# Chapter 5

# Stereochemistry

NEPHAR Organic Chemistry
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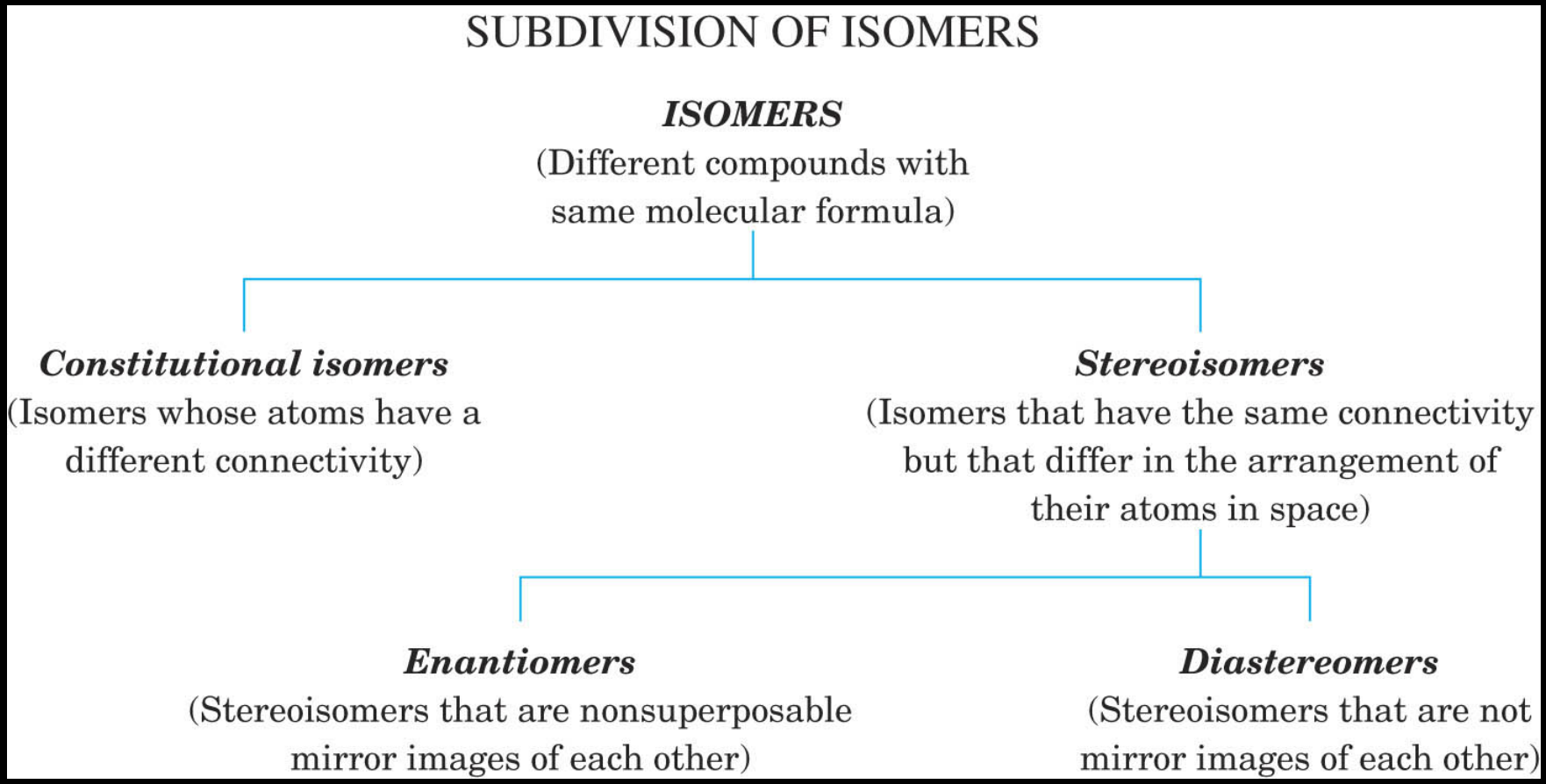
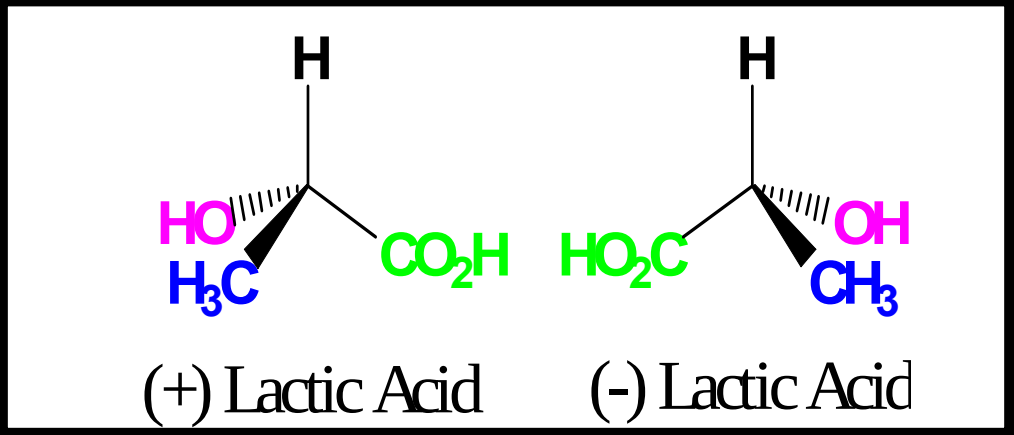
# 5.1 Isomerism: Constitutional Isomers and Stereoisomers

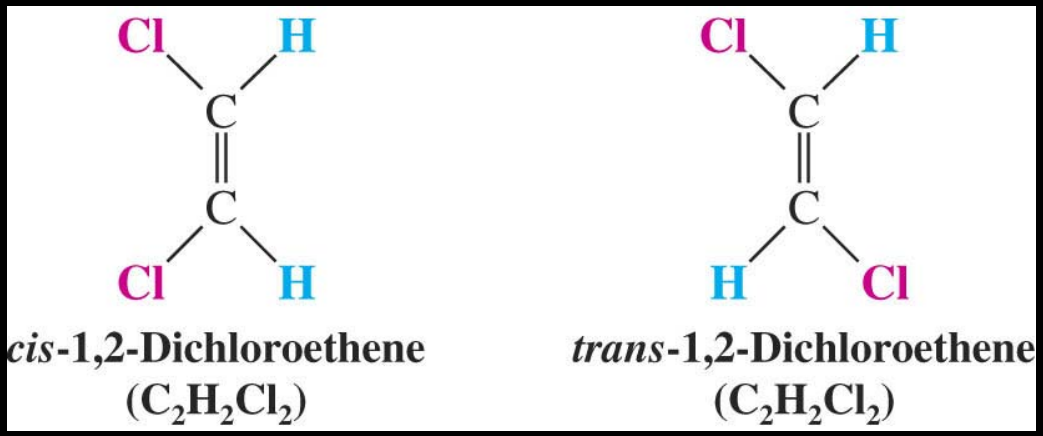
- **Stereoisomers are isomers with the same molecular formula and same connectivity of atoms but different arrangement of atoms in space**



- **Example of Enantiomers :** Lactic acid




- **Example Diastereomers :** cis and trans double bond isomers



# 5.2 Enantiomers and Chiral Molecules

➔ **Chiral molecule**

- Not superposable on its mirror image
- Can exist as a pair of enantiomers

➔ **Pair of enantiomers**

- A chiral molecule and its mirror image

➔ **Achiral molecule**

- Superposable on its mirror image

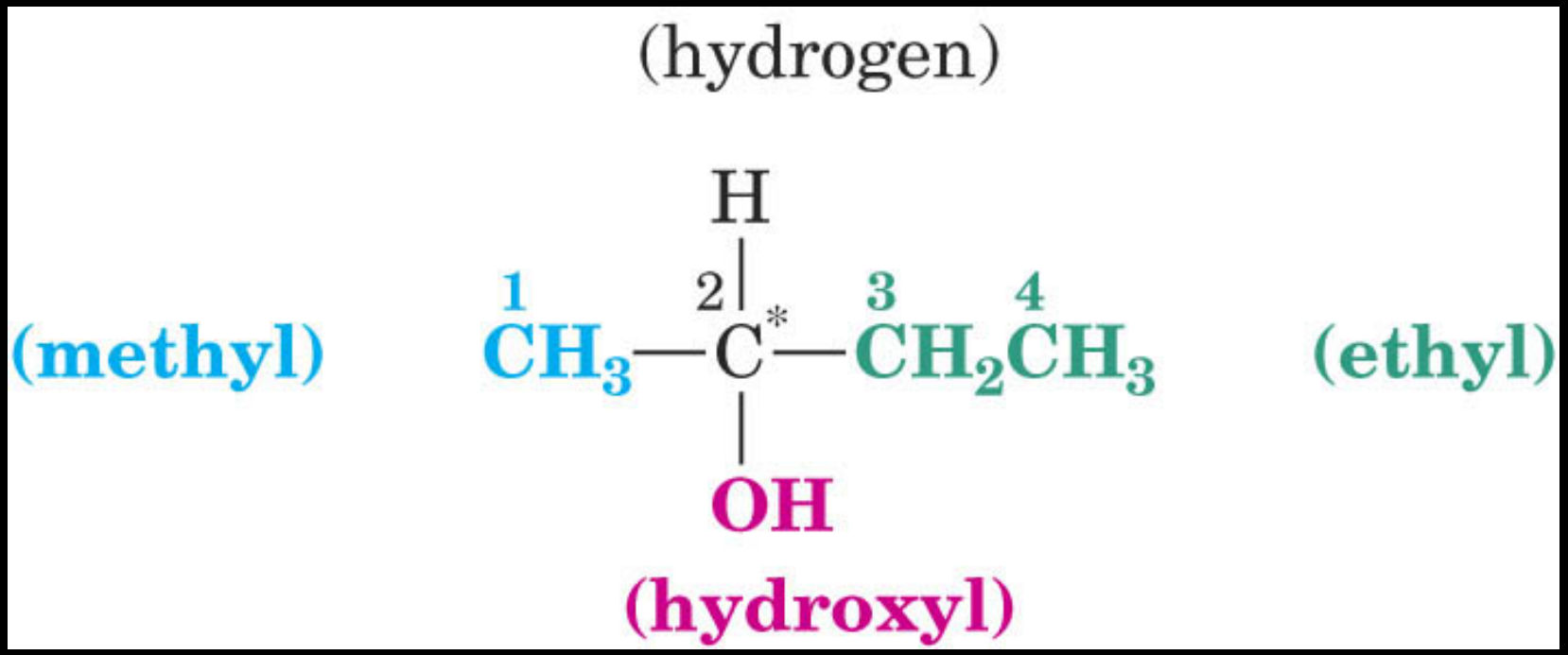
# Chiral Molecule

- A molecule with a single tetrahedral carbon bonded to four different groups will always be chiral
- A molecule with more than one tetrahedral carbon bonded to four different groups is not always chiral
- Switching two groups at the tetrahedral center leads to the enantiomeric molecule in a molecule with one tetrahedral carbon

# Stereogenic Center

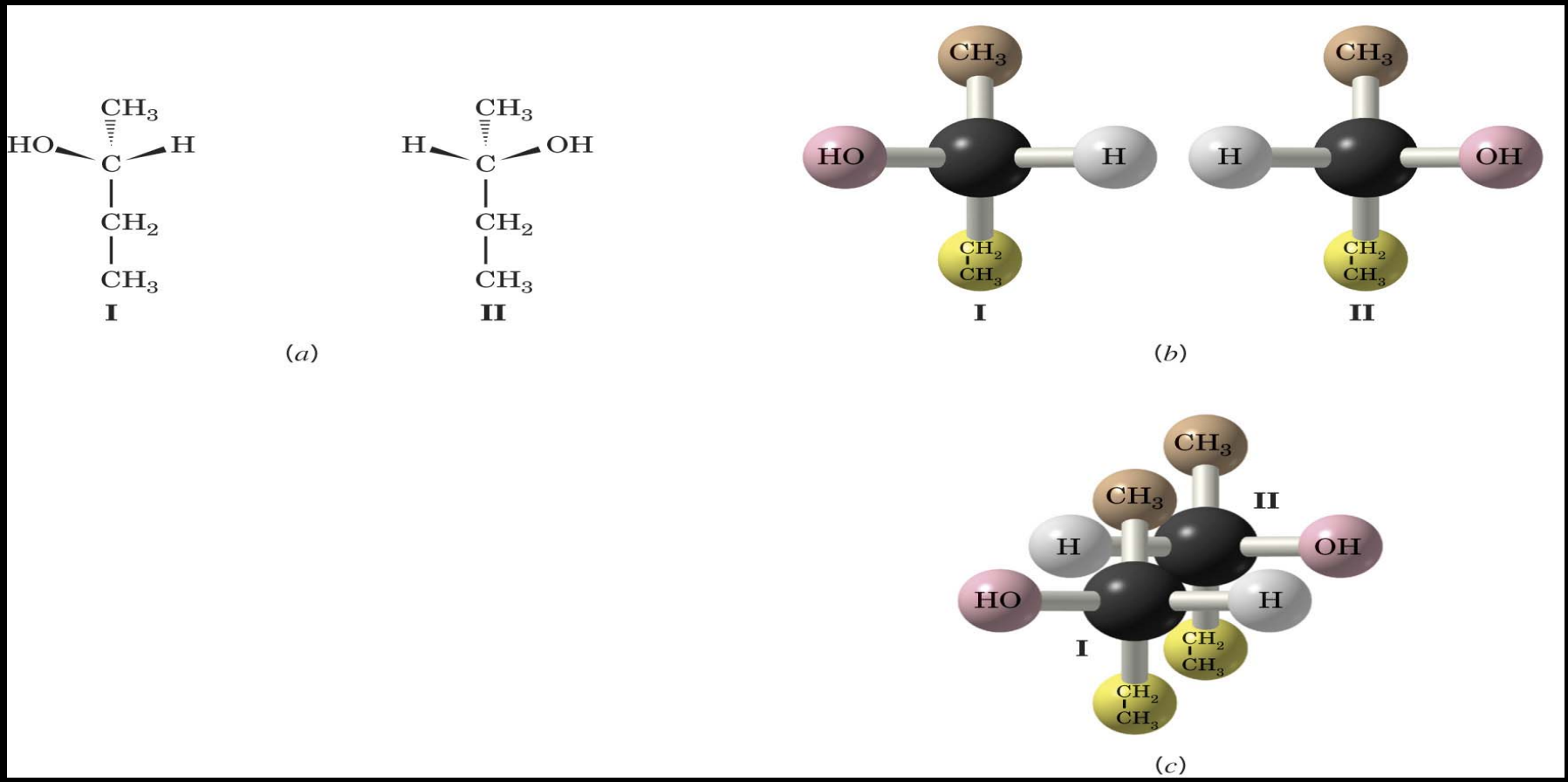
- An atom bearing groups of such nature that an interchange of any two groups will produce a stereoisomer
- Carbons at a tetrahedral stereogenic center are designated with an asterisk (*)

**Example**: 2-butanol



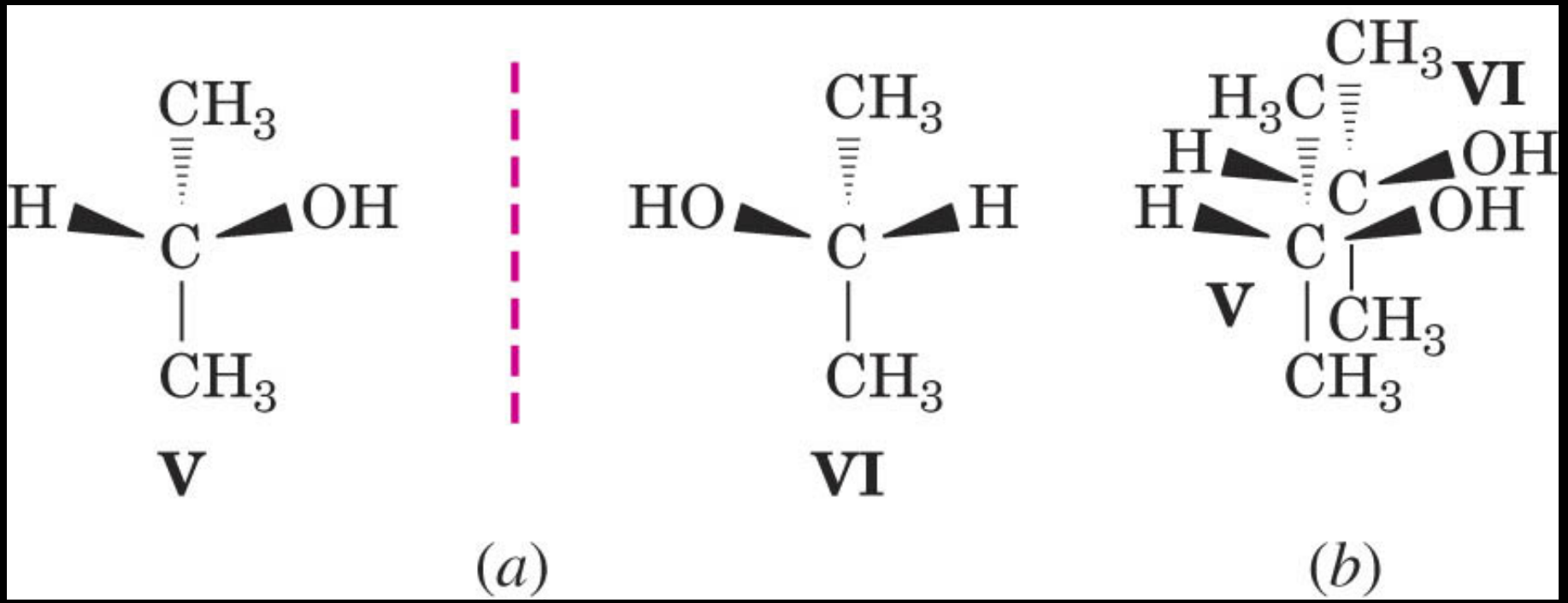
**Example**: 2-butanol

- I and II are mirror images of each other (figures a and b)
- I and II are not superposable and so are enantiomers (figure c)
- 2-butanol is a chiral molecule



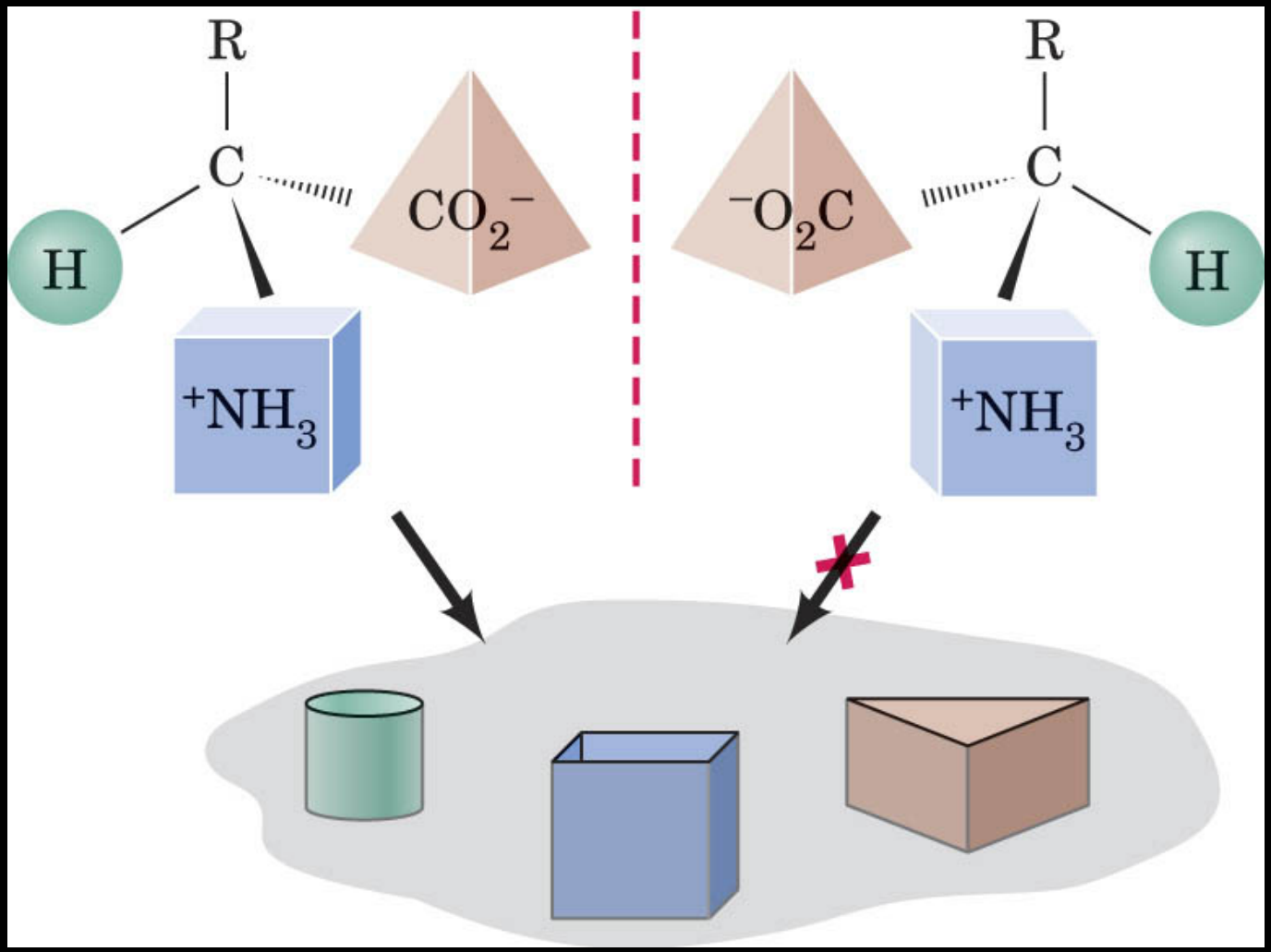
**Example**: (2-propanol) example of achiral?
Need to have 4 different substituent.

**Not chiral**



# 5.3 The Biological Importance of Chirality

➔The binding specificity of a chiral receptor site for a chiral molecule is usually only favorable in one way

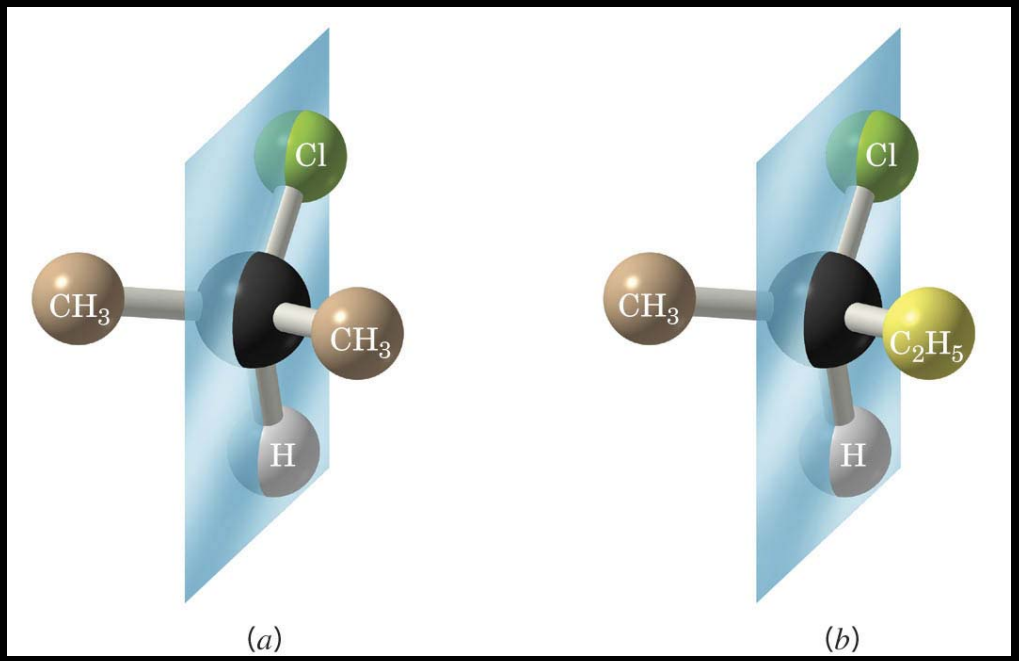


# 5.5 Tests for Chirality: Planes of Symmetry

- An imaginary plane that bisects a molecule in such a way that the two halves of the molecule are mirror images of each other
- A molecule with a plane of symmetry cannot be chiral

➔**Example**

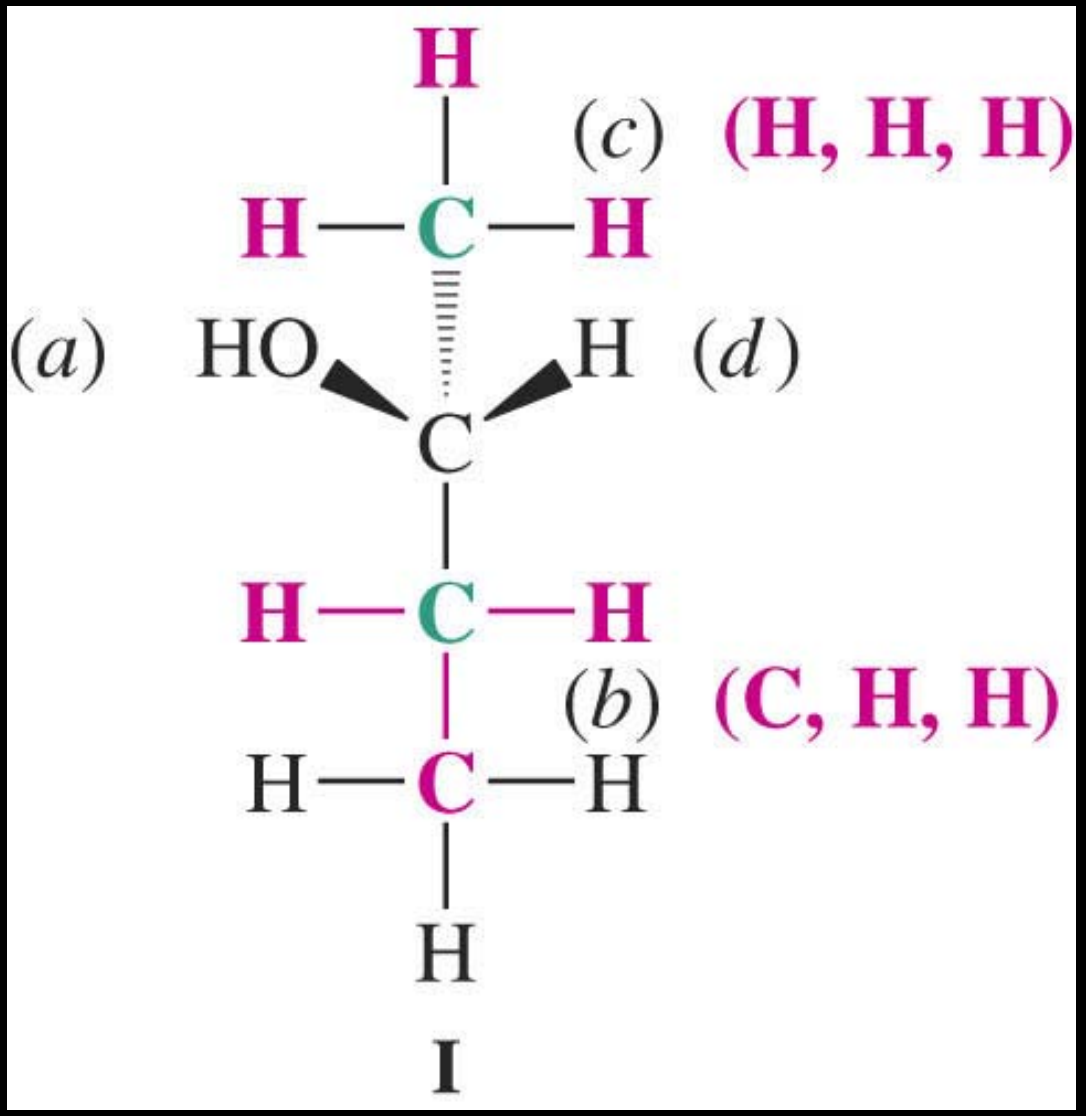
2-chloropropane **(a)** has a plane of symmetry but 2-chlorobutane **(b)** does not



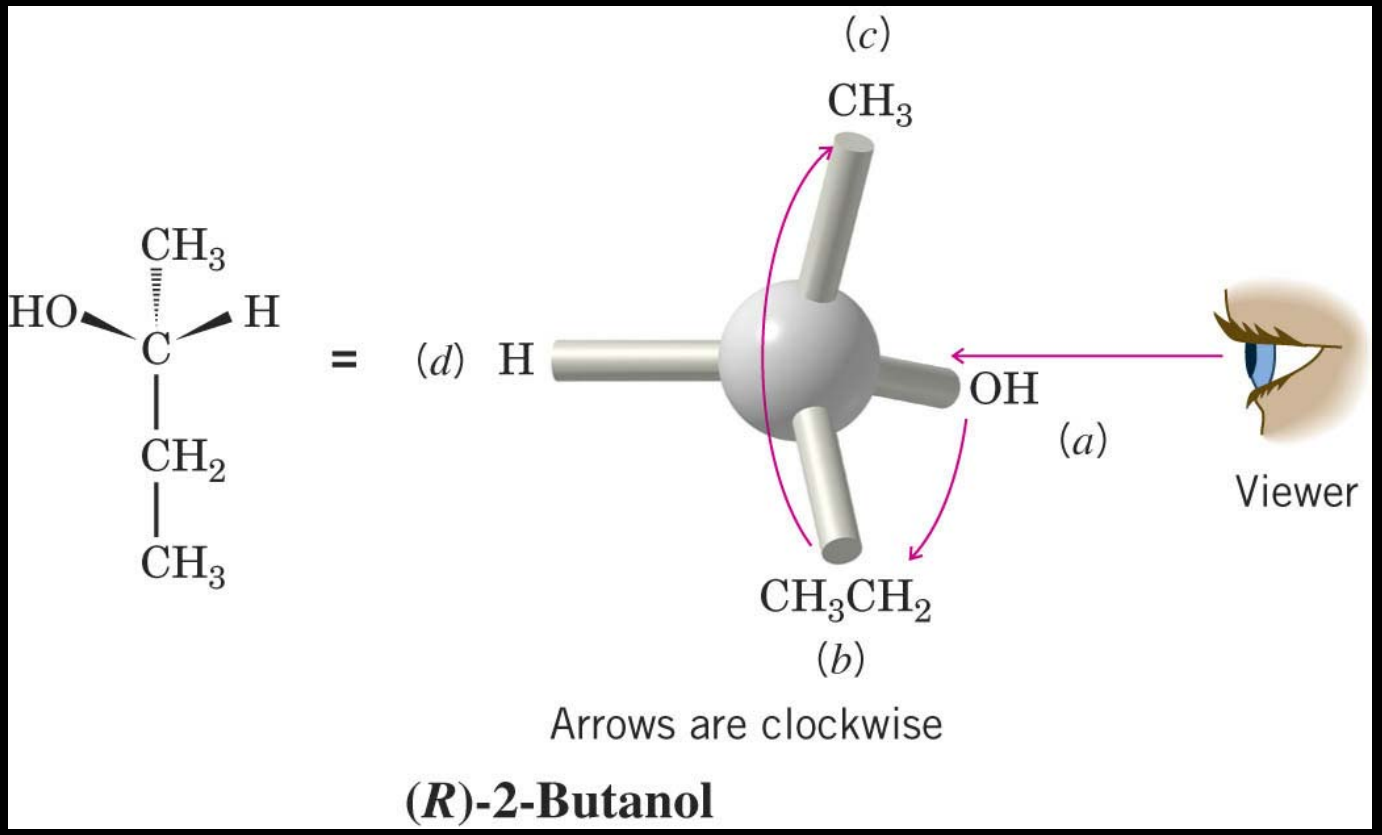
# 5.6 Nomenclature of Enantiomers: The *R,S* System

- Also called the Cahn-Ingold-Prelog system
- The four groups attached to the stereogenic carbon are assigned priorities from highest (a) to lowest (d)
- Priorities are assigned as follows
  - Atoms directly attached to the stereogenic center are compared
  - Atoms with higher atomic number are given higher priority
  - If priority cannot be assigned based on directly attached atoms, the next layer of atoms is examined

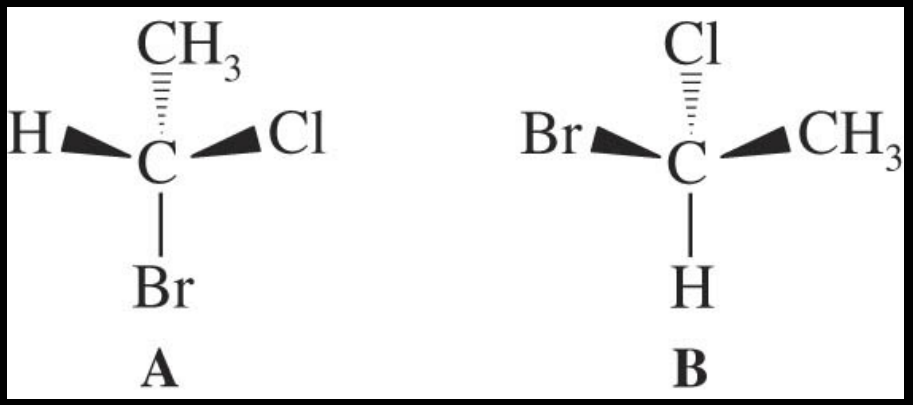
# Example



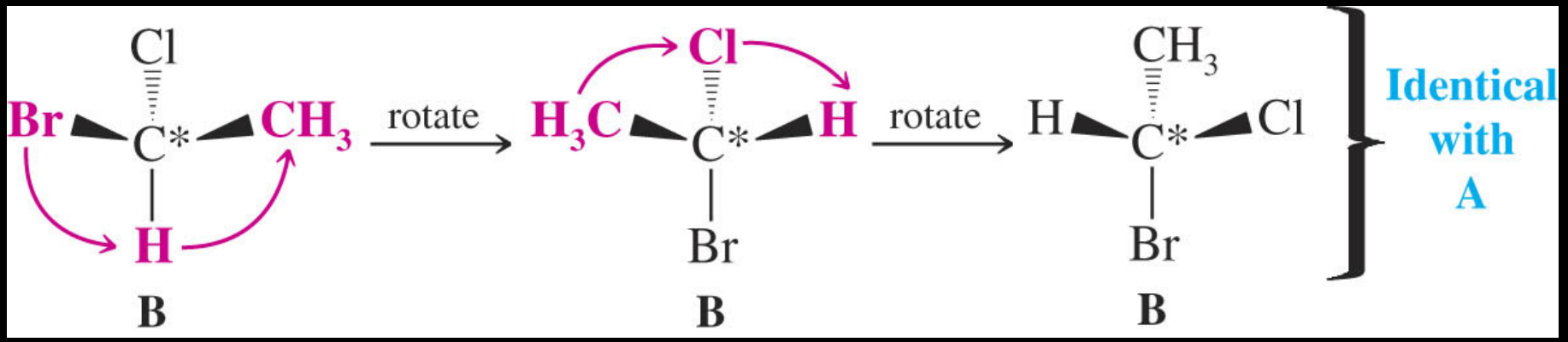
- The molecule is rotated to put the **lowest priority group back**
  - ➔ If the groups descend in priority (a,b then c) in **clockwise** direction the enantiomer is ***R***
  - ➔ If the groups descend in priority in **counterclockwise** direction the enantiomer is ***S***



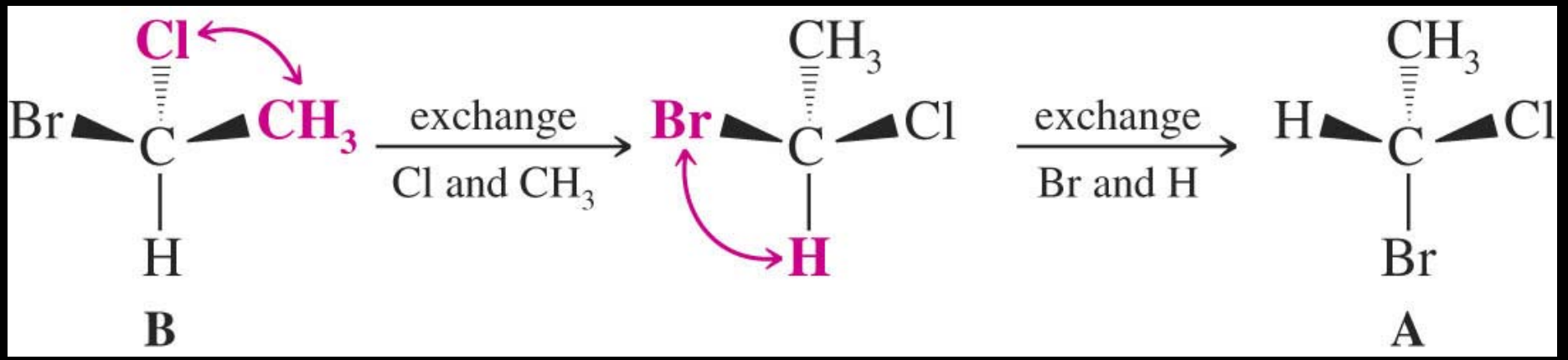
- **Problem: Are A and B identical or enantiomers?**




➔ **Manipulate B to see if it will become superposable with A**



- Exchange 2 groups to try to convert B into A
- One exchange of groups leads to the enantiomer of B
- Two exchanges of groups leads back to B

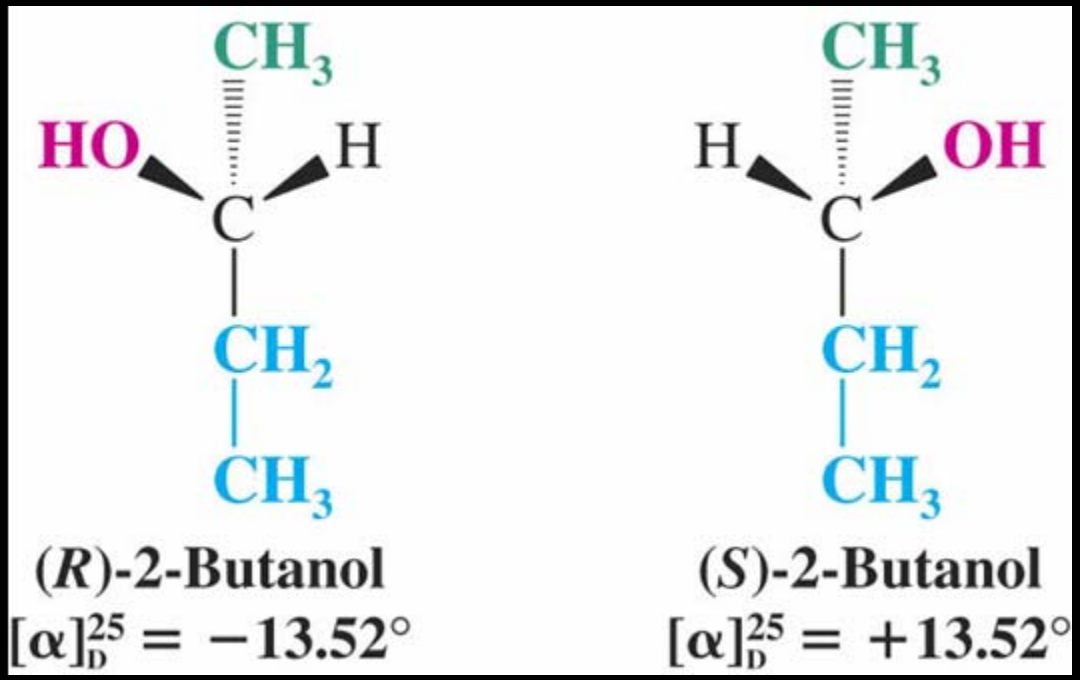


# 5.7 Properties of Enantiomers: Optical Activity

- Enantiomers have almost all identical physical properties (melting point, boiling point, density)

- However enantiomers rotate the plane of plane-polarized light in equal but opposite directions

- The specific rotation of the two pure enantiomers of 2-butanol are equal but opposite




- There is no straightforward correlation between the *R,S* designation of an enantiomer and the direction [(+) or (-)]in which it rotates plane polarized light

# Racemic mixture

- A 1:1 mixture of enantiomers
- No net optical rotation
- Often designated as (±)

(±)-2-butanol or as (±)-$CH_3CH_2CHOHCH_3$

# Racemic Forms and Enantiomeric Excess

- Often a mixture of enantiomers will be enriched in one enantiomer
  - ➔One can measure the **enantiomeric excess** (**ee**)

$$\%\ \text{Enantiomeric excess} = \frac{\text{moles of one enantiomer} - \text{moles of other enantiomer}}{\text{total moles of both enantiomers}} \times 100$$

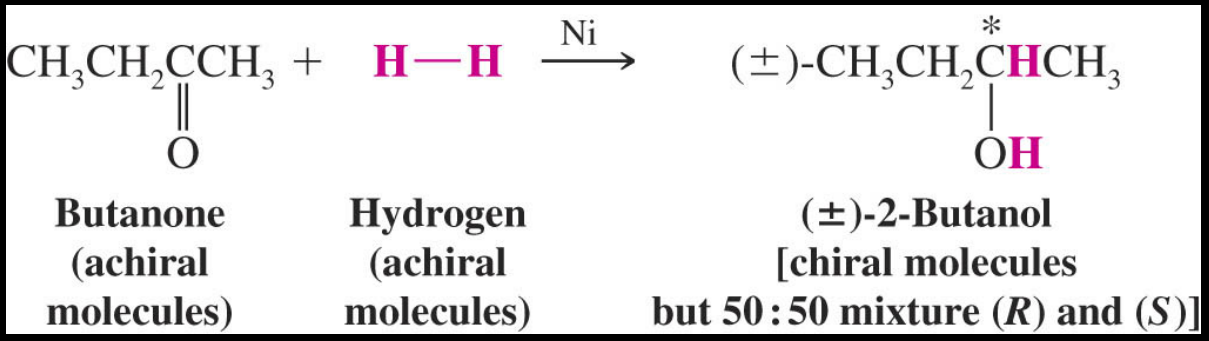
$$\%\ \text{Enantiomeric excess*} = \frac{\text{observed specific rotation}}{\text{specific rotation of the pure enantiomer}} \times 100$$

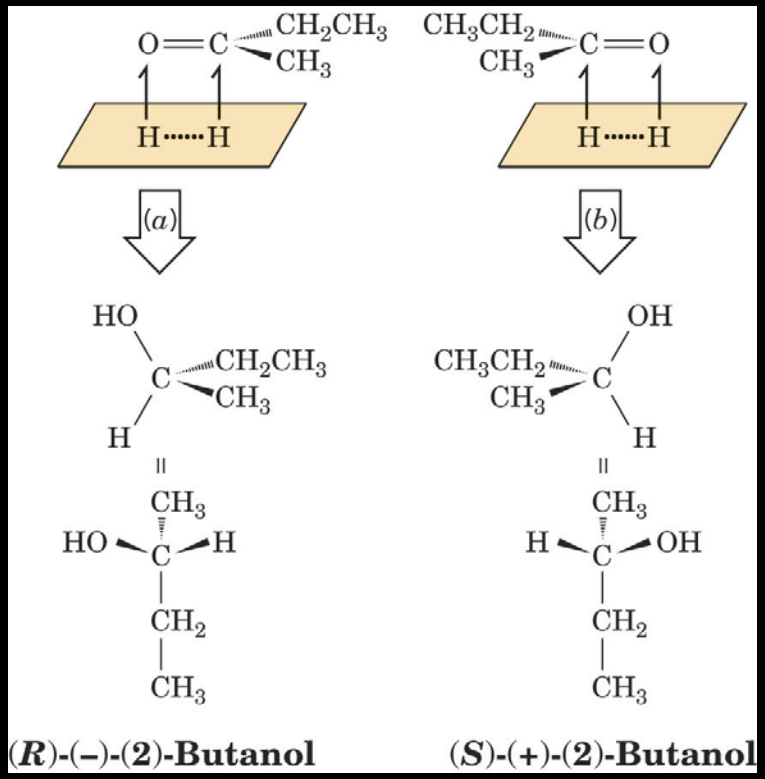
- Example : The optical rotation of a sample of 2-butanol is +6.76°. What is the enantiomeric excess?

$$\text{Enantiomeric excess} = \frac{+6.76^\circ}{+13.52^\circ} \times 100 = 50\%$$

# 5.9 The Synthesis of Chiral Molecules

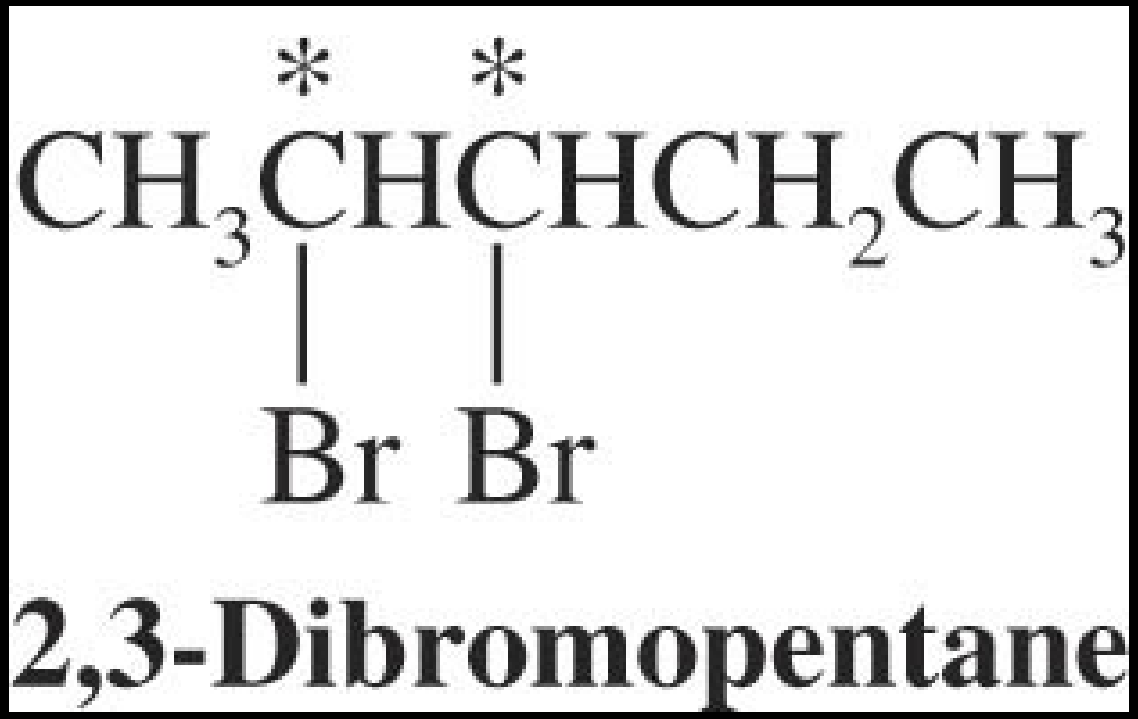
**Most chemical reactions which produce chiral molecules produce them in racemic form**

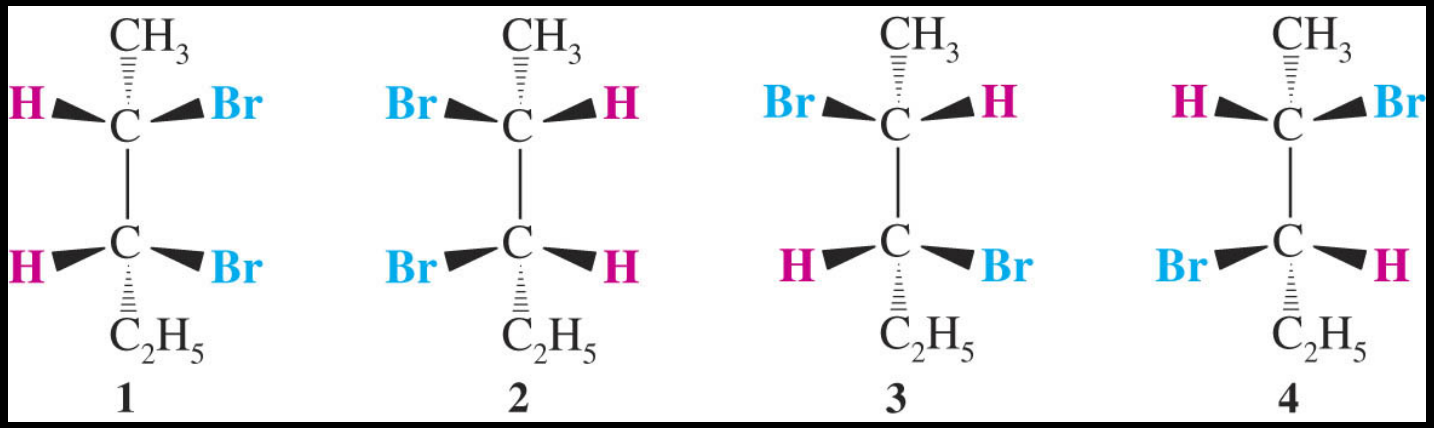


# Molecules with More than One Stereogenic Center

- The maximum number of stereoisomers available will not exceed $2^n$, where n is equal to the number of tetrahedral stereogenic centers



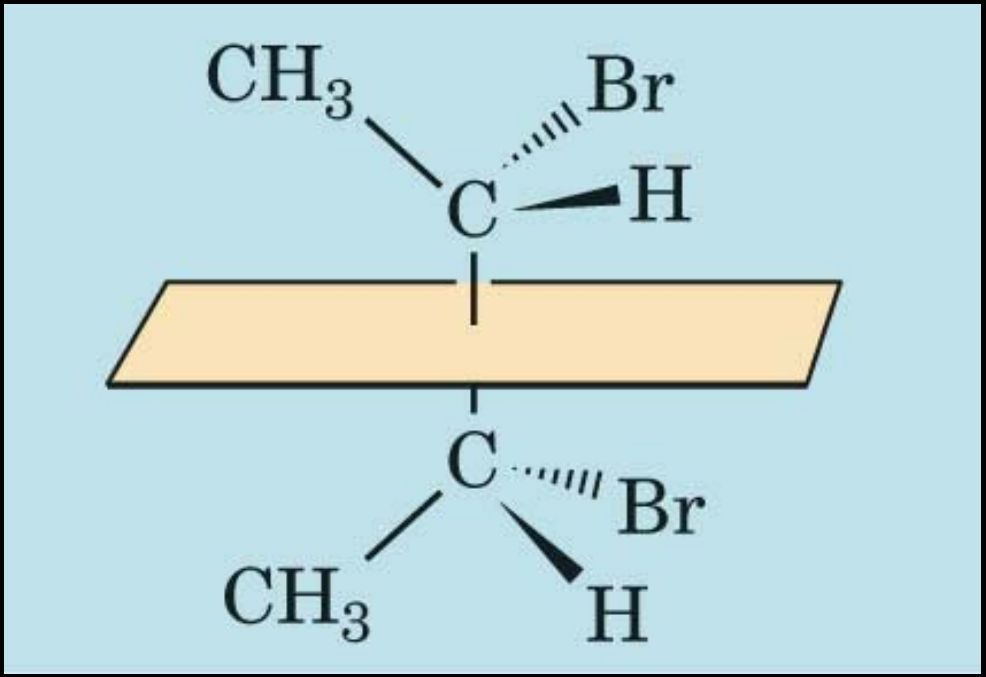



- There are two pairs of enantiomers (1, 2) and (3,4)
  - ➔Enantiomers are not easily separable so 1 and 2 cannot be separated from each other
- Diastereomers: stereoisomers which are not mirror images of each other
  - ➔For instance 1 and 3 or 1 and 4
  - ➔Have different physical properties and can be separated

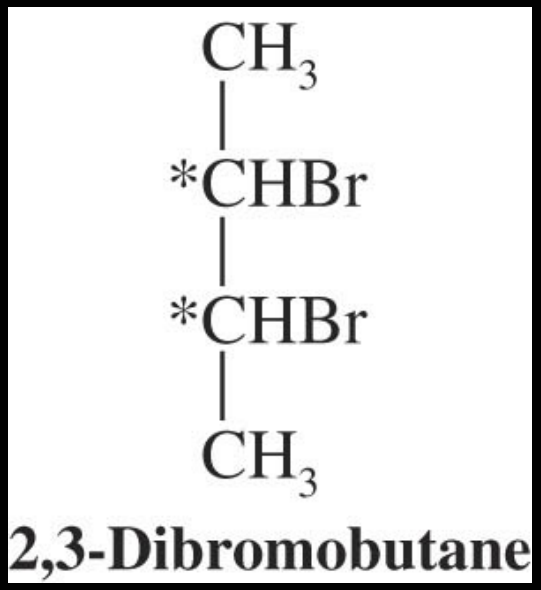
- **Meso Compound**

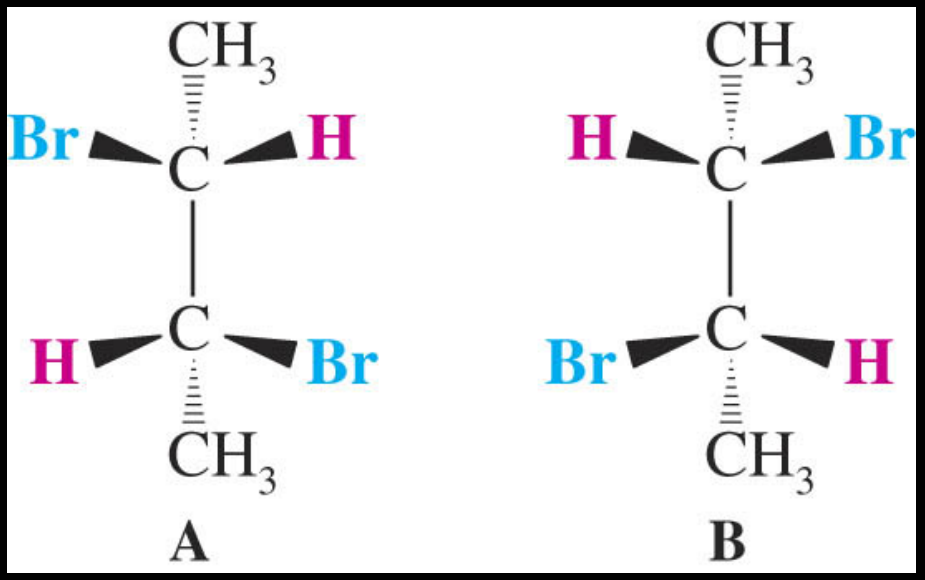
  achiral despite the presence of stereogenic centers

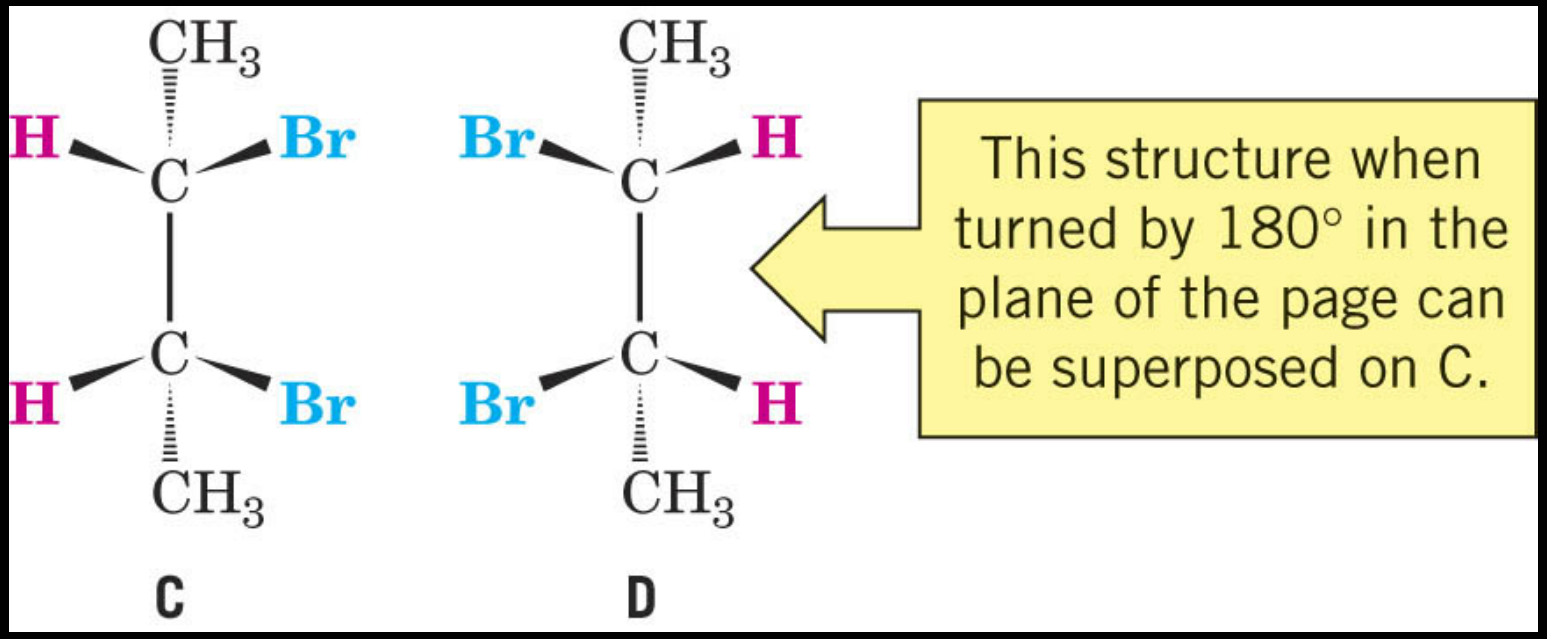
  - ➔ Not optically active
  - ➔ Superposable on its mirror image
  - ➔ Has a plane of symmetry



# Example for Meso Compounds

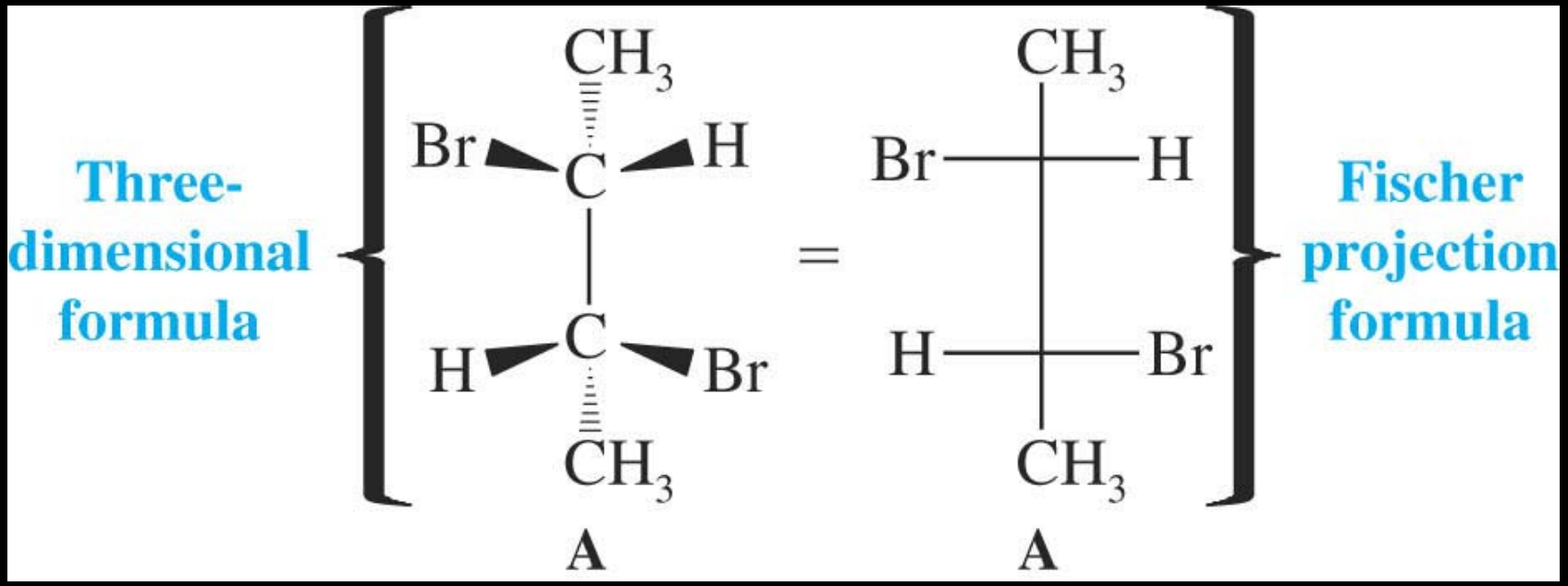


# Fischer Projection Formulas

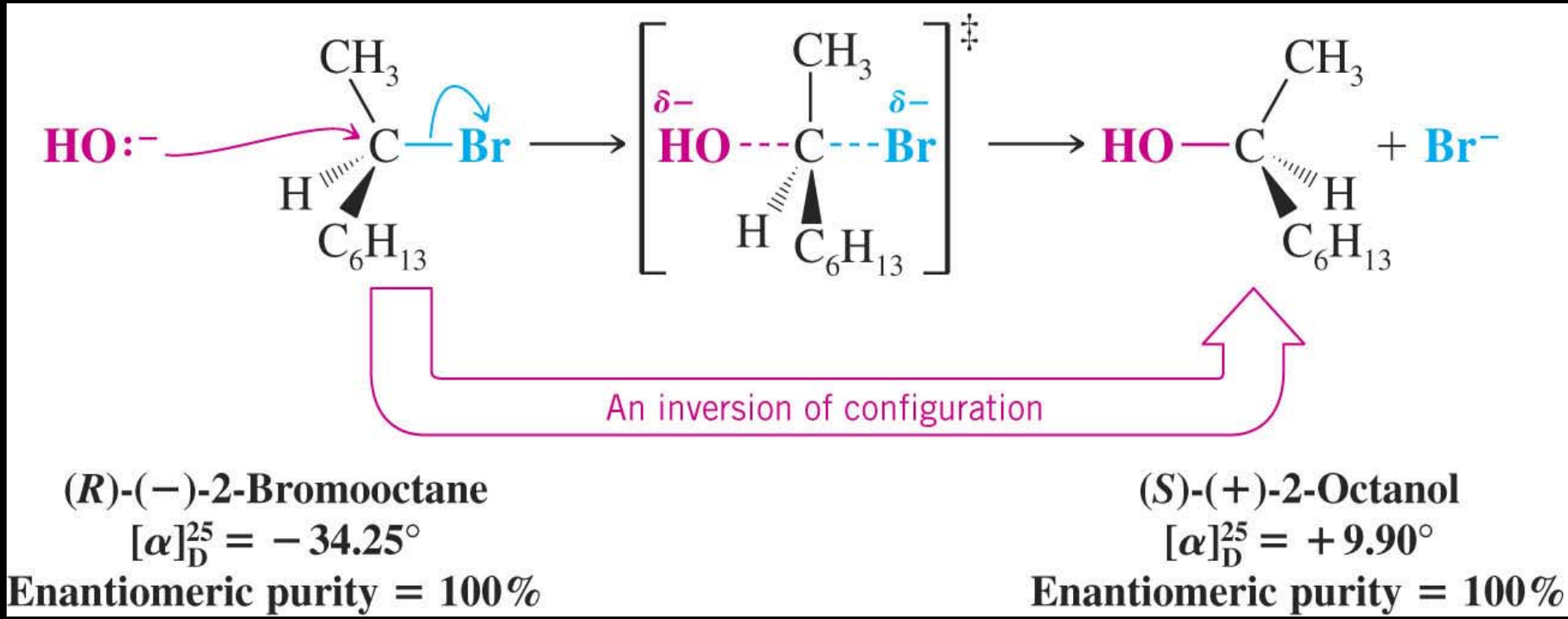
- A 2-dimensional representation of chiral molecules
  - ➔Vertical lines represent bonds that project behind the plane of the paper
  - ➔Horizontal lines represent bonds that project out of the plane of the paper



# 6.9 The Stereochemistry of $S_N2$ Reactions

➔ **Stereochemistry can be controlled in $S_N2$ reactions**

- **Backside attack of nucleophile results in an inversion of configuration**




**(*R*)-(−)-2-Bromooctane**
$[\alpha]_D^{25} = -34.25°$
**Enantiomeric purity = 100%**

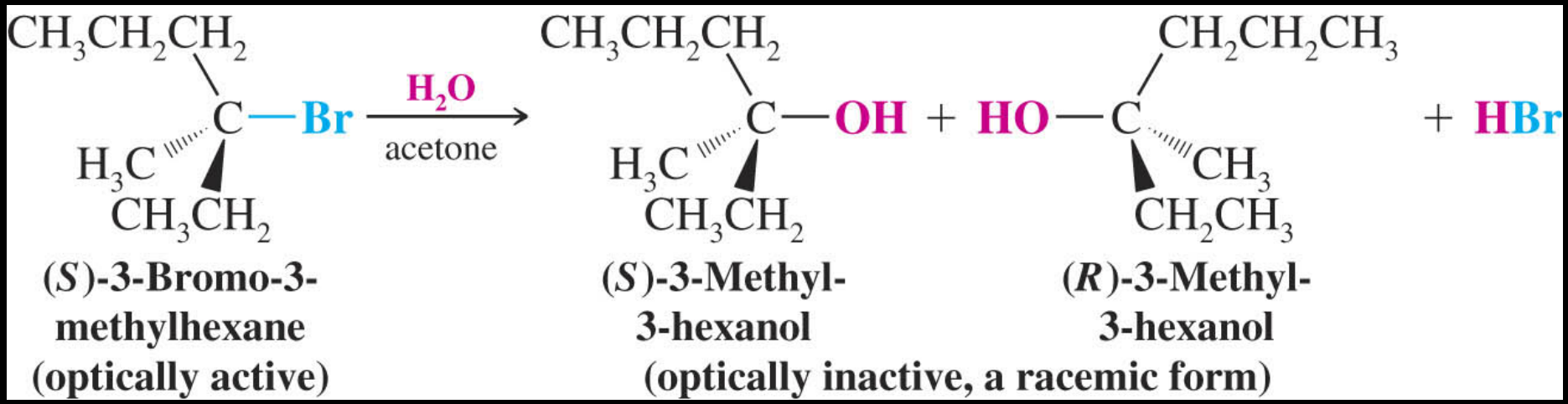
**(*S*)-(+)-2-Octanol**
$[\alpha]_D^{25} = +9.90°$
**Enantiomeric purity = 100%**

# 6.13 The Stereochemistry of $S_N1$ Reactions

➔When the leaving group leaves from a stereogenic center of an optically active compound in an $S_N1$ reaction, racemization will occur

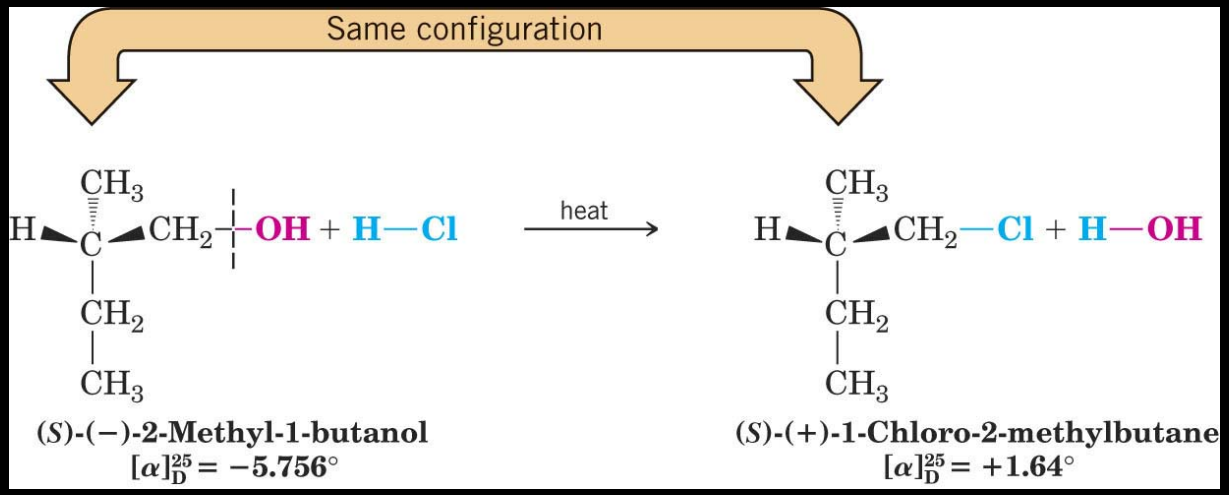
- This is because an achiral carbocation intermediate is formed

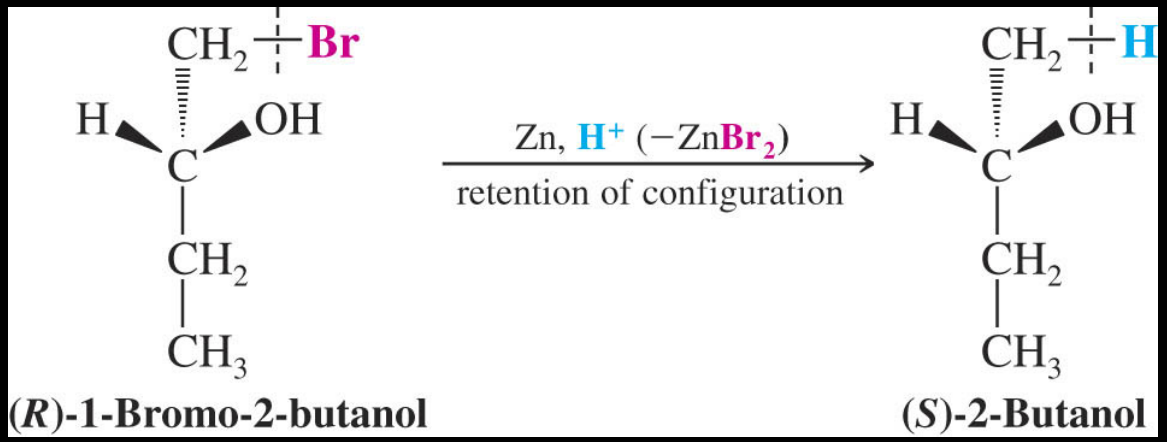
**Racemization**: transformation of an optically active compound to a racemic mixture



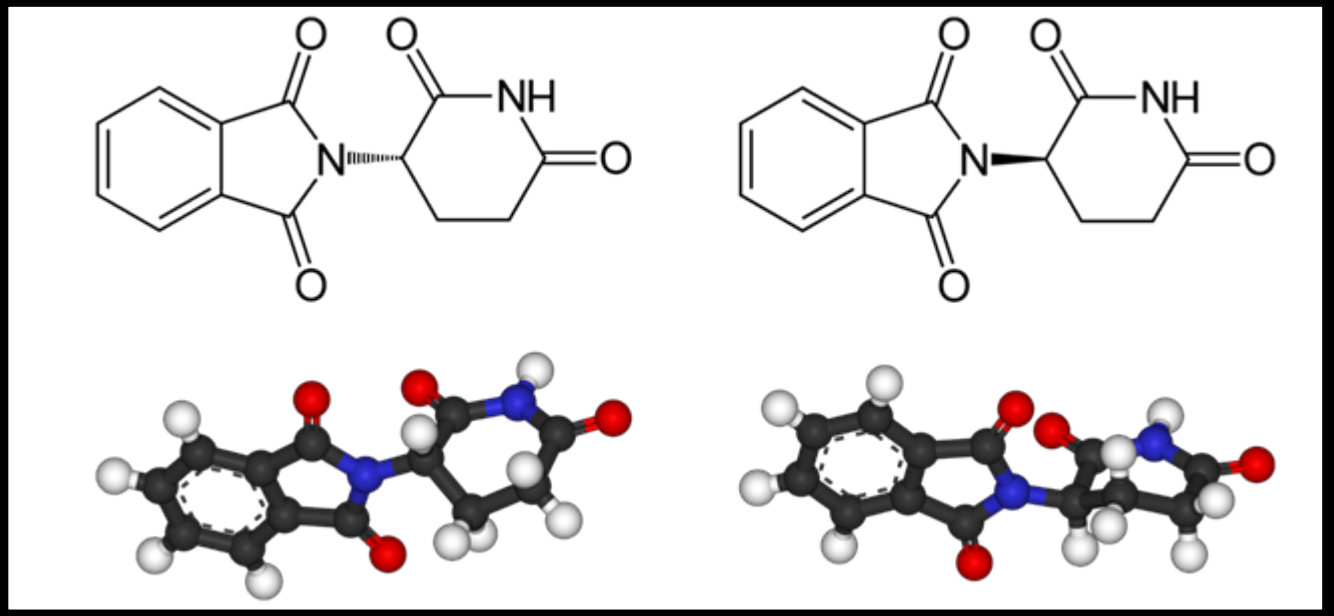
## ♦ Relating Configurations through Reactions in which No Bonds to the Stereogenic Carbon are Broken

➔A reaction which takes place in a way that no bonds to the stereogenic carbon are broken is said to proceed with ***retention of configuration***



# Example of Importance of Enantiomers in Drugs




The two enantiomers of thalidomide:
(*S*)-thalidomide (*R*)-thalidomide

Thalidomide is racemic – it contains both left- and right-handed isomers in amounts.
The (*R*) enantiomer is effective against morning sickness. The (*S*) is teratogenic and causes birth defects