30

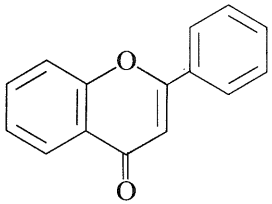
NATURAL PRODUCTS. BIOSYNTHESIS

For an organic chemist, a *natural product* is one that is produced by a living organism. This definition encompasses many compounds already discussed, such as carbohydrates, proteins, lipids, and nucleic acids, all of which play an important and primary role in metabolic reactions. However, there are other organic compounds produced naturally, some of extraordinary complexity, which are not primary metabolites. Organic chemists always have been fascinated by the great diversity of these substances and particularly those that can be isolated from plants or are produced by microorganisms. Many of these compounds, such as the alkaloids and mold metabolites, do not seem to have any obvious metabolic or evolutionary function. In fact, some compounds may be formed as the result of a "metabolic accident" or are by-products of the synthesis machinery of the cellular enzymes. Regardless of their utility to the parent organism, their value to man as drugs, herbs, flavorings, poisons, dyes, and so on is undisputed.

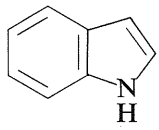
30-1 CLASSIFICATION OF NATURAL PRODUCTS

There are several ways to categorize natural products. They may be grouped according to a recurring structural feature. *Flavonoid compounds,* for example, are oxygenated derivatives of the aromatic ring structure **1**; likewise, alka-

loids having an indole ring, **2**, are called *indole alkaloids:*



1, flavone



2, indole

Or they may be grouped according to the genus of their plant source (morphine and codeine, Section 23-2, are examples of *opium alkaloids*), or by their physiological effects (antimicrobials, antibiotics, analgesics), or by similarities in the route by which they are synthesized by the organism (biosynthesis). The structural and biosynthetic classifications make the most sense to the chemist and is the organization chosen here.

30-2 APPROACHES TO THE STUDY OF NATURAL PRODUCTS

Chemists have a compelling curiosity to discover what compounds Nature provides, but to obtain this information it is necessary to isolate compounds from their natural source and to determine their structures. This is seldom an easy task, especially when the compound of interest is present at low concentrations such that enormous quantities of source material are required to extract even a few micrograms of the desired product. In this circumstance a high degree of skill and technology is required in both the isolation procedures and the subsequent investigations to establish the chemical structure.

A second objective is the total synthesis of the compound from smaller molecules. Indeed, in the classical approach to structure determination, a structure was assigned to a natural product through chemical degradation studies to smaller, identifiable molecules. However, the assigned structure was not regarded as fully confirmed until the compound was synthesized and shown to be identical in all respects (composition, configuration, conformation) with the natural compound. This approach persists, although the enormous impact of modern methods of separation and spectroscopic analysis has made it possible to determine structure beyond a reasonable doubt in almost all cases without recourse to synthesis.

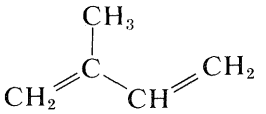
Nevertheless, the synthesis of natural products continues to be important. It provides new methodology, new reactions and techniques. It also provides alternative sources of natural compounds and offers routes to related but unnatural analogs. In the case of a useful drug, the synthetic objective is to find a related structure that is more potent at lower dosages with fewer side effects than the natural compound.

Yet another area of investigation in natural-product chemistry concerns the way in which the compound is synthesized biologically—that is, the *biosynthesis* of the compound. These are experimentally difficult studies and

involve first identifying the starting materials (biological precursors). This can be done by feeding the organism isotopically labeled compounds suspected of being precursors and then determining where and how much of the labeled material is incorporated into the natural product. Ultimately, each step in the synthesis should be elucidated and each enzyme isolated and the entire sequence reconstructed in a cell-free system. From experiments of this type we now have a rather good understanding of the biosynthesis of fatty acids, terpenes, and steroids.

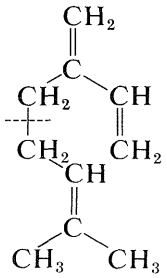
30-3 ISOPRENOID COMPOUNDS

The odor of a freshly crushed mint leaf, like many plant odors, is due to the presence in the plant of volatile C_{10} and C_{15} compounds, which are called **terpenes.** Isolation of these substances from the various parts of plants, even from the wood in some cases, by steam distillation or ether extraction gives what are known as **essential oils.** These are widely used in perfumery, as food flavorings and medicines, and as solvents. Among the typical essential oils are those obtained from cloves, roses, lavender, citronella, eucalyptus, peppermint, camphor, sandalwood, cedar, and turpentine. Such substances are of interest to us here because, as was pointed out by Wallach in 1887 and reemphasized by Ruzicka in 1935, the components of the essential oils can be regarded as derived from isoprene:

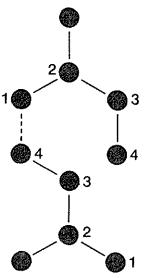


isoprene
(2-methyl-1,3-butadiene, C_5H_8)

Not only are the carbon skeletons of these substances divisible into isoprene units, but the terpene hydrocarbons are usually exact multiples of C_5H_8. An example is myrcene ($C_{10}H_{16}$), which occurs in the oils of bay and verbena and has a carbon skeleton divisible into two **isoprene units.** (Also see Exercise 3-19.)



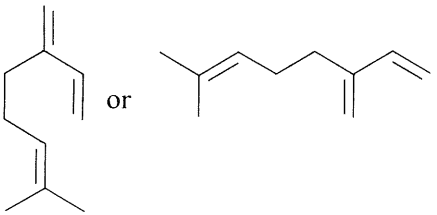
myrcene



The connection between the isoprene units in myrcene is between the 1- and 4-positions; this turns out to be more common than 1,1 and 4,4 linkages.

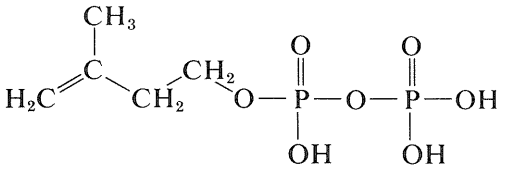
30-3A Terpene Hydrocarbons

A wide variety of cyclic terpene hydrocarbons are known and, as multiples of C_5H_8, these have fewer double bonds than the open-chain terpenes. Because it is time consuming to show all the carbon and hydrogen atoms of such substances, the structures often are drawn in a convenient shorthand notation wherein the carbon–carbon bonds are represented by lines, carbon atoms being understood at the junctions or the ends of lines. By this notation, myrcene can be represented by formulas such as the following:



The left semicyclic structural formula is useful to show relationships with the open-chain (acyclic) and cyclic terpene hydrocarbons.

A number of terpene hydrocarbons are shown in Table 30-1. The designation "terpene" is by custom specifically reserved for the C_{10} compounds, the C_{15} compounds being known as sesquiterpenes, the C_{20} as *diterpenes,* C_{30} as *triterpenes,* and so on. It should be apparent from Table 30-1 that the C_{10} and C_{15} compounds, which are the important components of essential oils, in reality are members of a much larger class of substances with carbon skeletons made up of isoprene units and occurring in both plants *and* animals. It is common to refer to all members of the group as isoprenoid compounds. The so-called *isoprene rule,* which correlates the structures of these substances, speaks for their synthesis in living systems from some common precursor with five carbon atoms. We can characterize the isoprenoid compounds as being *biogenetically* related. Isoprene itself does not occur naturally and appears to play no part in biosynthesis. The actual five-carbon intermediate appears to be isopentenyl pyrophosphate, and the role of this substance in biosynthesis will be discussed later:



isopentenyl pyrophosphate

or

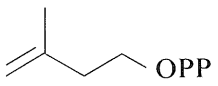
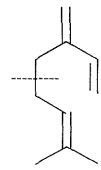
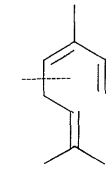
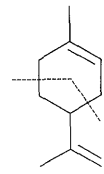
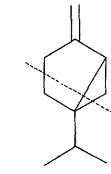
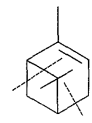
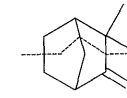
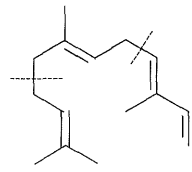
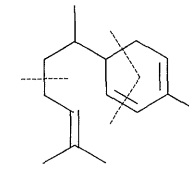
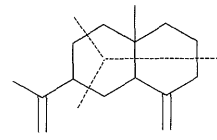
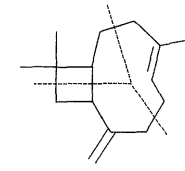
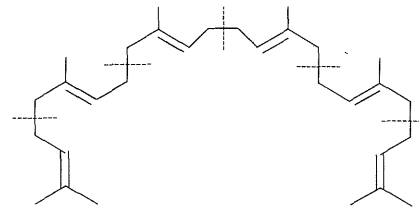
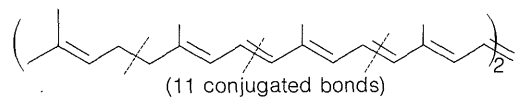


Table 30-1
Some Isoprenoid Hydrocarbons[a]

Type	Name and origin	Structure	Name and origin	Structure
terpene, $C_{10}H_{16}$	**myrcene**; bayberry wax; oils of bay, verbena		**ocimene**; oil of *Ocimum basilicum*	
	limonene; oils of lemon, orange		**sabinene**; oil of savin	
	α-pinene; oil of turpentine		**camphene**; oil of ginger, citronella	
sesqui-terpene, $C_{15}H_{24}$	**α-farnesene**; oil of citronella		**zingiberene**; oil of ginger	
	β-selinene; oil of celery		**caryophyllene**; oil of cloves	
triterpene, $C_{30}H_{50}$	**squalene**; shark-liver oil			
tetraterpene, $C_{40}H_{56}$	**lycopene**; plant pigment; tomatoes, pyracantha	 (11 conjugated bonds)		

[a]Also see β-carotene (Section 2-1) and natural rubber (Section 13-4).

Exercise 30-1 **a.** Write out all of the possible carbon skeletons for *acyclic* terpene and sesquiterpene hydrocarbons that follow the isoprene rule. Do not consider double-bond position isomers.
b. Do the same for monocyclic terpenes with a six-membered ring.

Exercise 30-2 The terpene known as alloöcimene ($C_{10}H_{16}$) shows λ_{max} at 288 nm and gives among other products 1 mole of 2-propanone and 1 mole of ethanal on ozonization. What is a likely structure for alloöcimene? Show your reasoning.

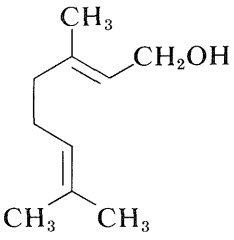
Exercise 30-3 Write structures for each of the optical and cis-trans isomers that would be expected for the following isoprenoid compounds (refer to Table 30-1):

a. myrcene **d.** zingiberene **g.** camphene
b. α-farnesene **e.** sabinene **h.** selinene
c. limonene **f.** α-pinene **i.** caryophyllene

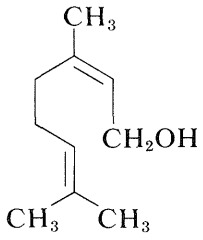
Exercise 30-4* Optically active camphene racemizes on heating with weak acids. Write a mechanism for this racemization that is in harmony with the acid-catalyzed character of the reaction. (We suggest that you review Sections 8-9B and 15-5E.)

30-3B Oxygenated Isoprenoid Compounds

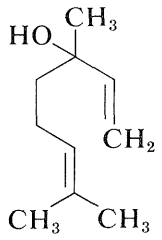
A great profusion of oxygen-containing isoprenoid compounds are known. Of particular importance in the acyclic series are the alcohols geraniol, nerol, and linaloöl, and the aldehydes geranial (citral *a*), neral (citral *b*), and citronellal:



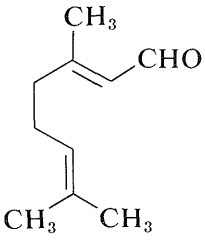
geraniol



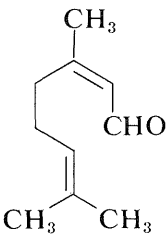
nerol



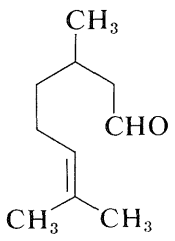
linaloöl



geranial
(citral *a*)



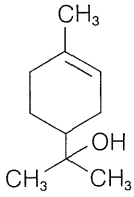
neral
(citral *b*)



citronellal

The alcohols occur in oil of rose and other flower essences. They have geranium or rose odors and are important perfume ingredients. The aldehydes have much stronger citruslike odors and occur as major or minor constituents in many essential oils, such as oil of citronella, oil of lemon, and so on.

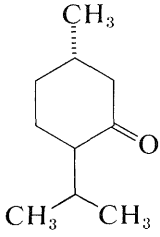
Exercise 30-5 a. Nerol and geraniol cyclize under the influence of acid to yield α-terpineol. How could the relative ease of cyclization of these alcohols, coupled with other reactions, be used to establish the configurations at the double bond of geraniol, nerol, geranial, and neral? Write a mechanism for the cyclizations.



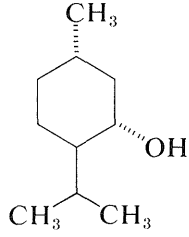
α-terpineol

b. Acidic cyclization of optically active linaloöl produces optically active α-terpineol. Explain how this can come about.

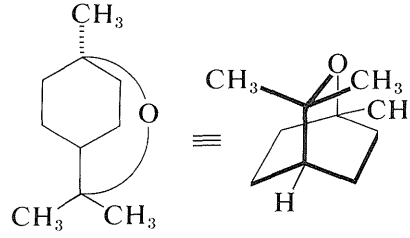
Monocyclic and bicyclic oxygenated terpenes include some familiar and interesting substances such as menthone and menthol from peppermint oil, 1,8-cineole from eucalyptus, and ascaridole, which is a naturally occurring peroxide from chenopodium oil:



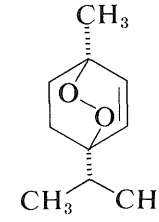
menthone



menthol

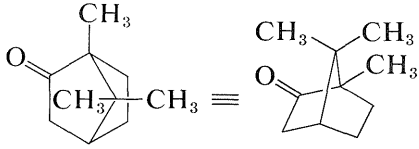


1,8-cineole



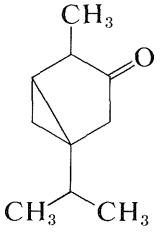
ascaridole

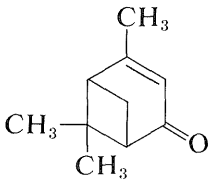
Camphor is a particularly well-known bicyclic terpene ketone, which has uses in medicine and as a plasticizer for nitrocellulose (Section 20-7):

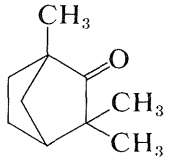


camphor

For many years, the principal source of camphor was the Formosan camphor tree. It now can be synthesized on a large scale from α-pinene (see Exercise 30-7). Some of the other types of naturally occurring bicyclic ketones follow:

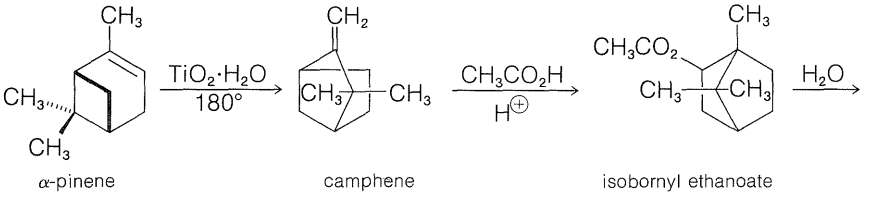

thujone

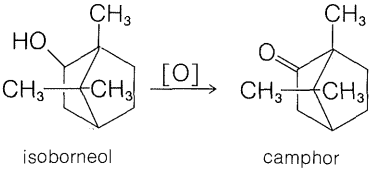

verbenone


fenchone

Exercise 30-6 Reduction of the ketone group of (—)-menthone, which has its alkyl groups trans to one another, gives two products, known as (—)-menthol and (+)-neomenthol. These two substances differ considerably in their reactions. (+)-Neomenthol undergoes dehydration either in methanoic acid or when treated with phosphorus pentachloride, whereas (—)-menthol gives a methanoate ester with methanoic acid and a chloride with phosphorus pentachloride. What is the relationship between neomenthol and menthol, and why do they behave differently with methanoic acid and phosphorus pentachloride? What is the likely structure of the menthene from dehydration of neomenthol? (Review Sections 8-8D, 12-3D, and 12-5.)

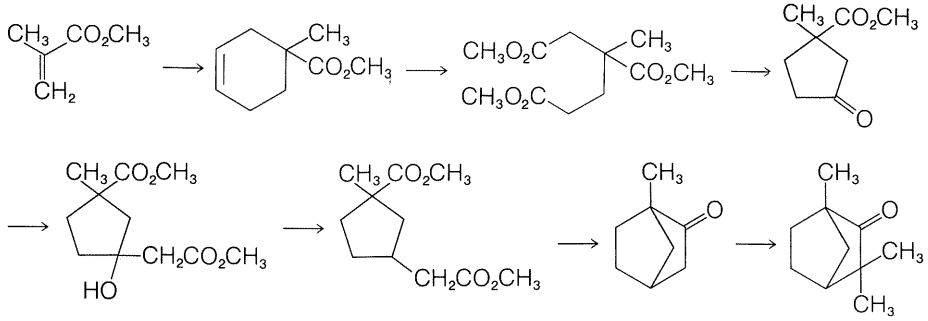
Exercise 30-7* Camphor can be made on an industrial scale from α-pinene (turpentine) by the following reactions, some of which involve carbocation rearrangements of a type particularly prevalent in the bicyclic terpenes and the scourge of the earlier workers in the field trying to determine terpene structures.


α-pinene camphene isobornyl ethanoate

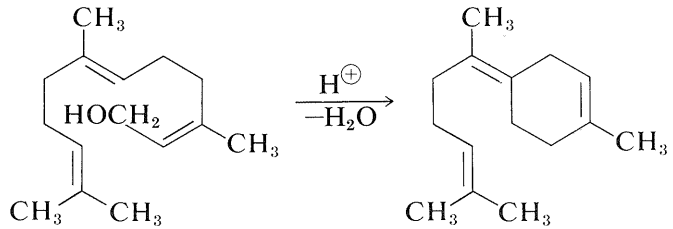

isoborneol camphor

Write mechanisms for the rearrangement reactions, noting that hydrated titanium oxide is an acidic catalyst.

Exercise 30-8 One route for the synthesis of D,L-fenchone is through the following steps. Show the reagents, conditions, and important reaction intermediates you expect would be successful in achieving each of the indicated transformations, noting that more than one step may be required (all the reactions necessary have been described in previous chapters).

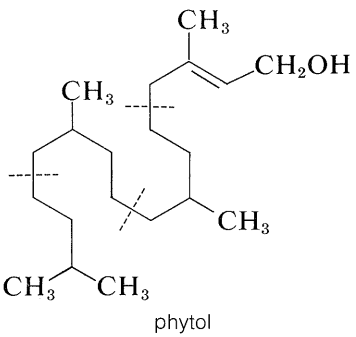


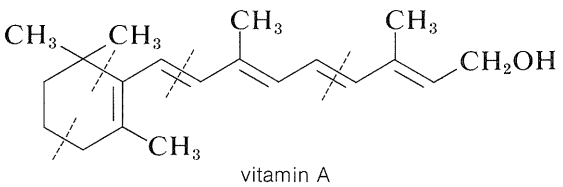
Higher oxygenated terpenes include the sesquiterpene alcohol, farnesol, which has a lily-of-the-valley odor and occurs in ambrette-seed oil. On acid dehydration it gives α-farnesene (Table 30-1) under some conditions, and bisabolene (a component of oil of bergamot) under others:



As we shall see, cyclization reactions of this general type seem to be important in terpene biosynthesis. The 6,7-*trans*-farnesol has been shown to have hormone action in some insects. It acts to regulate the changes from caterpillar to cocoon to moth.

Two important *diterpene alcohols* are vitamin A (Section 28-7) and phytol, which occurs as an ester of the propanoic acid side-chain of chlorophyll (Figure 20-6):

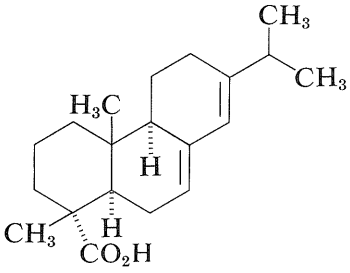




The phytyl group appears also as a side chain in vitamin K_1 (Section 26-2B).

β-Carotene (Section 2-1) has vitamin A activity and apparently is oxidized in the body at the central double bond to give one mole of vitamin A.

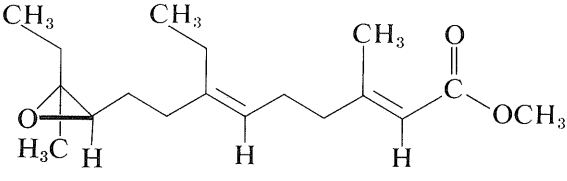
The *diterpene acid*, abietic acid, is a major constituent of rosin, which is obtained as a nonvolatile residue in the manufacture of turpentine by steam distillation of pine oleoresin or shredded pine stumps. Abietic acid is used extensively in varnishes and as its sodium salt in laundry soaps.



abietic acid

30-3C Isoprenoid Compounds of Animal Origin

A number of compounds important to animal physiology have been identified as isoprenoid compounds. Notable examples are vitamin A, retinal (Section 28-7), and squalene (Table 30-1). Also, terpene hydrocarbons and oxygenated terpenes have been isolated from insects and, like farnesol, show hormonal and pheromonal activity. As one example, the juvenile hormone isolated from *Cecropia* silk moths has the structure shown in **3**:



Cecropia juvenile hormone, **3**

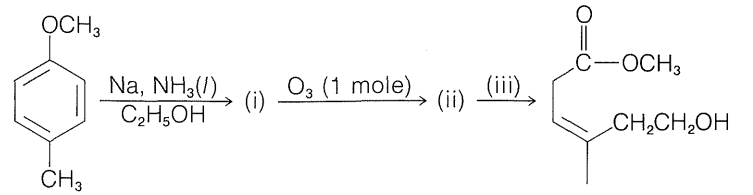
The structure was established by an impressive combination of chemical, spectroscopic, and synthetic methods with about 200μg of pure compound isolated from the abdomens of a myriad of male moths.[1] (Some aspects of synthetic work on juvenile hormone are incorporated in Exercise 30-9.)

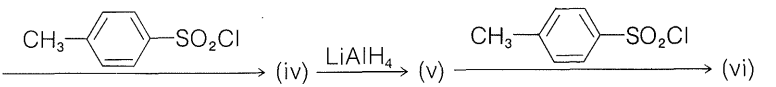
> Juvenile hormone plays a critical role in maintaining the juvenile or larval stage of insects, and if its secretion is not controlled, normal development to the adult stage is prevented. Use of hormones or substances with hormonelike activity to control insect populations is an area of intense research interest and activity.[2] The secretion of juvenile hormone is controlled by other hormones originating in the brain (brain hormone) and the phthoracic gland (moulting hormone, ecdysone; see Table 30-2).

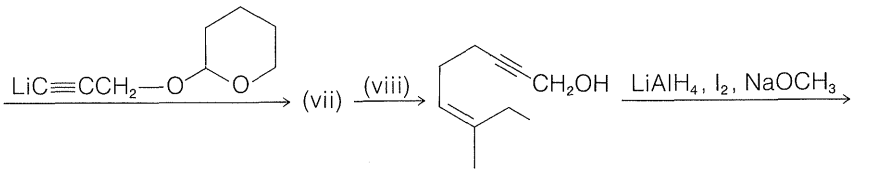
[1]A summary of the structure proof is reported by H. Röller, K. H. Dahn, C. C. Sweely, and B. M. Trost, *Angew. Chem.* (Intl. Ed.) **6,** 179 (1967); B. M. Trost, *Accts. Chem. Res.* **3,** 120 (1970).

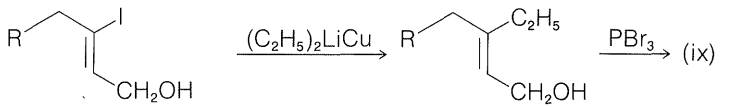
[2]C. E. Berkoff, *J. Chem. Educ.* **48,** 577 (1971).

Exercise 30-9 The synthesis of *Cecropia* juvenile hormone outlined below was designed by E. J. Corey and co-workers. Draw in the structure of the product (as i, ii, etc.) at each stage where this has been omitted, and write above the arrows the reagents and conditions necessary to accomplish reactions where these have been omitted. (To save space, the abbreviation R and R′ are used to designate parts of the structure that do not change in later steps.)

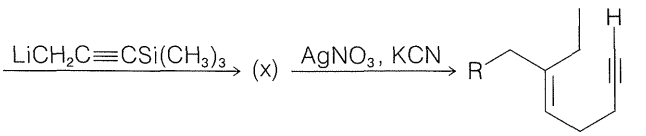


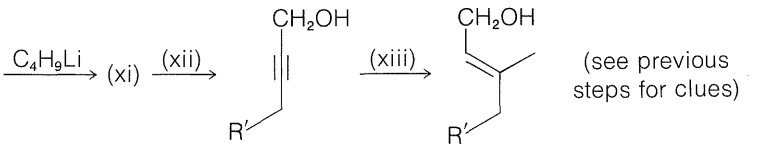




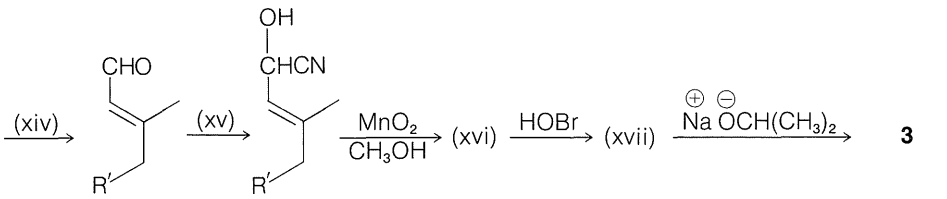


R = —$CH_2CH{=}C(CH_3)C_2H_5$



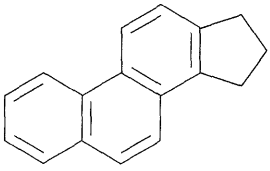


R′ = —$CH_2CH{=}C(C_2H_5)CH_2R$



30-4 STEROIDS

The term **steroid** applies to compounds containing a hydrogenated cyclopentanophenanthrene carbon skeleton:



cyclopentanophenanthrene

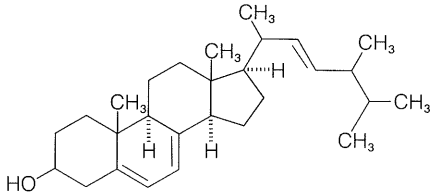
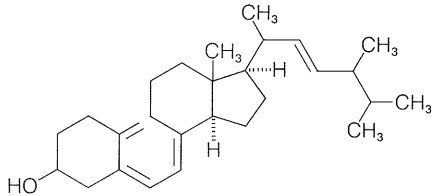
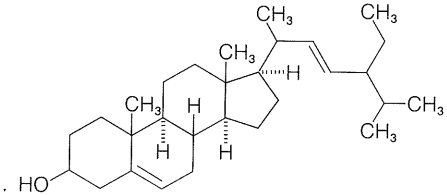
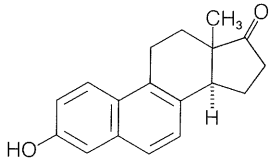
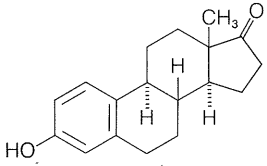
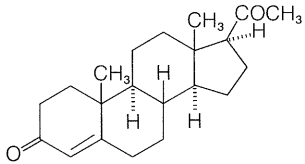
Most steroids are alcohols, and accordingly are named as **sterols.** Important examples include cholesterol, ergosterol, estradiol, stigmasterol, and other representative sterols given in Table 30-2. As you can see from their structures, most possess the same ring skeleton but vary considerably in their peripheral structural features, stereochemistry, and in the degree of ring unsaturation.

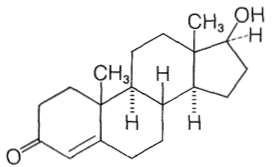
Sterols are widely distributed in both plants and animals. Many are of vital importance to animal physiology, such as cholesterol, the bile acids, vitamin D, sex hormones, and corticoid hormones. Many have value as medicinals, such as the cardiac glycosides, hormones, and steroidal antibiotics. The occurrence and physiological properties of representative steroids are included in Table 30-2.

30-4A Cholesterol

Cholesterol is an unsaturated alcohol of formula $C_{27}H_{45}OH$ that has long been known to be the principal constituent of human gall stones and has received notoriety in recent years for its connection with circulatory ailments, particularly hardening of the arteries. Cholesterol, either free or in the form of esters, actually is widely distributed in the body, particularly in nerve and brain tissue, of which it makes up about one sixth of the dry weight. The function of cholesterol in the body is not understood; experiments with labeled cholesterol indicate that cholesterol in nerve and brain tissue is not rapidly equilibrated with cholesterol administered in the diet. Two things are clear: Cholesterol is synthesized in the body and its metabolism is regulated by a highly specific set of enzymes. The high specificity of these enzymes may be judged from the fact that the very closely related plant sterols, such as sitosterol, are not metabolized by the higher animals, even though they have the same

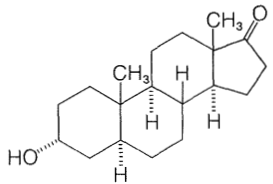
Table 30-2
Representative Steroids

Structure and name[a]	Occurrence and physiological properties	Structure and name[a]	Occurrence and physiological properties
 ergosterol	sterol of yeast, gives vitamin D_2 when irradiated (see Section 28-2F)	 vitamin D_2	antirachitic factor, formed by ultraviolet irradiation of ergosterol (Section 28-2F)
 stigmasterol	plant sterol, soybean oil	 equilenin	female sex hormone of horse, regulates sexual cycle
 estrone	human estrogenic hormone, the corresponding C17 alcohol (OH *trans* to the C13 methyl) is even more active (estradiol)	 progesterone	human pregnancy hormone, secreted by the corpus luteum



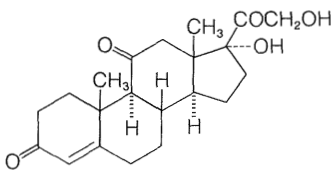
testosterone

male sex hormone, regulates development of reproductive organs and secondary sex characteristics



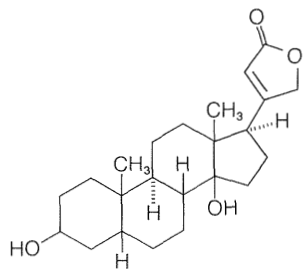
androsterone

androgenic hormone of less potency than testosterone



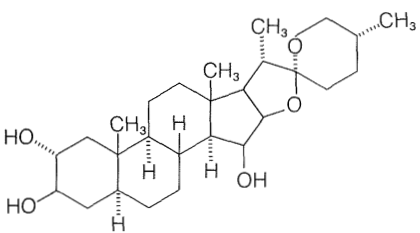
cortisone

hormone of adrenal cortex, once used for treatment of arthritis, 6- and 9-fluoro derivatives have higher activity and fewer side effects



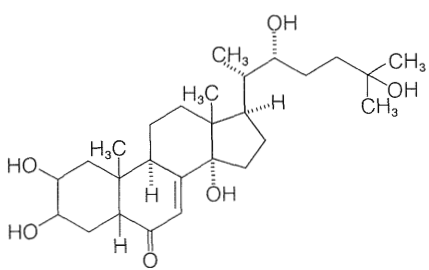
digitoxigenen

as a complex glycoside at the 3-hydroxyl in digitalis plants, potent cardiac poison, used in small doses to regulate heart action



digitogenin

a saponin, occurs as a complex glycoside (glucose, galactose, and xylose) in digitalis plants[b]



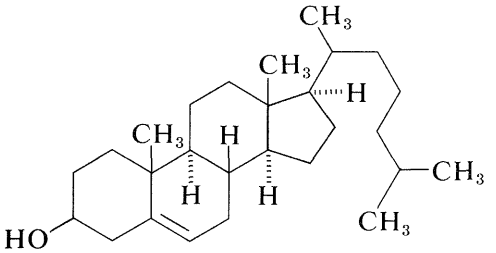
α-ecdysone

molting hormone of *Cecropia silk moth*

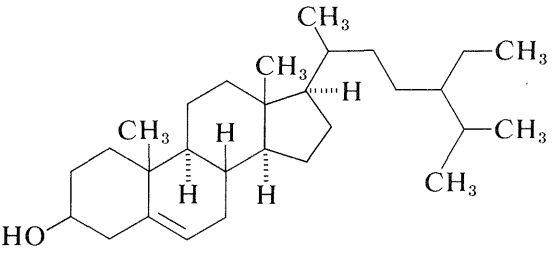
[a]The stereochemistry of the B/C and C/D ring junctions are as in cholesterol and the cholic acids; A/B stereochemistry is indicated where necessary. See p. 1474 for numbering system used for steroids.

[b]Digitogenin as the glycoside, digitonin, has the remarkable property of forming insoluble precipitates with the sterols having the 3-hydroxyl equatorial, but not those in which the hydroxyl is axial.

stereochemical configuration of all the groups in the ring and differ in structure only near the end of the side chain:

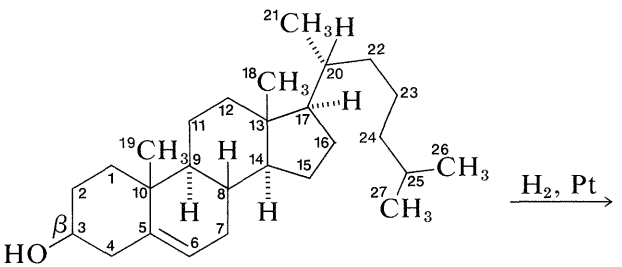


cholesterol

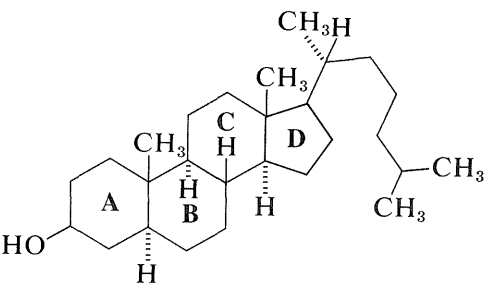


sitosterol

The accepted numbering system for the steroid nucleus and attached side chains is illustrated for cholesterol in **4**. The methyl groups at the junction of rings **A** and **B** (C10) and rings **C** and **D** (C13) are called *angular* methyls. To avoid misinterpretation of structure and stereochemistry, methyl groups and hydrogens at ring junctions should be explicitly written as CH_3 or H. The stereochemistry is specified by a solid line if the atom or group is *above* the ring plane (β), and by a dashed line if *below* the ring plane (α). Thus compound **5**, 5α-cholestan-3β-ol, which is obtained by the reduction of cholesterol, implies in the name that the hydroxyl at C3 is above the ring plane and that the hydrogen at C5 is below the ring plane (i.e., the **A**/**B** rings, have the *trans*-decalin stereochemistry; Section 12-9).



cholesterol, **4**



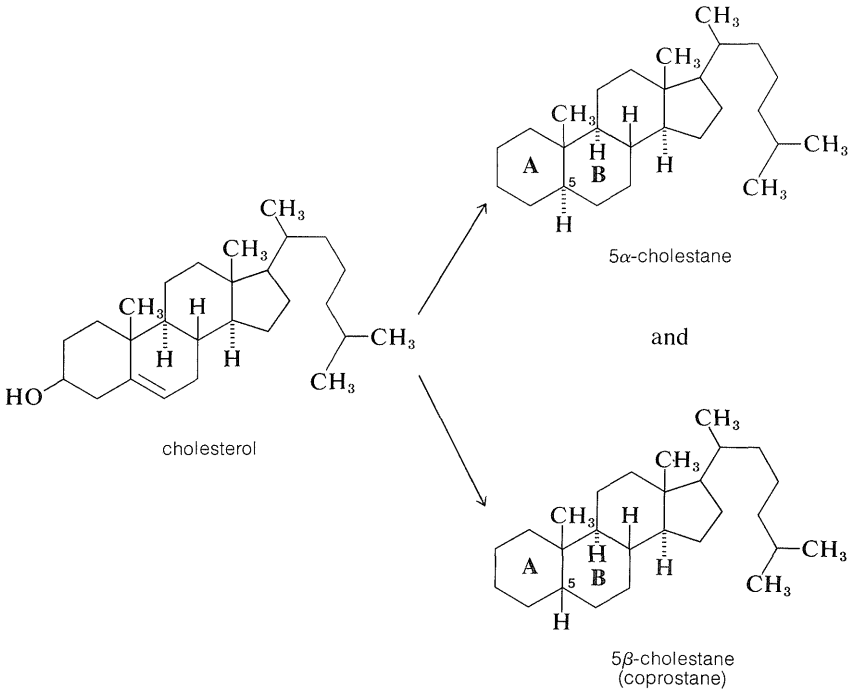
5α-cholestan-3β-ol, **5**

30-4B Structure of Cholesterol

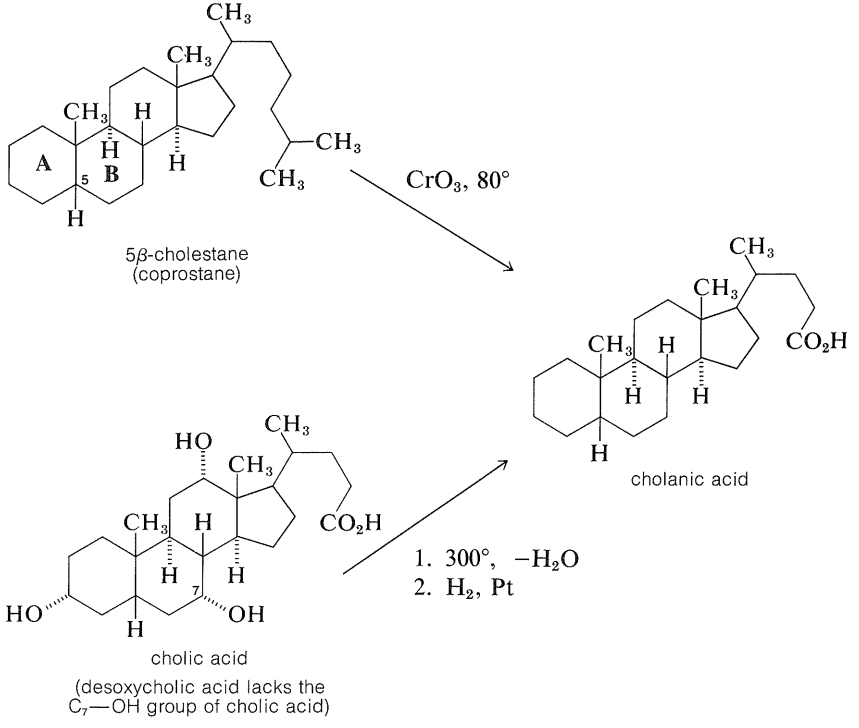
Although cholesterol was recognized as an individual chemical substance in 1812, all aspects of its structure and stereochemical configuration were not settled until about 1955. The structural problem was a very difficult one, because most of cholesterol is saturated and not easily degraded. Fortunately, cholesterol is readily available, so that it was possible to use rather elaborate degradative sequences, which would have been quite out of the question with some of the rarer natural products.

The first step in the elucidation of the structure of cholesterol was the determination of the molecular formula, first incorrectly as $C_{26}H_{44}O$ in 1859 and then correctly as $C_{27}H_{46}O$ in 1888. The precision required to distinguish between these two formulas is quite high, because $C_{26}H_{44}O$ has 83.80% C and 11.90% H, whereas $C_{27}H_{46}O$ has 83.87% C and 11.99% H. Cholesterol was shown in 1859 to be an alcohol by formation of ester derivatives and in 1868 to possess a double bond by formation of a dibromide. By 1903 the alcohol function was indicated to be secondary by oxidation to a ketone rather than an aldehyde. The presence of the hydroxyl group and double bond when combined with the molecular formula showed the presence of four carbocyclic rings. Further progress was only possible by oxidative degradation.

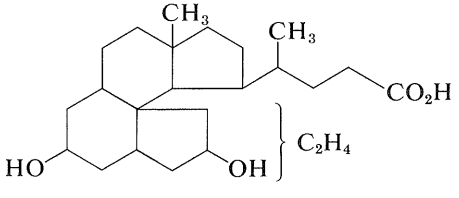
The structure proof for cholesterol paralleled that for two other important steroids, the so-called *bile acids,* cholic and desoxycholic acid, which function to help solubilize fats in the intestinal tract. Proof that cholesterol and the bile acids have the same general ring system was achieved by dehydration and reduction of cholesterol to two different hydrocarbons, 5α-*cholestane* and 5β-*cholestane* (*coprostane*), which differ only in the stereochemistry of the junction between rings **A** and **B:**



Oxidation of 5β-cholestane, but not 5α-cholestane, gave an acid that turned out to be identical with *cholanic acid* obtained by dehydration of cholic acid at 300° followed by hydrogenation:



Once the connection between cholesterol and the bile acids was established, further work on the structure proof was directed towards degradation experiments on the bile acids which, with their hydroxyl groups on rings **B** and **C**, offered more possible degradation reactions than cholesterol. Outstanding contributions toward the structure proof were made by the German chemists H. Wieland and A. Windaus, both of whom were honored by the award of the Nobel Prize in chemistry. Wieland received the award in 1927 and Windaus in 1928. Despite their many years of effort, the structure proposed by Windaus in 1928 for desoxycholic acid was only tentative and was unspecific as to the location of two carbons.



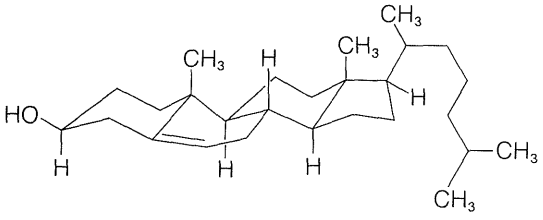
Windaus structure for desoxycholic acid (1928)

Serious doubt as to the correctness of the Windaus structure came as a result of an x-ray study of ergosterol by J. D. Bernal in 1932. He pointed out that the x-ray evidence indicated ergosterol to be a long, rather flat molecule. Steroids

with the ring system corresponding to the Windaus structure would have a globular shape. This observation stimulated further work and a re-examination of the evidence that eventually led to the correct structure. The details of this research may be found elsewhere.[3]

Exercise 30-10 How many optical isomers are possible for cholic acid?

Exercise 30-11 Assuming cholesterol has the following stereochemical configuration, draw a similar configurational structure for cholic acid (including the hydroxyl groups).



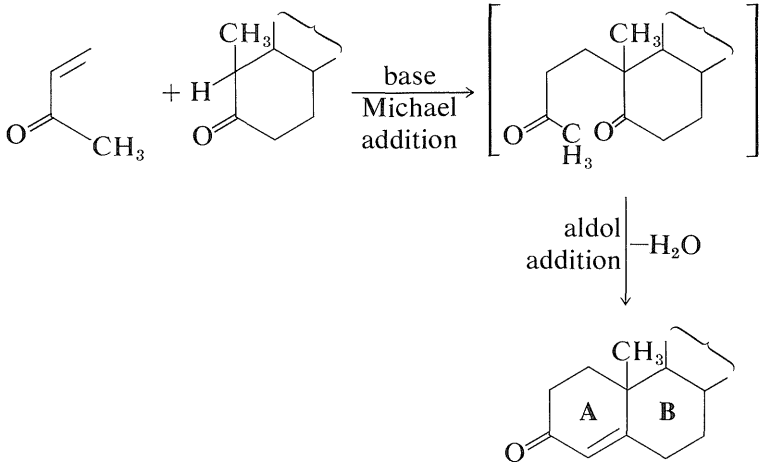
Exercise 30-12 Reduction of the double bond of cholesterol can be carried out so as to produce either 5α- or 5β-cholestanol. Equilibration of 5α-cholestanol with a trace of 5α-cholestanone and base (Section 16-4E) gives 90% 5α-cholestanol and 10% of a stereoisomer known as epicholestanol. Similar equilibration of 5β-cholestanol (in the presence of 5β-cholestanone) gives 10% 5β-cholestanol and 90% of a stereoisomer of 5β-cholestanol known as epicoprostanol. Write the configurations of each of these compounds and explain the orders of stabilities that are observed.

30-4C Synthesis of Steroids

One of the most notable achievements of the 1950's was the total synthesis of a number of important steroids, including estrone, cholesterol, cortisone, androsterone, and testosterone (see Supplementary Exercises). The courses of some of these syntheses are extraordinarily complex and involve large numbers of steps. Although they have not surpassed Nature in providing practical quantities of synthetic steroids, they have led to the development of key reactions of general use in organic synthesis. An especially useful reaction for building fused ring systems is the so-called *Robinson annelation reaction* developed by Sir Robert Robinson (Nobel Prize, 1947) and J. W. Cornforth

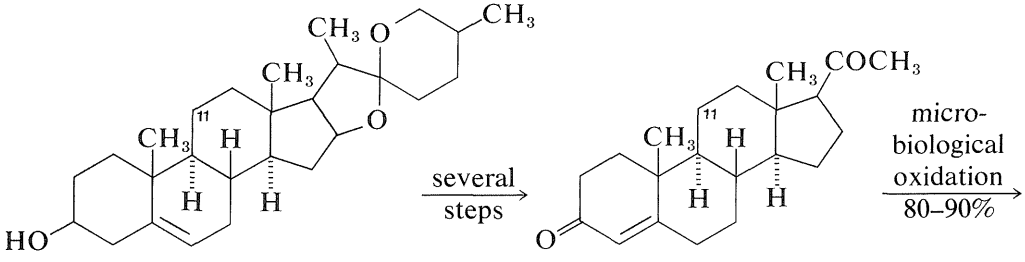
[3]See, for example, the excellent and authoritative account given by L. F. Fieser and M. Fieser, *Steroids,* Van Nostrand Reinhold Co., New York, 1959, Chapter 3.

(Nobel Prize, 1975). The reaction involves a Michael addition to an α,β-unsaturated ketone immediately followed by an aldol addition:

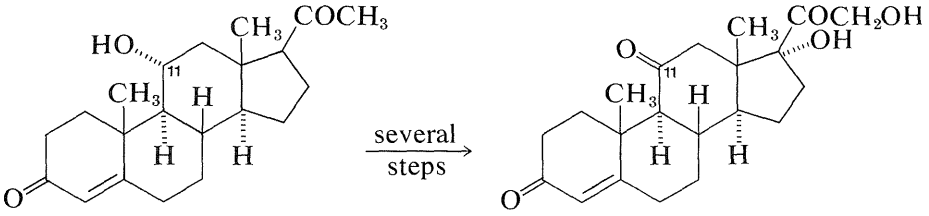


The pharmacological importance of many natural steroids has stimulated much synthetic work in an effort to obtain practical quantities of naturally occurring and unnatural steroids. Oftentimes a combination of biosynthesis and organic synthesis works best. For example, the need for large quantities of cortisone derivatives for therapeutic use in treatment of arthritis and similar metabolic diseases has led to intensive research on synthetic approaches for methods of producing steroids with oxygen functions at C11, which is not a particularly common point of substitution in steroids.

An efficient way of doing this is by microbiological oxidation. Cortisone can be manufactured on a relatively large scale from the saponin, diosgenin, which is isolated from tubers of a Mexican yam of the genus *Dioscorea*. Diosgenin is converted to progesterone, then by a high-yield (80–90%) oxidation with the mold, *Rhizopus nigricans*, to 11-hydroxyprogesterone and finally to cortisone:

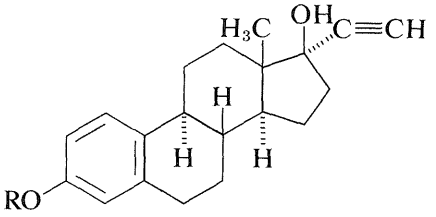


diosgenin progesterone



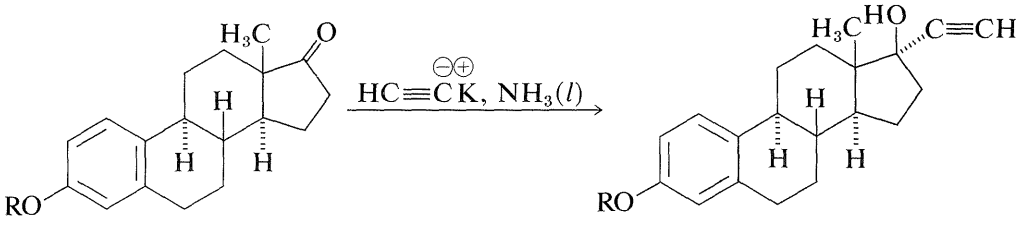
cortisone

Especially important steroid derivatives in use today are the synthetic estrogens, 17-α-ethynylestradiol and its 3-OCH_3 derivative, mestranol:



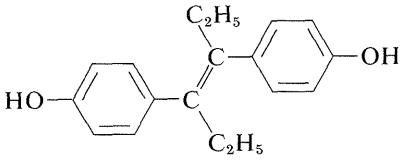
R = H, 17α-ethynylestradiol
R = CH_3, mestranol

Both of these compounds have potent estrogenic activity (inhibit ovulation) and are widely used as oral contraceptives. They are synthesized from the natural estrogen, estrone, by the following reaction:



R = H, estrone
R = CH_3, estrone methyl ether

A compound known as diethylstilbestrol (DES) also exhibits estrogenic activity even though it is unrelated structurally to steroidal estrogens. It has acquired notoriety as a possible cause of uterine cancer. Diethylstilbestrol has been used extensively as an additive in cattle and chicken feed because it gives a greater gain in weight for a given amount of feed.

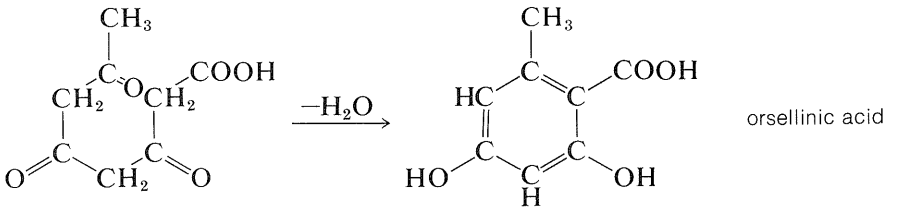


diethylstilbestrol

30-5 BIOSYNTHESIS

30-5A Fatty Acids

The idea that ethanoic acid (acetic acid) is a possible common starting material for the biosynthesis of many organic compounds was first proposed by Collie (1893) on purely structural grounds. He recognized a structural connection between a linear chain of recurring CH_3CO units (a polyketomethylene chain, $CH_3COCH_2COCH_2COCH_2CO$—) and certain cyclic natural products. In the example given below, orsellinic acid is represented as if it were derived from a chain of four CH_3CO units by a condensation-cyclization reaction:



orsellinic acid

Experimental verification of Collie's hypothesis came many years later when isotopic hydrogen and carbon (^2H, ^3H, ^{13}C, and ^{14}C) became available. Tracer studies showed that long-chain fatty acids are made by plants and animals from CH_3CO units by successively linking together the carbonyl group of one to the methyl group of another (K. Bloch and F. Lynen, Nobel Prize, 1964). If ethanoic acid supplied to the organism is labeled at the carboxyl group with ^{14}C ($\overset{*}{C}$), the fatty acid has the label at alternate carbons:

$$CH_3\overset{*}{C}H_2CH_2\overset{*}{C}H_2CH_2\overset{*}{C}H_2CH_2\overset{*}{C}H_2CH_2\overset{*}{C}H_2CH_2\overset{*}{C}H_2CH_2\overset{*}{C}H_2CH_2\overset{*}{C}O_2H$$

However, if the carbon of the methyl group is labeled, the product comes out labeled at the other set of alternate carbons:

$$\overset{*}{C}H_3CH_2\overset{*}{C}H_2CH_2\overset{*}{C}H_2CH_2\overset{*}{C}H_2CH_2\overset{*}{C}H_2CH_2\overset{*}{C}H_2CH_2\overset{*}{C}H_2CH_2\overset{*}{C}H_2CO_2H$$

Ethanoic acid is activated for biosynthesis by combination with the thiol, coenzyme A (**CoASH**, Figure 18-7) to give the thioester, ethanoyl (acetyl) coenzyme A (CH_3COS**CoA**). You may recall that the metabolic degradation of fats also involves this coenzyme (Section 18-8F) and it is tempting to assume that fatty acid biosynthesis is simply the reverse of fatty acid metabolism to CH_3COS**CoA**. However, this is not quite the case. In fact, it is a general observation in biochemistry that primary metabolites are synthesized by different routes from those by which they are metabolized (for example, compare the pathways of carbon in photosynthesis and metabolism of carbohydrates, Sections 20-9,10).

A brief description of the main events in fatty-acid biosynthesis follows, and all of these steps must be understood to be under control of appropriate enzymes and their coenzymes even though they are omitted here.

The CH_3CO group of ethanoyl coenzyme A is first transferred to a protein having a free thiol (SH) group to make another thioester, represented here as CH_3COS—**ACP**, where **ACP** stands for Acyl-Carrier-Protein. The growing carbon chain remains bound to this protein throughout the synthesis:

$$CH_3COSCoA + HS\text{—}ACP \longrightarrow CH_3COS\text{—}ACP + CoASH$$

Carboxylation of CH_3COS—**ACP** yields a propanedioyl thioester, **6**, which then undergoes a Claisen condensation with a second mole of CH_3COS—**ACP** accompanied by decarboxylation to yield a 3-oxobutanoyl thioester, **7**:

$$CH_3COS\text{—}ACP + CO_2 \xrightarrow{\text{biotin}} HO_2CCH_2COS\text{—}ACP$$

propanedionyl thioester, **6**
(malonyl thioester)

$$CH_3COS\text{—}ACP + HO_2CCH_2COS\text{—}ACP \xrightarrow[-HSACP]{-CO_2} CH_3COCH_2COS\text{—}ACP$$

3-oxobutanoyl thioester, **7**
(acetoacetyl thioester)

Reduction of the ketone group of the thioester (by NADPH) leads to a thiol ester of a four-carbon carboxylic acid. Repetitive condensations with thioester **6** followed by reduction eventually lead to fatty acids. Each repetition increases the chain length by two carbons:

$$CH_3COCH_2COS\text{—}ACP \xrightarrow[-H_2O]{[H]} CH_3CH_2CH_2COS\text{—}ACP \xrightarrow{\text{etc.}} CH_3(CH_2)_{2n}CO_2H$$

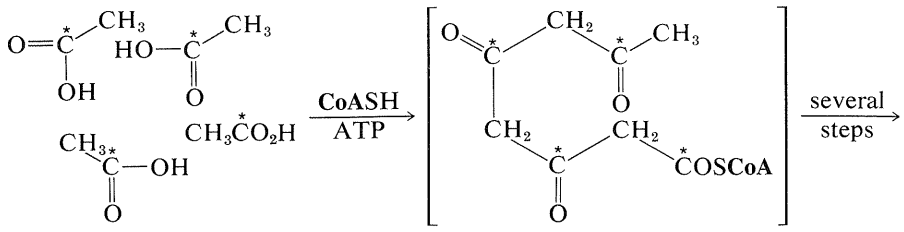
fatty acid

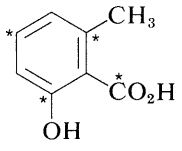
The preceding scheme is representative of fatty acid biosynthesis in plants, animals, and bacteria. The major difference is that plant and bacterial fatty acids usually contain more double bonds (or even triple bonds) than do animal fatty acids.

30-5B Biosynthesis of Aromatic Rings

Collie's hypothesis that aromatic compounds are made biologically from ethanoic acid was greatly expanded by A. J. Birch to include an extraordinary number of diverse compounds. The generic name "acetogenin" has been suggested as a convenient classification for ethanoate (acetate)-derived natural products, but the name "polyketides" also is used. Naturally occurring aromatic compounds and quinones are largely made in this way. An example is 2-hydroxy-6-methylbenzoic acid formed as a metabolite of the mold *Penicillium urticae;*

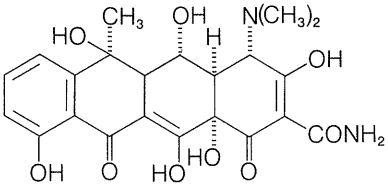
using ^{14}C-carboxyl-labeled ethanoic acid, the label has been shown to be at the positions indicated below:





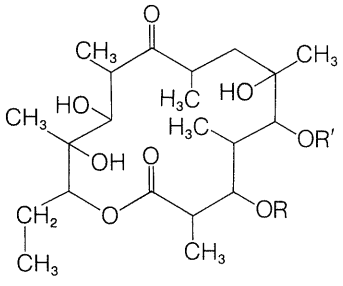
2-hydroxy-
6-methylbenzoic acid

Exercise 30-13 a. The structure of Terramycin (an oxytetracycline antibiotic) is shown below. This substance is a mold metabolite and shows extensive incorporation of ^{14}C when $CH_3—^{14}CO_2H$ is introduced into the culture medium. Indicate positions expected for introduction of the ^{14}C-label in Terramycin using $CH_3—^{14}CO_2H$.



Terramycin
(oxytetracycline)

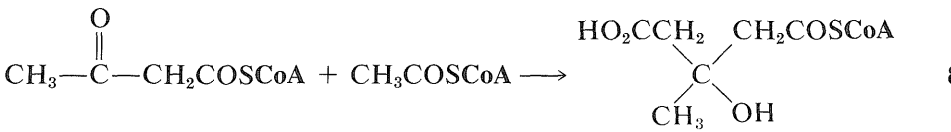
b. Erythromycin A is an example of a large group of antibiotics known as **macrolides.** They are medium-ring lactones. Erythromycin A is biosynthesized from propanoate. Show the expected distribution of deuterium and ^{14}C labels in erythromycin grown in a medium containing $CD_3CH_2{}^{14}CO_2H$.



Erythromycin A
(R and R′ are sugars)

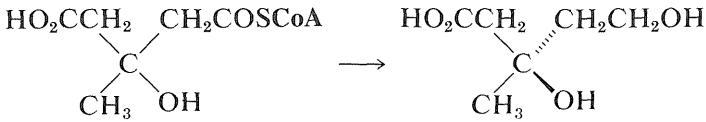
30-5C Terpene Biosynthesis

The biosynthesis of terpenes clearly follows a somewhat different course from fatty acids in that branched-chain compounds are formed. One way that this can come about is for 2-oxobutanoyl coenzyme A to undergo an aldol addition at the keto carbonyl group with the ethanoyl coenzyme A to give the 3-methyl-3-hydroxypentanedioic acid derivative, **8**:



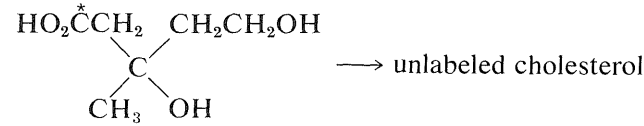
8

The next step is reduction of one of the carboxyl groups of **8** to give mevalonic acid:



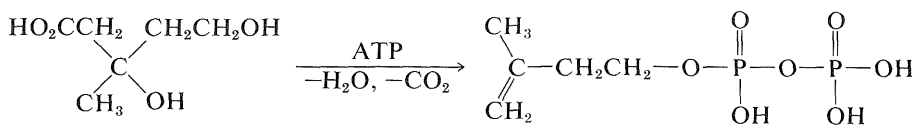
8 mevalonic acid (*R* enantiomer)

This substance has been shown by tracer studies to be an efficient precursor of terpenes and steroids. Mevalonic acid has six carbon atoms, whereas the isoprene unit has only five. Therefore, if mevalonic acid is the precursor of isoprene units, it must lose one carbon atom at some stage. Synthesis of mevalonic acid labeled at the carboxyl group with ^{14}C, and use of this material as a starting material for production of cholesterol, gives *unlabeled* cholesterol. Therefore, the carboxyl carbon is the one that is lost:



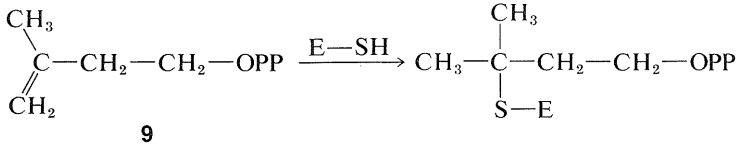
carboxyl-labeled mevalonic acid

Formation of the "biological isoprene unit" from mevalonic acid has been shown to proceed by stepwise phosphorylation of both alcohol groups, then elimination and decarboxylation to yield 3-methyl-3-butenyl pyrophosphate, **9** (often called Δ^3-isopentenyl pyrophosphate):



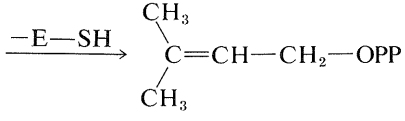
9

The coupling of the five-carbon units, **9**, to give isoprenoid compounds has been suggested to proceed by the following steps. First, isomerization of the double bond is effected by an enzyme (E) carrying an SH group:



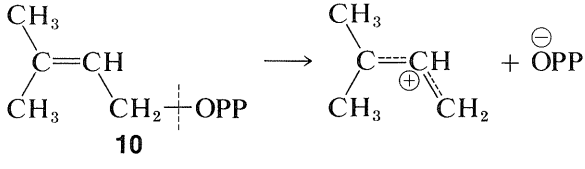
9

[OPP = pyrophosphate]

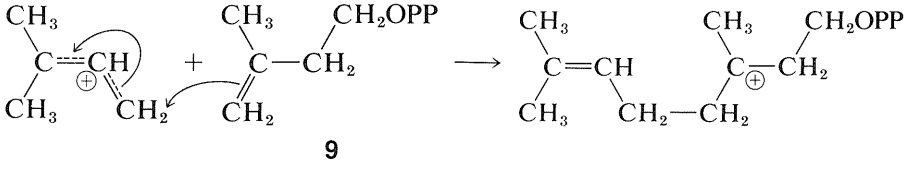


10

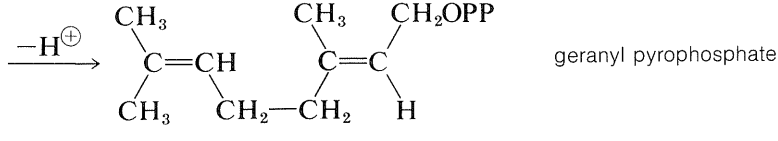
The ester, **10**, then becomes connected to the double bond of a molecule of **9**, probably in an enzyme-induced carbocation type of polymerization (Section 10-8B):



10



9



geranyl pyrophosphate

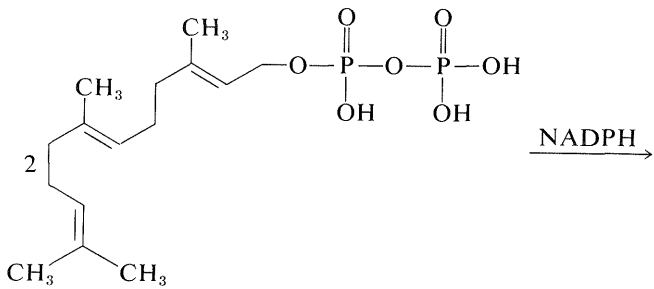
The product of the combination of two units of the pyrophosphate, **9**, through this sequence is **geranyl pyrophosphate** if, as shown, the proton is lost to give a trans double bond. Formation of a cis double bond would give neryl pyrophosphate (Section 30-3B).

Exercise 30-14 Show the position(s) of an isotopic carbon label such as ^{14}C in geranyl pyrophosphate biosynthesized from carboxyl-labeled $CH_3C^*O_2H$ by way of **8** and **9**.

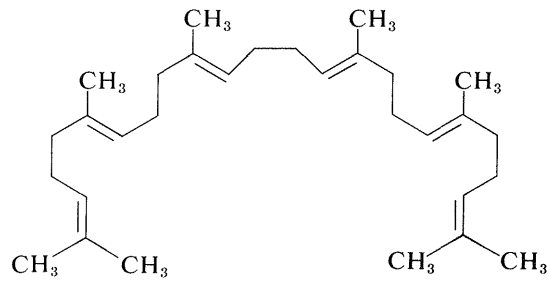
Exercise 30-15 Show by a reasonable mechanism how myrcene, ocimene, and limonene might arise from CH_3CO_2H by way of the pyrophosphate ester, **9**.

Suppose one started with CH_3CO_2H labeled at the methyl with ^{14}C; where would each product be labeled?

Continuation of the head-to-tail addition of five-carbon units to geranyl (or neryl) pyrophosphate can proceed in the same way to farnesyl pyrophosphate and so to gutta-percha (or natural rubber). At some stage, a new process must be involved because, although many isoprenoid compounds are head-to-tail type polymers of isoprene, others, such as squalene, lycopene, and β- and γ-carotene (Table 30-1), are formed differently. Squalene, for example, has a structure formed from head-to-head reductive coupling of two farnesyl pyrophosphates:



farnesyl pyrophosphate



squalene

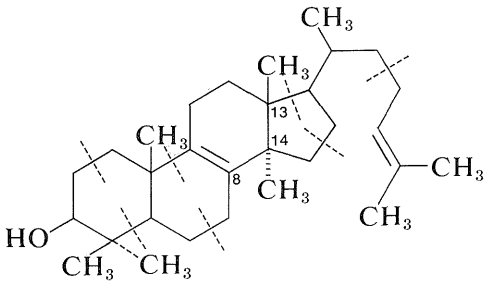
Since squalene can be produced from farnesyl pyrophosphate with NADPH and a suitable enzyme system, the general features of the above scheme for terpene biosynthesis are well supported by experiment.

In summary, the sequence from ethanoate to squalene has been traced as

ethanoyl coenzyme A ⟶ mevalonic acid ⟶ isopentenyl pyrophosphate
⟶ farnesyl pyrophosphate ⟶ squalene

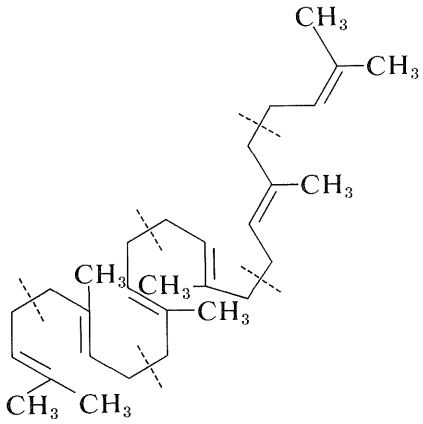
30-5D Cholesterol Biosynthesis

Isotopic labeling experiments show that cholesterol is derived from ethanoate by way of squalene and lanosterol. The evidence for this is that homogenized liver tissue is able to convert labeled squalene to labeled lanosterol and thence to labeled cholesterol. The conversion of squalene to lanosterol is particularly interesting because, although squalene is divisible into isoprene units, lanosterol is not—a methyl being required at C8 and not C13:



lanosterol

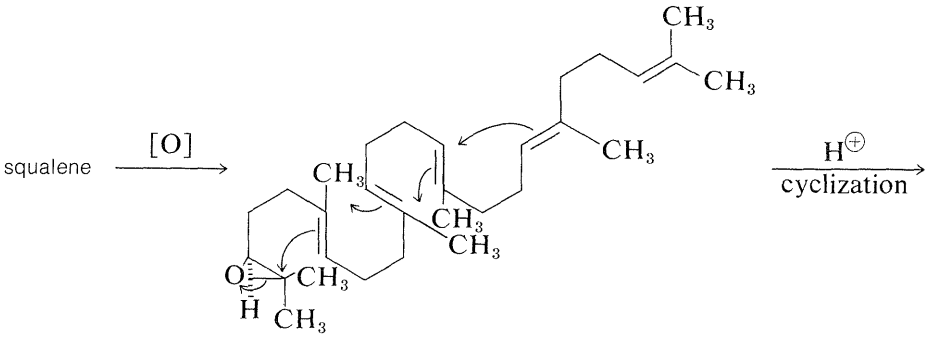
As a result, some kind of rearrangement must be required to get from squalene to lanosterol. The nature of this rearrangement becomes clearer if we write the squalene formula so as to take the shape of lanosterol:



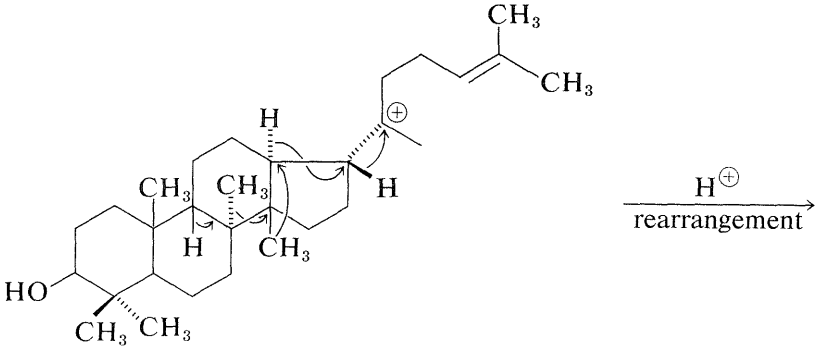
squalene

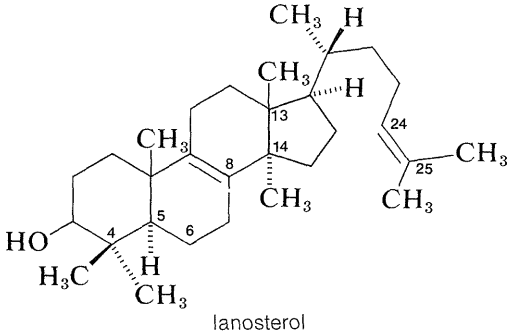
When squalene is written in this form, we see that it is beautifully constructed for cyclization to lanosterol. The key intermediate that initiates the cyclization is the 2,3-epoxide of squalene. Enzymatic cleavage of the epoxide ring is fol-

lowed by cyclization and then manifold hydride (H :) and methide (CH_3:) shifts to give lanosterol:



2,3-squalene oxide





lanosterol

The evidence is strong that the biosynthesis of lanosterol actually proceeds by a route of this type. With squalene made from either methyl- or carboxyl-labeled ethanoate, all the carbons of lanosterol and cholesterol are labeled just

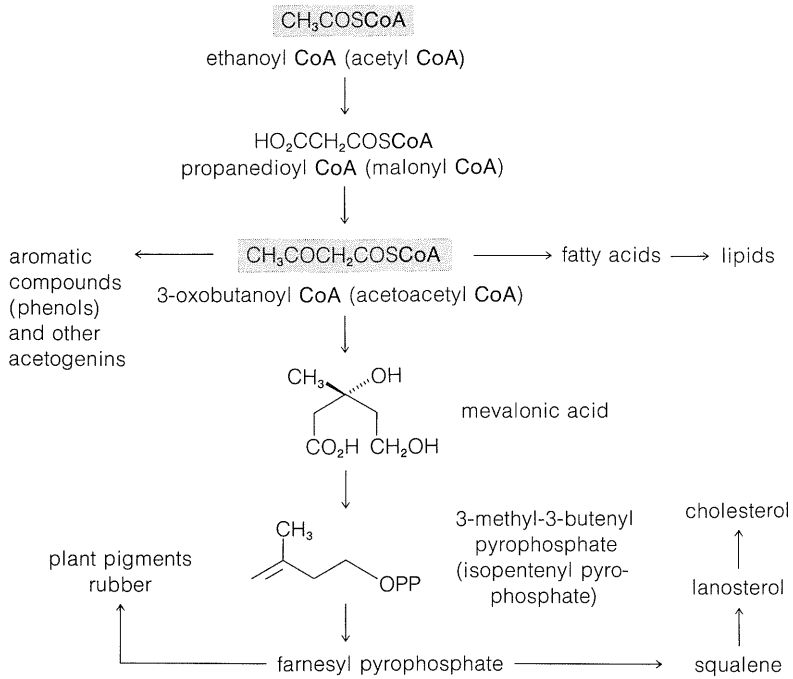


Figure 30-1 Summary of biosynthetic pathways to fatty acids, terpenes, and steroids

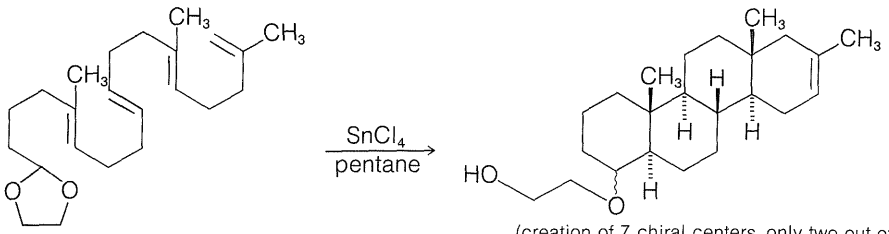
as predicted from the mechanism. Furthermore, ingenious double-labeling experiments have shown that the methyl at C13 of lanosterol is the one that was originally located at C14, whereas the one at C14 is the one that came from C8.

The conversion of lanosterol to cholesterol involves removal of the three methyl groups at the 4,4- and 14-positions, shift of the double bond at the **B/C** junction to between C5 and C6, and reduction of the C24–C25 double bond. The methyl groups are indicated by tracer experiments to be eliminated by oxidation to carbon dioxide.

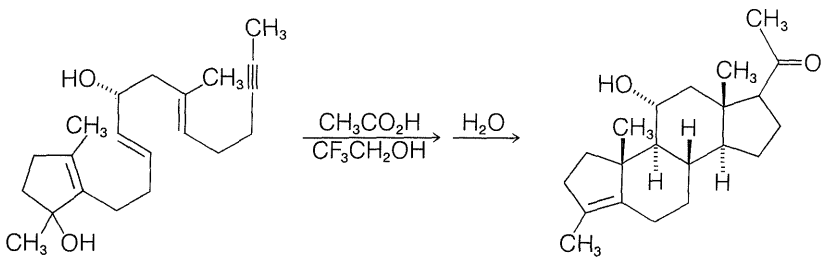
The biosynthetic connection between ethanoyl coenzyme A and the complex natural products briefly discussed is summarized in Figure 30-1.

Exercise 30-16 An ingenious and highly practical synthetic procedure for forming the steroid ring system has been developed by W. S. Johnson that closely mimics the squalene cyclization without the need for enzymes. The cyclizations occur by carbocationic intermediates under rather strictly defined conditions that are designed to prevent the reactants from being diverted to nucleophilic substitution or elimination

products until the desired additions have occurred. Devise a course for each of the following Johnson cyclization reactions:



(creation of 7 chiral centers, only two out of 64 D,L possible mixtures were formed)



(intermediate for cortisone synthesis)

30-6 SOME NITROGEN-CONTAINING NATURAL PRODUCTS

30-6A Alkaloids

Basic nitrogen compounds in plants are classified as alkaloids. Several examples were given previously of this large and remarkably heterogeneous class of compounds, many of which have very complex structures (Section 23-2). It is difficult to give a coherent account of alkaloid chemistry in the limited space available to us here.

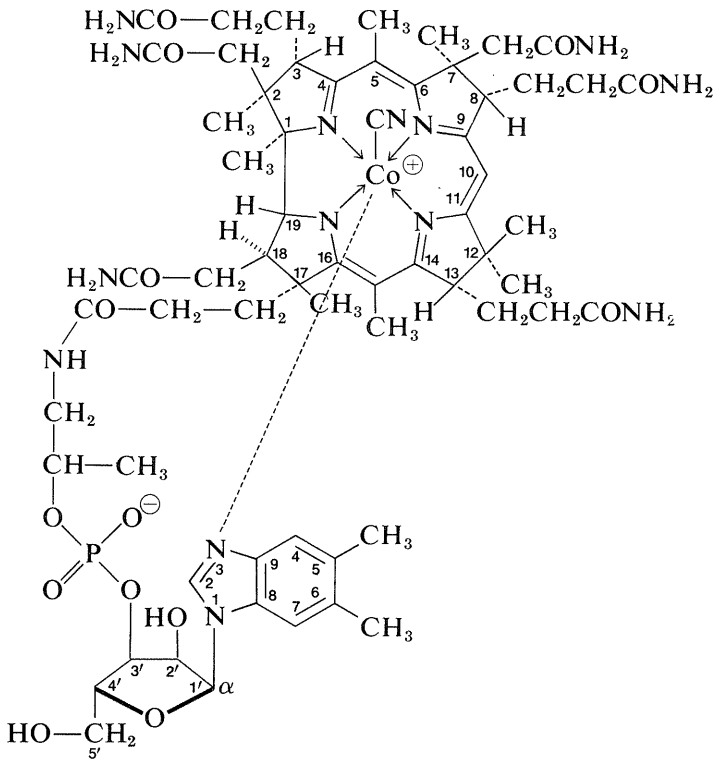
The **biosynthesis of alkaloids** has been extensively studied, and although for a time it was thought that alkaloids arose primarily from amino acid precursors, strong evidence now is available that ethanoate also is involved. The mode of alkaloid biosynthesis is not yet as well understood as that of the terpenes and steroids. One experimental problem is the difficulty of feeding suitably labeled precursors to plants.

30-6B Vitamin B_{12}

Vitamin B_{12} is the nutritional factor required for the prevention of pernicious anemia. Its structure was determined in 1956 through the chemical studies

of Alexander Todd (Nobel Prize, 1957) and the x-ray diffraction studies of Dorothy Hodgkin (Nobel Prize, 1964). It is one of the most complex natural products known, yet it has features that are not unfamiliar. It is related to the metalloporphyrins discussed previously (Section 25-8B), but the ring system surrounding the cobalt atom has one less carbon bridging two of the nitrogen-containing rings than the porphyrin ring of heme or chlorophyll. The B_{12} ring system is called a **corrin** ring, and the vitamin is a cobalt-corrin complex.

The corrin ring includes methyl, ethanamide, and propanamide groups, and one of these is linked through a nucleotide residue to the cobalt atom. There are five nitrogen ligands around the cobalt, and a sixth ligand is attached through carbon—here a cyano group—so that an alternate name for vitamin B_{12} is *cyanocobalamin:*

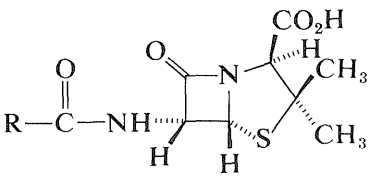


vitamin B_{12} (cyanocobalamin form)

A total synthesis of vitamin B_{12} was announced in 1972, as the result of a collaborative effort between R. B. Woodward (Harvard) and A. Eschenmoser (Zurich). The synthesis was completed after 11 years of effort involving 100 co-workers from 19 countries. A number of important techniques and reactions of synthetic value were developed during the course of this work, including the principle of conservation of orbital symmetry (the Woodward–Hoffman rules, Section 21-10). The biochemical action of vitamin B_{12} is considered in Chapter 31.

30-6C Penicillins and Cephalosporins

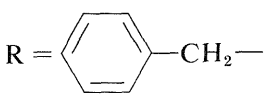
The first antibiotics of medicinal value were discovered by Alexander Fleming in 1929 as metabolites of the microorganism *Penicillium notatum*. They became known as **penicillins,** but their development as useful drugs was slow in coming. However, the urgent need for nontoxic antibiotics was recognized during World War II, and resulted in a team effort by English and American scientists to develop efficient methods for preparing penicillin by fermentation and to undertake clinical and chemical studies. By 1943, penicillin was available in quantity for the treatment of war wounded. By 1945, the basic structure and stereochemistry was deduced through chemical degradation and x-ray diffraction studies:



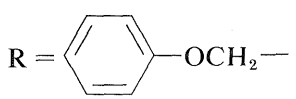
penicillin

The structure is unusual in that it has a four-membered cyclic amide ring (β-lactam). It was the first example to be discovered of a natural product with this ring structure.

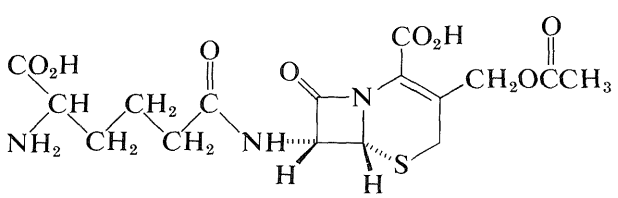
Fermentation can produce penicillins that differ only in the nature of the side-chain group R. The common natural penicillin is penicillin G, in which R = phenylmethyl (benzyl):

penicillin G 

penicillin F $R = CH_3CH_2CH{=}CHCH_2-$

penicillin V 

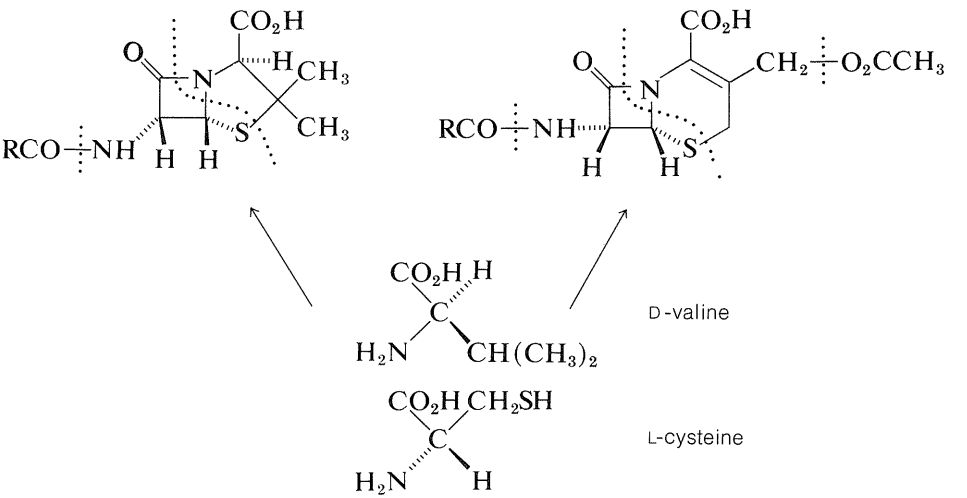
The cephalosporins are antibiotics produced by the bacterial strain *cephalosporium*. They are closely related to the penicillins. Thus cephalosporin C has a β-lactam ring but a six-membered sulfur-containing ring:



cephalosporin C

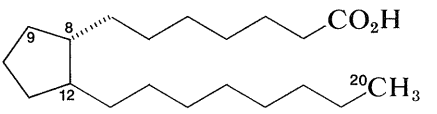
Both the cephalosporins and the penicillins owe their antibacterial action to their ability to block bacterial cell-wall biosynthesis. Cephalosporin C is less active than the penicillins, but is less susceptible to enzymatic destruction by β-lactamases, which are enzymes that cleave the lactam ring. In fact, the so-called resistance of *staph* bacteria to penicillins is attributed to the propagation of strains that produce β-lactamase. Numerous semisynthetic penicillins and cephalosporins have been made in the hope of finding new broad-spectrum antibiotics with high activity but with greater β-lactam stability. Several of these are in clinical use.

The total synthesis of penicillin V was achieved by J. C. Sheehan (1957) and of cephalosporin by R. B. Woodward (1966). Biosynthetic routes have been worked out in part, and the precursors to both ring systems are L-cysteine and D-valine:



30-7 PROSTAGLANDINS

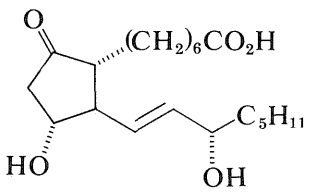
Some of the most recent and exciting developments in the field of natural products are related to the compounds known as **prostaglandins.** All are oxygenated unsaturated derivatives of prostanoic acid, which is a C_{20} fatty acid in which there is a cyclopentane ring formed by connecting the C8 and C12 positions:



prostanoic acid

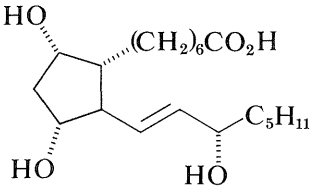
There are two main types of prostaglandins that differ in the oxygen function at C9, which is a carbonyl in Series E (PGE) and hydroxyl in Series F (PGF). Examples follow:

PGE

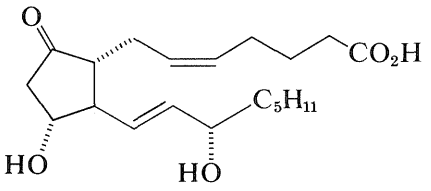


prostaglandin E_1

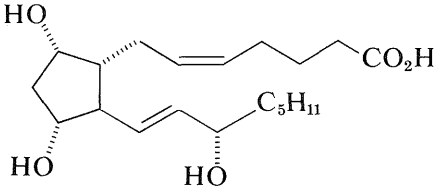
PGF



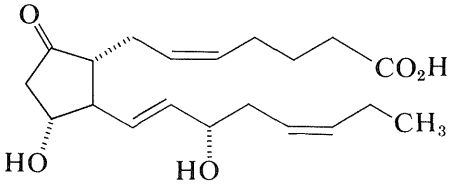
prostaglandin $F_{1\alpha}$



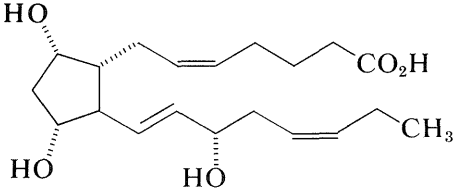
prostaglandin E_2



prostaglandin $F_{2\alpha}$



prostaglandin E_3

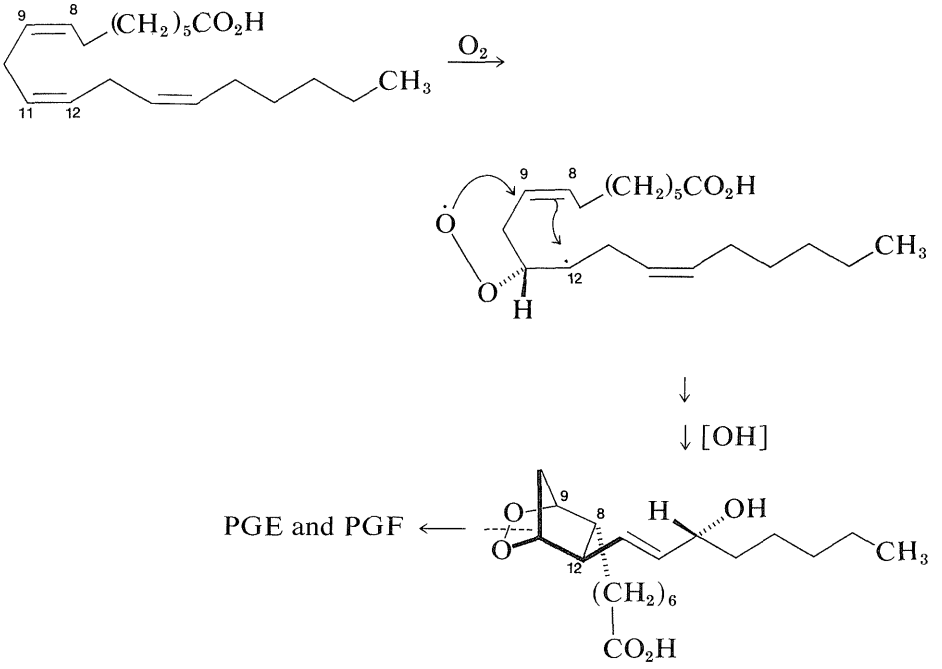


prostaglandin $F_{3\alpha}$

Prostaglandins are found in low concentrations distributed in a large number of organs, tissues, and body fluids of mammals. They exhibit a broad spectrum of physiological activity and are remarkably potent. Their precise biological role is not entirely clear, but they are known to induce strong contractions of smooth muscle tissue (lungs, uterus) and to lower blood pressure and sodium levels. Prostaglandins also have been implicated in the control of pituitary hormones released from the hypothalamus, and in the incidence of "pain" as a response to fever and inflammation. In fact, the analgesic property of aspirin possibly may result from the inhibition of prostaglandin biosynthesis. Although prostaglandins are not yet in extensive clinical use, their wide-ranging physiological effects hold promise that they will become useful drugs for the treatment of high blood pressure, thrombosis, respiratory disease, hypertension, ulcers, and in the regulation of fertility in both men and women.

A number of brilliant total syntheses of natural prostaglandins have been developed and these also have provided a number of interesting prostaglandin analogs (see Exercise 30-24). The biosynthesis of prostaglandins proceeds by oxygenation at C11 of unsaturated fatty acids. This is followed by

cyclization (probably as the result of a radical addition mechanism) to a bicyclic peroxide. Cleavage of the peroxide ring leads to prostaglandins:



Additional Reading

K. Nakanishi, T. Goto, S. Itô, S. Natori, and S. Nozoe, *Natural Products Chemistry,* Academic Press, Inc., New York, Volume 1 (1974); Volume 2 (1975).

P. Bernfeld, *Biogenesis of Natural Compounds,* 2nd ed., Pergamon Press, Inc., Elmsford, N.Y., 1967.

N. M. Packter, *Biosynthesis of Acetate-derived Compounds,* John Wiley & Sons, Inc., New York, 1973.

J. H. Richards and J. B. Hendrickson, *The Biosynthesis of Steroids, Terpenes, and Acetogenins,* W. A. Benjamin, Inc., Menlo Park, Calif., 1964.

J. B. Hendrickson, *The Molecules of Nature,* W. A. Benjamin, Inc., Menlo Park, Calif., 1965.

E. W. Horton, "Prostaglandins—Tomorrow's Drugs," *Chemical Society Reviews* 4, 589 (1975).

L. J. Mulheirn and P. J. Ramm, "The Biosynthesis of Sterols," *Chemical Society* Reviews 2, 259 (1972).

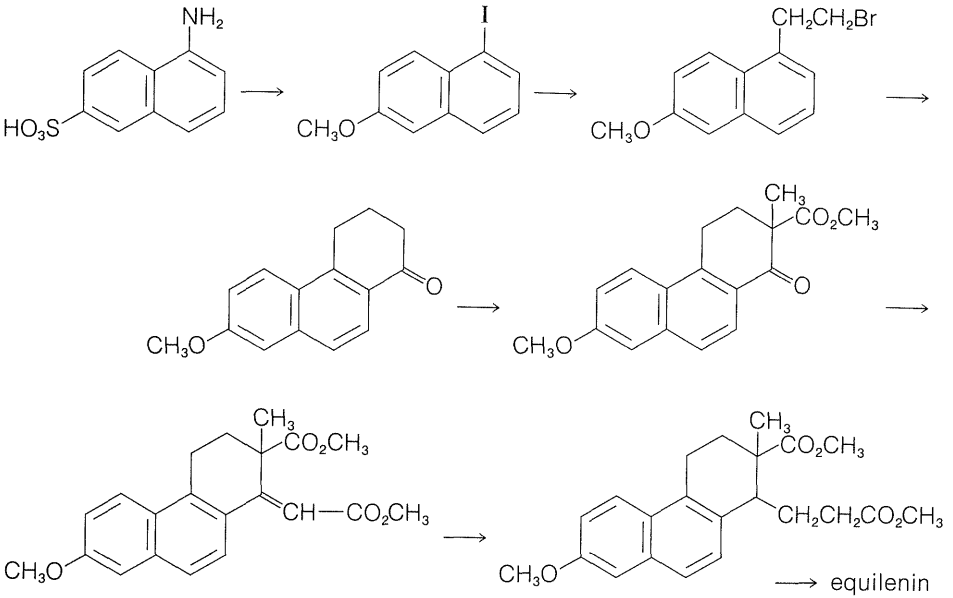
M. Goodman and P. Morehouse, *Organic Molecules in Action,* Gordon and Breach, New York, 1973.

J. W. Cornforth, "Asymmetry and Enzyme Action" (Nobel Lecture), *Science* **193**, 121 (1976).

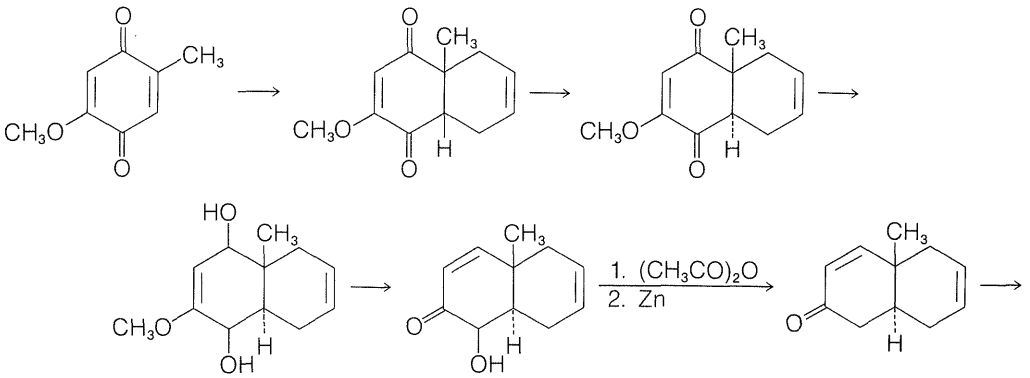
Supplementary Exercises

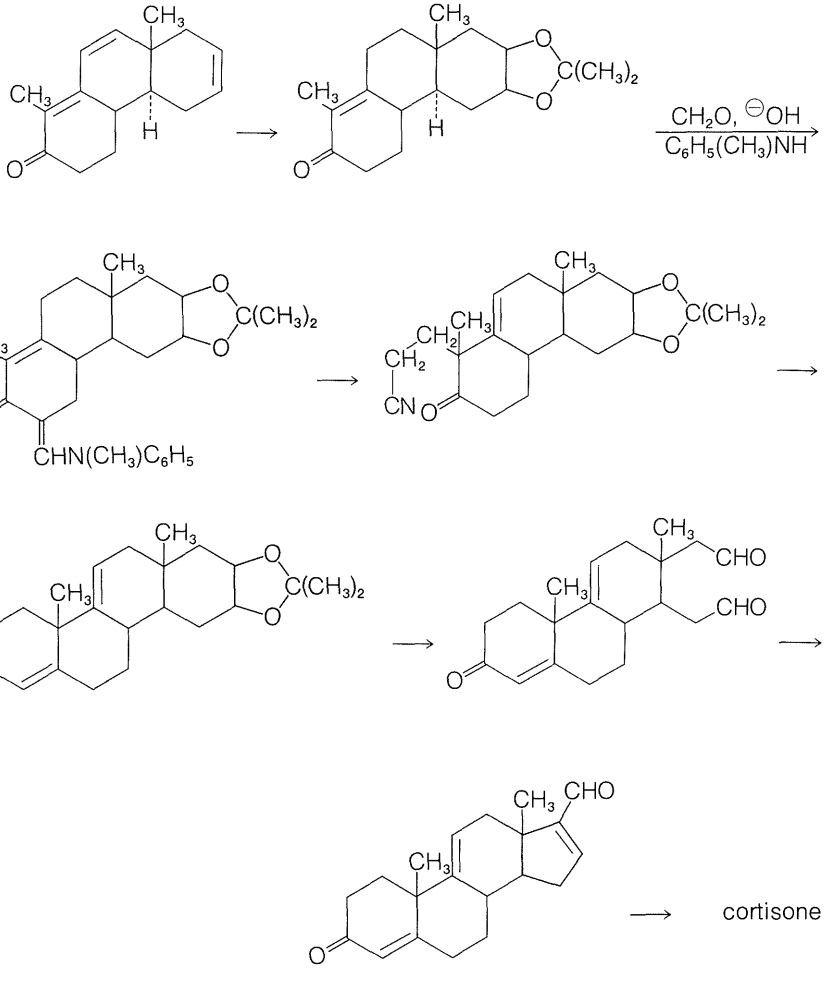
The following problems illustrate the steps taken in several important syntheses of naturally occurring substances. Show the reagents, conditions, and important intermediates you expect to be successful in achieving each of the indicated transformations, noting that more than one step may be required. Except where conditions and reagents already are supplied, all the reactions necessary have been discussed in previous chapters. We suggest that the reasons for the stereospecificity of the reactions (if any) be considered carefully. See Table 30-2 for steroid structures.

30-17 Equilenin was synthesized by Bachmann, Cole, and Wilds in 1939. This was the first total synthesis of a steroid. The route follows:

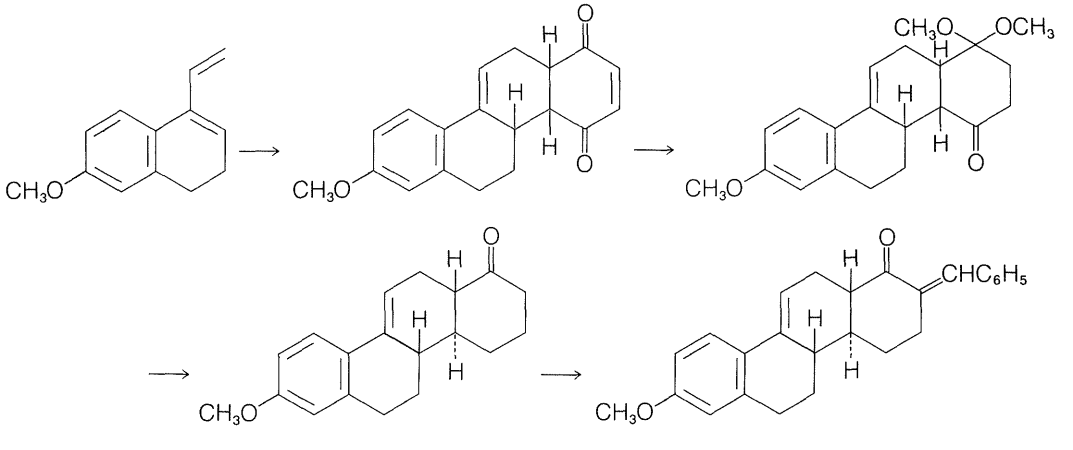


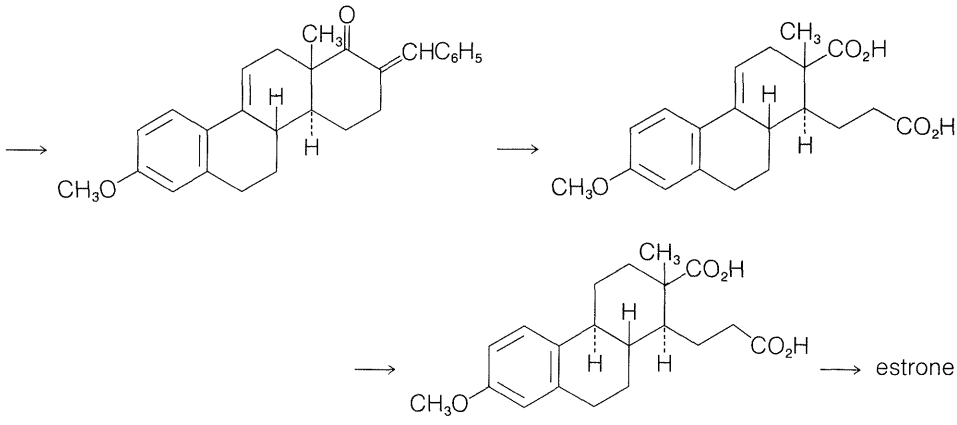
30-18 The total synthesis of cortisone has been achieved from an intermediate prepared by Woodward and co-workers in 1951 by the following route:



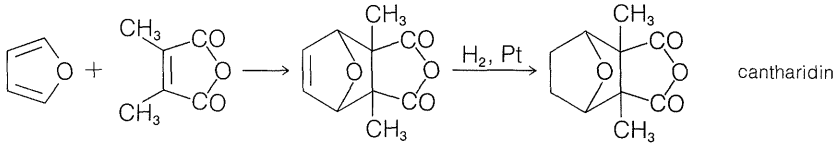


30-19 W. S. Johnson and co-workers have produced several elegant syntheses of estrone. One of the shortest and most stereospecific follows:



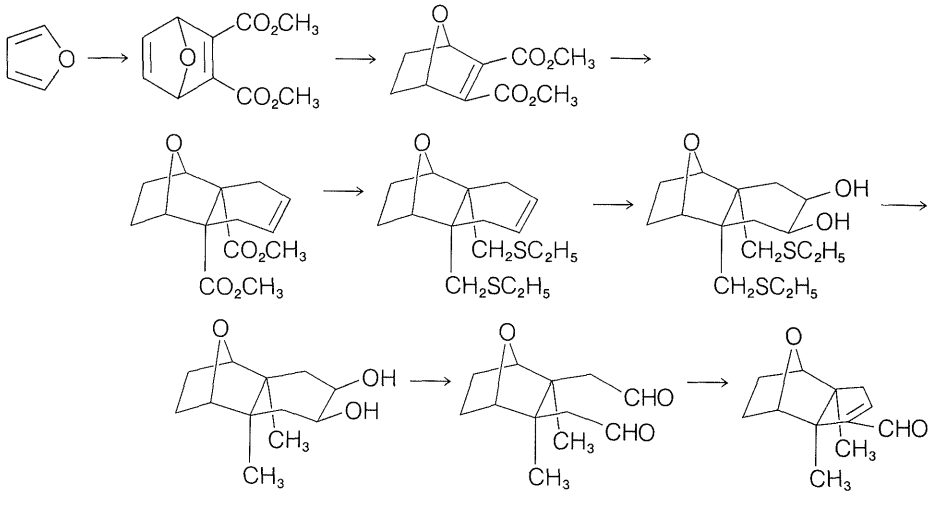


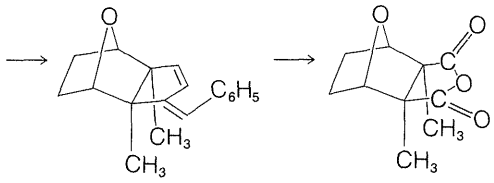
30-20 Cantharidin, a bicyclic "head-to-head" monoterpene (Section 30-3A) that is the irritant principle of the Spanish fly, would seem to be easy to synthesize by hydrogenation of the Diels-Alder adduct of dimethylbutenedioic anhydride and oxacyclopentadiene (furan):



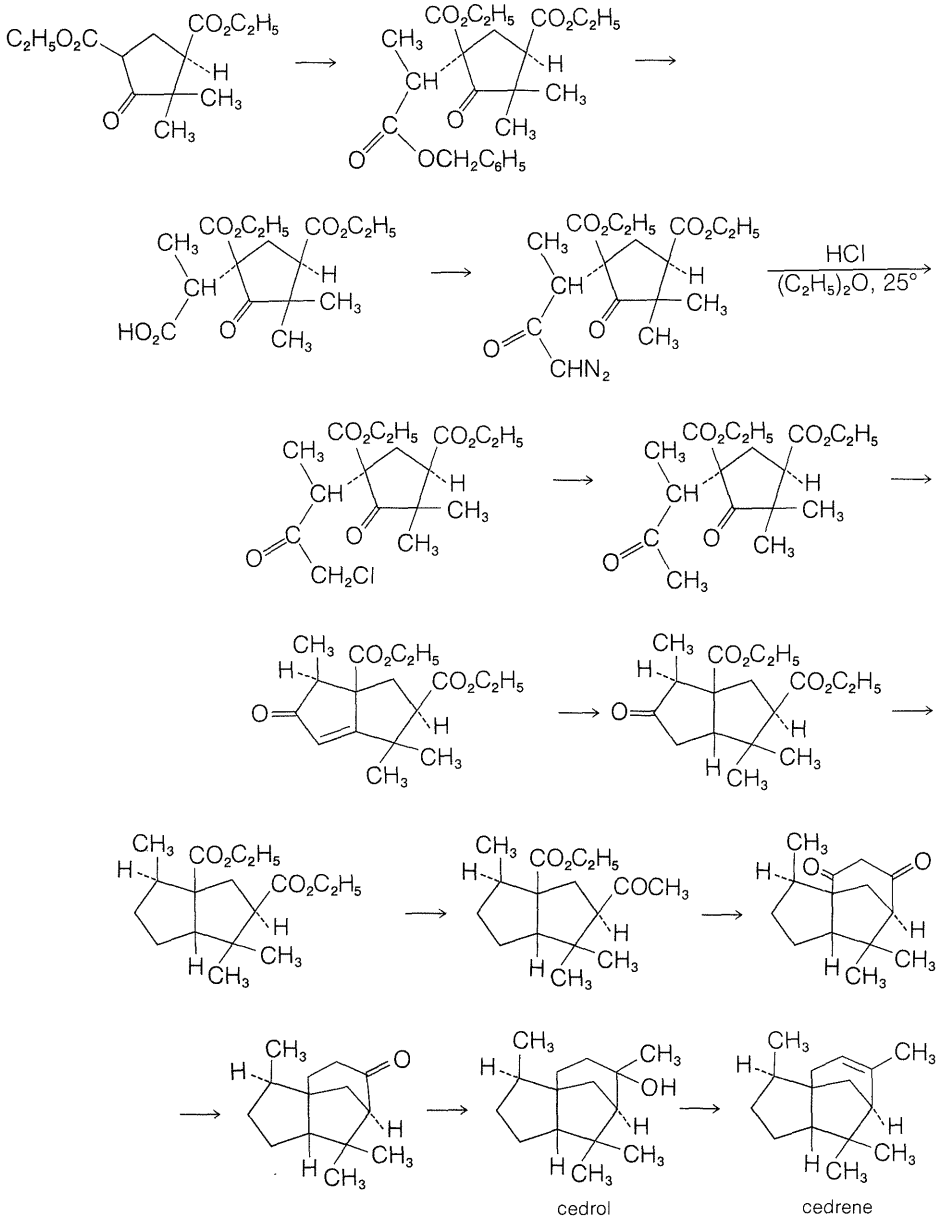
However, this route fails because the Diels–Alder reaction with the particular set of reagents has a very unfavorable equilibrium constant. Even if the addition were successful, it is possible also that the stereochemistry (**exo** or **endo**) of the adduct would not be the same as that of the natural product.

An ingenious synthesis of cantharadin that gives the correct stereochemistry was reported by Stork, van Tamelen, Friedman, and Burgstahler (1953) by way of the following intermediates:

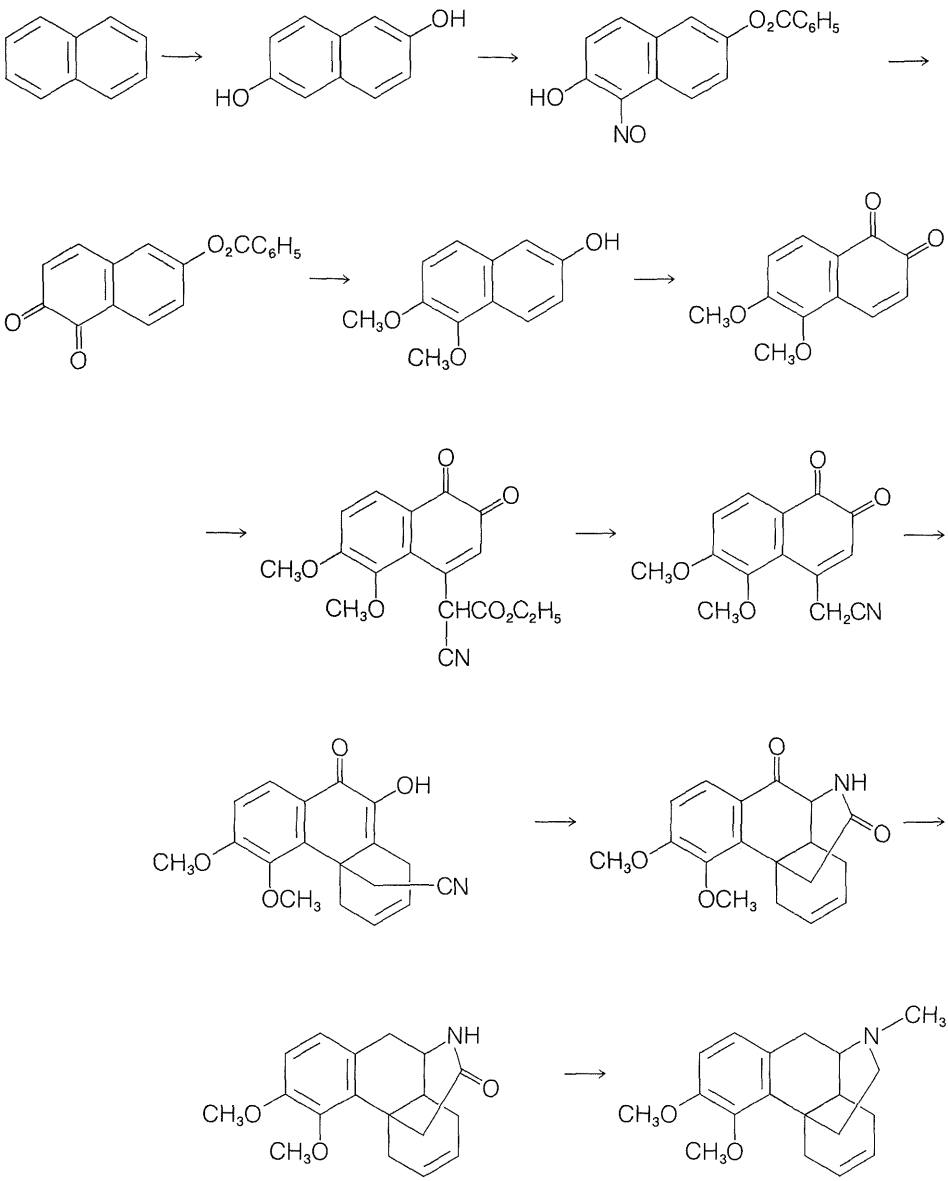


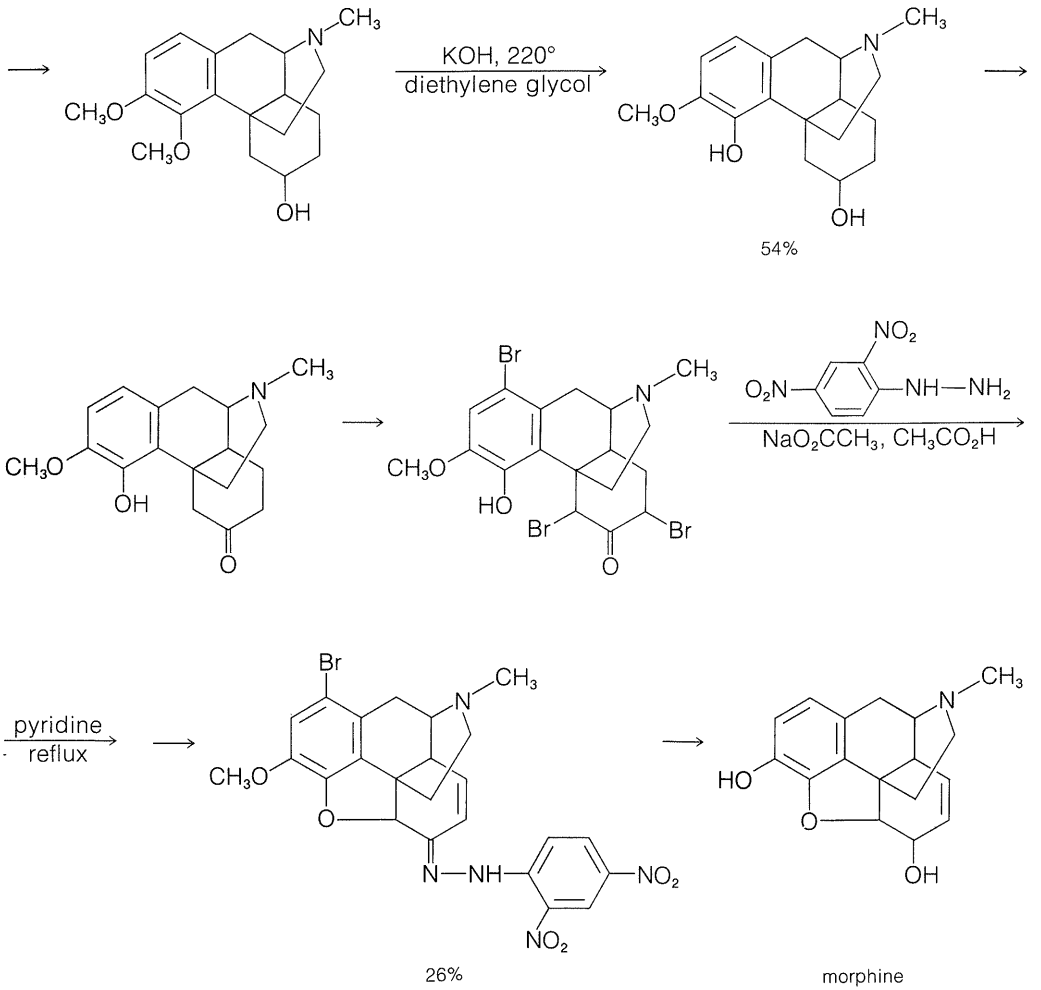


30-21 Cedrene (oil of cedar) has been synthesized by Stork and Clarke (1955) by way of the following intermediates:



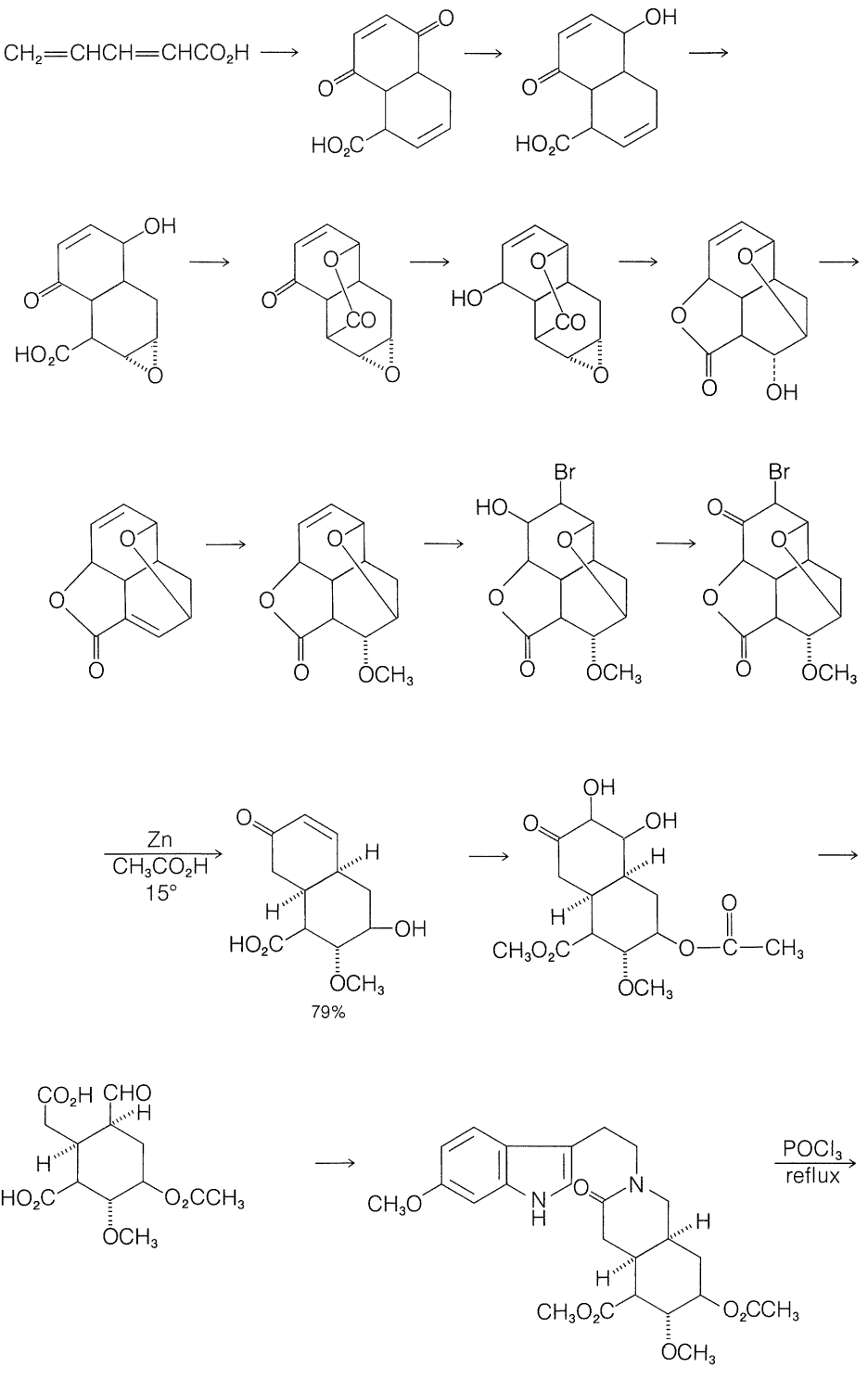
30-22 A synthesis of the alkaloid morphine (Section 23-2) was completed by Gates and Tschudi in 1952 by way of the following key intermediates, starting from naphthalene. Show the reagents, conditions, and important reaction intermediates that you expect would be successful in achieving each of the indicated transformations, noting that **more than one** synthetic step may be required between each key compound and considering carefully the order in which the operations should be carried out. Indicate those reactions that may be expected to give mixtures of stereo- or position-isomers. All the reactions involved have analogy in reactions that have been discussed in this or previous chapters, except where the conditions and reagents are specified.

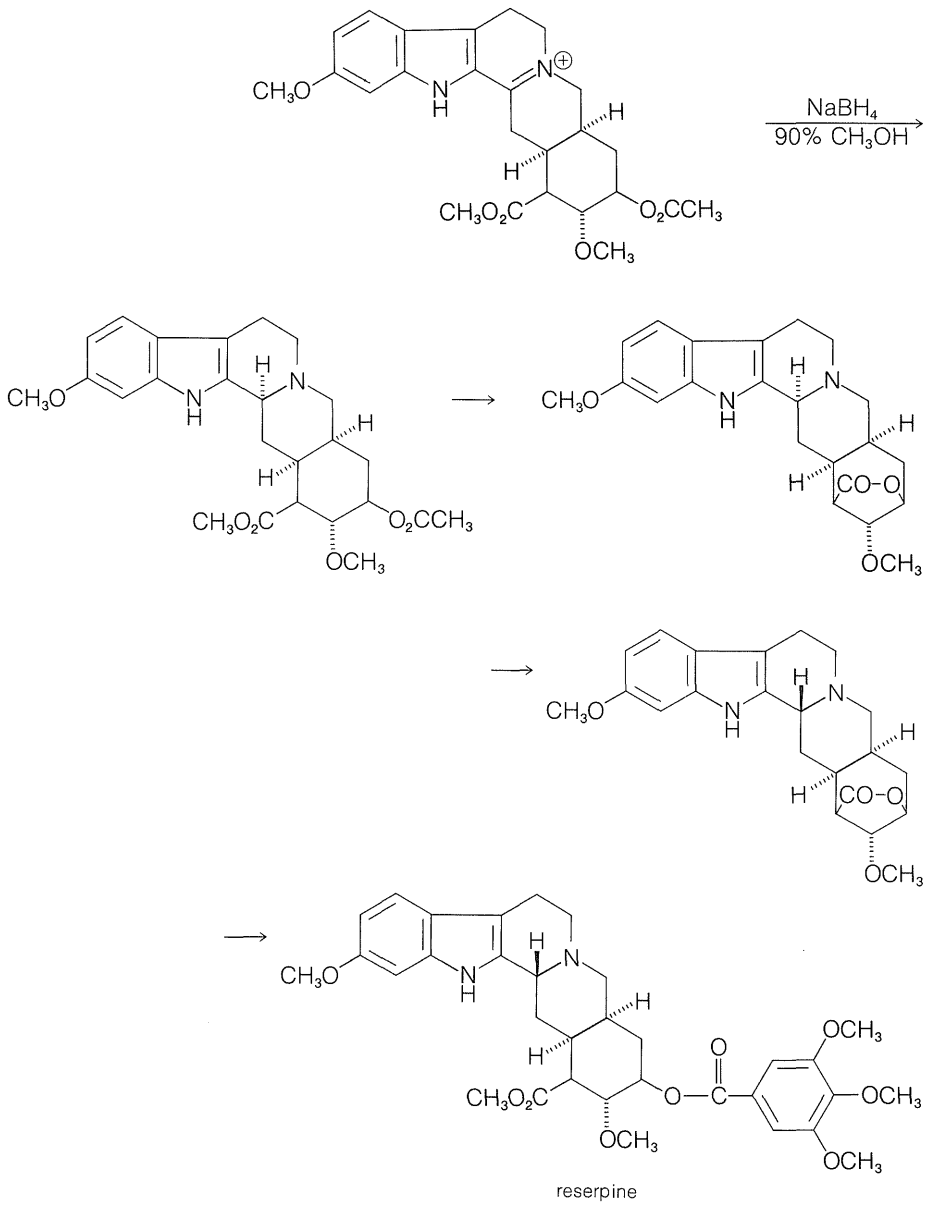




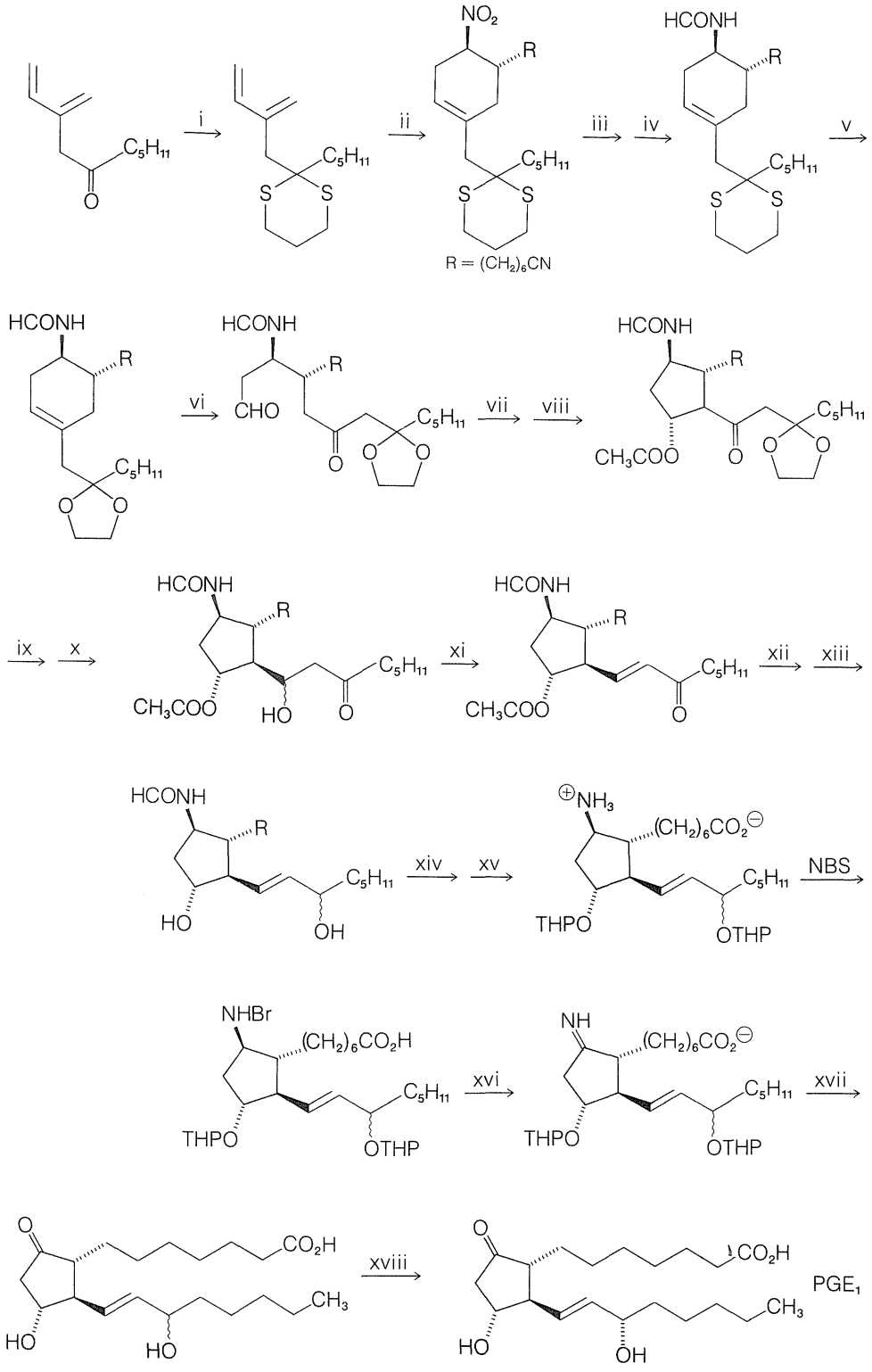
30-23 Synthesis of the alkaloid reserpine was reported in 1956 by R. B. Woodward and co-workers through the following intermediates from 2,4-pentadienoic acid. Show the reagents, conditions, and important reaction intermediates that you expect would be successful in achieving each of the indicated transformations, noting that **more than one** synthetic step may be required between each key compound and considering carefully the order in which the operations should be carried out. Indicate those reactions that may be expected to give mixtures of stereo- or position-isomers. All the reactions involved have analogy in reactions that have been discussed in this or previous chapters, except where the reagents and conditions are specified. The beauty of this synthesis lies in the control that it provides over the stereochemistry of the transformations involved, and it is worthwhile to give this detailed attention (with the aid of models, if possible).

Reserpine has important clinical use in the treatment of high blood pressure (hypertension) and also as a tranquilizer for the emotionally disturbed.


CH2=CHCH=CHCO2H
HO2C
OH
CO
HO
Br
OCH3
Zn
CH3CO2H
15°
79%
CO2H
CHO
O2CCH3
CH3O
POCl3
reflux



30-24 The need for adequate amounts of prostaglandins has led to several total syntheses of these substances. A stereospecific synthesis reported by E. J. Corey and co-workers in 1968 is outlined below. Complete the sequence as in Exercise 30-9 by showing the reagents and conditions needed for each step. Note that ≀ implies a mixture of epimers.


i
ii
iii
iv
v
vi
vii
viii
ix
x
xi
xii
xiii
xiv
xv
NBS
xvi
xvii
xviii
R = (CH2)6CN
PGE1