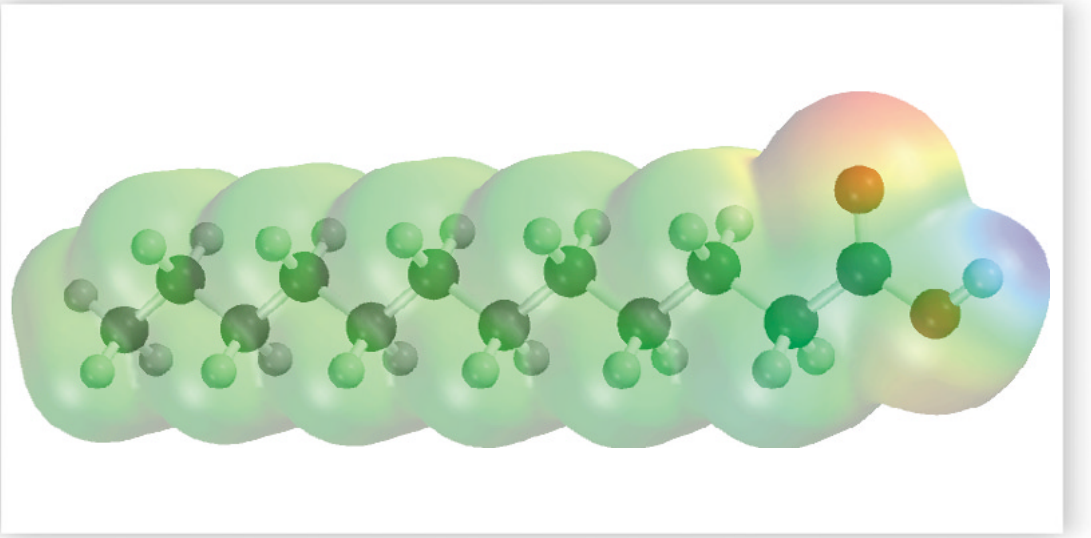


CHAPTER 26

LIPIDS

Lipids differ from the other classes of naturally occurring biomolecules (carbohydrates, proteins, and nucleic acids) in that they are more soluble in non-to-weakly polar solvents (diethyl ether, hexane, dichloromethane) than they are in water. They include a variety of structural types, a collection of which is introduced in this chapter.

In spite of the number of different structural types, lipids share a common biosynthetic origin in that they are ultimately derived from glucose. During one stage of carbohydrate metabolism, called *glycolysis,* glucose is converted to lactic acid. Pyruvic acid is an intermediate.

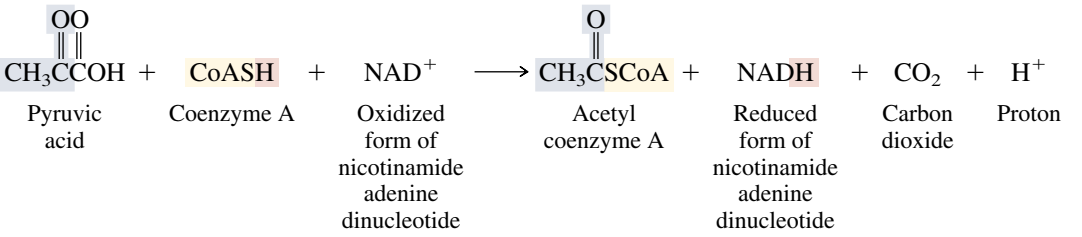
$$\underset{\text{Glucose}}{C_6H_{12}O_6} \longrightarrow \underset{\text{Pyruvic acid}}{CH_3\overset{\overset{O}{\|}}{C}CO_2H} \longrightarrow \underset{\text{Lactic acid}}{CH_3\overset{\overset{OH}{|}}{C}HCO_2H}$$

In most biochemical reactions the pH of the medium is close to 7. At this pH, carboxylic acids are nearly completely converted to their conjugate bases. Thus, it is common practice in biological chemistry to specify the derived carboxylate anion rather than the carboxylic acid itself. For example, we say that glycolysis leads to *lactate* by way of *pyruvate.*

Pyruvate is used by living systems in a number of different ways. One pathway, the one leading to lactate and beyond, is concerned with energy storage and production. This is not the only pathway available to pyruvate, however. A significant fraction of it is converted to acetate for use as a starting material in the biosynthesis of more complex substances, especially lipids. By far the major source of lipids is *biosynthesis* via acetate and this chapter is organized around that theme. We'll begin by looking at the reaction in which acetate (two carbons) is formed from pyruvate (three carbons).

26.1 ACETYL COENZYME A

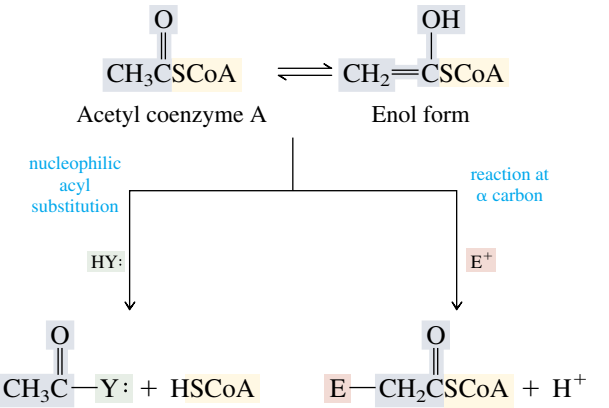
The form in which acetate is used in most of its important biochemical reactions is **acetyl coenzyme A** (Figure 26.1*a*). Acetyl coenzyme A is a *thioester* (Section 20.12). Its formation from pyruvate involves several steps and is summarized in the overall equation:



Coenzyme A was isolated and identified by Fritz Lipmann, an American biochemist. Lipmann shared the 1953 Nobel Prize in physiology or medicine for this work.

All the individual steps are catalyzed by enzymes. NAD^+ (Section 15.11) is required as an oxidizing agent, and coenzyme A (Figure 26.1*b*) is the acetyl group acceptor. Coenzyme A is a *thiol;* its chain terminates in a *sulfhydryl* (—SH) group. Acetylation of the sulfhydryl group of coenzyme A gives acetyl coenzyme A.

As we saw in Chapter 20, thioesters are more reactive than ordinary esters toward nucleophilic acyl substitution. They also contain a greater proportion of enol at equilibrium. Both properties are apparent in the properties of acetyl coenzyme A. In some reactions it is the carbonyl group of acetyl coenzyme A that reacts; in others it is the α-carbon atom.



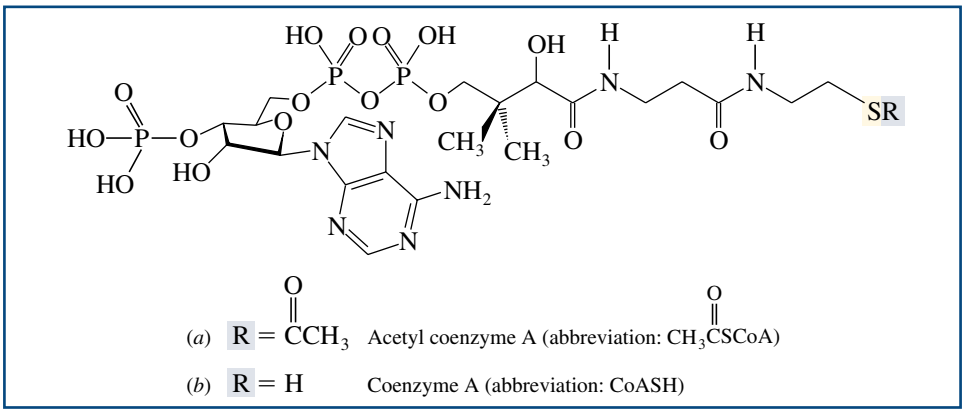


FIGURE 26.1 Structures of (*a*) acetyl coenzyme A and (*b*) coenzyme A.

We'll see numerous examples of both reaction types in the following sections. Keep in mind that in vivo reactions (reactions in living systems) are enzyme-catalyzed and occur at rates that are far greater than when the same transformations are carried out in vitro ("in glass") in the absence of enzymes. In spite of the rapidity with which enzyme-catalyzed reactions take place, the nature of these transformations is essentially the same as the fundamental processes of organic chemistry described throughout this text.

Fats are one type of lipid. They have a number of functions in living systems, including that of energy storage. Although carbohydrates serve as a source of readily available energy, an equal weight of fat delivers over twice the amount of energy. It is more efficient for an organism to store energy in the form of fat because it requires less mass than storing the same amount of energy in carbohydrates or proteins.

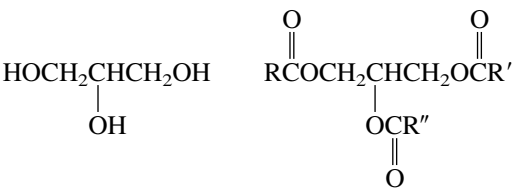
How living systems convert acetate to fats is an exceedingly complex story, one that is well understood in broad outline and becoming increasingly clear in detail as well. We will examine several aspects of this topic in the next few sections, focusing mostly on its structural and chemical features.

26.2 FATS, OILS, AND FATTY ACIDS

Fats and oils are naturally occurring mixtures of *triacylglycerols,* also called *triglycerides.* They differ in that fats are solids at room temperature and oils are liquids. We generally ignore this distinction and refer to both groups as fats.

An experiment describing the analysis of the triglyceride composition of several vegetable oils is described in the May 1988 issue of the *Journal of Chemical Education* (pp. 464–466).

Triacylglycerols are built on a glycerol framework.



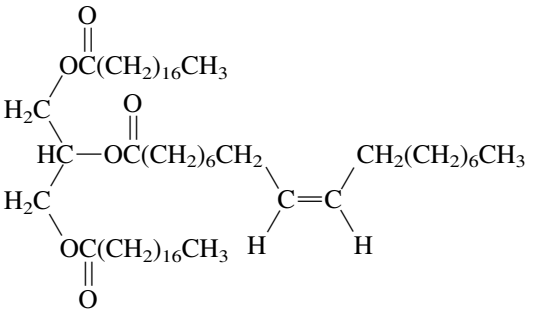
Glycerol A triacylglycerol

All three acyl groups in a triacylglycerol may be the same, all three may be different, or one may be different from the other two.

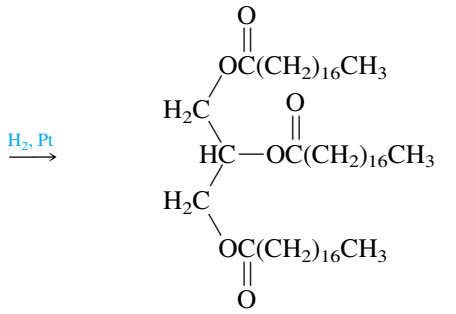
Figure 26.2 shows the structures of two typical triacylglycerols, 2-oleyl-1,3-distearylglycerol (Figure 26.2*a*) and tristearin (Figure 26.2*b*). Both occur naturally—in cocoa butter, for example. All three acyl groups in tristearin are stearyl (octadecanoyl) groups. In 2-oleyl-1,3-distearylglycerol, two of the acyl groups are stearyl, but the one in the middle is oleyl (*cis*-9-octadecenoyl). As the figure shows, tristearin can be prepared by catalytic hydrogenation of the carbon–carbon double bond of 2-oleyl-1,3-distearylglycerol. Hydrogenation raises the melting point from 43°C in 2-oleyl-1,3-distearylglycerol to 72°C in tristearin and is a standard technique in the food industry for converting liquid vegetable oils to solid "shortenings." The space-filling models of the two show the flatter structure of tristearin, which allows it to pack better in a crystal lattice than the more irregular shape of 2-oleyl-1,3-distearylglycerol permits. This irregular shape is a direct result of the cis double bond in the side chain.

Strictly speaking, the term "fatty acid" is restricted to those carboxylic acids that occur naturally in triacylglycerols. Many chemists and biochemists, however, refer to all unbranched carboxylic acids, irrespective of their origin and chain length, as fatty acids.

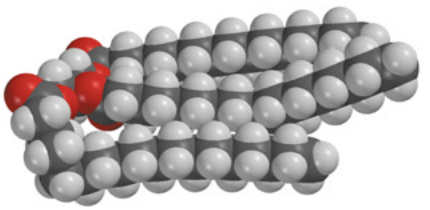
Hydrolysis of fats yields glycerol and long-chain **fatty acids.** Thus, tristearin gives glycerol and three molecules of stearic acid on hydrolysis. Table 26.1 lists a few representative fatty acids. As these examples indicate, most naturally occurring fatty acids possess an even number of carbon atoms and an unbranched carbon chain. The carbon



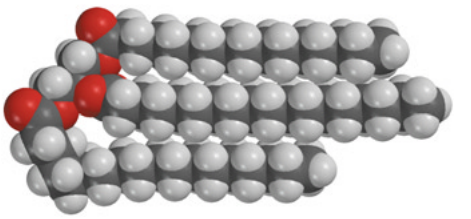
2-Oleyl-1,3-distearylglycerol (mp 43°C)



Tristearin (mp 72°C)



(*a*)



(*b*)

FIGURE 26.2 The structures of two typical triacylglycerols. (*a*) 2-Oleyl-1,3-distearylglycerol is a naturally occurring triacylglycerol found in cocoa butter. The cis double bond of its oleyl group gives the molecule a shape that interferes with efficient crystal packing. (*b*) Catalytic hydrogenation converts 2-oleyl-1,3-distearylglycerol to tristearin. Tristearin has a higher melting point than 2-oleyl-1,3-distearylglycerol.

TABLE 26.1 Some Representative Fatty Acids

Structural formula	Systematic name	Common name
Saturated fatty acids		
$CH_3(CH_2)_{10}COOH$	Dodecanoic acid	Lauric acid
$CH_3(CH_2)_{12}COOH$	Tetradecanoic acid	Myristic acid
$CH_3(CH_2)_{14}COOH$	Hexadecanoic acid	Palmitic acid
$CH_3(CH_2)_{16}COOH$	Octadecanoic acid	Stearic acid
$CH_3(CH_2)_{18}COOH$	Icosanoic acid	Arachidic acid
Unsaturated fatty acids		
$CH_3(CH_2)_7CH{=}CH(CH_2)_7COOH$	(*Z*)-9-Octadecenoic acid	Oleic acid
$CH_3(CH_2)_4CH{=}CHCH_2CH{=}CH(CH_2)_7COOH$	(9*Z*,12*Z*)-9,12-Octadecadienoic acid	Linoleic acid
$CH_3CH_2CH{=}CHCH_2CH{=}CHCH_2CH{=}CH(CH_2)_7COOH$	(9*Z*,12*Z*,15*Z*)-9,12,15-Octadecatrienoic acid	Linolenic acid
$CH_3(CH_2)_4CH{=}CHCH_2CH{=}CHCH_2CH{=}CHCH_2CH{=}CH(CH_2)_3COOH$	(5*Z*,8*Z*,11*Z*,14*Z*)-5,8,11,14-Icosatetraenoic acid	Arachidonic acid

chain may be saturated or it can contain one or more double bonds. When double bonds are present, they are almost always cis. Acyl groups containing 14–20 carbon atoms are the most abundant in triacylglycerols.

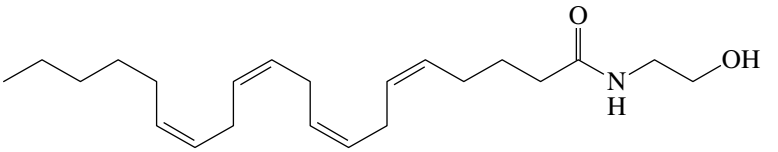
Instead of being a triacyl ester of glycerol, the fat substitute olestra is a mixture of hexa-, hepta-, and octaacyl esters of sucrose in which the acyl groups are derived from fatty acids. Olestra has many of the physical and taste properties of a fat but is not metabolized by the body and contributes no calories. For more about olestra, see the April 1997 issue of the *Journal of Chemical Education,* pp. 370–372.

PROBLEM 26.1 What fatty acids are produced on hydrolysis of 2-oleyl-1,3-distearylglycerol? What other triacylglycerol gives the same fatty acids and in the same proportions as 2-oleyl-1,3-distearylglycerol?

A few fatty acids with trans double bonds (trans fatty acids) occur naturally, but the major source of trans fats comes from the processing of natural fats and oils. In the course of hydrogenating some of the double bonds in a triacylglycerol, stereoisomerization can occur, converting cis double bonds to trans. Furthermore, the same catalysts that promote hydrogenation promote the reverse process—*dehydrogenation*—by which new double bonds, usually trans, are introduced in the acyl group.

The September 1997 issue of the *Journal of Chemical Education* (pp. 1030–1032) contains an article entitled "Trans Fatty Acids."

Fatty acids occur naturally in forms other than as glyceryl triesters, and we'll see numerous examples as we go through the chapter. One recently discovered fatty acid derivative is *anandamide.*



Anandamide

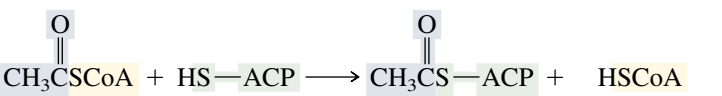
Anandamide is an ethanolamine ($H_2NCH_2CH_2OH$) amide of arachidonic acid (see Table 26.1). It was isolated from pig's brain in 1992 and identified as the substance that normally binds to the "cannabinoid receptor." The active component of marijuana, Δ^9-tetrahydrocannabinol (THC), must exert its effect by binding to a receptor, and scientists had long wondered what compound in the body was the natural substrate for this binding site. Anandamide is that compound, and it is now probably more appropriate to speak of cannabinoids binding to the anandamide receptor instead of vice versa. Anandamide seems to be involved in moderating pain. Once the identity of the "endogenous cannabinoid" was known, scientists looked specifically for it and found it in some surprising places—chocolate, for example.

Other than that both are lipids, there are no obvious structural similarities between anandamide and THC.

Fatty acids are biosynthesized by way of acetyl coenzyme A. The following section outlines the mechanism of fatty acid biosynthesis.

26.3 FATTY ACID BIOSYNTHESIS

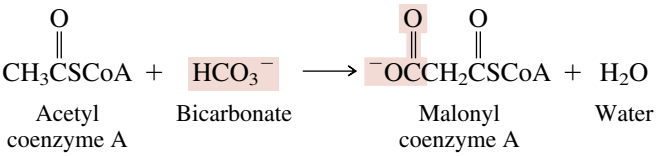
We can describe the major elements of fatty acid biosynthesis by considering the formation of butanoic acid from two molecules of acetyl coenzyme A. The "machinery" responsible for accomplishing this conversion is a complex of enzymes known as **fatty acid synthetase.** Certain portions of this complex, referred to as **acyl carrier protein (ACP),** bear a side chain that is structurally similar to coenzyme A. An important early step in fatty acid biosynthesis is the transfer of the acetyl group from a molecule of acetyl coenzyme A to the sulfhydryl group of acyl carrier protein.



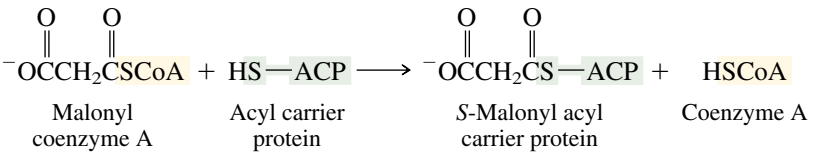
Acetyl coenzyme A | Acyl carrier protein | *S*-Acetyl acyl carrier protein | Coenzyme A

PROBLEM 26.2 Using HSCoA and HS—ACP as abbreviations for coenzyme A and acyl carrier protein, respectively, write a structural formula for the tetrahedral intermediate in the preceding reaction.

A second molecule of acetyl coenzyme A reacts with carbon dioxide (actually bicarbonate ion at biological pH) to give malonyl coenzyme A:



Formation of malonyl coenzyme A is followed by a nucleophilic acyl substitution, which transfers the malonyl group to the acyl carrier protein as a thioester.

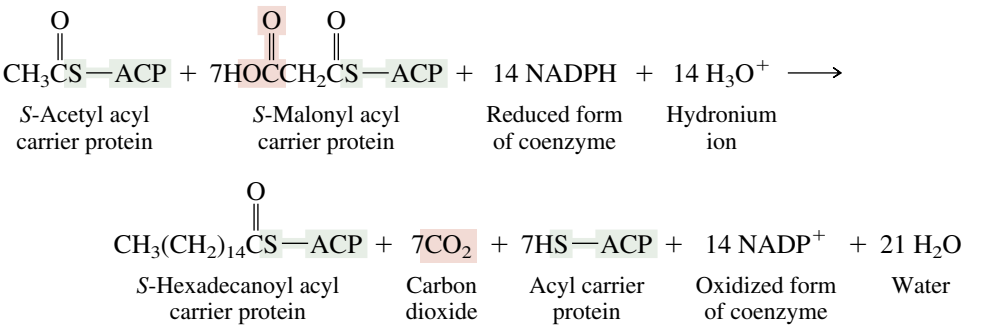


When both building block units are in place on the acyl carrier protein, carbon–carbon bond formation occurs between the α-carbon atom of the malonyl group and the carbonyl carbon of the acetyl group. This is shown in step 1 of Figure 26.3. Carbon–carbon bond formation is accompanied by decarboxylation and produces a four-carbon acetoacetyl (3-oxobutanoyl) group bound to acyl carrier protein.

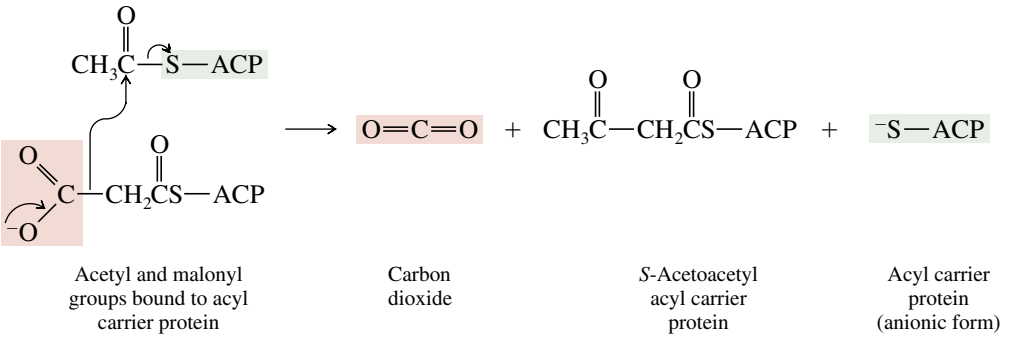
The acetoacetyl group is then transformed to a butanoyl group by the reaction sequence illustrated in steps 2 to 4 of Figure 26.3.

The four carbon atoms of the butanoyl group originate in two molecules of acetyl coenzyme A. Carbon dioxide assists the reaction but is not incorporated into the product. The same carbon dioxide that is used to convert one molecule of acetyl coenzyme A to malonyl coenzyme A is regenerated in the decarboxylation step that accompanies carbon–carbon bond formation.

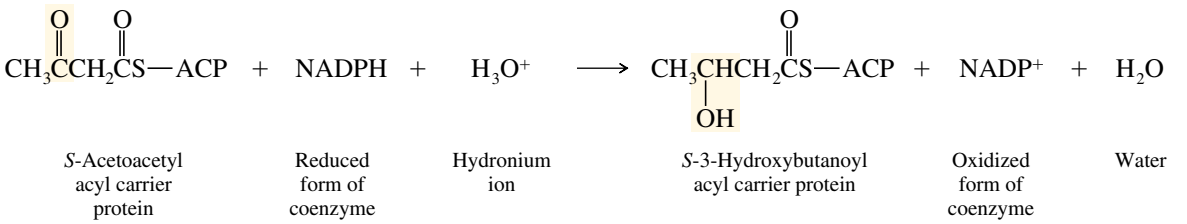
Successive repetitions of the steps shown in Figure 26.3 give unbranched acyl groups having 6, 8, 10, 12, 14, and 16 carbon atoms. In each case, chain extension occurs by reaction with a malonyl group bound to the acyl carrier protein. Thus, the biosynthesis of the 16-carbon acyl group of hexadecanoic (palmitic) acid can be represented by the overall equation:



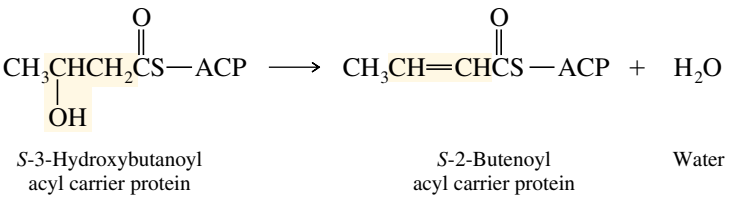
Step 1: An acetyl group is transferred to the α carbon atom of the malonyl group with evolution of carbon dioxide. Presumably decarboxylation gives an enol, which attacks the acetyl group.



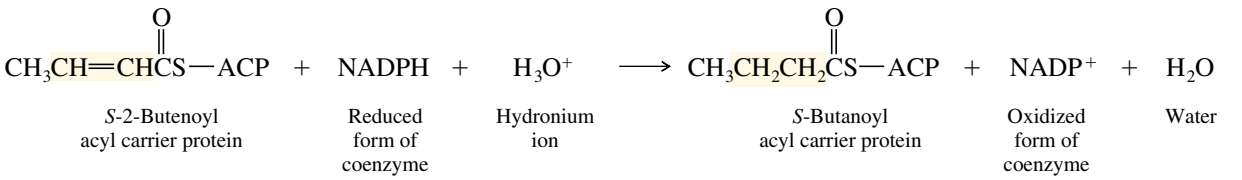
Step 2: The ketone carbonyl of the acetoacetyl group is reduced to an alcohol function. This reduction requires NADPH as a coenzyme. (NADPH is the phosphate ester of NADH and reacts similarly to it.)



Step 3: Dehydration of the β-hydroxy acyl group.



Step 4: Reduction of the double bond of the α, β-unsaturated acyl group. This step requires NADPH as a coenzyme.



PROBLEM 26.3 By analogy to the intermediates given in steps 1–4 of Figure 26.3, write the sequence of acyl groups that are attached to the acyl carrier protein in the conversion of

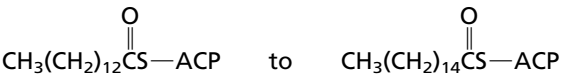
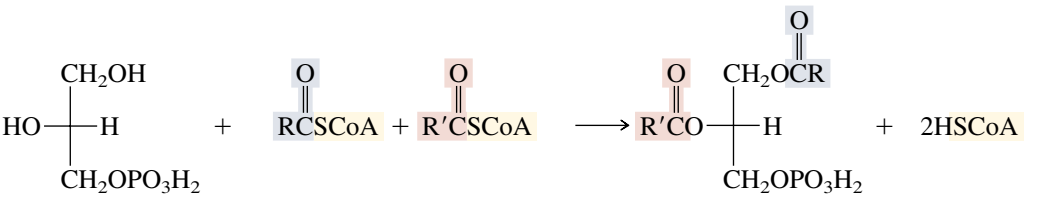


FIGURE 26.3 Mechanism of biosynthesis of a butanoyl group from acetyl and malonyl building blocks.

This phase of fatty acid biosynthesis concludes with the transfer of the acyl group from acyl carrier protein to coenzyme A. The resulting acyl coenzyme A molecules can then undergo a number of subsequent biological transformations. One such transformation is chain extension, leading to acyl groups with more than 16 carbons. Another is the introduction of one or more carbon–carbon double bonds. A third is acyl transfer from sulfur to oxygen to form esters such as triacylglycerols. The process by which acyl coenzyme A molecules are converted to triacylglycerols involves a type of intermediate called a *phospholipid* and is discussed in the following section.

26.4 PHOSPHOLIPIDS

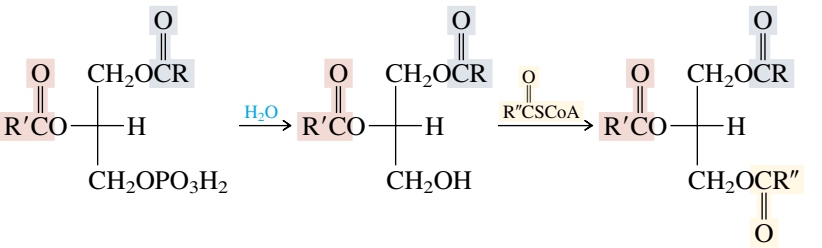
Triacylglycerols arise, not by acylation of glycerol itself, but by a sequence of steps in which the first stage is acyl transfer to L-glycerol 3-phosphate (from reduction of dihydroxyacetone 3-phosphate, formed as described in Section 25.21). The product of this stage is called a **phosphatidic acid.**



L-Glycerol 3-phosphate | Two acyl coenzyme A molecules (R and R′ may be the same or they may be different) | Phosphatidic acid | Coenzyme A

PROBLEM 26.4 What is the absolute configuration (*R* or *S*) of L-glycerol 3-phosphate? What must be the absolute configuration of the naturally occurring phosphatidic acids biosynthesized from it?

Hydrolysis of the phosphate ester function of the phosphatidic acid gives a diacylglycerol, which then reacts with a third acyl coenzyme A molecule to produce a triacylglycerol.

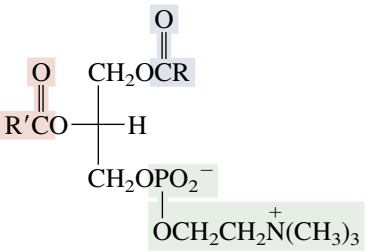


Phosphatidic acid | Diacylglycerol | Triacylglycerol

Phosphatidic acids not only are intermediates in the biosynthesis of triacylglycerols but also are biosynthetic precursors of other members of a group of compounds called **phosphoglycerides** or **glycerol phosphatides.** Phosphorus-containing derivatives of lipids are known as **phospholipids,** and phosphoglycerides are one type of phospholipid.

Lecithin is added to foods such as mayonnaise as an emulsifying agent to prevent the fat and water from separating into two layers.

One important phospholipid is **phosphatidylcholine,** also called *lecithin.* Phosphatidylcholine is a mixture of diesters of phosphoric acid. One ester function is derived from a diacylglycerol, whereas the other is a choline [$-OCH_2CH_2\overset{+}{N}(CH_3)_3$] unit.



Phosphatidylcholine
(R and R′ are usually
different)

Phosphatidylcholine possesses a polar "head group" (the positively charged choline and negatively charged phosphate units) and two nonpolar "tails" (the acyl groups). Under certain conditions, such as at the interface of two aqueous phases, phosphatidylcholine forms what is called a *lipid bilayer,* as shown in Figure 26.4. Because there are two long-chain acyl groups in each molecule, the most stable assembly has the polar groups solvated by water molecules at the top and bottom surfaces and the lipophilic acyl groups directed toward the interior of the bilayer.

Phosphatidylcholine is one of the principal components of cell membranes. These membranes are composed of lipid bilayers analogous to those of Figure 26.4. Nonpolar materials can diffuse through the bilayer from one side to the other relatively easily; polar materials, particularly metal ions such as Na^+, K^+, and Ca^{2+}, cannot. The transport of metal ions through a membrane is usually assisted by certain proteins present in the lipid bilayer, which contain a metal ion binding site surrounded by a lipophilic exterior. The metal ion is picked up at one side of the lipid bilayer and delivered at the other, surrounded at all times by a polar environment on its passage through the hydrocarbon-like interior of the membrane. Ionophore antibiotics such as monensin (Section 16.4) disrupt the normal functioning of cells by facilitating metal ion transport across cell membranes.

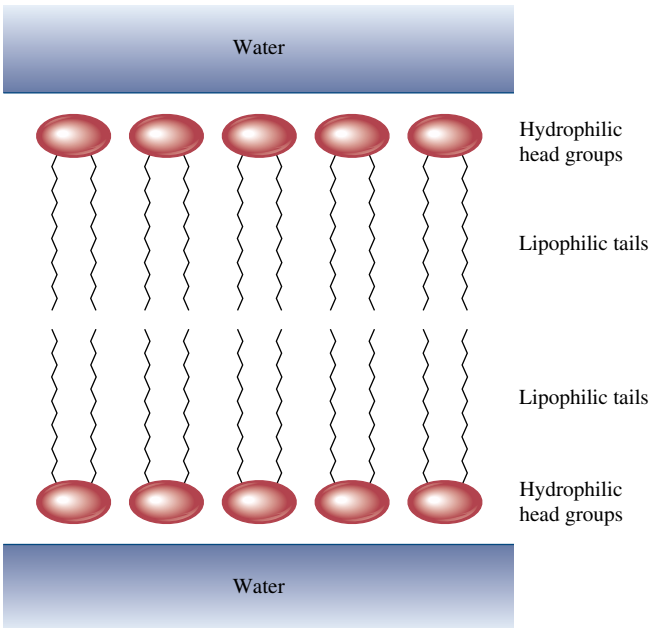


FIGURE 26.4 Cross section of a phospholipid bilayer.

26.5 WAXES

Waxes are water-repelling solids that are part of the protective coatings of a number of living things, including the leaves of plants, the fur of animals, and the feathers of birds. They are usually mixtures of esters in which both the alkyl and acyl group are unbranched and contain a dozen or more carbon atoms. Beeswax, for example, contains the ester triacontyl hexadecanoate as one component of a complex mixture of hydrocarbons, alcohols, and esters.

Triacontyl hexadecanoate

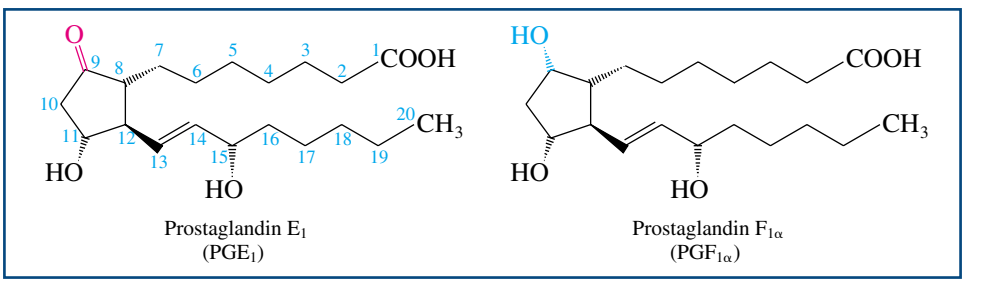
PROBLEM 26.5 Spermaceti is a wax obtained from the sperm whale. It contains, among other materials, an ester known as *cetyl palmitate,* which is used as an emollient in a number of soaps and cosmetics. The systematic name for cetyl palmitate is *hexadecyl hexadecanoate.* Write a structural formula for this substance.

Fatty acids normally occur naturally as esters; fats, oils, phospholipids, and waxes all are unique types of fatty acid esters. There is, however, an important class of fatty acid derivatives that exists and carries out its biological role in the form of the free acid. This class of fatty acid derivatives is described in the following section.

26.6 PROSTAGLANDINS

Research in physiology carried out in the 1930s established that the lipid fraction of semen contains small amounts of substances that exert powerful effects on smooth muscle. Sheep prostate glands proved to be a convenient source of this material and yielded a mixture of structurally related substances referred to collectively as **prostaglandins.** We now know that prostaglandins are present in almost all animal tissues, where they carry out a variety of regulatory functions.

Prostaglandins are extremely potent substances and exert their physiological effects at very small concentrations. Because of this, their isolation was difficult, and it was not until 1960 that the first members of this class, designated PGE_1 and $PGF_{1\alpha}$ (Figure 26.5), were obtained as pure compounds. More than a dozen structurally related prostaglandins have since been isolated and identified. All the prostaglandins are 20-carbon carboxylic acids and contain a cyclopentane ring. All have hydroxyl groups at C-11 and C-15 (for the numbering of the positions in prostaglandins, see Figure 26.5). Prostaglandins belonging to the F series have an additional hydroxyl group at C-9, and a carbonyl function is



Prostaglandin E_1 (PGE_1) Prostaglandin $F_{1\alpha}$ ($PGF_{1\alpha}$)

FIGURE 26.5 Structures of two representative prosta-glandins. The numbering scheme is illustrated in the structure of PGE_1.

present at this position in the various PGEs. The subscript numerals in their abbreviated names indicate the number of double bonds.

Prostaglandins are believed to arise from unsaturated C_{20}-carboxylic acids such as arachidonic acid (see Table 26.1). Mammals cannot biosynthesize arachidonic acid directly. They obtain linoleic acid (Table 26.1) from vegetable oils in their diet and extend the carbon chain of linoleic acid from 18 to 20 carbons while introducing two more double bonds. Linoleic acid is said to be an **essential fatty acid,** forming part of the dietary requirement of mammals. Animals fed on diets that are deficient in linoleic acid grow poorly and suffer a number of other disorders, some of which are reversed on feeding them vegetable oils rich in linoleic acid and other *polyunsaturated fatty acids.* One function of these substances is to provide the raw materials for prostaglandin biosynthesis.

Arachidonic acid gets its name from *arachidic acid,* the saturated C_{20} fatty acid isolated from peanut *(Arachis hypogaea)* oil.

PROBLEM 26.6 Arachidonic acid is the biosynthetic precursor to PGE_2. The structures of PGE_1 (see Figure 26.5) and PGE_2 are identical except that PGE_2 has one more double bond than PGE_1. Suggest a reasonable structure for PGE_2.

Physiological responses to prostaglandins encompass a variety of effects. Some prostaglandins relax bronchial muscle, others contract it. Some stimulate uterine contractions and have been used to induce therapeutic abortions. PGE_1 dilates blood vessels and lowers blood pressure; it inhibits the aggregation of platelets and offers promise as a drug to reduce the formation of blood clots.

The long-standing question of the mode of action of aspirin has been addressed in terms of its effects on prostaglandin biosynthesis. Prostaglandin biosynthesis is the body's response to tissue damage and is manifested by pain and inflammation at the affected site. Aspirin has been shown to inhibit the activity of an enzyme required for prostaglandin formation. Aspirin reduces pain and inflammation—and probably fever as well—by reducing prostaglandin levels in the body.

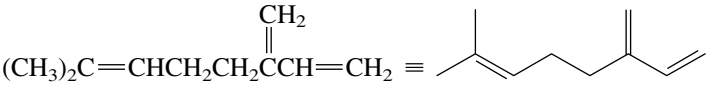
Much of the fundamental work on prostaglandins and related compounds was carried out by Sune Bergström and Bengt Samuelsson of the Karolinska Institute (Sweden) and by Sir John Vane of the Wellcome Foundation (Great Britain). These three shared the Nobel Prize for physiology or medicine in 1982. Bergström began his research on prostaglandins because he was interested in the oxidation of fatty acids. That research led to the identification of a whole new class of biochemical mediators. Prostaglandin research has now revealed that other derivatives of oxidized polyunsaturated fatty acids, structurally distinct from the prostaglandins, are also physiologically important. These fatty acid derivatives include, for example, a group of substances known as the **leukotrienes,** which have been implicated as mediators in immunological processes.

26.7 TERPENES: THE ISOPRENE RULE

The word "essential" as applied to naturally occurring organic substances can have two different meanings. For example, as used in the previous section with respect to fatty acids, *essential* means "necessary." Linoleic acid is an "essential" fatty acid; it must be included in the diet in order for animals to grow properly because they lack the ability to biosynthesize it directly.

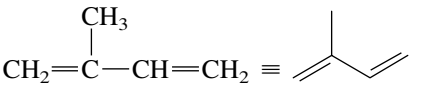
"Essential" is also used as the adjective form of the noun "essence." The mixtures of substances that make up the fragrant material of plants are called *essential oils* because they contain the essence, that is, the odor, of the plant. The study of the composition of essential oils ranks as one of the oldest areas of organic chemical research. Very often, the principal volatile component of an essential oil belongs to a class of chemical substances called the **terpenes.**

Myrcene, a hydrocarbon isolated from bayberry oil, is a typical terpene:

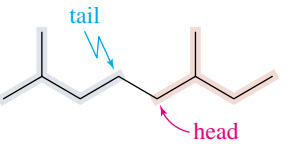


Myrcene

The structural feature that distinguishes terpenes from other natural products is the **isoprene unit.** The carbon skeleton of myrcene (exclusive of its double bonds) corresponds to the head-to-tail union of two isoprene units.



Isoprene
(2-methyl-1,3-butadiene)

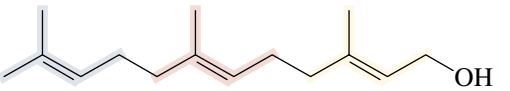


Two isoprene units
linked head to tail

There are more than 23,000 known isoprenoid compounds.

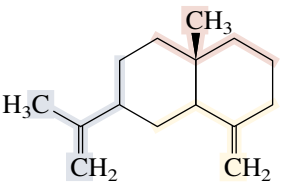
Terpenes are often referred to as *isoprenoid* compounds. They are classified according to the number of carbon atoms they contain, as summarized in Table 26.2.

Although the term "terpene" once referred only to hydrocarbons, current usage includes functionally substituted derivatives as well. Figure 26.6 presents the structural formulas for a number of representative terpenes. The isoprene units in some of these are relatively easy to identify. The three isoprene units in the sesquiterpene **farnesol,** for example, are indicated as follows in color. They are joined in a head-to-tail fashion.



Isoprene units in farnesol

Many terpenes contain one or more rings, but these also can be viewed as collections of isoprene units. An example is α-selinene. Like farnesol, it is made up of three isoprene units linked head to tail.

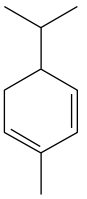


Isoprene units in α-selinene

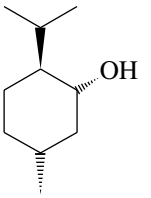
TABLE 26.2 Classification of Terpenes

Class	Number of carbon atoms
Monoterpene	10
Sesquiterpene	15
Diterpene	20
Sesterpene	25
Triterpene	30
Tetraterpene	40

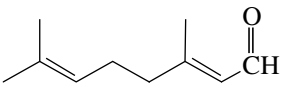
Monoterpenes



α-Phellandrene
(eucalyptus)

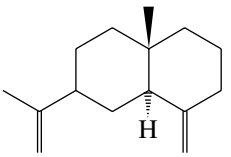


Menthol
(peppermint)

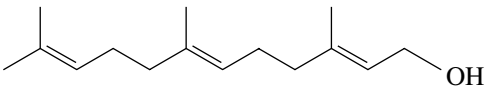


Citral
(lemon grass)

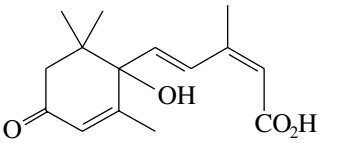
Sesquiterpenes



α-Selinene
(celery)

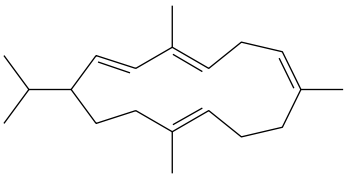


Farnesol
(ambrette)

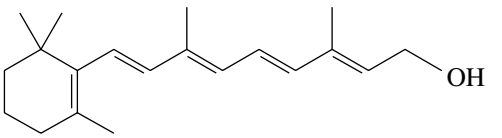


Abscisic acid
(a plant hormone)

Diterpenes

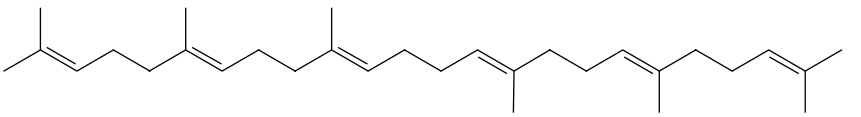


Cembrene
(pine)



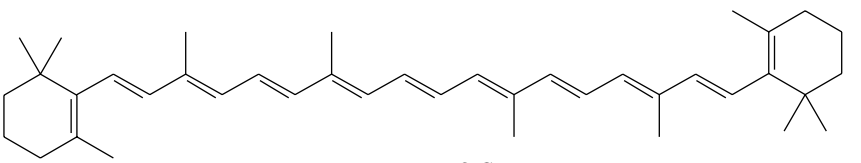
Vitamin A
(present in mammalian tissue and fish oil;
important substance in the chemistry of vision)

Triterpenes



Squalene
(shark liver oil)

Tetraterpenes

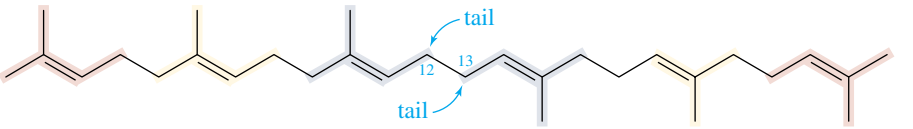


β-Carotene
(present in carrots and other vegetables;
enzymes in the body cleave β-carotene to vitamin A)

FIGURE 26.6 Some representative terpenes and related natural products. Structures are customarily depicted as carbon skeleton formulas when describing compounds of isoprenoid origin.

PROBLEM 26.7 Locate the isoprene units in each of the monoterpenes, sesquiterpenes, and diterpenes shown in Figure 26.6. (In some cases there are two equally correct arrangements.)

Tail-to-tail linkages of isoprene units sometimes occur, especially in the higher terpenes. The C(12)—C(13) bond of squalene unites two C_{15} units in a tail-to-tail manner. Notice, however, that isoprene units are joined head to tail within each C_{15} unit of squalene.



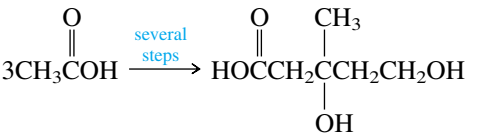
Isoprene units in squalene

PROBLEM 26.8 Identify the isoprene units in β-carotene (see Figure 26.6). Which carbons are joined by a tail-to-tail link between isoprene units?

The German chemist Otto Wallach (Nobel Prize in chemistry, 1910) established the structures of many monoterpenes and is credited with recognizing that they can be viewed as collections of isoprene units. Leopold Ruzicka of the Swiss Federal Institute of Technology (Zürich), in his studies of sesquiterpenes and higher terpenes, extended and refined what we now know as the **isoprene rule.** He was a corecipient of the Nobel Prize in chemistry in 1939. Although exceptions to it are known, the isoprene rule is a useful guide to terpene structures and has stimulated research in the biosynthetic origin of these compounds. It is a curious fact that terpenes contain isoprene units but isoprene does not occur naturally. What is the *biological isoprene unit,* how is it biosynthesized, and how do individual isoprene units combine to give terpenes?

26.8 ISOPENTENYL PYROPHOSPHATE: THE BIOLOGICAL ISOPRENE UNIT

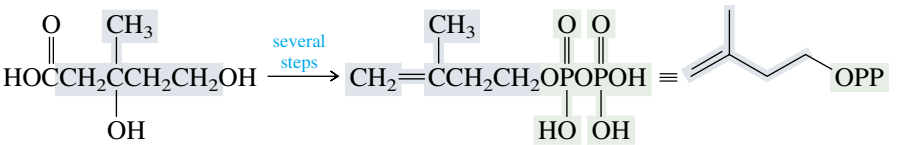
Isoprenoid compounds are biosynthesized from acetate by a process that involves several stages. The first stage is the formation of *mevalonic acid* from three molecules of acetic acid:



Acetic acid Mevalonic acid

In the second stage, mevalonic acid is converted to *3-methyl-3-butenyl pyrophosphate (isopentenyl pyrophosphate):*

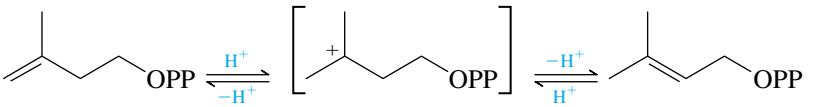
It is convenient to use the symbol —OPP to represent the pyrophosphate group.



Mevalonic acid Isopentenyl pyrophosphate

Isopentenyl pyrophosphate is the biological isoprene unit; it contains five carbon atoms connected in the same order as in isoprene.

Isopentenyl pyrophosphate undergoes an enzyme-catalyzed reaction that converts it, in an equilibrium process, to *3-methyl-2-butenyl pyrophosphate (dimethylallyl pyrophosphate):*

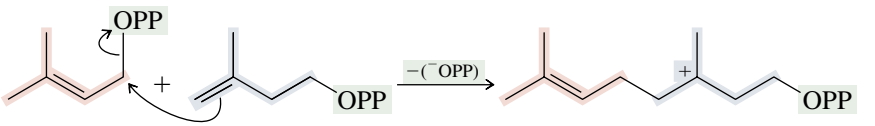


Isopentenyl pyrophosphate — Carbocation intermediate — Dimethylallyl pyrophosphate

Isopentenyl pyrophosphate and dimethylallyl pyrophosphate are structurally similar—both contain a double bond and a pyrophosphate ester unit—but the chemical reactivity expressed by each is different. The principal site of reaction in dimethylallyl pyrophosphate is the carbon that bears the pyrophosphate group. Pyrophosphate is a reasonably good leaving group in nucleophilic substitution reactions, especially when, as in dimethylallyl pyrophosphate, it is located at an allylic carbon. Isopentenyl pyrophosphate, on the other hand, does not have its leaving group attached to an allylic carbon and is far less reactive than dimethylallyl pyrophosphate toward nucleophilic reagents. The principal site of reaction in isopentenyl pyrophosphate is the carbon–carbon double bond, which, like the double bonds of simple alkenes, is reactive toward electrophiles.

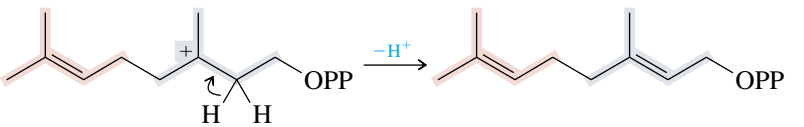
26.9 CARBON–CARBON BOND FORMATION IN TERPENE BIOSYNTHESIS

The chemical properties of isopentenyl pyrophosphate and dimethylallyl pyrophosphate are complementary in a way that permits them to react with each other to form a carbon–carbon bond that unites two isoprene units. Using the π electrons of its double bond, isopentenyl pyrophosphate acts as a nucleophile and displaces pyrophosphate from dimethylallyl pyrophosphate.



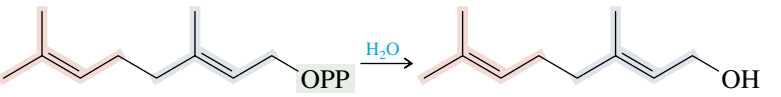
Dimethylallyl pyrophosphate — Isopentenyl pyrophosphate — Ten-carbon carbocation

The tertiary carbocation formed in this step can react according to any of the various reaction pathways available to carbocations. One of these is loss of a proton to give a double bond.



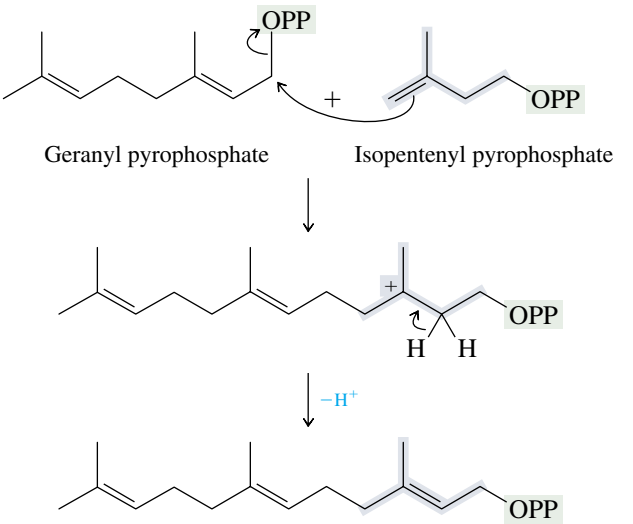
Geranyl pyrophosphate

The product of this reaction is *geranyl pyrophosphate.* Hydrolysis of the pyrophosphate ester group gives *geraniol,* a naturally occurring monoterpene found in rose oil.



Geranyl pyrophosphate Geraniol

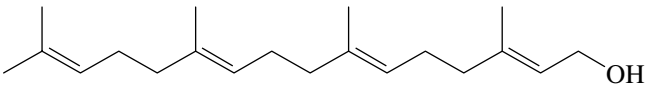
Geranyl pyrophosphate is an allylic pyrophosphate and, like dimethylallyl pyrophosphate, can act as an alkylating agent toward a molecule of isopentenyl pyrophosphate. A 15-carbon carbocation is formed, which, on deprotonation, gives *farnesyl pyrophosphate.*



Farnesyl pyrophosphate

Hydrolysis of the pyrophosphate ester group converts farnesyl pyrophosphate to the corresponding alcohol *farnesol* (see Figure 26.6 for the structure of farnesol).

A repetition of the process just shown produces the diterpene geranylgeraniol from farnesyl pyrophosphate.



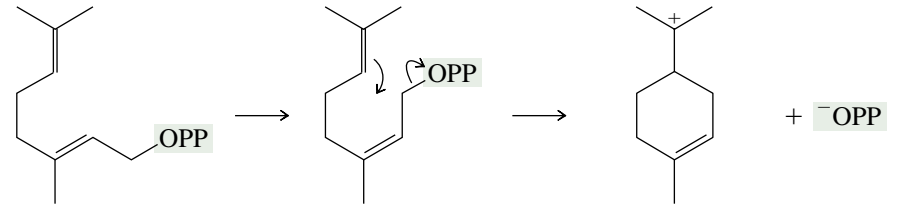
Geranylgeraniol

PROBLEM 26.9 Write a sequence of reactions that describes the formation of geranylgeraniol from farnesyl pyrophosphate.

The higher terpenes are formed not by successive addition of C_5 units but by the coupling of simpler terpenes. Thus, the triterpenes (C_{30}) are derived from two molecules of farnesyl pyrophosphate, and the tetraterpenes (C_{40}) from two molecules of geranylgeranyl pyrophosphate. These carbon–carbon bond-forming processes involve tail-to-tail couplings and proceed by a more complicated mechanism than that just described.

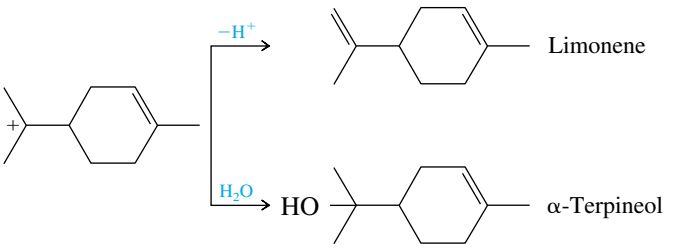
The enzyme-catalyzed reactions that lead to geraniol and farnesol (as their pyrophosphate esters) are mechanistically related to the acid-catalyzed dimerization of alkenes discussed in Section 6.21. The reaction of an allylic pyrophosphate or a carbocation with a source of π electrons is a recurring theme in terpene biosynthesis and is invoked to explain the origin of more complicated structural types. Consider, for

example, the formation of cyclic monoterpenes. *Neryl pyrophosphate,* formed by an enzyme-catalyzed isomerization of the *E* double bond in geranyl pyrophosphate, has the proper geometry to form a six-membered ring via intramolecular attack of the double bond on the allylic pyrophosphate unit.

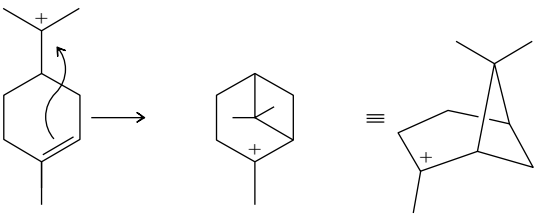


Geranyl pyrophosphate Neryl pyrophosphate Tertiary carbocation

Loss of a proton from the tertiary carbocation formed in this step gives *limonene,* an abundant natural product found in many citrus fruits. Capture of the carbocation by water gives *α-terpineol,* also a known natural product.



The same tertiary carbocation serves as the precursor to numerous bicyclic monoterpenes. A carbocation having a bicyclic skeleton is formed by intramolecular attack of the π electrons of the double bond on the positively charged carbon.



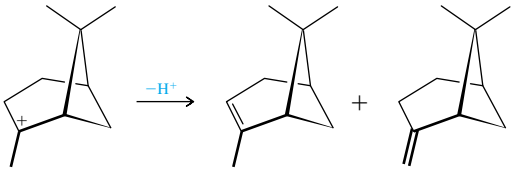
Bicyclic carbocation

This bicyclic carbocation then undergoes many reactions typical of carbocation intermediates to provide a variety of bicyclic monoterpenes, as outlined in Figure 26.7.

PROBLEM 26.10 The structure of the bicyclic monoterpene borneol is shown in Figure 26.7. Isoborneol, a stereoisomer of borneol, can be prepared in the laboratory by a two-step sequence. In the first step, borneol is oxidized to camphor by treatment with chromic acid. In the second step, camphor is reduced with sodium borohydride to a mixture of 85% isoborneol and 15% borneol. On the basis of these transformations, deduce structural formulas for isoborneol and camphor.

Analogous processes involving cyclizations and rearrangements of carbocations derived from farnesyl pyrophosphate produce a rich variety of structural types in the sesquiterpene series. We will have more to say about the chemistry of higher terpenes,

A. Loss of a proton from the bicyclic carbocation yields α-pinene and β-pinene. The pinenes are the most abundant of the monoterpenes. They are the main constituents of turpentine.



B. Capture of the carbocation by water, accompanied by rearrangement of the bicyclo-[3.1.1] carbon skeleton to a bicyclo[2.2.1] unit, yields borneol. Borneol is found in the essential oil of certain trees that grow in Indonesia.

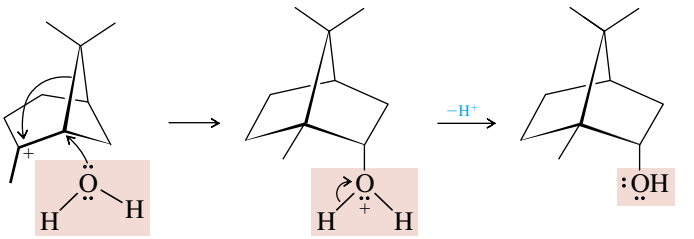
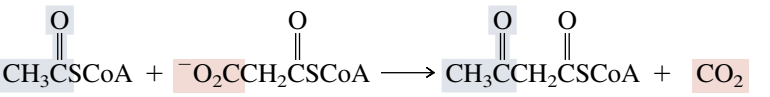


FIGURE 26.7 Two of the reaction pathways available to the C_{10} bicyclic carbocation formed from neryl pyrophosphate. The same carbocation can lead to monoterpenes based on either the bicyclo[3.1.1] or the bicyclo[2.2.1] carbon skeleton.

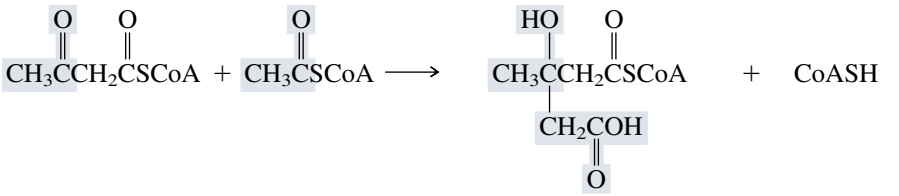
especially the triterpenes, later in this chapter. For the moment, however, let's return to smaller molecules in order to complete the picture of how isoprenoid compounds arise from acetate.

26.10 THE PATHWAY FROM ACETATE TO ISOPENTENYL PYROPHOSPHATE

The introduction to Section 26.8 pointed out that mevalonic acid is the biosynthetic precursor of isopentenyl pyrophosphate. The early steps in the biosynthesis of mevalonate from three molecules of acetic acid are analogous to those in fatty acid biosynthesis (Section 26.3) except that they do not involve acyl carrier protein. Thus, the reaction of acetyl coenzyme A with malonyl coenzyme A yields a molecule of acetoacetyl coenzyme A.

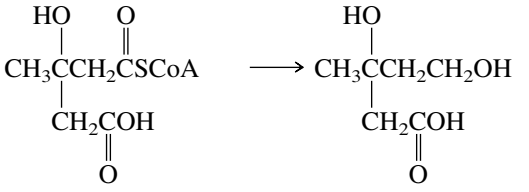


Carbon–carbon bond formation then occurs between the ketone carbonyl of acetoacetyl coenzyme A and the α carbon of a molecule of acetyl coenzyme A.



Acetoacetyl coenzyme A | Acetyl coenzyme A | 3-Hydroxy-3-methylglutaryl coenzyme A (HMG CoA) | Coenzyme A

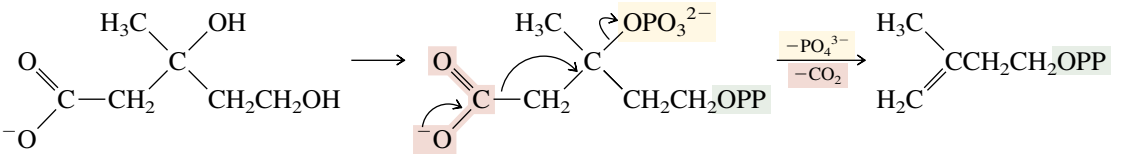
The product of this reaction, 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA), has the carbon skeleton of mevalonic acid and is converted to it by enzymatic reduction.



3-Hydroxy-3-methylglutaryl coenzyme A (HMG CoA) | Mevalonic acid

Some of the most effective cholesterol-lowering drugs act by inhibiting the enzyme that catalyzes this reaction.

In keeping with its biogenetic origin in three molecules of acetic acid, mevalonic acid has six carbon atoms. The conversion of mevalonate to isopentenyl pyrophosphate involves loss of the "extra" carbon as carbon dioxide. First, the alcohol hydroxyl groups of mevalonate are converted to phosphate ester functions—they are enzymatically *phosphorylated,* with introduction of a simple phosphate at the tertiary site and a pyrophosphate at the primary site. Decarboxylation, in concert with loss of the tertiary phosphate, introduces a carbon–carbon double bond and gives isopentenyl pyrophosphate, the fundamental building block for formation of isoprenoid natural products.



Mevalonate | (Unstable; undergoes rapid decarboxylation with loss of phosphate) | Isopentenyl pyrophosphate

Much of what we know concerning the pathway from acetate to mevalonate to isopentenyl pyrophosphate to terpenes comes from "feeding" experiments, in which plants are grown in the presence of radioactively labeled organic substances and the distribution of the radioactive label is determined in the products of biosynthesis. To illustrate, eucalyptus plants were allowed to grow in a medium containing acetic acid enriched with ^{14}C in its methyl group. *Citronellal* was isolated from the mixture of monoterpenes produced by the plants and shown, by a series of chemical degradations, to contain the radioactive ^{14}C label at carbons 2, 4, 6, and 8, as well as at the carbons of both branching methyl groups.

Citronellal occurs naturally as the principal component of citronella oil and is used as an insect repellent.

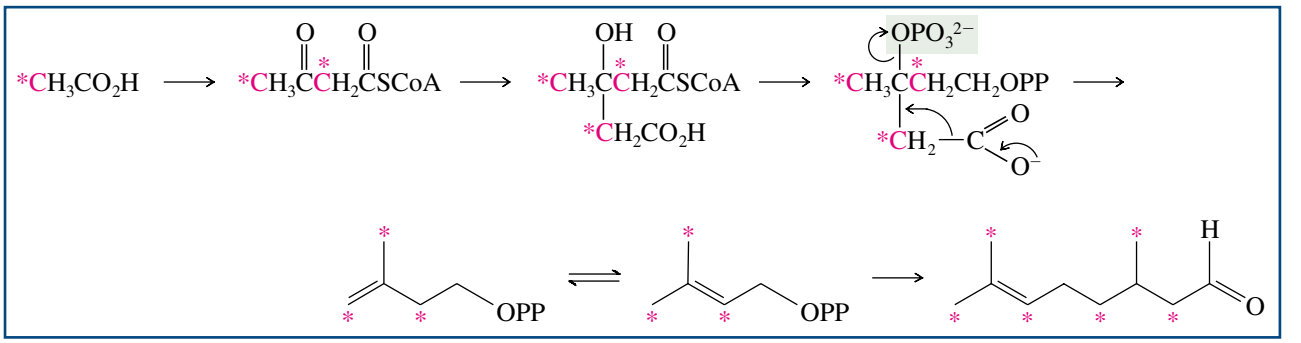
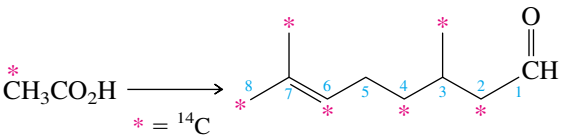


FIGURE 26.8 Diagram showing the distribution of the ^{14}C label (*C) in citronellal biosynthesized from acetate in which the methyl carbon was isotopically enriched with ^{14}C.



Citronellal

Figure 26.8 traces the ^{14}C label from its origin in acetic acid to its experimentally determined distribution in citronellal.

PROBLEM 26.11 How many carbon atoms of citronellal would be radioactively labeled if the acetic acid used in the experiment were enriched with ^{14}C at C-1 instead of at C-2? Identify these carbon atoms.

A more recent experimental technique employs ^{13}C as the isotopic label. Instead of locating the position of a ^{14}C label by a laborious degradation procedure, the ^{13}C NMR spectrum of the natural product is recorded. The signals for the carbons that are enriched in ^{13}C are far more intense than those corresponding to carbons in which ^{13}C is present only at the natural abundance level.

Isotope incorporation experiments have demonstrated the essential correctness of the scheme presented in this and preceding sections for terpene biosynthesis. Considerable effort has been expended toward its detailed elaboration because of the common biosynthetic origin of terpenes and another class of acetate-derived natural products, the steroids.

26.11 STEROIDS: CHOLESTEROL

Cholesterol is the central compound in any discussion of steroids. Its name is a combination of the Greek words for "bile" *(chole)* and "solid" *(stereos)* preceding the characteristic alcohol suffix *-ol.* It is the most abundant steroid present in humans and the most important one as well, since all other steroids arise from it. An average adult has over 200 g of cholesterol; it is found in almost all body tissues, with relatively large amounts present in the brain and spinal cord and in gallstones. Cholesterol is the chief constituent of the plaque that builds up on the walls of arteries in atherosclerosis.

Cholesterol was isolated in the eighteenth century, but its structure is so complex that its correct constitution was not determined until 1932 and its stereochemistry not

verified until 1955. Steroids are characterized by the tetracyclic ring system shown in Figure 26.9*a*. As shown in Figure 26.9*b*, cholesterol contains this tetracyclic skeleton modified to include an alcohol function at C-3, a double bond at C-5, methyl groups at C-10 and C-13, and a C_8H_{17} side chain at C-17. Isoprene units may be discerned in various portions of the cholesterol molecule, but the overall correspondence with the isoprene rule is far from perfect. Indeed, cholesterol has only 27 carbon atoms, three too few for it to be classed as a triterpene.

Animals accumulate cholesterol from their diet, but are also able to biosynthesize it from acetate. The pioneering work that identified the key intermediates in the complicated pathway of cholesterol biosynthesis was carried out by Konrad Bloch (Harvard) and Feodor Lynen (Munich), corecipients of the 1964 Nobel Prize for physiology or medicine. An important discovery was that the triterpene *squalene* (see Figure 26.6) is an intermediate in the formation of cholesterol from acetate. Thus, *the early stages of cholesterol biosynthesis are the same as those of terpene biosynthesis* described in Sections 26.8–26.10. In fact, a significant fraction of our knowledge of terpene biosynthesis is a direct result of experiments carried out in the area of steroid biosynthesis.

How does the tetracyclic steroid cholesterol arise from the acyclic triterpene squalene? Figure 26.10 outlines the stages involved. It has been shown that the first step is oxidation of squalene to the corresponding 2,3-epoxide. Enzyme-catalyzed ring opening of this epoxide in step 2 is accompanied by a cyclization reaction, in which the electrons of four of the five double bonds of squalene 2,3-epoxide are used to close the A, B, C, and D rings of the potential steroid skeleton. The carbocation that results from the cyclization reaction of step 2 is then converted to a triterpene known as *lanosterol* by the rearrangement shown in step 3. Step 4 of Figure 26.10 simply indicates the structural changes that remain to be accomplished in the transformation of lanosterol to cholesterol.

Lanosterol is one component of lanolin, a mixture of many substances that coats the wool of sheep.

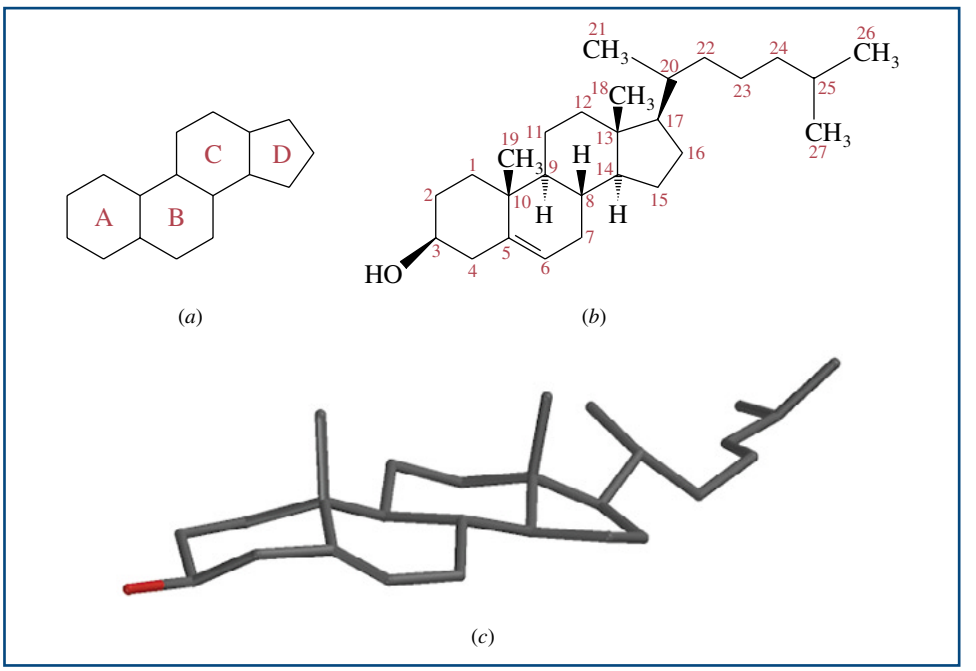
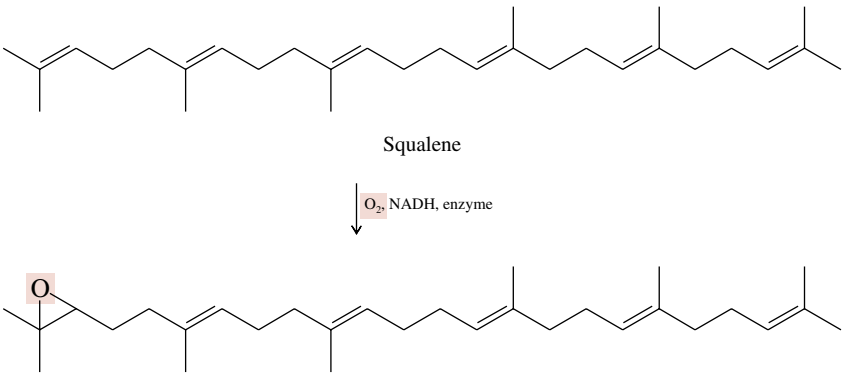
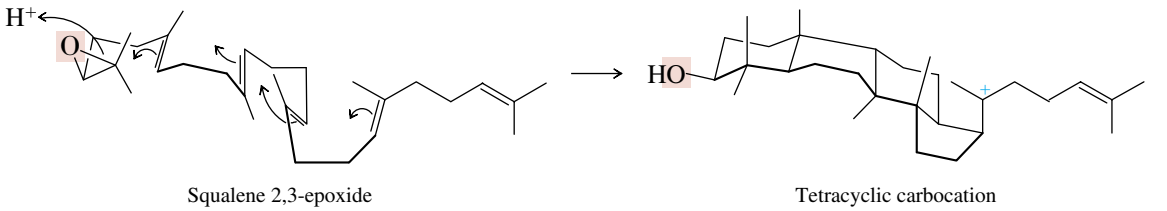


FIGURE 26.9 (*a*) The tetracyclic ring system characteristic of steroids. The rings are designated A, B, C, and D as shown. (*b*) and (*c*) The structure of cholesterol. A unique numbering system is used for steroids and is indicated in the structural formula.

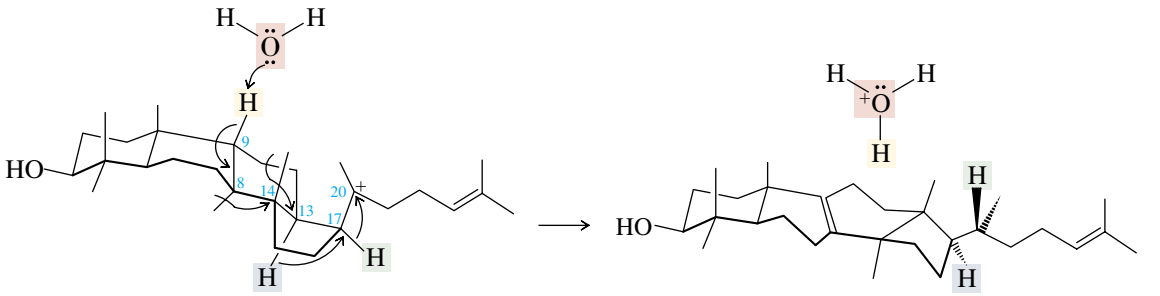
Step 1: Squalene undergoes enzymic oxidation to the 2,3-epoxide. This reaction has been described earlier, in Section 16.14.



Step 2: Cyclization of squalene 2,3-epoxide, shown in its coiled form, is triggered by ring opening of the epoxide. Cleavage of the carbon–oxygen bond is assisted by protonation of oxygen and by nucleophilic participation of the π electrons of the neighboring double bond. A series of ring closures leads to the tetracyclic carbocation shown.



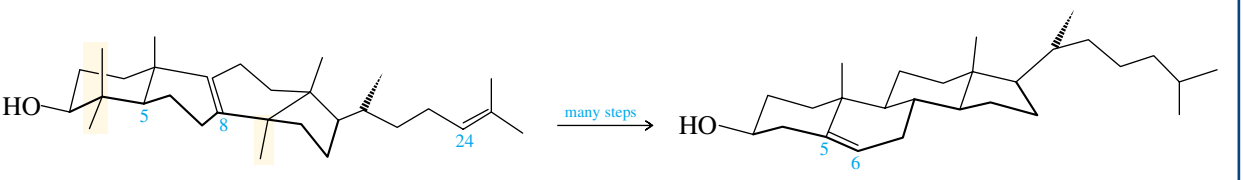
Step 3: Rearrangement of the tertiary carbocation formed by cyclization produces lanosterol. Two hydride shifts, from C-17 to C-20 and from C-13 to C-17, are accompanied by methyl shifts from C-14 to C-13 and from C-8 to C-14. A double bond is formed at C-8 by loss of the proton at C-9.



—Cont.

FIGURE 26.10 The biosynthetic conversion of squalene to cholesterol proceeds through lanosterol. Lanosterol is formed by a cyclization reaction of squalene-2,3-epoxide.

Step 4: A series of enzyme-catalyzed reactions converts lanosterol to cholesterol. The three highlighted methyl groups in the structural formula of lanosterol are lost via separate multistep operations, the C-8 and C-24 double bonds are reduced, and a new double bond is introduced at C-5.



Lanosterol Cholesterol

FIGURE 26.10 Cont.

PROBLEM 26.12 The biosynthesis of cholesterol as outlined in Figure 26.10 is admittedly quite complicated. It will aid your understanding of the process if you consider the following questions:

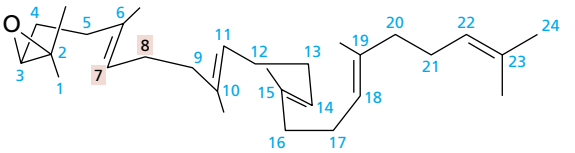
(a) Which carbon atoms of squalene 2,3-epoxide correspond to the doubly bonded carbons of cholesterol?

(b) Which two hydrogen atoms of squalene 2,3-epoxide are the ones that migrate in step 3?

(c) Which methyl group of squalene 2,3-epoxide becomes the methyl group at the C, D ring junction of cholesterol?

(d) What three methyl groups of squalene 2,3-epoxide are lost during the conversion of lanosterol to cholesterol?

SAMPLE SOLUTION (a) As the structural formula in step 4 of Figure 26.10 indicates, the double bond of cholesterol unites C-5 and C-6 (steroid numbering). The corresponding carbons in the cyclization reaction of step 2 in the figure may be identified as C-7 and C-8 of squalene 2,3-epoxide (systematic IUPAC numbering).



Coiled form of squalene 2,3-epoxide

PROBLEM 26.13 The biosynthetic pathway shown in Figure 26.10 was developed with the aid of isotopic labeling experiments. Which carbon atoms of cholesterol would you expect to be labeled when acetate enriched with ^{14}C in its methyl group ($^{14}CH_3COOH$) is used as the carbon source?

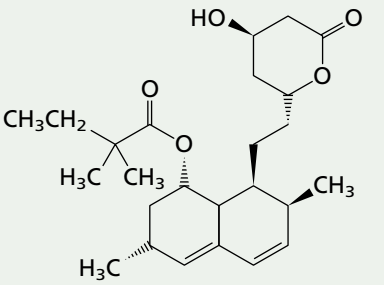
Once formed in the body, cholesterol can undergo a number of transformations. A very common one is acylation of its C-3 hydroxyl group by reaction with coenzyme A derivatives of fatty acids. Other processes convert cholesterol to the biologically important steroids described in the following sections.

GOOD CHOLESTEROL? BAD CHOLESTEROL? WHAT'S THE DIFFERENCE?

Cholesterol is biosynthesized in the liver, transported throughout the body to be used in a variety of ways, and returned to the liver where it serves as the biosynthetic precursor to other steroids. But cholesterol is a lipid and isn't soluble in water. How can it move through the blood if it doesn't dissolve in it? The answer is that it doesn't dissolve, but is instead carried through the blood and tissues as part of a *lipoprotein* (lipid + protein = lipoprotein).

The proteins that carry cholesterol from the liver are called low-density lipoproteins, or LDLs; those that return it to the liver are the *high-density lipoproteins,* or HDLs. If too much cholesterol is being transported by LDL, or too little by HDL, the extra cholesterol builds up on the walls of the arteries causing atherosclerosis. A thorough physical examination nowadays measures not only total cholesterol concentration but also the distribution between LDL and HDL cholesterol. An elevated level of LDL cholesterol is a risk factor for heart disease. LDL cholesterol is "bad" cholesterol. HDLs, on the other hand, remove excess cholesterol and are protective. HDL cholesterol is "good" cholesterol.

The distribution between LDL and HDL cholesterol depends mainly on genetic factors, but can be altered. Regular exercise increases HDL and reduces LDL cholesterol, as does limiting the amount of saturated fat in the diet. Much progress has been made in developing new drugs to lower cholesterol. The *statin* class, beginning with lovastatin in 1988 followed by simvastatin in 1991 have proven especially effective.

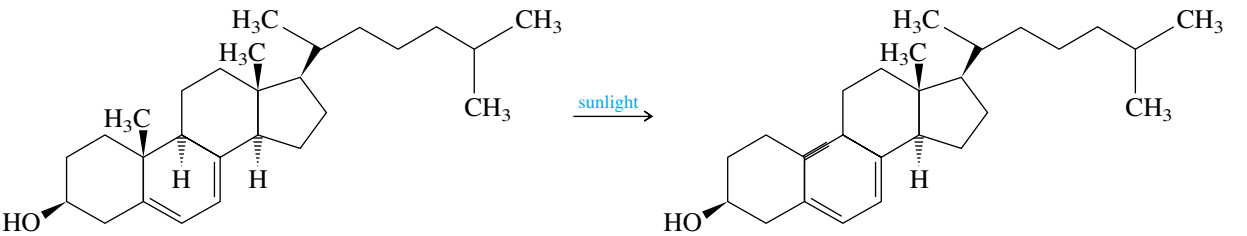


Simvastatin

The statins lower cholesterol by inhibiting the enzyme 3-hydroxy-3-methylglutaryl coenzyme A reductase, which is required for the biosynthesis of mevalonic acid (see Section 26.10). Mevalonic acid is an obligatory precursor to cholesterol, so less mevalonic acid translates into less cholesterol.

26.12 VITAMIN D

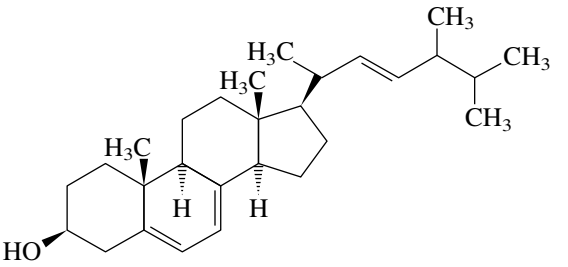
A steroid very closely related structurally to cholesterol is its 7-dehydro derivative. 7-Dehydrocholesterol is formed by enzymic oxidation of cholesterol and has a conjugated diene unit in its B ring. 7-Dehydrocholesterol is present in the tissues of the skin, where it is transformed to vitamin D_3 by a sunlight-induced photochemical reaction.



7-Dehydrocholesterol Vitamin D_3

Vitamin D_3 is a key compound in the process by which Ca^{2+} is absorbed from the intestine. Low levels of vitamin D_3 lead to Ca^{2+} concentrations in the body that are insufficient to support proper bone growth, resulting in the bone disease called *rickets.*

Rickets was once more widespread than it is now. It was thought to be a dietary deficiency disease because it could be prevented in children by feeding them fish liver oil. Actually, rickets is an environmental disease brought about by a deficiency of sunlight. Where the winter sun is weak, children may not be exposed to enough of its light to convert the 7-dehydrocholesterol in their skin to vitamin D_3 at levels sufficient to promote the growth of strong bones. Fish have adapted to an environment that screens them from sunlight, and so they are not directly dependent on photochemistry for their vitamin D_3 and accumulate it by a different process. Although fish liver oil is a good source of vitamin D_3, it is not very palatable. Synthetic vitamin D_3, prepared from cholesterol, is often added to milk and other foods to ensure that children receive enough of the vitamin for their bones to develop properly. *Irradiated ergosterol* is another dietary supplement added to milk and other foods for the same purpose. Ergosterol, a steroid obtained from yeast, is structurally similar to 7-dehydrocholesterol and, on irradiation with sunlight or artificial light, is converted to vitamin D_2, a substance analogous to vitamin D_3 and comparable with it in antirachitic activity.

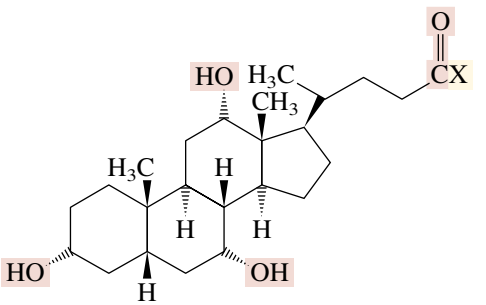


Ergosterol

PROBLEM 26.14 Suggest a reasonable structure for vitamin D_2.

26.13 BILE ACIDS

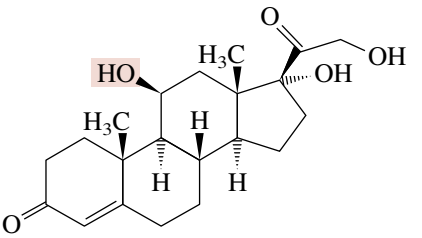
A significant fraction of the body's cholesterol is used to form **bile acids.** Oxidation in the liver removes a portion of the C_8H_{17} side chain, and additional hydroxyl groups are introduced at various positions on the steroid nucleus. *Cholic acid* is the most abundant of the bile acids. In the form of certain amide derivatives called **bile salts,** of which *sodium taurocholate* is one example, bile acids act as emulsifying agents to aid the digestion of fats. Bile salts have detergent properties similar to those of salts of long-chain fatty acids and promote the transport of lipids through aqueous media.



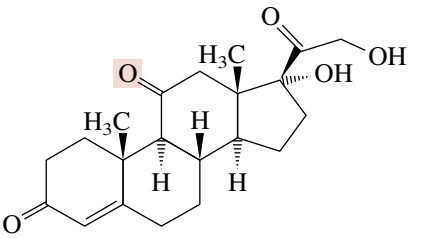
X = OH: cholic acid
X = $NHCH_2CH_2SO_3Na$: sodium taurocholate

26.14 CORTICOSTEROIDS

The outer layer, or *cortex,* of the adrenal gland is the source of a large group of substances known as **corticosteroids.** Like the bile acids, they are derived from cholesterol by oxidation, with cleavage of a portion of the alkyl substituent on the D ring. *Cortisol* is the most abundant of the corticosteroids, but *cortisone* is probably the best known. Cortisone is commonly prescribed as an antiinflammatory drug, especially in the treatment of rheumatoid arthritis.



Cortisol



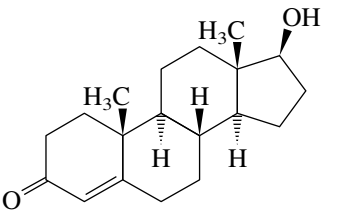
Cortisone

Many antiitch remedies contain dihydrocortisone.

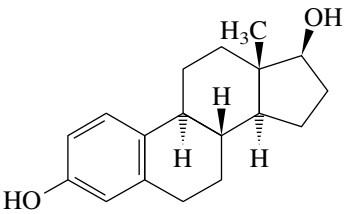
Corticosteroids exhibit a wide range of physiological effects. One important function is to assist in maintaining the proper electrolyte balance in body fluids. They also play a vital regulatory role in the metabolism of carbohydrates and in mediating the allergic response.

26.15 SEX HORMONES

Hormones are the chemical messengers of the body; they are secreted by the endocrine glands and regulate biological processes. Corticosteroids, described in the preceding section, are hormones produced by the adrenal glands. The sex glands—testes in males, ovaries in females—secrete a number of hormones that are involved in sexual development and reproduction. *Testosterone* is the principal male sex hormone; it is an **androgen.** Testosterone promotes muscle growth, deepening of the voice, the growth of body hair, and other male secondary sex characteristics. Testosterone is formed from cholesterol and is the biosynthetic precursor of estradiol, the principal female sex hormone, or **estrogen.** *Estradiol* is a key substance in the regulation of the menstrual cycle and the reproductive process. It is the hormone most responsible for the development of female secondary sex characteristics.



Testosterone



Estradiol

Testosterone and estradiol are present in the body in only minute amounts, and their isolation and identification required heroic efforts. In order to obtain 0.012 g of estradiol for study, for example, 4 tons of sow ovaries had to be extracted!

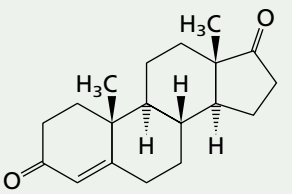
A separate biosynthetic pathway leads from cholesterol to *progesterone,* a female sex hormone. One function of progesterone is to suppress ovulation at certain stages of

ANABOLIC STEROIDS

As we have seen in this chapter, steroids have a number of functions in human physiology. Cholesterol is a component part of cell membranes and is found in large amounts in the brain. Derivatives of cholic acid assist the digestion of fats in the small intestine. Cortisone and its derivatives are involved in maintaining the electrolyte balance in body fluids. The sex hormones responsible for masculine and feminine characteristics as well as numerous aspects of pregnancy from conception to birth are steroids.

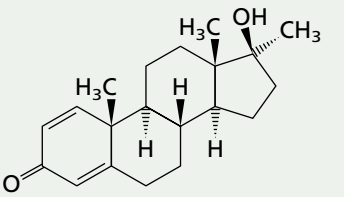
In addition to being an androgen, the principal male sex hormone testosterone promotes muscle growth and is classified as an **anabolic** steroid hormone. Biological chemists distinguish between two major classes of metabolism: **catabolic** and **anabolic** processes. Catabolic processes are degradative pathways in which larger molecules are broken down to smaller ones. Anabolic processes are the reverse; larger molecules are synthesized from smaller ones. Although the body mainly stores energy from food in the form of fat, a portion of that energy goes toward producing muscle from protein. An increase in the amount of testosterone, accompanied by an increase in the amount of food consumed, will cause an increase in the body's muscle mass.

Androstenedione, a close relative of testosterone, reached the public's attention in connection with Mark McGwire's successful bid to break Roger Maris' home run record in the summer of 1998. Androstenedione differs from testosterone in having a carbonyl group in the D ring where testosterone has a hydroxyl group. McGwire admitted to taking androstenedione, which is available as a nutritional supplement in health food stores and doesn't violate any of the rules of Major League Baseball. A controversy ensued as to the wisdom of androstenedione being sold without a prescription and the fairness of its use by athletes. Although the effectiveness of androstenedione as an anabolic steroid has not been established, it is clearly not nearly as potent as some others.

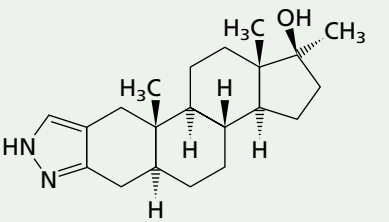


Androstenedione

The pharmaceutical industry has developed and studied a number of anabolic steroids for use in veterinary medicine and in rehabilitation from injuries that are accompanied by deterioration of muscles. The ideal agent would be one that possessed the anabolic properties of testosterone without its androgenic (masculinizing) effects. Methandrostenolone *(Dianabol)* and *stanozolol* are among the many synthetic anabolic steroids that require a prescription.



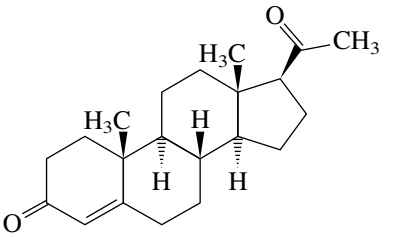
Dianabol



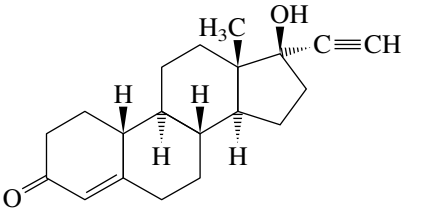
Stanozolol

Some scientific studies indicate that the gain in performance obtained through the use of anabolic steroids is small. This may be a case, though, in which the anecdotal evidence of the athletes may be closer to the mark than the scientific studies. The scientific studies are done under ethical conditions in which patients are treated with "prescription-level" doses of steroids. A 240-pound offensive tackle ("too small" by today's standards) may take several anabolic steroids at a time at 10–20 times their prescribed doses in order to weigh the 280 pounds he (or his coach) feels is necessary. The price athletes pay for gains in size and strength can be enormous. This price includes emotional costs (friendships lost because of heightened aggressiveness), sterility, testicular atrophy (the testes cease to function once the body starts to obtain a sufficient supply of testosterone-like steroids from outside), and increased risk of premature death from liver cancer or heart disease.

the menstrual cycle and during pregnancy. Synthetic substances, such as *norethindrone,* have been developed that are superior to progesterone when taken orally to "turn off" ovulation. By inducing temporary infertility, they form the basis of most oral contraceptive agents.



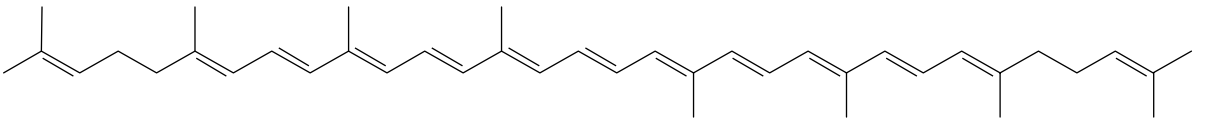
Progesterone



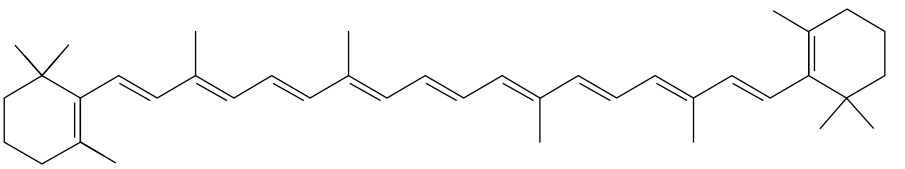
Norethindrone

26.16 CAROTENOIDS

Carotenoids are natural pigments characterized by a tail-to-tail linkage between two C_{20} units and an extended conjugated system of double bonds. They are the most widely distributed of the substances that give color to our world and occur in flowers, fruits, plants, insects, and animals. It has been estimated that biosynthesis from acetate produces approximately a hundred million tons of carotenoids per year. The most familiar carotenoids are lycopene and β-carotene, pigments found in numerous plants and easily isolable from ripe tomatoes and carrots, respectively.



Lycopene



β-Carotene

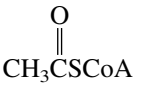
Carotenoids absorb visible light (Section 13.19) and dissipate its energy as heat, thereby protecting the organism from any potentially harmful effects associated with sunlight-induced photochemistry. They are also indirectly involved in the chemistry of vision, owing to the fact that β-carotene is the biosynthetic precursor of vitamin A, also known as retinol, a key substance in the visual process.

The structural chemistry of the visual process, beginning with β-carotene, was described in the boxed essay entitled "Imines in Biological Chemistry" in Chapter 17.

26.17 SUMMARY

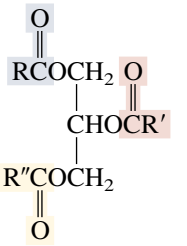
Section 26.1 Chemists and biochemists find it convenient to divide the principal organic substances present in cells into four main groups: *carbohydrates, proteins, nucleic acids,* and **lipids.** Structural differences separate carbohydrates from proteins, and both of these are structurally distinct from nucleic acids. Lipids, on the other hand, are characterized by a *physical*

property, their solubility in nonpolar solvents, rather than by their structure. In this chapter we have examined lipid molecules that share a common biosynthetic origin in that all their carbons are derived from acetic acid (acetate). The form in which acetate occurs in many of these processes is a thioester called acetyl coenzyme A.



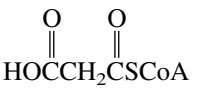
Abbreviation for acetyl coenzyme A
(for complete structure, see Figure 26.1)

Section 26.2 Acetyl coenzyme A is the biosynthetic precursor to the **fatty acids,** which most often occur naturally as esters. **Fats** and **oils** are glycerol esters of long-chain carboxylic acids. Typically, these chains are unbranched and contain even numbers of carbon atoms.



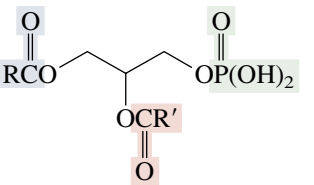
Triacylglycerol
(R, R′, and R″ may be the same or different)

Section 26.3 The biosynthesis of fatty acids follows the pathway outlined in Figure 26.3. Malonyl coenzyme A is a key intermediate.



Malonyl coenzyme A

Section 26.4 **Phospholipids** are intermediates in the biosynthesis of triacylglycerols from fatty acids and are the principal constituents of cell membranes.

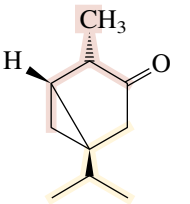


A phospholipid

Section 26.5 **Waxes** are mixtures of substances that usually contain esters of fatty acids and long-chain alcohols.

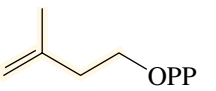
Section 26.6 A group of compounds called **prostaglandins** are powerful regulators of biochemical processes. They are biosynthesized from C_{20} fatty acids. The structures of two representative prostaglandins are shown in Figure 26.5.

Section 26.7 **Terpenes** are said to have structures that follow the isoprene rule in that they can be viewed as collections of isoprene units.



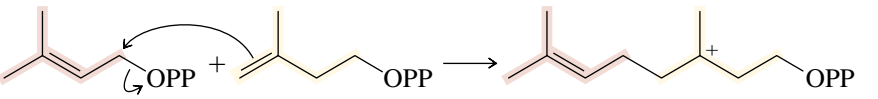
β-Thujone: a toxic monoterpene present in absinthe

Section 26.8 Terpenes and related *isoprenoid* compounds are biosynthesized from *isopentenyl pyrophosphate.*

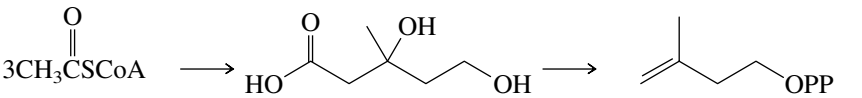


Isopentenyl pyrophosphate is the "biological isoprene unit."

Section 26.9 Carbon–carbon bond formation between isoprene units can be understood on the basis of nucleophilic attack of the π electrons of a double bond on a carbocation or an allylic carbon that bears a pyrophosphate leaving group.



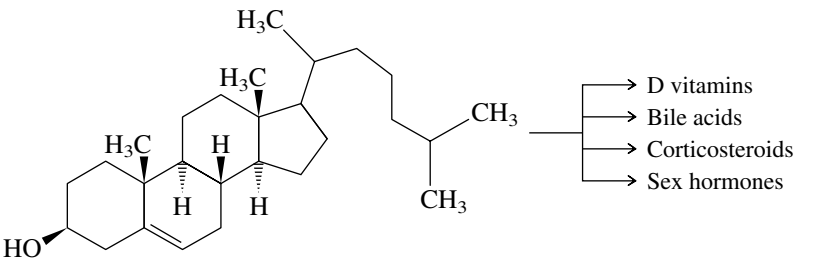
Section 26.10 The biosynthesis of isopentenyl pyrophosphate begins with acetate and proceeds by way of *mevalonic acid.*



Acetyl coenzyme A Mevalonic acid Isopentenyl pyrophosphate

Section 26.11 The triterpene *squalene* is the biosynthetic precursor to cholesterol by the pathway shown in Figure 26.10.

Sections 26.12–26.15 Most of the steroids in animals are formed by biological transformations of cholesterol.



Cholesterol

Section 26.16 **Carotenoids** are tetraterpenes. They have 40 carbons and numerous double bonds. Many of the double bonds are conjugated, causing carotenes to absorb visible light and be brightly colored. They are often plant pigments.

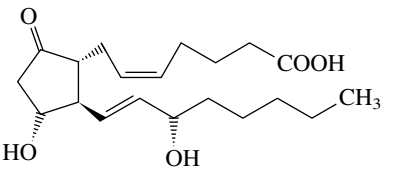
PROBLEMS

26.15 Identify the carbon atoms expected to be labeled with ^{14}C when each of the following substances is biosynthesized from acetate enriched with ^{14}C in its methyl group:

(a) $CH_3(CH_2)_{14}CO_2H$

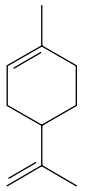
Palmitic acid

(b)



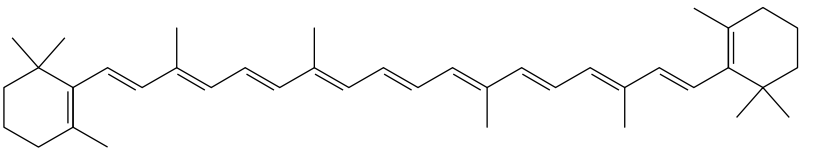
PGE_2

(c)



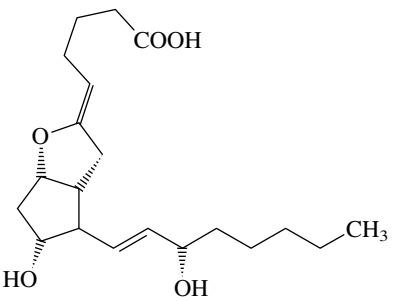
Limonene

(d)



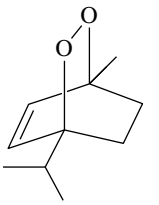
β-Carotene

26.16 The biosynthetic pathway to prostaglandins leads also to a class of physiologically potent substances known as *prostacyclins.* Which carbon atoms of the prostacyclin shown here would you expect to be enriched in ^{14}C if it were biosynthesized from acetate labeled with ^{14}C in its methyl group?

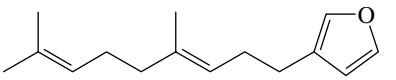


26.17 Identify the isoprene units in each of the following naturally occurring substances:

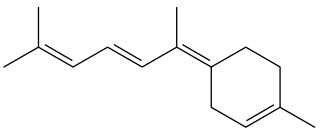
(a) *Ascaridole,* a naturally occurring peroxide present in chenopodium oil:



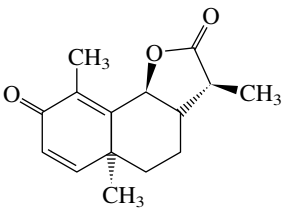
(b) *Dendrolasin,* a constituent of the defense secretion of a species of ant:



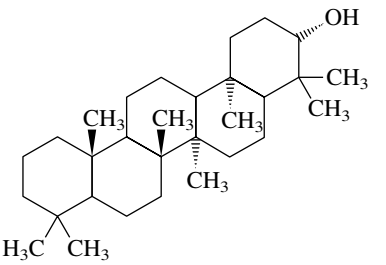
(c) *γ-Bisabolene,* a sesquiterpene found in the essential oils of a large number of plants:



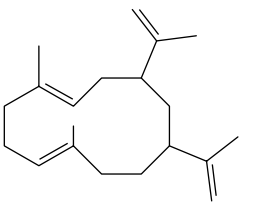
(d) *α-Santonin,* an anthelmintic substance isolated from artemisia flowers:



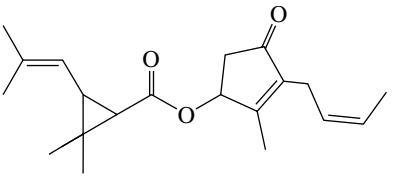
(e) *Tetrahymanol,* a pentacyclic triterpene isolated from a species of protozoans:



26.18 *Cubitene* is a diterpene present in the defense secretion of a species of African termite. What unusual feature characterizes the joining of isoprene units in cubitene?



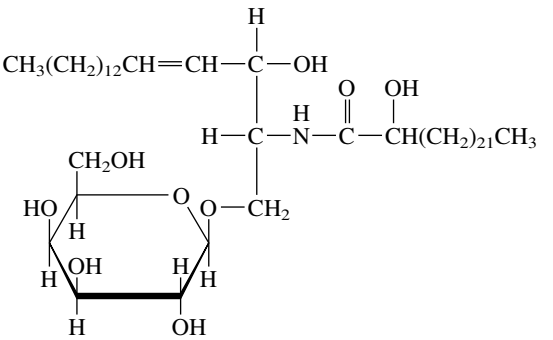
26.19 *Pyrethrins* are a group of naturally occurring insecticidal substances found in the flowers of various plants of the chrysanthemum family. The following is the structure of a typical pyrethrin, *cinerin I* (exclusive of stereochemistry):



(a) Locate any isoprene units present in cinerin I.

(b) Hydrolysis of cinerin I gives an optically active carboxylic acid, (+)-chrysanthemic acid. Ozonolysis of (+)-chrysanthemic acid, followed by oxidation, gives acetone and an optically active dicarboxylic acid, (−)-caronic acid ($C_7H_{10}O_4$). What is the structure of (−)-caronic acid? Are the two carboxyl groups cis or trans to each other? What does this information tell you about the structure of (+)-chrysanthemic acid?

26.20 *Cerebrosides* are found in the brain and in the myelin sheath of nerve tissue. The structure of the cerebroside *phrenosine* is



(a) What hexose is formed on hydrolysis of the glycoside bond of phrenosine? Is phrenosine an α- or a β-glycoside?

(b) Hydrolysis of phrenosine gives, in addition to the hexose in part (*a*), a fatty acid called *cerebronic acid,* along with a third substance called *sphingosine.* Write structural formulas for both cerebronic acid and sphingosine.

26.21 Each of the following reactions has been reported in the chemical literature and proceeds in good yield. What are the principal organic products of each reaction? In some of the exercises more than one diastereomer may be theoretically possible, but in such instances one diastereomer is either the major product or the only product. For those reactions in which one diastereomer is formed preferentially, indicate its expected stereochemistry.

(a) $CH_3(CH_2)_7C{\equiv}C(CH_2)_7COOH + H_2 \xrightarrow{\text{Lindlar Pd}}$

(b) $CH_3(CH_2)_7C{\equiv}C(CH_2)_7COOH \xrightarrow[2.\ H^+]{1.\ Li,\ NH_3}$

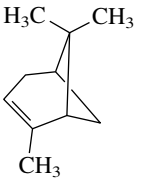
(c) $(Z)\text{-}CH_3(CH_2)_7CH{=}CH(CH_2)_7\overset{\overset{O}{\|}}{C}OCH_2CH_3 + H_2 \xrightarrow{Pt}$

(d) $(Z)\text{-}CH_3(CH_2)_5\underset{\underset{OH}{|}}{C}HCH_2CH{=}CH(CH_2)_7\overset{\overset{O}{\|}}{C}OCH_3 \xrightarrow[2.\ H_2O]{1.\ LiAlH_4}$

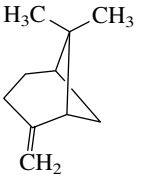
(e) (*Z*)-$CH_3(CH_2)_7CH{=}CH(CH_2)_7COOH$ + $C_6H_5CO_2OH$ ⟶

(f) Product of part (e) + H_3O^+ ⟶

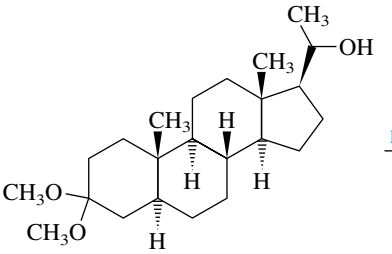
(g) (*Z*)-$CH_3(CH_2)_7CH{=}CH(CH_2)_7COOH$ $\xrightarrow[2.\ H^+]{1.\ OsO_4,\ (CH_3)_3COOH,\ HO^-}$

(h) 

$\xrightarrow[2.\ H_2O_2,\ HO^-]{1.\ B_2H_6,\ \text{diglyme}}$

(i) 

$\xrightarrow[2.\ H_2O_2,\ HO^-]{1.\ B_2H_6,\ \text{diglyme}}$

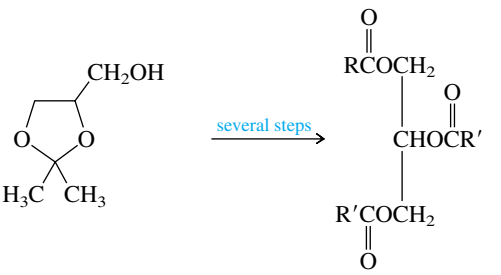
(j) 

$\xrightarrow{HCl,\ H_2O}$ $C_{21}H_{34}O_2$

26.22 Describe an efficient synthesis of each of the following compounds from octadecanoic (stearic) acid using any necessary organic or inorganic reagents:

(a) Octadecane
(b) 1-Phenyloctadecane
(c) 3-Ethylicosane
(d) Icosanoic acid
(e) 1-Heptadecanamine
(f) 1-Octadecanamine
(g) 1-Nonadecanamine

26.23 A synthesis of triacylglycerols has been described that begins with the substance shown.

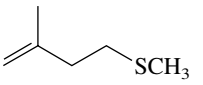


4-(Hydroxymethyl)-2,2-dimethyl-1,3-dioxolane

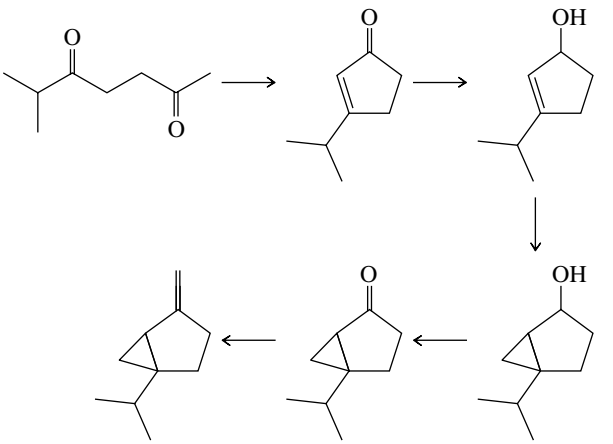
Triacylglycerol

Outline a series of reactions suitable for the preparation of a triacylglycerol of the type illustrated in the equation, where R and R′ are different.

26.24 The isoprenoid compound shown is a scent marker present in the urine of the red fox. Suggest a reasonable synthesis for this substance from 3-methyl-3-buten-1-ol and any necessary organic or inorganic reagents.

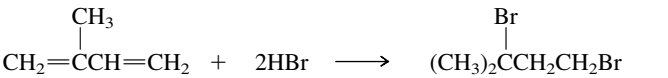


26.25 *Sabinene* is a monoterpene found in the oil of citrus fruits and plants. It has been synthesized from 6-methyl-2,5-heptanedione by the sequence that follows. Suggest reagents suitable for carrying out each of the indicated transformations.



Sabinene

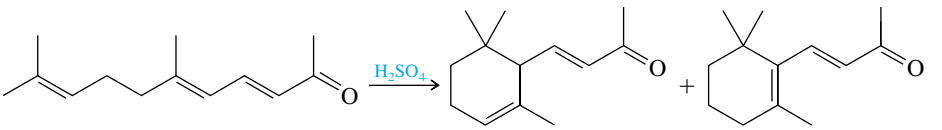
26.26 Isoprene has sometimes been used as a starting material in the laboratory synthesis of terpenes. In one such synthesis, the first step is the electrophilic addition of 2 moles of hydrogen bromide to isoprene to give 1,3-dibromo-3-methylbutane.



2-Methyl-1,3-butadiene (isoprene) | Hydrogen bromide | 1,3-Dibromo-3-methylbutane

Write a series of equations describing the mechanism of this reaction.

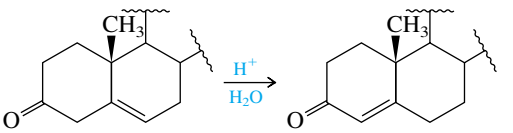
26.27 The ionones are fragrant substances present in the scent of iris and are used in perfume. A mixture of α- and β-ionone can be prepared by treatment of pseudoionone with sulfuric acid.



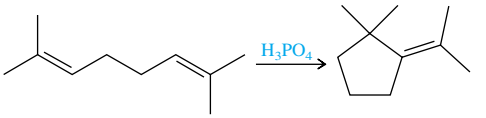
Pseudoionone | α-Ionone | β-Ionone

Write a stepwise mechanism for this reaction.

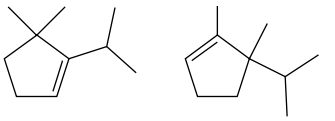
26.28 β,γ-Unsaturated steroidal ketones represented by the partial structure shown here are readily converted in acid to their α,β-unsaturated isomers. Write a stepwise mechanism for this reaction.



26.29 (a) Suggest a mechanism for the following reaction.



(b) The following two compounds are also formed in the reaction given in part (a). How are these two products formed?



(*Note:* The solution to this problem is not given in the *Solutions Manual and Study Guide*. It is discussed in detail, however, in a very interesting article on pages 541–542 of the June 1995 issue of the *Journal of Chemical Education.*)

26.30 The compound shown is *diethylstilbestrol* (DES); it has a number of therapeutic uses in estrogen-replacement therapy. DES is not a steroid, but can adopt a shape that allows it to mimic estrogens such as estradiol (p. 1040) and bind to the same receptor sites. Construct molecular models of DES and estradiol that illustrate this similarity in molecular size, shape, and location of polar groups.