

Stereochemistry - Chirality

Chapter 5

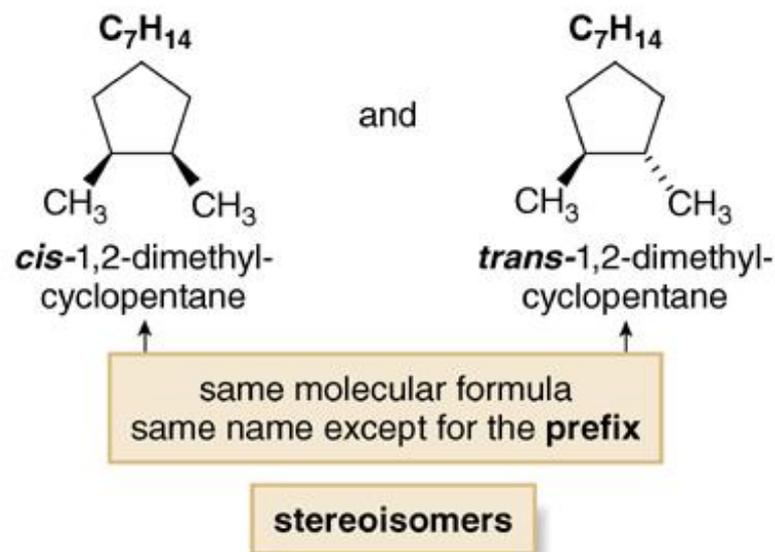
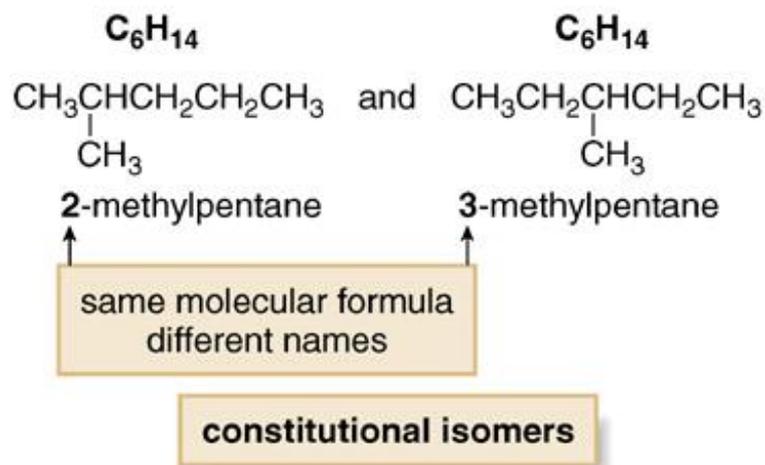
Organic Chemistry, *8th Edition*

John E. McMurry

Isomerism

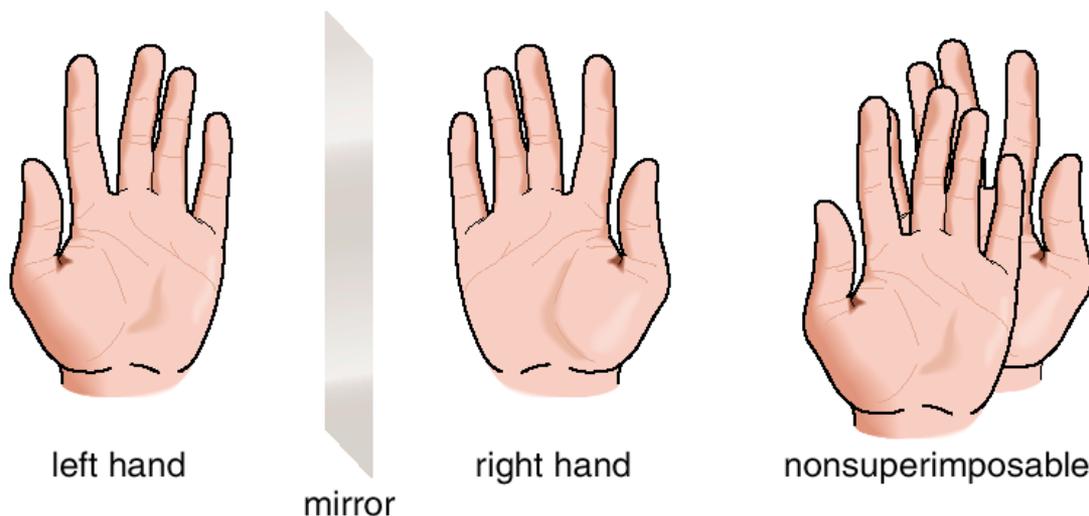
- The two major classes of isomers are **constitutional** isomers and **stereoisomers**.
 - ➡ **Constitutional/structural isomers** have different IUPAC names, different physical and chemical properties, and may have different functional groups.
 - ➡ **Stereoisomers** differ only in the way the atoms are oriented in space. They have identical IUPAC names (except for a prefix like *cis* or *trans*). They always have the same functional group(s).
- A particular three-dimensional arrangement is called a **configuration**. **Stereoisomers differ in configuration.**

Stereoisomers



Chirality

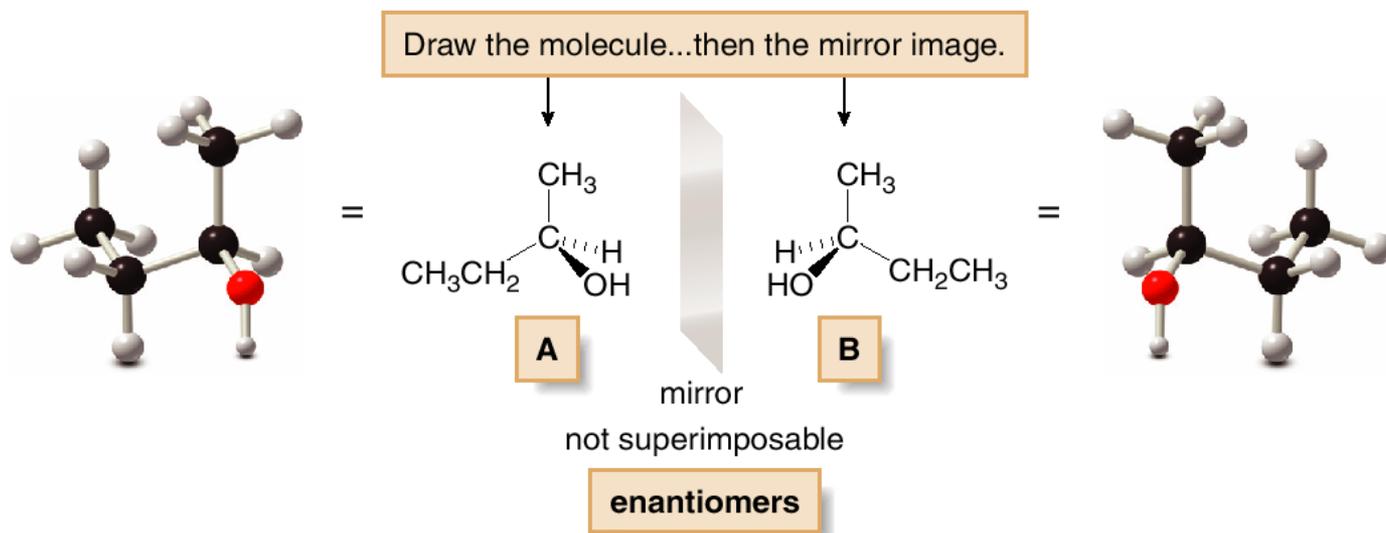
- Every object has a mirror image: mirror images may or may not be **superimposable**.
- Some molecules are like hands. Left and right hands are mirror images, but they are not identical, or **superimposable**.



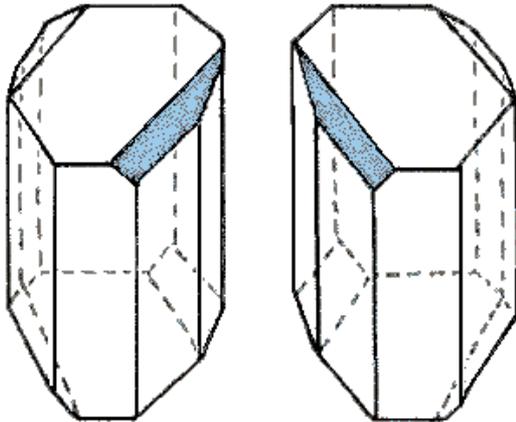
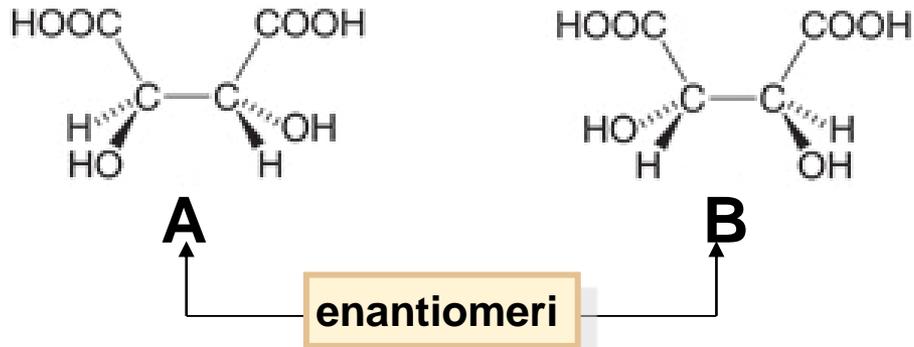
- A molecule (or object) that is *not* superimposable on its mirror image is said to be *chiral*.

Chirality

- A and B are stereoisomers—specifically, they are **enantiomers**.
- A carbon atom with four different groups is a tetrahedral **stereogenic center**.



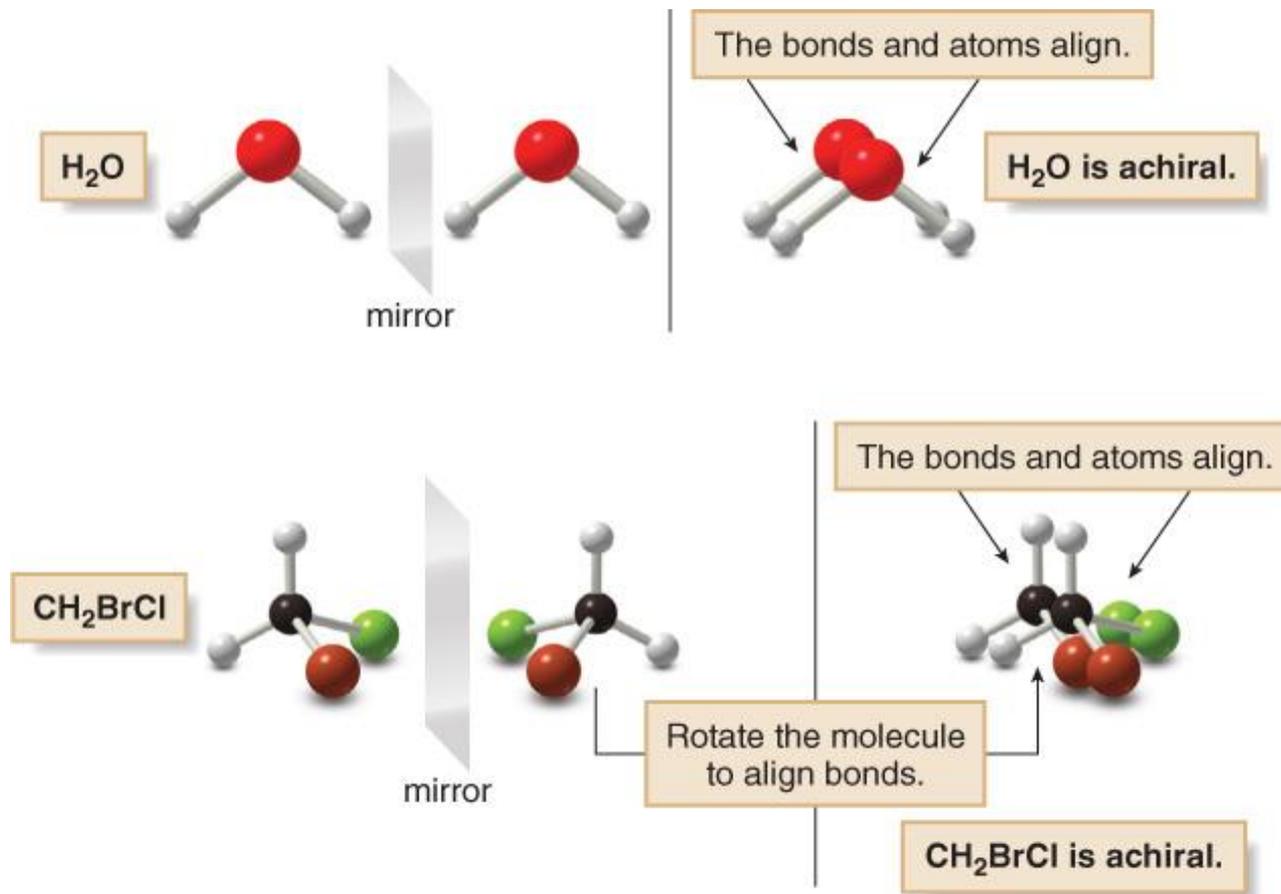
Tartaric acid



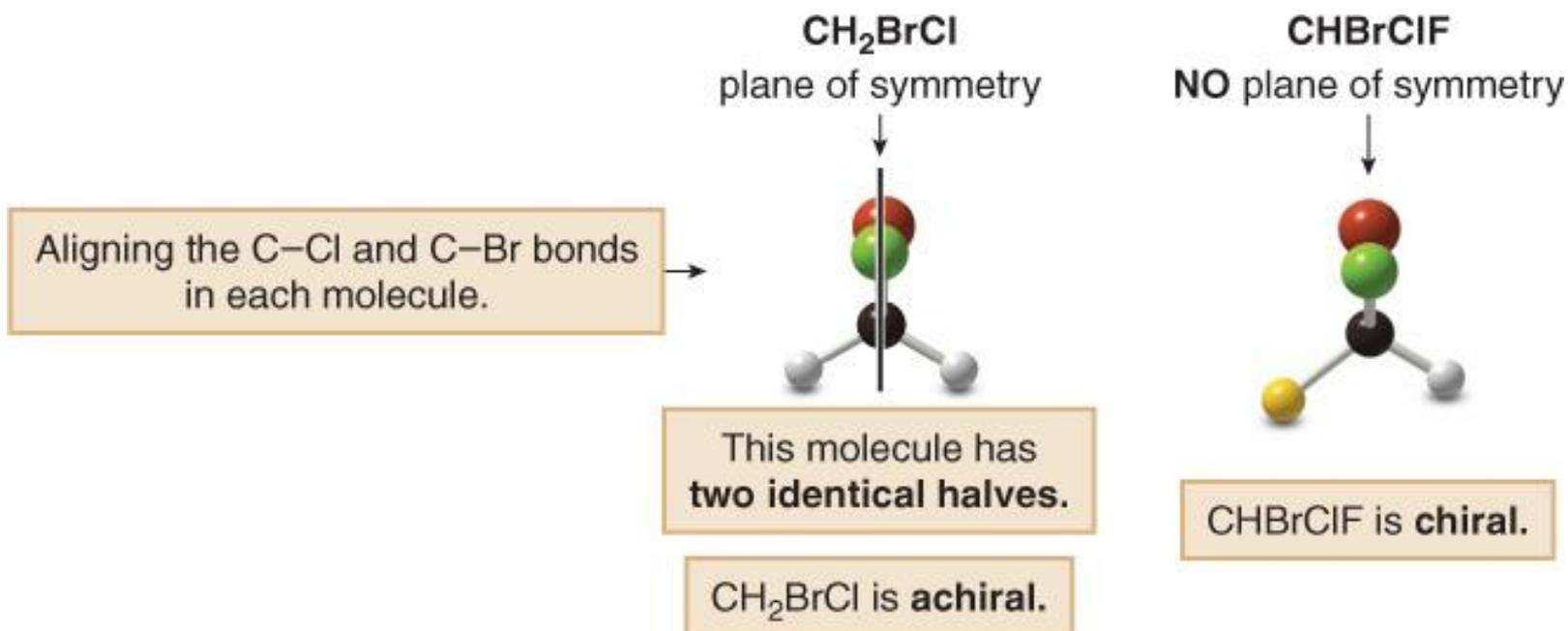
Louis Pasteur



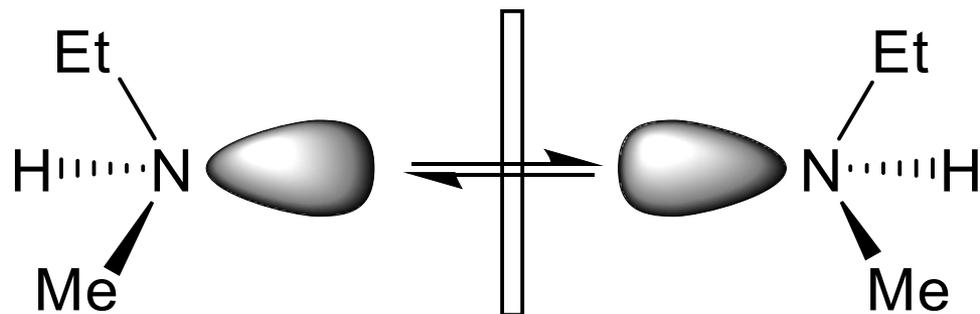
Chirality



Chirality and Symmetry

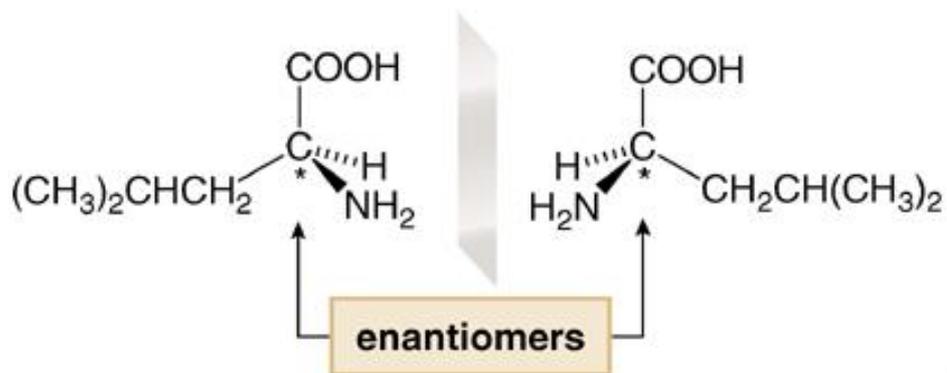


Amines are Achiral



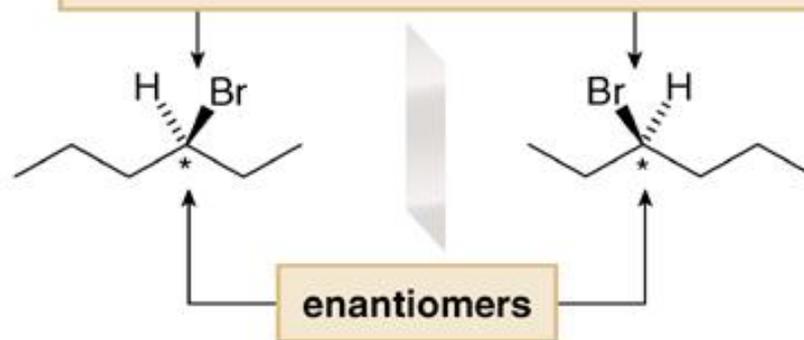
Stereogenic Centers

Leucine, an amino acid



3-Bromohexane

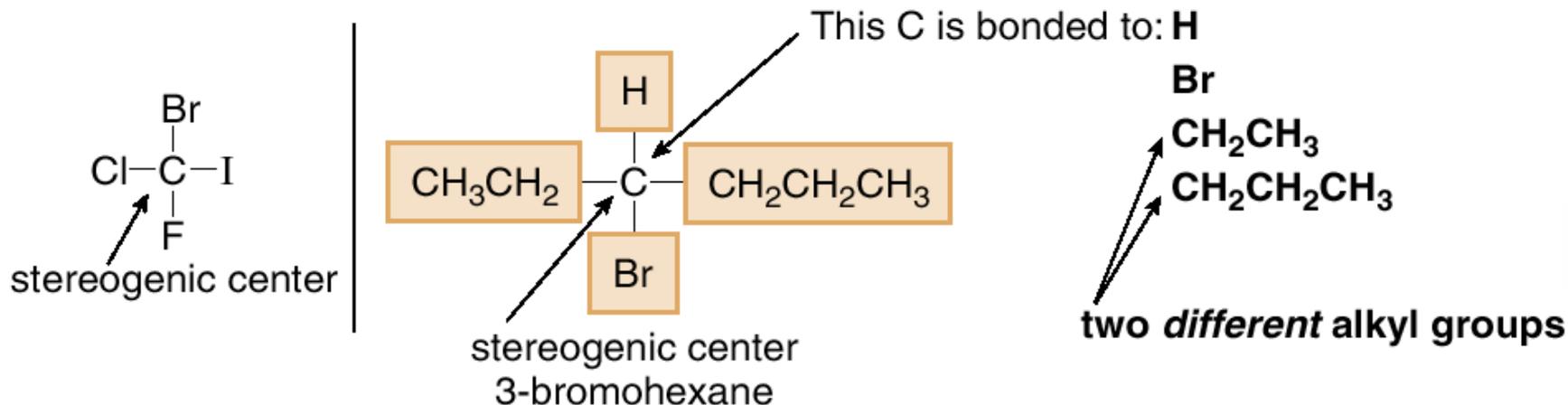
Remember: H and Br are directly aligned, one behind the other.



[* = stereogenic center]

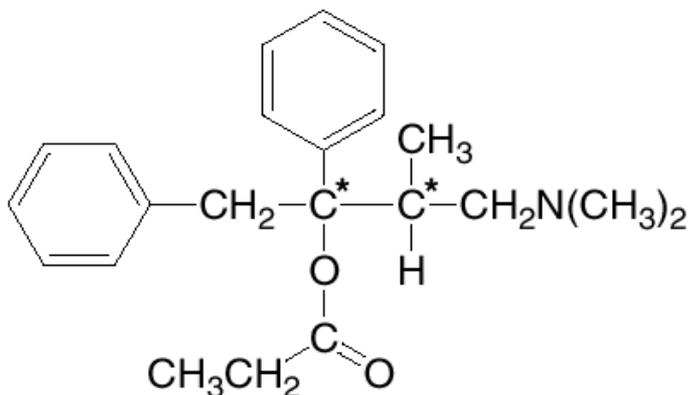
Stereogenic Centers

- To locate a stereogenic center, examine each tetrahedral carbon atom in a molecule, and look at the four groups—not the four atoms—bonded to it.
- Always omit from consideration all C atoms that cannot be tetrahedral stereogenic centers. These include
 - ➡ CH₂ and CH₃ groups
 - ➡ Any *sp* or *sp*² hybridized C

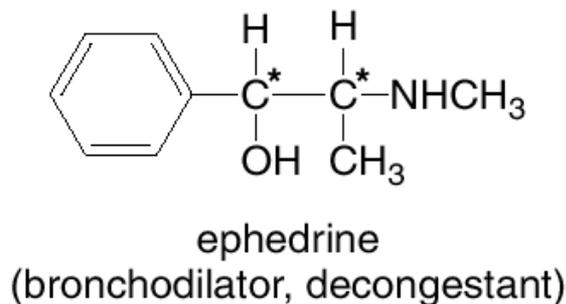


Stereogenic Centers

- Larger organic molecules can have two, three or even hundreds of stereogenic centers.

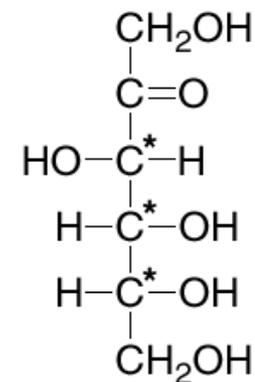


propoxyphene
Trade name: Darvon
(analgesic)



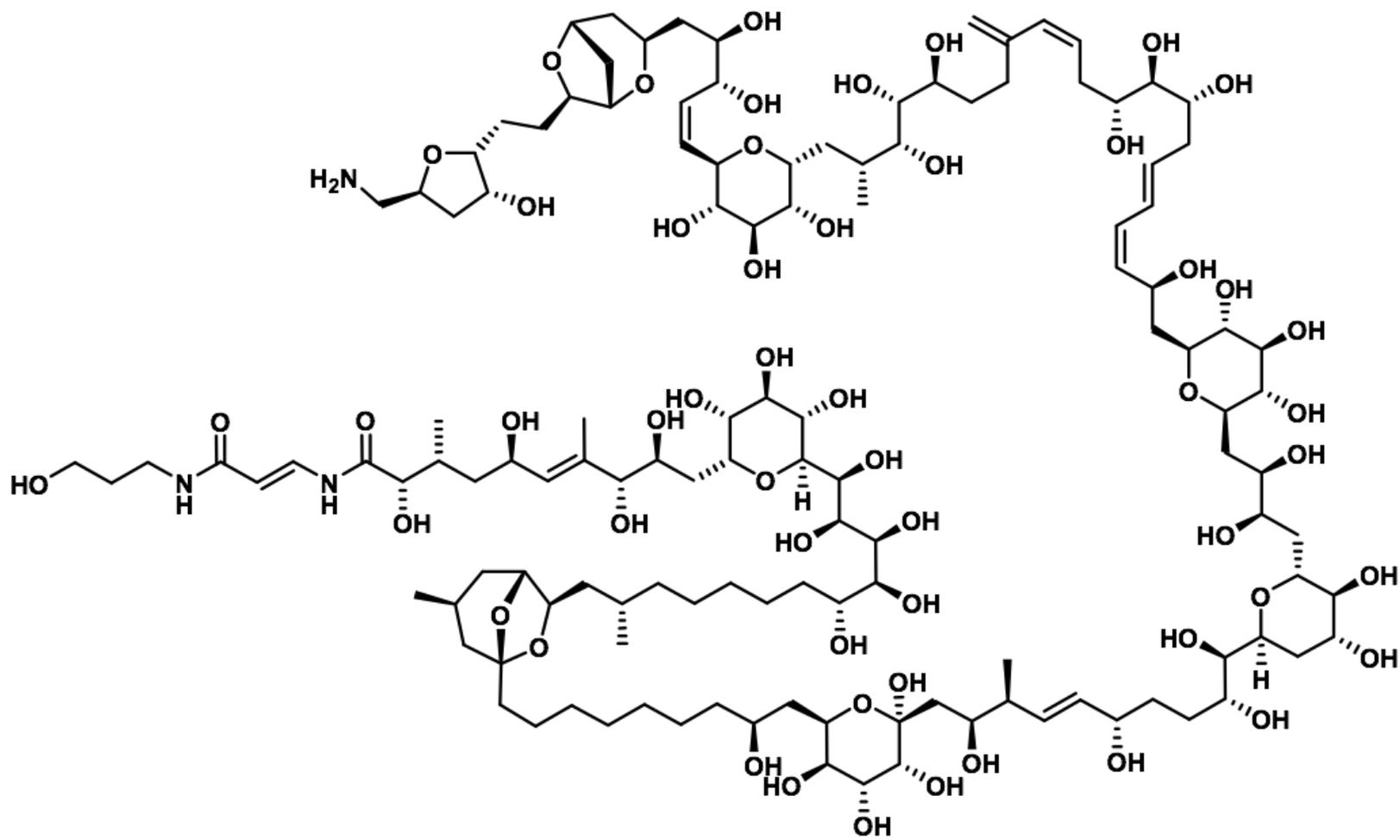
ephedrine
(bronchodilator, decongestant)

[* = stereogenic center]



fructose
(a simple sugar)

Stereogenic Centers

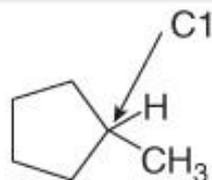


Palytoxin: 64 chiral centers

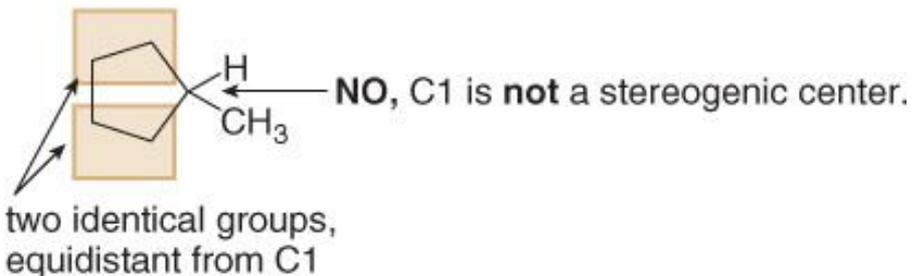
Cyclic Compounds

- Stereogenic centers may also occur at carbon atoms that are part of a ring.
- To find stereogenic centers on ring carbons, always draw the rings as flat polygons, and look for tetrahedral carbons that are bonded to four different groups.

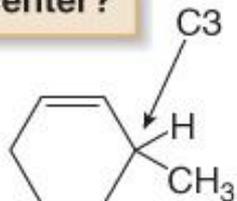
Is C1 a stereogenic center?



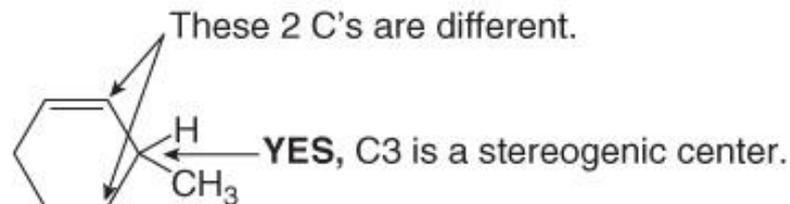
methylcyclopentane



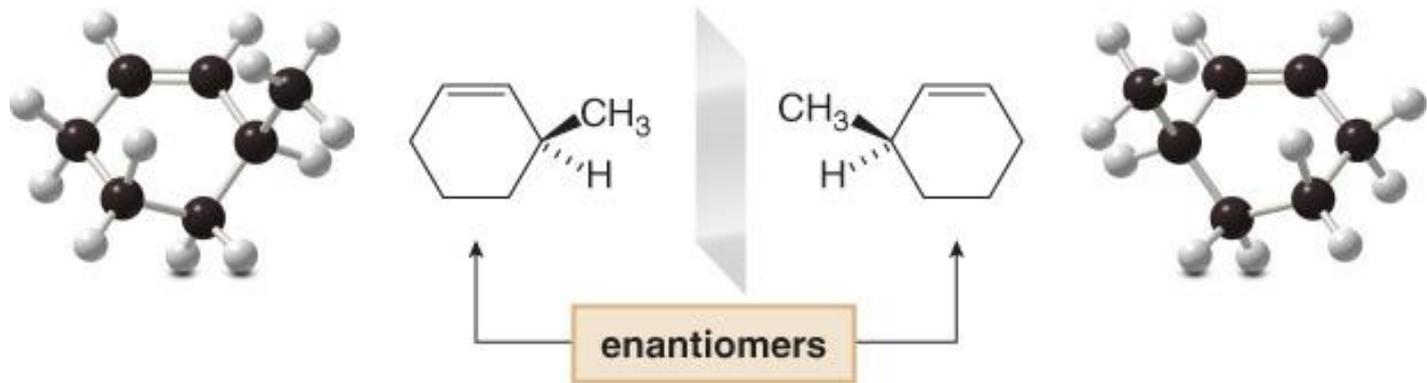
Is C3 a stereogenic center?



3-methylcyclohexene



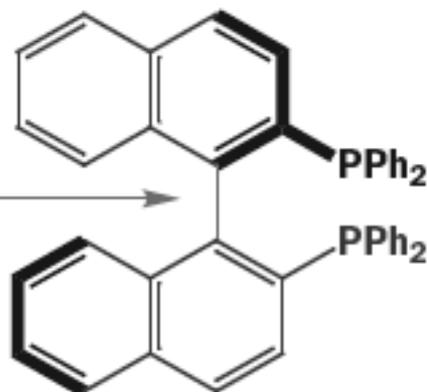
Cyclic Compounds



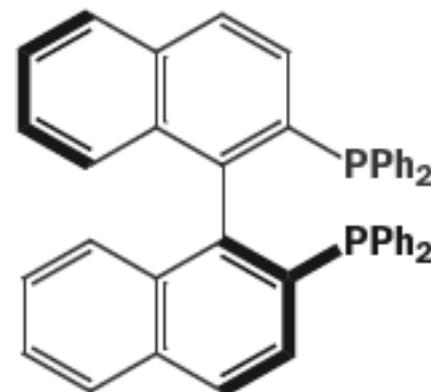
Stereoisomerism from Hindered Rotation

Binaphthalenes

steric hindrance means rotation about this bond is restricted

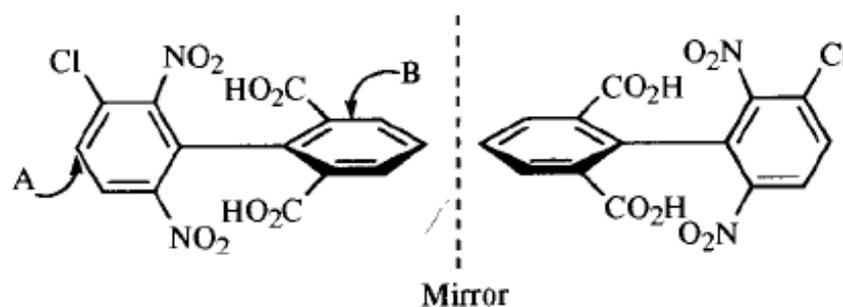
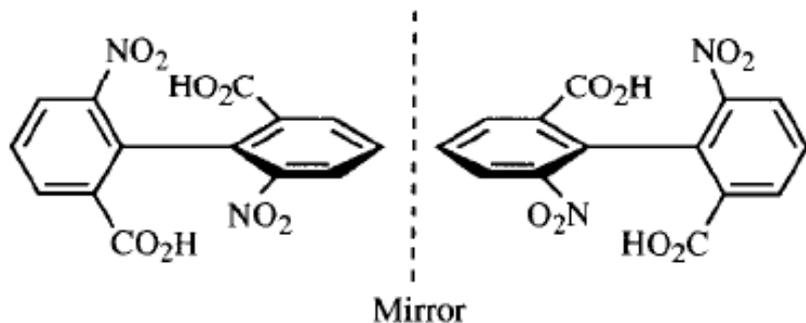


(R)-BINAP

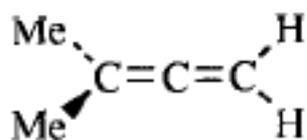
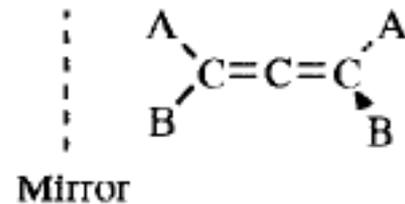
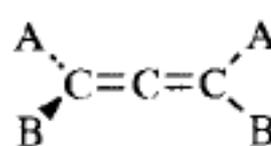
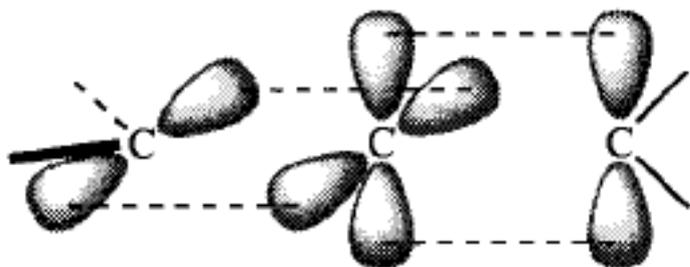


(S)-BINAP

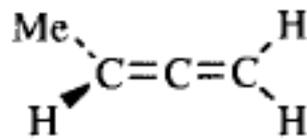
Biphenyl



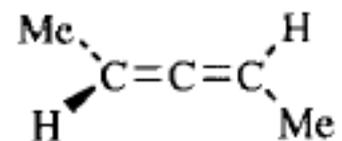
Allenes



Inactive

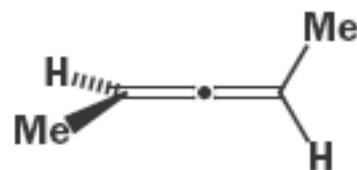


Inactive



Active

Enantiomers

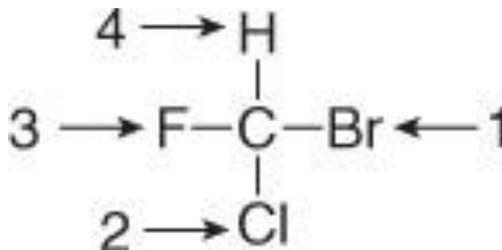


Chirality and Symmetry

- A stereogenic center is a sufficient but not necessary condition for chirality.
- With one stereogenic center, a molecule will always be chiral.
- With two or more stereogenic centers, a molecule may or may not be chiral.
- Achiral molecules usually contain a **plane of symmetry** but chiral molecules do not.
- A plane of symmetry is a **mirror plane** that cuts the molecule in half, so that one half of the molecule is a reflection of the other half.

Cahn-Ingold-Prelog System

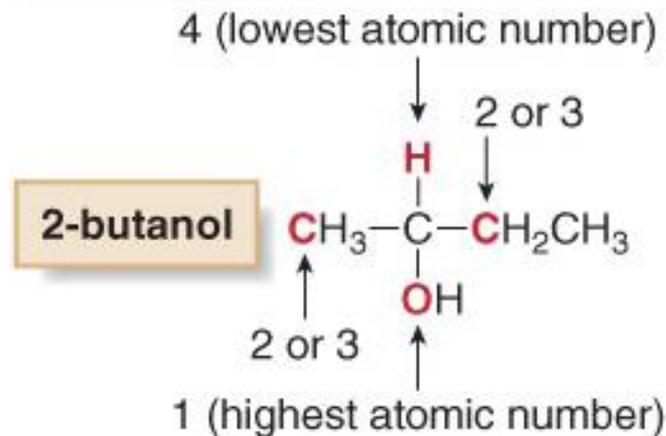
- Naming enantiomers with the prefixes *R* or *S* is called the Cahn-Ingold-Prelog system.
- **Priority rule 1.** The atom of highest atomic number gets the highest priority (1).



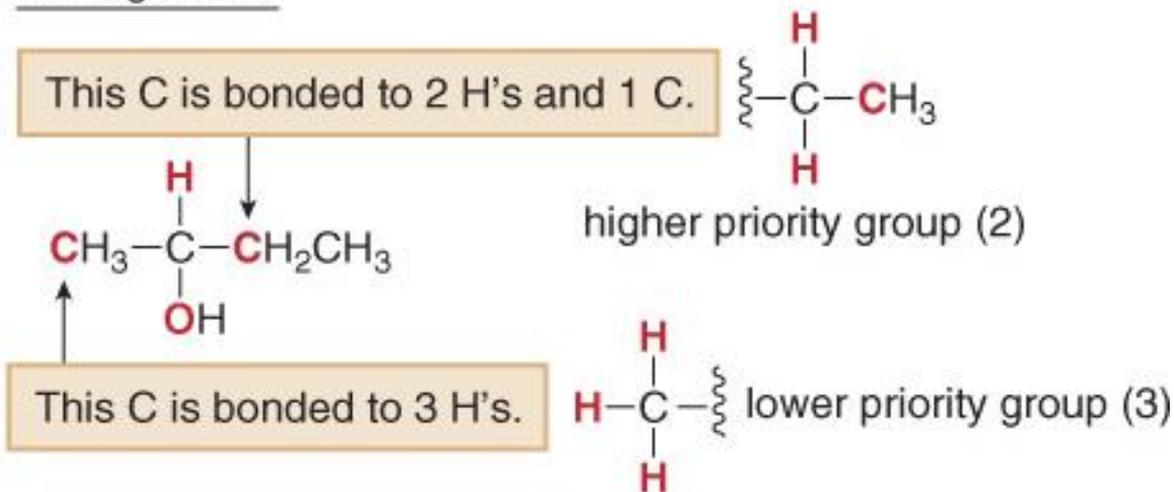
Cahn-Ingold-Prelog System

- **Priority rule 2.** If two atoms on a stereogenic center are the same, assign priority based on the atomic number of the atoms bonded to these atoms. *One* atom of higher atomic number determines the higher priority.

Following rule 1:



Adding rule 2:



Cahn-Ingold-Prelog System

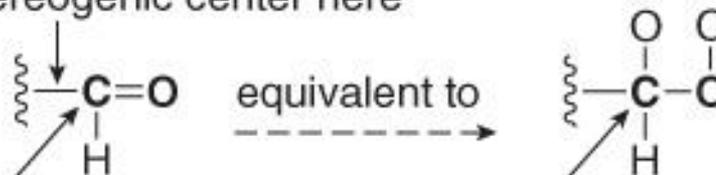
- **Priority rule 3.** If two isotopes are bonded to the stereogenic center, assign priorities in order of decreasing mass number. Thus, in comparing the three isotopes of hydrogen, the order of priorities is:

	Mass number	Priority
T (tritium)	3 (1 proton + 2 neutrons)	1
D (deuterium)	2 (1 proton + 1 neutron)	2
H (hydrogen)	1 (1 proton)	3

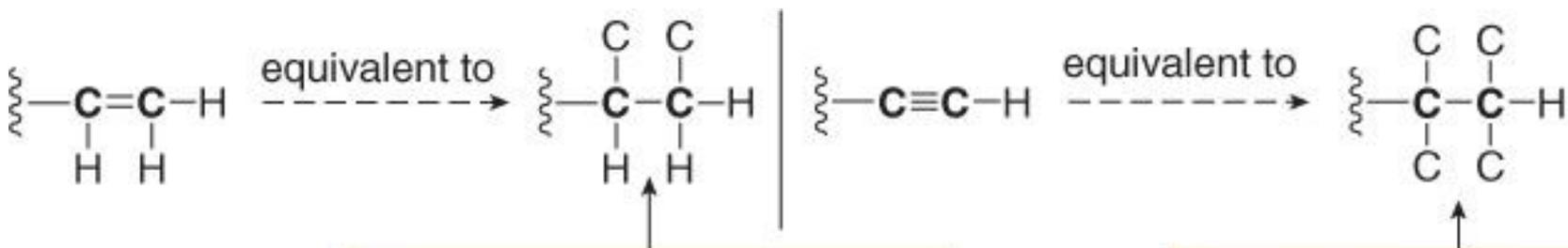
Cahn-Ingold-Prelog System

- **Priority rule 4.** To assign a priority to an atom that is part of a multiple bond, treat a multiply bonded atom as an equivalent number of singly bonded atoms. For example, the C of a C=O is considered to be bonded to two O atoms.

bonded to a stereogenic center here



Consider this C bonded to 2 O's.



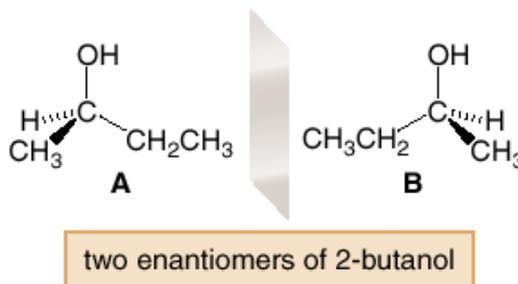
Each atom in the **double** bond is drawn **twice**.

Each atom in the **triple** bond is drawn **three** times.

Cahn-Ingold-Prelog System

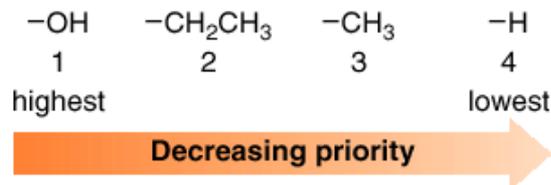
How To Assign *R* or *S* to a Stereogenic Center

Example Label each enantiomer as *R* or *S*.



Step [1] Assign priorities from 1 to 4 to each group bonded to the stereogenic center.

- The priorities for the four groups around the stereogenic center in 2-butanol were given in Rule 2, on page 172.

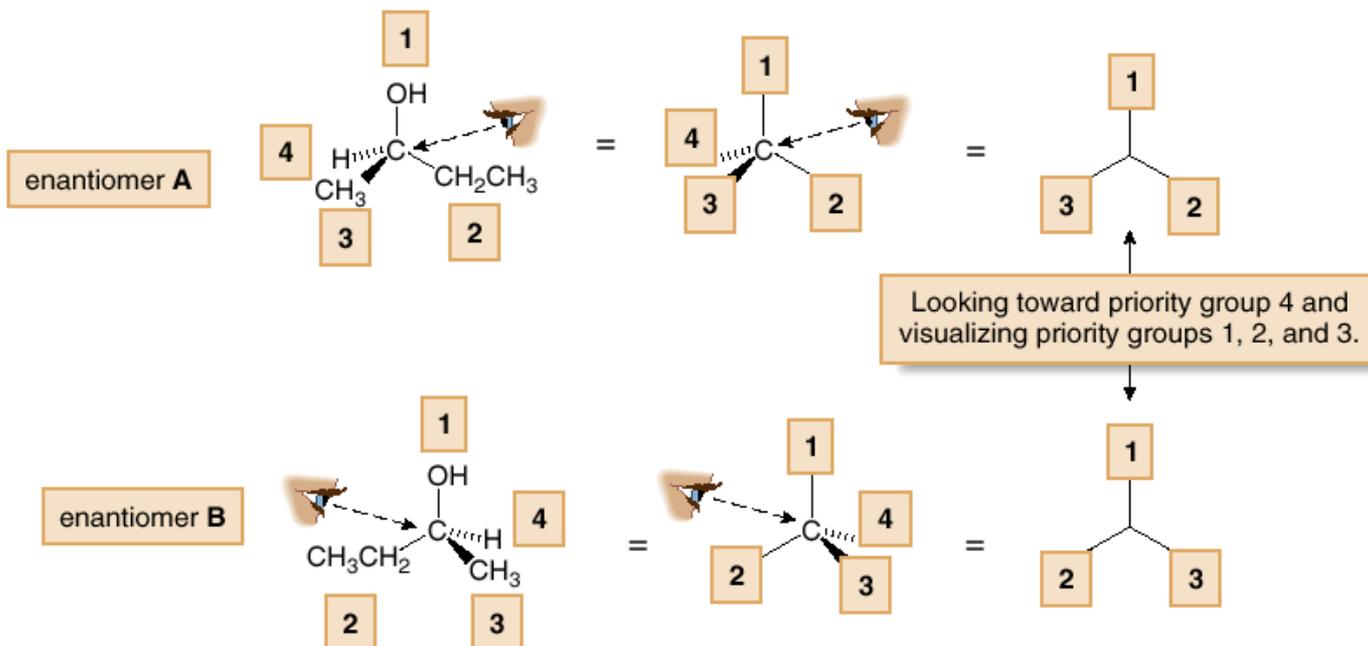


Cahn-Ingold-Prelog System

How To, continued . . .

Step [2] Orient the molecule with the lowest priority group (4) back (on a dash), and visualize the relative positions of the remaining three groups (priorities 1, 2, and 3).

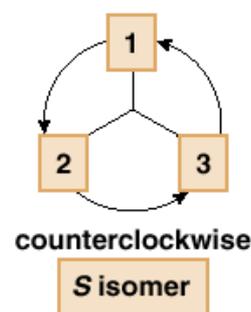
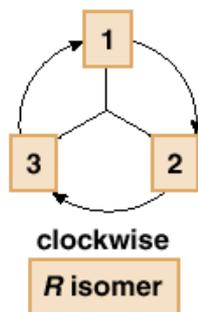
- For each enantiomer of 2-butanol, look toward the lowest priority group, drawn behind the plane, down the C–H bond.



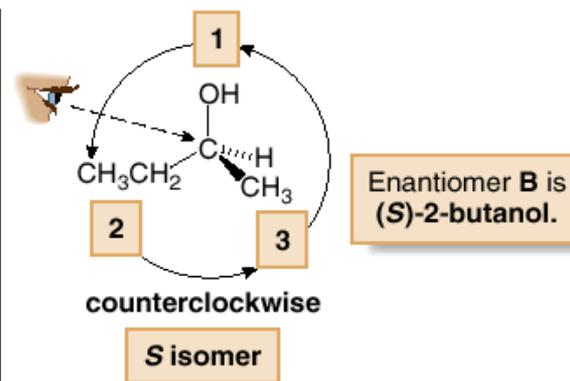
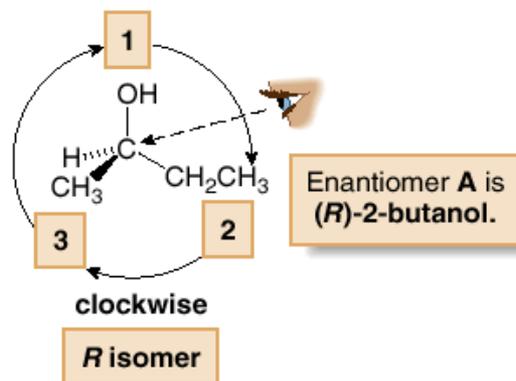
Cahn-Ingold-Prelog System

Step [3] Trace a circle from priority group 1 → 2 → 3.

- If tracing the circle goes in the **clockwise** direction—to the right from the noon position—the isomer is named **R**.
- If tracing the circle goes in the **counterclockwise** direction—to the left from the noon position—the isomer is named **S**.

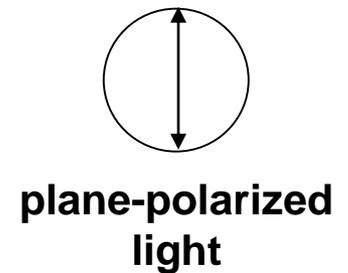
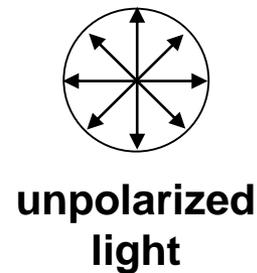
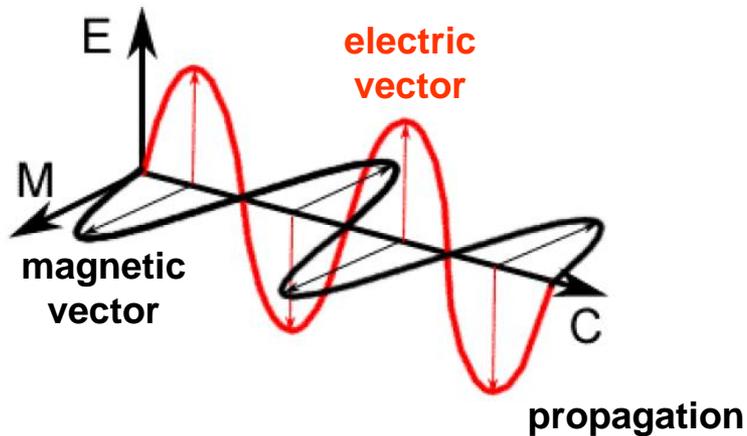


- The letters *R* or *S* precede the IUPAC name of the molecule. For the enantiomers of 2-butanol:



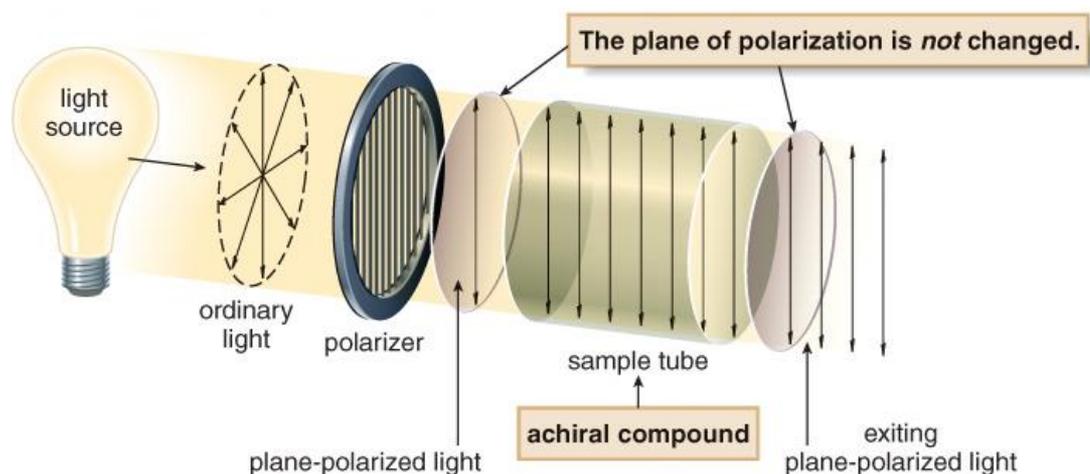
Optical Activity

- The physical properties of two enantiomers are identical except for how they interact with plane-polarized light.
- In **ordinary light** the electric vector oscillates in all planes perpendicular to the propagation direction.
- In **plane polarized light** the vector oscillates in a single plane. Polarized light is obtained with a polarizer.



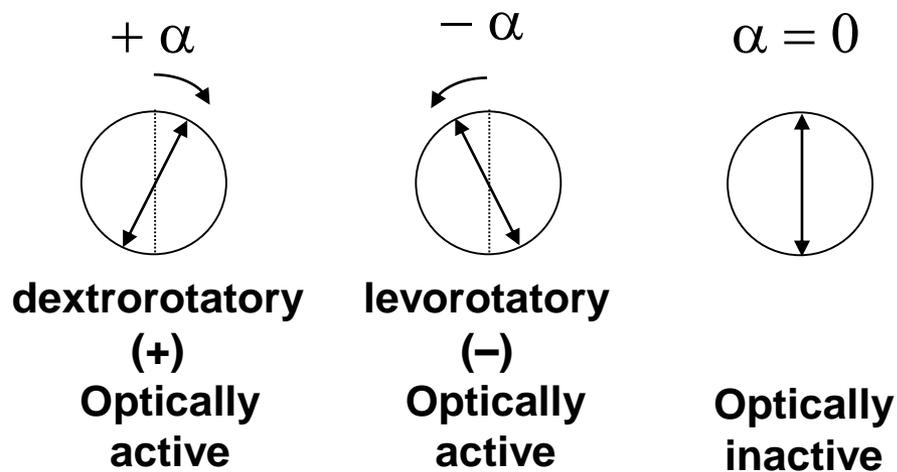
Optical Activity

- In a **polarimeter** polarized light travels through a sample tube containing an organic compound.
- With **achiral** compounds, the light that exits the sample tube remains unchanged. A compound that does not change the plane of polarized light is said to be **optically inactive**.



Optical Activity

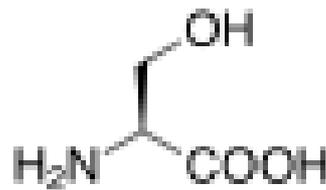
- Two enantiomers rotate plane-polarized light to an equal extent but in **opposite directions**.



- No relationship** exists between *R* and *S* prefixes and the (+) and (-) designations that indicate optical rotation.



(S)-(+)



(S)-(-)

Optical Activity

- **Specific rotation** is a standardized physical constant for the amount that a chiral compound rotates plane-polarized light. Specific rotation $[\alpha]$ is defined using a specific sample tube length (l , in dm), concentration (c in g/mL for pure liquids [=d]; g/100mL for solutions), temperature (generally 25°C) and wavelength (generally 589 nm).

$$\text{specific rotation} = [\alpha] = \frac{\alpha}{l \times c}$$

α = observed rotation (°)

l = length of sample tube (dm)

c = concentration (g/ml or g/100ml)

$$\left[\begin{array}{l} \text{dm} = \text{decimeter} \\ 1 \text{ dm} = 10 \text{ cm} \end{array} \right]$$

Racemic Mixtures

- An equal amount of two enantiomers is called a **racemic mixture** or a **racemate**. A racemic mixture is optically inactive. Because two enantiomers rotate plane-polarized light to an equal extent but in opposite directions, the rotations cancel, and no rotation is observed.

Property	(+) Enantiomer	(-) Enantiomer	Racemic mixture
melting point	identical		may be different
boiling point	identical		may be different
optical rotation	+ α	- α	0

Optical Purity

- **Enantiomeric excess (optical purity)** is a measurement of how much one enantiomer is present in excess of the racemic mixture.

$ee = \% \text{ of one enantiomer} - \% \text{ of the other enantiomer.}$

- The enantiomeric excess can also be calculated if the specific rotation $[\alpha]$ of a mixture and the specific rotation $[\alpha]$ of a pure enantiomer are known.

$ee = ([\alpha] \text{ mixture} / [\alpha] \text{ pure enantiomer}) \times 100.$

Enantiomeric excess

$$\text{e.e.} = \frac{[\text{S}] - [\text{R}]}{[\text{S}] + [\text{R}]} \times 100$$

[S] = concentration of enantiomer S

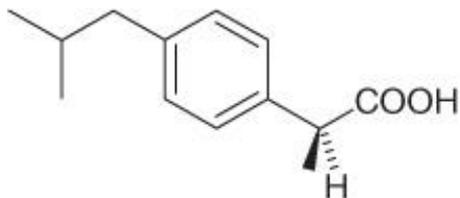
[R] = concentration of enantiomer R

(e.e.) with respect to relative % of the two enantiomers :

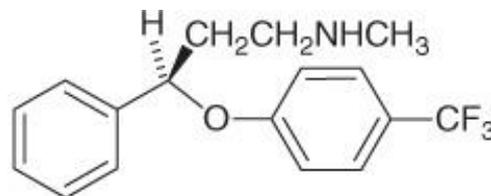
[S]	e.e.
50	00
60	20
70	40
80	60
90	80
95	90
98	94
99	98

Chemical Properties of Enantiomers

- Two enantiomers have exactly the same chemical properties except for their reaction with chiral non-racemic reagents.
- Many drugs are chiral and often must react with a chiral receptor or chiral enzyme to be effective. One enantiomer of a drug may effectively treat a disease whereas its mirror image may be ineffective or toxic.

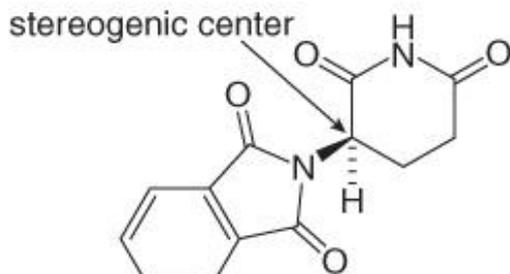


(S)-ibuprofen
anti-inflammatory agent

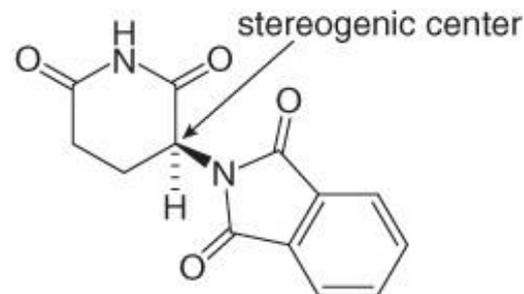


(R)-fluoxetine
antidepressant

Two enantiomers of thalidomide

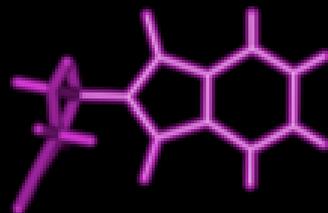
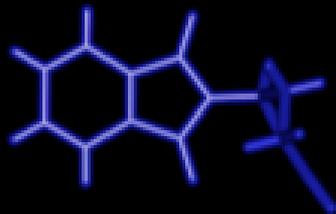
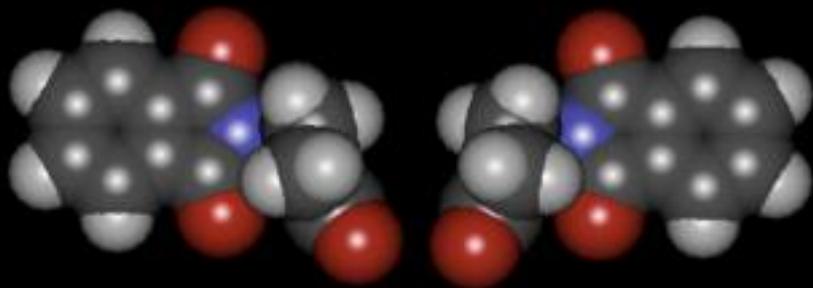


anti-nausea drug



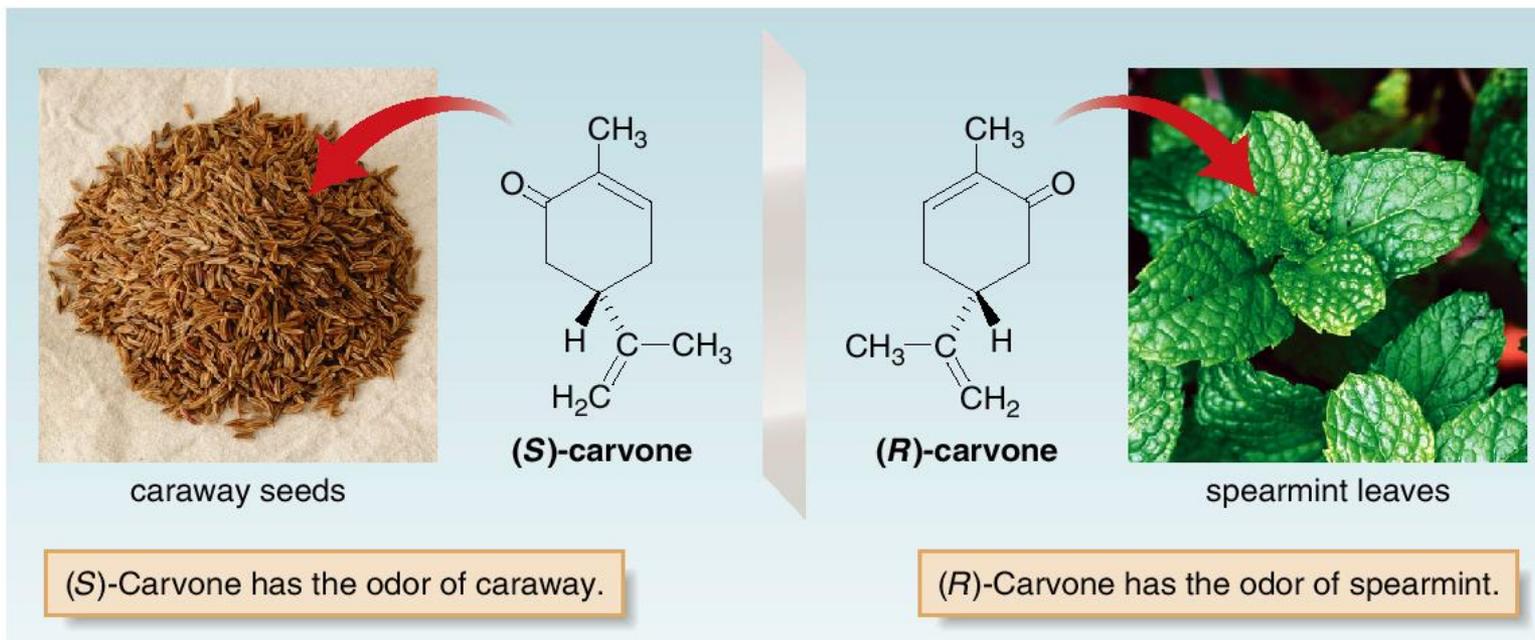
teratogen

Thalidomide



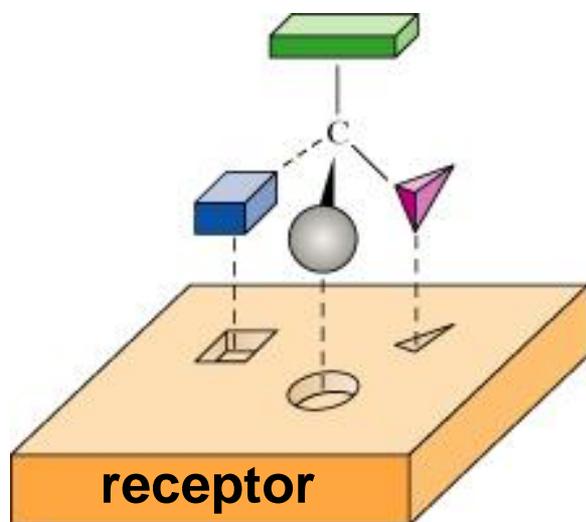
Chemical Properties of Enantiomers

- Research suggests that the odor of a particular molecule is determined more by its shape than by the presence of a particular functional group.
- Because enantiomers interact with chiral smell receptors, some enantiomers have different odors.

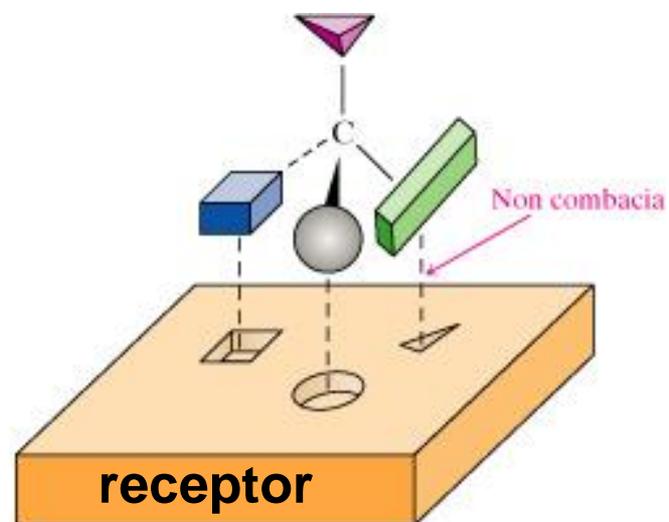


Chiral Recognition

3 point theory:

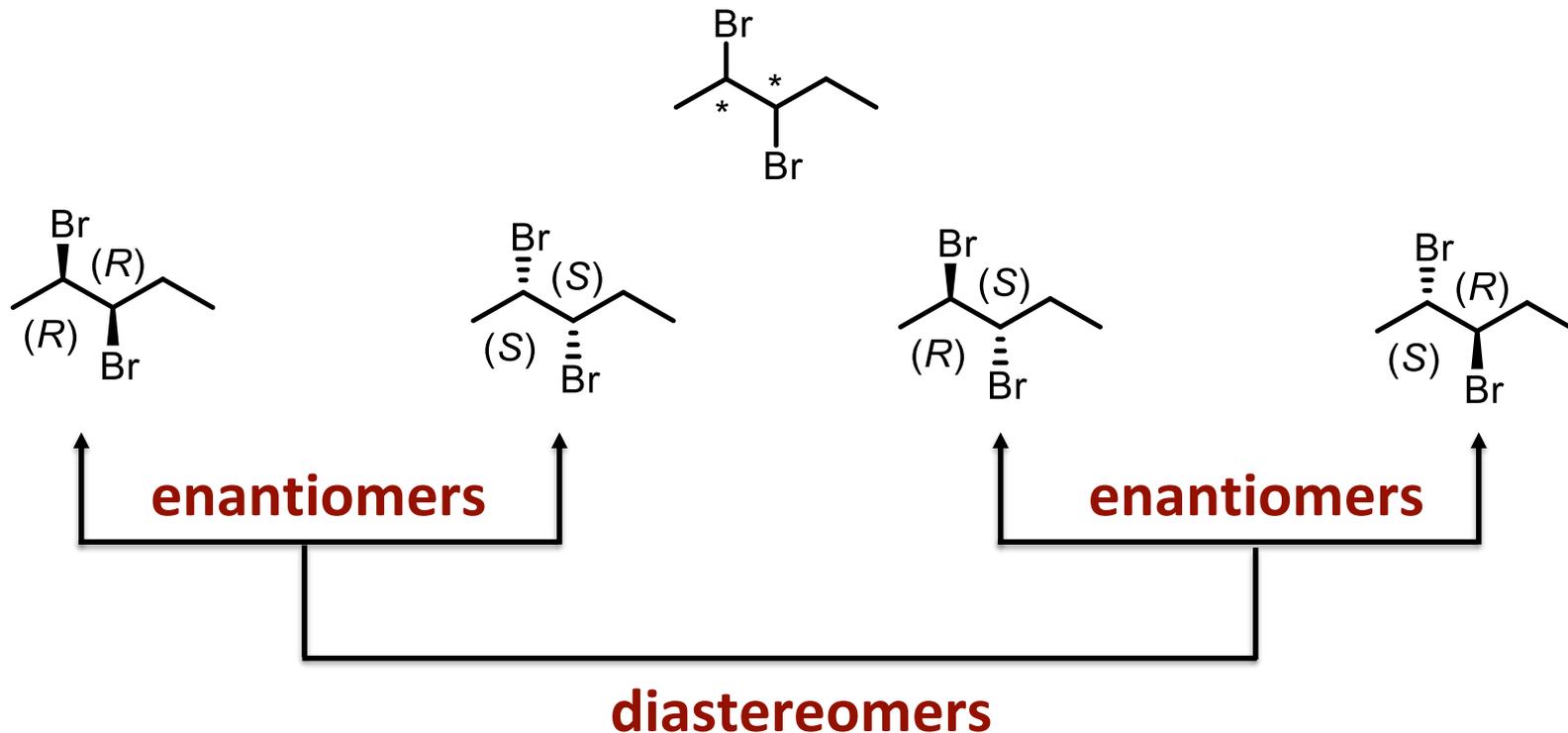


(a)

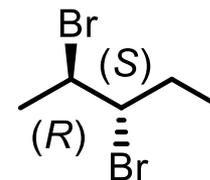
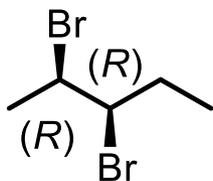


(b)

Diastereomers

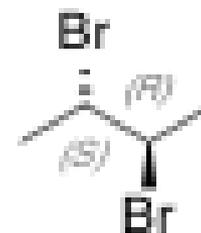
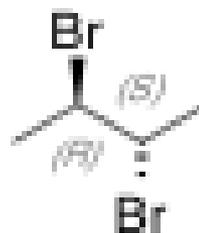
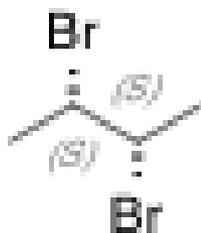
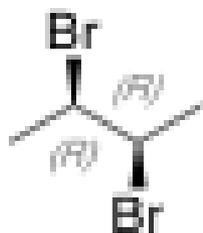
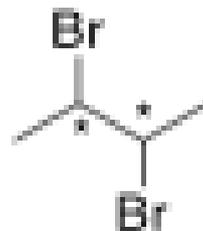


- When a compound has more than one stereogenic center, *R* and *S* configurations must be assigned to each of them.



(2*S*,3*R*)-2,3-dibromopentane

Meso Compounds

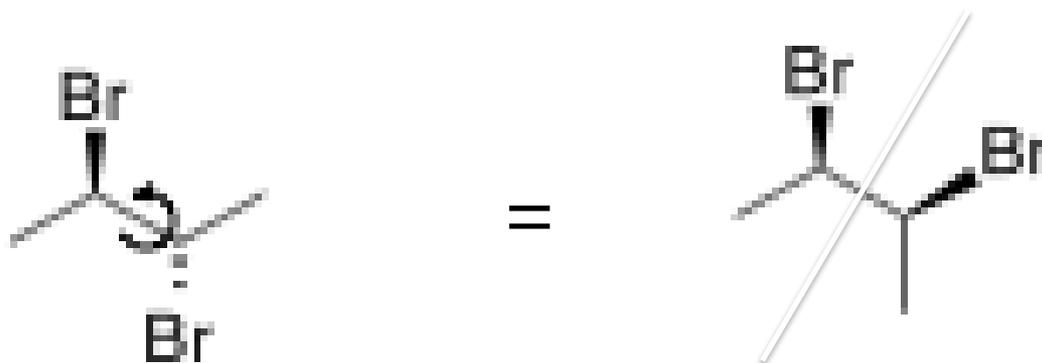


enantiomers

identical

diastereomers

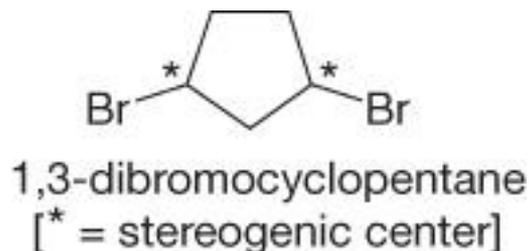
Meso Compounds



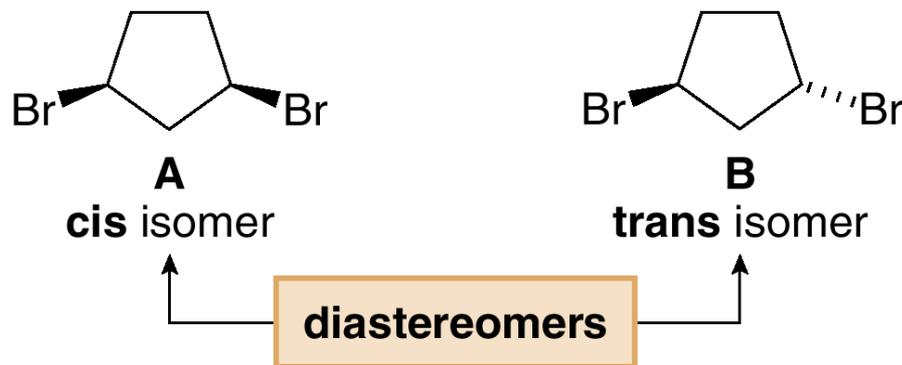
- Meso compounds contain a plane of symmetry, and are **achiral**.

Diastereomers

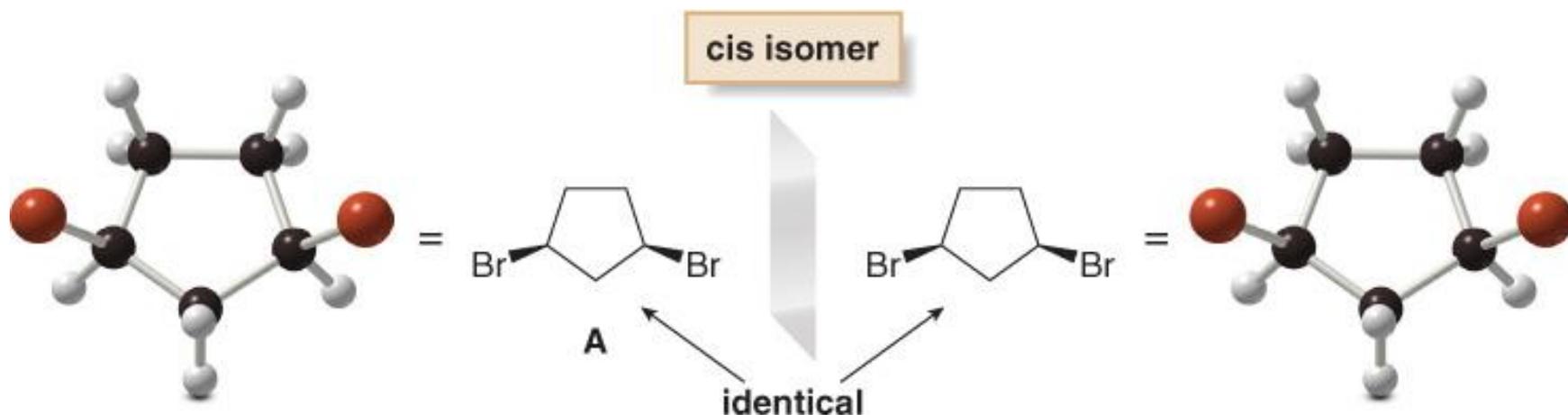
- Consider 1,3-dibromocyclopentane. Since it has two stereogenic centers, it has a maximum of four stereoisomers.



- cis* isomer (A) and *trans* isomer (B) are stereoisomers but not mirror images.

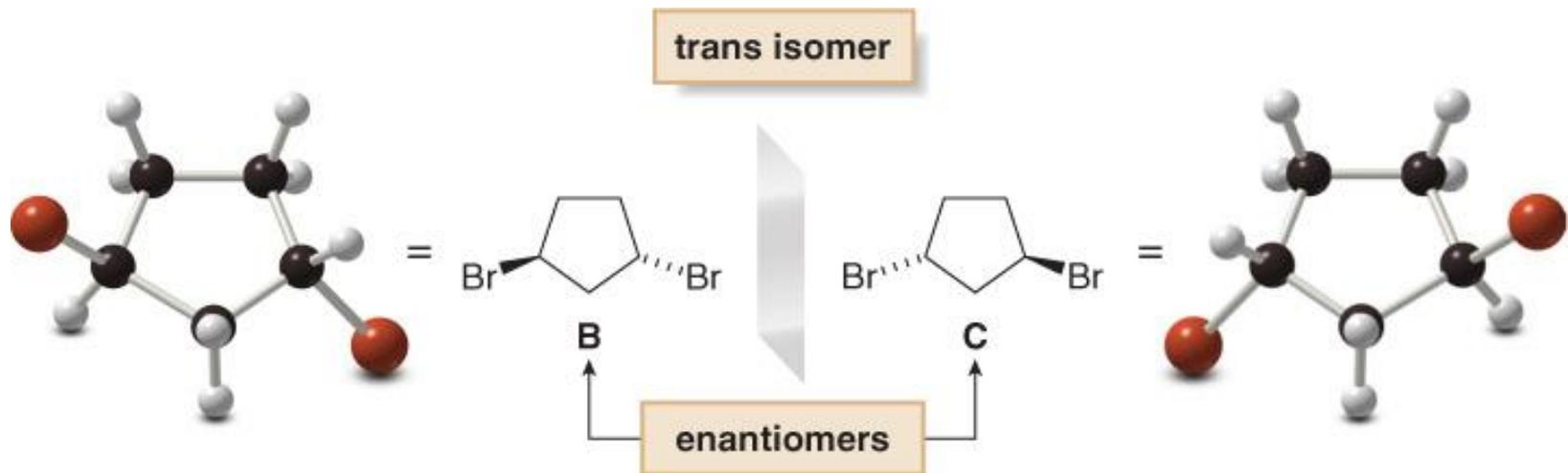


Diastereomers



- The *cis* isomer is superimposable on its mirror image, making the images identical. Thus, A is an achiral meso compound.

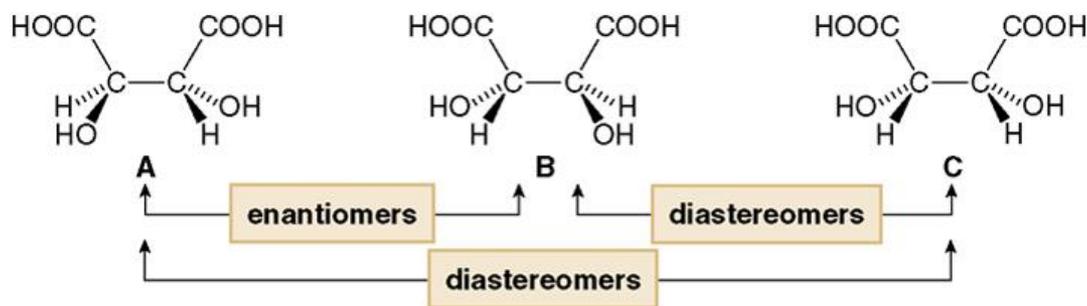
Diastereomers



- The trans isomer is not superimposable on its mirror image, labeled C, making B and C different compounds. B and C are enantiomers.

Diastereomers

- Diastereomers have different physical properties, and therefore can be separated by common physical techniques.

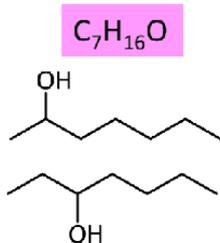


Property	A	B	C	A + B (1:1)
melting point (°C)	171	171	146	206
solubility (g/100 mL H ₂ O)	139	139	125	139
[α]	+13	-13	0	0
<i>R,S</i> designation	<i>R,R</i>	<i>S,S</i>	<i>R,S</i>	—
<i>d,l</i> designation	<i>d</i>	<i>l</i>	none	<i>d,l</i>

- The physical properties of **A** and **B** differ from their diastereomer **C**.
- The physical properties of a racemic mixture of **A** and **B** (last column) can also differ from either enantiomer and diastereomer **C**.
- C** is an achiral meso compound, so it is optically inactive; [α] = 0.

Isomeria

Isomeri
Composti differenti con la stessa formula molecolare

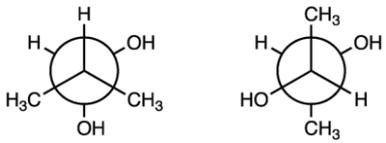
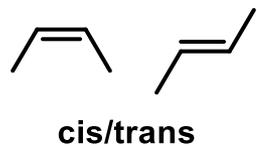
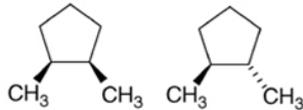
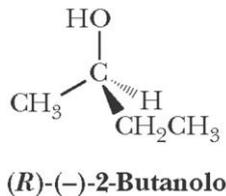
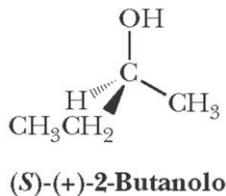
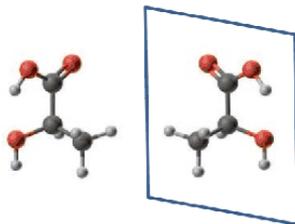


Isomeri costituzionali
Isomeri i cui atomi hanno una diversa connettività

Stereoisomeri
Isomeri i cui atomi hanno la stessa connettività, ma un diverso orientamento nello spazio

Enantiomeri
Stereoisomeri le cui molecole sono **immagini speculari** non sovrapponibili

Diastereoisomeri
Stereoisomeri le cui molecole **non sono immagini speculari**

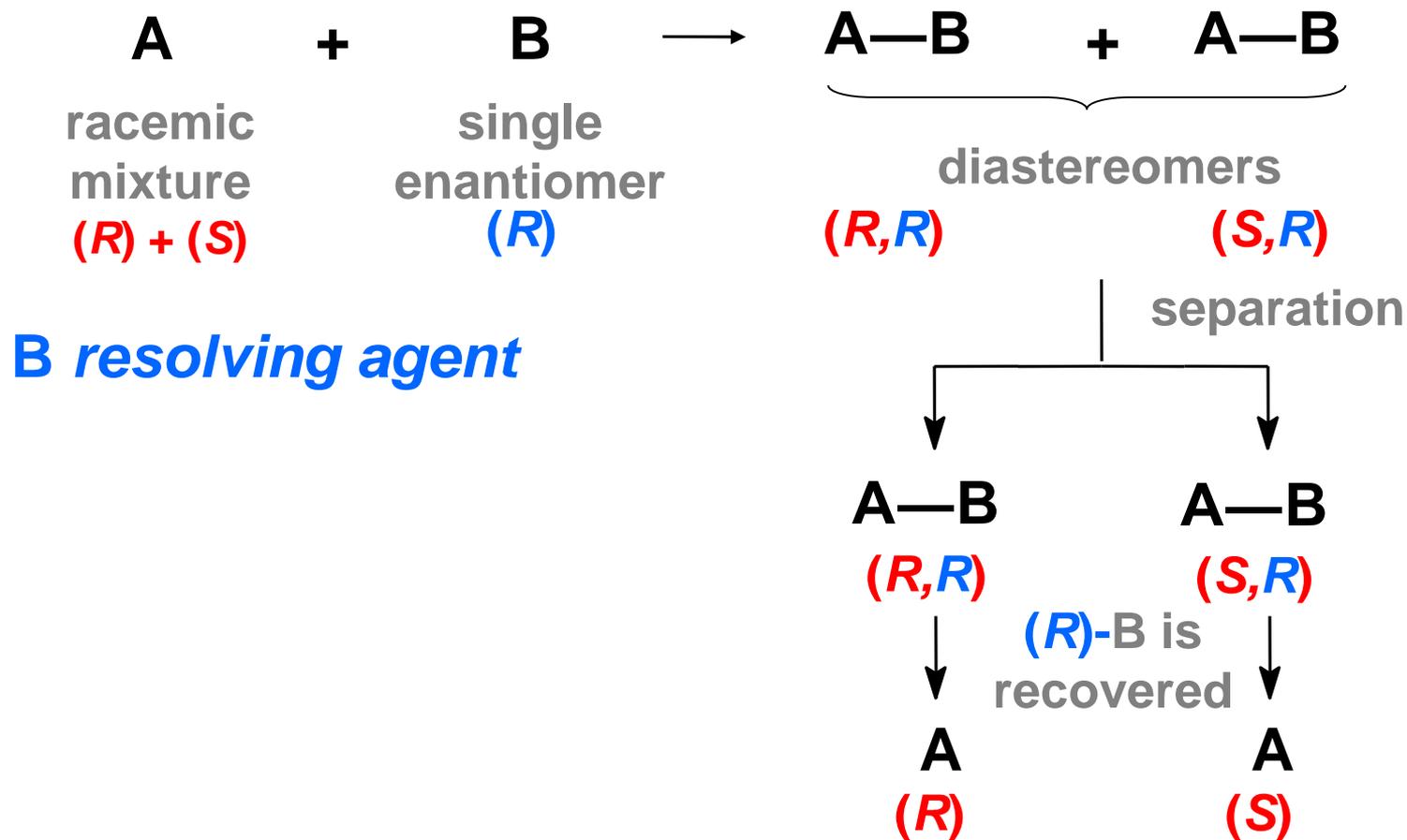


Conformeri
Stereoisomeri che si formano per rotazione attorno a un legame semplice

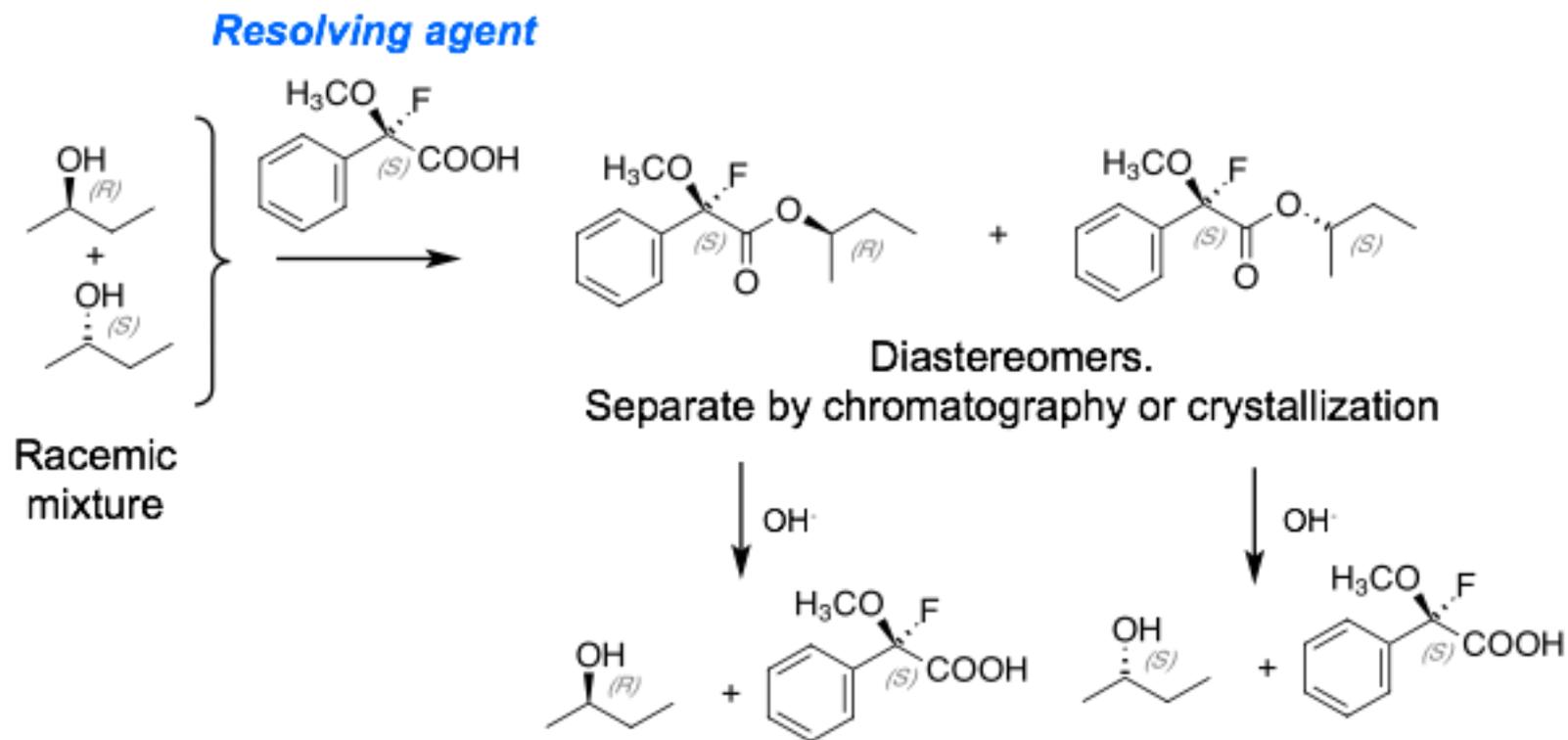
Separation of Enantiomers

- Enantiomers have identical physical properties and can not be separated by conventional physical techniques (distillation, crystallization, etc).
- The separation of enantiomers in a racemic mixture is called **resolution**.

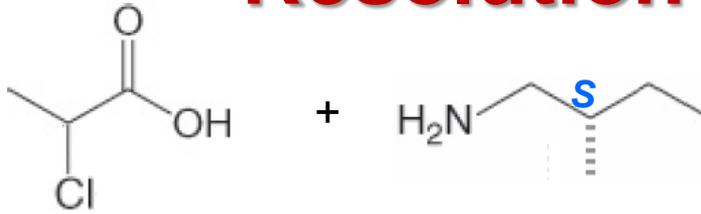
Resolution of Enantiomers



Resolution of Enantiomers

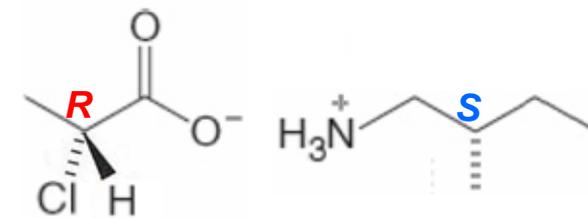


Resolution of Enantiomers



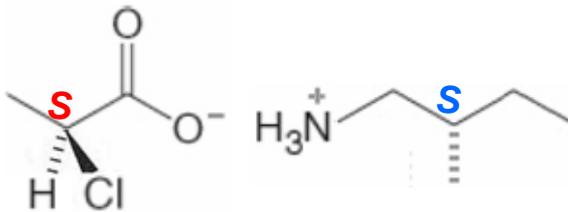
Racemic mixture
(R) + (S)

Resolving agent



(R,S)

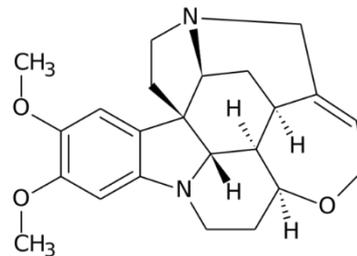
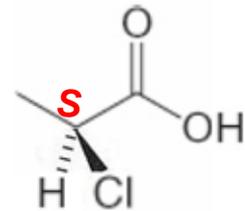
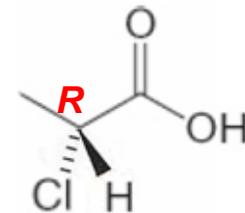
+



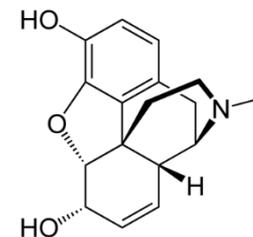
(S,S)

1) Separation of
diastereoisomeric
salts

2) HCl



Brucina (2,3-dimetossistricnina)



morfina