CHIRAL DRUGS

Chemistry and Biological Action

Edited by
GUO-QIANG LIN
QI-DONG YOU
JIE-FEI CHENG

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Introduction

The book consists of 11 chapters. The first part of the book introduces the general concept of chirality and its impact on drug discovery and development. The history and the trends of chiral drug development, the technologies for the preparation of chiral drugs, and the industrial applications of chiral technologies are discussed. This part covers three important chiral technologies, namely, asymmetric synthesis, biocatalytic process, and chiral resolution, and discusses their impact on chiral drug development. Without question, fluorine atoms play an important role in chiral drug discovery and development. The significance and the preparation of fluorine-containing chiral drugs are the topic of a separate chapter.

The second part of the book mainly deals with some unique aspects of chiral drugs in terms of pharmaceutical, pharmacological, and toxicological properties. For instance, pharmacology, pharmacokinetic properties, and toxicology of chiral drugs are discussed in comparison with racemic drugs. Additionally, computational modeling as applied to chiral drug discovery and development is discussed. This part of the book provides a general knowledge of design, synthesis, screening, and pharmacology from the preclinical point of view, hoping to raise interest from a broad range of readers.

Finally, Chapter 11 covers 25 representative chiral drugs that have been approved or are in advanced clinical trials. Some natural products are not included. The most important criteria for their selection are the involvement of chiral processes during their preparation and the significance of chirality in their development. Every entry contains the trade name, chemical name and properties, a

representative synthetic pathway, pharmacological characterizations, and references.

This book is intended to introduce chemists to pharmacological aspects of drug development and to form a fruitful cooperation among academic synthetic chemists, medicinal chemists, pharmaceutical scientists, and pharmacologists from the pharmaceutical and biotechnology industries. The references after each chapter will give readers an opportunity for further reading on the topics discussed. This is the first book of its kind to combine synthetic organic chemistry, medicinal chemistry, process chemistry, and pharmacology in the context of chiral drug discovery and development.

Chapter 1

Overview of Chirality and Chiral Drugs

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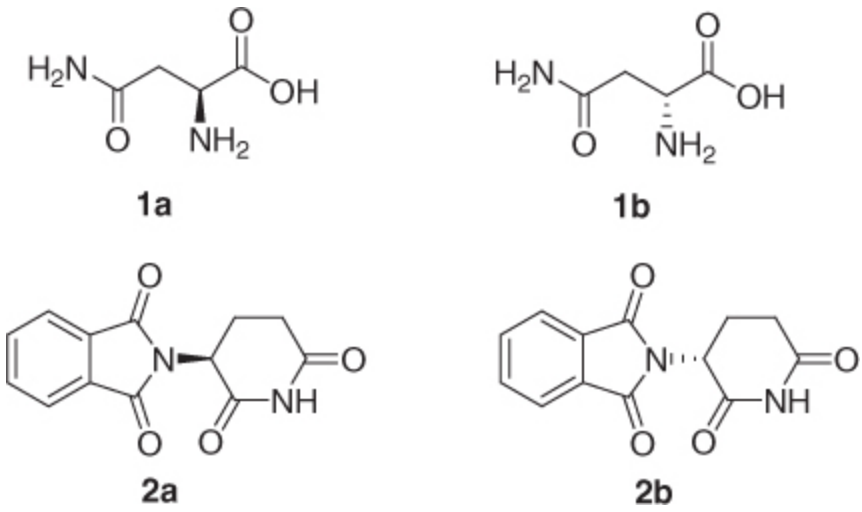
1.1 Introduction

The pharmacological activity of a drug depends mainly on its interaction with biological matrices or drug targets such as proteins, nucleic acids, and biomembranes (e.g., phospholipids and glycolipids). These biological matrices display complex three-dimensional structures that are capable of recognizing specifically a drug molecule in only one of the many possible arrangements in the three-dimensional space, thus determining the binding mode and the affinity of a drug molecule. As the drug target is made of

small fragments with chirality, it is understandable that a chiral drug molecule may display biological and pharmacological activities different from its enantiomer or its racemate counterpart when interacting with a drug target. In vivo pharmacokinetic processes (ADME) may also contribute to the observed difference in in vivo pharmacological activities or toxicology profiles. One of the earliest observations on the taste differences associated with two enantiomers of asparagines was made in 1886 by Piutti (1). Colorless crystalline asparagine is the amide form of aspartic or aminosuccinic acid and is found in the cell sap of plants in two isomeric forms, levo- and dextro-asparagin. The *l*-form exists in asparagus, beet-root, wheat, and many seeds and is tasteless, while the *d*-form is sweet. Thalidomide is another classical example. It was first synthesized as a racemate in 1953 and was widely prescribed for morning sickness from 1957 to 1962 in the European countries and Canada. This led to an estimated over 10,000 babies born with defects (2). It was argued that if one of the enantiomers had been used instead of the racemate, the birth defects could have been avoided as the *S* isomer caused teratogenesis and induced fatal malformations or deaths in rodents while the *R* isomer exhibited the desired analgetic properties without side effects (3). Subsequent tests with rabbits proved that both enantiomers have desirable and undesirable activities and the chiral center is easily racemized in vivo (4). Recent identification of thalidomide's target solved the long-standing controversies (5). The chirality story about thalidomide, although not true, has indeed had great impact on modern chiral drug discovery and development (Fig. 1.1).

Figure 1.1 Asparagine (**1**) and thalidomide (**2**).

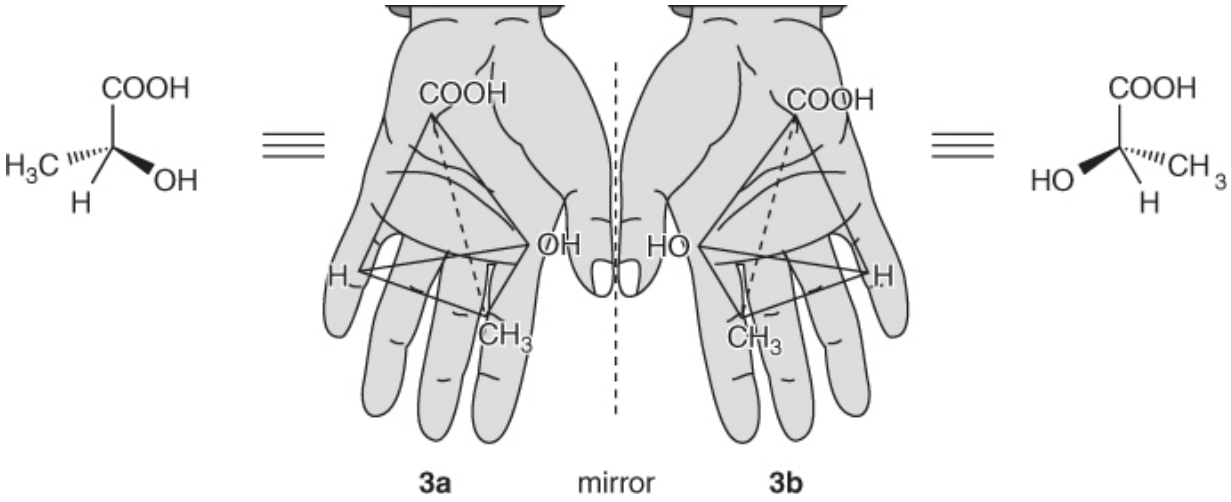


1.2 Overview of Chirality

1.2.1 Superimposability

Chirality is a fundamental property of three-dimensional objects. The word “chiral” is derived from the Greek word *cheir*, meaning hand, or “handedness” in a general sense. The left and right hands are mirror images of each other no matter how the two are arranged. A chiral molecule is the one that is not superimposable with its mirror image. Accordingly, an achiral compound has a superimposable mirror image. Two possible mirror image forms are called enantiomers and are exemplified by the right-handed and left-handed forms of lactic acids in Figure 1.2. Formally, a chiral molecule possesses either an asymmetric center (usually carbon) referred to as a chiral center or an asymmetric plane (planar chirality).

Figure 1.2 Mirror images of lactic acid.



In an achiral environment, enantiomers of a chiral compound exhibit identical physical and chemical properties, but they rotate the plane of polarized light in opposite directions and react at different rates with a chiral compound or with an achiral compound in a chiral environment. A chiral drug is a chiral molecule with defined pharmaceutical/pharmacological activities and utilities. The description “chiral drug” does not indicate specifically whether a drug is racemic, single-enantiomeric, or a mixture of stereoisomers. Instead, it simply implies that the drug contains chiral centers or has other forms of chirality, and the enantiomeric composition is not specified by this terminology.

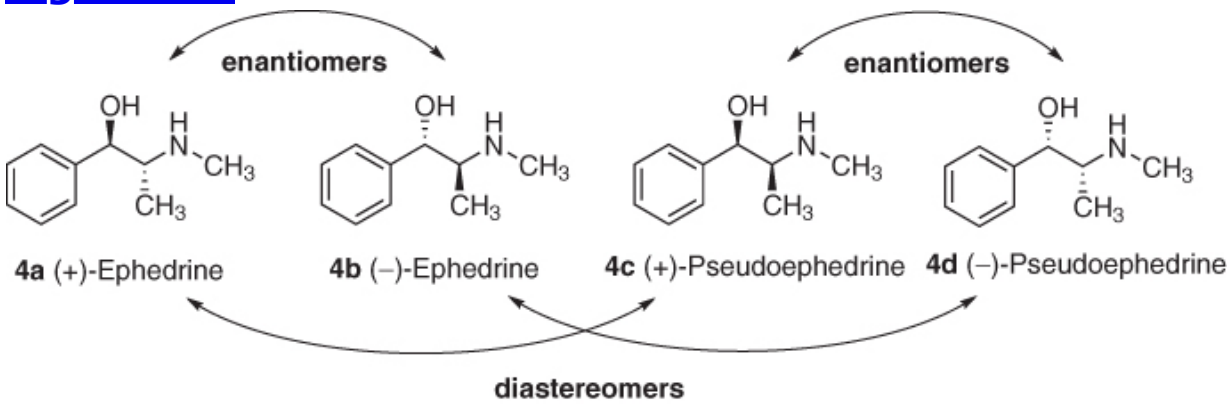
1.2.2 Stereoisomerism

In chemistry, there are two major forms of isomerism: constitutional (structural) isomerism and stereoisomerism. Isomers are chemical species (or molecular entities) that have the same stoichiometric molecular formula but different constitutional formulas or different stereochemical formulas. In structural isomers, the atoms and functional groups are joined together in different ways. On the other hand, stereoisomers are compounds that have the same atoms connected in the same order but differ from each

other in the way that the atoms are oriented in space. They include enantiomers and diastereomers, the latter indicating compounds that contain two or more chiral centers and are not superimposable with their mirror image. Diastereomers also include the nonoptical isomers such as *cis-trans* isomers.

Many molecules, particularly many naturally derived compounds, contain more than one chiral center. In general, a compound with *n* chiral centers will have 2^n possible stereoisomers. Thus 2-methylamino-1-phenylpropanol with two chiral centers could have a total of four possible stereoisomers. Among these, there are two pairs of enantiomers and two pairs of diastereomers. This relationship is exemplified by ephedrines (**4a, 4b**) and pseudoephedrines (**4c, 4d**) shown in Figure 1.3. In certain cases, one of the stereoisomeric forms of a molecule containing two or more chiral centers could display a superimposable mirror image, which is referred to as a *meso* isomer.

Figure 1.3 Enantiomers and diastereomers.



1.2.3 Absolute Configuration

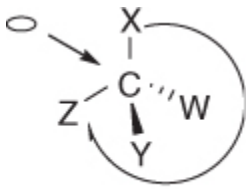
It is important to define the absolute configuration of a chiral molecule in order to understand its function in a biological system. Many biological activities are exclusive to one specific absolute configuration. Without a good

understanding of absolute configuration of a molecule, it often is hard to understand its chemical and biological behavior. As mentioned above, two enantiomers of a chiral compound will have identical chemical and physical properties such as the same boiling/melting points and solubility in a normal achiral environment.

The *R*/*S* nomenclature or Cahn–Ingold–Prelog (CIP) system for defining absolute configuration is the most widely used system in the chemistry community. The key to this system is the CIP priority rule, which defines the substituent priority based on the following criteria: 1) Higher atomic number or higher atomic mass is given higher priority; 2) when the proximate atom of two or more of the substituents are the same, the atomic number of the next atom determines the priority; 3) double bonds or triple bonds are counted as if they were split into two or three single bonds, respectively; 4) *cis* is given higher priority than *trans*; 5) long pair electrons are regarded as an atom with atomic number 0; and 6) proximal groups have higher priority than distal groups.

The carbon atom in compound **5** (Fig. 1.4) is defined as a chiral center if the four substituents (X, Y, Z, and W) around the center are different. If the molecule is oriented in a way that the lowest-priority group W is pointed away from the observer and the other three groups have a priority sequence X→Y→Z in a clockwise direction, the chiral center will have a *R* configuration; otherwise it is defined as an *S* configuration. The *R*/*S* system can be used for other chiral molecules without a chiral center (e.g., planar chirality) as well (6).

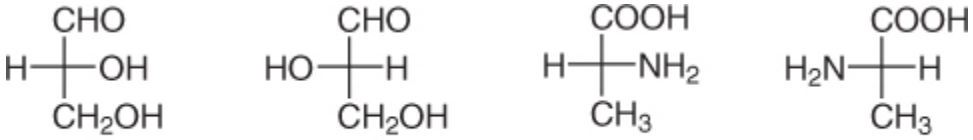
Figure 1.4 A central chiral system.



5

Fischer's convention with D or L prefix (small cap) is sometimes used for the description of the absolute configuration of a molecule, particularly for carbohydrates or amino acids. For example, D-glyceraldehyde **6a** by Fischer's convention is shown in Figure 1.5 and is identical to (*R*)-glyceraldehyde according to *CIP* rules. By relating compounds to glyceraldehydes, the absolute configuration of other compounds can be defined. For example, naturally occurring alanine **6d** is designated as L-form with an *S* configuration.

Figure 1.5 Structure of (D)- and (L)-glyceraldehyde and analogs.



6a **6b** **6c** **6d**

Enantiomers do differ from each other in rotating the plane-polarized light, which is referred to as optical activity or optical rotation. When an enantiomer rotates the plane of polarized light clockwise (as seen by a viewer toward whom the light is traveling), it is labeled as (+). Its mirror-image enantiomer is labeled as the (−) isomer. The (+) and (−) isomers have historically been termed *d*- and *l*-, respectively, with *d* for dextrorotatory and *l* for levorotatory rotation of the lights. This *d*/*l* system is now obsolete, and (+/–) should be used instead to specify the optical rotation. It should also be pointed out that the optical rotation (+/–) convention has no direct relation with the *R*/*S* or D/L systems. It is used in most cases for description of *relative*,

not *absolute* configuration. Thus compound **3b**, which rotates the plane-polarized light in a clockwise direction, is denoted as *R*-(+)-lactic acid, while the enantiomer (**3a**) is referred to *S*-(–)-lactic acid.

Absolute configuration is most commonly determined either by X-ray crystallography or through chemical conversion to a known compound with defined stereochemistry. Other instrumental procedures for determining absolute stereochemistry without derivatization include circular dichroism (CD), vibrational circular dichroism (VCD) (7), and optical rotator dispersion (ORD) or specific optical rotation. The NMR-based method for deducing the absolute configuration of secondary carbinol (alcohol) centers using the “modified Mosher method” (8) was first described by Kakisawa and co-workers (9). This modified Mosher ester analysis relies on the fact that the protons in diasteromeric α-methoxy-α-trifluoromethylphenylacetates display different arrays of chemical shifts in their ^{1}H NMR spectra. When correctly used and supported by appropriate data, the method can be used to determine the absolute configuration of a variety of compounds including alcohols, amines, and carboxylic acids (10). However, it is always advisable to examine the complete molecular topology in the neighborhood of the asymmetric carbon centers and confirm with another analytical method.

1.2.4 Determination of Enantiomer Composition (ee) and Diastereomeric Ratio (dr)

It is important to measure enantiomer composition and diastereomeric ratio for a chiral molecule, in particular a chiral drug, as the biological data may closely relate to the optical purity. The enantiomer composition of a sample is

described by enantiomeric excess, or *ee*%, which describes the excess of one enantiomer over the other. Correspondingly, the diastereomer composition of a diastereomer mixture is the measure of an extent of a particular diastereomer over the others. This is calculated as shown in Equations 1 and 2, respectively, for [*S*] > [*R*] (Fig. 1.6).

Figure 1.6 Method of calculating enantiomer or diastereomer excess.

$$ee\% = \frac{[S] - [R]}{[S] + [R]} \times 100\% \qquad \text{eq. 1}$$

$$de\% = \frac{[S^*S] - [S^*R]}{[S^*S] + [S^*R]} \times 100\% \qquad \text{eq. 2}$$

A chiral molecule containing only one enantiomeric form is regarded as optically pure or enantiopure or enantiomerically pure. Enantiomers can be separated via a process called resolution (Chapter 4), while in most cases diastereomers can be separated through chromatographic methods. A variety of methods for determination of optical purity or *ee*/de value are available (6). One of the widely used methods for analyzing chiral molecules is polarimetry. For any compound of which the optical rotation of the pure enantiomer is known, the *ee* can be determined simply from the observed rotation and calculated by Equations 3 and 4 (Fig. 1.7).

Figure 1.7 *ee* value is directly determined from the observed rotation.

$$[\alpha]_D^{20} = \frac{[\alpha]}{L(dm) \times c(g/100mL)} \times 100\% \qquad \textbf{Eq. 3}$$

$[\alpha]^D$ = measured rotation
L = path length of cell (dm)
c = concentration (g/100mL)
D = D line of wavelength of light used for measurement
20 = temperature

$$\text{ee \% (optical purity)} = \frac{[\alpha]_{obs}}{[\alpha]_{max}} \times 100\% \qquad \textbf{Eq. 4}$$

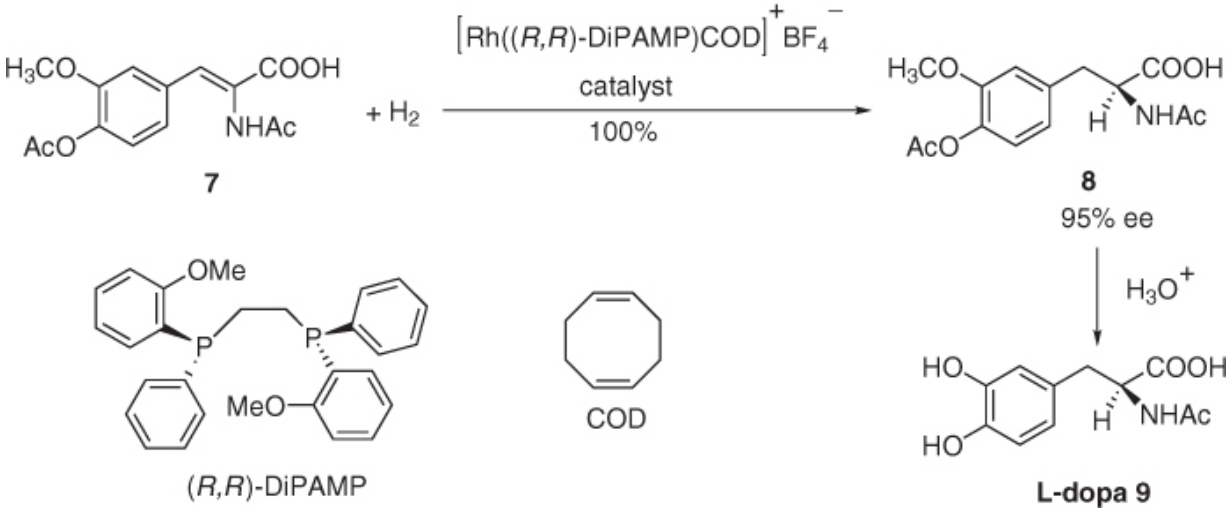
Chromatography with chiral stationary columns, for example, chiral high-pressure liquid chromatography (HPLC) or chiral gas chromatography (GC), has also been utilized extensively for analyzing and determining enantiomeric composition of a chiral compound. Nuclear magnetic resonance (NMR) spectroscopy can also be used to evaluate the enantiomeric purity in the presence of chiral shift reagents (6, 11) or through its diastereomer derivatives (e.g., Mosher's esters) (8).

1.3 General Strategies for Synthesis of Chiral Drugs

Asymmetric synthesis refers to the selective formation of a single stereoisomer and therefore affords superior atom economy. It has become the most powerful and commonly employed method for preparation of chiral drugs. Since the 1980s, there has been progress in many new technologies, in particular, the technology related to catalytic asymmetric synthesis, that allow the preparation of pure enatiomers in quantity. The first commercialized catalytic asymmetric synthesis, the Monsanto process of L-DOPA (**9**) (Fig. 1.8),

was established in 1974 by Knowles (12), who was awarded a Nobel Prize in Chemistry in 2001 along with Noyori and Sharpless. In the key step of the synthesis of L-DOPA, a gold standard drug for Parkinson disease, enamide compound **7** is hydrogenated in the presence of a catalytic amount of [Rh(*R,R*)-DiPAMP)COD]$^{+}BF_4^{-}$ complex, affording the protected amino acid **8** in quantitative yield and in 95% *ee*. A simple acid-catalyzed hydrolysis step completes the synthesis of L-DOPA (**9**).

Figure 1.8 Monsanto process of L-dopa (**9**).



The discovery of an atropisomeric chiral diphosphine, BINAP, by Noyori in 1980 (13) was revolutionary in the field of catalytic asymmetric synthesis. For example, the BINAP-Ru(II) complexes exhibit an extremely high chiral recognition ability in the hydrogenation of a variety of functionalized olefins and ketones. This transition metal catalysis is clean, simple, and economical to operate and hence is capable of conducting a reaction on a milligram to kilogram scale with a very high (up to 50%) substrate concentration in organic solvents. Both enantiomers can be synthesized with equal efficiency by choosing the appropriate enantiomers of the catalysts. It has been used in industrial production of compounds such as (*R*)-1,2- propanediol, (*S*)-naproxen, a chiral azetidinone intermediate for carbapenem synthesis,

and a β-hydroxylcarboxylic acid intermediate for the first-generation synthesis of Januvia (14) among others. The Sharpless–Katsuki epoxidation was also published in 1980 (15). It has also been used for the chiral drug synthesis on an industrial scale.

Chiral compounds can now be accessed in one of many different approaches: 1) via chiral resolution of a racemate (Chapter 4); 2) through asymmetric synthesis, either chemically or enzymatically (Chapters 2 and 3); and 3) through manipulation of chiral starting materials (chiral-pool material). In the early 1990s, most chiral drugs were derived from chiral-pool materials, and only 20% of all drugs were made via purely synthetic approaches. This has now been reversed, with only about 25% of drugs made from chiral pool and over 50% from other chiral technologies (16). The following is a brief account of catalytic enantioselective synthesis with commercial applications.

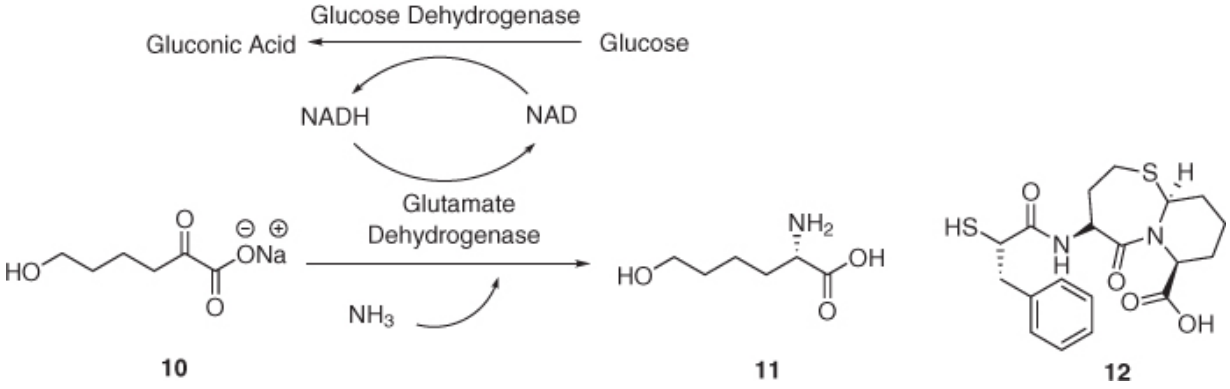
1.3.1 Enantioselective Synthesis via Enzymatic Catalysis

Enzyme-catalyzed reactions (biotransformation) are often highly enantioselective and regioselective, and they can be carried out at ambient temperature, atmospheric pressure, and at or near neutral pH. Most of the enzymes used in the asymmetric synthesis can be generated in large quantity with modern molecular biology approaches. The enzyme can be degraded biochemically, therefore eliminating any potential hazardous caused by the catalysis, providing a superior and environmentally friendly method for making chiral drug molecules. It is estimated that the value of pharmaceutical intermediates generated by using enzymatic reactions was $198 million in 2006 and is expected to reach $354.4 million by 2013 (17).

(*S*)-6-hydroxynorleucine (**11**) is a key intermediate for the synthesis of omapatrilat (**12**), an antihypertensive drug that acts by inhibiting angiotensin-converting enzyme (ACE) and neutral endopeptidase (NEP). **11** is prepared from 2-keto-6-hydroxyhexanoic acid **10** by reductive amination using beef liver glutamate dehydrogenase at 100 g/l substrate concentration. The reaction requires ammonia and NADH. NAD produced during the reaction is recycled to NADH by the oxidation of glucose to gluconic acid with glucose dehydrogenase from *Bacillus megaterium*. The reaction is complete in about 3 h with reaction yields of 92% and >99% *ee* for (*S*)-6-hydroxynorleucine **11** (Fig. 1.9) (18).

There are some exceptions and limitations to the enzymatic-catalyzed reactions. For example, the reaction type may be limited, and reactions may preferably be conducted in aqueous media and at low substrate concentration. However, a lot of new development in the technology of engineering enzymes have been witnessed recently (19). Enzymes can be immobilized and reused in many cycles. Selective mutations of an enzyme can alter the enzyme's performance or even make the opposite enantiomer formation possible.

Figure 1.9 Enzymatic synthesis of chiral synthon (*S*)-6-hydroxynorleucine (**11**).

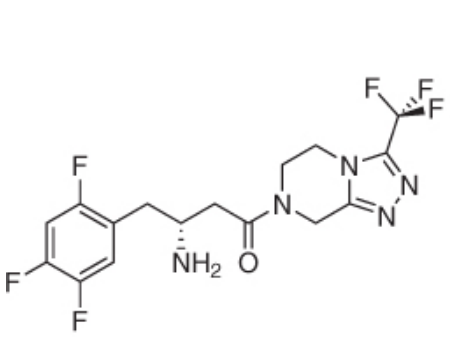


1.3.2 Enantioselective Synthesis via Organometallic Catalysis

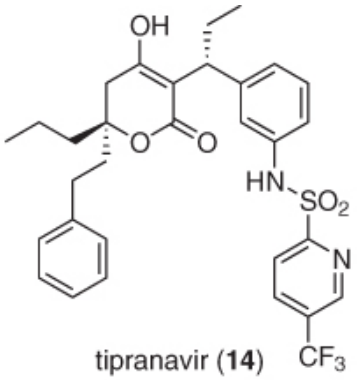
In asymmetric synthesis, a chiral agent should behave as a catalyst with enzymelike selectivity and turnover rate. Transition metal-based catalysts have been prevalent in organic synthesis for many years. Since the introduction of the Monsanto process of L-DOPA and BINAP-based ligands, asymmetric hydrogenation has become one of the most important processes in the pharmaceutical industry to synthesize key intermediates or active pharmaceutical ingredients. More than 3,000 chiral diphosphine and many monophosphine ligands have been reported, and approximately 1% of those ligands are currently commercially available (20). Besides the asymmetric hydrogenation of olefins, the ligand-mediate asymmetric hydrogenation of ketone to the corresponding alcohol (21) is becoming an indispensable alternative to other known processes such as transfer hydrogenation and biocatalytic and hydride reduction. However, a lot still remains to be improved in this field in terms of catalyst sensitivity to atmosphere, high cost, and possible toxicity.

Compounds **13**–**17** are examples that were generated via catalytic asymmetric hydrogenation. According to reference (22), they are sitagliptin (**13**), an oral diabetes drug, tipranavir (**14**), an HIV protease inhibitor, ramelteon (**15**), a sleep aid, aliskiren (**16**), which is a hypertension drug, and taranabant (**17**), the antiobesity agent (Fig. 1.10).

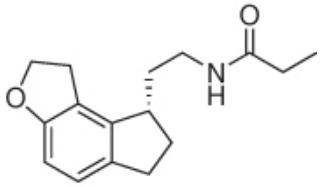
Figure 1.10 Example compounds generated via catalytic asymmetric hydrogenation.



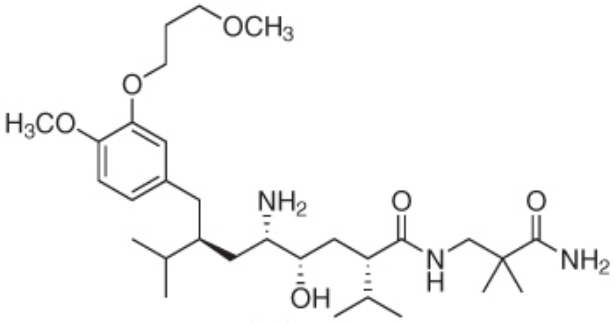
sitagliptin (**13**)



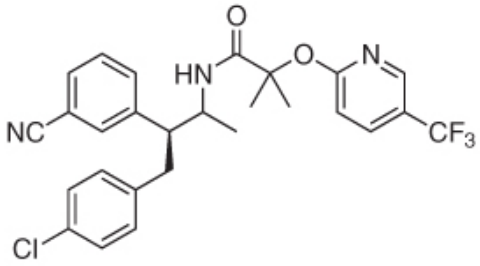
tipranavir (**14**)



ramelteon (**15**)



aliskiren (**16**)



taranabant (**17**)

1.3.3 Enantioselective Synthesis via Organocatalysis

Organocatalysts (23) have emerged as a powerful synthetic paradigm to complement organometallic- and enzyme-catalyzed asymmetric synthesis. Although examples of asymmetric organocatalysis appeared as early as the 1970s (24), the field was not born until the late 1990s and matured at the turn of the new century. Organocatalysis is now widely accepted as a new branch of enantioselective synthesis. A survey conducted by MacMillan (25) in 2008 showed only a few papers describing organocatalytic reactions before 2000, while the number of papers published in 2007 is close to 600. There have been a number of special issues of journals dedicated to asymmetric organocatalysis (26).

Organocatalysts are loosely defined as low-molecular-weight organic molecules having intrinsic catalytic activity. If