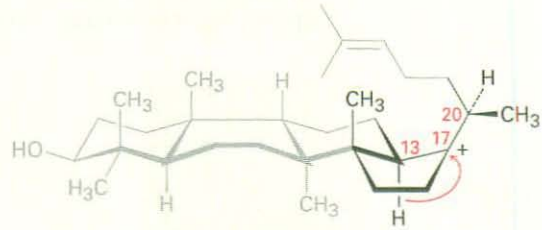


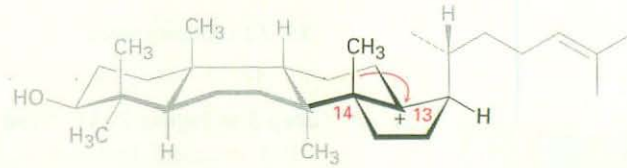
Figure 27.14 MECHANISM: Mechanism of the conversion of 2,3-oxidosqualene to lanosterol. Four cationic cyclizations are followed by four rearrangements and a final loss of H^+ from C9. The steroid numbering system is used for referring to specific positions in the intermediates (Section 27.6). Individual steps are explained in the text.

Protosteryl cation

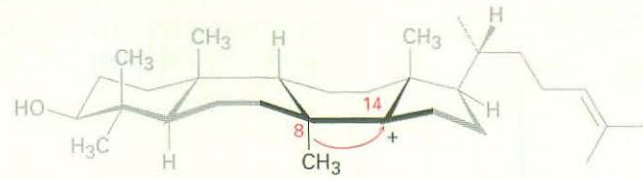
❺ Hydride migration from C17 to C20 occurs, establishing *R* stereochemistry at C20.



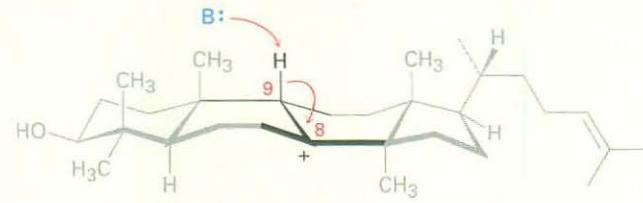
❻ A second hydride migration takes place, from C13 to C17, establishing the final 17β stereochemistry of the side chain.



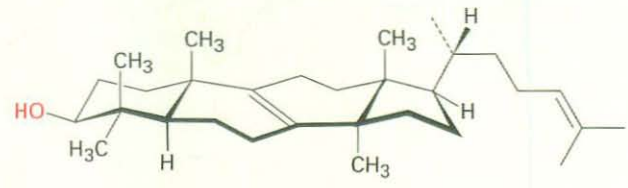
❼ Methyl migration from C14 to C13 occurs.



❽ A second methyl migration occurs, from C8 to C14.



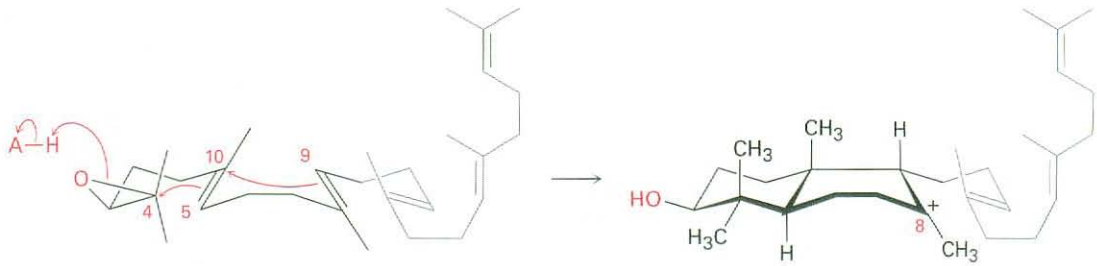
❾ Loss of a proton from C9 forms an 8,9 double bond and gives lanosterol.



Lanosterol

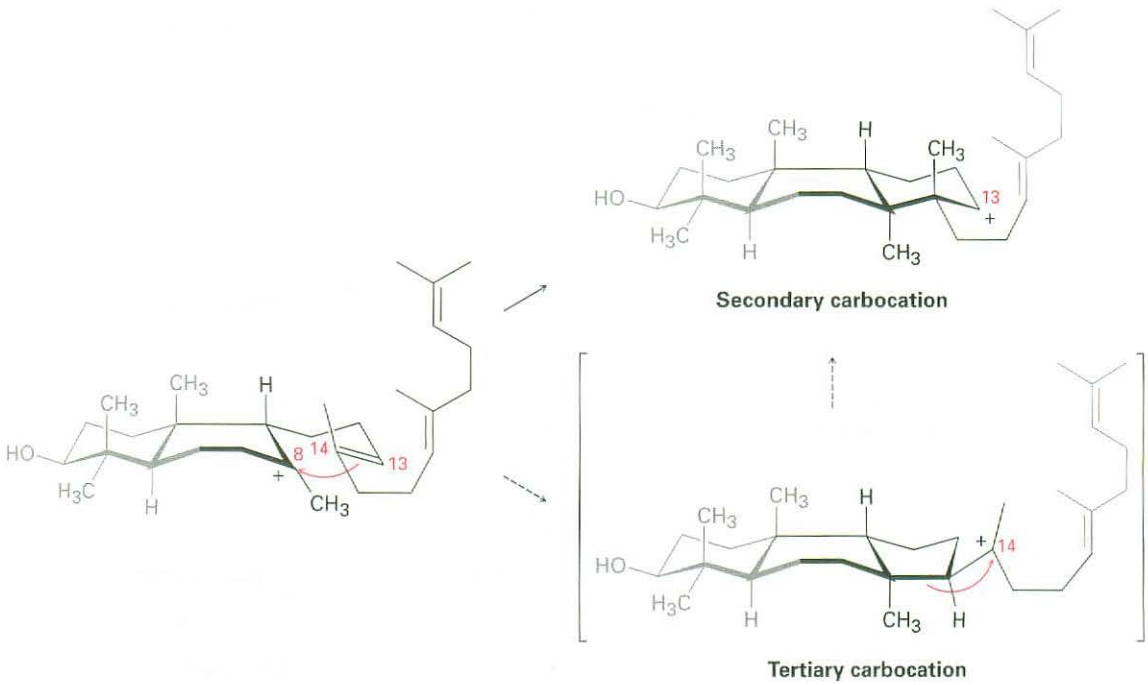
Figure 27.14 *(continued)*

Steps 1–2 of Figure 27.14: Epoxide Opening and Initial Cyclizations Cyclization is initiated in step 1 by protonation of the epoxide ring by an aspartic acid residue in the enzyme. Nucleophilic opening of the protonated epoxide by the nearby 5,10 double bond (steroid numbering; Section 27.6) then yields a tertiary carbocation at C10. Further addition of C10 to the 8,9 double bond in step 2 next gives a bicyclic tertiary cation at C8.



(3*S*)-2,3-Oxidosqualene

Step 3 of Figure 27.14: Third Cyclization The third cationic cyclization is somewhat unusual because it occurs with non-Markovnikov regiochemistry and gives a secondary cation at C13 rather than the alternative tertiary cation at C14. There is growing evidence, however, that the tertiary carbocation may in fact be formed initially and that the secondary cation arises by subsequent rearrangement. The secondary cation is probably stabilized in the enzyme pocket by the proximity of an electron-rich aromatic ring.

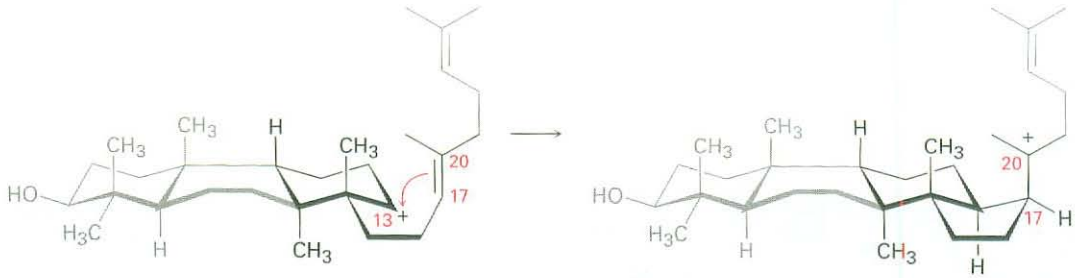


Secondary carbocation

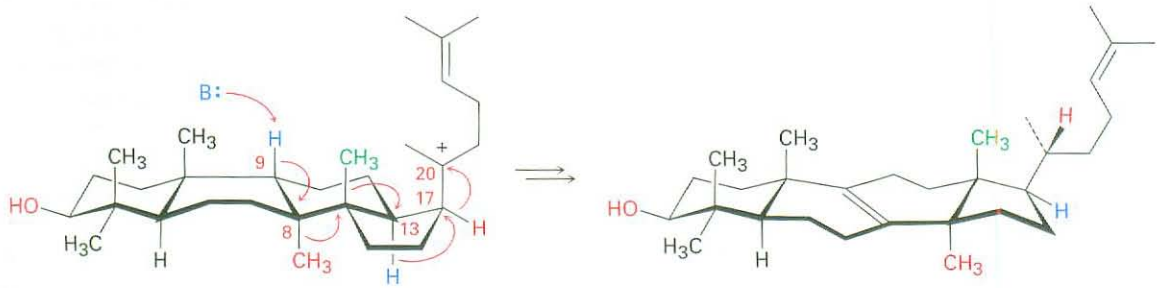
Tertiary carbocation

Step 4 of Figure 27.14: Final Cyclization The fourth and last cyclization occurs in step 4 by addition of the cationic center at C13 to the 17,20 double bond, giving what is known as the *protosteryl* cation. The side-chain alkyl group at

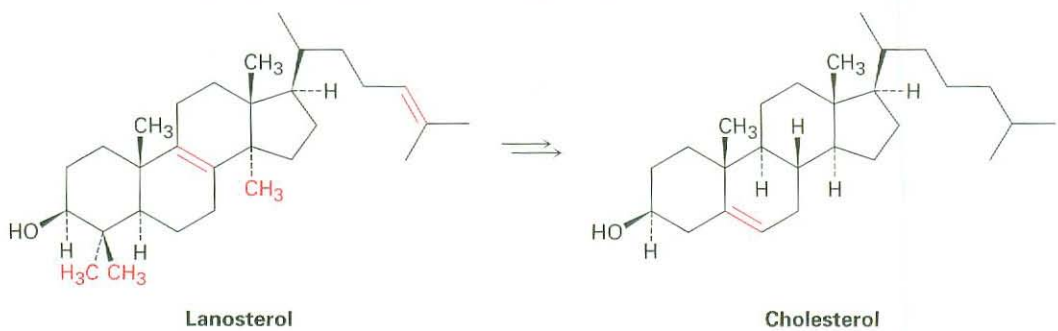
C17 has β (up) stereochemistry, although this stereochemistry is lost in step 5 and then reset in step 6.



Steps 5–9 of Figure 27.14: Carbocation Rearrangements Once the tetracyclic carbon skeleton of lanosterol has been formed, a series of carbocation rearrangements occur (Section 6.11). The first rearrangement, hydride migration from C17 to C20, occurs in step 5 and results in establishment of *R* stereochemistry at C20 in the side chain. A second hydride migration then occurs from C13 to C17 on the α (bottom) face of the ring in step 6 and reestablishes the 17β orientation of the side chain. Finally, two methyl group migrations, the first from C14 to C13 on the top (β) face and the second from C8 to C14 on the bottom (α) face, place the positive charge at C8. A basic histidine residue in the enzyme then removes the neighboring β proton from C9 to give lanosterol.



From lanosterol, the pathway for steroid biosynthesis continues on to yield cholesterol. Cholesterol then becomes a branch point, serving as the common precursor from which all other steroids are derived.



Problem 27.10 Compare the structures of lanosterol and cholesterol, and catalog the changes needed for the transformation.

Focus On . . .

Saturated Fats, Cholesterol, and Heart Disease

© Rob Friedman

It's hard to resist, but a high intake of saturated animal fat doesn't do much for your cholesterol level.

We hear a lot these days about the relationships between saturated fats, cholesterol, and heart disease. What are the facts? It's well established that a diet rich in saturated animal fats often leads to an increase in blood serum cholesterol, particularly in sedentary, overweight people. Conversely, a diet lower in saturated fats and higher in polyunsaturated fats leads to a lower serum cholesterol level. Studies have shown that a serum cholesterol level greater than 240 mg/dL (a desirable value is <200 mg/dL) is correlated with an increased incidence of coronary artery disease, in which cholesterol deposits build up on the inner walls of coronary arteries, blocking the flow of blood to the heart muscles.

A better indication of a person's risk of heart disease comes from a measurement of blood lipoprotein levels. *Lipoproteins* are complex molecules with both lipid and protein parts that transport lipids through the body. They can be divided into three types according to density, as shown in Table 27.3. Very-low-density lipoproteins (VLDLs) act primarily as carriers of triglycerides from the intestines to peripheral tissues, whereas low-density lipoproteins (LDLs) and high-density lipoproteins (HDLs) act as carriers of cholesterol to and from the liver. Evidence suggests that LDLs transport cholesterol as its fatty-acid ester *to* peripheral tissues, whereas HDLs remove cholesterol as its stearate ester *from* dying cells. If LDLs deliver more cholesterol than is needed, and if insufficient HDLs are present to remove it, the excess is deposited in arteries. Thus, a *low* level of *low*-density lipoproteins is good because it means that less cholesterol is being transported, and a *high* level of *high*-density lipoproteins is good because it means that more cholesterol is being removed. In addition, HDL contains an enzyme that has antioxidant properties, offering further protection against heart disease.

As a rule of thumb, a person's risk drops about 25% for each increase of 5 mg/dL in HDL concentration. Normal values are about 45 mg/dL for men and 55 mg/dL for women, perhaps explaining why premenopausal women appear to be somewhat less susceptible than men to heart disease.

Not surprisingly, the most important factor in gaining high HDL levels is a generally healthful lifestyle. Obesity, smoking, and lack of exercise lead to low HDL levels, whereas regular exercise and a sensible diet lead to high HDL levels. Distance runners and other endurance athletes have HDL levels nearly 50% higher than the general population. Failing that—not everyone wants to run 50 miles per week—diet is also important. Diets high in cold-water fish

(continued)

Table 27.3 Serum Lipoproteins

Name	Density (g/mL)	% Lipid	% Protein	Optimal (mg/dL)	Poor (mg/dL)
VLDL	0.940–1.006	90	10	—	—
LDL	1.006–1.063	75	25	<100	>130
HDL	1.063–1.210	60	40	>60	<40

like salmon and whitefish, raise HDL and lower blood cholesterol because these fish contain almost entirely polyunsaturated fat. Animal fat from red meat and cooking fats should be minimized because saturated fats and monounsaturated trans fats raise blood cholesterol.

SUMMARY AND KEY WORDS

eicosanoid, 1067
fat, 1061
fatty acid, 1061
hormone, 1082
lipid, 1060
lipid bilayer, 1067
micelle, 1064
oil, 1061
phospholipid, 1066
polyunsaturated fatty acid, 1061
prostaglandin, 1067
steroid, 1079
terpenoid, 1070
triacylglycerol, 1061
wax, 1061

Lipids are the naturally occurring materials isolated from plants and animals by extraction with nonpolar organic solvents. Animal **fats** and vegetable **oils** are the most widely occurring lipids. Both are **triacylglycerols**—triesters of glycerol with long-chain **fatty acids**. Animal fats are usually saturated, whereas vegetable oils usually have unsaturated fatty acid residues.

Phospholipids are important constituents of cell membranes and are of two kinds. *Glycerophospholipids*, such as phosphatidylcholine and phosphatidylethanolamine, are closely related to fats in that they have a glycerol backbone esterified to two fatty acids (one saturated and one unsaturated) and to one phosphate ester. *Sphingomyelins* have the amino alcohol sphingosine for their backbone.

Eicosanoids and **terpenoids** are still other classes of lipids. Eicosanoids, of which prostaglandins are the most abundant kind, are derived biosynthetically from arachidonic acid, are found in all body tissues, and have a wide range of physiological activity. Terpenoids are often isolated from the essential oils of plants, have an immense diversity of structure, and are produced biosynthetically from the five-carbon precursor isopentenyl diphosphate (IPP). Isopentenyl diphosphate is itself biosynthesized from 3 equivalents of acetate in the mevalonate pathway.

Steroids are plant and animal lipids with a characteristic tetracyclic carbon skeleton. Like the eicosanoids, steroids occur widely in body tissues and have a large variety of physiological activities. Steroids are closely related to terpenoids and arise biosynthetically from the triterpene lanosterol. Lanosterol, in turn, arises from cationic cyclization of the acyclic hydrocarbon squalene.

EXERCISES

Organic KNOWLEDGE TOOLS

ThomsonNOW™ Sign in at **www.thomsonedu.com** to assess your knowledge of this chapter's topics by taking a pre-test. The pre-test will link you to interactive organic chemistry resources based on your score in each concept area.

Online homework for this chapter may be assigned in Organic OWL.

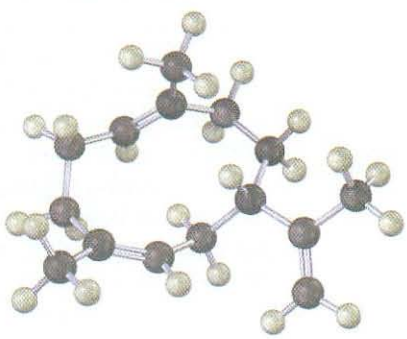
■ indicates problems assignable in Organic OWL.

VISUALIZING CHEMISTRY

(Problems 27.1–27.10 appear within the chapter.)

27.11 ■ The following model is that of cholic acid, a constituent of human bile. Locate the three hydroxyl groups, and identify each as axial or equatorial. Is cholic acid an A–B trans steroid or an A–B cis steroid?

27.12 Propose a biosynthetic pathway for the sesquiterpene helminthogermacrene from farnesyl diphosphate.



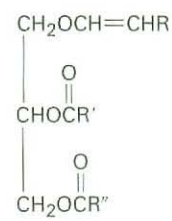
27.13 ■ Identify the following fatty acid, and tell whether it is more likely to be found in peanut oil or in red meat:

ADDITIONAL PROBLEMS

27.14 Fats can be either optically active or optically inactive, depending on their structure. Draw the structure of an optically active fat that yields 2 equivalents of stearic acid and 1 equivalent of oleic acid on hydrolysis. Draw the structure of an optically inactive fat that yields the same products.

27.15 Spermaceti, a fragrant substance from sperm whales, was much used in cosmetics until it was banned in 1976 to protect the whales from extinction. Chemically, spermaceti is cetyl palmitate, the ester of cetyl alcohol (n-$C_{16}H_{33}OH$) with palmitic acid. Draw its structure.

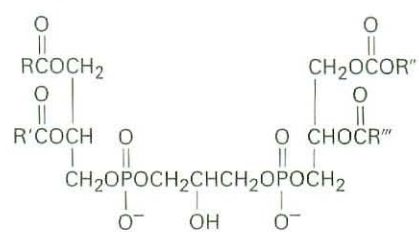
27.16 The *plasmalogens* are a group of lipids found in nerve and muscle cells. How do plasmalogens differ from fats?



A plasmalogen

27.17 What products would you obtain from hydrolysis of a plasmalogen (Problem 27.16) with aqueous NaOH? With H_3O^+?

27.18 *Cardiolipins* are a group of lipids found in heart muscles. What products would be formed if all ester bonds, including phosphates, were saponified by treatment with aqueous NaOH?



A cardiolipin

■ Assignable in OWL

27.19 ■ Stearolic acid, $C_{18}H_{32}O_2$, yields stearic acid on catalytic hydrogenation and undergoes oxidative cleavage with ozone to yield nonanoic acid and nonanedioic acid. What is the structure of stearolic acid?

27.20 ■ How would you synthesize stearolic acid (Problem 27.19) from 1-decyne and 1-chloro-7-iodoheptane?

27.21 ■ Show the products you would expect to obtain from reaction of glyceryl trioleate with the following reagents:

(a) Excess Br_2 in CH_2Cl_2
(b) H_2/Pd
(c) $NaOH/H_2O$
(d) O_3, then Zn/CH_3CO_2H
(e) $LiAlH_4$, then H_3O^+
(f) CH_3MgBr, then H_3O^+

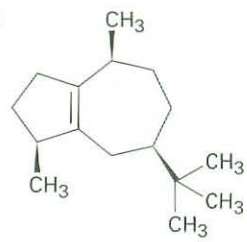
27.22 ■ How would you convert oleic acid into the following substances?

(a) Methyl oleate
(b) Methyl stearate
(c) Nonanal
(d) Nonanedioic acid
(e) 9-Octadecynoic acid (stearolic acid)
(f) 2-Bromostearic acid
(g) 18-Pentatriacontanone, $CH_3(CH_2)_{16}CO(CH_2)_{16}CH_3$

27.23 Cold-water fish like salmon are rich in *omega-3* fatty acids, which have a double bond three carbons in from the noncarboxyl end of the chain and have been shown to lower blood cholesterol levels. Draw the structure of 5,8,11,14,17-eicosapentaenoic acid, a common example. (Eicosane = $C_{20}H_{42}$.)

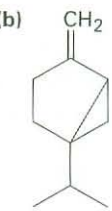
27.24 Without proposing an entire biosynthetic pathway, draw the appropriate precursor, either geranyl diphosphate or farnesyl diphosphate, in a conformation that shows a likeness to each of the following terpenoids:

(a)



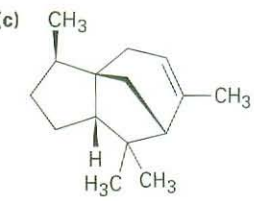
Guaiol

(b)



Sabinene

(c)



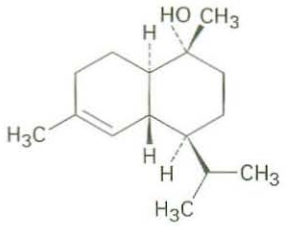
Cedrene

27.25 ■ Indicate by asterisks the chirality centers present in each of the terpenoids shown in Problem 27.24. What is the maximum possible number of stereoisomers for each?

27.26 ■ Assume that the three terpenoids in Problem 27.24 are derived biosynthetically from isopentenyl diphosphate and dimethylallyl diphosphate, each of which was isotopically labeled at the diphosphate-bearing carbon atom (C1). At what positions would the terpenoids be isotopically labeled?

27.27 ■ Assume that acetyl CoA containing a ^{14}C isotopic label in the carboxyl carbon atom is used as starting material for the biosynthesis of mevalonate, as shown in Figure 27.7. At what positions in mevalonate would the isotopic label appear?

27.28 ■ Assume that acetyl CoA containing a ^{14}C isotopic label in the carboxy carbon atom is used as starting material and that the mevalonate pathway i followed. Identify the positions in α-cadinol where the label would appear.

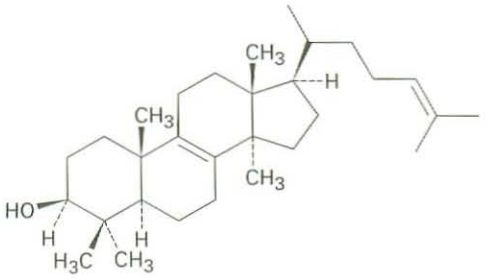


α-Cadinol

27.29 Assume that acetyl CoA containing a ^{14}C isotopic label in the carboxyl carbon atom is used as starting material and that the mevalonate pathway is followed. Identify the positions in squalene where the label would appear.

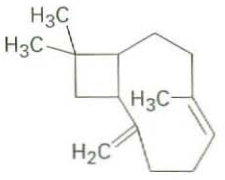
Squalene

27.30 Assume that acetyl CoA containing a ^{14}C isotopic label in the carboxyl carbon atom is used as starting material and that the mevalonate pathway is followed. Identify the positions in lanosterol where the label would appear.



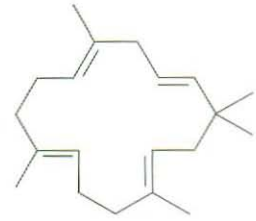
Lanosterol

27.31 Propose a mechanistic pathway for the biosynthesis of caryophyllene, a substance found in clove oil.



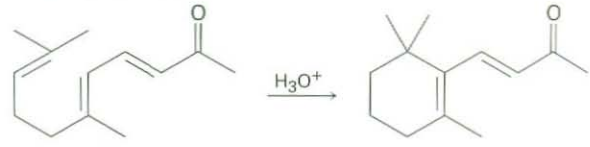
Caryophyllene

27.32 Flexibilene, a compound isolated from marine coral, is the only known terpenoid to contain a 15-membered ring. What is the structure of the acyclic biosynthetic precursor of flexibilene? Show the mechanistic pathway for the biosynthesis.



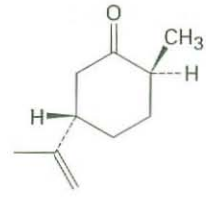
Flexibilene

27.33 ■ Suggest a mechanism by which ψ-ionone is transformed into β-ionone on treatment with acid.



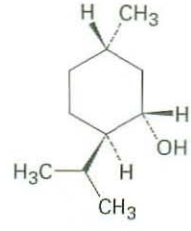
ψ-Ionone **β-Ionone**

27.34 ■ Draw the most stable chair conformation of dihydrocarvone.



Dihydrocarvone

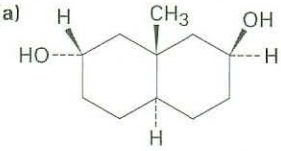
27.35 ■ Draw the most stable chair conformation of menthol, and label each substituent as axial or equatorial.



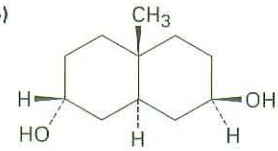
Menthol (from peppermint oil)

27.36 ■ As a general rule, equatorial alcohols are esterified more readily than axial alcohols. What product would you expect to obtain from reaction of the following two compounds with 1 equivalent of acetic anhydride?

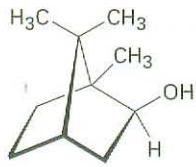
(a)



(b)

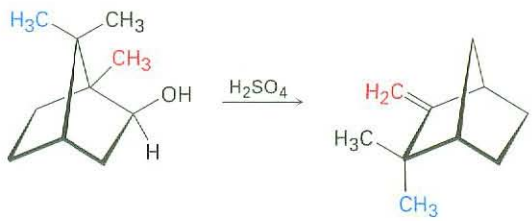


27.37 ■ Propose a mechanistic pathway for the biosynthesis of isoborneol. A carbocation rearrangement is needed at one point in the scheme.



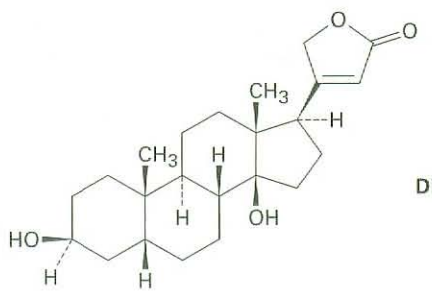
Isoborneol

27.38 ■ Isoborneol (Problem 27.37) is converted into camphene on treatment with dilute sulfuric acid. Propose a mechanism for the reaction, which involves a carbocation rearrangement.



Isoborneol **Camphene**

27.39 Digitoxigenin is a heart stimulant obtained from the purple foxglove *Digitalis purpurea* and used in the treatment of heart disease. Draw the three-dimensional conformation of digitoxigenin, and identify the two −OH groups as axial or equatorial.



Digitoxigenin

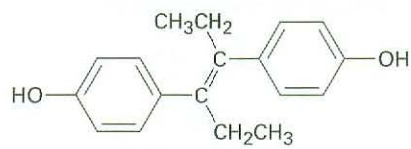
27.40 What product would you obtain by reduction of digitoxigenin (Problem 27.39) with $LiAlH_4$? By oxidation with pyridinium chlorochromate?

27.41 ■ Vaccenic acid, $C_{18}H_{34}O_2$, is a rare fatty acid that gives heptanal and 11-oxoundecanoic acid [$OHC(CH_2)_9CO_2H$] on ozonolysis followed by zinc treatment. When allowed to react with $CH_2I_2/Zn(Cu)$, vaccenic acid is converted into lactobacillic acid. What are the structures of vaccenic and lactobacillic acids?

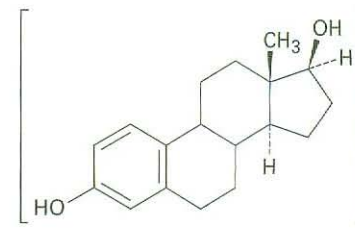
27.42 Eleostearic acid, $C_{18}H_{30}O_2$, is a rare fatty acid found in the tung oil used for finishing furniture. On ozonolysis followed by treatment with zinc, eleostearic acid furnishes one part pentanal, two parts glyoxal (OHC—CHO), and one part 9-oxononanoic acid [$OHC(CH_2)_7CO_2H$]. What is the structure of eleostearic acid?

27.43 Diterpenoids are derived biosynthetically from geranylgeranyl diphosphate (GGPP), which is itself biosynthesized by reaction of farnesyl diphosphate with isopentenyl diphosphate. Show the structure of GGPP, and propose a mechanism for its biosynthesis from FPP and IPP.

27.44 Diethylstilbestrol (DES) has estrogenic activity even though it is structurally unrelated to steroids. Once used as an additive in animal feed, DES has been implicated as a causative agent in several types of cancer. Show how DES can be drawn so that it is sterically similar to estradiol.



Diethylstilbestrol



Estradiol

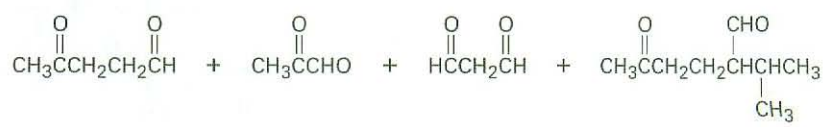
27.45 Propose a synthesis of diethylstilbestrol (Problem 27.44) from phenol and any other organic compound required.

27.46 ■ What products would you expect from reaction of estradiol (Problem 27.44) with the following reagents?

(a) NaH, then CH_3I (b) CH_3COCl, pyridine

(c) Br_2, $FeBr_3$ (d) Pyridinium chlorochromate in CH_2Cl_2

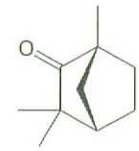
27.47 Cembrene, $C_{20}H_{32}$, is a diterpene hydrocarbon isolated from pine resin. Cembrene has a UV absorption at 245 nm, but dihydrocembrene ($C_{20}H_{34}$), the product of hydrogenation with 1 equivalent H_2, has no UV absorption. On exhaustive hydrogenation, 4 equivalents H_2 react, and octahydrocembrene, $C_{20}H_{40}$, is produced. On ozonolysis of cembrene, followed by treatment of the ozonide with zinc, four carbonyl-containing products are obtained:



Propose a structure for cembrene that is consistent with its formation from geranylgeranyl diphosphate.

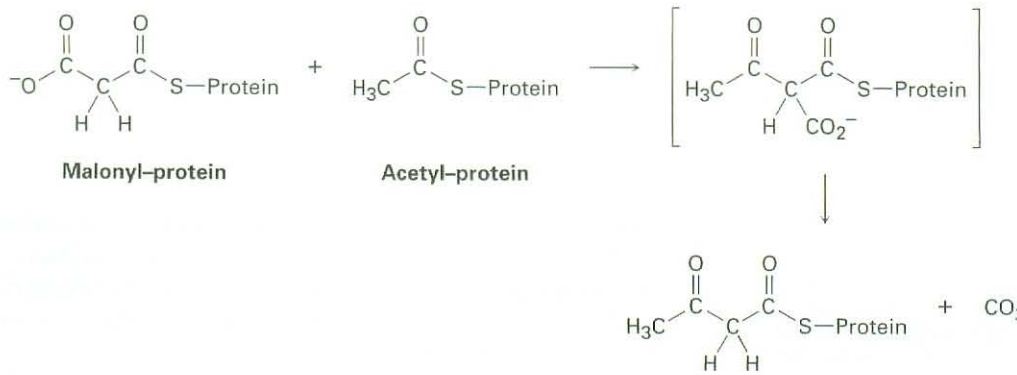
■ Assignable in OWL

27.48 α-Fenchone is a pleasant-smelling terpenoid isolated from oil of lavender. Propose a pathway for the formation of α-fenchone from geranyl diphosphate. A carbocation rearrangement is required.



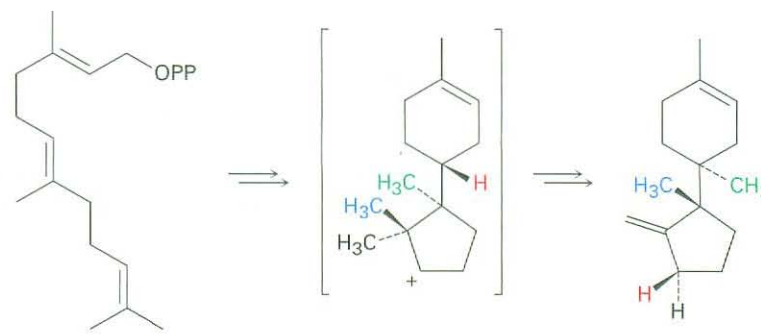
α-Fenchone

27.49 Fatty acids are synthesized by a multistep route that starts with acetate. The first step is a reaction between protein-bound acetyl and malonyl units to give a protein-bound 3-ketobutyryl unit. Show the mechanism, and tell what kind of reaction is occurring.



Malonyl–protein **Acetyl–protein** **3-Ketobutyryl–protein**

27.50 Propose a mechanism for the biosynthesis of the sesquiterpene trichodiene from farnesyl diphosphate. The process involves cyclization to give an intermediate secondary carbocation, followed by several carbocation rearrangements.



Farnesyl diphosphate (FPP) **Trichodiene**