# 1
# Chirality

## 1.1
## Introduction

A simple chiral molecule just contains one $sp^3$-hybridized carbon that connects four different groups, such as chiral molecule **1** ($R^1 \neq R^2 \neq R^3 \neq R^4$, Figure 1.1). Its mirror image structure, namely the enantiomer, is **2**, which has the same relative configuration (RC) but different absolute configuration (AC); for example, when $R^1 < R^2 < R^3 < R^4$, chiral molecule **1** has (*R*)-AC and **2** has (*S*)-AC. Both have the same chemical characteristics, such as the transition state (TS) barrier (reaction activation energy) in reactions in the absence of a chiral catalyst or a chiral auxiliary compound, and physical characteristics such as melting and boiling point and magnetic shielding constant for each corresponding atom. However, in a beam of circularly polarized light (CPL), the enantiomers exhibit opposite characteristics. For example, both have the same absolute optical rotation (OR) values, but their OR signs are reversed. The different optical characteristics are the basis allowing us to identify their AC.

As a widely known phenomenon, chirality, also named as handedness, brings out many mysteries that we have not known until now. For example, the L-amino acids were selected in peptide formation for the origin of life instead of D-amino acids. D-sugars were used instead of L-sugars. That is the amazing natural choice. Although we do not know why Nature selected different chiral molecules in life, it does not affect us in the study of the handedness of molecules and other materials.

Absolutely, because of the natural selection of L-amino acids and D-sugars in life formation, different chiral compounds must, logically, have different effects on the life process. Historically, a mixture of the (*R*) and (*S*) enantiomers (**3** and **4**) was used as a medicine for preventing vomiting in pregnant women in European countries – but not in America – in the 1960s. Many infants with deformed limbs were born. This was caused by a chiral chemical compound, (*S*)-thalidomide (**4**), which can be isomerized from (*R*)-**3** (Scheme 1.1) [1a–c]. In America, this tragic issue was avoided because Frances O. Kelsey in the Food and Drug Administration (FDA) could not find evidences from the documents handed by the pharmaceutical company to confirm that it was not harmless to the central nervous system.

*Organic Stereochemistry: Experimental and Computational Methods,* First Edition. Hua-Jie Zhu.

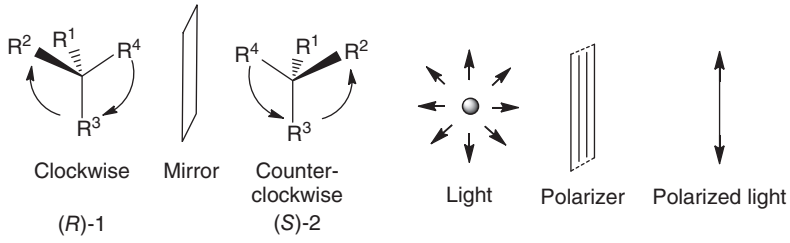
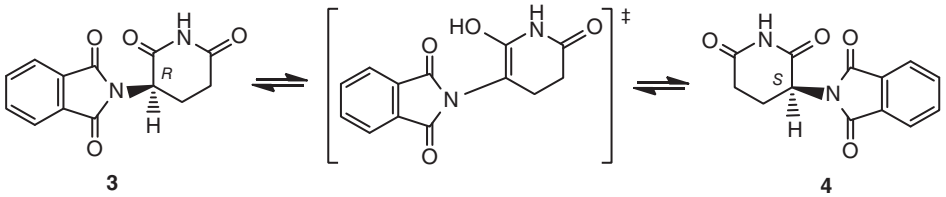


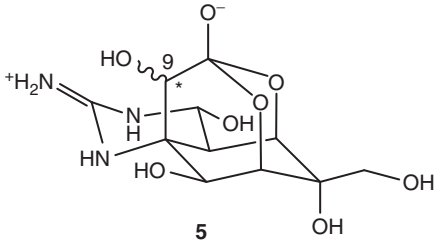

**Figure 1.1** Enantiomers and polarized light.




**Scheme 1.1** Isomerization of (*R*)-thalidomide to its (*S*)-enantiomer [1].

This doubt delayed the approval of this medicine for use in the United States, and just because of this action it saved many infants and families in the United States.

Tertodotoxin (**5**) is a strong toxic chiral compound that is isolated from globefish [1d]. The strong toxicity comes from the (*S*) AC of C9. Once C9 becomes (*R*) AC, its severe toxicity almost disappears.




More examples can be found with different bioactivities. Some pairs of enantiomers and their bioactivities are listed after their structures (Figure 1.2) [1e].

The different ACs of **6–19** result in different bioactivities. Obviously, it should be a big challenge to obtain various chiral compounds in organic stereochemistry. Generally, we can design and synthesize different chiral catalysts or auxiliary reagents to control the formation of stereogenic centers of a chiral compound. A well-known example is the use a chiral catalyst to control the asymmetric epoxidation of the C=C bond. This is called Sharpless epoxidation. For example, when L-diisopropyltartrate (**20**) was used as a catalyst, the product **22** could be achieved in 98% yield and 68% ee (Eq. (1.1)) [2].

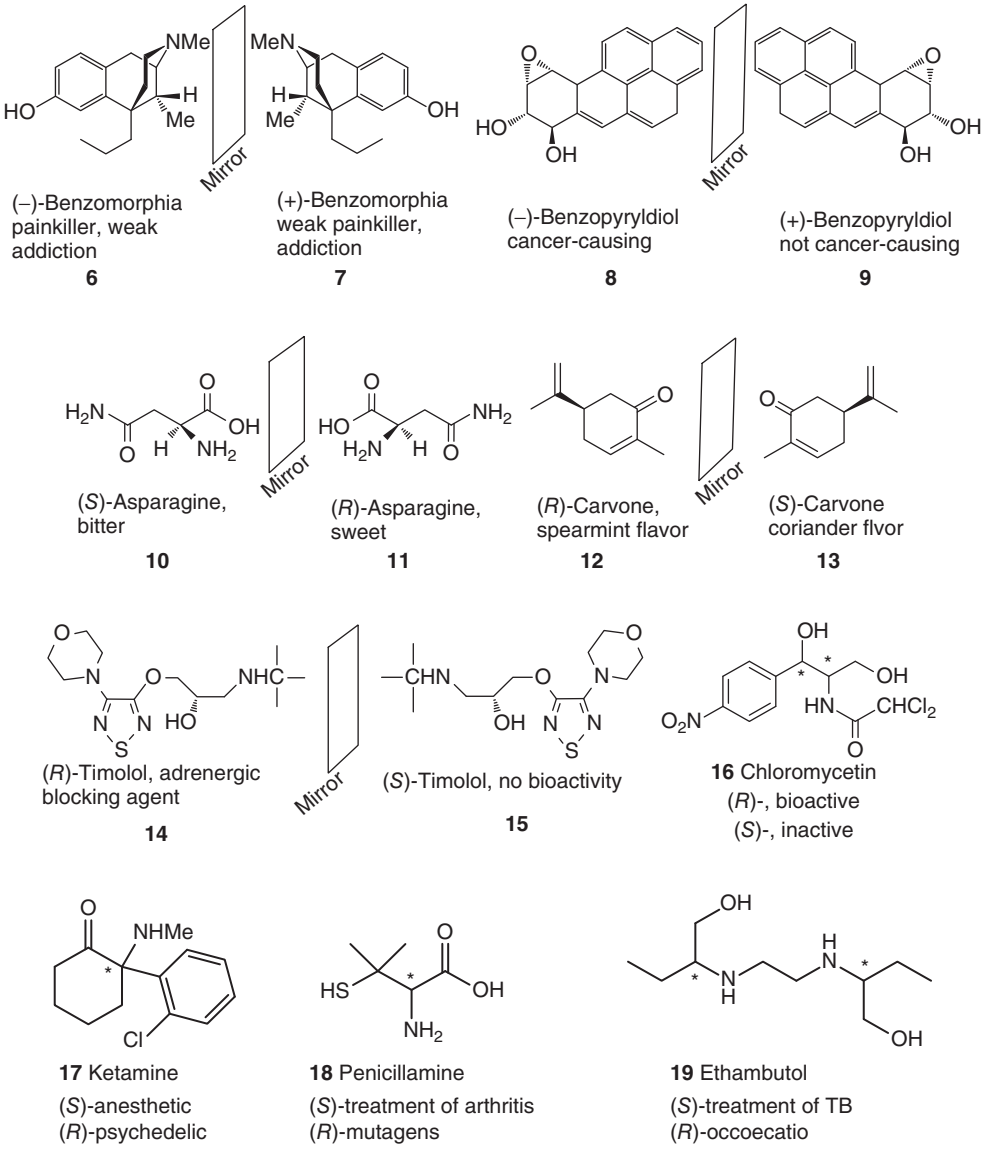
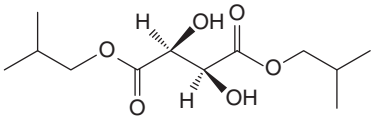
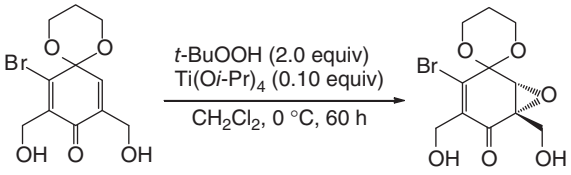



**Figure 1.2** Examples of enantiomers and their different bioactivities.

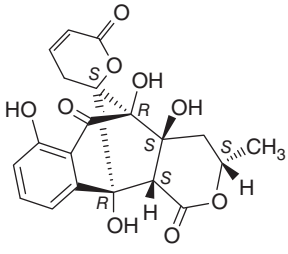


**20**

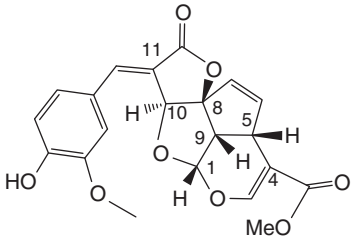



**21** **22** (1.1)

Another big challenge in organic stereochemistry is the identification of the AC of chiral compounds. The most convenient method is comparing the theoretical chiroptical spectrum to the experimental one. For example, the RC of compound **23** has been estimated by X-ray study as illustrated below; the experimental OR was +57.4 in methanol [3]. The computed OR for **23** with the same AC as the illustrated one was +74.3 in the gas phase, and this value decreased to 66.2 in methanol. This prediction is close to the recorded value of +57.4. Therefore, its AC was assigned as that illustrated below. Another example is that the predicted OR for (1*R*,5*S*,8*S*,9*S*,10*S*)-oruwacin (**24**) was −193. The experimental value was 193. Therefore, it was assigned as (1*S*,5*R*,8*R*,9*R*,10*R*) based on its OR value [4].



**23**

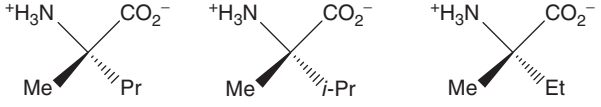



**24** Oruwacin

The study of chiral materials is an important branch in stereochemistry. By the reaction of a chiral molecule with a monomer, a chiral polymer can be formed. For example, the widely used (−)-menthyl methacrylate (MnMA, **25**, Eq. (1.2)) can undergo polymerization and afford the chiral polymer *P*-(−)-MnMA (**26**) [5].


**25** (–)-MnMA **26** *P*- (–)-MnMA (1.2)

The last but important issue is to understand the chirality selection for the formation of life in prebiotic Earth. That is about the origin of life. The process leading to its origin is extremely long. Where is the first chiral compound coming from in the long time? Evidence comes from the presence of chiral $\alpha$-methyl amino acids **27 – 29** in meteorites [6]. A reasonable hypothesis is that the chiral compounds led to the formation of other chiral molecules in the prebiotic Earth, and due to the effect of amplification reactions and other factors on the formation of chiral compounds, finally it led to the formation of L-amino acids that form the basis of the origin of life.




**27** 2.8% ee, (*S*) **28** 2.8% ee, (*S*) **29** 15.2% ee, (*S*)

As a general rule in organic chemistry, the formation of D- and L-amino acids without any catalyst would be in the ratio 1 : 1. This ratio, however, might not have been strictly 1 : 1 in the prebiotic Earth for some unknown reasons. A mixture of D- and L-amino acids with a tiny excess of the L-form could dissolve in water.

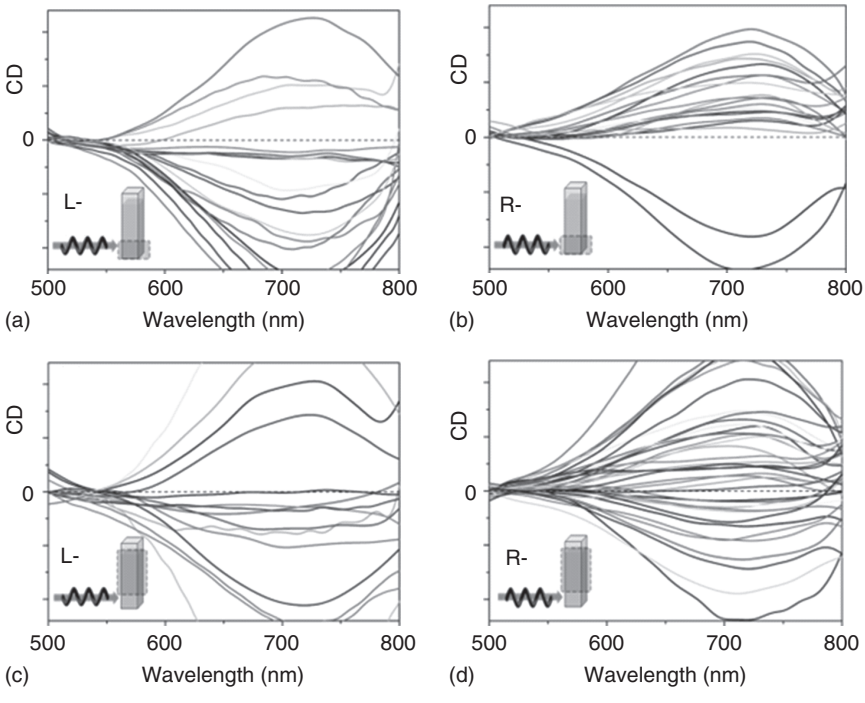


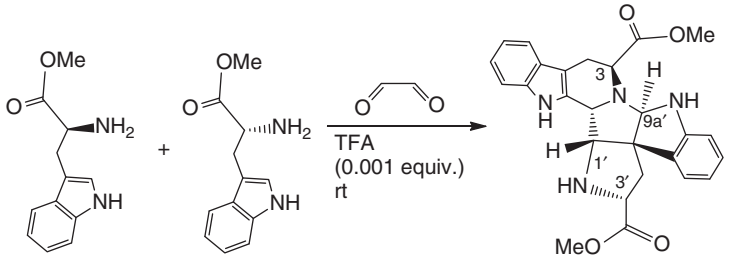

**Figure 1.3** Times of ECD experiments in solid state for (a) light-left circularly polarized light, (b) light-right CPL, (c) dark-left CPL, and (d) dark-right CPL. (Solution contains $[Cu(NH_3)_4]^{2+}$ (0.5 mmol), succinate (1.5 mmol), 4,4′-bipyridine (0.5 mmol), water (10 ml), and ethanol (10 ml).) [8]

Because of the different solubility of L- and D- salts from the respective amino acids, the mixing of D- and L- salts resulted in precipitation. This resulted in a solution with concentrated L-amino acid [7]. Thus, starting with a small excess of the L-amino acid, the final L-/D- ratio would increase.

Another example is that irradiation with right-CPL results in the possibility growing crystals with right-handed helical structure more than with left-handed helical structure from a $[Cu(NH_3)_4]^{2+}$-containing solution found through a statistical analysis of the Cotton effect of crystals (Figure 1.3) [8]. This might hint that the crystal could abstract one enantiomer and enrich its enantiomer in the solution.

In view point of chemists, a chemical procedure for choosing L-amino acids should be much more interesting in the study of the origin of life because this procedure is irreversible. A reversible procedure such as the deposition of salts of racemic amino acids is too short for the formation of chiral peptides.

Recently, it was reported that there is a chirality pairing recognition reaction, or molecular sex recognition reaction, which may enrich L-tryptophan if it has a small excessive quantity in a mixture of D and L-tryptophan. When (*R*)- and (*S*)-tryptophan methyl esters were used as the starting materials, L-tryptophan methyl ester tended to react with D-tryptophan methyl ester to form L-/D- products instead of the L-tryptophan methyl ester (Eq. (1.3)) [7].




L-**30** D-**31**

**32** L–D product, 50%
(**33** D–L product, 50%) (1.3)

Theoretically, this may disclose some secrets during the formation of life. For example, if L-tryptophan formed with a little more excess quantity than D-tryptophan, due to the molecule sex recognition reaction in oceanic era, the excessive quantity of L-amino acids might have been enriched after the formation of **32** and **33**. The enriched L-tryptophan may act as a first chiral source to promote the formation of other chiral compounds that were involved in life formation. This is the chemical procedure. It may be a starting point of a new chemistry: "Evolution Chemistry".

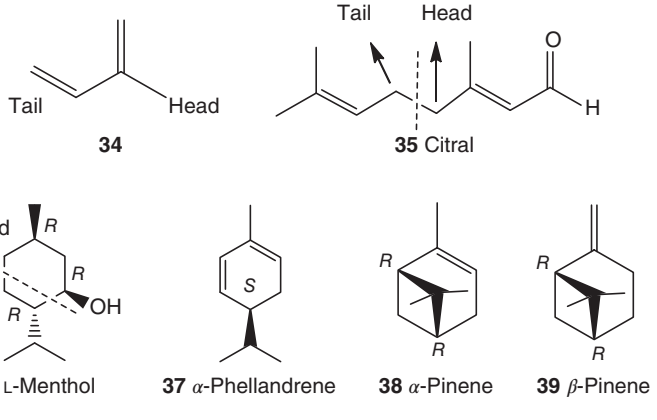
In this book, the key points include the (i) methods used for RC and AC assignment, (ii) design and synthesis of chiral catalysts, (iii) chemoselective and (iv) regioselective reactions, (v) diastereoselective reactions, and (vi) the total synthesis of bioactive natural products. Theoretical methods used in the experimental study are introduced in each later chapter.

## 1.2
## Tetrahedron of Carbon

The simple chiral molecule just contains one $sp^3$-hybridized carbon that connects four different groups, such as the chiral molecule **1** ($R^1 \neq R^2 \neq R^3 \neq R^4$). Because of different connections of the asymmetric centers to various atoms or groups, it forms various chiral compounds, such as terpenoids, flavonoids, alkaloids, glycosides, alkaloids, and so on. This is the basis of life evolution and survival.

### 1.2.1
### Terpenoids

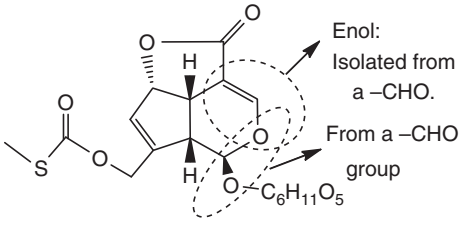
This is a large family of compounds showing various bioactivities. The basic unit is isopentadiene (**34**, also called isoprene) [9]. However, isopentadiene itself does not take part in the reaction directly in the body of plants. When it is converted into isopentenyl pyrophosphate (IPP) and dimethylallyl pyrophosphate (DMAPP), they can form various natural terpenoids. Structurally, the different connections, such as "head-to-head," "tail-to-tail," or "head-to-tail," are called the "isoprene rule." Two isopentadienes can form a linear (acyclic) monoterpenoid without a stereogenic center (**35**, "head-to-tail" connection) or a cyclic monoterpene, which generally has one or more stereogenic centers, such as L-menthol (**36**). Most monoterpenes with different functional groups are also the major components of essential oils (volatile oils) and exhibit different bioactivities.



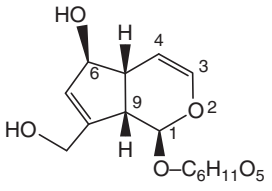

The prefix $\alpha$ or $\beta$ in the above does not refer to their stereochemistry; they are used to show the positions of double bond: for example, $\alpha$-pinene **38** and $\beta$-pinene **39.** However, in some textbooks – or some journals until now – both are used to express the configuration of a stereogenic center. One should be careful in reading reports from different journals. In this book, all stereogenic centers will be labeled as (*R*) or (*S*) except for the introduction of some structures from reports. In addition, L- and D- are used for the AC expression of amino acids or sugars.

When dealing with helical compounds, capital letters of *M* and *P* are used to show their stereochemistry. This will be introduced in the "Other Stereogenic Centers" section.

Some monoterpenes may contain two or more –CHO groups together so that are close enough in space like the paederoside **40** [9] and harpagoside **41**. Both aldehyde groups may undergo reaction with each other and form an iridoid, which can further react with a glucose to afford the iridoid glycoside (**41**). The AC of C1 may be controlled by the C9's AC in both structures (obeying the Cram rule).

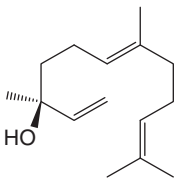



**40** paederoside

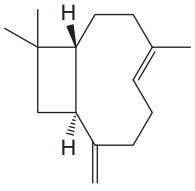



**41** Aucubin

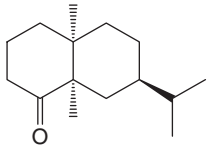
Three isopentadiene units can form the corresponding sesquiterpenes. They are widely distributed in nature with thousands of types. As with terpenoids, linear and cyclic sesquiterpenes with one or more rings are found in different species. Some representatives are the compounds **42**–**48** [9].



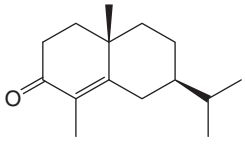
**42** Nerolidol



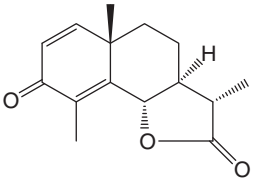
**43** *β*-Caryophyllene



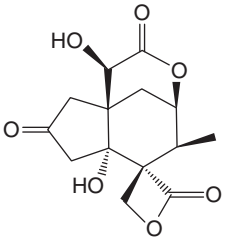
**44** Valeranone



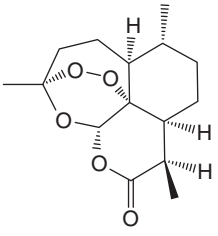
**45** Cyperone



**46** 1-*α*-Santonin
Strong ascarifuge

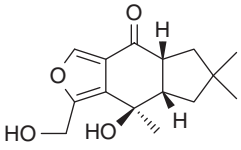


**47** *α*-Oxo-6-deoxyneo-anisatin
Strong toxic, $LD_{50}$ near 0.94 mg $kg^{-1}$

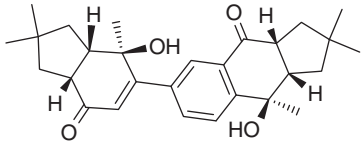


**48** Qinhaosu
Anti malaria

With the development of separation materials and technology, more and more skeletons were found from different materials. For example, the sterostreins A (**49**) and D (**50**) are furan-containing illudalanes, which were isolated from fungi [10]. Its dimeric compound stereostreins A exhibited antimalarial activity with an inhibitory concentration ($IC_{50}$) of 2.3 μg $ml^{-1}$.

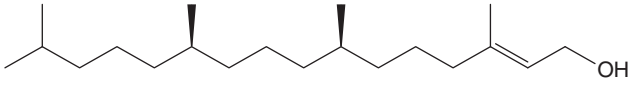


**49** Sterostreins D



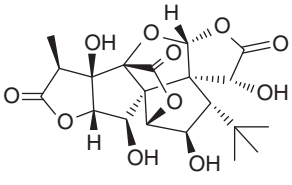
**50** Sterostreins A

Diterpenoids contain four isopentadiene units, which are classified as linear and cyclic structures. For example, an acyclic phytol (**51**), widely existing in chlorophyll, could be used as a starting material for the synthesis of vitamins E and $K_1$.

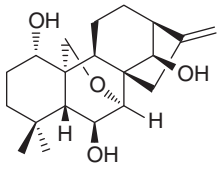


**51** Phytol

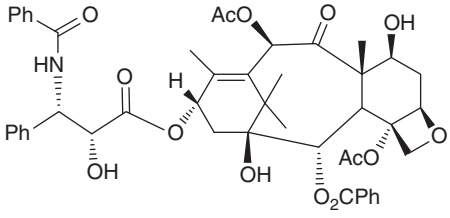
Because of the four isopentadiene units in diterpenes, their structural complexity is more than that of sesquiterpenes. Many bioactive compounds have been found, such as taxol (**54**), with strong antitumor activity. Some representatives are illustrated below (**52**–**58**).



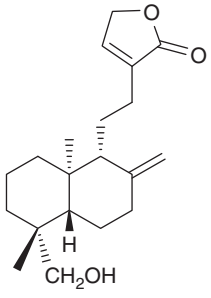
**52** Ginkgolide C
Cerebrovascular drug



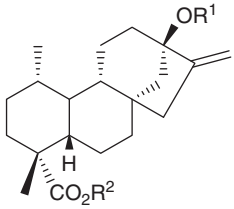
**53** Oridnin
Anti-cancer



**54** Taxol, anti-cancer



**55**
Neo-andrographolide



Intense sweetener

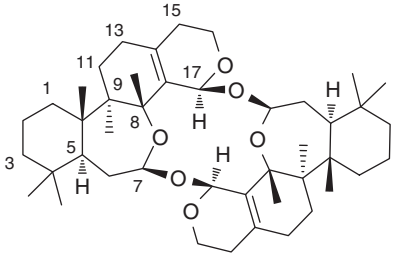
**56** Stevioside
**57** Stevioside A
**58** Stevioside D

| | $R^1$ | $R^2$ |
|---|---|---|
| **56** Stevioside | glc $^{2\text{-}1*}$ glc | glc |
| **57** Stevioside A | glc $^{2\text{-}1}$ glc, $^{3\text{-}1}$ glc | glc |
| **58** Stevioside D | glc $^{2\text{-}1}$ glc, $^{3\text{-}1}$ glc | glc$^{2\text{-}1}$ glc |

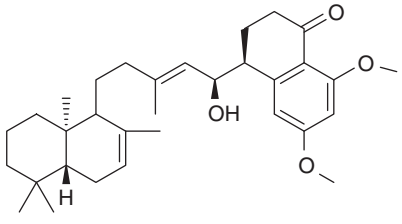
*Note: glc$^{2-1}$ glc means that the –OH on C2 of the first glucose connects to the –OH on C1 of next glucose to form an ether (–O–) structure.

New skeletons of diterpenes have been found recently, such as a macrocyclic diterpene with a $C_2$ symmetric axis, and schaffnerine (**59**) [11], which has slight

bioactivity. A smaller structure, actinoranone (**60**), was obtained that exhibited significant cytotoxicity to the HCT-116 human colon cancer cells, with an $LD_{50}$ of 2.0 μg $ml^{-1}$ [12]. The structures here belong to diterpenoids. However, it is not easy to find the connection model, either "head to head" or "head to tail" or "tail to tail" at first sight.

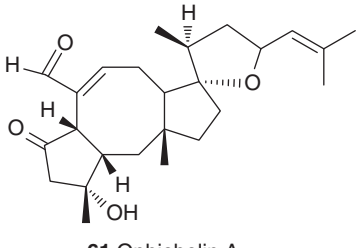


**59** Schaffnerine

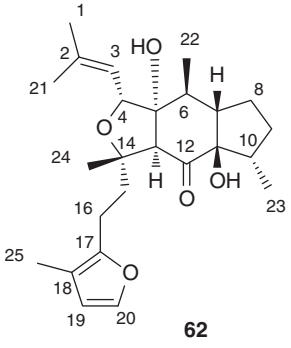


**60** Actinoranone

Sesterterpenoids consist of five isopentadiene units. They are not frequently reported. A traditional sesterterpenoid **61** and a recently reported compound **62** [13] are shown below.

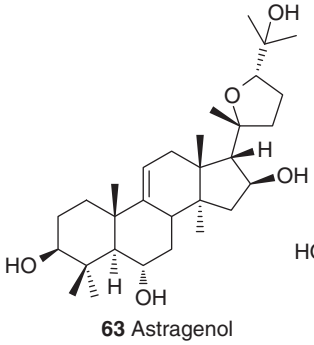


**61** Ophiobolin A

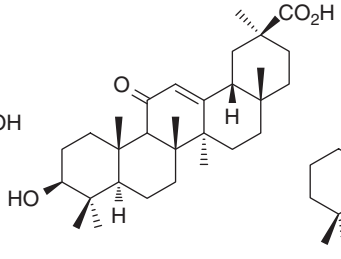


**62**

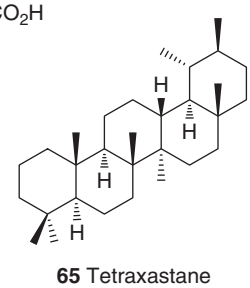
Triterpenoids have six isopentadiene units. They include various backbones with different bioactivities. Some of them have been developed as medicines. Some typical structures are illustrated below (**63**–**67**).



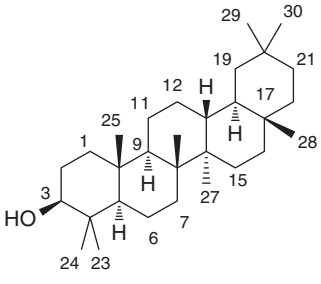
**63** Astragenol



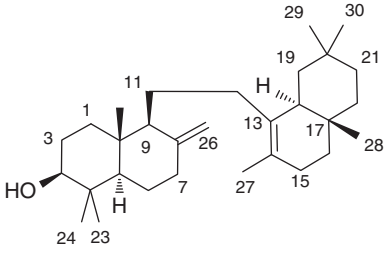
**64** Glycyrrhetinic acid
Anti-inflammation



**65** Tetraxastane




**66** oleana-3β-ol



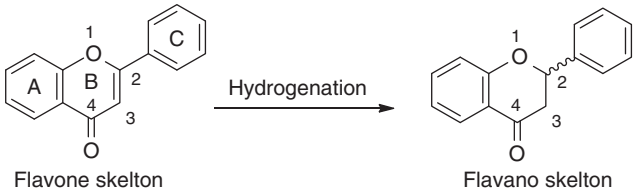

**67** 8,14-*seco*-oleana-8(26),13-dien-3β-ol

In order to name a triterpene, we need to look at its precursor. For example, as a typical triterpene, oleane-3*β*-ol (**66**) must be the precursor of **67** [14], which has the skeleton name "oleana" inside. By analyzing the disconnected positions (C8 and C14), it can be named as 8,14-*seco*-oleana-8(26),13-dien-3*β*-ol.

Be careful that "*β*" here is used to name the configuration of C3. To avoid mistaking the same symbol with different concepts in structural study, it is suggested that you use (*R*) or (*S*) to assign the C3's configuration. For the example of **67**, C3 has the (*S*) configuration.

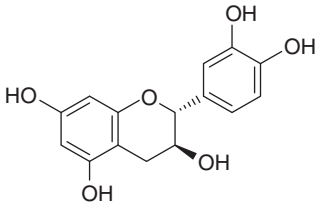
### 1.2.2 Flavonoids

Flavonoids, which generally have a characteristic yellow color, are widely distributed in nature. The general skeleton contains two phenyl rings, as in **68**. Most flavonoids have no chirality. The double bond at C2 and C3 may be hydrogenated to afford flavano or flavanone. The stereogenic centers may form in unequal quantities if the hydrogenation happens in a chiral environment. Its basic characteristic is six carbons on ring A, three carbons on ring B, and six carbons on ring C, and it forms C6–C3–C6 unit connections. When there is a –OH on C3 in **68**, it belongs to flavanol. Once it is on C3 in **69**, it is named as flavanonol.

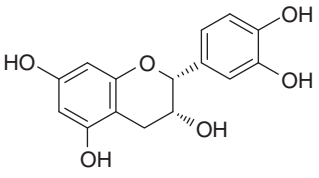



Flavone skelton **68** Flavano skelton **69** (1.4)

Many flavanonols show different but good activity in humans. For example, (+)-catechin (**70**) is used as a liver protection medicine (its commercial name in European market is Categen) its isomer **71** was also reported with similar bioactivity. The study of their AC is difficult because the isomers easily convert to each other. To report its structure with RC or racemic structures is also acceptable in studies.

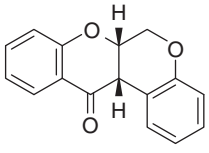



**70** (+)-Catechin

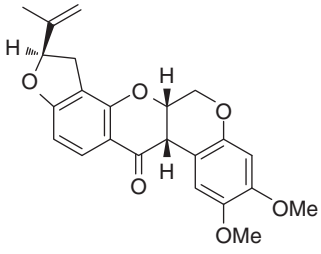



**71** (–)-Epicatechin

There are many flavanols derived from the "standard" flavano skeleton. For example, rotenoids have a basic skeleton (**72**) [9] with a fixed AC, whereas the others, such as rotenone (**73**), have almost the same backbone of **72**. It has strong toxicity against fish (when the concentration of rutenone in water reaches ~0.08 ppm, it will lead to fish stupor or death) and flies. But it is harmless to humans and animals.

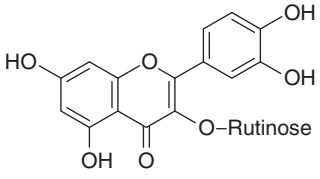



Skeleton of rotenoids
**72**

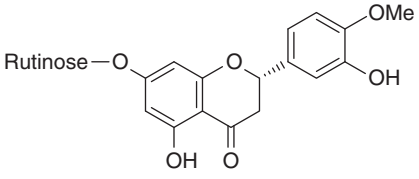



**73** Rotenone

The hydroxyl group of a flavone or flavanone undergoes condensation reaction with a sugar to form glycoside, which derivatizes with chirality. For example, the flavone rutin is a derivative of rutinose. It can be used to assist in antihypertension treatment.



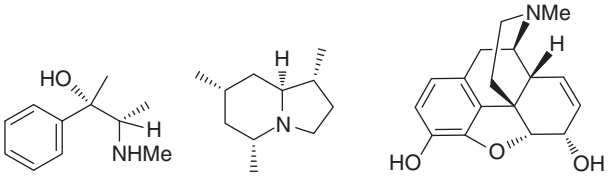

**74** Rutin




**75** Hesperidin

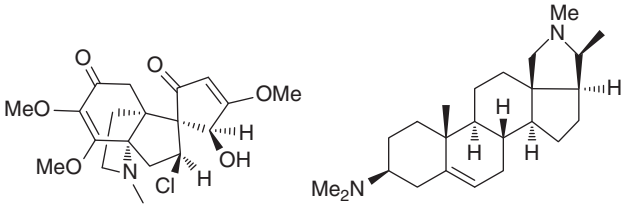
### 1.2.3 Alkaloids

Alkaloids are very important compounds in modern organic chemistry. Many alkaloids have strong bioactivity; for example, ephedrine (**76**) is well known for its effect in relieving cough and asthma. Others, such as morphine (**78**), are also famous for their bioactivities. Alkaloids bring many benefits for modern pharmaceutical industry.



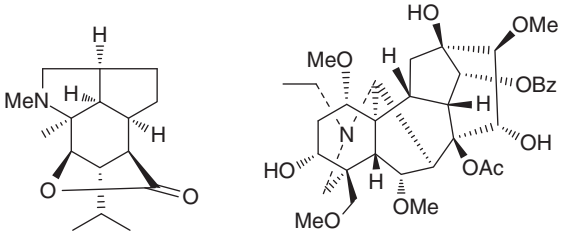

**76** L-ephedrine **77** Dendroprimine **78** Morphine

In many cases, alkaloids have very complex structures. For example, acutumine (**79**) has five stereogenic centers; it is not usual for a Cl atom in the molecule. Other alkaloids, such as conessine (**80**), which are derived from steroids, belong to steroidal alkaloids.




**79** Acutumine **80** Conessine

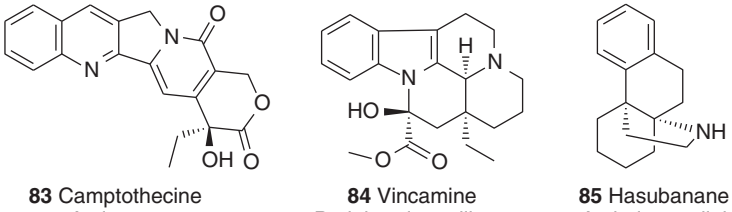
Alkaloids with a terpenoid skeleton are widely reported. Their structural complexity is a big stumbling block for organic chemists when assigning their AC. Two traditional structures are illustrated below [9].




**81** Dendrobine
Sesquiterpene alkaloid

**82** Aconitine
Diterpene alkaloid

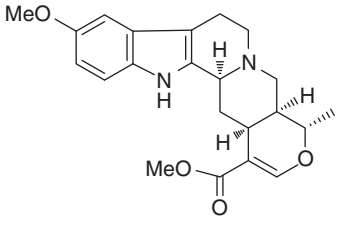
There are hundreds of alkaloids reported until now. Some of them are valuable lead compounds for the pharmaceutical study. Some alkaloid structures are illustrated below.



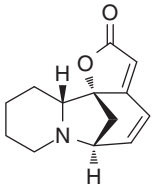

**83** Camptothecine
Antitumor

**84** Vincamine
Peripheral asodilator

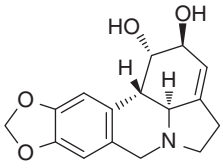
**85** Hasubanane
Anti-plasmodial




**86** Arisine




**87** Securinine
Central stimulant

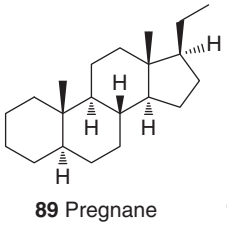



**88** Lycorine
Antitumor

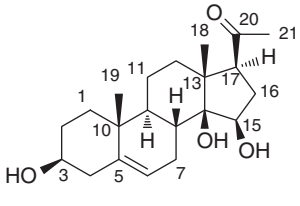
### 1.2.4
### Steroids

Steroids form an important kind of natural compounds with various bioactivities. They can be mainly classified as $C_{21}$-steroids, steroidal saponin, and so on.

$C_{21}$-steroids, as the name implies, have 21 carbons in a basic skeleton of pregnane or its isomer. As pointed out earlier, $\beta$ was used to label the configuration of **91**. If it is labeled as (*R*) or (*S*), it should be (3*S*,8*R*,9*S*,10*R*,13*R*,14*S*,15*R*,17*S*).

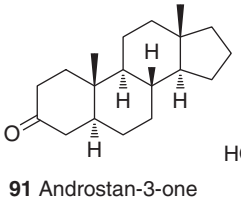



**89** Pregnane

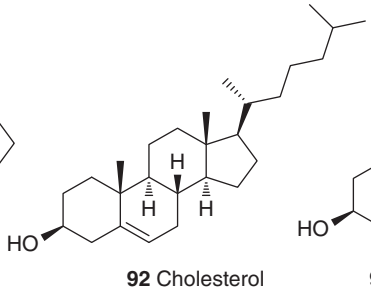



**90** 3$\beta$,14$\beta$,15$\beta$-Trihydroxypregn-5-en-20-one

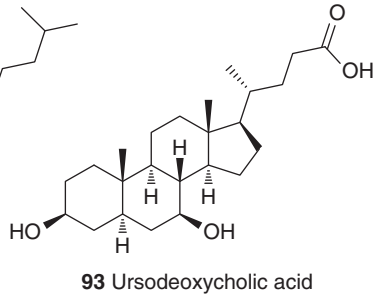
Other steroids, such as androstan-3-one (**91**), cholesterol (**92**), ursodeoxycholic acid (**93**), mestanolone (**94**), formestane (**95**), and enicillitone (**96**), are listed below [15]. These are some representatives among the huge number of steroids.



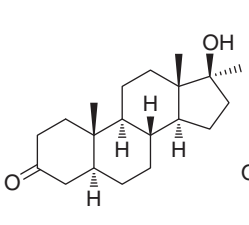

**91** Androstan-3-one



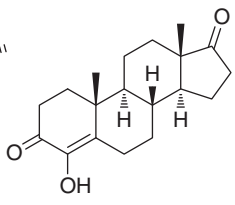

**92** Cholesterol



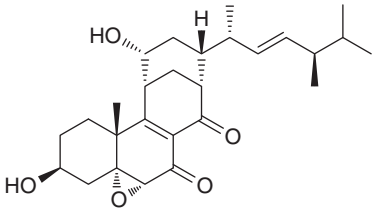

**93** Ursodeoxycholic acid




**94** Mestanolone




**95** Formestane

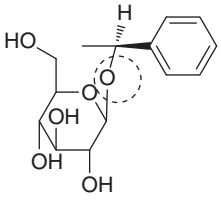



**96** Penicillitone

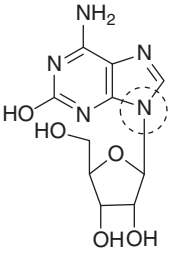
1.2.5
**Glycosides**

When a sugar reacts with an –OH-containing compound (such as a terpenoid, a teroid, and so on), the product is called a glycoside. Therefore, glycosides contain two moieties; one is an aglycone (like terpene, alkaloid), and the other is a sugar moiety. Until now, hundreds and thousands of glycosides have been found and reported all over the world. Most of them have definite bioactivities. Because of their interesting activities, researchers have paid much attention to this kind of products.

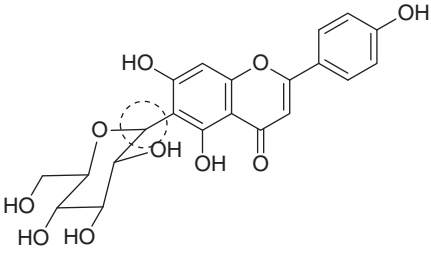
The group –OH can be replaced by one –NH, –CH, or –SH. After the replacement, it forms the corresponding *N*-glycosides and *C*-glycosides, respectively, such as crotonide (**98**) and isovitexin (**99**). It clearly shows that there are two moieties: a sugar and an aglycone.




**97** Prunasin
O-glycoside

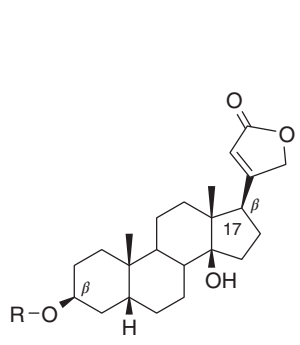



**98** Crotonide
N-glycoside

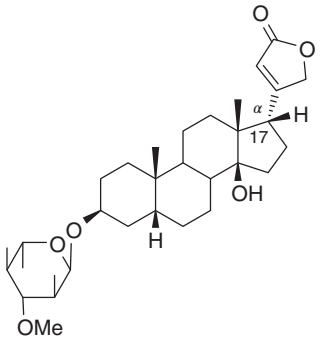



**99** iso-Vitexin
C-glycoside

The –OH is hidden for clarity in the structures in some reports (101). As one of the most important steroidal glycosides, cardiac glycosides have been attracting the attention of many researchers. Traditionally, the configuration of glycosides in some positions is named as $\alpha$ or $\beta$. For example, naturally, most cardiac glycosides have $\beta$ configuration at C3 and C17. If C17 has $\beta$ orientation, H17 will have $\alpha$ orientation (**100**). However, a glycoside such as **101** has $\beta$ orientation on H17, which is named as 17$\beta$-*H*-neriifolin.




**100** R = differnet glucose moiety



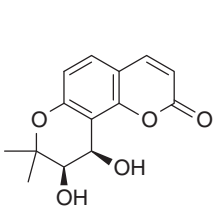

**101** 17$\beta$H-neriifolin

The difficulty is to convert the $\alpha$ or $\beta$ configuration to the corresponding (*R*) or (*S*) at the beginning. Researchers must understand that the use of $\alpha$ or $\beta$ is out of tradition. With the development of organic stereochemistry, it is possible to change traditional habits to use (*R*) or (*S*) in AC study, although it may take a lot of time.

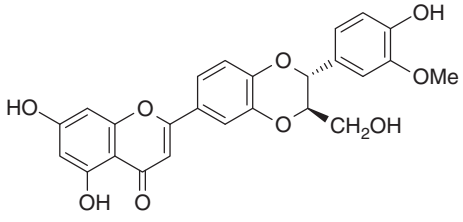
### 1.2.6 Others

There are many different chiral compounds found in nature. However, amino acids and sugars are not included in the text. They are important organic matter. There are some special books dealing with them.

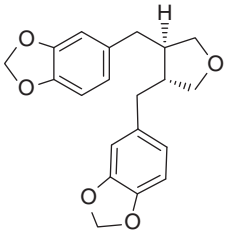
For a quick look at the chiral compounds, their structures are illustrated below.



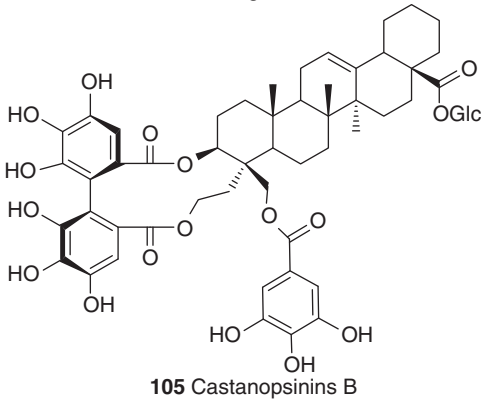

**102** Khellactone
Coumarinoids




**103** Silymarin
New lignanoids




**104** Cobebin
Lignanoids

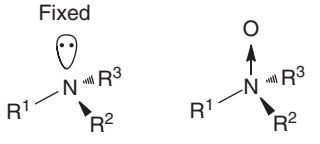



**105** Castanopsinins B

The pretty chiral materials exhibit a very colorful picture in front of chemists. Finding newer chiral compounds and their uses is an interesting task. The assignment of their AC then becomes a big challenge in modern science.

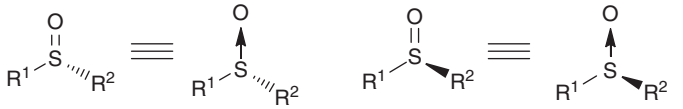
## 1.3 Other Stereogenic Centers

The earliest discovery of chirality is the chiral $sp^3$ C atom. It is also regarded as C-chirality. There is another kind of chiral compounds in which the stereogenic centers are located on the N, P, or S atom. For example, when the lone electrons on the N atom are fixed, like quaternary ammonium salts (the substituents on N are not equivalent) or N–O compounds, chirality of N atom is formed.



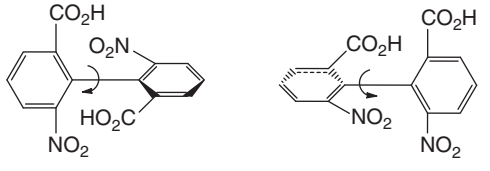

**106** **107**

$R^1 \neq R^2 \neq R^3$ in the N-chirality compounds shown above. Compared to the instability of the N-chirality in absence of some acidic reagents, sulfoxide's chirality (S-chirality) can exist stably at room temperature and can be used widely in asymmetric synthesis. Other atoms, such as P, can also form the corresponding P-chirality. Their AC nomenclature is the same as that in C-chirality compounds.




**108** **109**

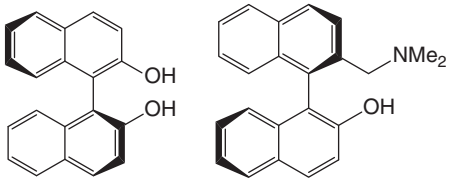
Among the different chiral compounds, one kind of compounds has chirality due to the rotation restriction (limitation) of the C–C single bond [16]; the early reported racemic 6,6′-dinitro-[1,1′-bipheyl]-2,2′-dicarboxylic acid has two ACs in solution, which can be separated from each other. This is axis chirality or axial chirality, and the compounds are atropisomers.




**110** **111**

The widely used single-bond rotation-limited chiral compounds are derived from [1,1′-binaphthalene]-2,2′-diol (**112**). The number of chiral catalysts derived from it may be over a hundred, and some of them, such as (*R*)-2′-((dimethylamino)methyl)-[1,1′-binaphthalen]-2-ol (**113**), exhibit very high

enantioselectivity in different reactions, giving up to 90% ee in the enantioselective addition of diethylzinc to aldehydes [17].



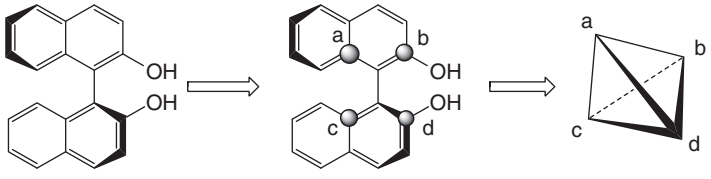

(*S*)-**112** (*R*)-**113**

The rule to name the AC for binaphthyl-containing chiral axial compounds is almost the same as used for chiral carbon tetrahedron structures. Chiral compound **112** was used as an example [18]. First, we can "concentrate" on the corresponding part as a point. For **112**, it can be labeled as the four points as in structure **A**. Then to convert it to a tetrahedron (**B**), obviously, the group point a should be smaller than the group point b (a < b) and c < d (Figure 1.4).

Then, we can put point a in a "rotation" circle center (**D**). In this case, point a is regarded as the smallest, and the point b, which is located on the same molecular moiety, will be regarded as the largest. Therefore, b > d > c. It forms a counterclockwise configuration and named as (*S*) for **112** (Figure 1.5).

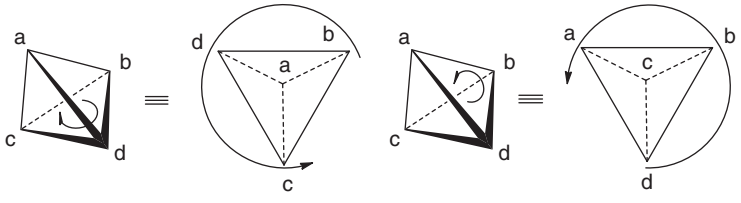
Of course, we can regard point c as the smallest one; then point d is the largest. We can draw another "rotation circle" (**F**). The order is d > b > a. It is also the counterclockwise configuration, and assigned as (*S*) for structure **112**.

There is another method to name its AC. Compound **112** could be "seen" along the axial direction to make sure its AC. Interested readers can find more details in




**112** **A** **B**

**Figure 1.4** Conversion of axial binapthanol to a tetrahedron structure [18].




**C** **D** **E** **F**

**Figure 1.5** Two equal tetrahedron structure conversion.

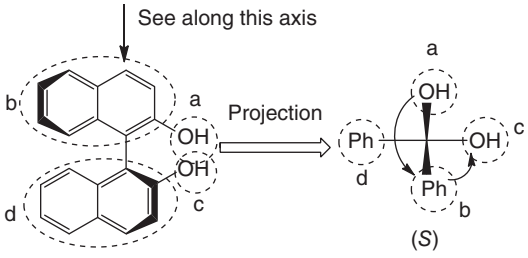



**Figure 1.6** Diagrammatic sketch of the projection structure from **112** [18].

Ref. [19]. Although the nomenclature is different, the final result is the same. For example, **112** can be "seen" as in Figure 1.6.

In this rule, for example, if the starting point is a hydroxyl group a, then it needs to go to phenyl group at point b, and then to another hydroxyl group at point c. The final result is the same: (*S*)-AC.

However, practically, it may be easy to go from point a, then to c, and finally to point b since the two hydroxyl groups are equal, and lead to a wrong (*R*)-AC. To avoid this error, we can apply the rule mentioned above to this case. We use **112** again as an example. If point a is regarded as the biggest, then point b must be regarded as the smallest, the second hydroxyl group c is the second largest, and point d is the smaller one. It forms a circle with the direction from point a to point c and finally to point d (Figure 1.7).

Substituted propadiene derivatives also have chirality. However, because of their instability at room temperature, they are rarely studied alone. However, as a kind of chiral compound, its academic significance cannot be ignored. Its nomenclature can be illustrated as in Figure 1.8. Here, point a is regarded as the largest, then, automatically, point b on the same atom C is the smallest, and the rotation direction is from a to c to d. It is (*R*)-AC in this case.

Spiro compounds have similar nomenclature. We need to "see" the structure from the top through spiro point. It can be found that the chiral compound **115** has (*R*)-AC. The largest point and the smallest point should be on the same side (Figure 1.9) [18].

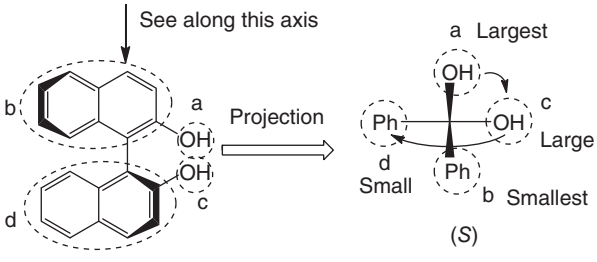



**Figure 1.7** Diagrammatic sketch of the projection structure from **112** [18].

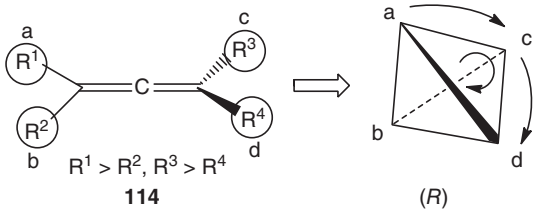



**Figure 1.8** Diagrammatic sketch of projection structure from **114** [18].

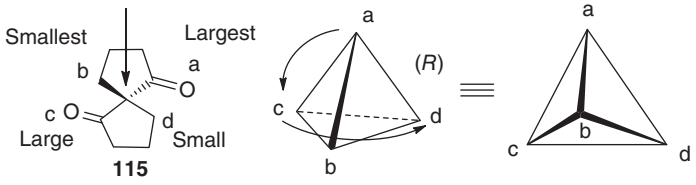



**Figure 1.9** Diagrammatic sketch of **115** to the tetrahedron structure [18].

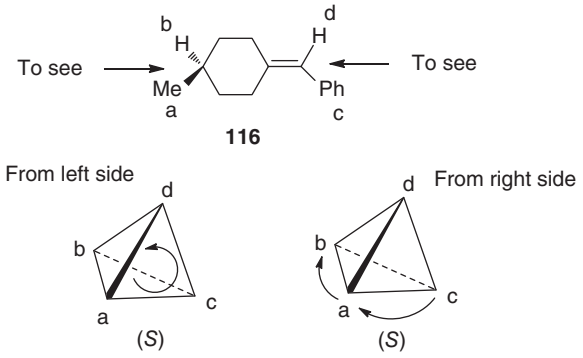
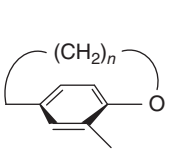


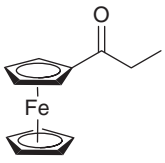

**Figure 1.10** Diagrammatic sketch of **116** to the tetrahedron structure [18].

Other similar chiral structures may derive from it, for example, (*S*)-((4-methyl cyclohexylidene)methyl)benzene **116**. In this case, Ph is larger than Me, However, if we see it from the left, point a can be regarded as the largest and point b as the smallest; then the rotation direction is from a to c to d, and it has (*S*) AC (Figure 1.10). We could see it from the right side too: then the rotation direction is from c to a to b, and it has (*S*) AC. The conclusion is the same.

Other chiral molecules include planar chirality compounds (**117**), chiral ferrocenes (**118**), and other chiral metallic complexes. This is a very interesting area that involves the chelation of different metallic ions with various organic ligands. This is not a major topic in organic stereochemistry; the corresponding research belongs to coordination chemistry.

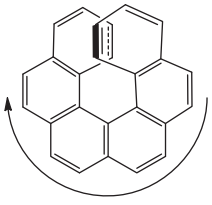



117

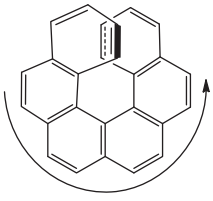



118

The final nonstandard chiral molecule is the helix structure. The study was well reported in the 1960s. This type of chiral compound has different nomenclatures: *M* or *P*. One needs to see it from the top. If the rotation direction is clockwise, it is labeled as *P*, and if it is counterclockwise the direction is *M*. This kind of chiral compound generally has large OR values. For example, the following two helix hexahelicenes have ORs of ~3700°. The difference may be due to measurement errors.



**119** *P*-(–)-Hexahelicene
$[\alpha]_D$ – 3640° [18b]



**120** *M*-(+)-Hexahelicene
$[\alpha]_D$ + 3707° [18c]

The DNA chain is a well-known helix biopolymer; it is the most important representative among all helical chiral compounds although it is a biopolymer. The synthesis of the similar bioactive compounds may be an interesting but challenging task.

## 1.4 Optical Characteristics

In polarized light, enantiomers exhibit reversed optical characteristics. Just like their OR, others like electronic circular dichroism (ECD), vibrational circular dichroism (VCD), or Raman optical activity (ROA) also exhibits reversed characteristics.

OR is one of the earliest discoveries in organic chemistry. Since its discovery, many excellent chemists have developed this knowledge. Now, OR is one of the very general parameters for characterizing chiral compounds in various reports not only because of its easy measurement but also its wide catholicity. Most compounds have definite OR values that can be easily recorded with reliable resolution. It is absolutely necessary to know more about these characteristics.

### 1.4.1 Measurement of OR

Since the first separation of the left-handed enantiomer of sodium ammonium tartrate from the right-handed one by Louis Pasteur, many enantiomers have been prepared. The optically pure chiral compounds provided researchers great opportunities to study the relationship between OR and the molecular configuration. Many theories have been proposed to explain the OR phenomenon. These will be introduced in the following chapters. The general setup for determining OR is shown in Figure 1.11.

The change in the angle $\alpha$ of a beam of polarized light depends on the wavelength of light. At the same time, its size also depends on the length of the cell and the solution concentration when the temperature and solvent are fixed. The specific rotatory power $[\alpha]^t$ is proportional the values of the measured rotation $\alpha$ (Eq. (1.5)) as

$$[\alpha]^t = \frac{\alpha}{l \times c} \tag{1.5}$$

where $c$ is the concentration with unit in g per 100 ml in most cases, $\alpha$ is the measured rotation value, $l$ is the length of cell (10.0 cm in most OR setups), and $t$ represents the temperature. When the D line of sodium light (589.6 nm) is used for OR determination, the specific rotatory power is written as $[\alpha]_D^t$ . In general, the specific rotatory power is simply called OR.

The molar rotation $[M]_D^t$ has the following relationship with $[\alpha]_D^t$ :

$$[M]_D^t = \frac{[\alpha]_D^t \times M}{100} \tag{1.6}$$

where $M$ is the molecular weight.

In many asymmetric synthesis studies, "optical purity" is used to characterize the chiral compound's content in percentage. It needs a 100% pure chirality compound as the OR standard value. For example, if one enantiomer has the OR value of 100, and if the synthesized product has the OR value of 80, its optical purity is 80% o.p. or 80% op. This is popular in many studies. It is equal to the enantiomer excess (ee%) theoretically. However, because of measurement errors, both values will not be equal but very close.

Determination of OR is inexpensive and convenient. Most chiral compounds have large enough OR values, and therefore it is more convenient to use OR for AC

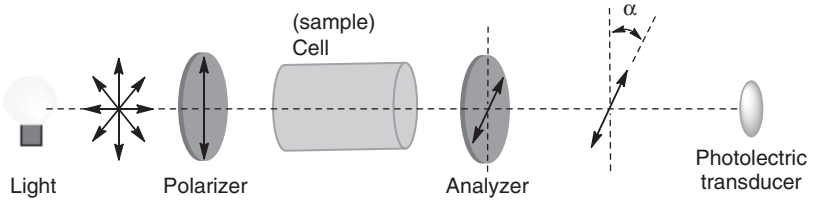
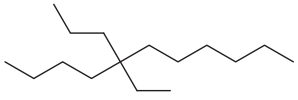



**Figure 1.11** General optical setup of OR.

determination. However, some chiral molecules may have a very small OR value. In some cases, it is too small to be examined correctly. For example, 5-ethyl 5-propyl-undecane (**121**) has an extremely small OR; its absolute OR value is <0.001 between 280 and 580 nm [20].



**121**

When the wavelength of light is changed from that of the D line of sodium to others, the recorded OR values under different wavelengths provide (ORD). The used wavelengths include 578, 546, 436, and 365 nm. Different setups may use different wavelengths for ORD determination.

The OR magnitudes may undergo a small change when one or more stereogenic centers change in some chiral molecules with two more such centers. This leads to difficulty in identifying the AC by comparing its experimental OR with the predicted OR. In this case, if a compound has double bonds that have UV absorption near the stereogenic centers, it is a good way to measure its ECD and compare its experimental ECD with the calculated ECD.

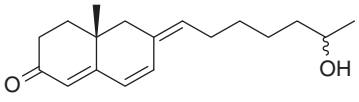
### 1.4.2 ECD and Its Definition

Left- and right-CPL may cause the phase of polarized light to change, and this produces the OR. On the other hand, the absorption of the left-handed and right-handed enantiomers of polarized light may be different, and this absorption difference ($\Delta\varepsilon$) can be measured as ECD.

$$\Delta\varepsilon = \varepsilon_L - \varepsilon_R \tag{1.7}$$

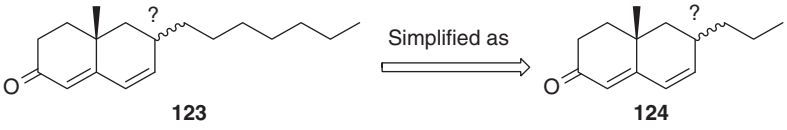
In the UV–vis region, where the wavelength of polarized light extends from 180 to 800 nm, mostly from 200 to 500 nm is used for determining the ECD of organic chiral compounds. It simply shows that the contribution to ECD is from the electrons (excited state).

ECD is used for AC study of chiral compounds with stereogenic centers close to functional groups, such as C=O and C=C, that have UV absorptions. Therefore, if a chiral molecule has no such UV-absorbing functional groups, it is extremely difficult to use ECD to determine its AC correctly. Even if there is a double bond in a molecule, if the stereogenic center is too far away from this double bond, for example, **122**, it is still difficult to use ECD to assign its AC for the carbon connected to the –OH.




**122**

This looks like a shortcoming in AC determination. However, it may bring us some benefits in the AC study in some cases. For example, it is possible to use ECD to assign the AC for **123.** In the normal case, the number of theoretical conformations may be up to ($3^6$) 486 when the rings are assumed not to change. We can use model **124** to study the AC of **123** in practice (Scheme 1.2). In this case, the theoretical number may decrease to 9. This could greatly reduce the computation time.




**123** **124**

**Scheme 1.2** Simplified model for chiral compound **123** with long side chain.

1.4.3
**Outline of VCD**

When a molecule has no UV–vis absorption and its OR value is not large enough, it is difficult to assign its AC if there is no assistance from VCD . As a recently developed technique, its application is not broad enough as ECD's. However, it has big application potential in this area.

As mentioned above, absorption of the left- and right-handed enantiomers of polarized light is different in a chiral environment. This absorption difference happens mostly from 500 to 8000 $cm^{-1}$ producing VCD. Theoretically, it can be used for all chiral compounds' AC assignment since all molecules have various vibrations. The difference of the vibration of bonds near the stereogenic centers gives rise to different VCD spectra due to different vibration vectors. The illustrative diagram of a VCD setup is shown in Figure 1.12.

The vibrational modes of bonds in chiral molecules are different based on their conformational structures in solution, including the interactions among several

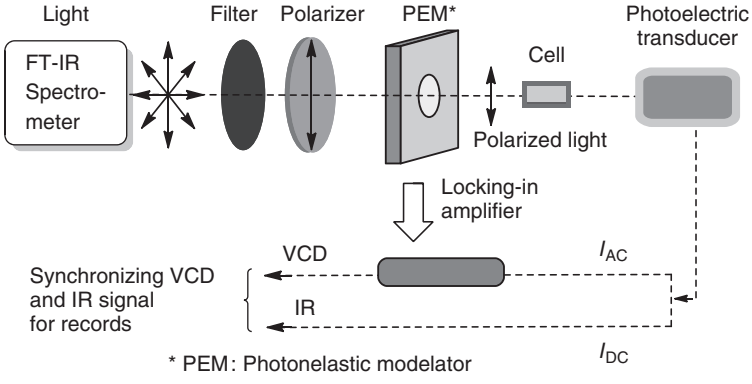



**Figure 1.12** Diagrammatic sketch of VCD equipment [21].

molecules. For example, if two or two more chiral compounds interact in a solution, it is a very good way to study their interaction conformations.

On the other hand, just because of this characteristic, it is sometimes found that the predicted VCD does not agree well with the experimental VCD when a chiral molecule has two or two more hydroxyl groups, especially when the two –OH groups are close enough. The –OH may form strong H-bonds between two molecules or among several molecules. These "dimers" or "trimers" might have a different VCD structure from that of their monomer. This causes a disagreement between the calculated and experimental VCD spectra. Therefore, the enriched VCD signal is an advantage for intermolecular interaction studies, but sometimes it is disadvantageous to understand the differences between the computed and experimental VCD results.

### 1.4.4 Outline of ROA

ROA clearly states that the optical characteristics recorded in experiments involve Raman scattering. The physical variable is the *scattering cross section* when polarized light passes through a chiral sample in a solution or solid [21]. The formula for computing the difference of scattering cross section is very similar to those in ECD or VCD computations:

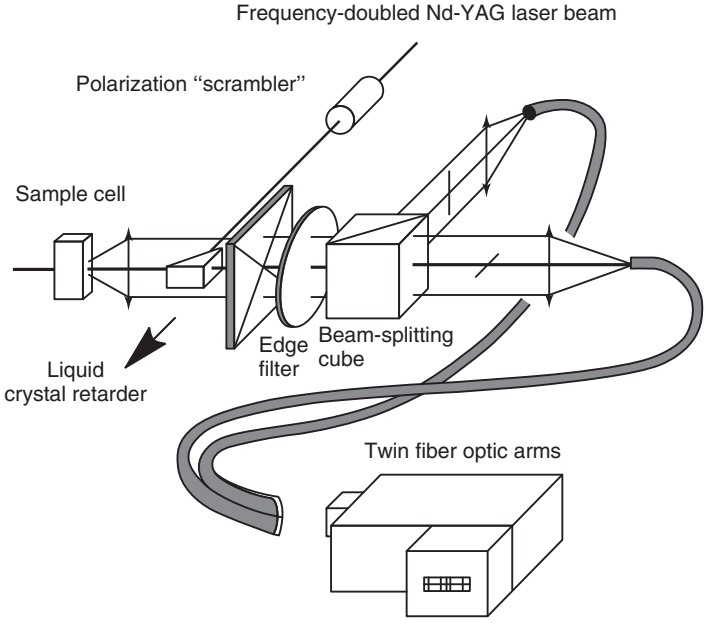



**Figure 1.13** Diagrammatic sketch for Hug's SCP (scattered circular polarization) backscattering ROA instrument upon which the BioTools *ChiralRAMAN* instrument is based. The double-headed arrows represent lenses. Copied from Ref. [22].

$$\Delta A = A_L - A_R \tag{1.8}$$

where $A$ is the scattering cross section, $A_L$ and $A_R$ are the scattering cross sections to the corresponding left-handed (circularly) and right-handed (circularly) polarized light, respectively.

The wavelength range in ROA also is mostly 200–4000 $cm^{-1}$ as used in organic chemistry. This is also depends on the requirement of measuring a sample. The traditional instrument for ROA measurements is illustrated in Figure 1.13.

Both VCD and ROA involve vibrational transitions in molecules involving internal normal modes of vibrational motion, such as the stretching and angle-bending of chemical bonds, and as forms of optical activity. Indeed, both VCD and ROA are also intensity differences between left- and right- circularly polarized IR. The quantum theory of VCD and ROA can be found in many specific references, and comprehensive descriptions of all aspects of VOA can be found in the books by Nafie, Barron, and Stephens, Devlin and Cheeseman. See more details in the corresponding chapters.

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