Pharmaceutical Organic Chemistry-1

Chapter-5: Stereoisomerism

Chirality & Stereochemistry

- An object is ***achiral*** (not chiral) if the object and its mirror image are identical

- A ***chiral*** object is one that cannot be superposed on its mirror image

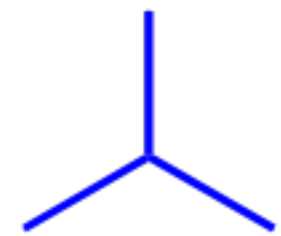
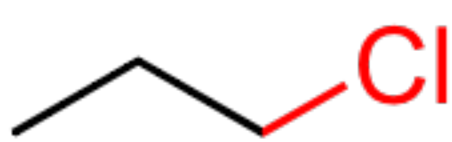
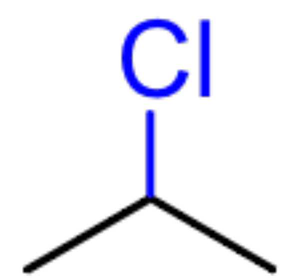
1. Isomerism: Constitutional Isomers & Stereoisomers

1A. Constitutional Isomers

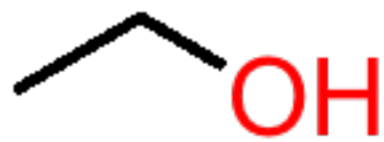
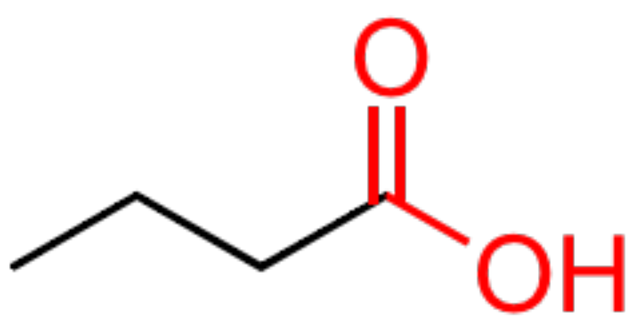
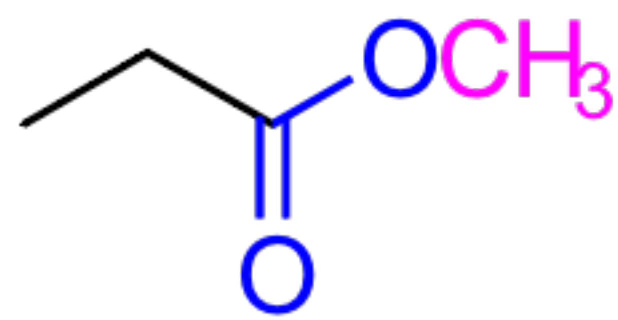
❖ **Isomers**: different compounds that have the same molecular formula

- **Constitutional isomers**: isomers that have the same molecular formula but different connectivity –their atoms are connected in a different order

❖ Examples

Molecular Formula	Constitutional Isomers		
C_4H_{10}	 Butane	and	 2-Methylpropane
C_3H_7Cl	 1-Chloropropane	and	 2-Chloropropane

❖ Examples

Molecular Formula	Constitutional Isomers		
C_2H_6O	 Ethanol	and	$CH_3{-}O{-}CH_3$ Methoxymethane
$C_4H_8O_2$	 Butanoic acid	and	 Methyl propanoate

1B. Stereoisomers

- Stereoisomers are **NOT** constitutional isomers

- **Stereoisomers** have their atoms connected in the same sequence but they differ in the arrangement of their atoms in space. The consideration of such spatial aspects of molecular structure is called ***stereochemistry***

1C. Enantiomers & Diastereomers

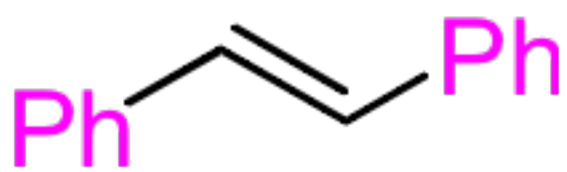
- Stereoisomers can be subdivided into two general categories: *enantiomers* & *diasteromers*
  - **Enantiomers** – stereoisomers whose molecules are nonsuperposable mirror images of each other
  - **Diastereomers** – stereoisomers whose molecules are not mirror images of each other

- Geometrical isomers (*cis* & *trans* isomers) are:
  - *Diastereomers*

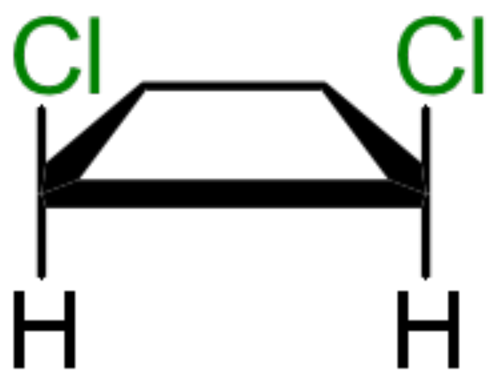
e.g.

(*cis*)

and

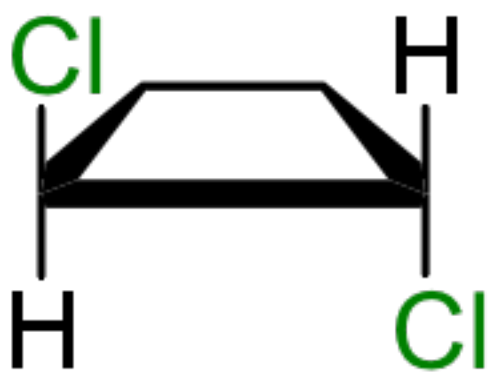


(*trans*)



(*cis*)

and



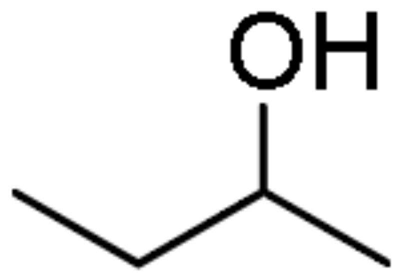
(*trans*)

Subdivision of Isomers

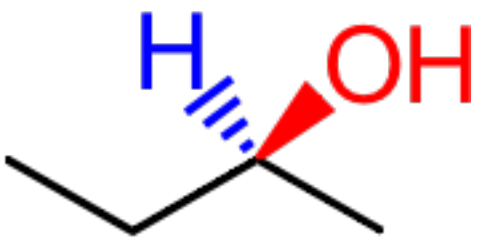
- **Isomers**
  (different compounds with same molecular formula)
  - **Constitutional Isomers**
    (isomers whose atoms have a different connectivity)
  - **Stereoisomers**
    (isomers that have the same connectivity but differ in spatial arrangement of their atoms)
    - **Enantiomers**
      (stereoisomers that are nonsuperposable mirror images of each other)
    - **Diastereomers**
      (stereoisomers that are NOT mirror images of each other)

2. Enantiomers and Chiral Molecules

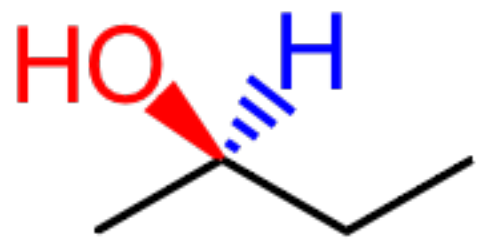
- Enantiomers occur only with compounds whose molecules are **chiral**
- A chiral molecule is one that is **NOT** superposable on its mirror image
- The relationship between a chiral molecule and its mirror image is one that is ***enantiomeric***. A chiral molecule and its mirror image are said to be enantiomers of each other



(2-Butanol)

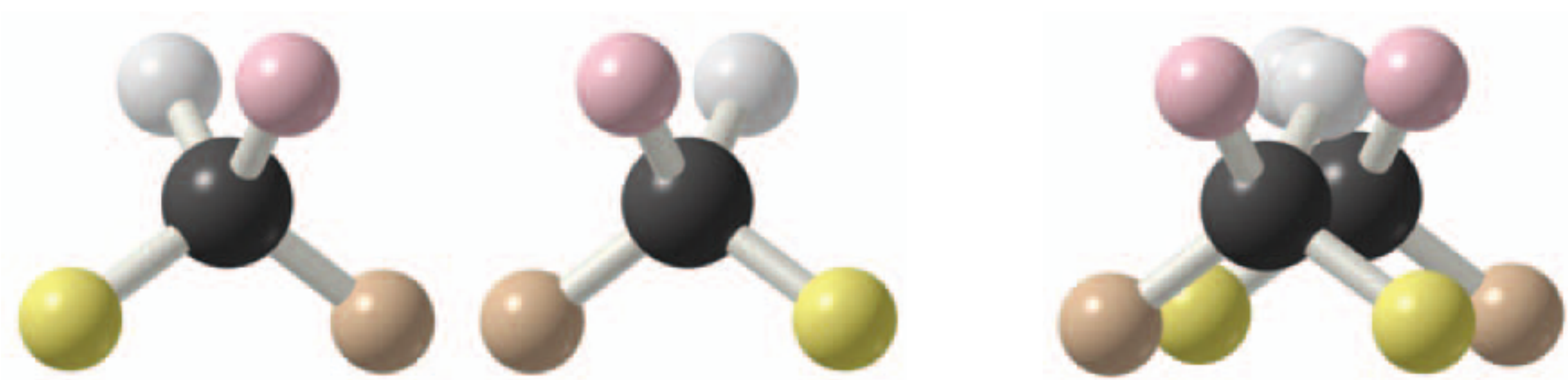


(I)



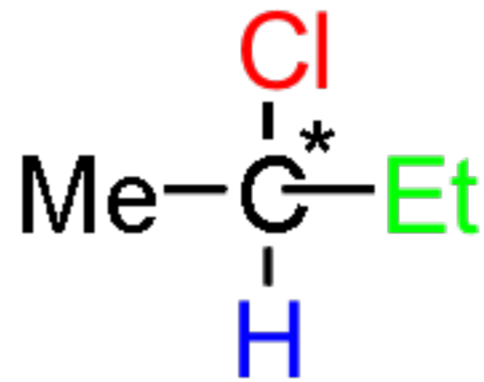
(II)

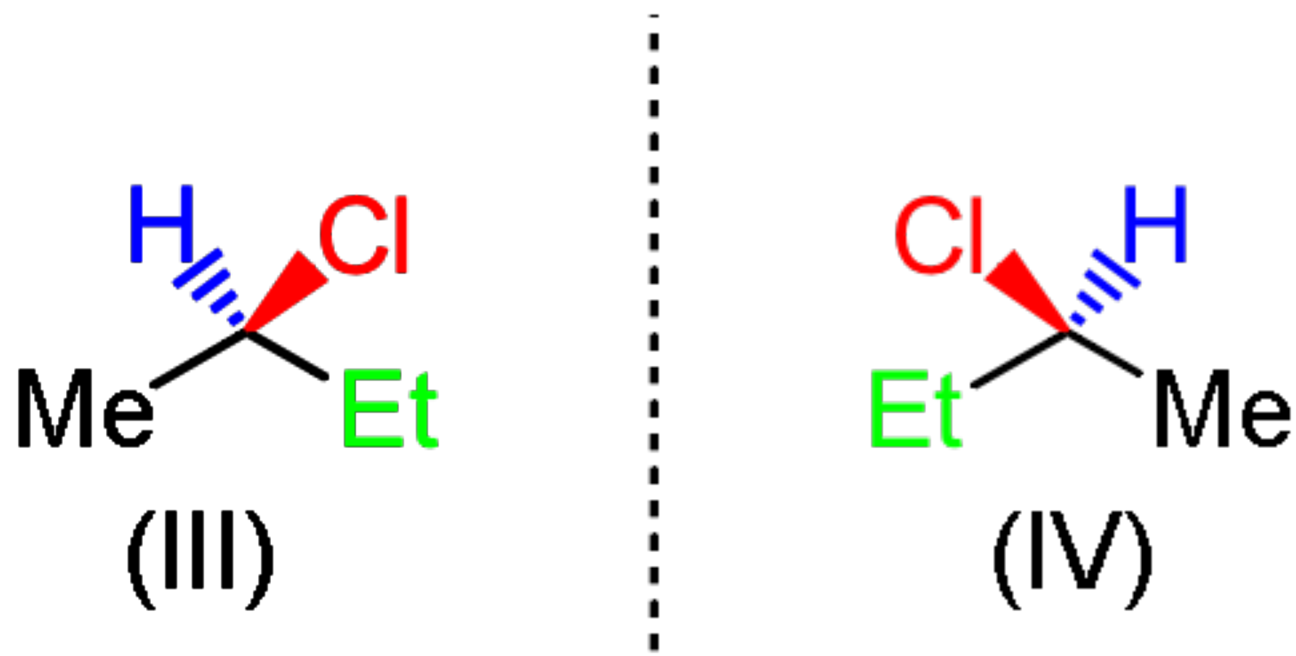
(I) and (II) are nonsuperposable mirror images of each other



3. A Single Chirality Center Causes a Molecule to Be Chiral

- The most common type of chiral compounds that we encounter are molecules that contain a carbon atom bonded to *four different groups*. Such a carbon atom is called an *asymmetric carbon* or a ***chiral center*** and is usually designated with an asterisk (*)

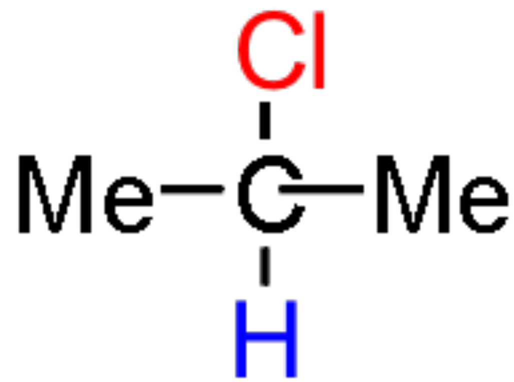


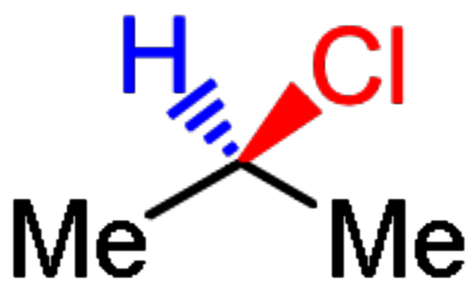


(III) (IV)

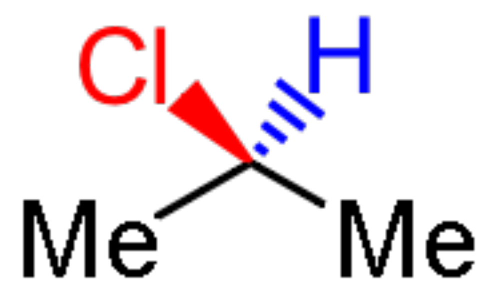
mirror

(III) and (IV) are nonsuperposable mirror images of each other





(V)



(VI)

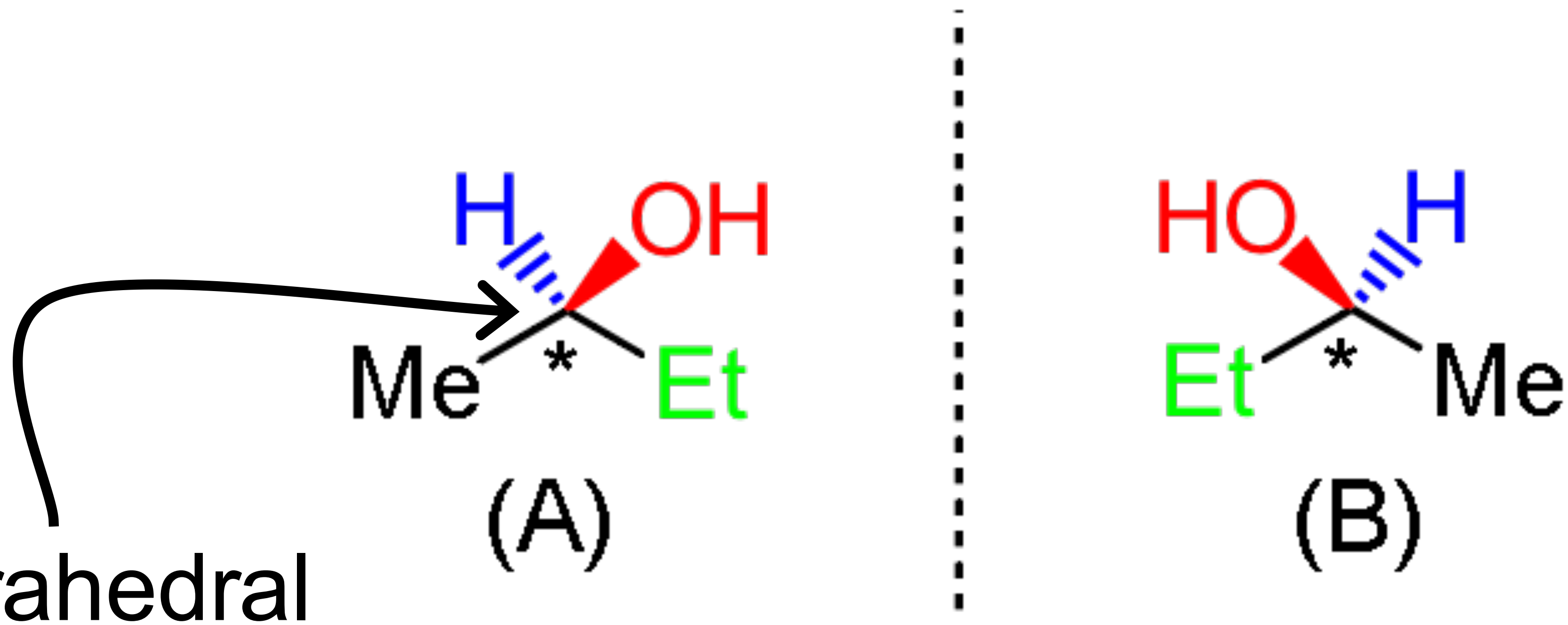
mirror

(V) and (VI) are superposable

⇒ not enantiomers ⇒ **achiral**

3A. Tetrahedral vs. Trigonal Stereogenic Centers

- Chirality centers are ***tetrahedral stereogenic*** centers



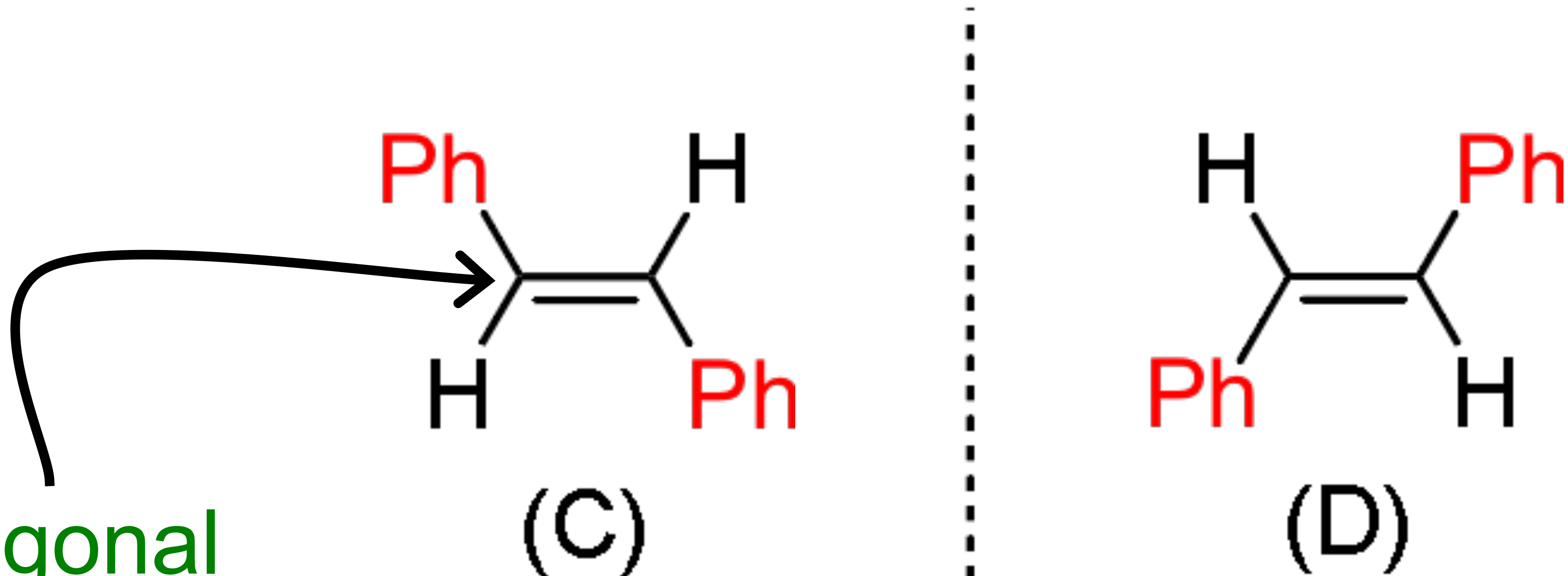
(A) (B)

Tetrahedral stereogenic center
⇒ chiral

mirror

(A) & (B) are enantiomers

- *Cis* and *trans* alkene isomers contain trigonal stereogenic centers



(C) (D)

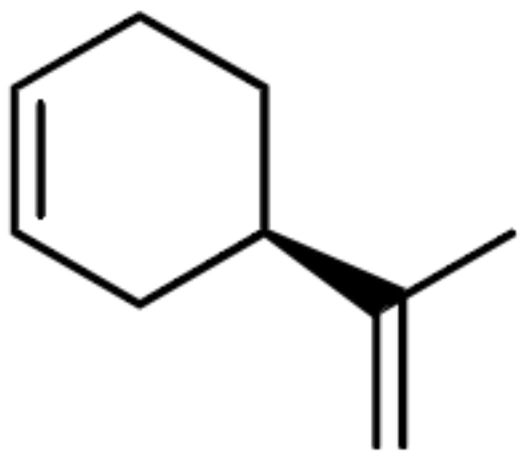
mirror

Trigonal stereogenic center

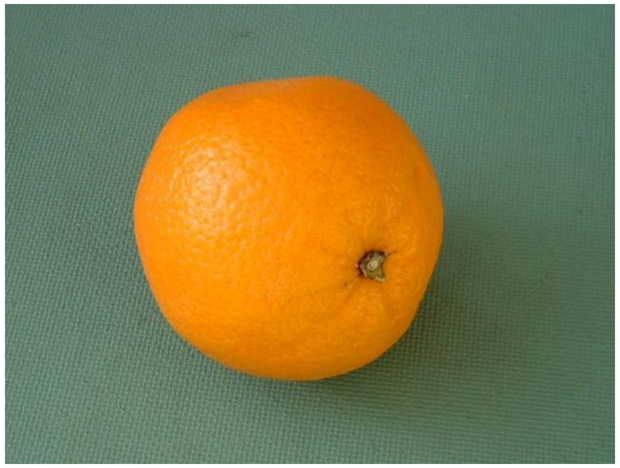
⇒ achiral

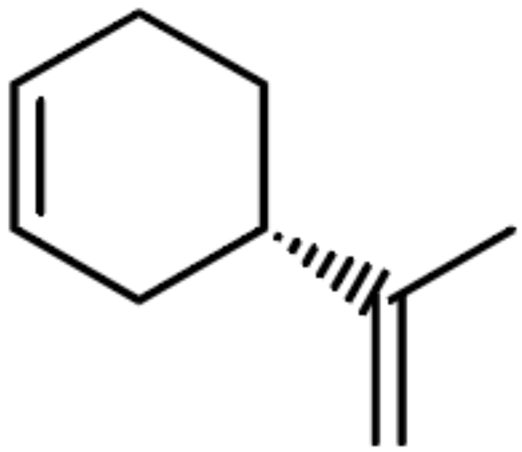
(C) & (D) are identical

4. More about the Biological Importance of Chirality



(+)-Limonene
(limonene enantiomer found in oranges)





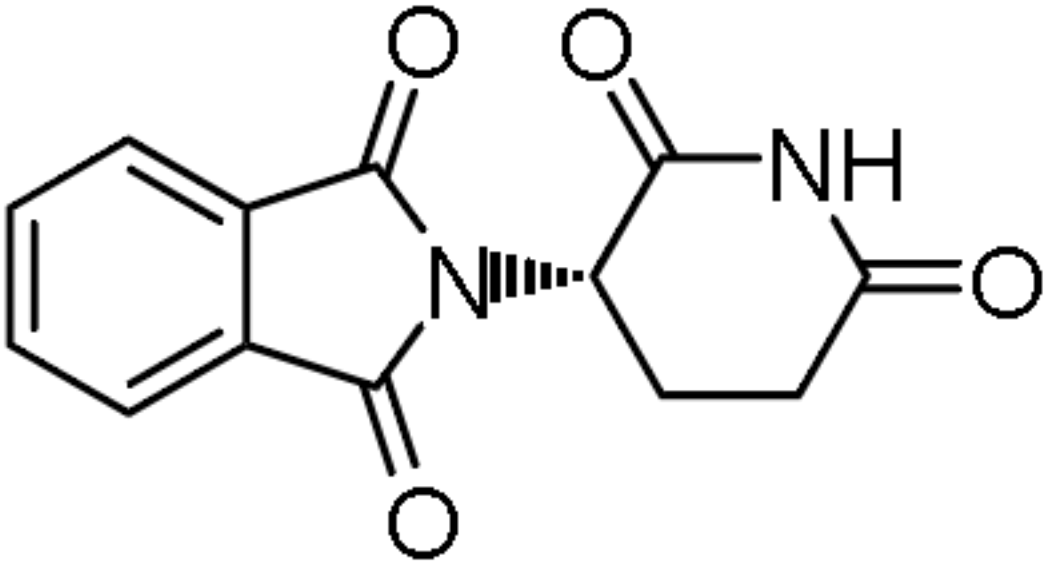
(-)-Limonene
(limonene enantiomer found in lemons)

Thalidomide

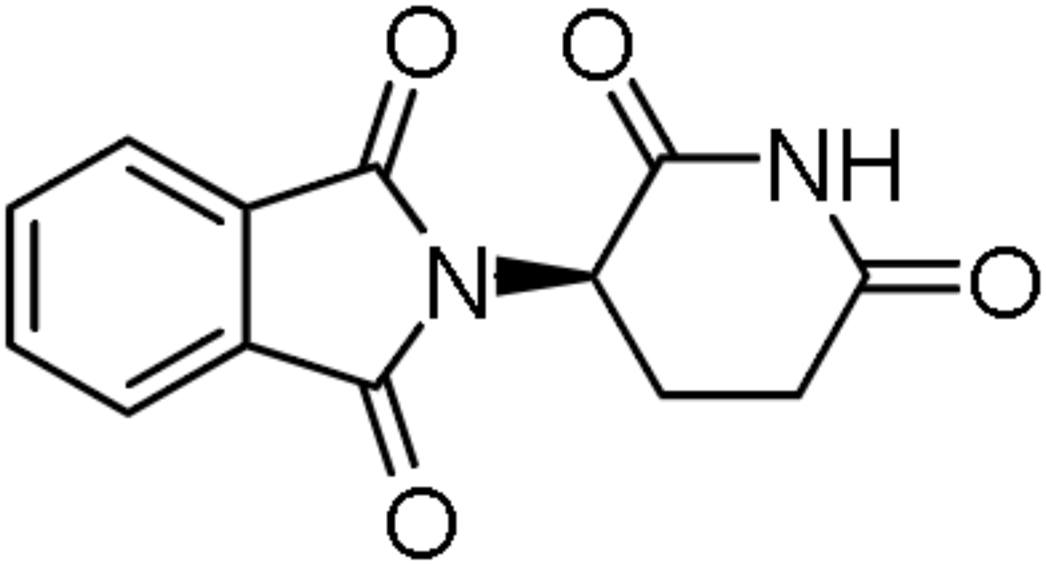
- The activity of drugs containing chirality centers can vary between enantiomers, sometimes with serious or even tragic consequences

- For several years before 1963 thalidomide was used to alleviate the symptoms of morning sickness in pregnant women

- In 1963 it was discovered that thalidomide (sold as a mixture of both enantiomers) was the cause of horrible birth defects in many children born subsequent to the use of the drug



Thalidomide
(cures morning sickness)

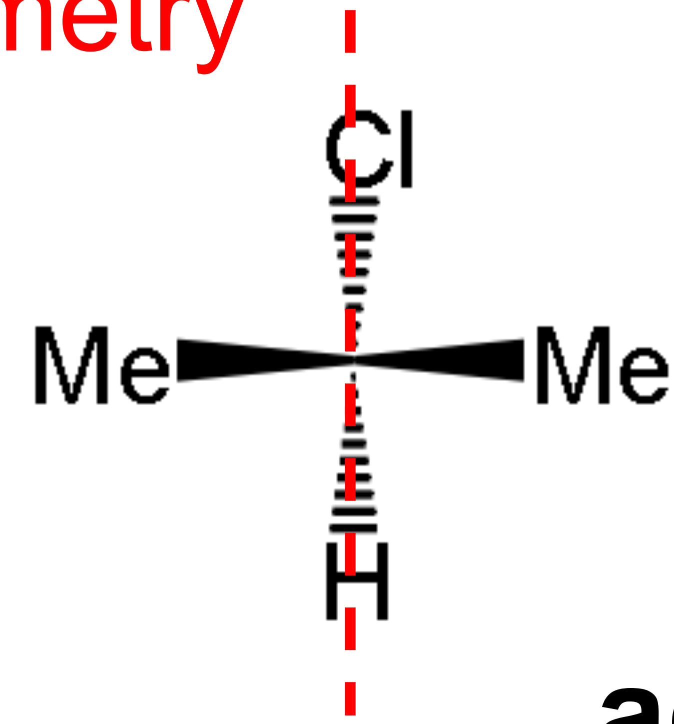


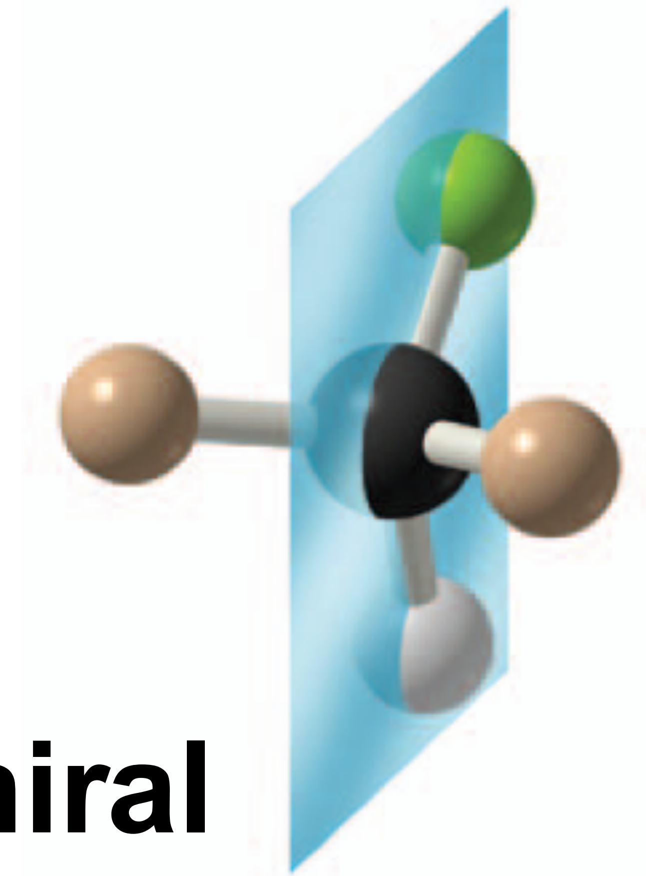
enantiomer of Thalidomide
(causes birth defects)

5. How to Test for Chirality: Planes of Symmetry

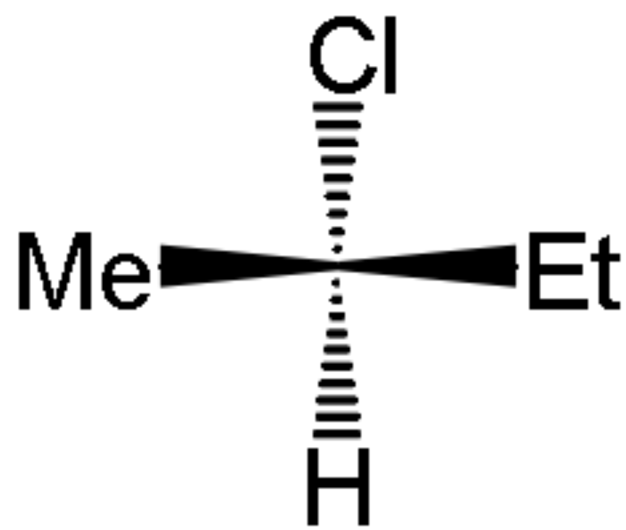
- A molecule will not be chiral if it possesses a plane of symmetry
- A plane of symmetry (mirror plane) is an imaginary plane that bisects a molecule such that the two halves of the molecule are mirror images of each other
- All molecules with a plane of symmetry in their most symmetric conformation are ***achiral***

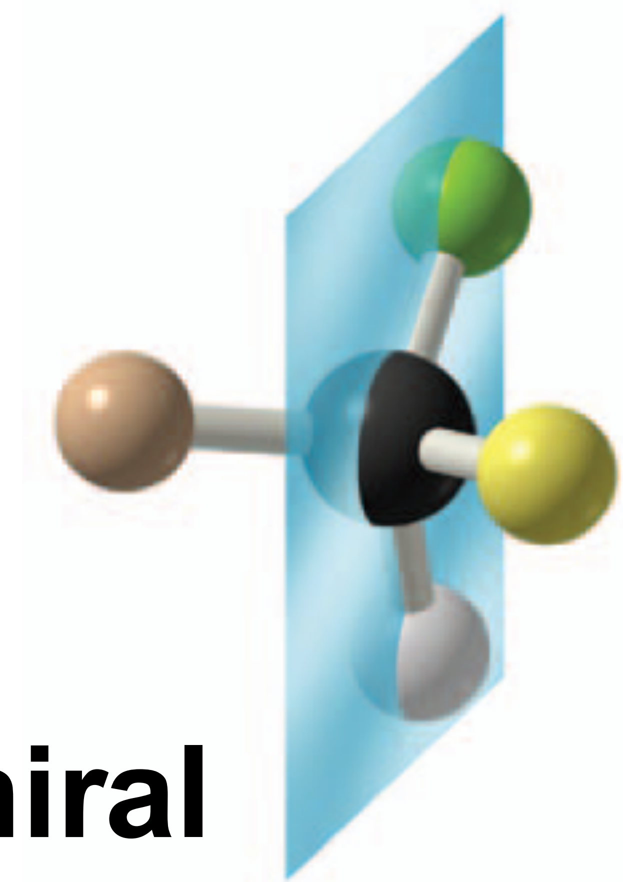
Plane of symmetry





achiral



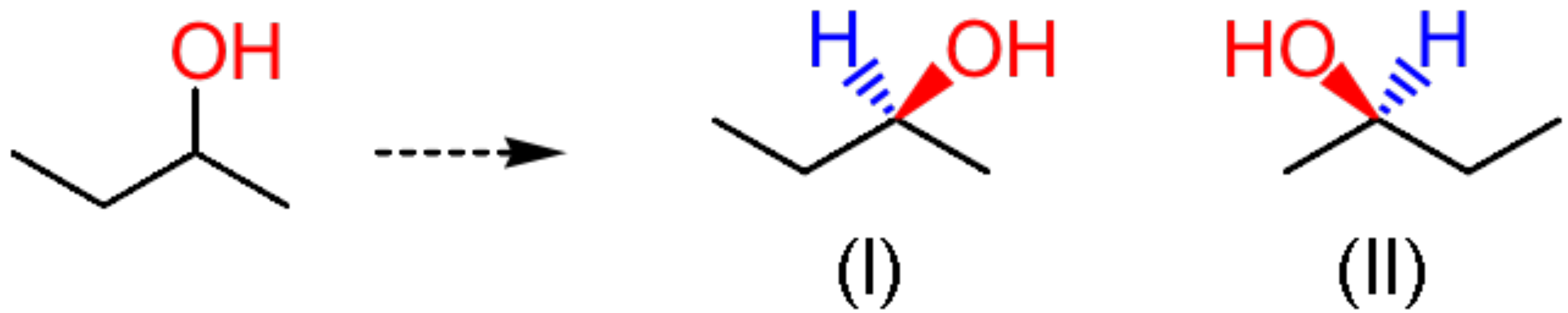


No plane of symmetry

chiral

6. Naming Enantiomers: *R*,*S*-System

Recall:



- Using only the IUPAC naming that we have learned so far, these two enantiomers will have the same name:
  - **2-Butanol**
- This is undesirable because each compound must have its own distinct name

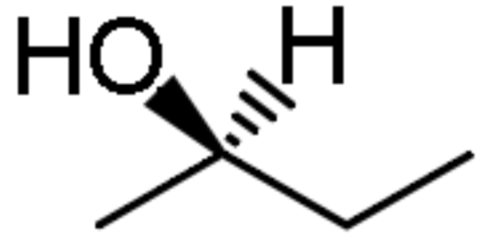
6A. How to Assign (R) and (S) Configurations

- Rule 1
  - Assign priorities to the four different groups on the stereocenter from highest to lowest (priority bases on atomic number, the higher the atomic number, the higher the priority)

- Rule 2
  - When a priority cannot be assigned on the basis of the atomic number of the atoms that are directly attached to the chirality center, then the next set of atoms in the unassigned groups is examined. This process is continued until a decision can be made.

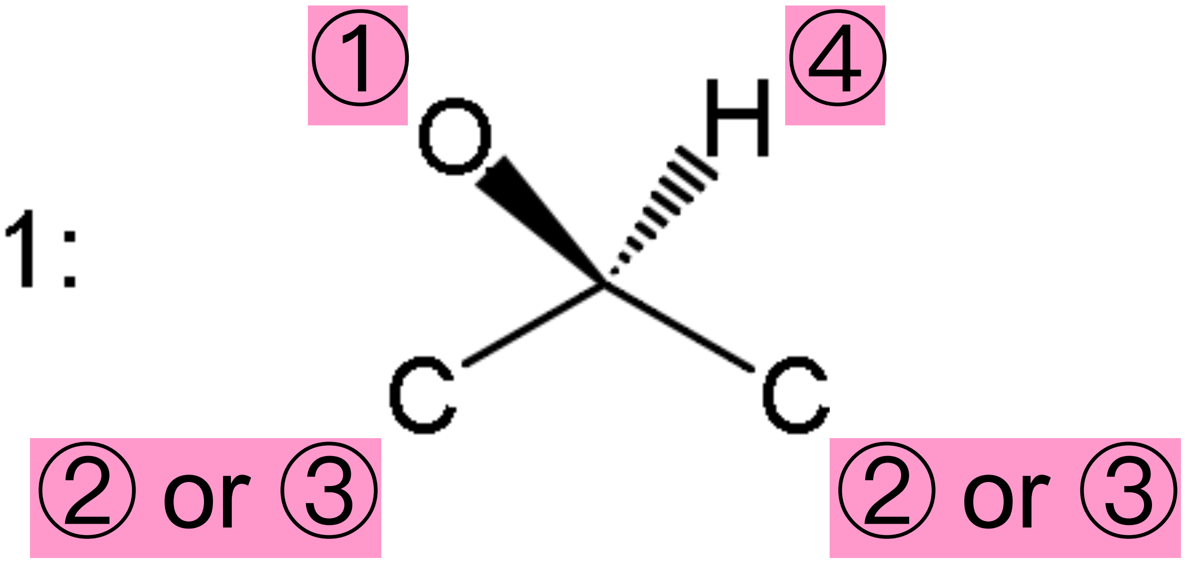
- Rule 3
  - Visualize the molecule so that the lowest priority group is directed away from you, then trace a path from highest to lowest priority. If the path is a clockwise motion, then the configuration at the asymmetric carbon is (*R*). If the path is a counter-clockwise motion, then the configuration is (*S*)

❖ Example

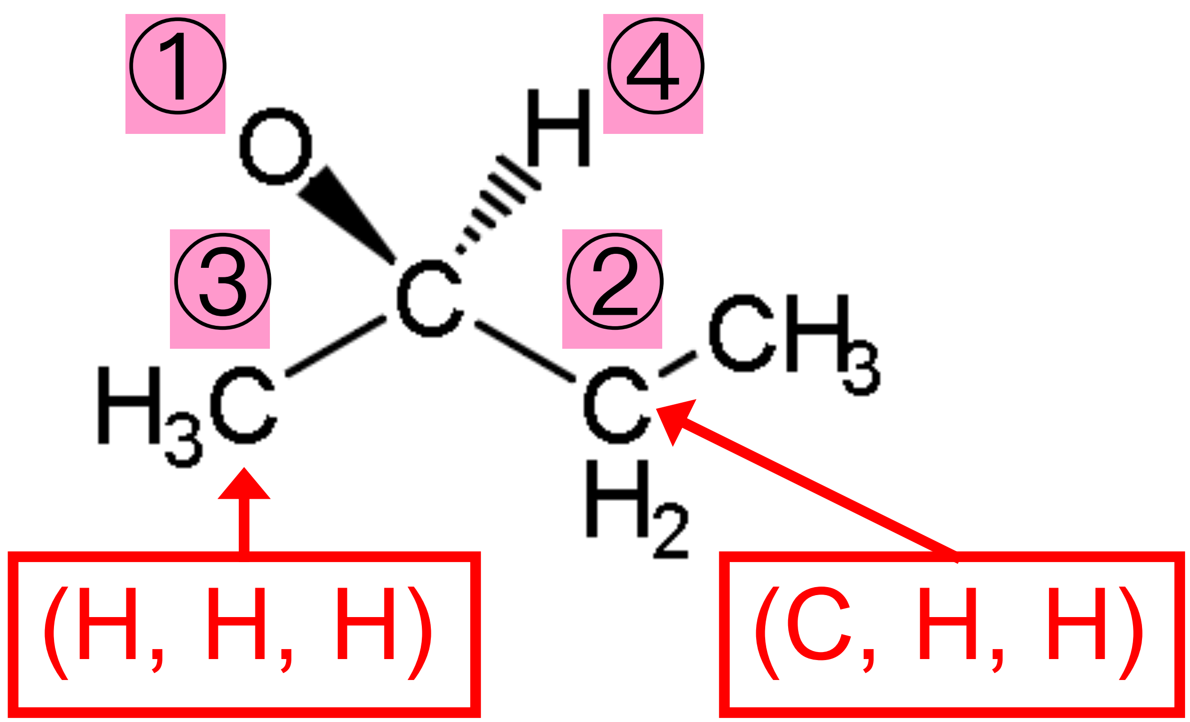


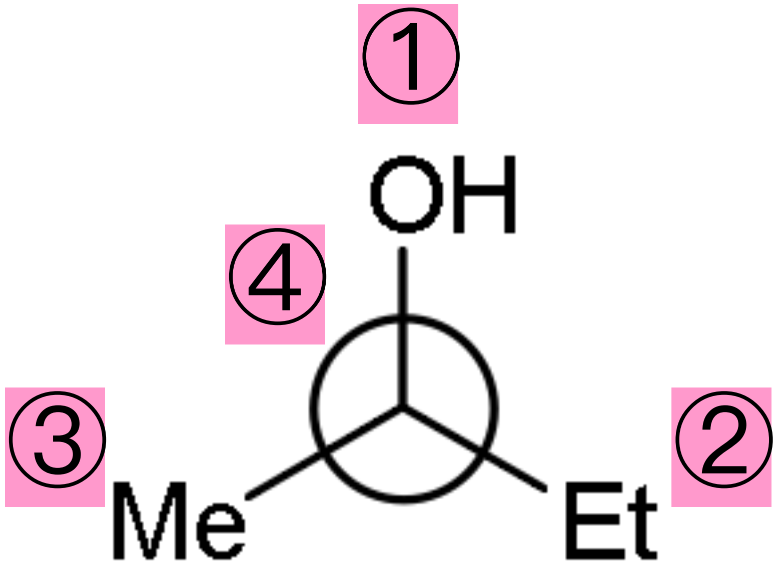
(2-Butanol)

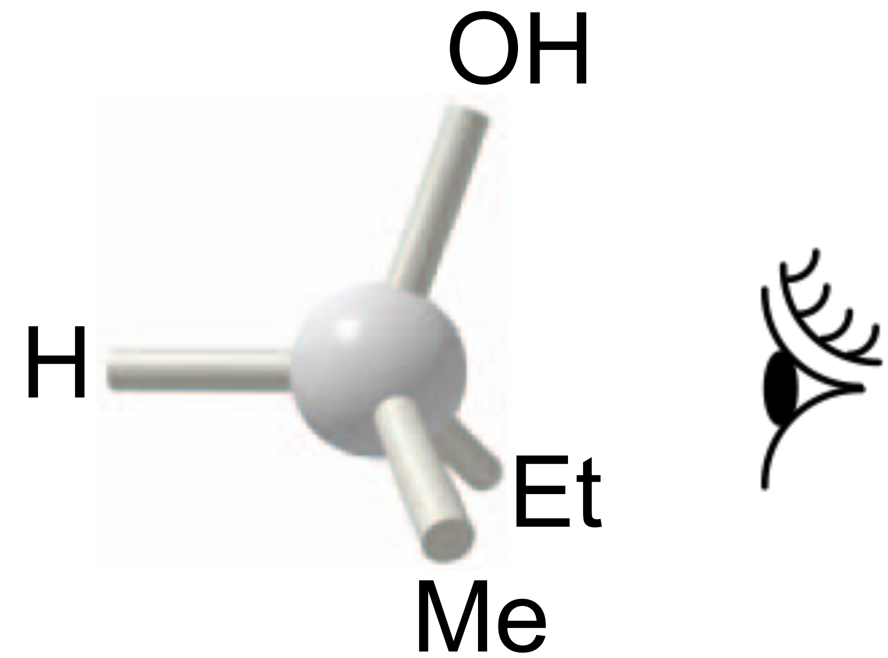
Step 1:

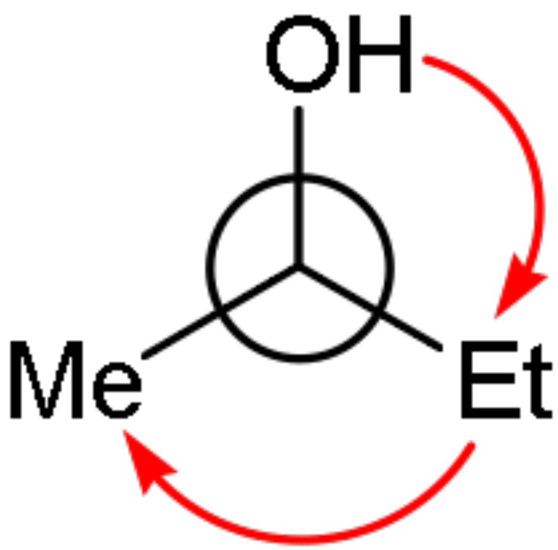


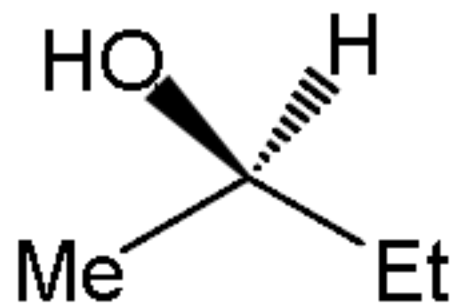
Step 2:











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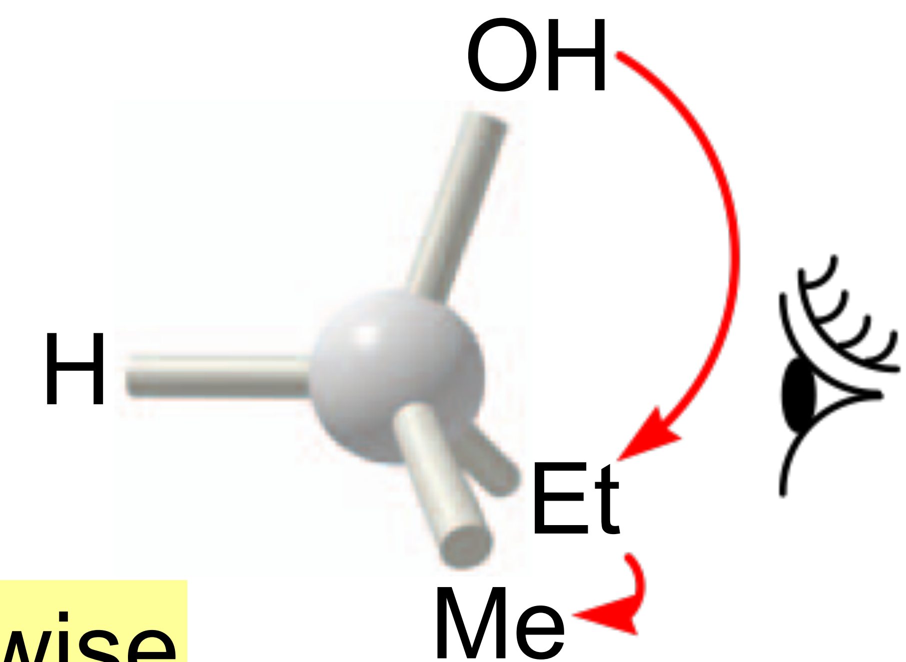
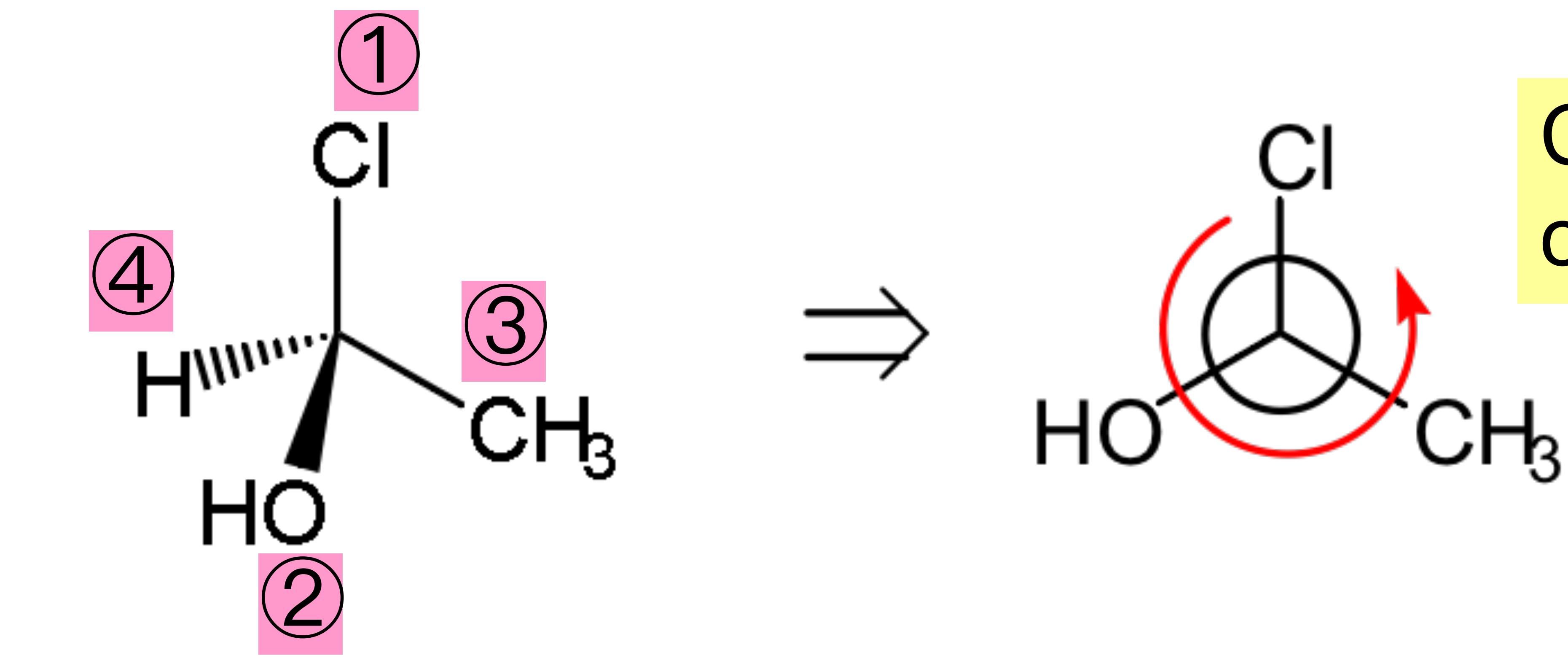


Arrows are clockwise

(*R*)-2-Butanol

❈ Other examples

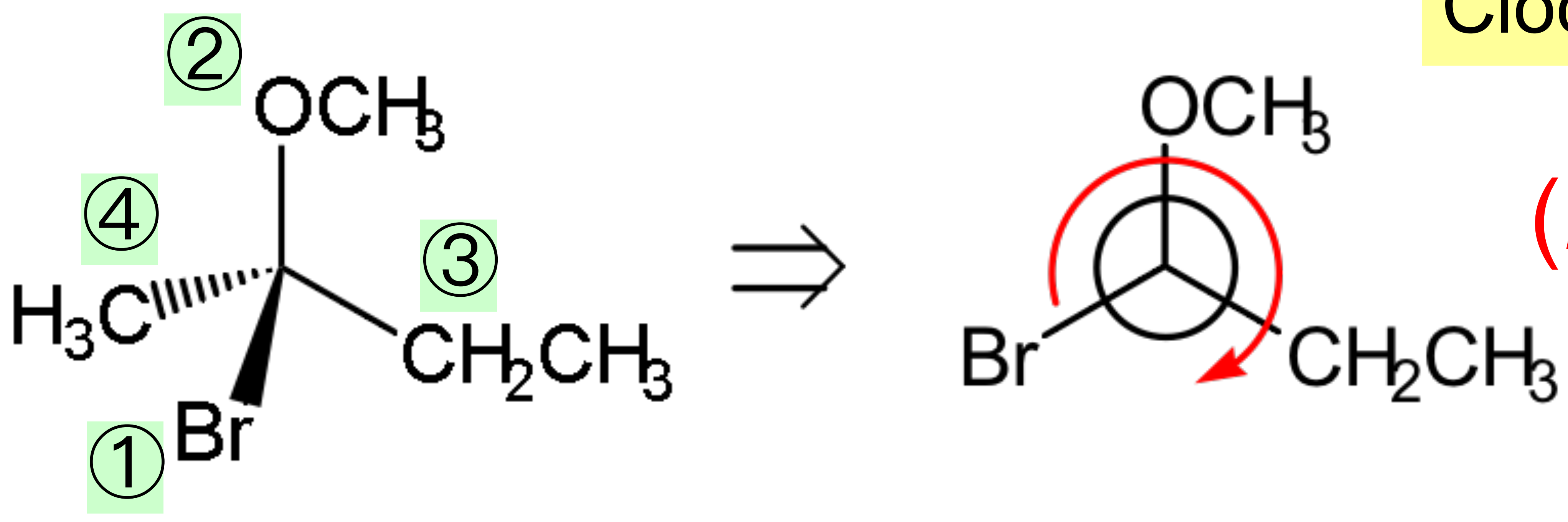


Counter-clockwise

(*S*)

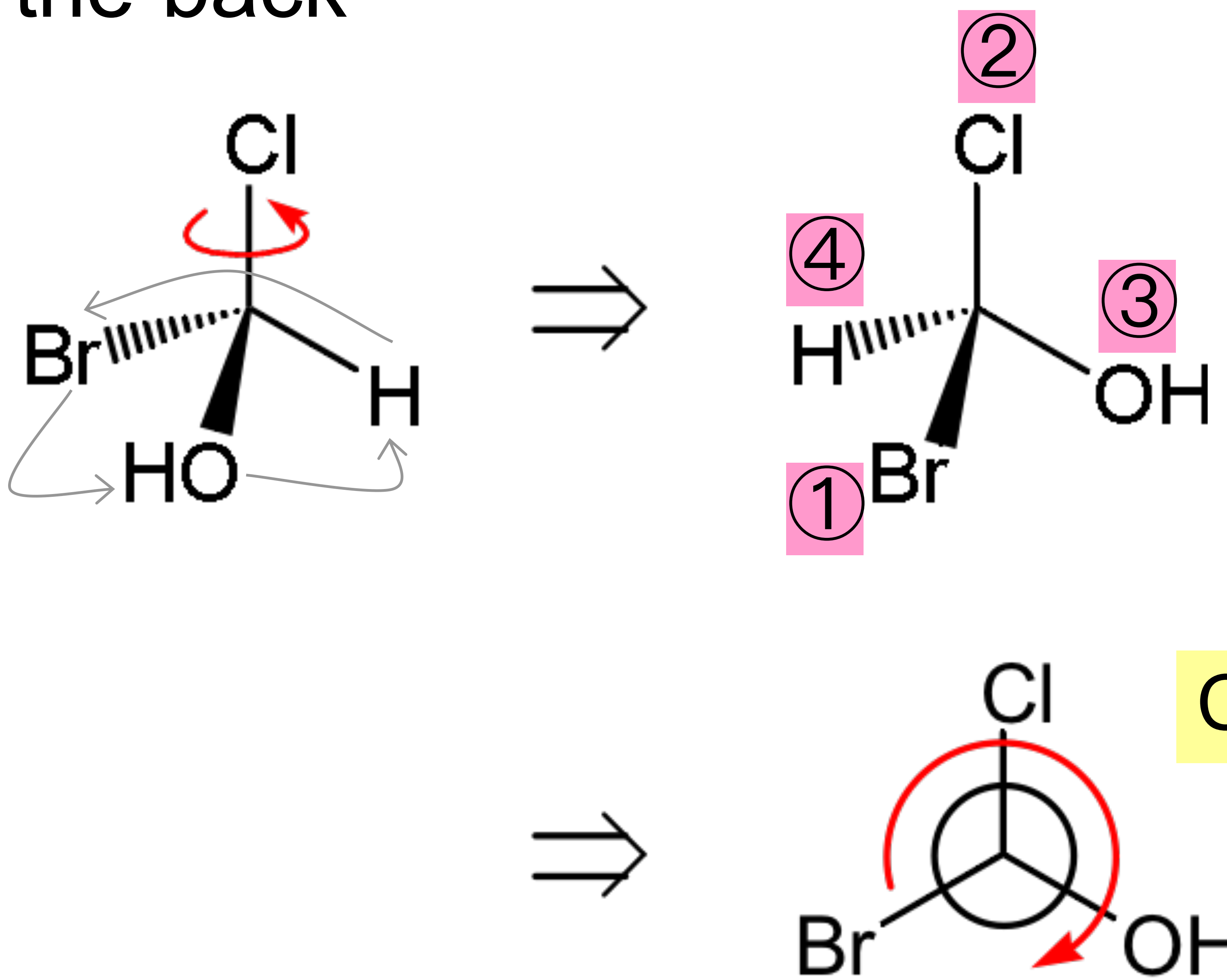
Clockwise

(*R*)



❈ Other examples

- Rotate C–Cl bond such that H is pointed to the back

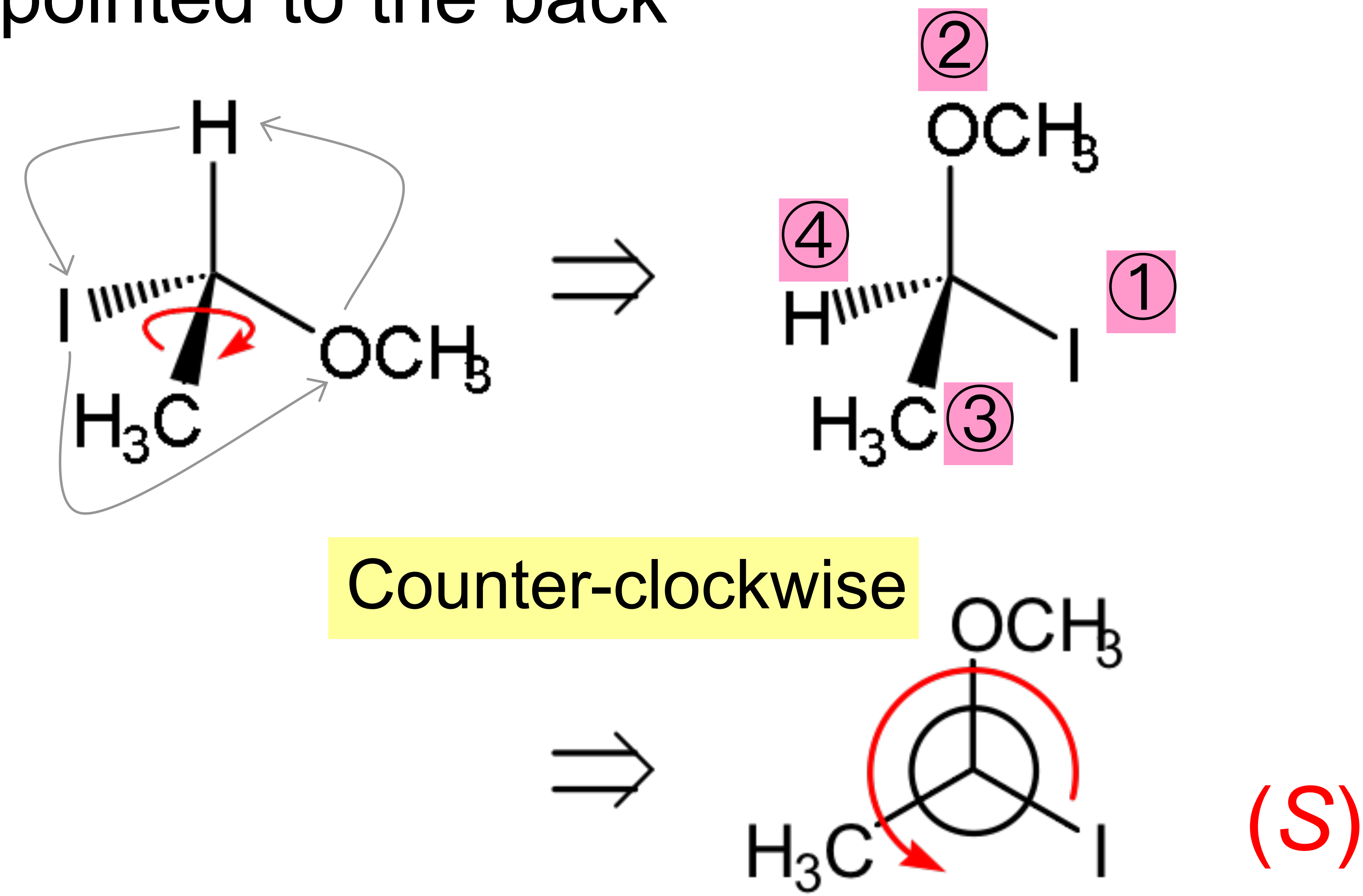


Clockwise

(*R*)

Other examples

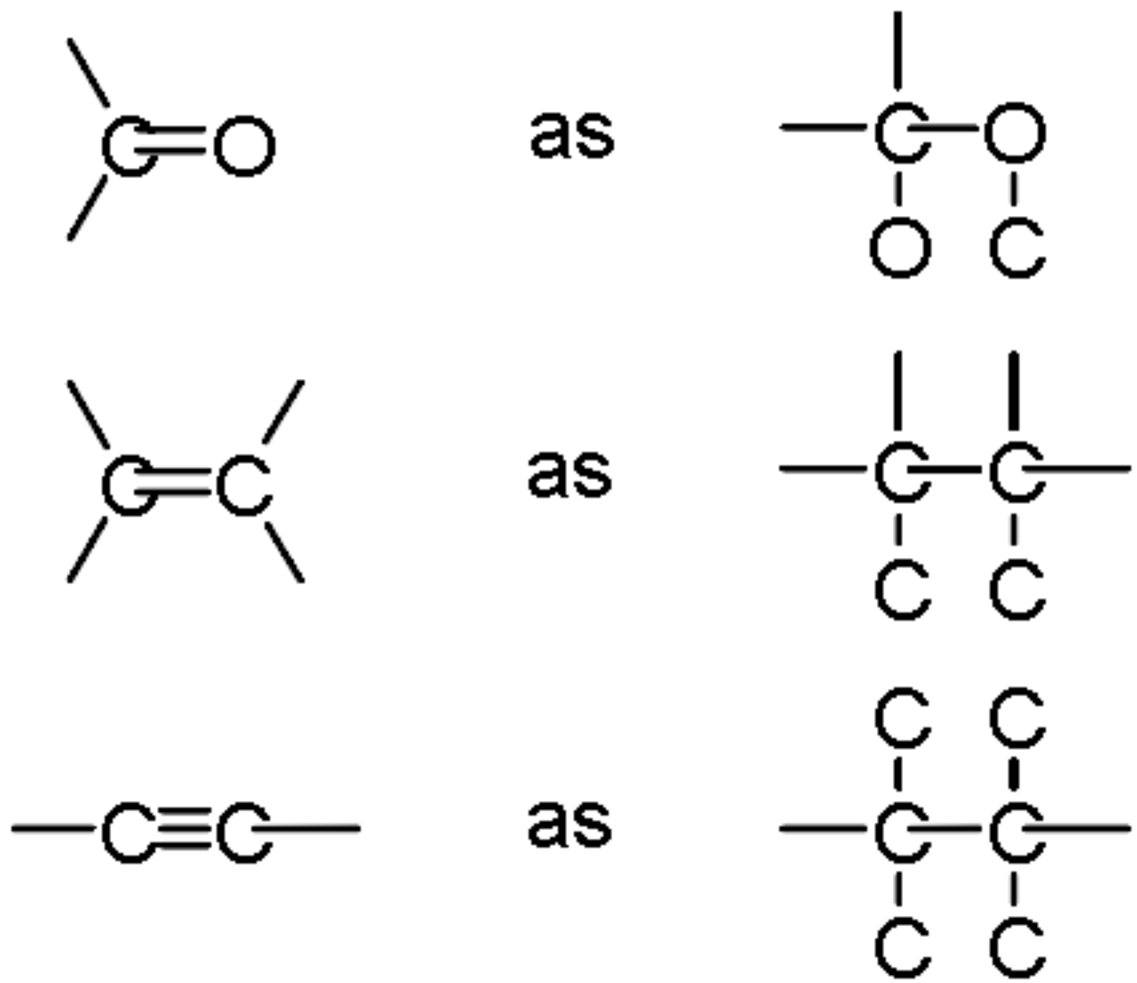
- Rotate C–CH_3 bond such that H is pointed to the back



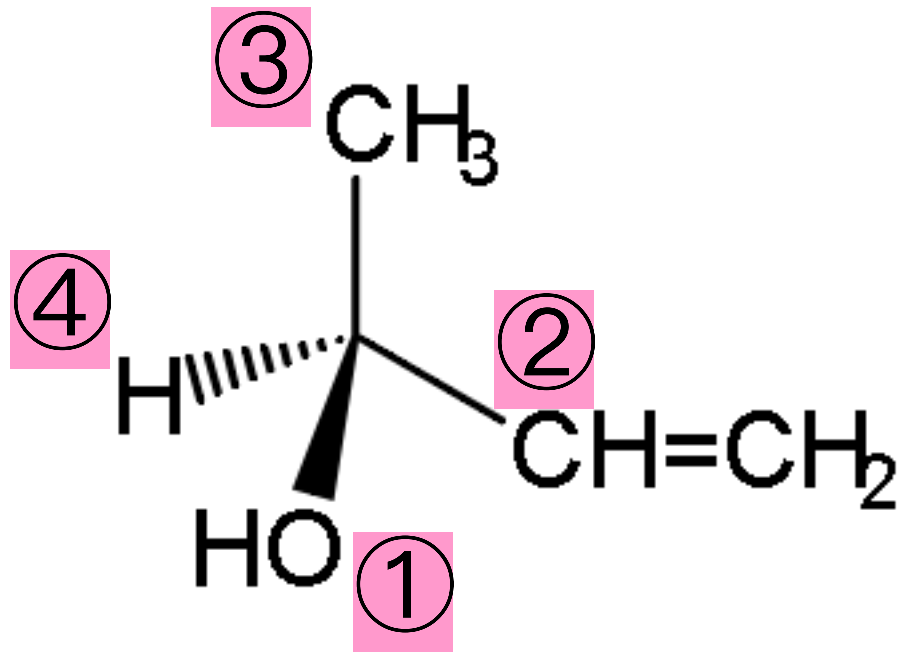
Rule 4

- For groups containing double or triple bonds, assign priorities as if both atoms were duplicated or triplicated

e.g.



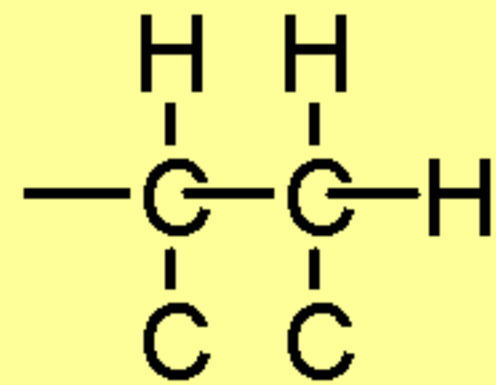
❖ Example



(S)

Compare $—CH_3$ & $—CH{=}CH_2$:

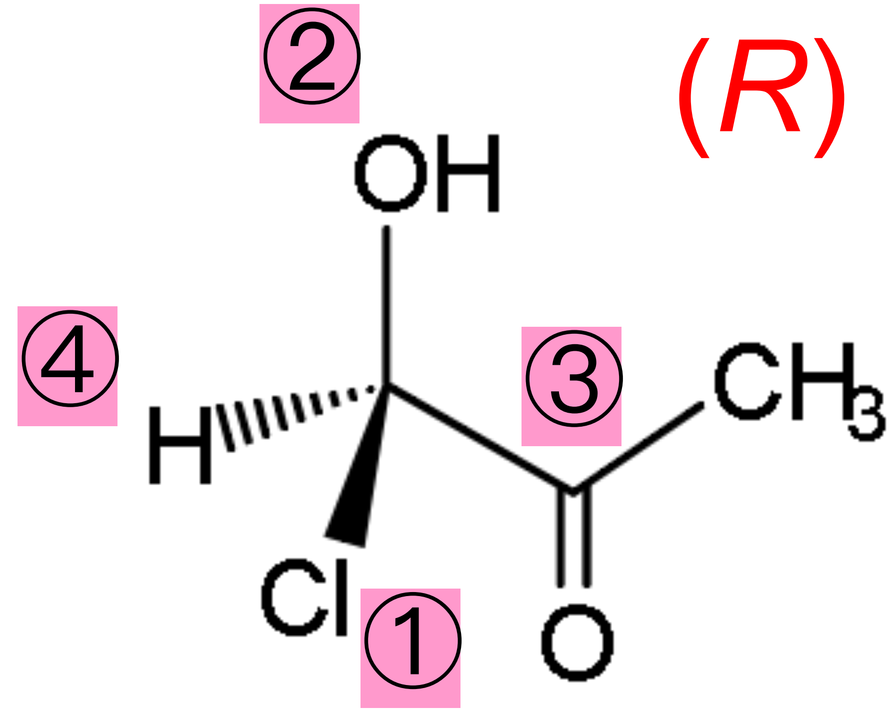
$—CH{=}CH_2$ equivalent to

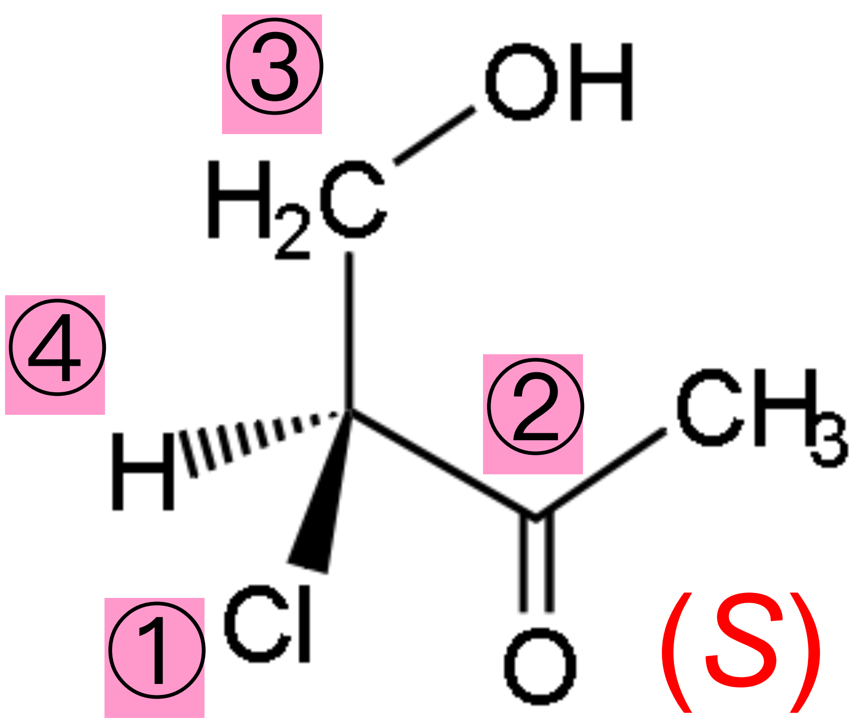


Thus, $—CH_3 \Rightarrow (H, H, H)$

$—CH{=}CH_2 \Rightarrow (C, C, H)$

- Other examples



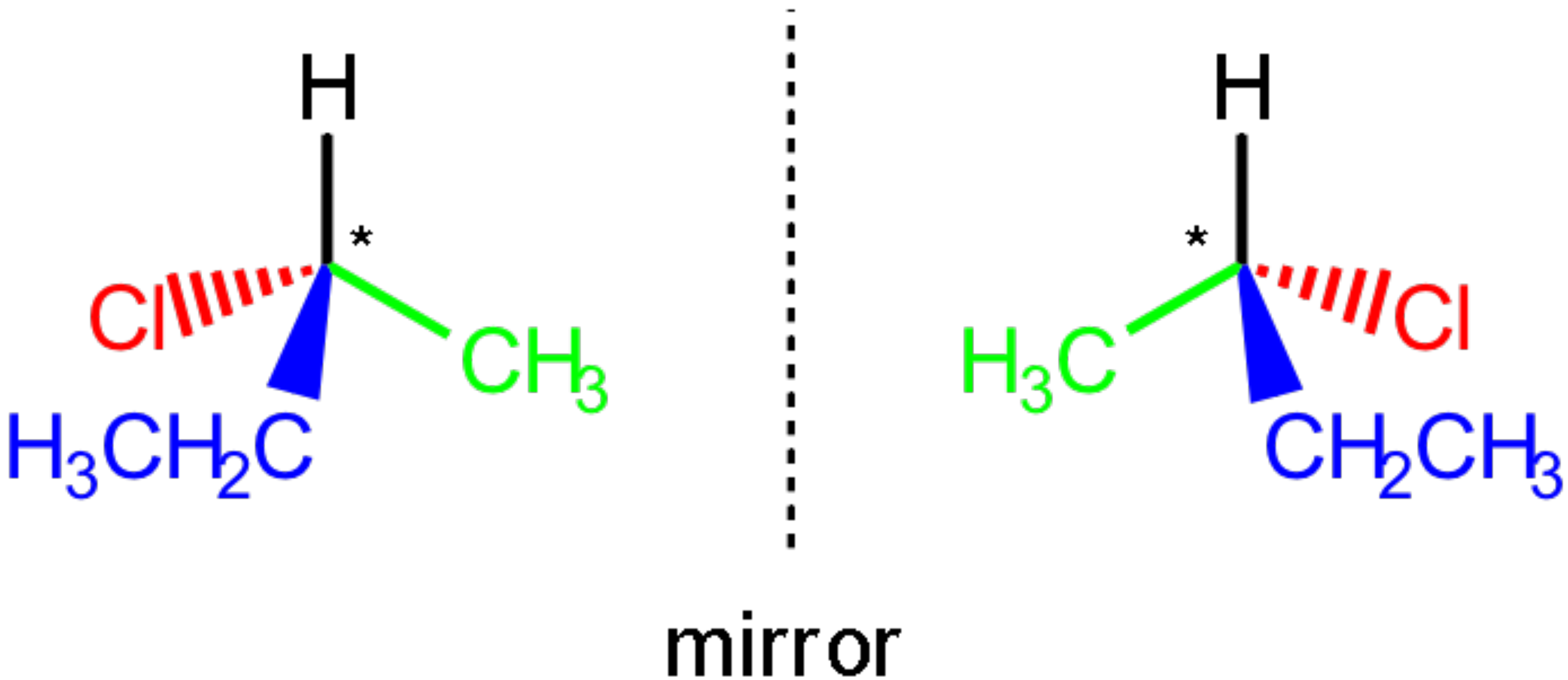


② C ⇒ (O, O, C)

③ C ⇒ (O, H, H)

7. Properties of Enantiomers: Optical Activity

- Enantiomers
  - Mirror images that are not superposable



- Enantiomers have identical physical properties (e.g. melting point, boiling point, refractive index, solubility etc.)

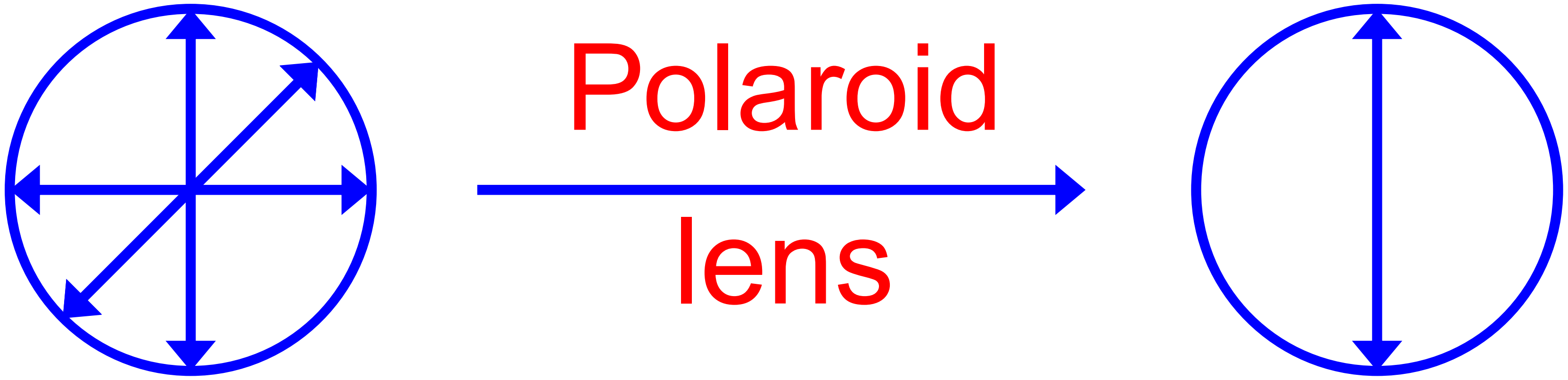
Compound	bp (^{o}C)	mp (^{o}C)
(*R*)-2-Butanol	99.5	
(*S*)-2-Butanol	99.5	
(+)-(*R,R*)-Tartaric Acid		168 – 170
(–)-(*S,S*)-Tartaric Acid		168 – 170
(+/–)-Tartaric Acid		210 – 212

- Enantiomers
  - Have the same chemical properties (except reaction/interactions with chiral substances)
  - Show different behavior only when they interact with other chiral substances
  - Turn plane-polarized light on opposite direction

- Optical activity
  - The property possessed by chiral substances of rotating the plane of polarization of plane-polarized light

7A. Plane-Polarized Light

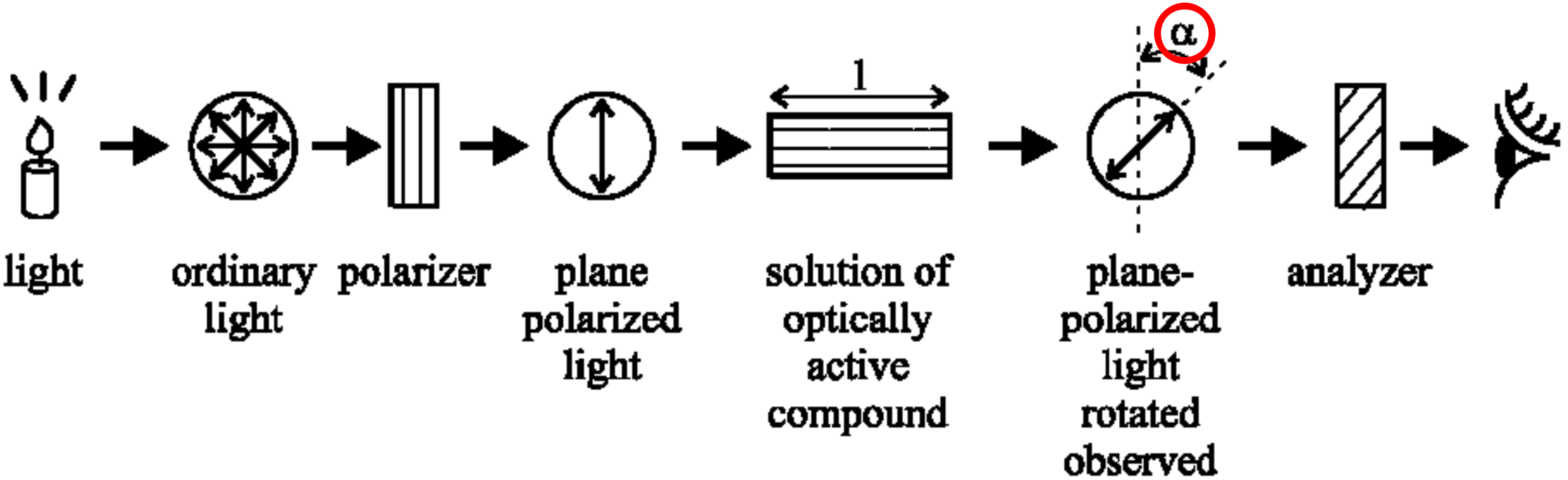
- The electric field (like the magnetic field) of light is oscillating in all possible planes
- When this light passes through a polarizer (Polaroid lens), we get plane-polarized light (oscillating in only one plane)



7B. The Polarimeter

- A device for measuring the optical activity of a chiral compound

α = observed optical rotation



7C. Specific Rotation

observed rotation

temperature

$$[\alpha]_D^{25} = \frac{\alpha}{c \times \ell}$$

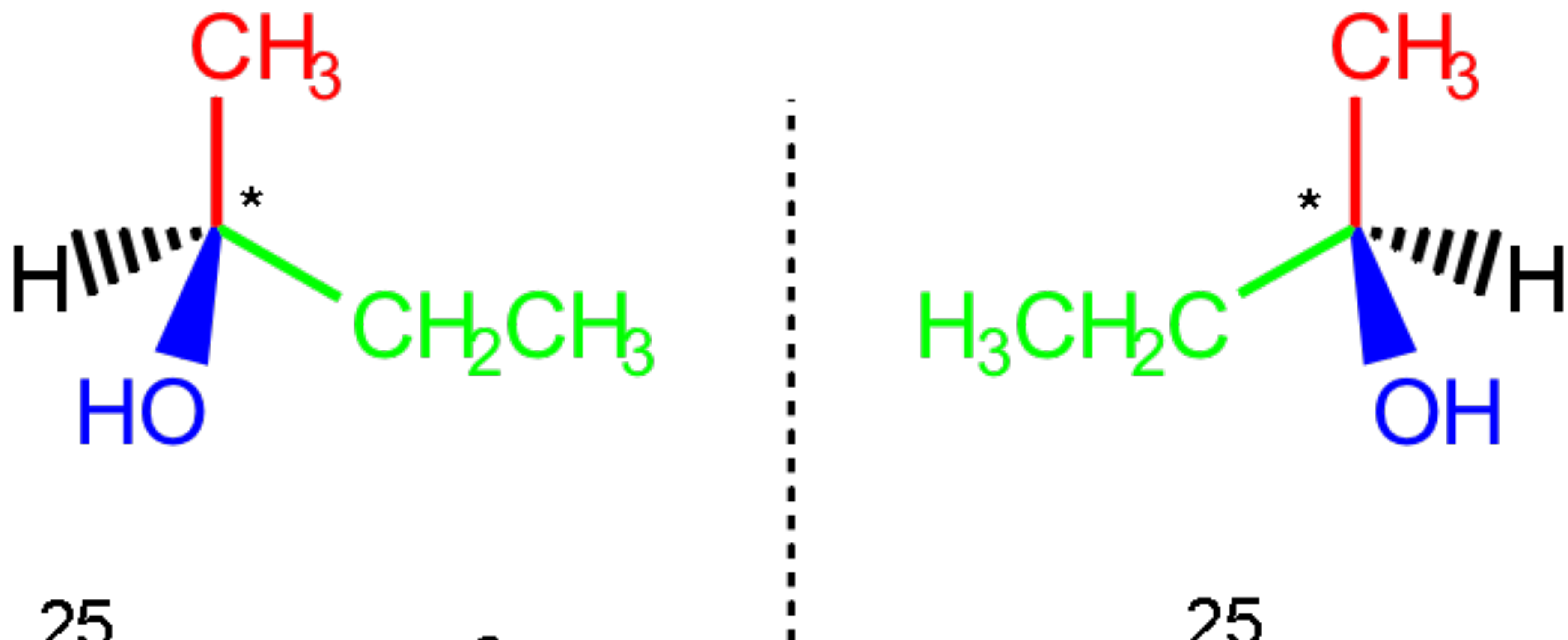
wavelength of light (e.g. D-line of Na lamp, λ=589.6 nm)

concentration of sample solution in g/mL

length of cell in dm (1 dm = 10 cm)

- The value of α depends on the particular experiment (since there are different concentrations with each run)
  - But specific rotation [α] should be the same regardless of the concentration

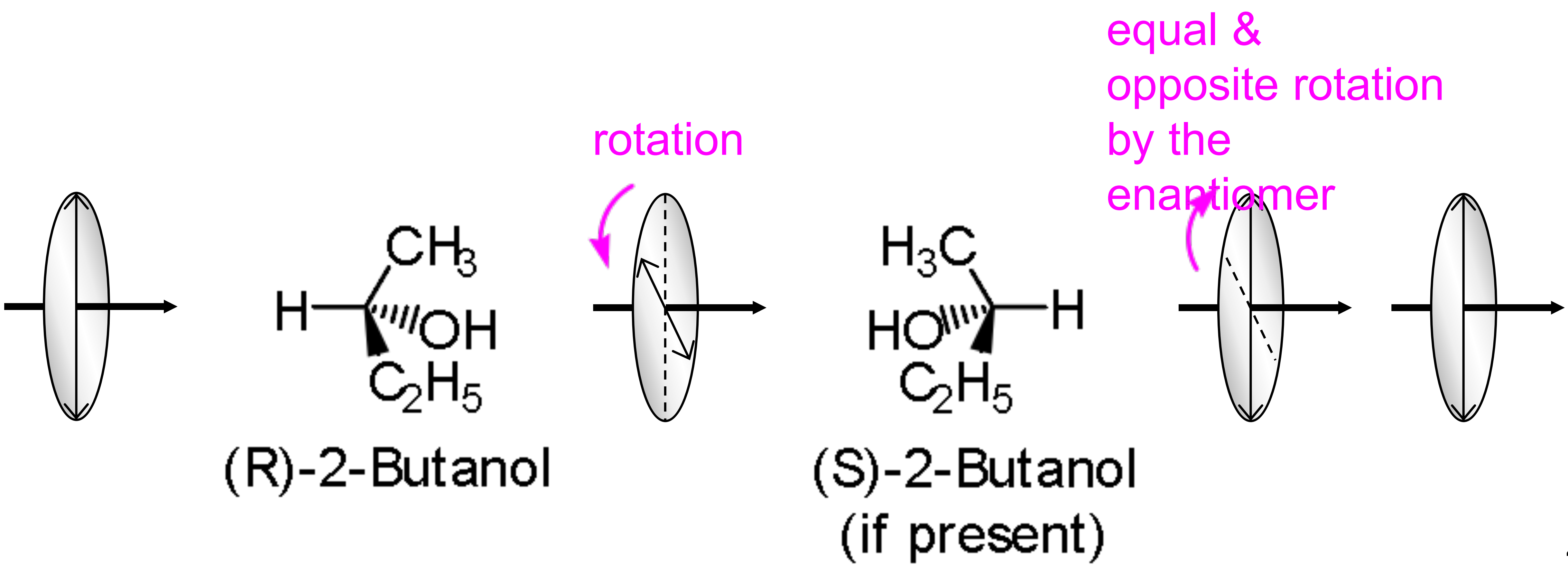
- Two enantiomers should have the same value of specific rotation, but the signs are opposite



$[\alpha]_D^{25} = +\ 13.5^\circ$ mirror $[\alpha]_D^{25} = -\ 13.5^\circ$

8A. Racemic Forms

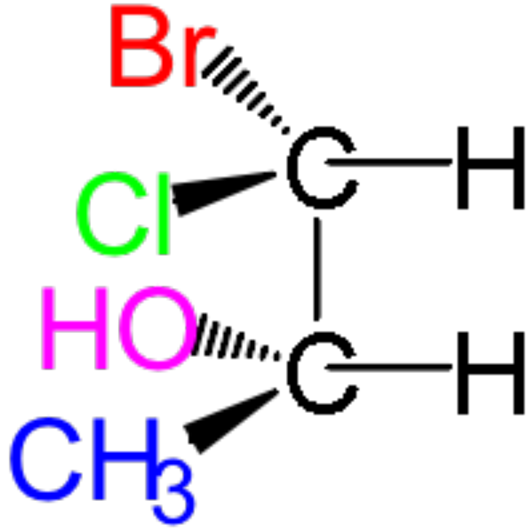
- An equimolar mixture of two enantiomers is called a racemic mixture (or *racemate* or *racemic form*)
- A racemic mixture causes no net rotation of plane-polarized light

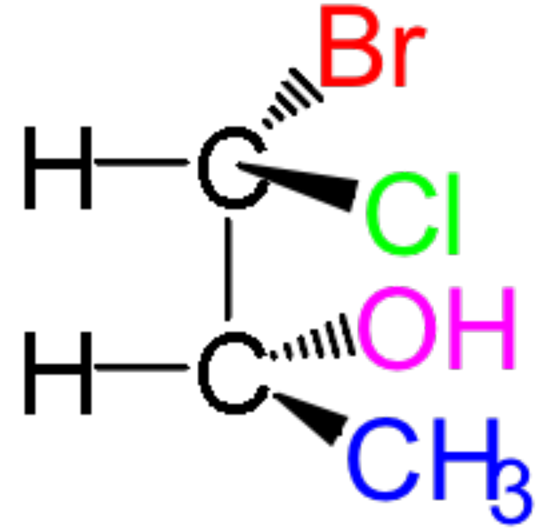


10. Molecules with More than One Chirality Center

- Diastereomers
  - Stereoisomers that are not enantiomers
  - Unlike enantiomers, diastereomers usually have substantially different chemical and physical properties

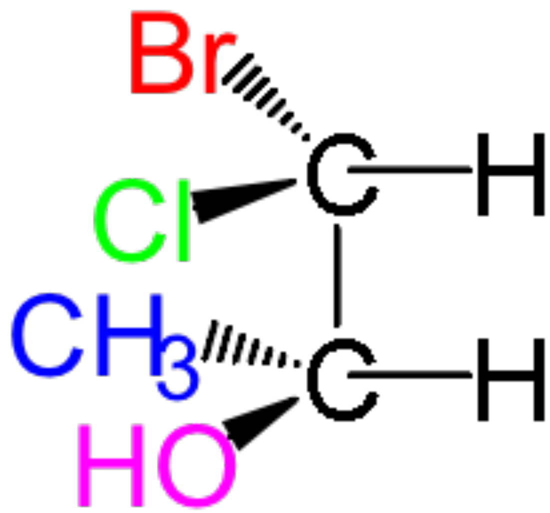
(I)

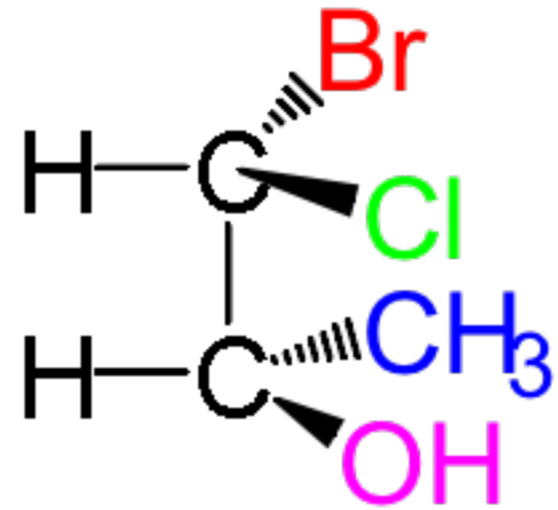




(II)

(III)

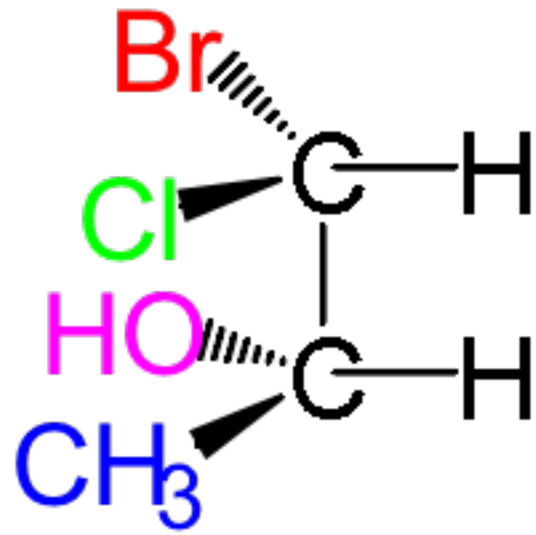


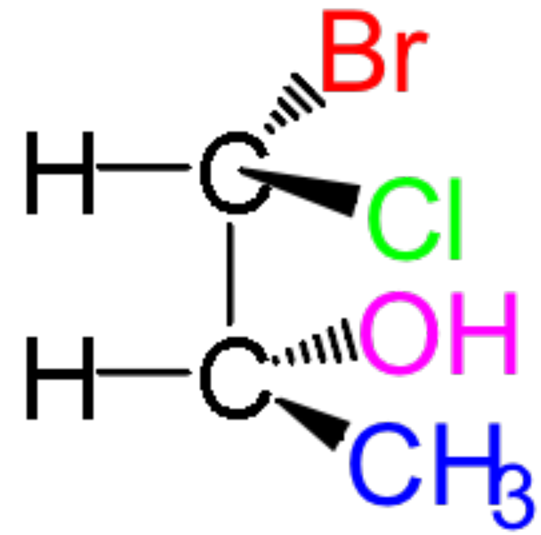


(IV)

Note: In compounds with *n* tetrahedral stereocenters, the maximum number of stereoisomers is 2^n.

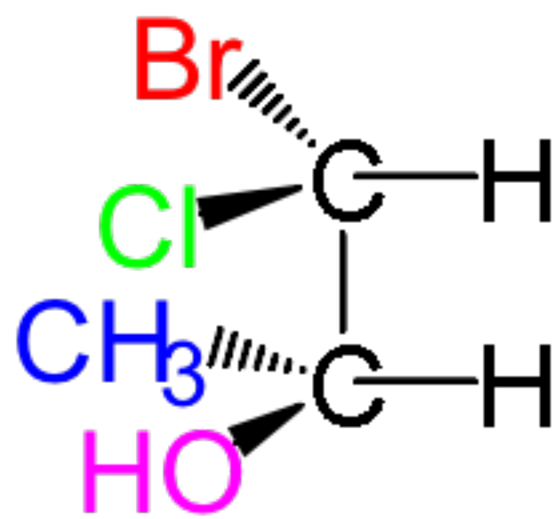
(I)

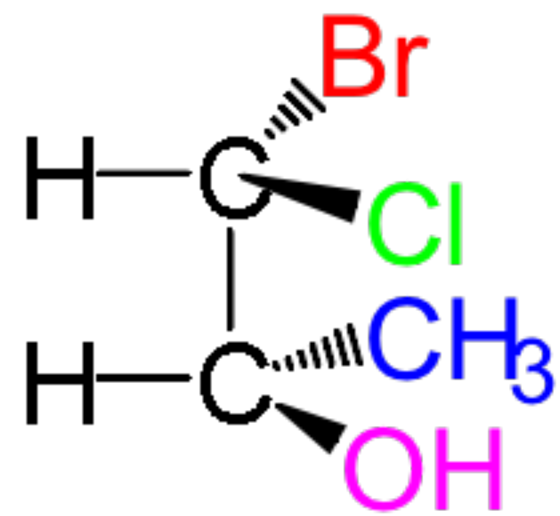




(II)

(III)

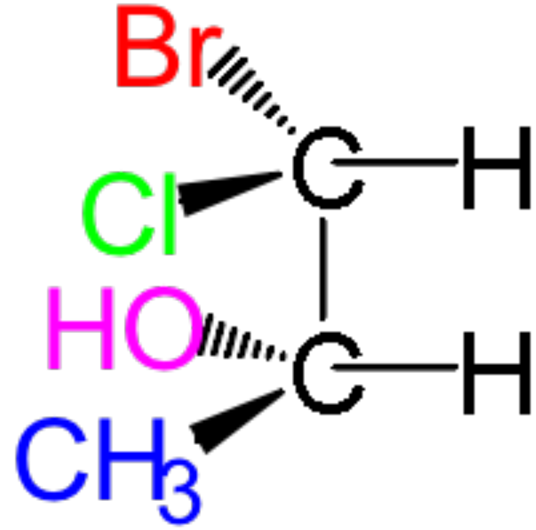


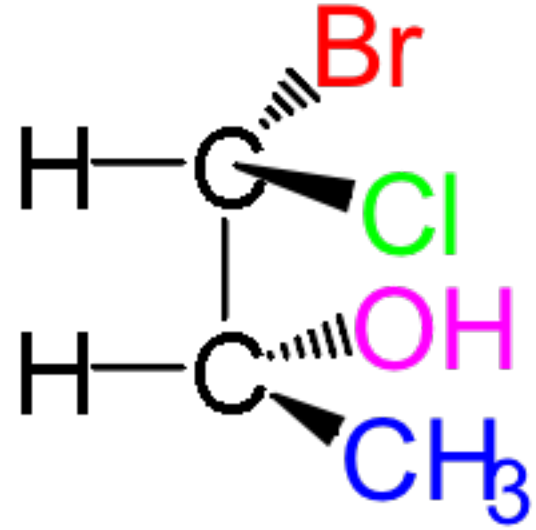


(IV)

- (I) & (II) are enantiomers to each other
- (III) & (IV) are enantiomers to each other

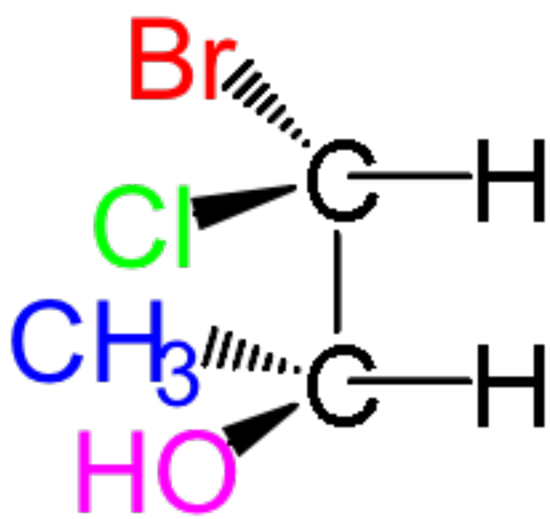
(I)

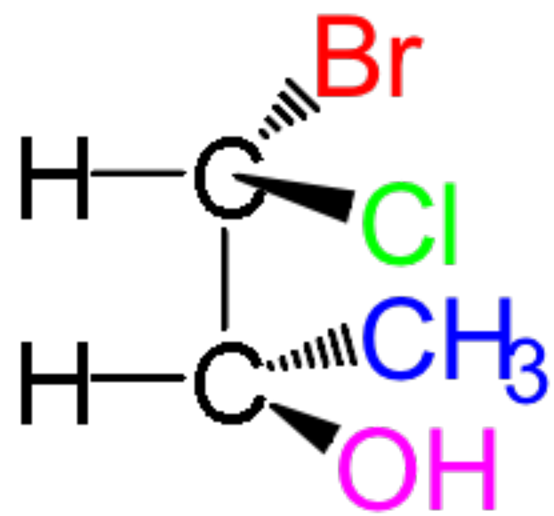




(II)

(III)





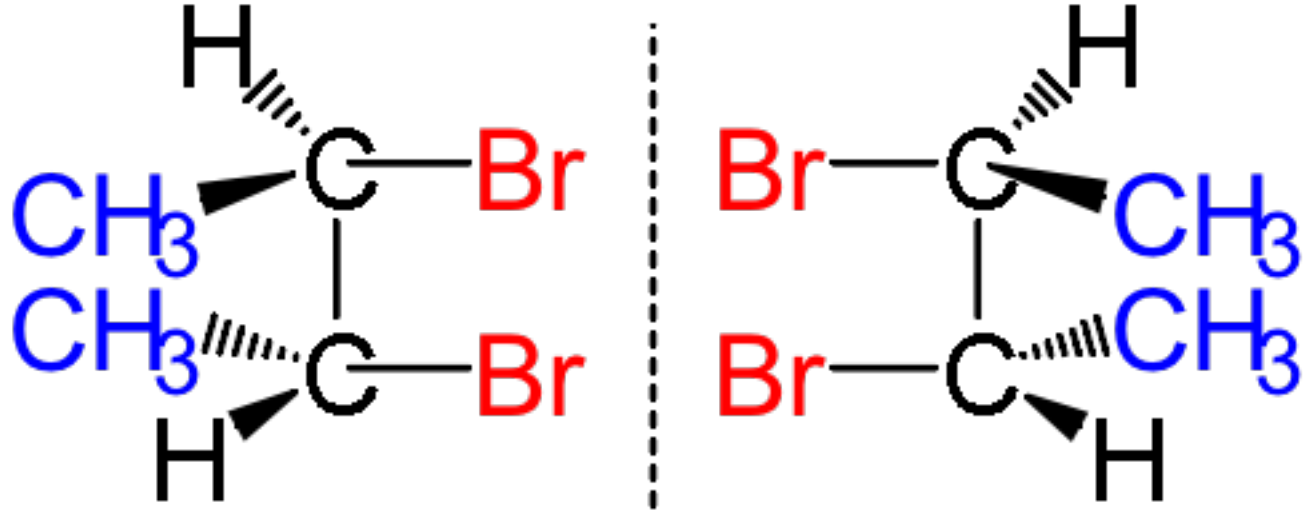
(IV)

- Diastereomers to each other:
  - (I) & (III), (I) & (IV), (II) & (III), (II) & (IV)

10A. <u>Meso Compounds</u>

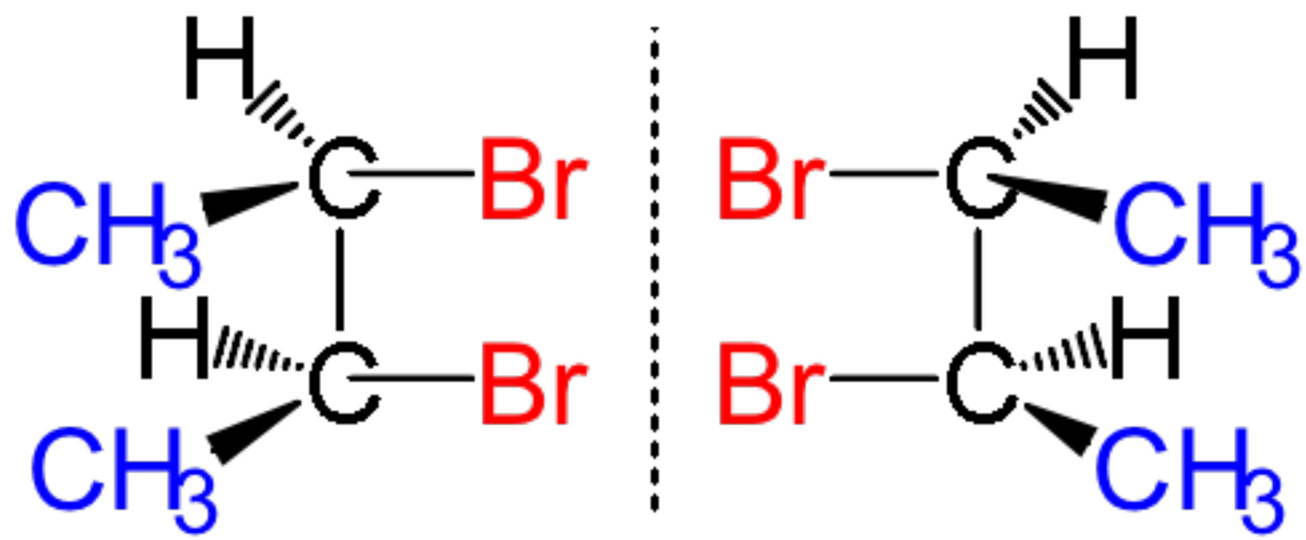
- Compounds with two stereocenters do not always have four stereoisomers ($2^2 = 4$) since some molecules are achiral (not chiral), even though they contain stereocenters
- For example, 2,3-dichlorobutane has two stereocenters, but only has 3 stereoisomers (not 4)

(I)



(II)

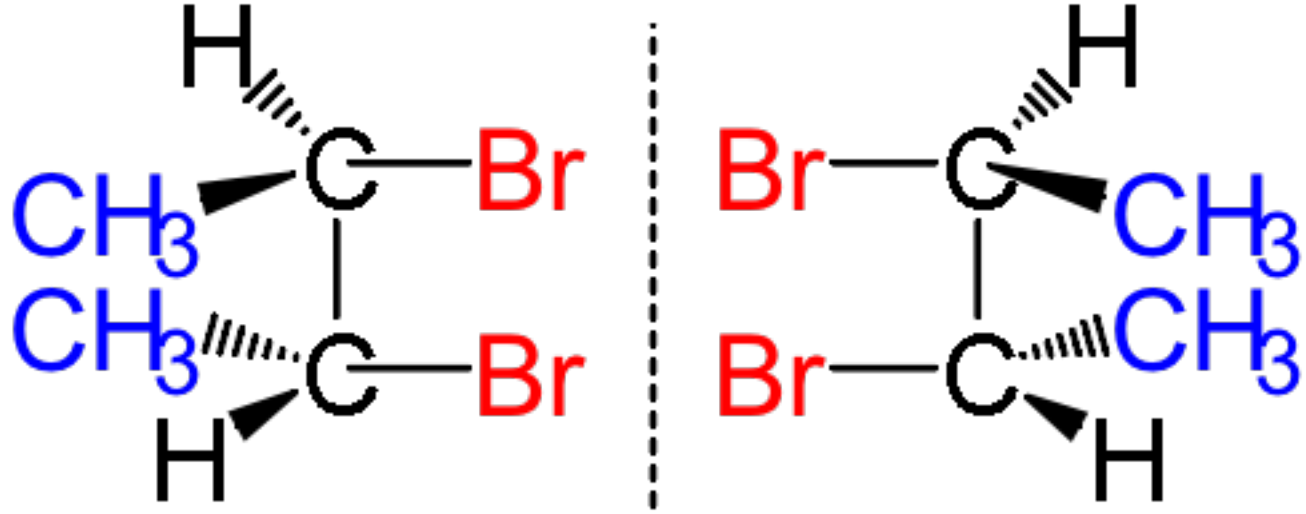
(III)



(IV)

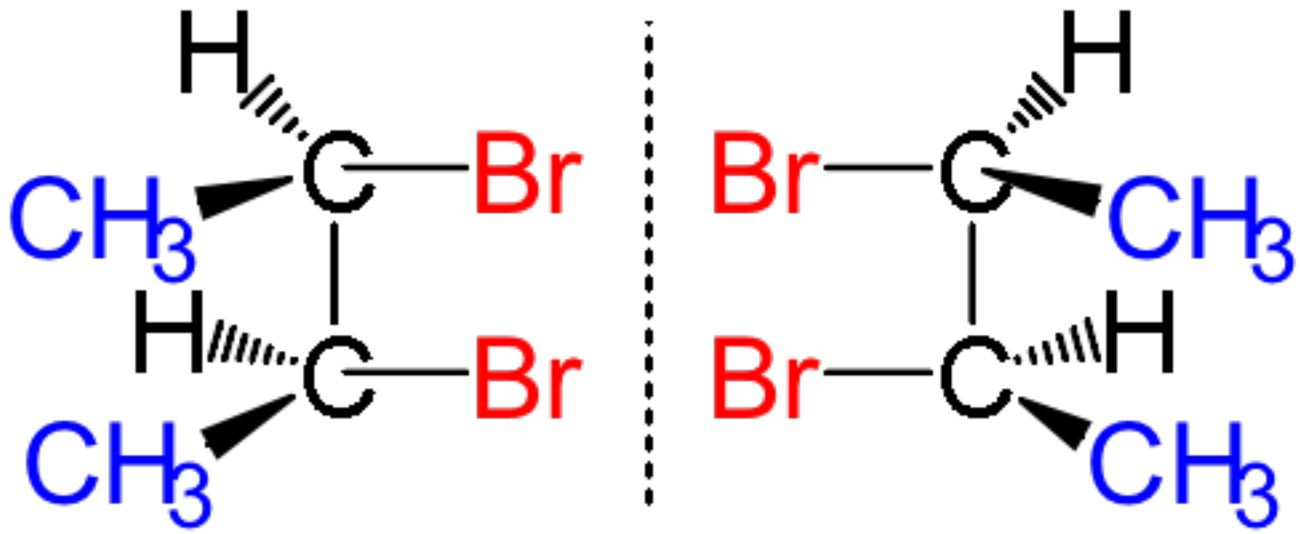
Note: (III) contains a plane of symmetry, is a meso compound, and is achiral ([α] = 0°).

(I)



(II)

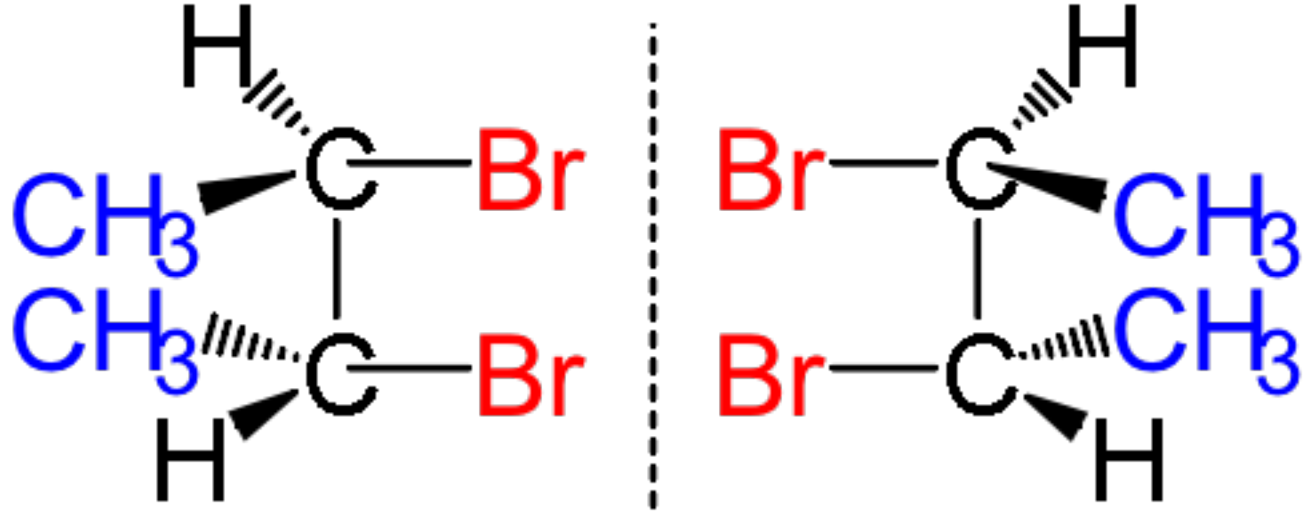
(III)



(IV)

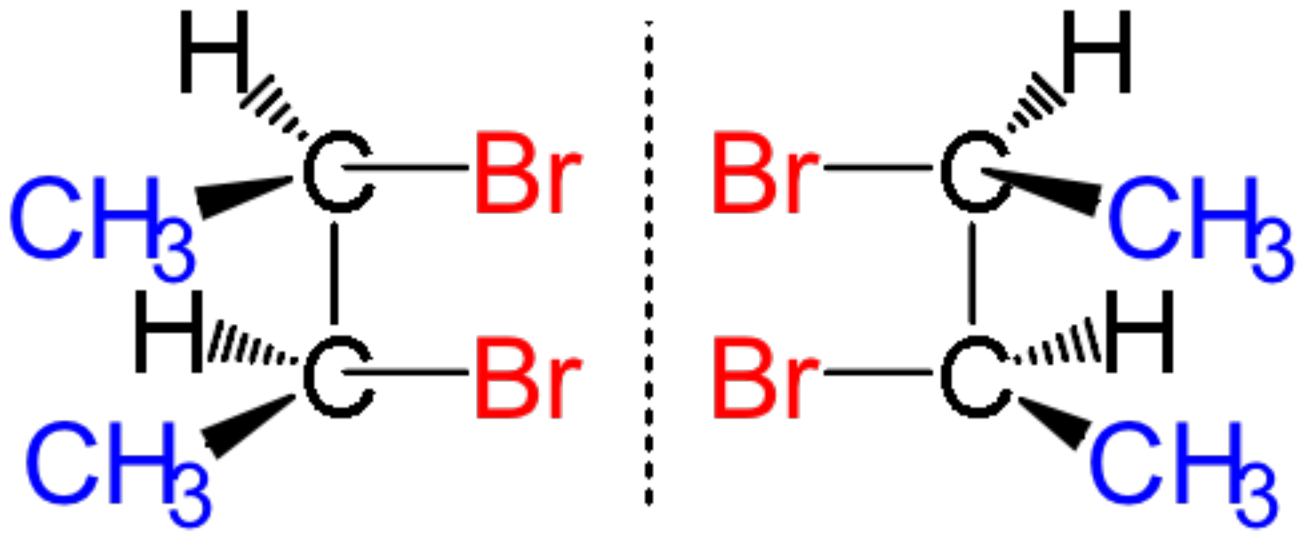
- (I) & (II) are enantiomers to each other and chiral
- (III) & (IV) are identical and achiral

(I)



(II)

(III)

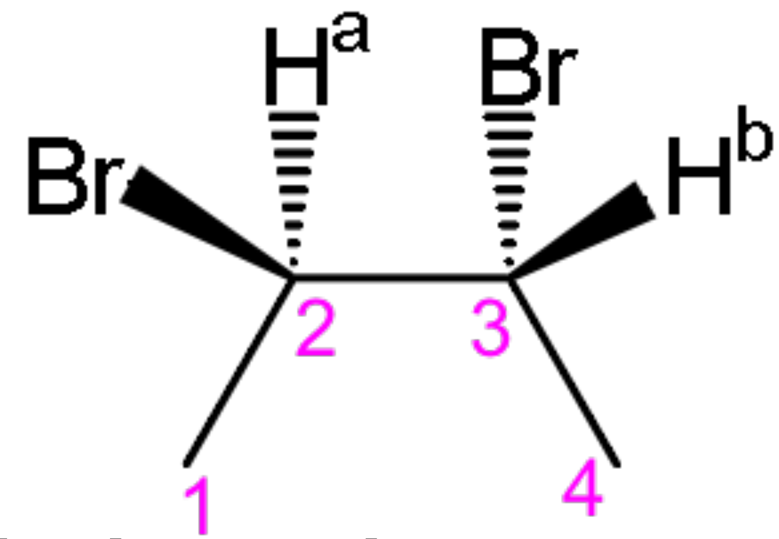


(IV)

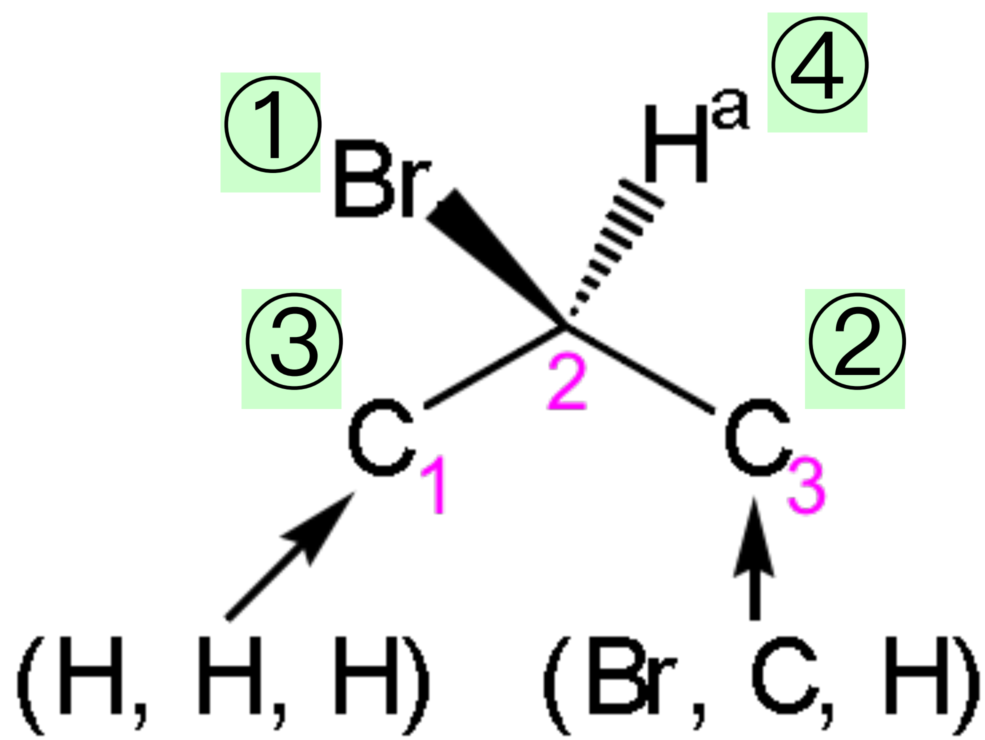
- ❈ (I) & (III), (II) & (III) are diastereomers
- ❈ Only 3 stereoisomers:
  - (I) & (II) {enantiomers}, (III) {meso}

10B. How to Name Compounds with More than One Chirality Center

- 2,3-Dibromobutane

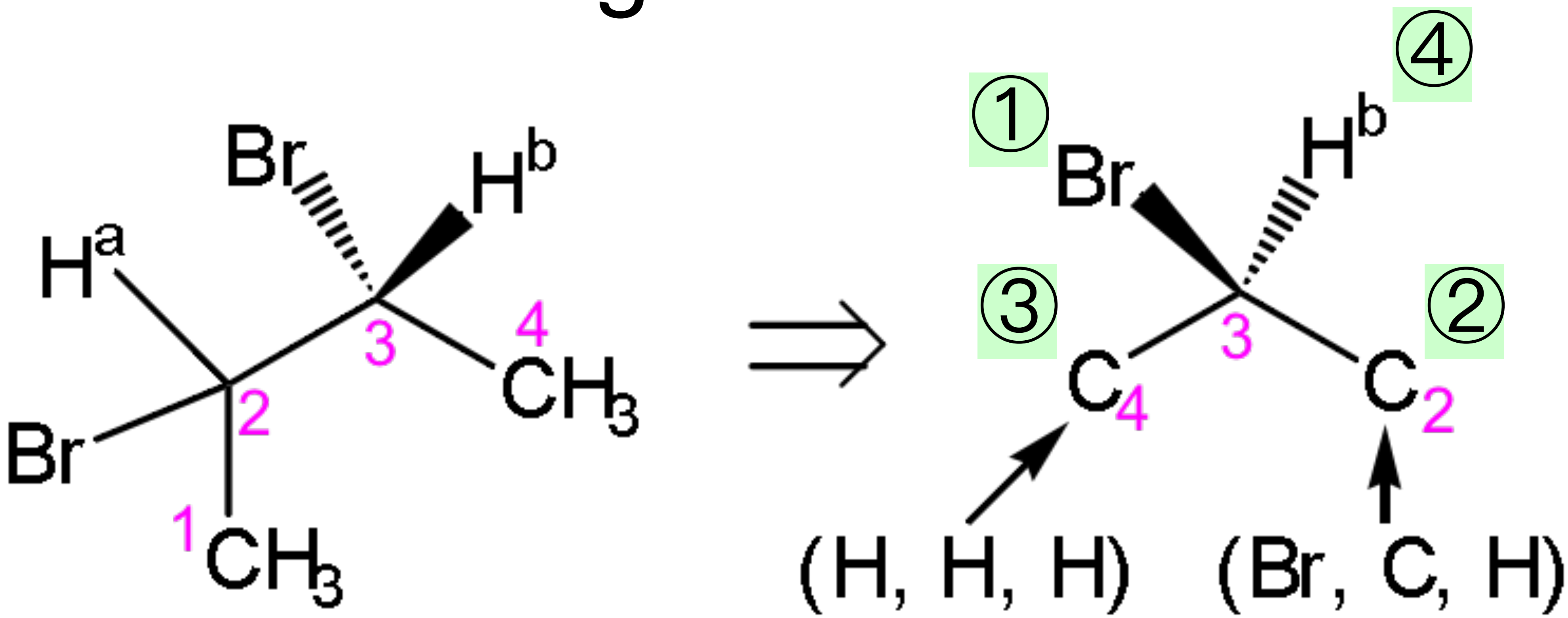


- Look through C2–H[a] bond



C2: *(R)* configuration

- Look through C3–H[b] bond



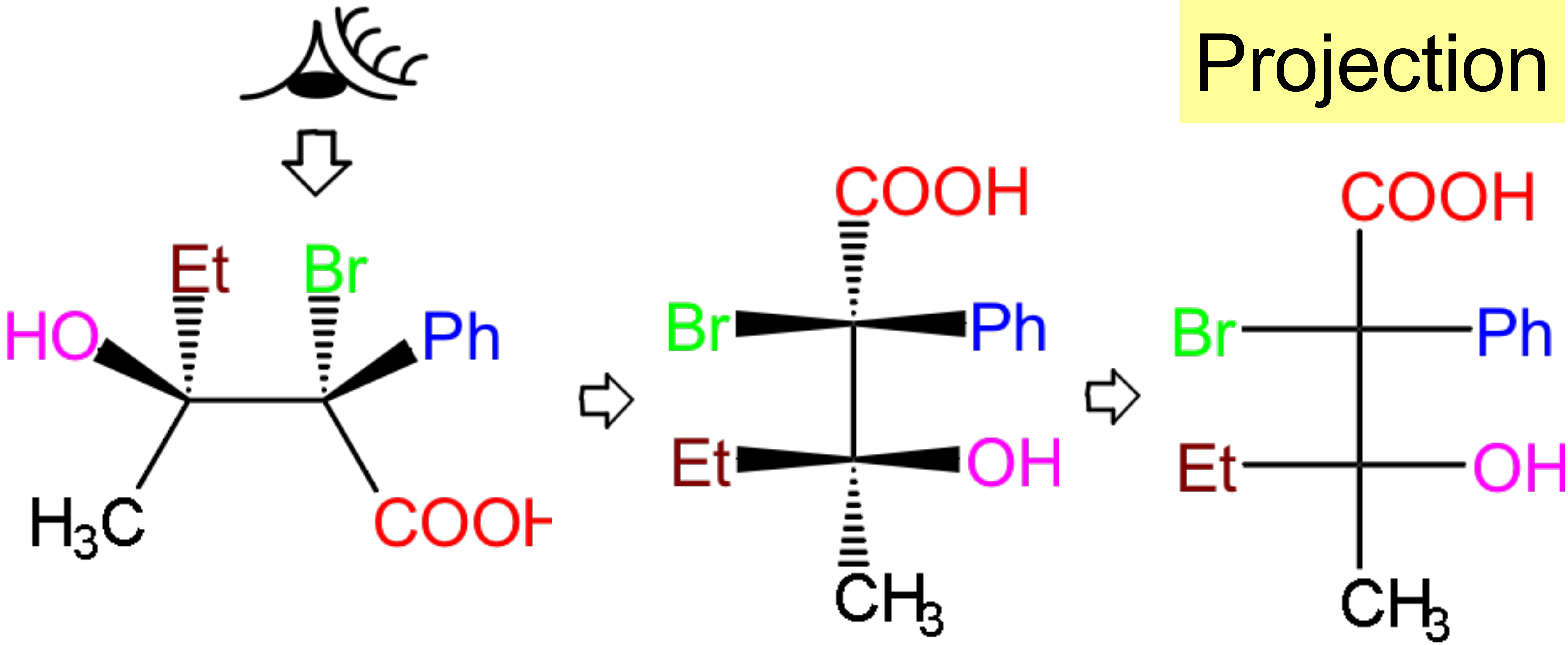
C3: *(R)* configuration

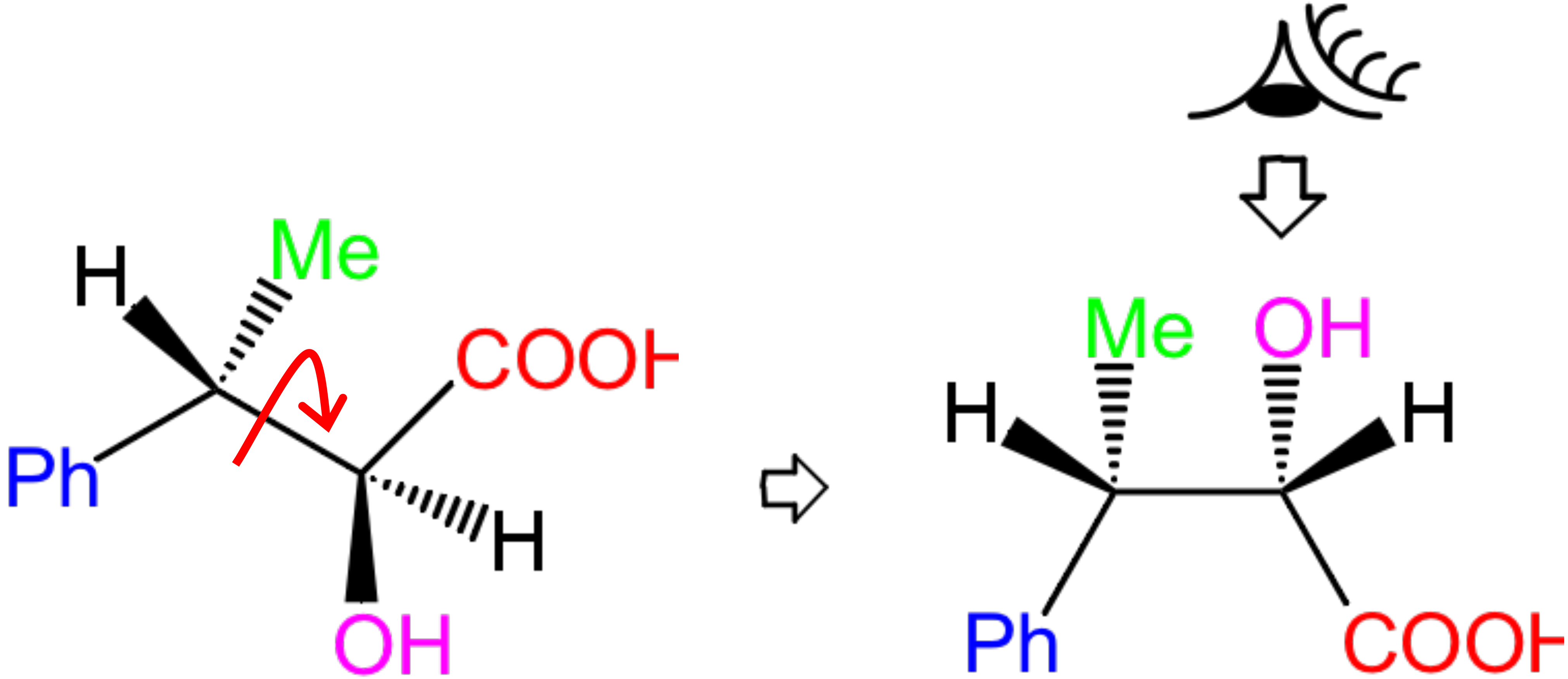
- Full name:
  - *(2R, 3R)*-2,3-Dibromobutane

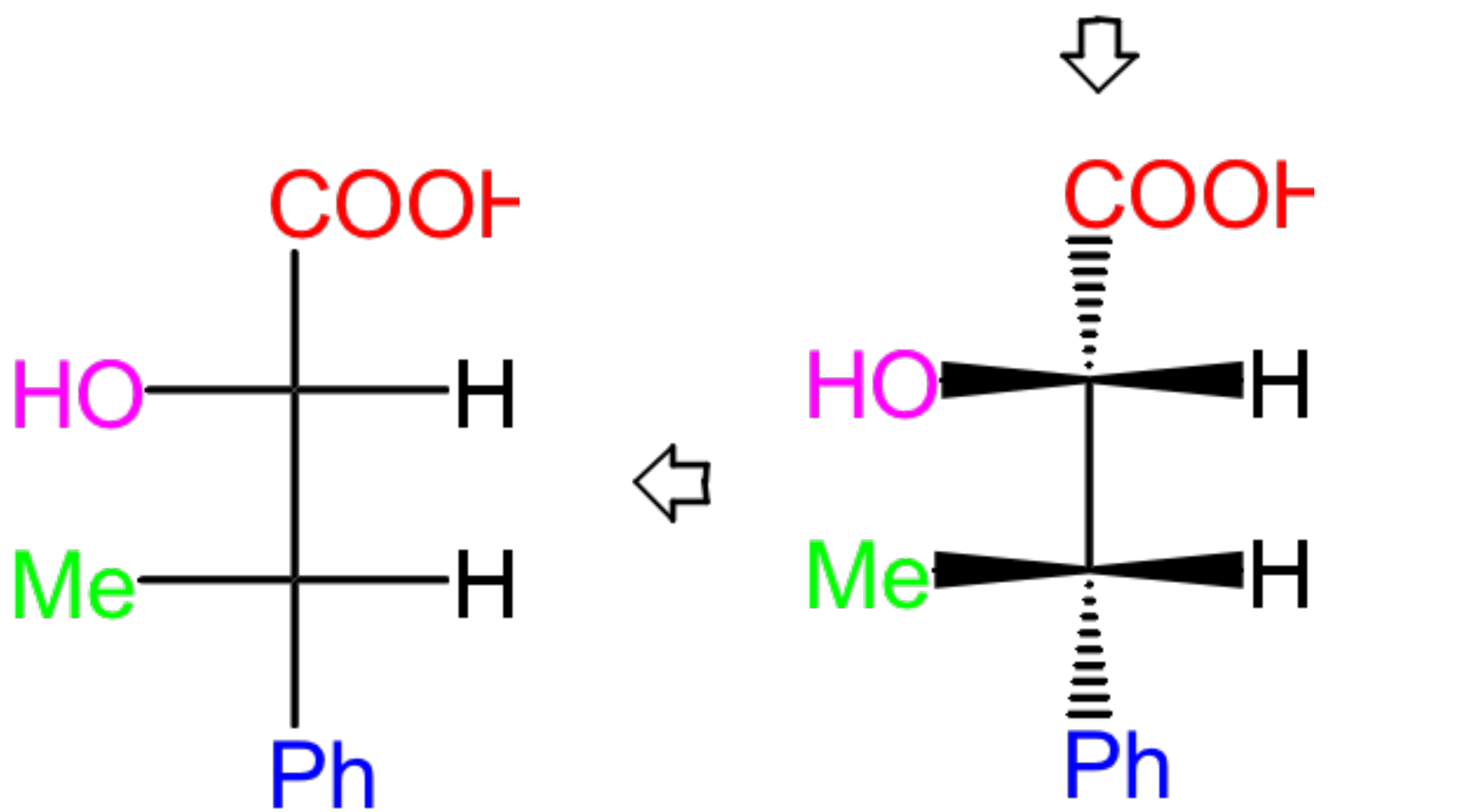
11. Fischer Projection Formulas

11A. How To Draw and Use Fischer Projections

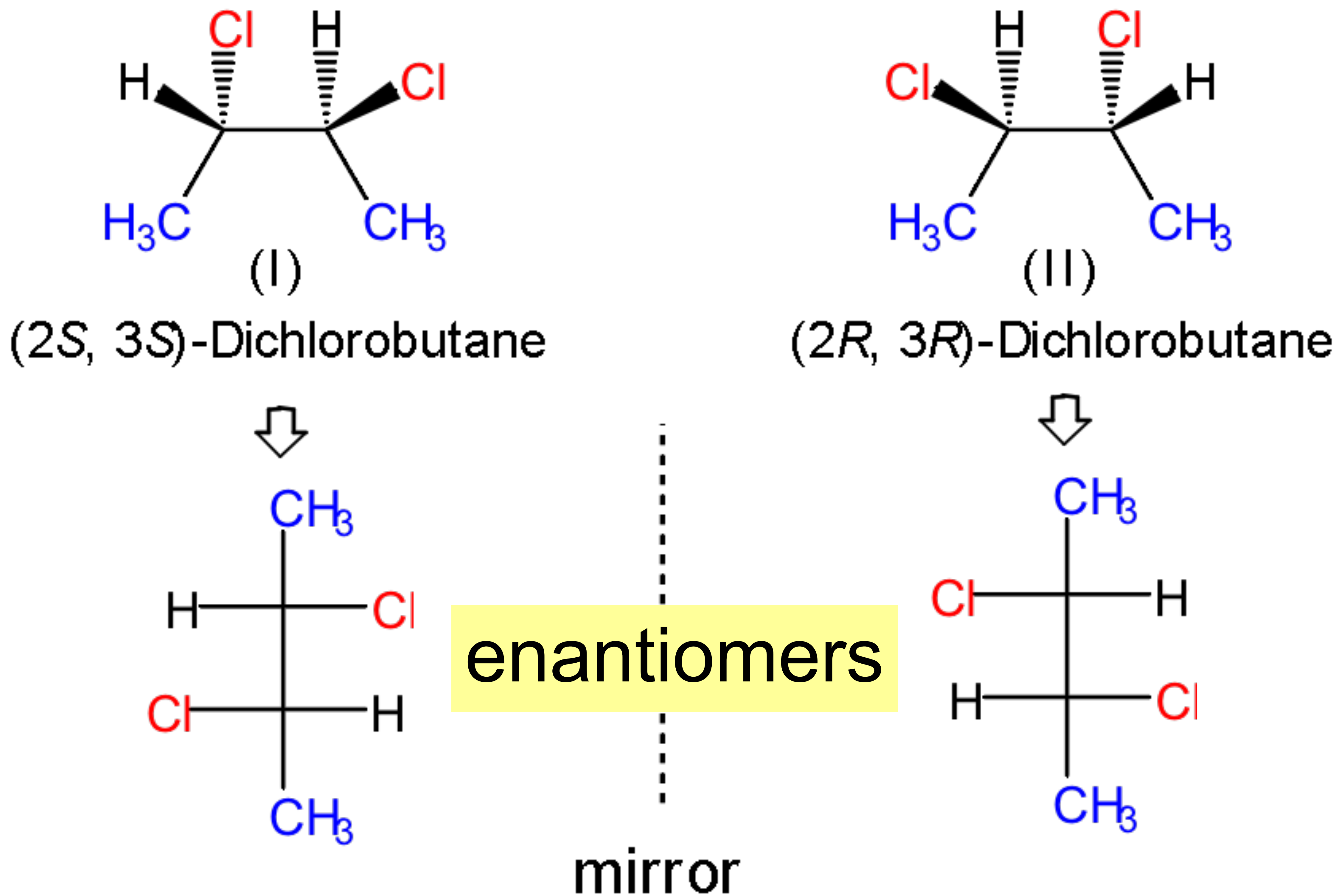
Fischer Projection



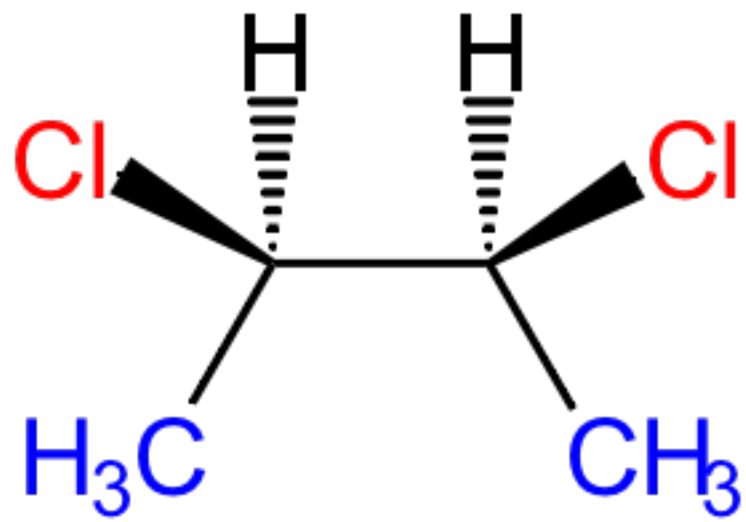




Fischer Projection

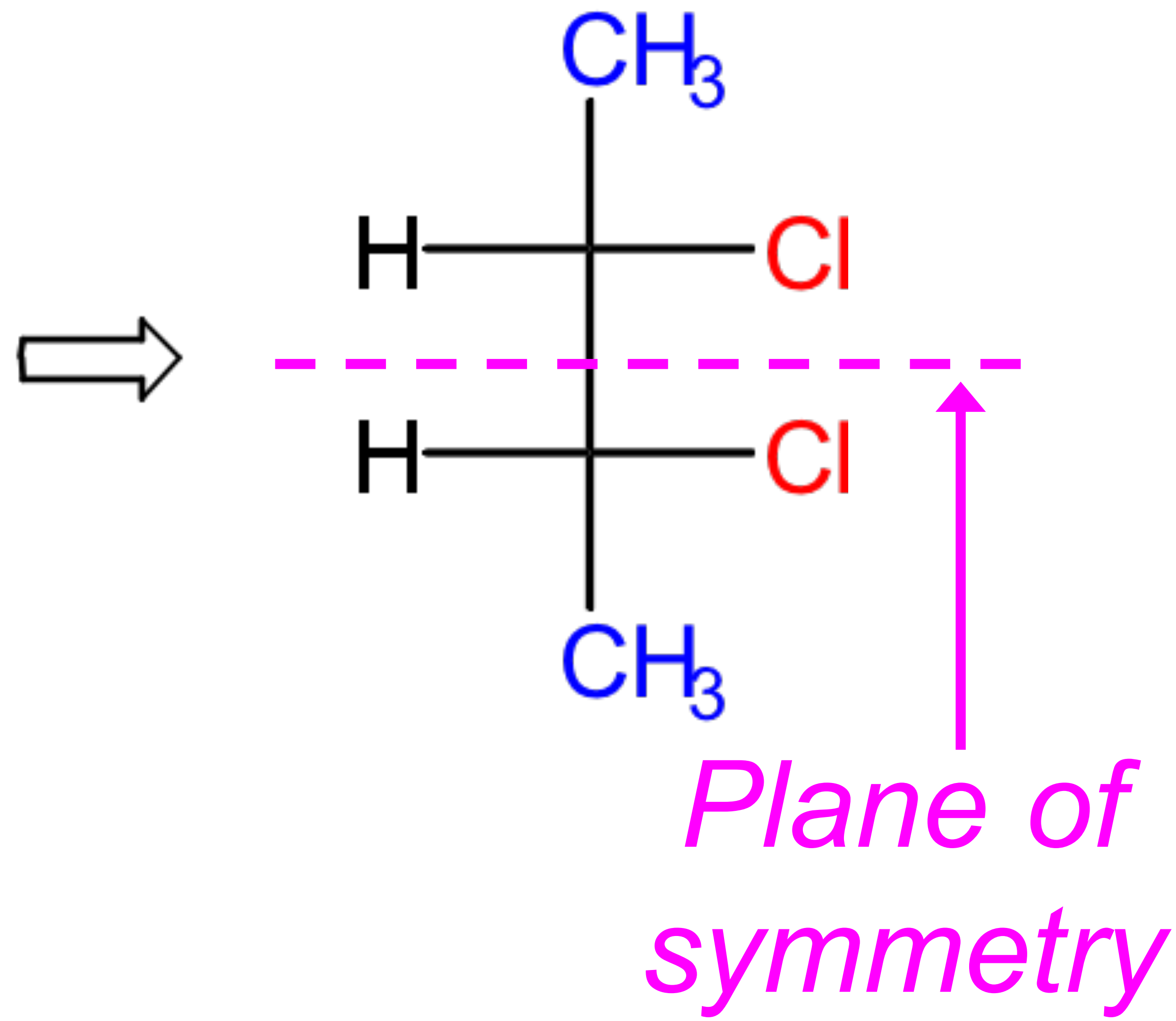


❖ (I) and (II) are both chiral and they are enantiomers with each other



(III)

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

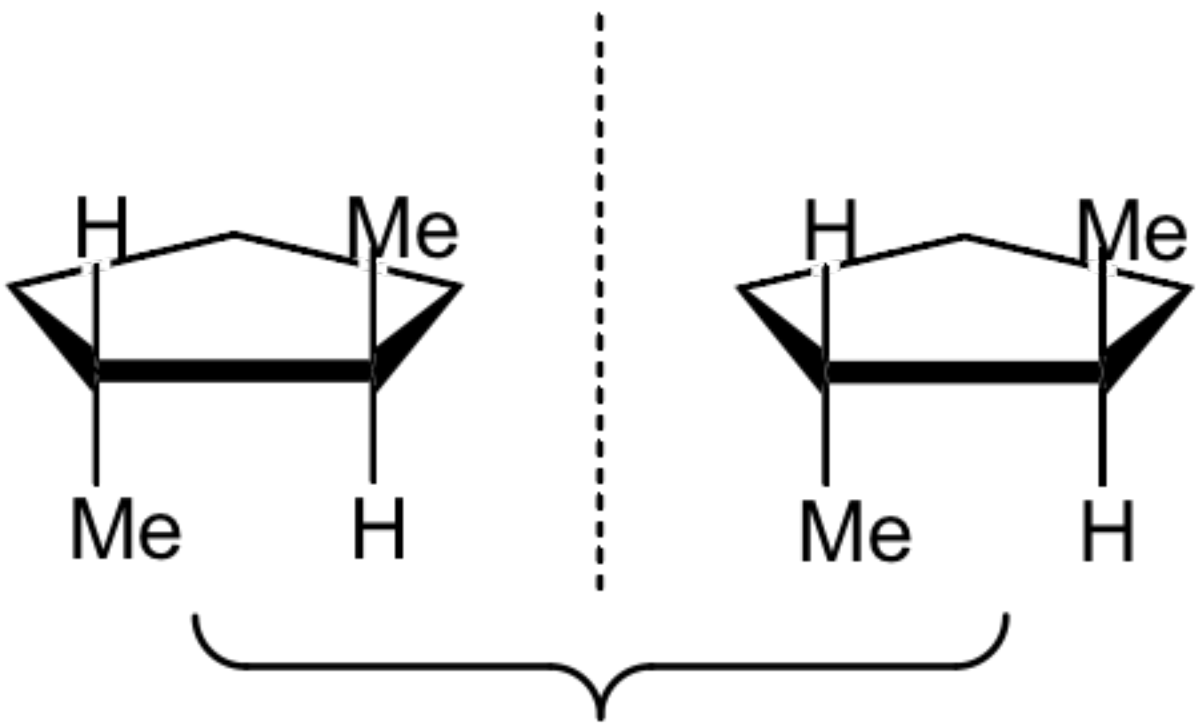


- (III) is achiral (a meso compound)
- (III) and (I) are diastereomers to each other

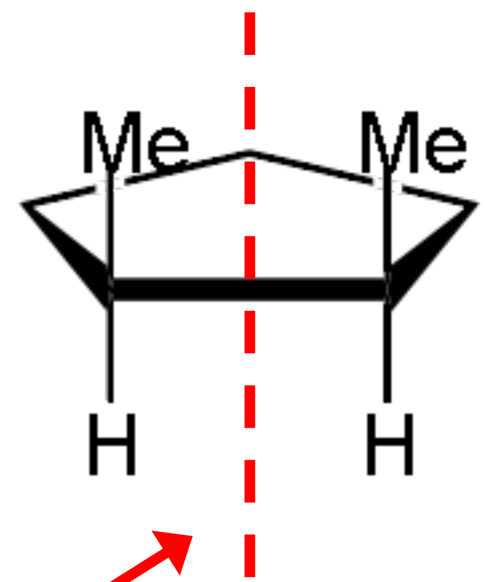
12. Stereoisomerism of Cyclic Compounds

a meso compound
achiral

mirror



enantiomers

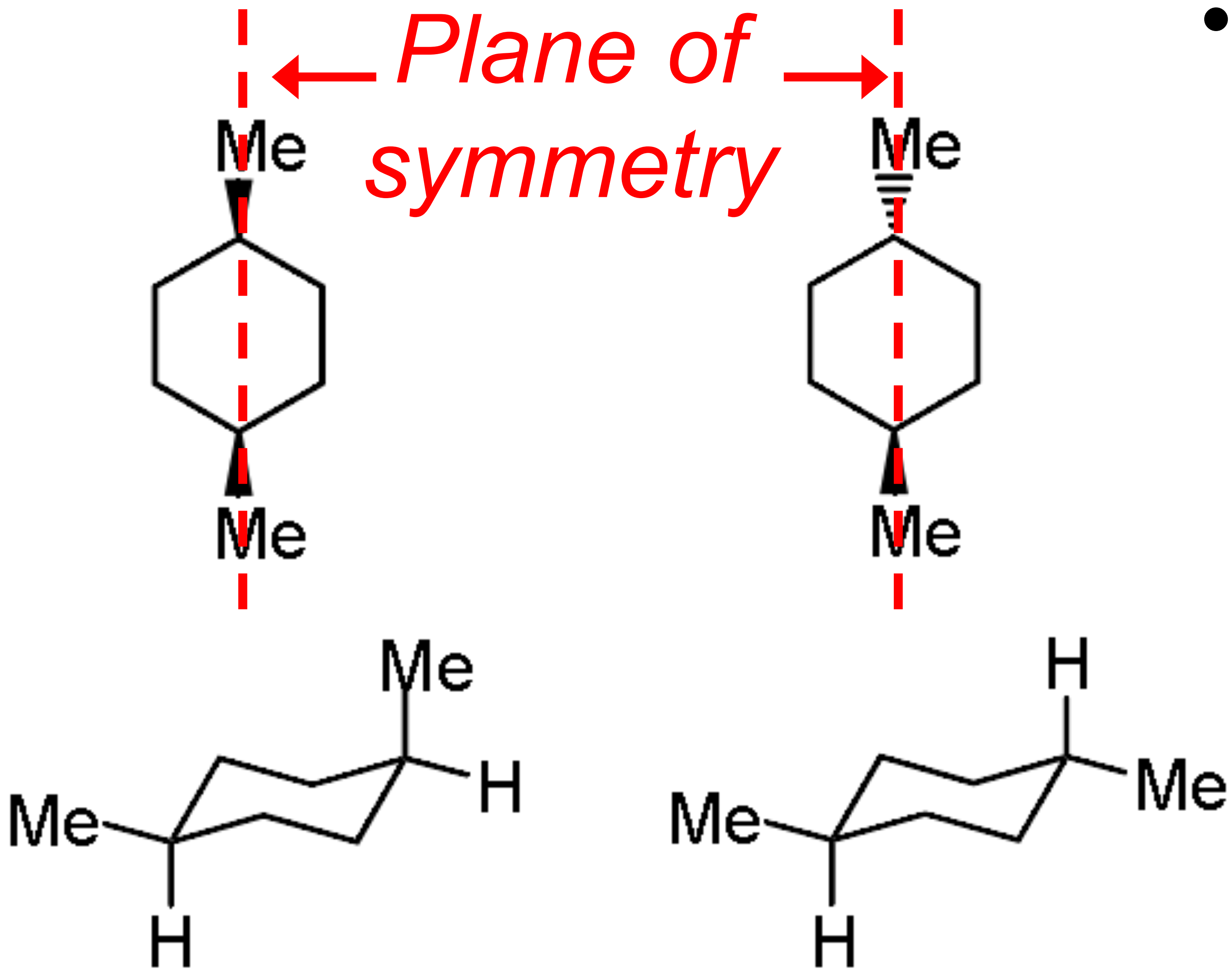


Plane of symmetry

12A. Cyclohexane Derivatives

❖ 1,4-Dimethylcyclohexane

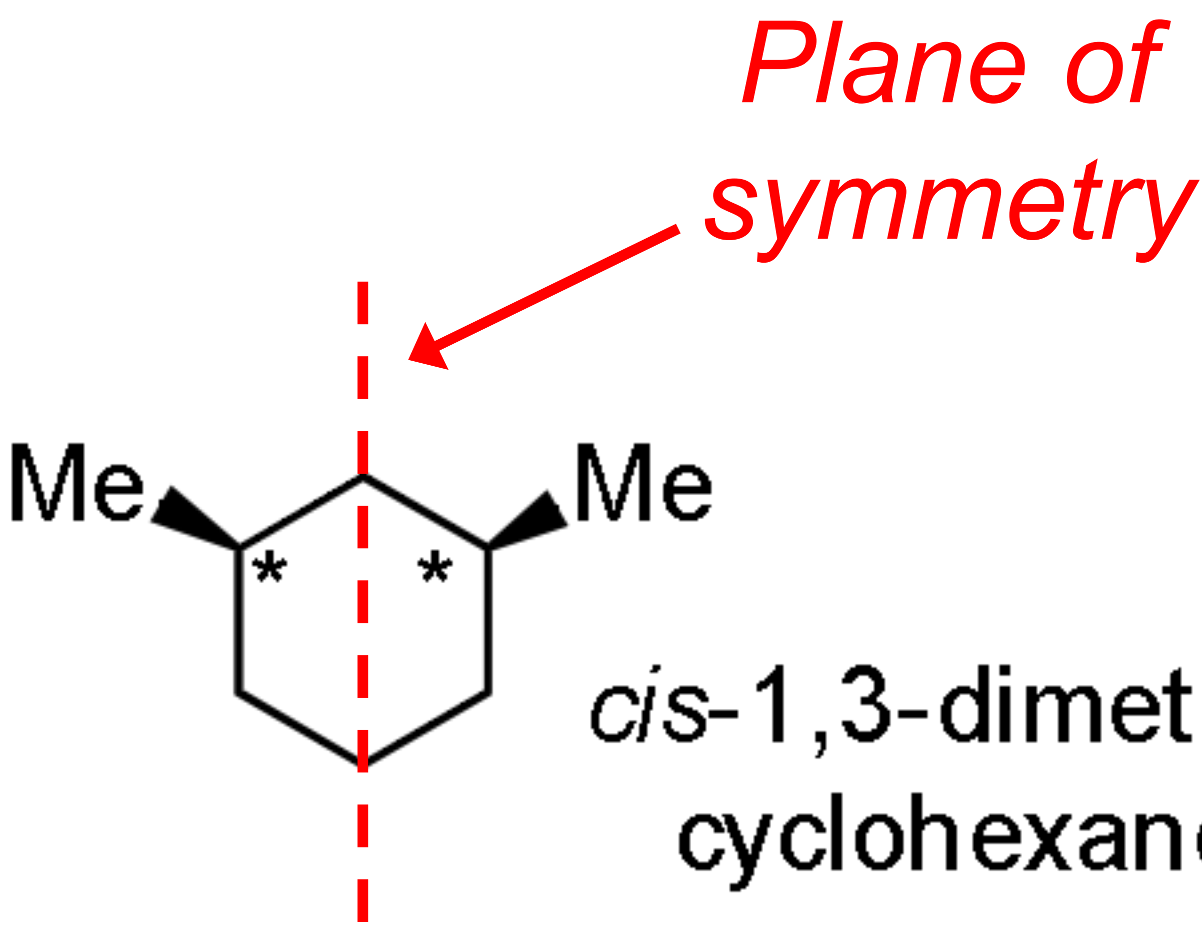
- Both *cis*- & *trans*-1,4-dimethylcyclo-hexanes are ***achiral*** and optically inactive



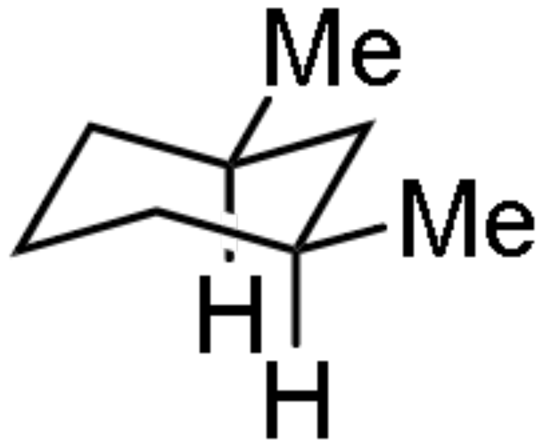
cis-1,4-dimethyl cyclohexane

trans-1,4-dimethyl cyclohexane

❈ 1,3-Dimethylcyclohexane



cis-1,3-dimethyl cyclohexane

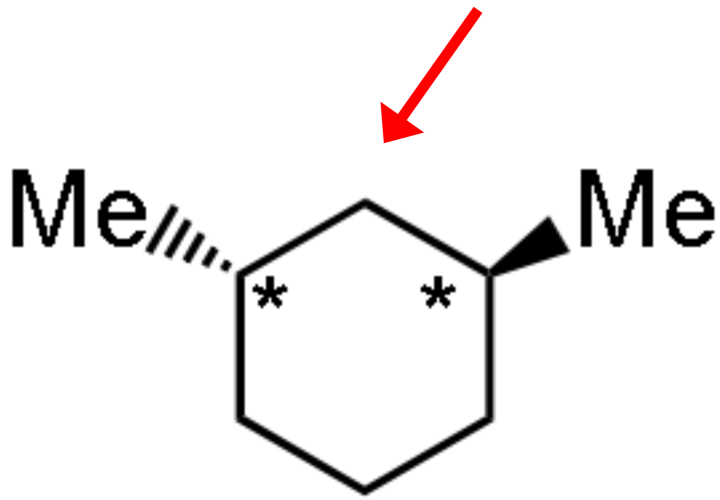


(meso)

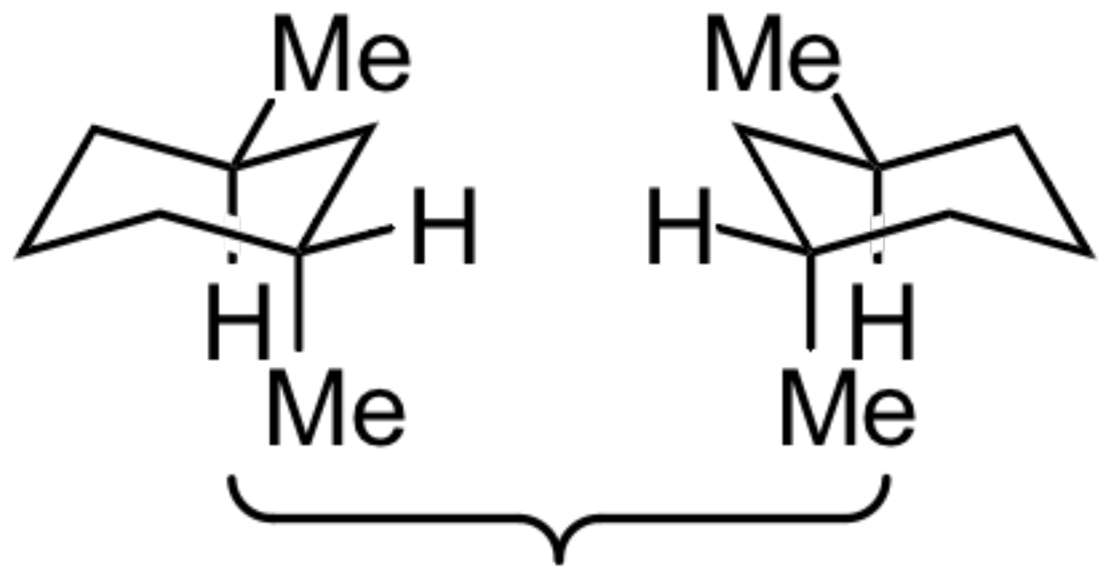
- *cis*-1,3-Dimethylcyclohexane has a plane of symmetry and is a meso compound

❖ 1,3-Dimethylcyclohexane

***NO** plane of symmetry*



trans-1,3-dimethyl cyclohexane

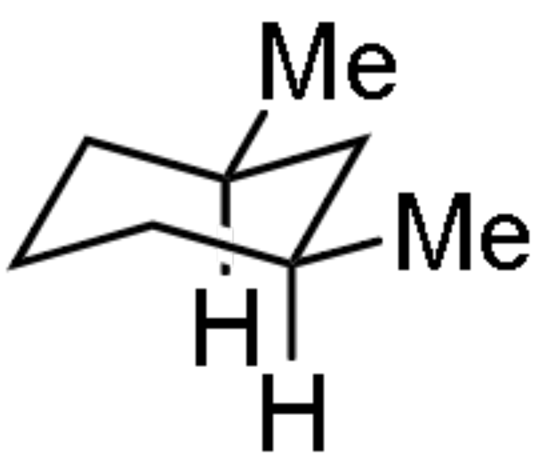


enantiomers

- *trans*-1,3-Dimethylcyclohexane exists as a pair of enantiomers

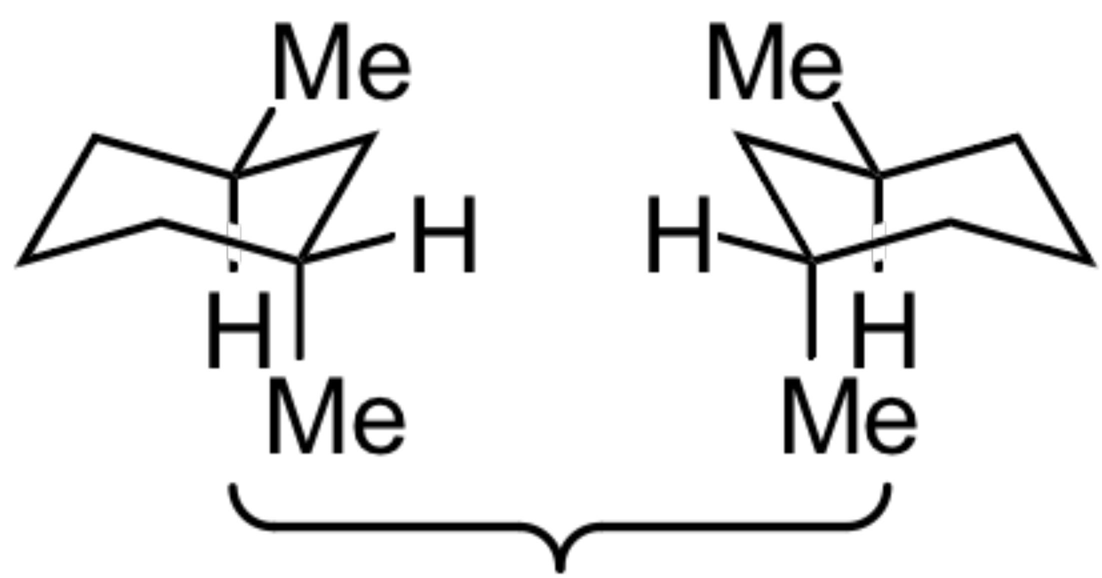
- 1,3-Dimethylcyclohexane
  - Has two chirality centers but only ***three*** stereoisomers

cis-1,3-dimethyl
cyclohexane



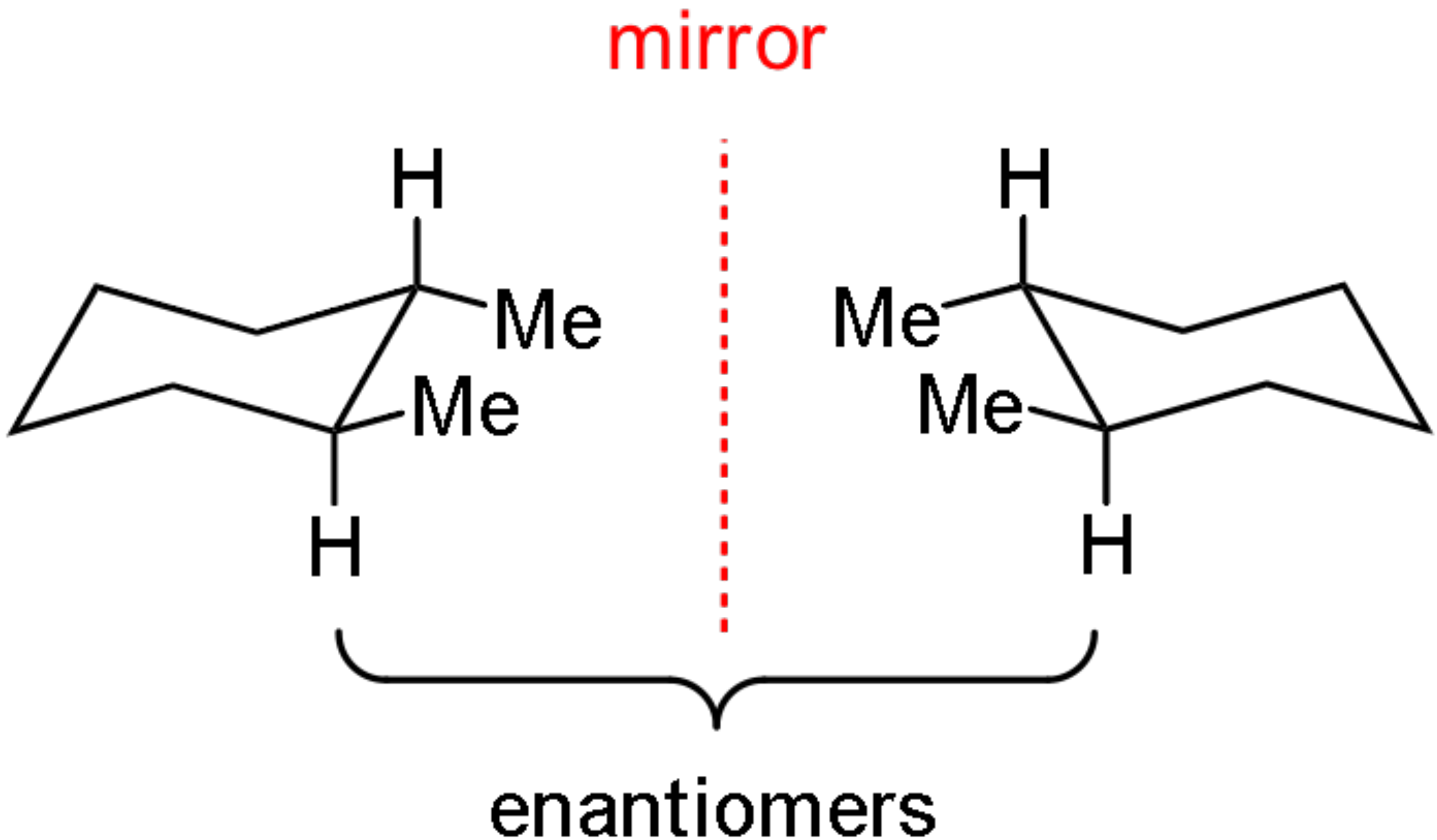
(meso)

trans-1,3-dimethyl
cyclohexane



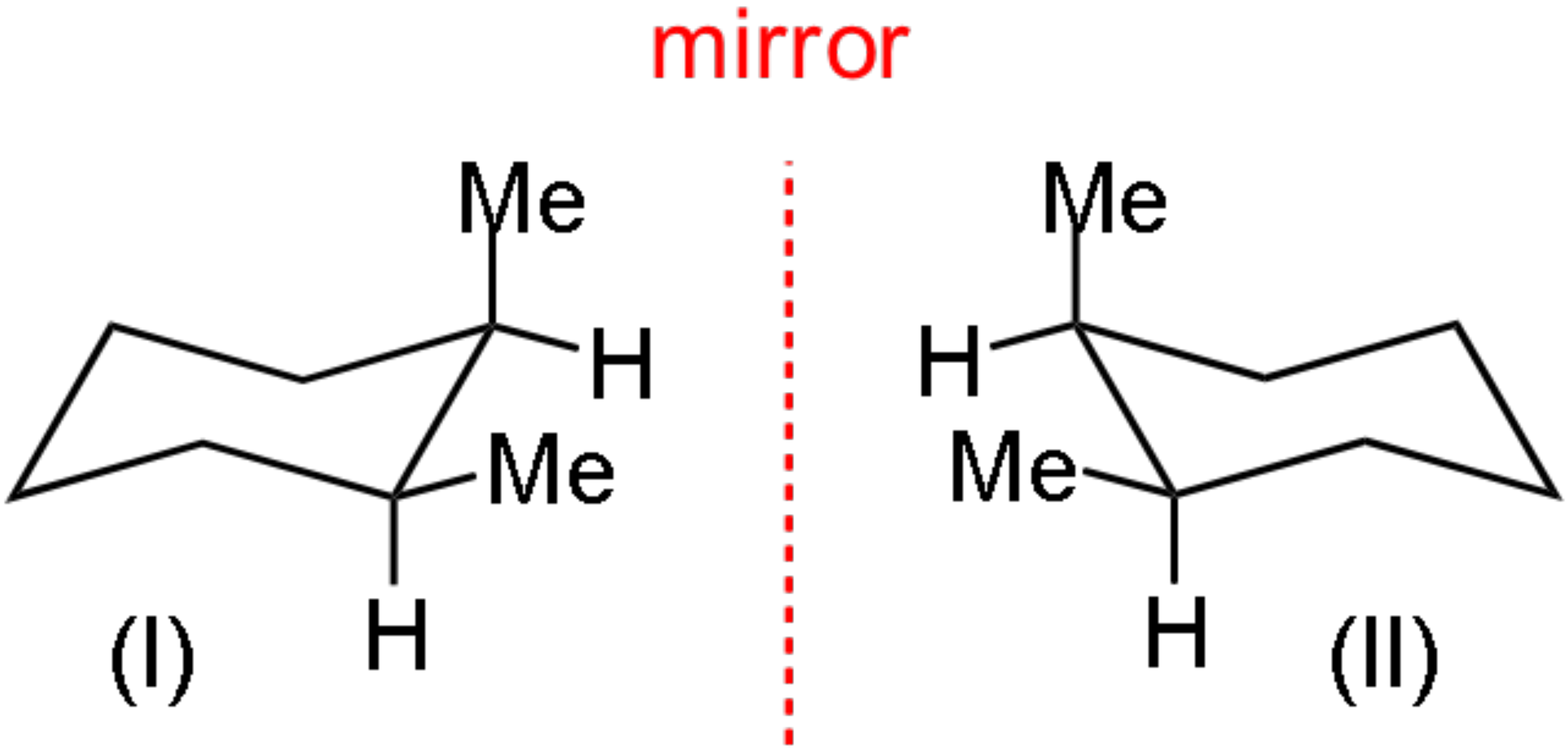
enantiomers

❖ 1,2-Dimethylcyclohexane



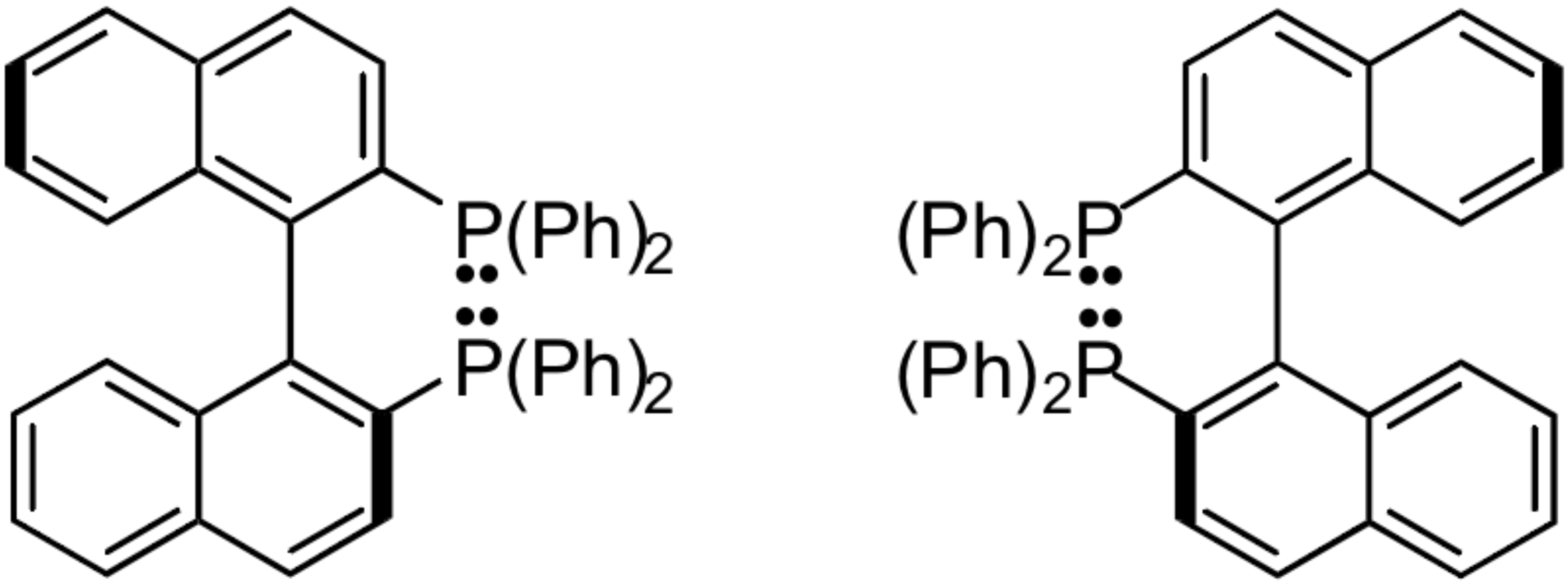
- *trans*-1,2-Dimethylcyclohexane exists as a pair of enantiomers

- 1,2-Dimethylcyclohexane
  - With *cis*-1,2-dimethylcyclohexane the situation is quite complicated



  - (I) and (II) are enantiomers to each other

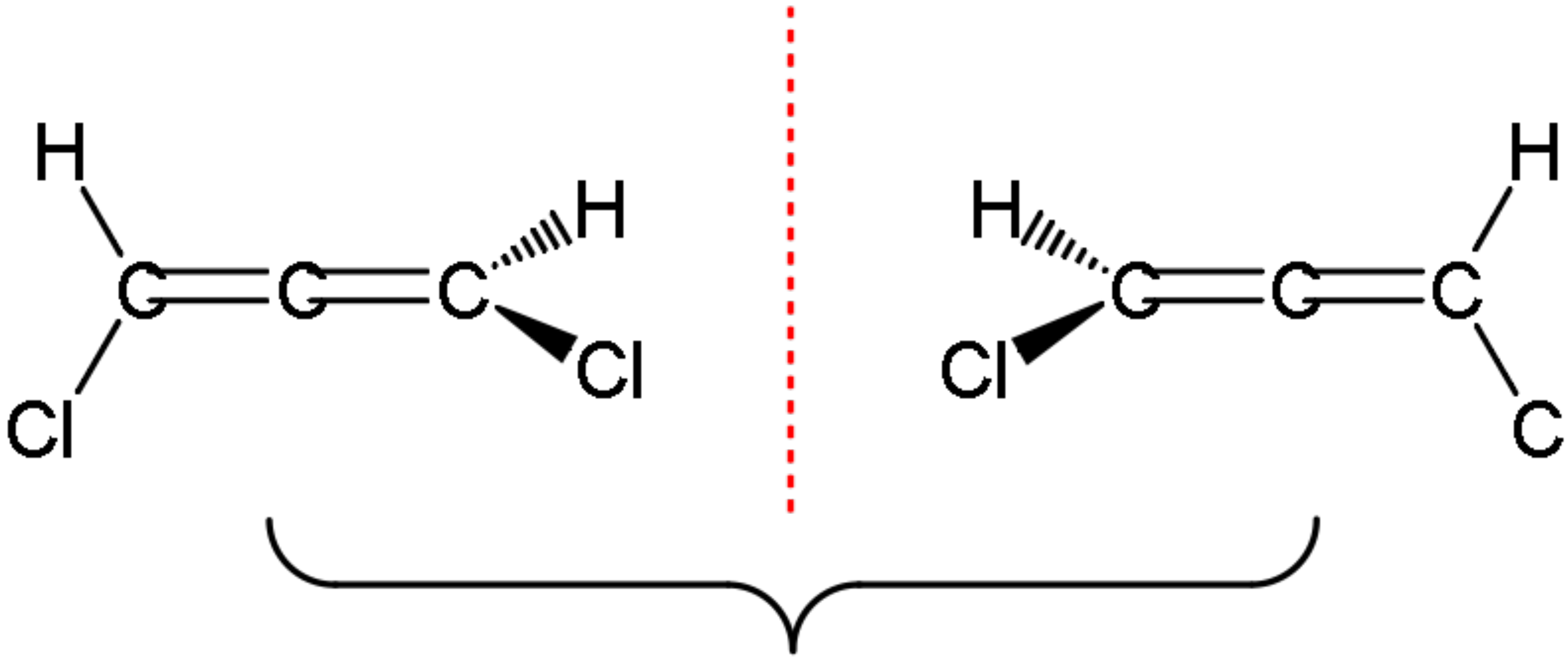
13. Chiral Molecules That Do Not Possess a Chirality Center



(S)-BINAP (R)-BINAP

enantiomers

mirror



enantiomers