27.7 Biosynthesis of Steroids

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

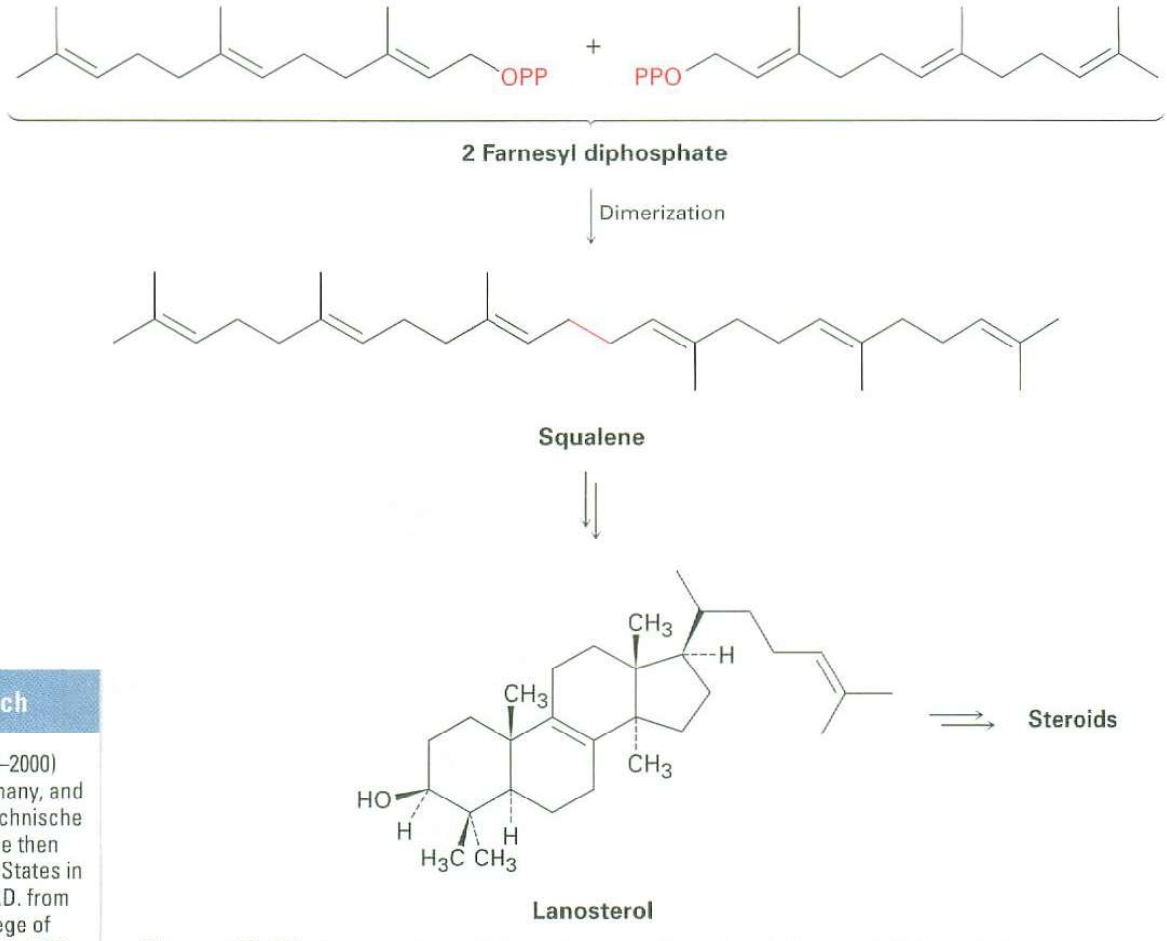
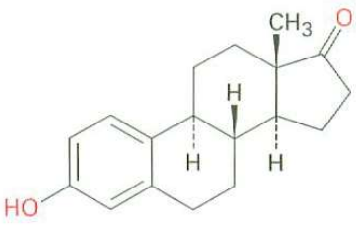


Figure 27.12 An overview of steroid biosynthesis from farnesyl diphosphate.

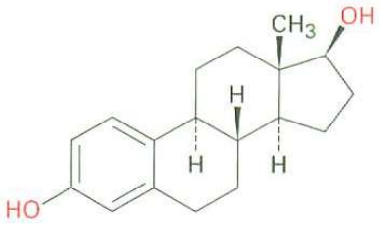
Konrad Emil Bloch

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

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

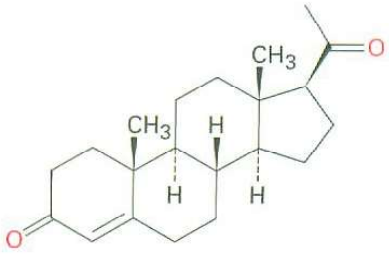


Estrone



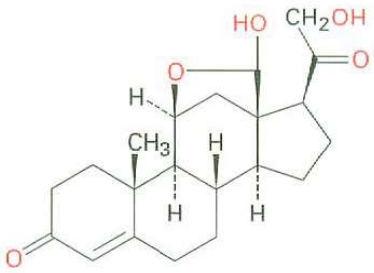
Estradiol

(Estrogens)

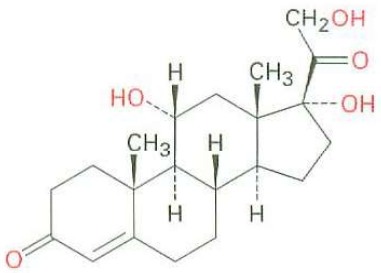


Progesterone
(a progestin)

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

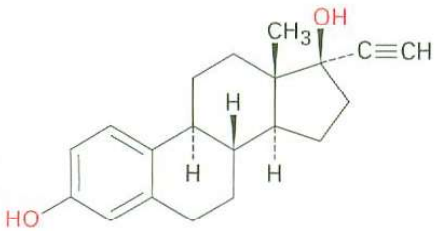


Aldosterone
(a mineralocorticoid)

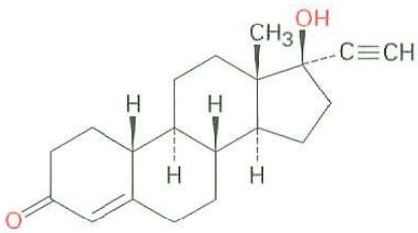


Hydrocortisone
(a glucocorticoid)

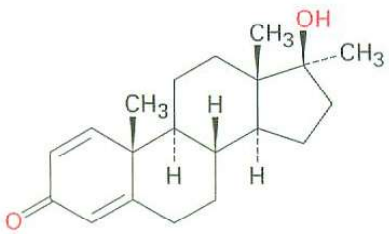
Synthetic Steroids In addition to the many hundreds of steroids isolated from plants and animals, thousands more have been synthesized in pharmaceutical laboratories in a search for new drugs. Among the best-known synthetic steroids are the oral contraceptives and anabolic agents. Most birth-control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



Ethynylestradiol
(a synthetic estrogen)

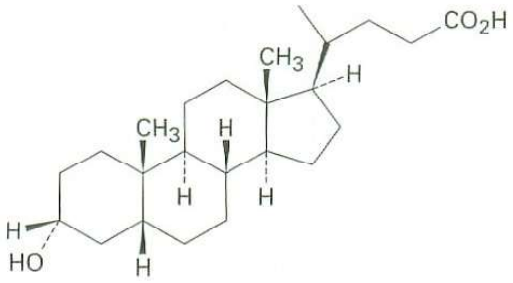


Norethindrone
(a synthetic progestin)



Methandrostenolone
(Dianabol)

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

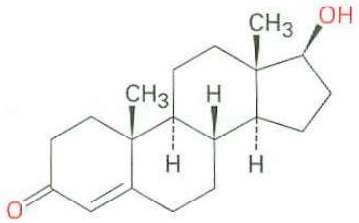


Lithocholic acid

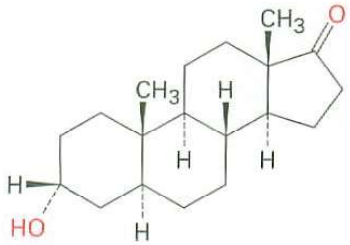
Steroid Hormones

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

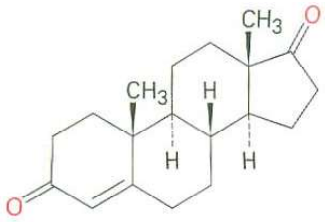
Sex Hormones Testosterone and androsterone are the two most important male sex hormones, or *androgens*. Androgens are responsible for the development of male secondary sex characteristics during puberty and for promoting tissue and muscle growth. Both are synthesized in the testes from cholesterol.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



Testosterone



Androsterone



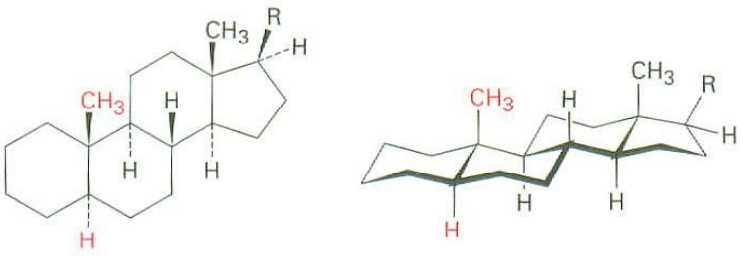
Androstenedione

(Androgens)

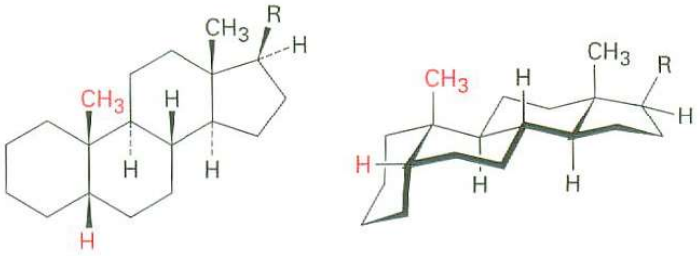
Estrone and estradiol are the two most important female sex hormones, or *estrogens*. Synthesized in the ovaries from testosterone, estrogenic hormones are responsible for the development of female secondary sex characteristics and for regulation of the menstrual cycle. Note that both have a benzene-like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

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

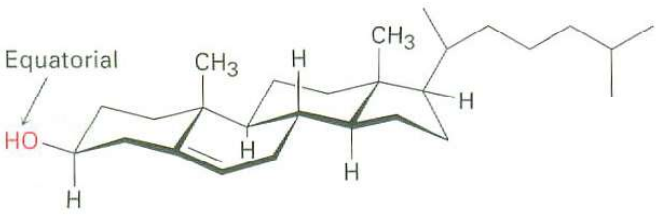
An A–B trans steroid

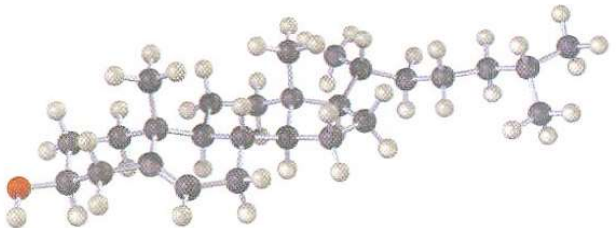


An A–B cis steroid



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

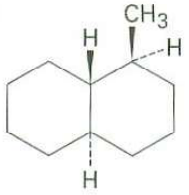




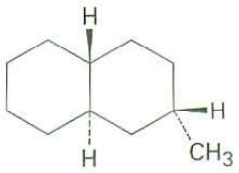
Cholesterol

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

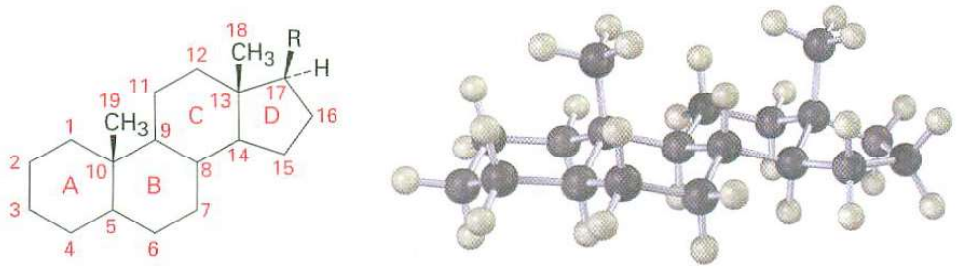
(a)



(b)



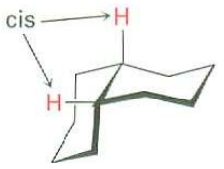
prevented by their rigid geometry from undergoing the usual cyclohexane ring-flips (Section 4.6).

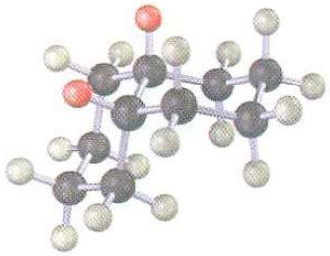


A steroid
(R = various side chains)

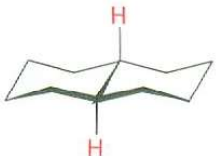
Two cyclohexane rings can be joined in either a cis or a trans manner. With cis fusion to give *cis*-decalin, both groups at the ring-junction positions (the *angular* groups) are on the same side of the two rings. With trans fusion to give *trans*-decalin, the groups at the ring junctions are on opposite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

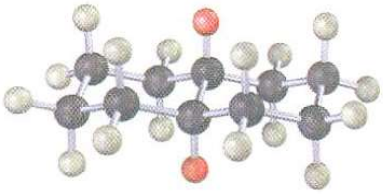
***cis*-Decalin**





***trans*-Decalin**

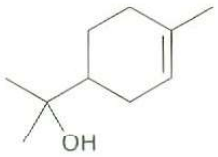




As shown in Figure 27.11, steroids can have either a cis or a trans fusion of the A and B rings, but the other ring fusions (B–C and C–D) are usually trans. An A–B trans steroid has the C19 angular methyl group up, denoted β, and the hydrogen atom at C5 down, denoted α, on opposite sides of the molecule.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

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

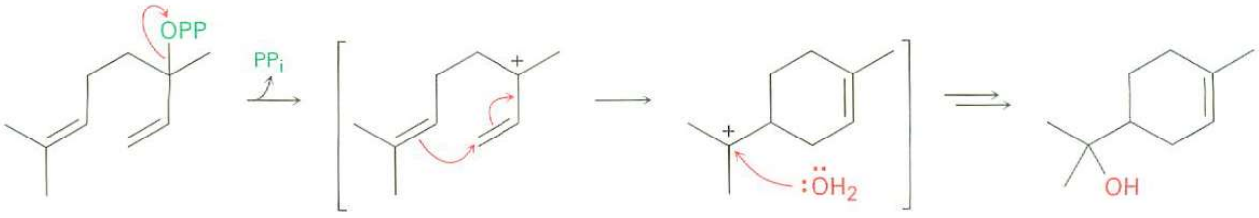
Propose a mechanistic pathway for the biosynthesis of α-terpineol from geranyl diphosphate.



α-Terpineol

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

Solution

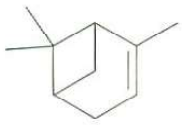


Linalyl diphosphate

α-Terpineol

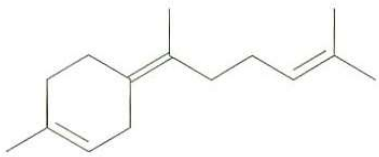
Problem 27.7 Propose mechanistic pathways for the biosynthetic formation of the following terpenes:

(a)



α-Pinene

(b)



γ-Bisabolene

27.6 Steroids

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

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