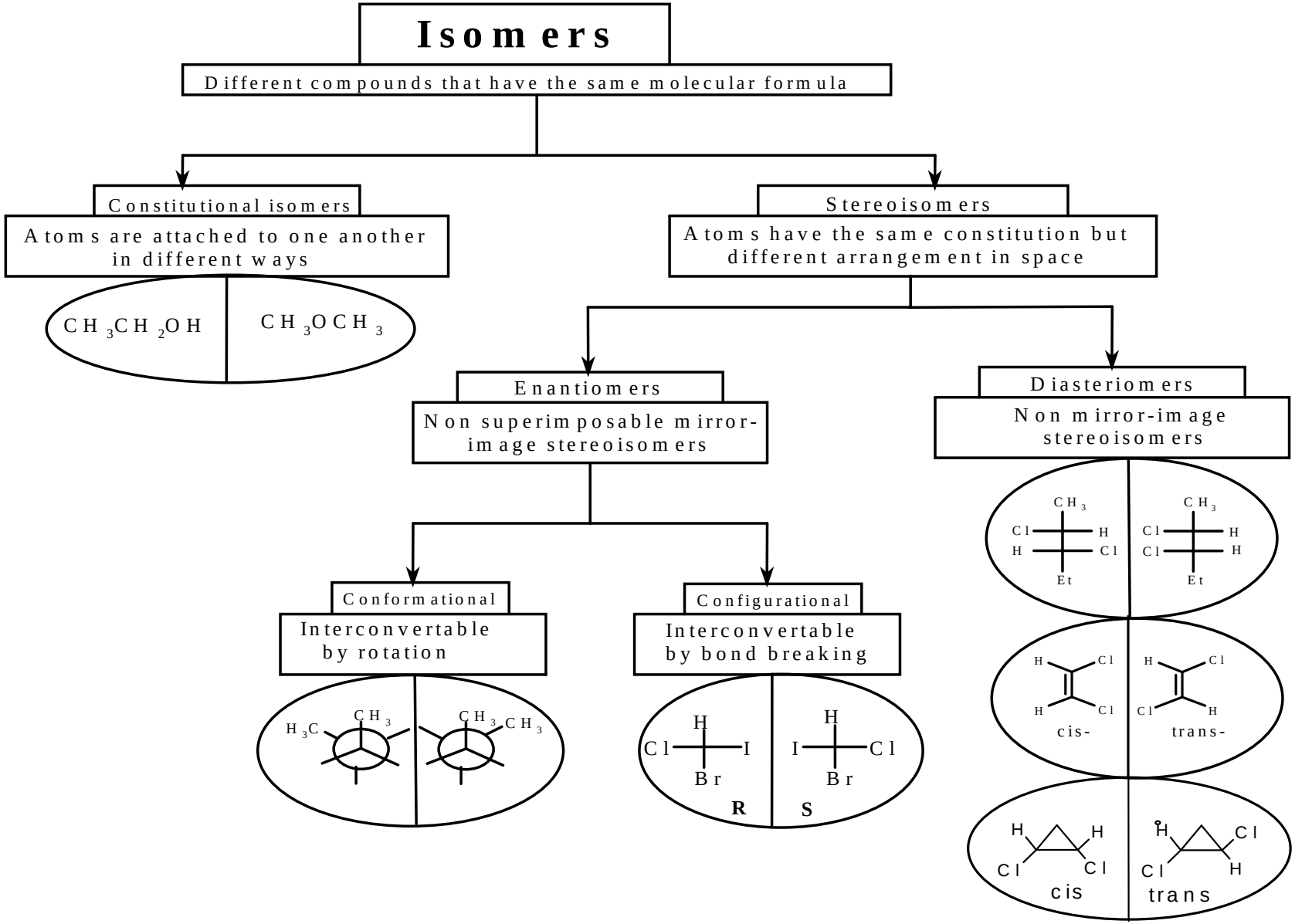
Stereochemistry

Stereochemistry:

That part of the science which deals with structure *in three dimensions*

Stereochemistry

Isomers: different compounds having the same molecular formula



Isomers – different compounds with the same molecular formula.

Structural Isomers – isomers that differ in which atoms are bonded to which atoms.

eg. C_4H_{10} $CH_3CH_2CH_2CH_3$ *n*-butane CH_3CHCH_3 (with CH_3) isobutane

constitutional isomers

CH_3CH_2OH and CH_3OCH_3
ethanol dimethyl ether

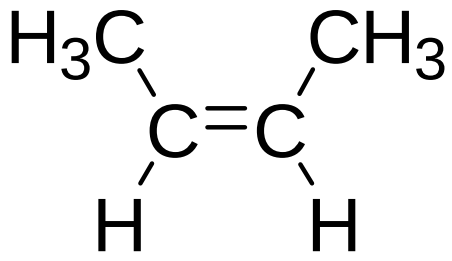
$CH_3CH_2CH_2CH_2Cl$ and $CH_3CH_2CHCH_3$ (with Cl)
1-chlorobutane 2-chlorobutane

$CH_3CH_2CH_2CH_2CH_3$ and $CH_3CHCH_2CH_3$ (with CH_3)
pentane isopentane

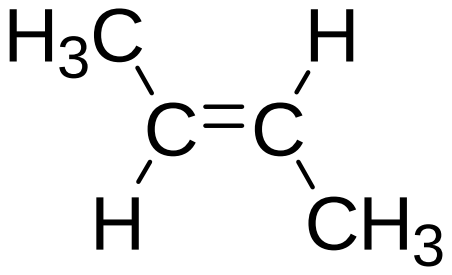
CH_3CCH_3 (with O) and CH_3CH_2CH (with O)
acetone propionaldehyde

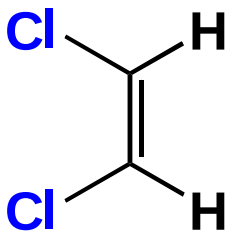
Stereoisomers – isomers that differ in the way the atoms are oriented in space, but <u>not</u> in which atoms are bonded to which atoms.

eg. *cis*-2-butene

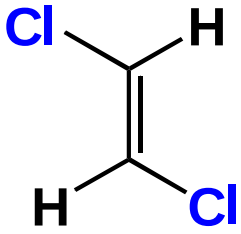


trans-2-butene





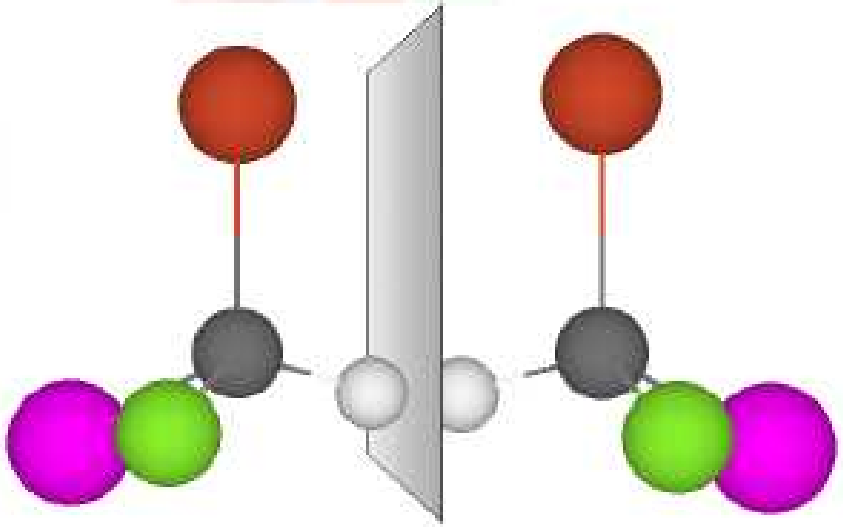
***cis*-1,2-Dichloroethene**



***trans*-1,2-Dichloroethene**

$C_2H_2Cl_2$

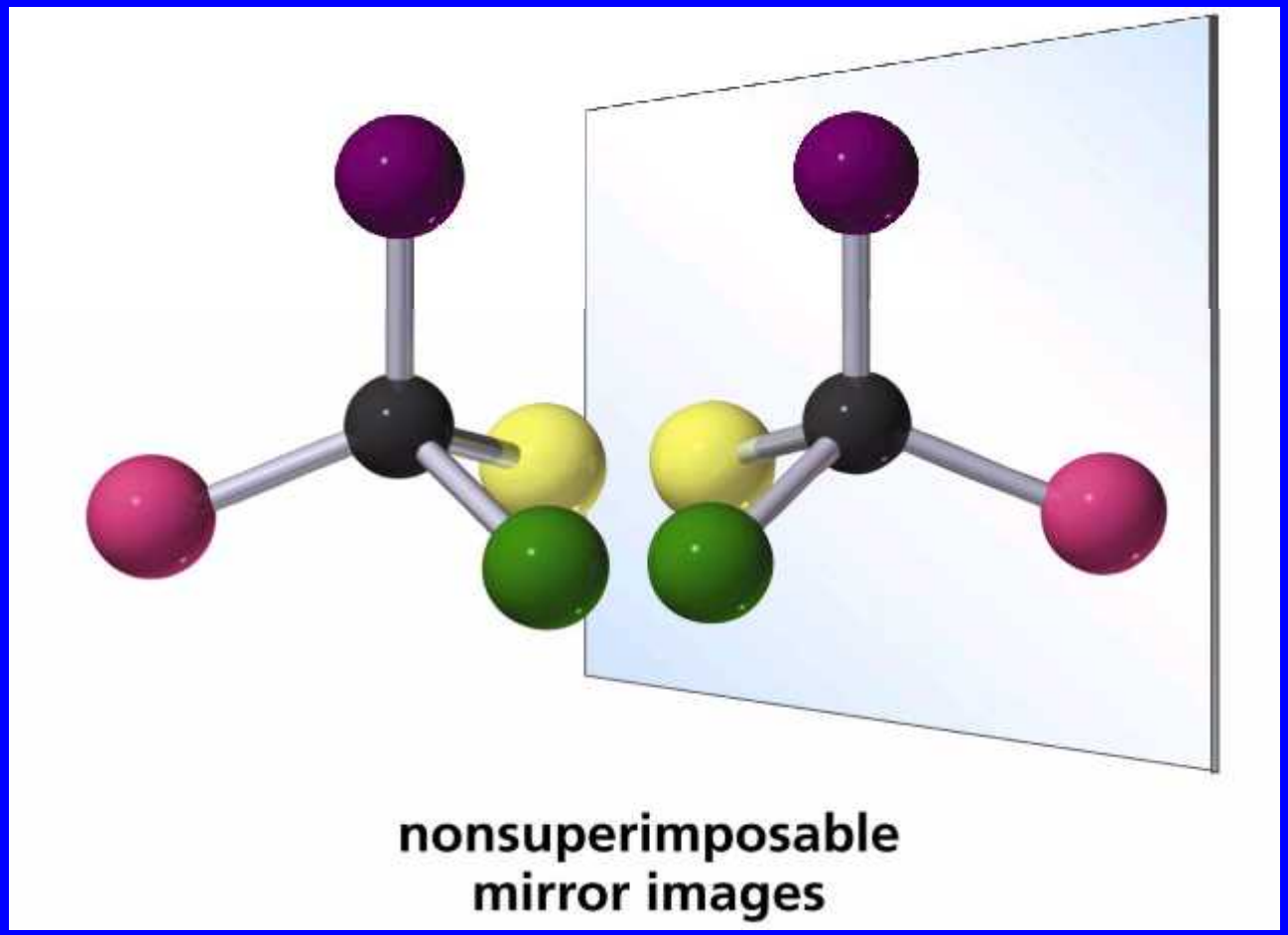
A carbon which is attached to four different substituents is called a chiral carbon...and a pair of non-superimposible mirror images are called enantiomers.

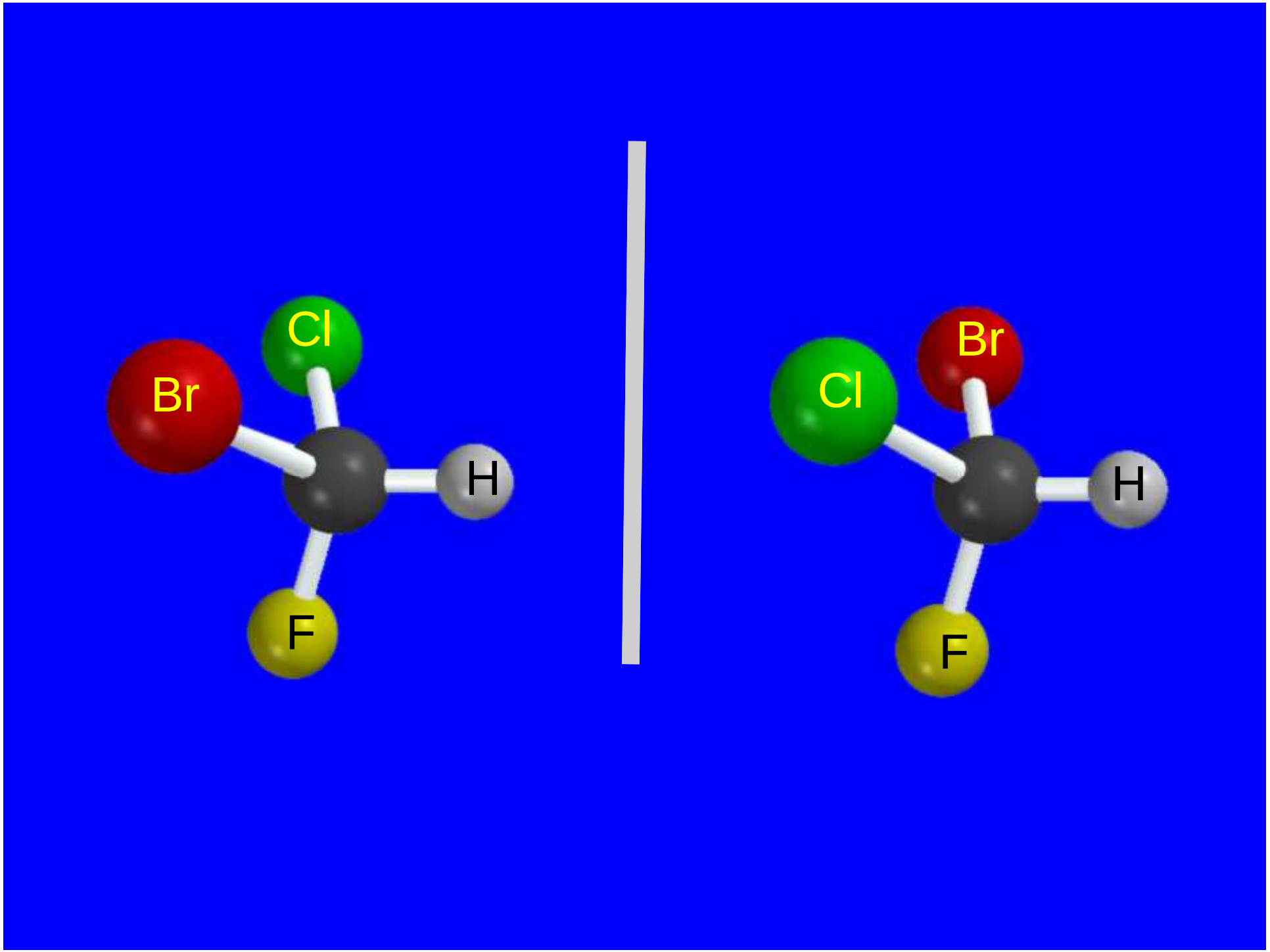


...a pair of enantiomers

Chirality Center

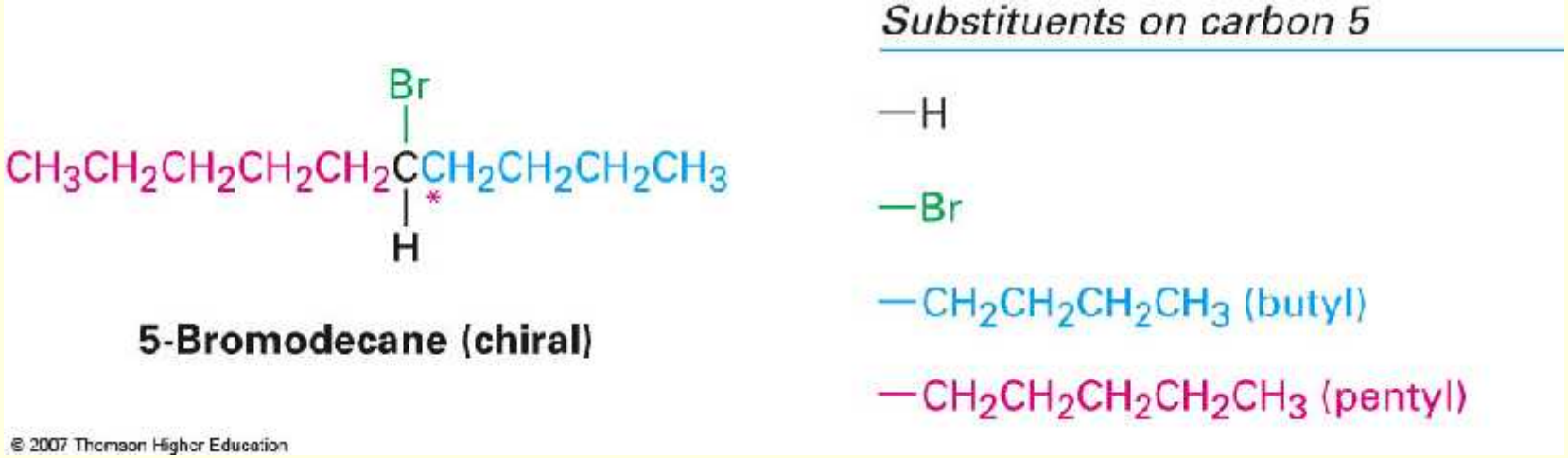
Carbon has four different groups attached



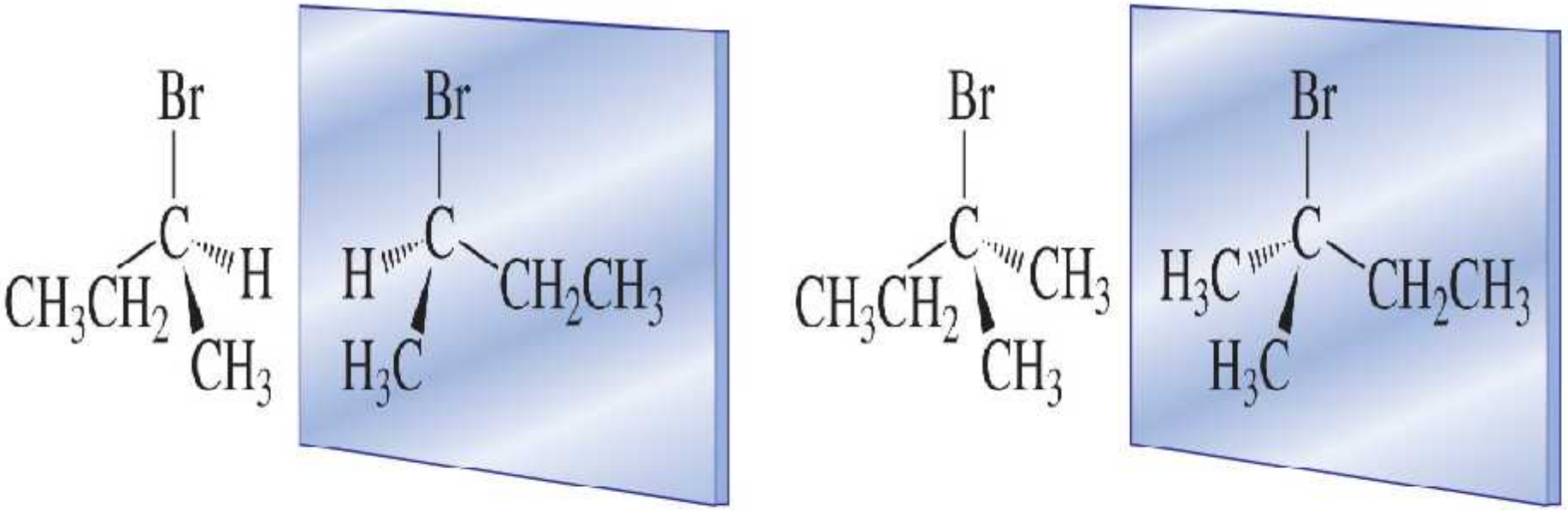

Cl
Br
H
F
Br
Cl
H
F

Chiral Centers

- A point in a molecule where four different groups (or atoms) are attached to carbon is called a **chiral center**
- There are two nonsuperimposable ways that 4 different groups (or atoms) can be attached to one carbon atom
- A chiral molecule usually has at least one chiral center



Chiral vs achiral



a chiral molecule

nonsuperimposable mirror image

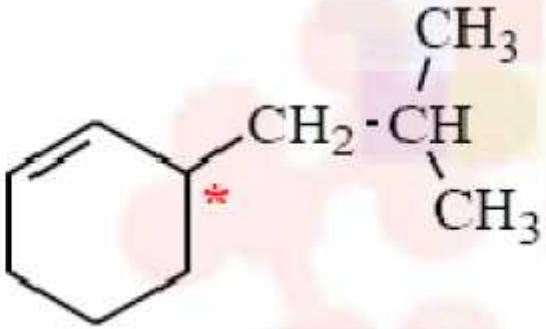
enantiomers

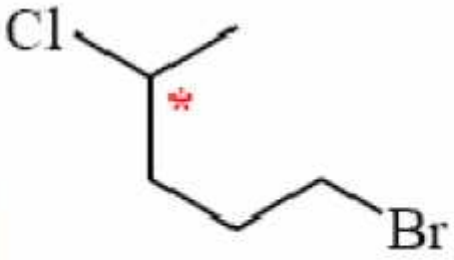
an achiral molecule

superimposable mirror image

identical molecules

For each of the molecules shown below, indicate each of the chiral centers with an asterisk (*)





NOMENCLATURE OF ENANTIOMERS: THE (*R-S*) *SYSTEM*

- (*R) and (S) are from the Latin words rectus and sinister:*
- i) *R configuration: clockwise (rectus, "**right")***
- ii) *S configuration: counterclockwise (sinister, "**left")***

Priority (Cahn-Ingold-Prelog) Rules

Rule 1:

- Look at the atoms directly attached to the chiral carbon and assign priority based on highest atomic number (O > N > C > H)

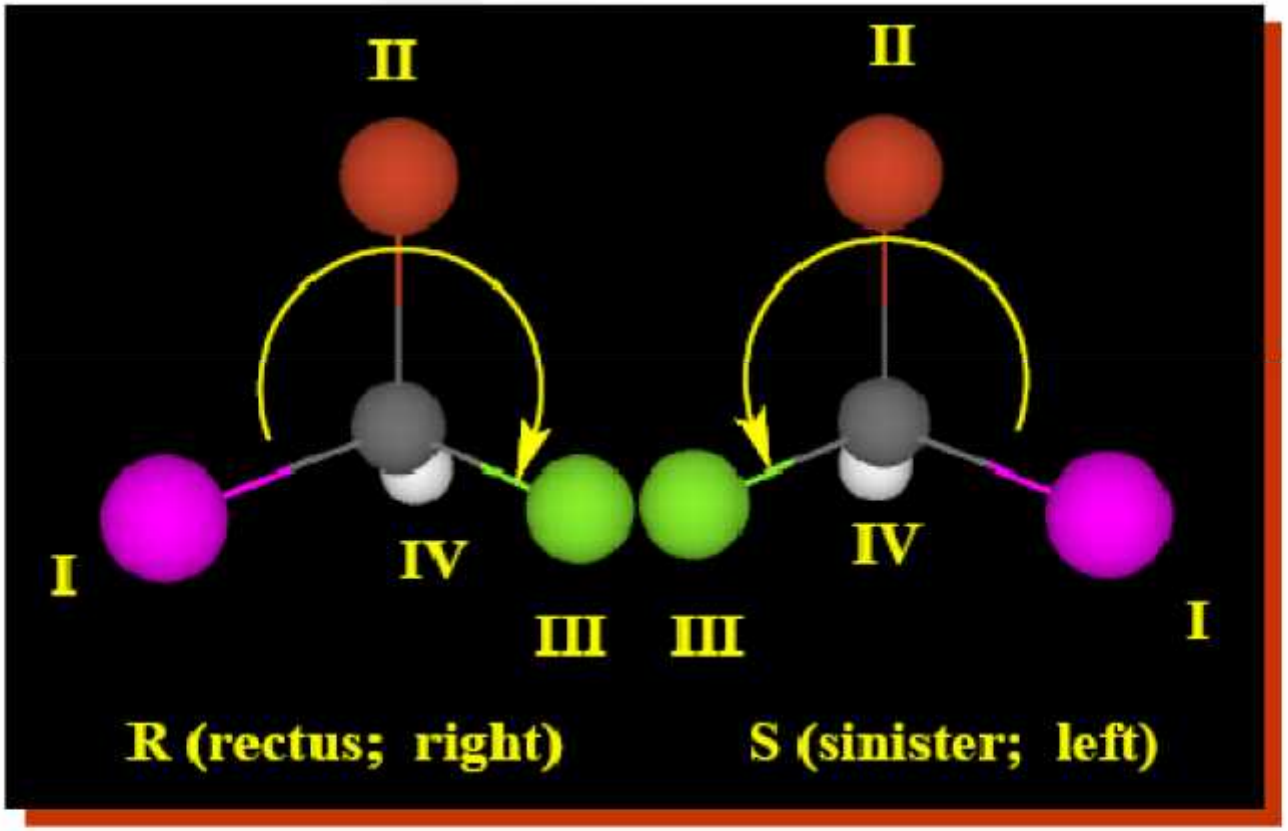
Rule 2:

- If decision can't be reached by ranking the first atoms in the substituents, look at the second, third, or fourth atoms until difference is found

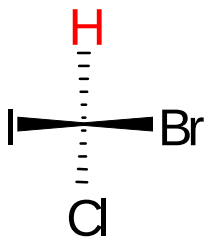
Rule 3:

- Multiple-bonded atoms are equivalent to the same number of single-bonded atoms

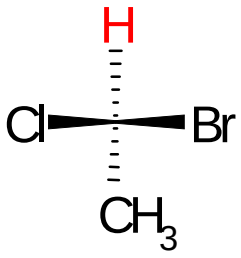
Assigning Absolute Configuration



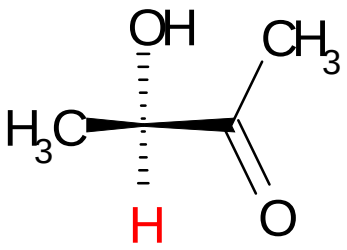
Examples



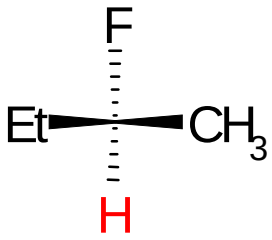
R



S



R



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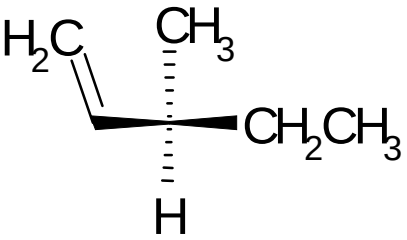

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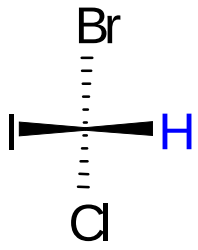

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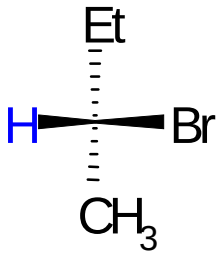

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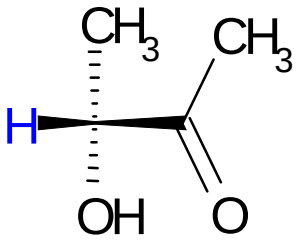
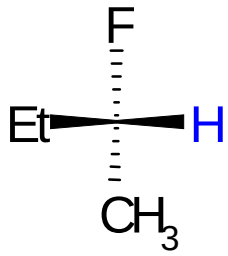
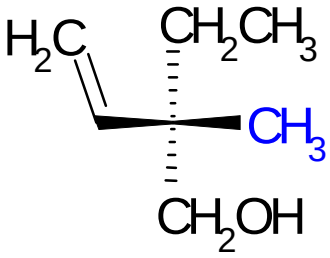


R



R



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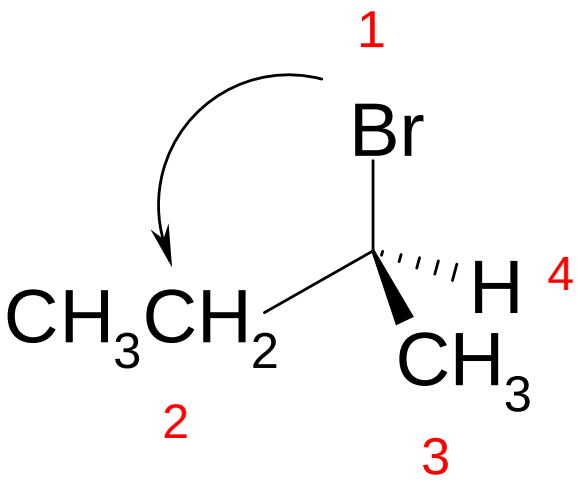
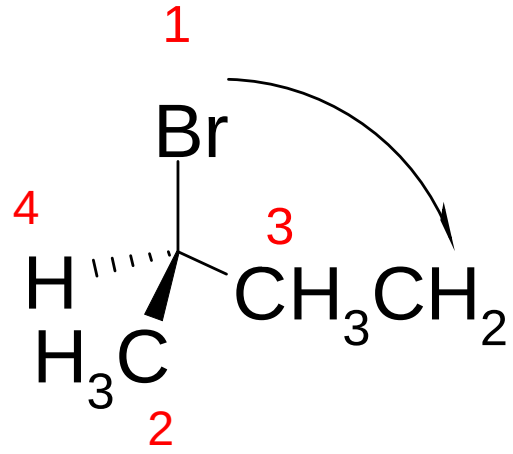
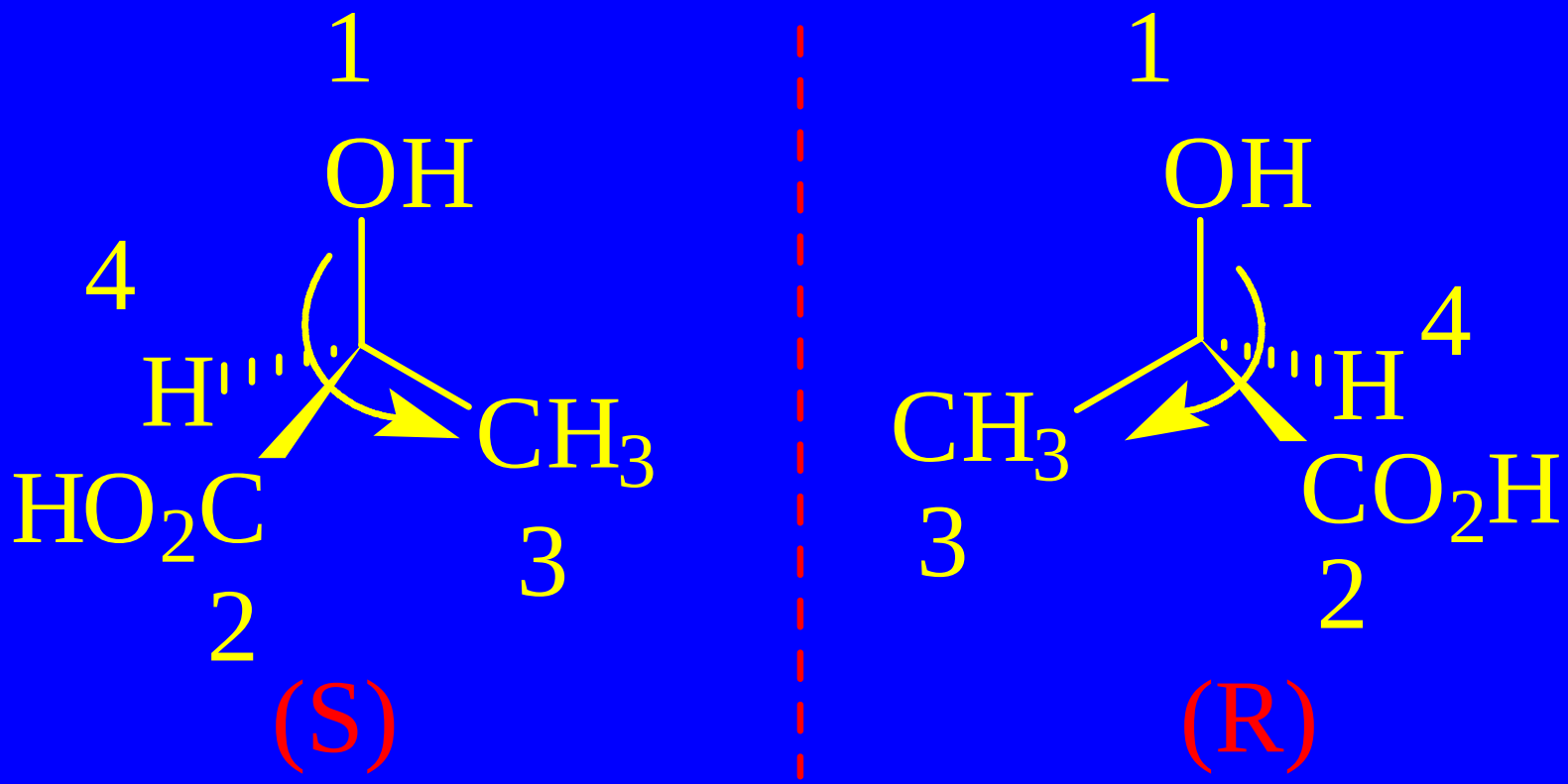


(S)-2-bromobutane



(R)-2-bromobutane

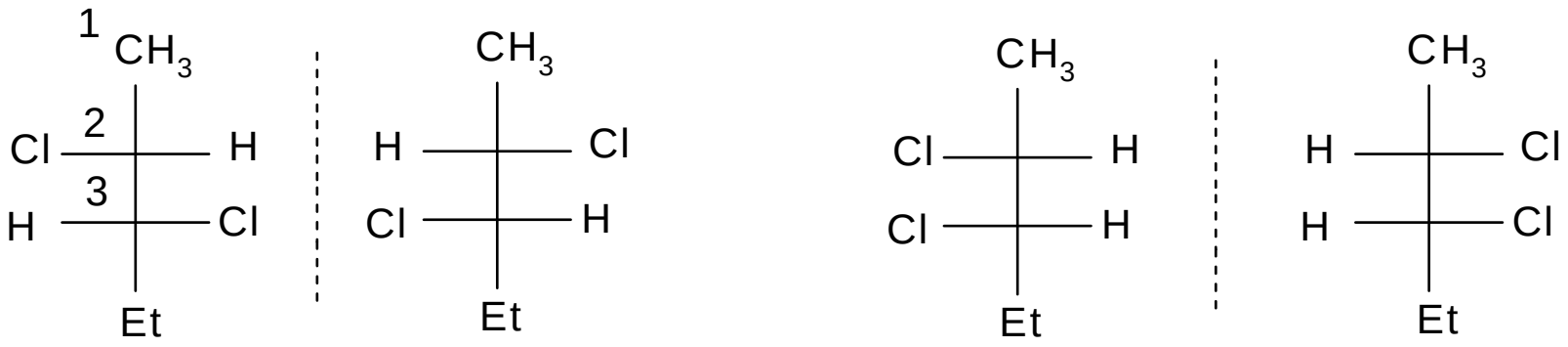
Lactic Acid



C.I.P. Priorities

Low	High
—— $CH_2CH_2CH_3$	—— $CH(CH_3)_2$
—— CH_2CH_2OH	—— $CH_2C(=O)H$
—— $CH_2CH_2CH_3$	—— $CH{=}CH_2$
—— CO_2H	—— CH_2Cl
—— CH_2CH_2Br	—— $CH(CH_3)_2$

Compounds with more than one stereogenic center; (Diasteriomers)



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

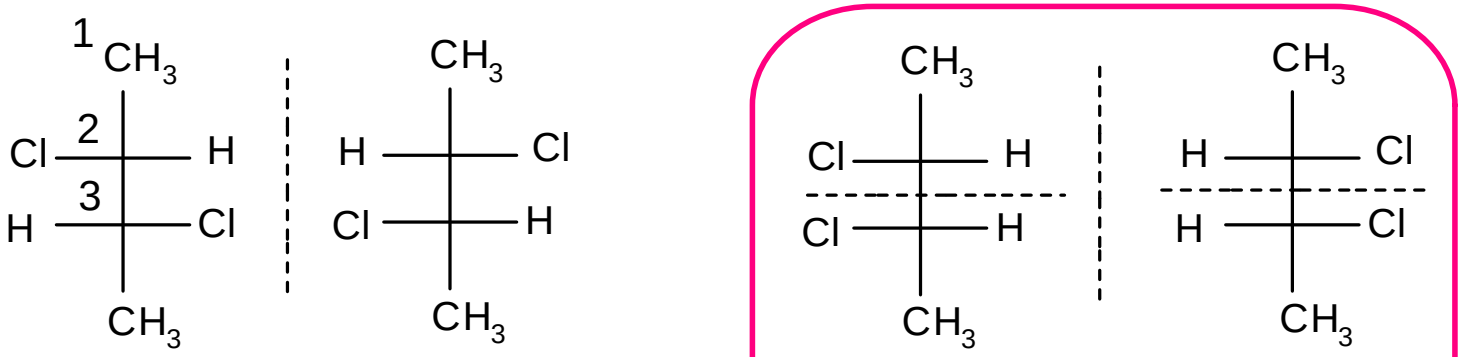
1 **2** **3** **4**

1 and **2** are enantiomers, **3** and **4** are also enantiomers

1 and **3** , **1** and **4**, **2** and **3**, **2** and **4** are diastereomers

Diastereomers are non mirror image stereoisomers

If a molecule has n different stereogenic centers, it may exist in a maximum of 2^n stereisomeric forms. There will be a maximum of 2^n / 2pairs of enantiomers. in the above case 2 stereogenic centers, 2 pairs of enantiomers, 4 stereoisomers



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

1 **2** **3** **4**

same compound

1 and **2** are enantiomers, **3** and **4** are the same compound (Meso structure)

1 and **3** , **2** and **3**, are diastereomers

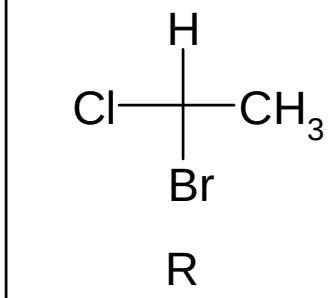
Diastereomers are non mirror image stereoisomers

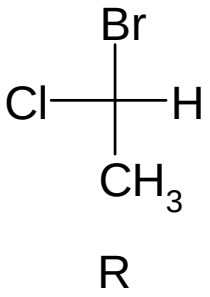
1 pair of enantiomers and a total of 3 isomers

A meso compound: is an achiral (optically inactive) diastereomer of a compound with stereogenic centers. Its stereogenic centers have opposite configurations. One half of the molecule is the mirror image of the other half

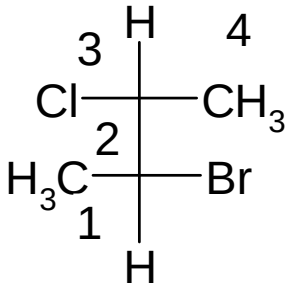
Example

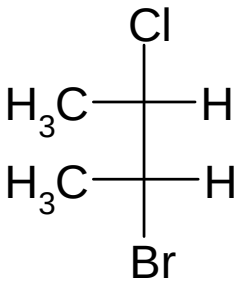
What is the relation between the following co





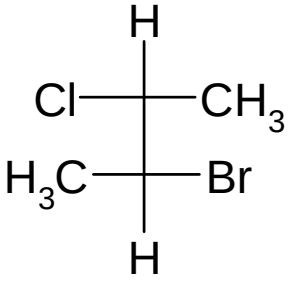
same compound

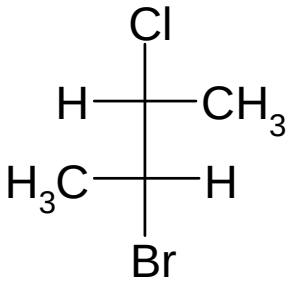




(2S,3S) (2R,3S)

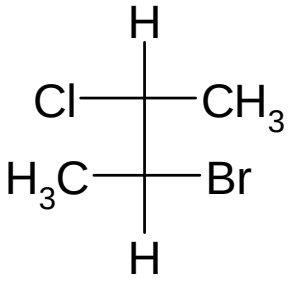
Diastereomers

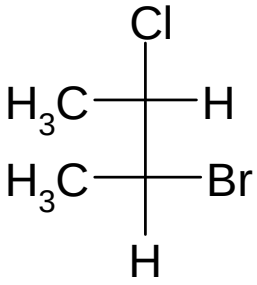




(2S,3S) (2R,3R)

Enantiomers





(2S,3S) (2S,3S)

Same compound

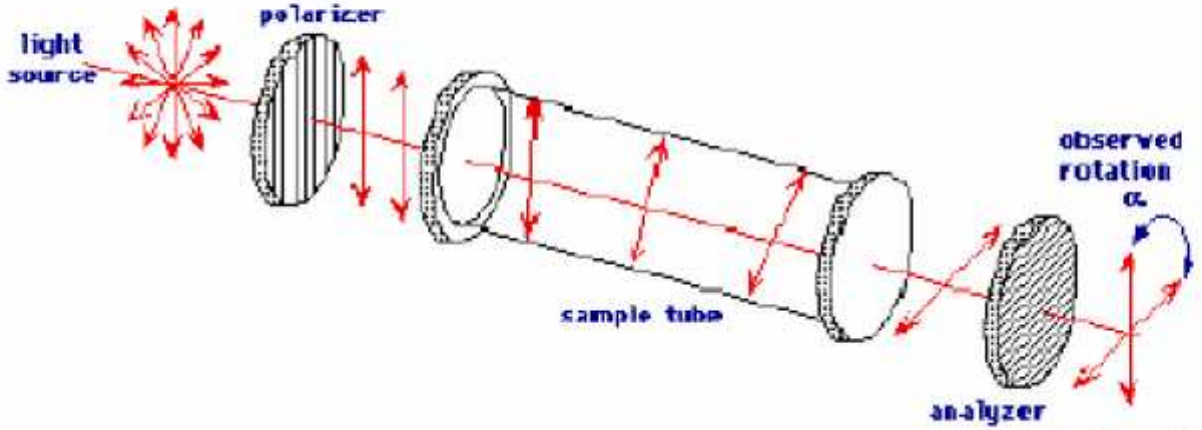
- **Properties of enantiomers and diastereomers**
- **A) Enantiomers**
- Have the same physical properties except for direction of rotation of plane polarized light
- Have the same chemical properties except for their reaction with other chiral molecules
- (This usually seen in their biological activity)
- **B) Diastereomers**
- Have different physical properties
- Similar chemical properties

Specific Rotation, [α]

$$[\alpha]_D = \frac{\text{Observed Rotation (degrees)}}{\text{Path length, } l\text{, (dm)} \times \text{Concentration, } C\text{ (g/mL)}} = \frac{\alpha}{l \times C}$$

The Specific Rotation is equal to the observed rotation (α) divided by the the pathlength of the cell *(l)* in dm, multiplied by the concentration *(C)* in g/mL

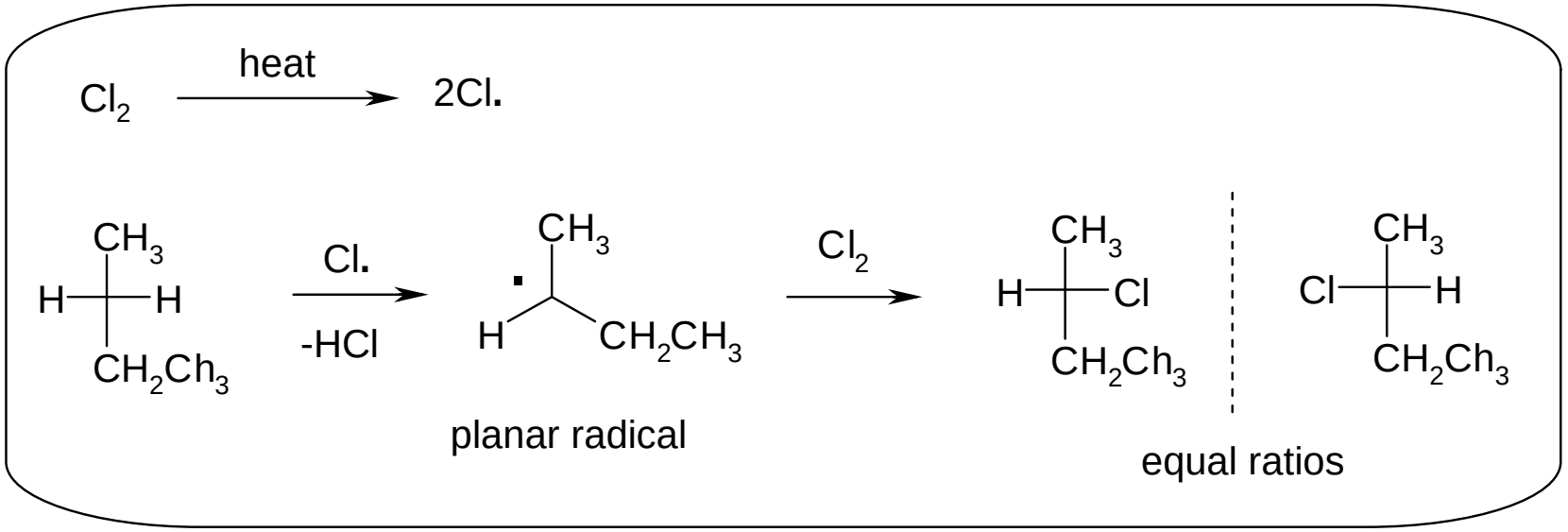
The subscript D refers to the wavelength of light used (the sodium "D-line")

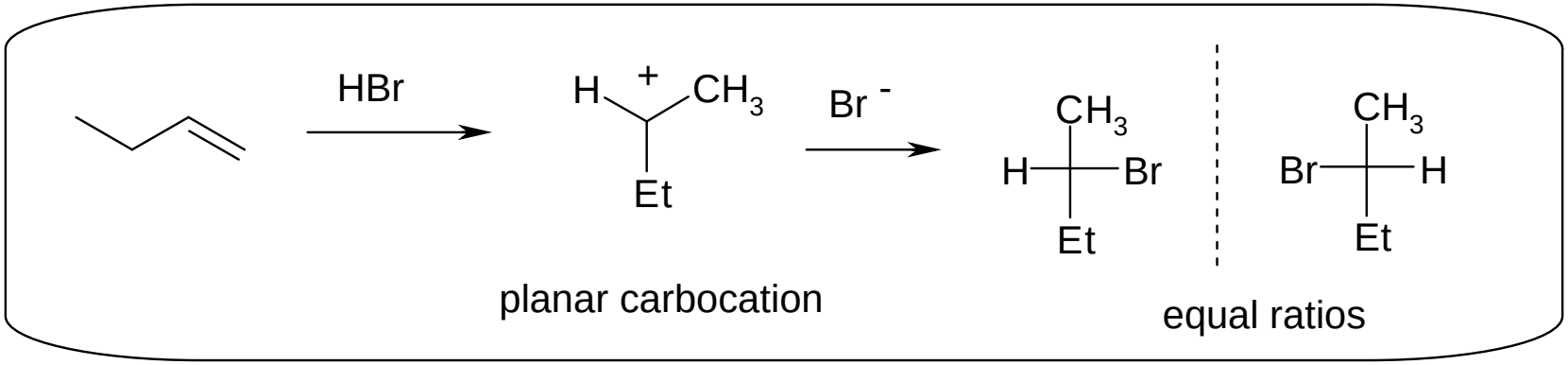


- **A chiral molecule** is one that is optically active

- **A racemic mixture** (racemic modification) is one with equal ratios of enantiomers (50:50 mixture)

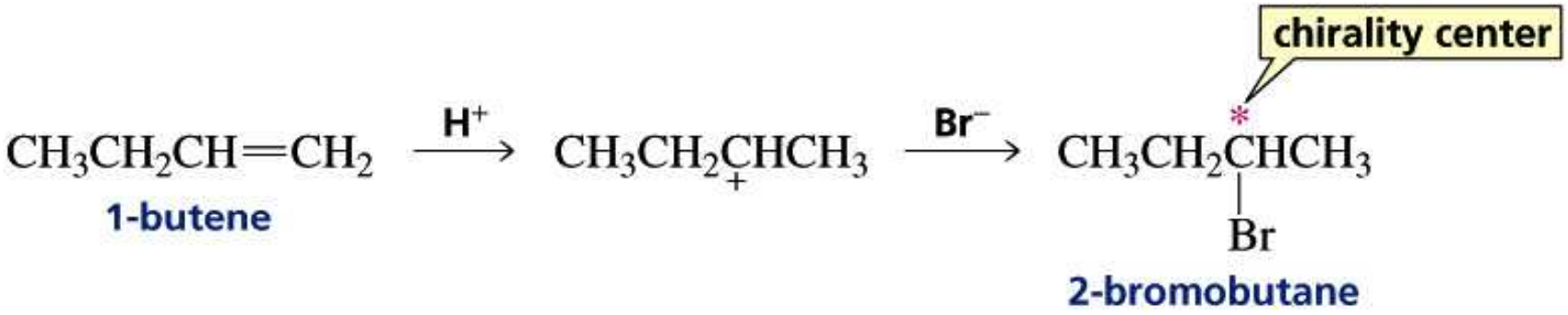
- **Chemical reactions of stereoisomers**
- **1) Generation of a chiral center**





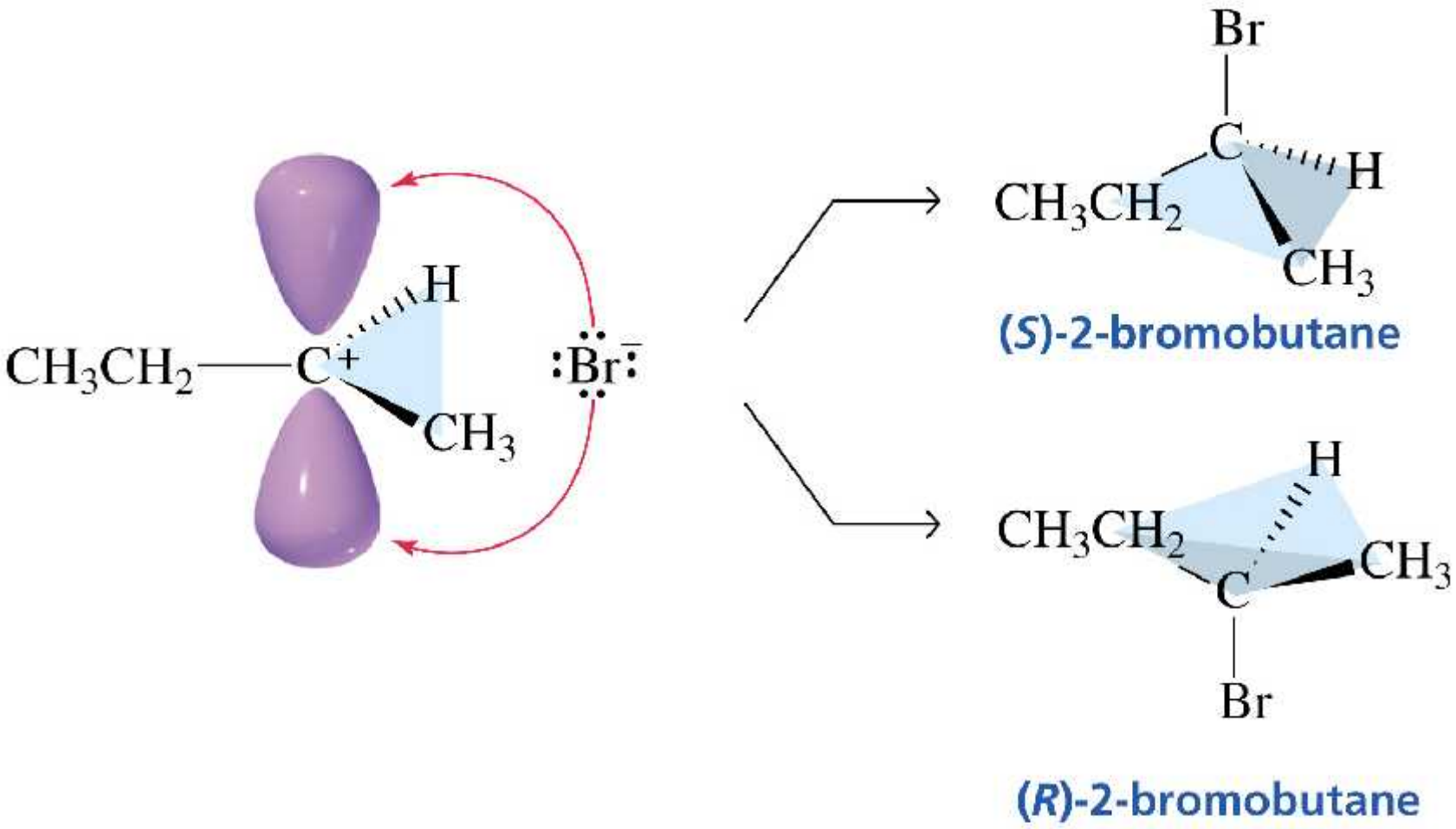
product is optically inactive → racemic modification

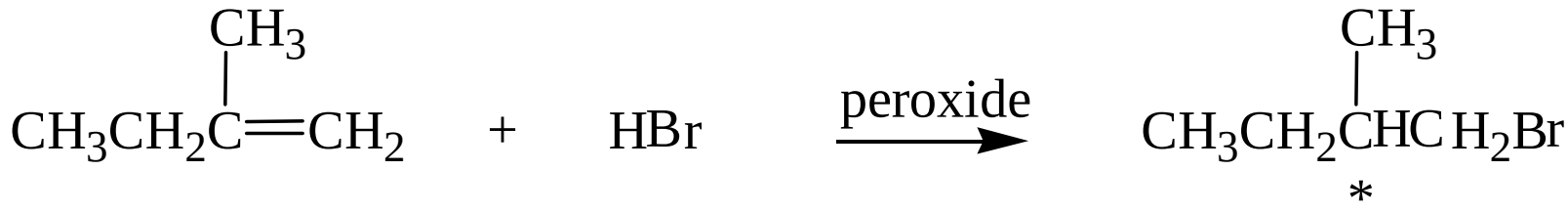
Stereochemistry of Electrophilic Addition Reactions of Alkenes



What is the absolute configuration of the product?

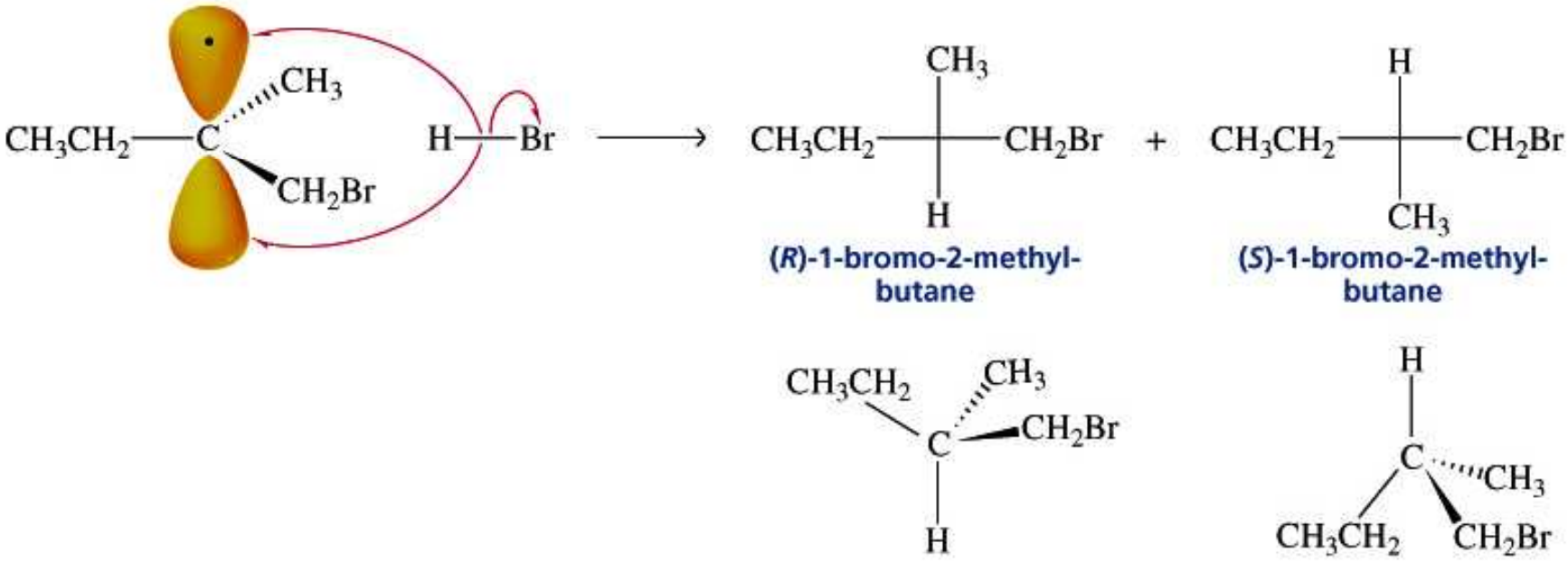
Addition reactions that form one asymmetric carbon



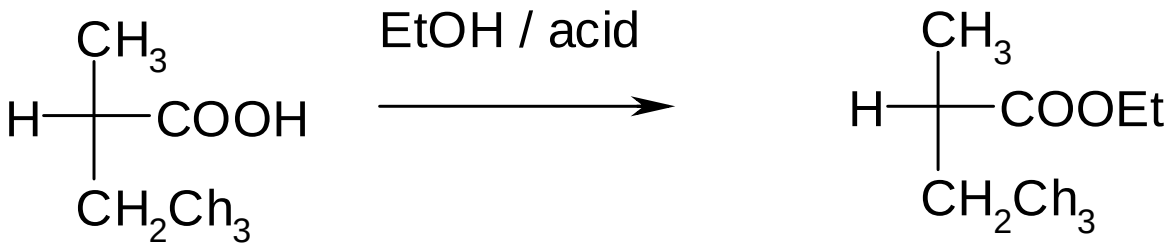


2-methyl-1-butene

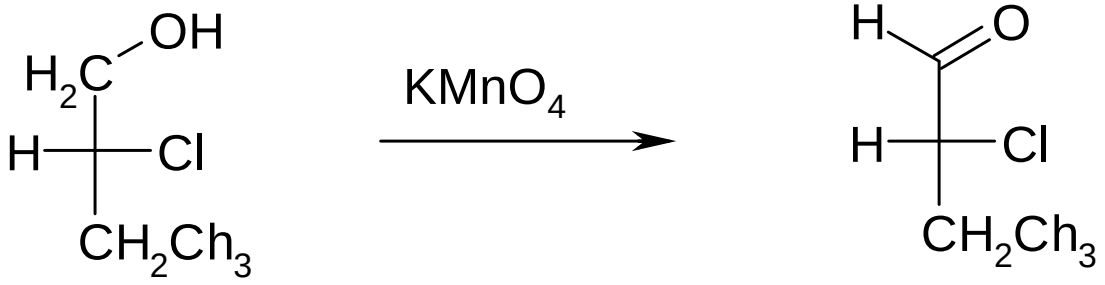
1-bromo-2-methylbutane



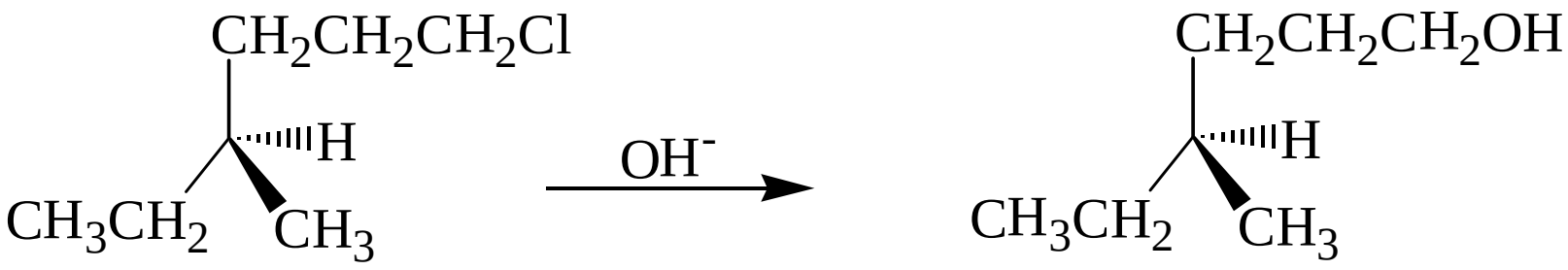
Reaction away from a chiral center

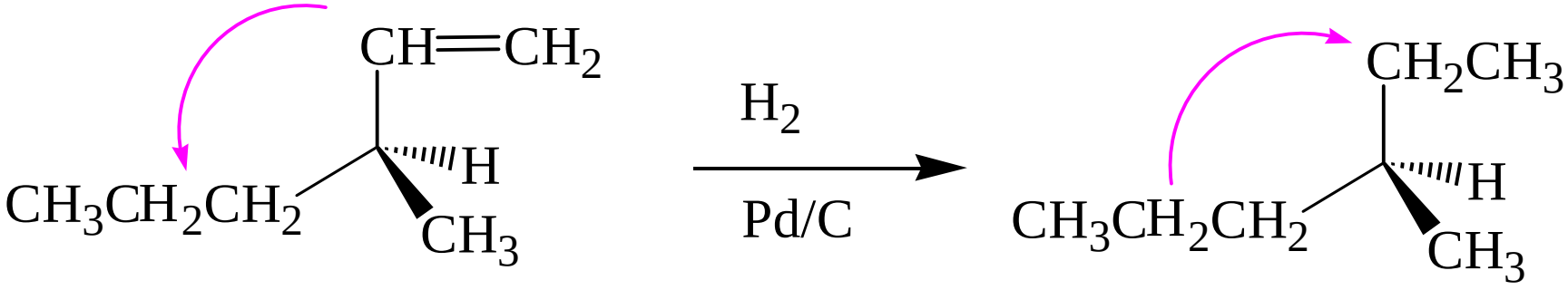


retention of configuration



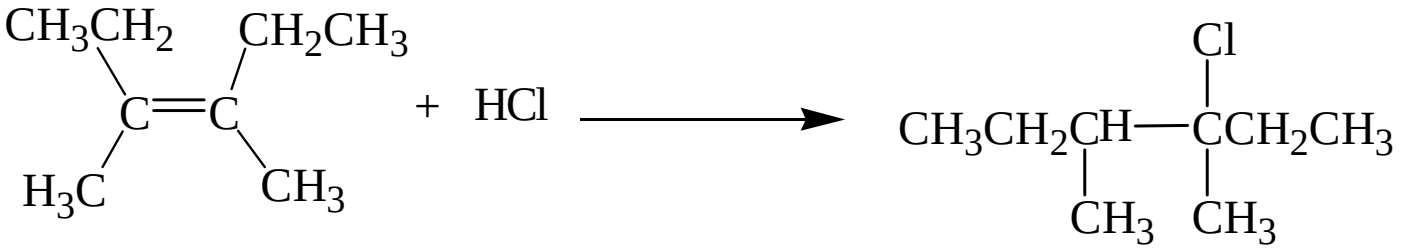
retention of configuration

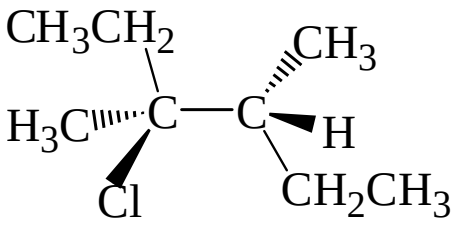

CH2CH2CH2Cl
H
CH3CH2
CH3
OH-
CH2CH2CH2OH
H
CH3CH2
CH3

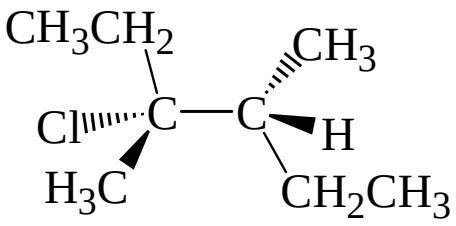

CH=CH2
H
CH3CH2CH2
CH3
H2
Pd/C
CH2CH3
H
CH3CH2CH2
CH3

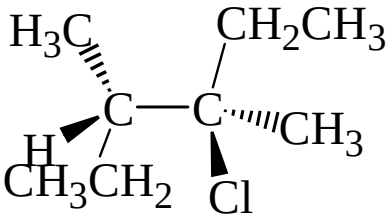
Addition reactions that form two asymmetric carbons

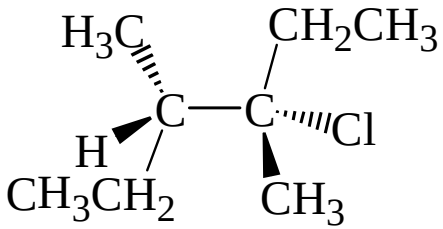
A carbocation reaction intermediate









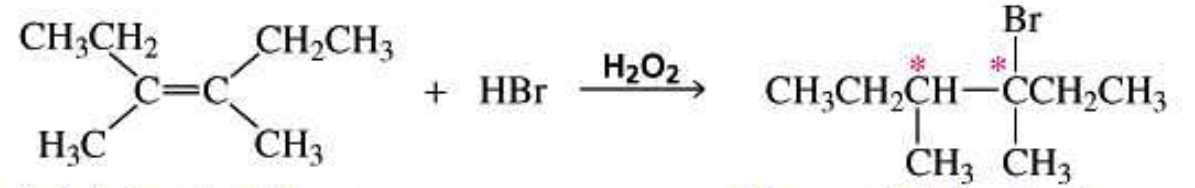


Two substituents added to the same side of the double bond: syn

Two substituents added to opposite sides of the double bond: anti

Addition reactions that form two asymmetric carbons

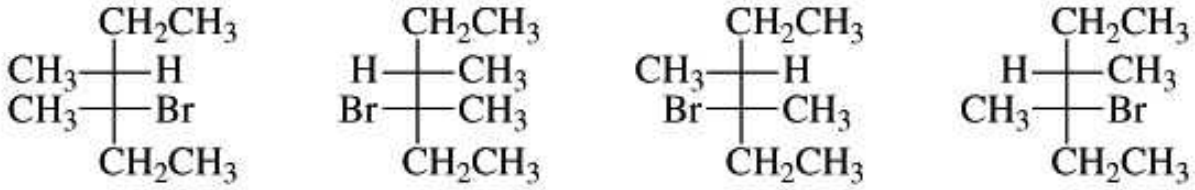
A radical reaction intermediate



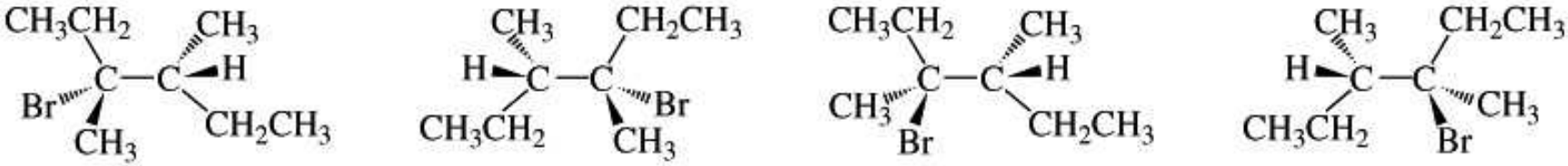
cis-3,4-dimethyl-3-hexene

3-bromo-3,4-dimethylhexane

stereochemistry of the product

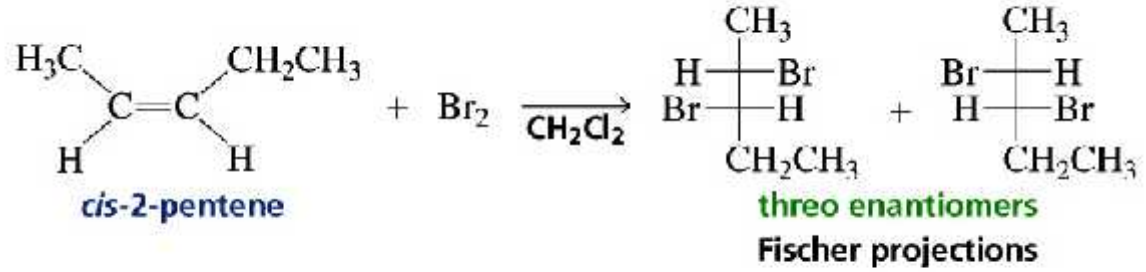


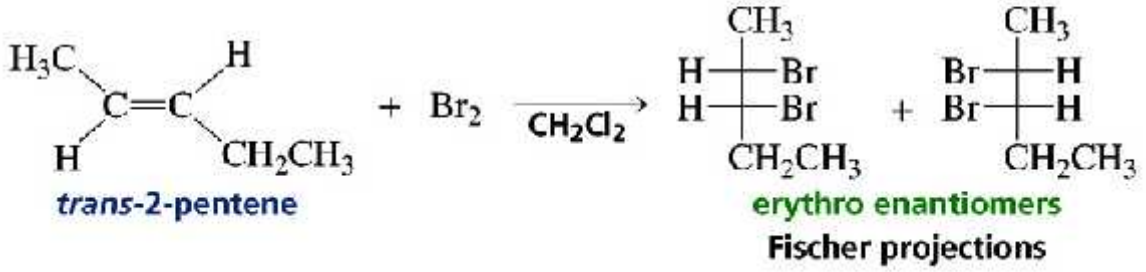
Fischer projections of the stereoisomers of the product

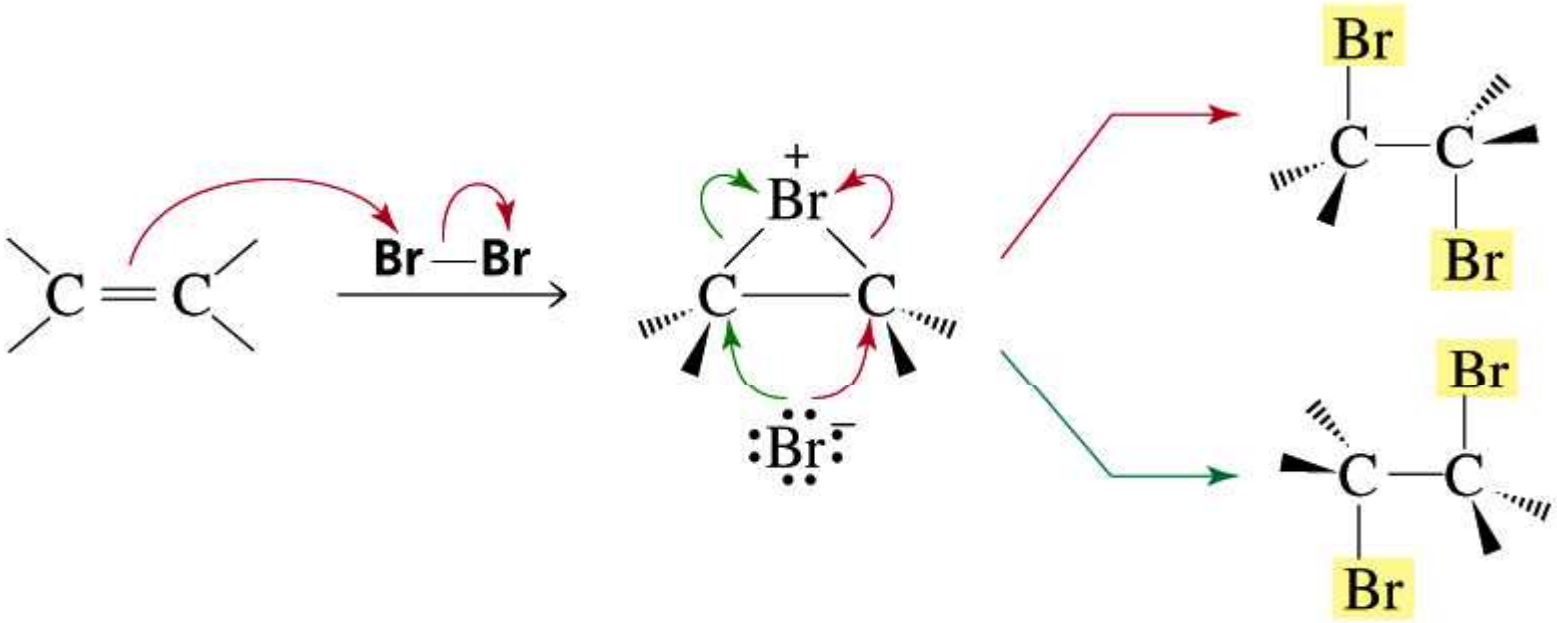


perspective formulas of the stereoisomers of the product

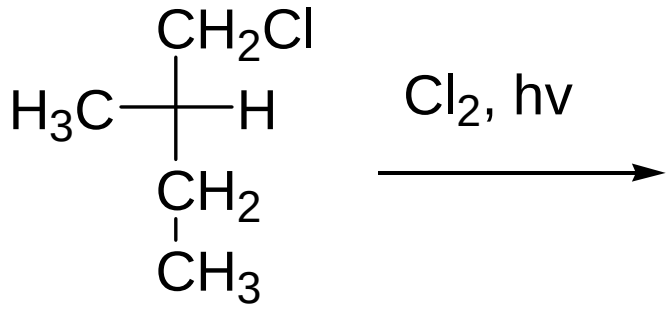
Addition reactions that form a bromonium ion intermediate (anti addition)







addition of Br_2 is an anti addition

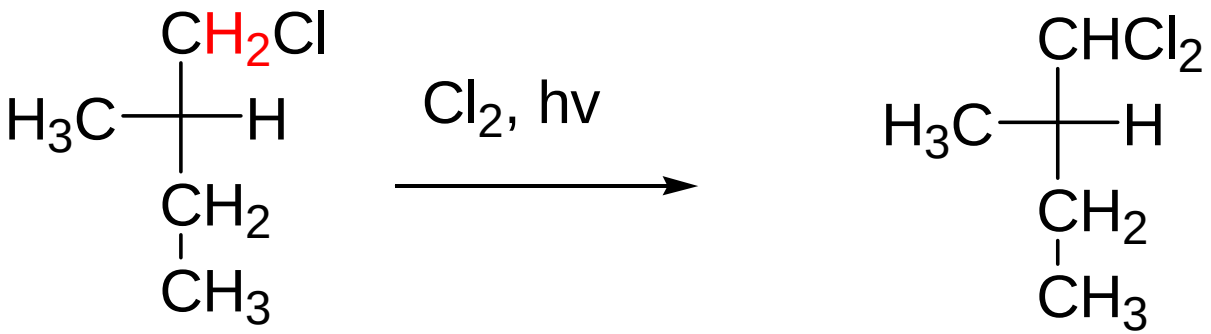


Cl_2, hv

$C_5H_{10}Cl_2$ + HCl

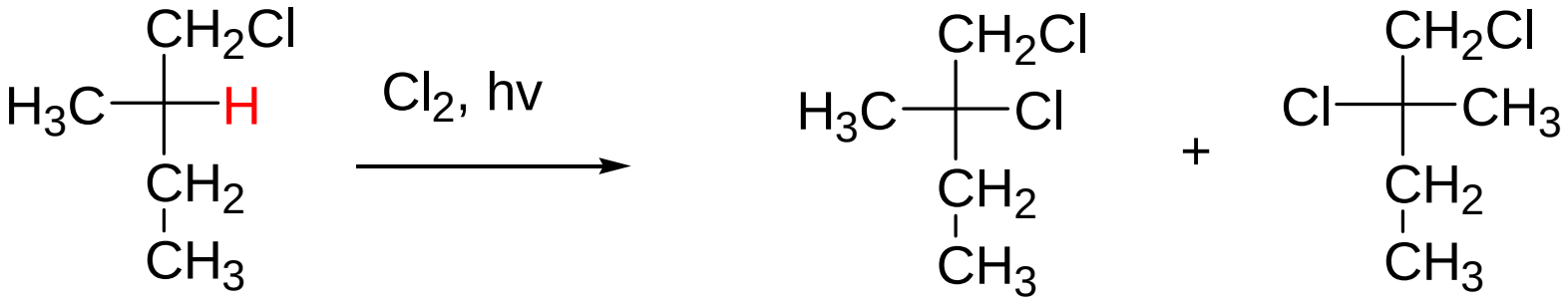
(*S*)-(-)-1-chloro-2-methylbutane

six fractions:
four optically active
two optically inactive



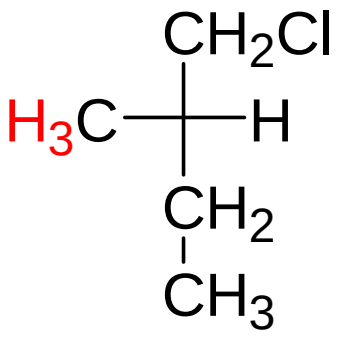
A

No bonds to the chiral center are broken, configuration is retained. Product is optically active

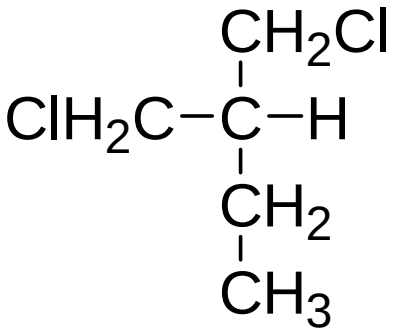


B

A bond is broken to the chiral center. Stereochemistry depends on the mechanism. Here, the intermediate free radical is flat and a racemic modification is formed. This fraction is optically inactive.

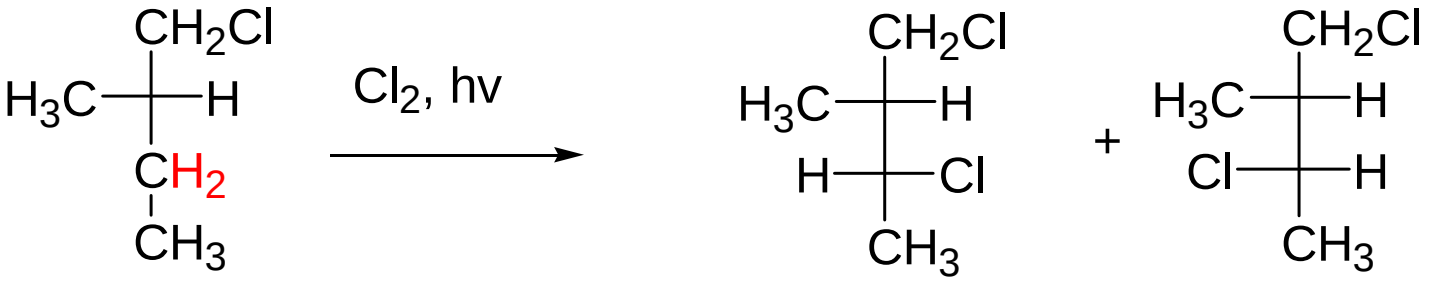


Cl_2, hv



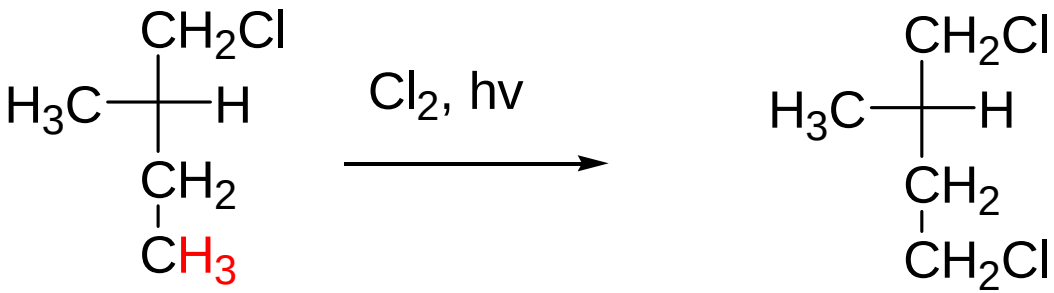
C

The product no longer has a chiral center. It is achiral and optically inactive.



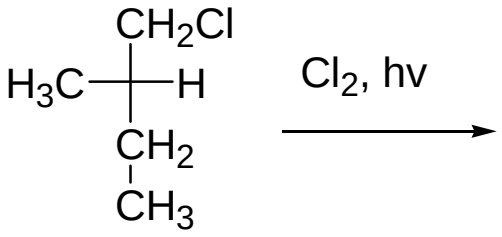
D E

No bond is broken to the chiral center and a new chiral center is formed. The products are diastereomers and each fraction is optically active.



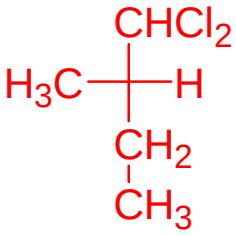
F

No bonds to the chiral center are broken, configuration is retained. Product is optically active

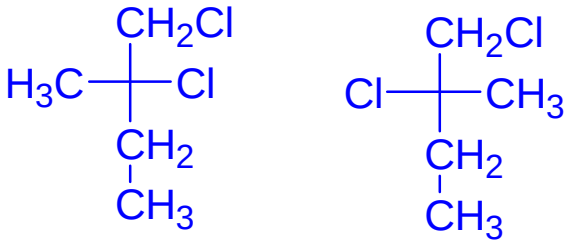


Cl_2, hv

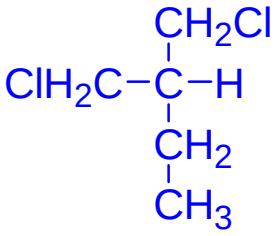
(*S*)-(-)-1-chloro-2-methylbutane



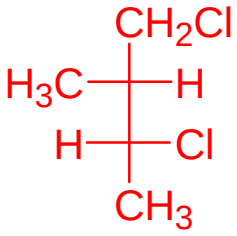
A



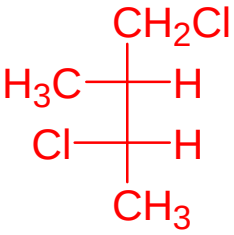
B



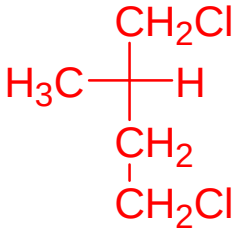
C



D



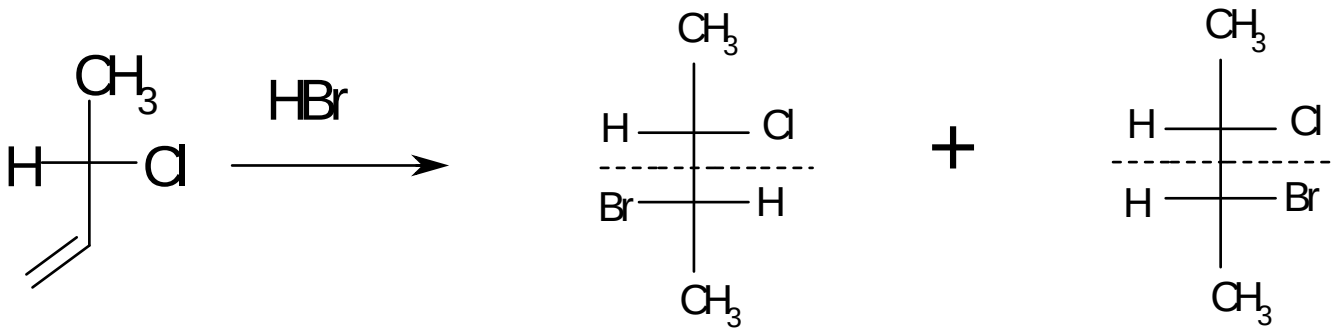
E



F

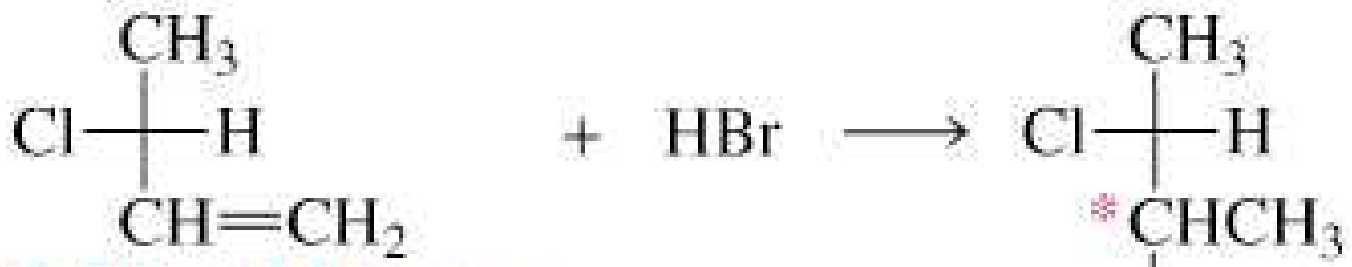
optically active
optically inactive

Generation of a second chiral center



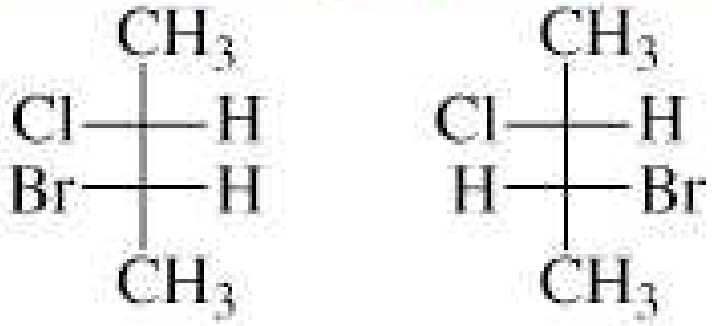
Diastereomeric products at different rates and in unequal amounts

Addition reactions that form an additional asymmetric carbon



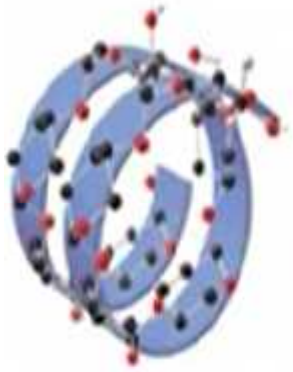
(R)-3-chloro-1-butene

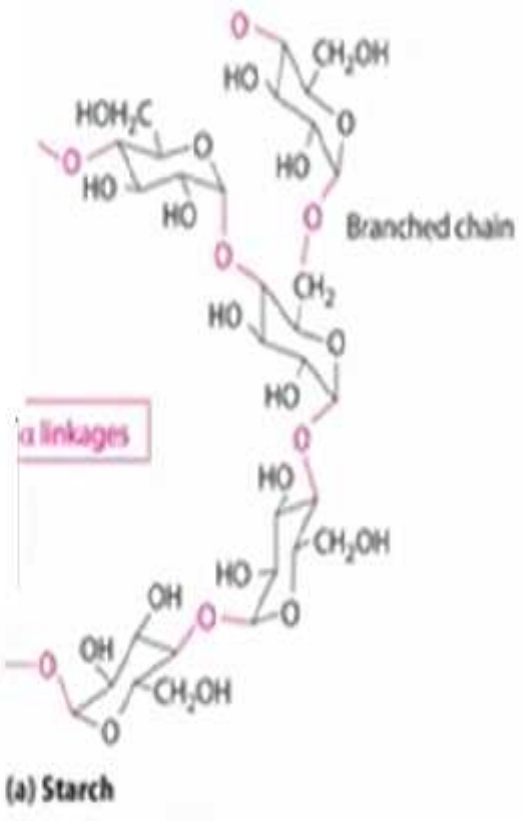
stereochemistry of the product

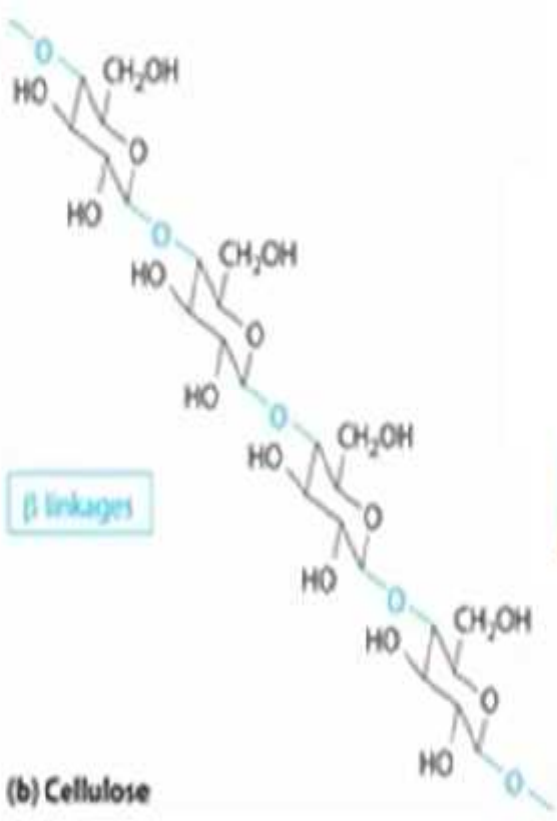


a pair of diastereomers

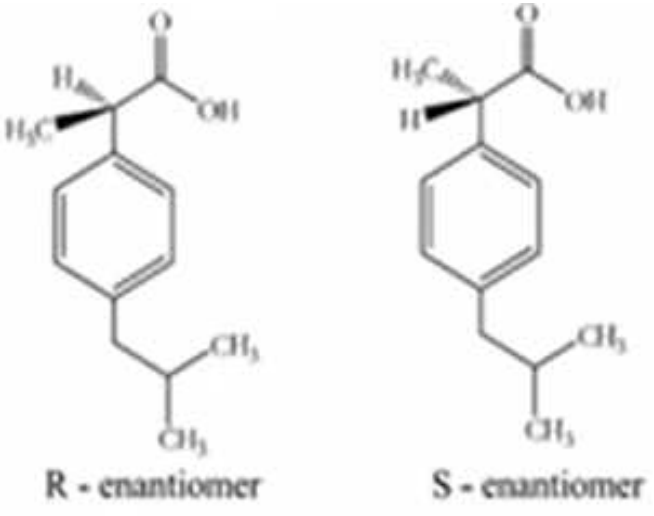
importance of stereochemistry in pharmaceutical



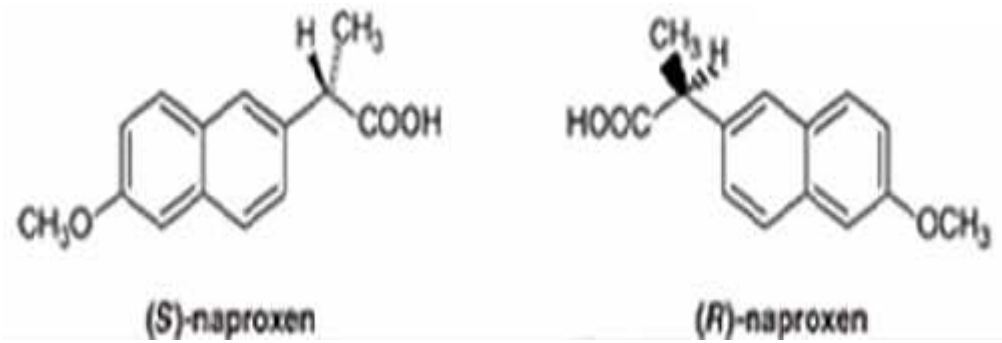




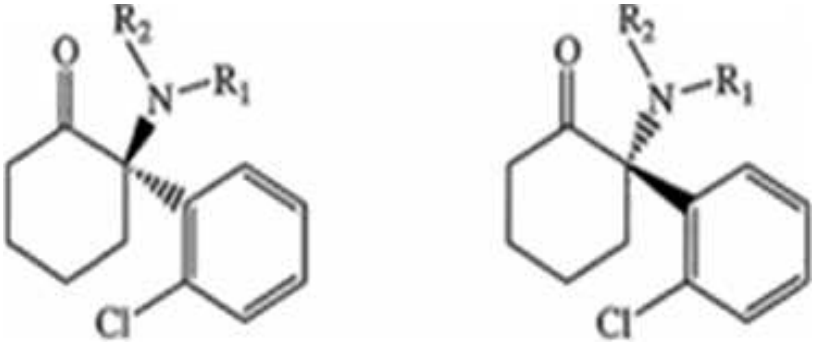
Ibuprofen

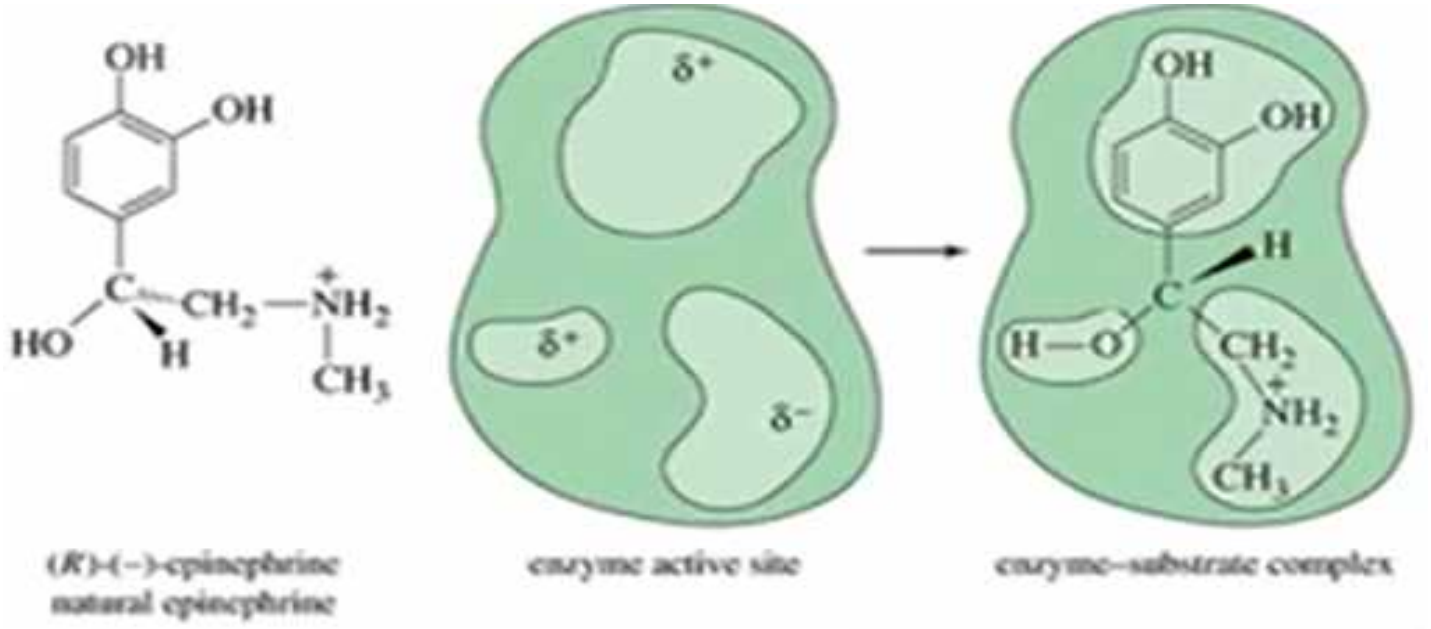


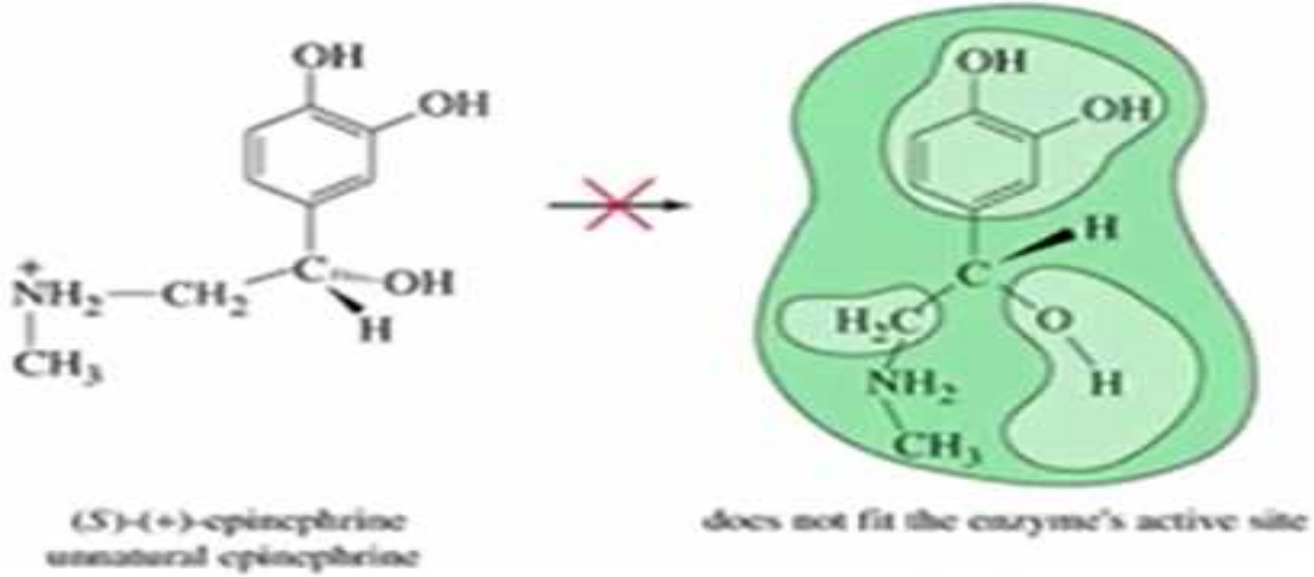
Naproxen



Ketamine




OH
OH
HO
H
CH2
NH2
CH3
δ+
δ+
δ−
H—O
(R)-(−)-epinephrine
natural epinephrine
enzyme active site
enzyme–substrate complex


OH
OH
NH2
CH2
CH3
H
H2C
O
(S)-(+)-epinephrine
unnatural epinephrine
does not fit the enzyme's active site