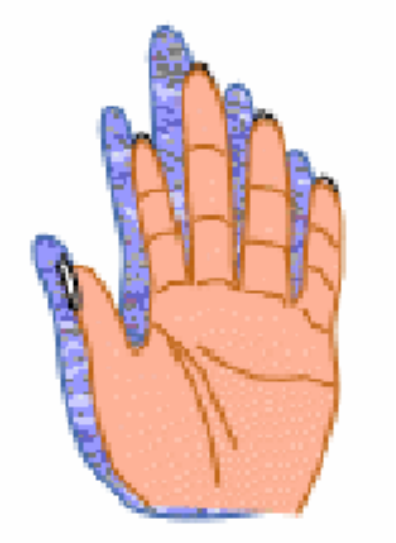
Handedness: plays a major role in organic chemistry as a direct consequence of tetrahedral sp^3-carbon

most molecules in biological systems and drugs are handed

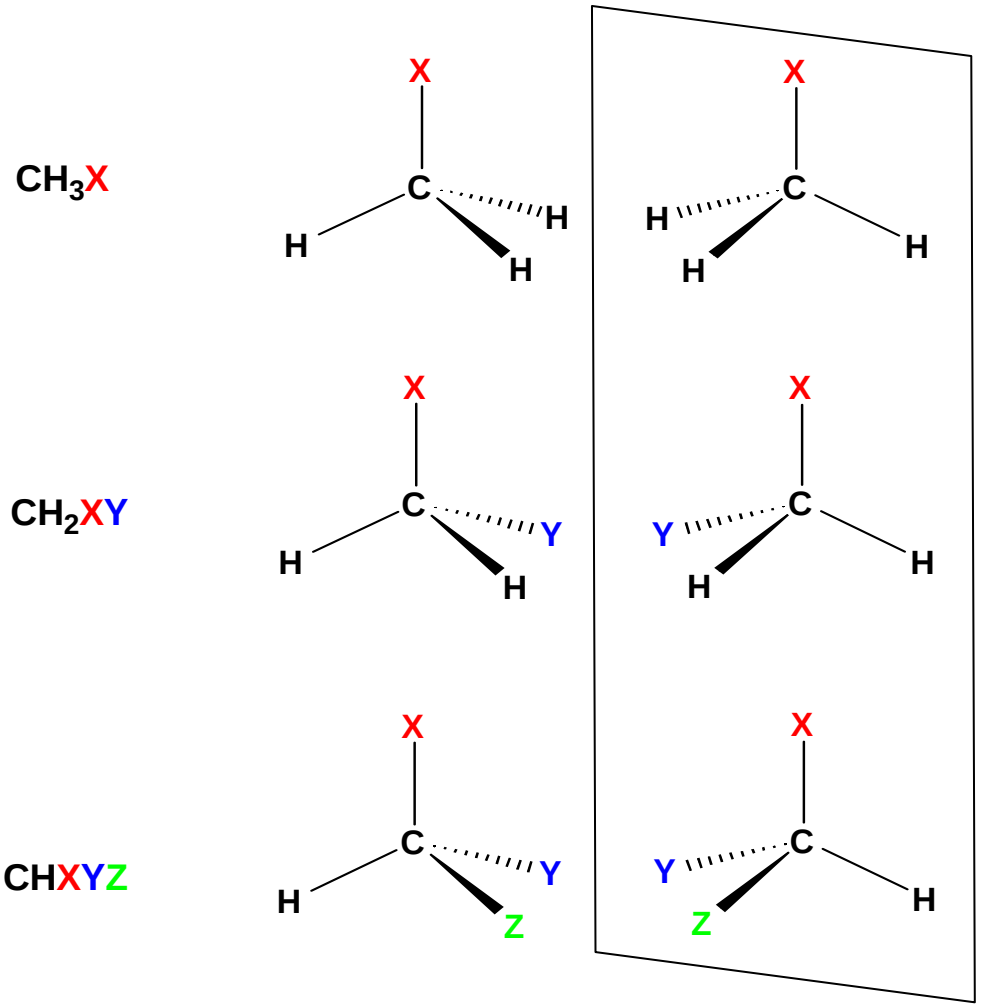
left hand
with right glove



right hand
with left glove

9.1 Enantiomers and the Tetrahedral Carbon

tetrahedral carbon and their mirror images



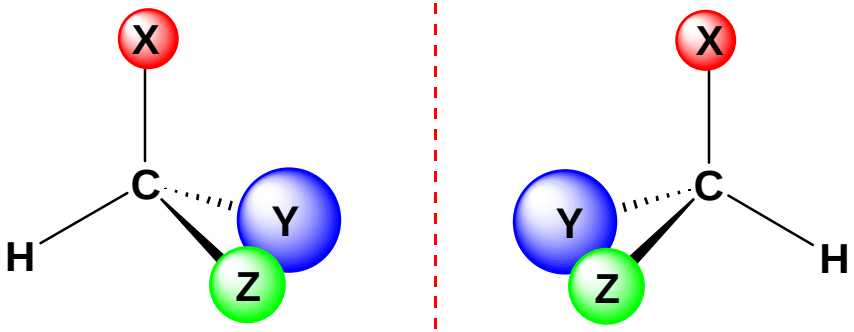
identical to its mirror image

identical to its mirror image

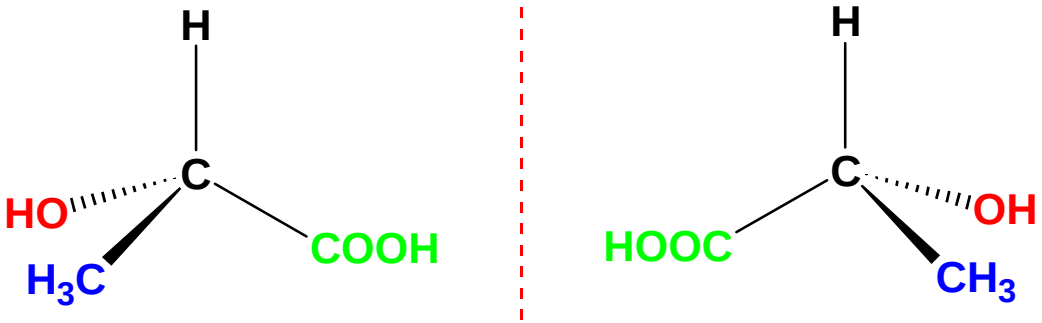
Not identical

Enantiomer: mirror-image molecules that are not superimposable

CHXYZ



mirror



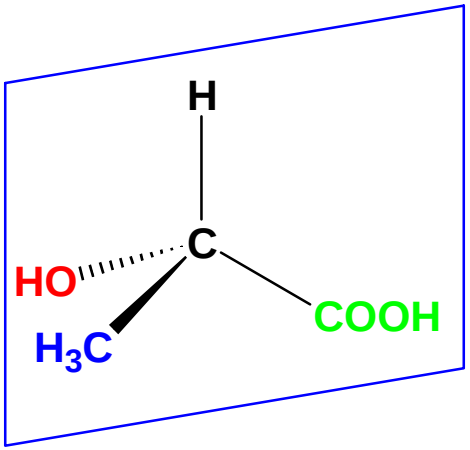
(+)-Lactic acid

(-)-Lactic acid

9.2 The Reason for Handedness in Molecules: Chirality

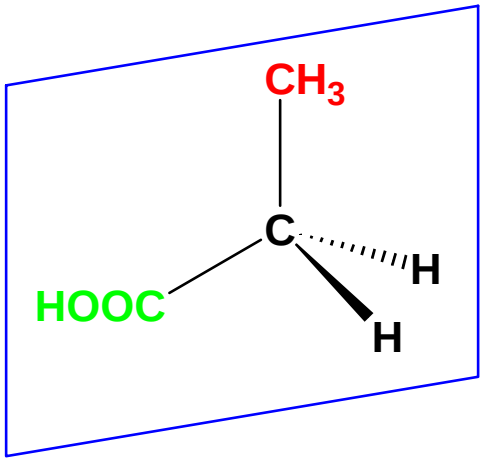
Chiral: molecules that are not superimposable with their mirror images are chiral
; two enamtiomers exist

Plane of symmetry : a molecule is not chiral if it contains a plane of symmetry



NOT symmetry plane

(+)-Lactic acid



symmetry plane

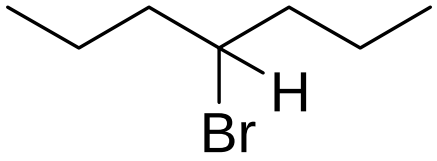
Propanoic acid

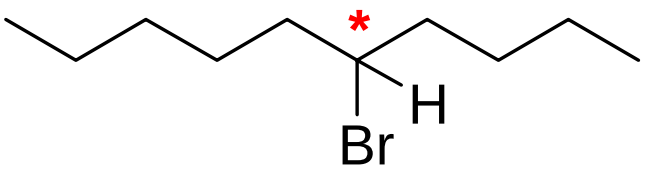
Achiral: superimposable with their mirror images

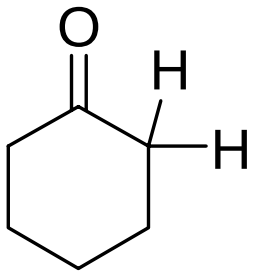
Chiral center: carbons with four different groups are referred to as chirality centers (**asymmetric center** or **stereogenic center**)
; marked by an asterisk (*)

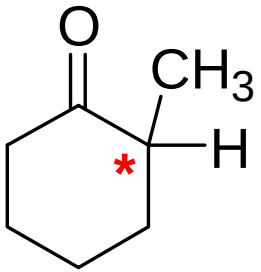
Note that chirality is a property of the entire molecule, whereas a chiral center is a structural feature within the molecule that gives rise to chirality

Practice :

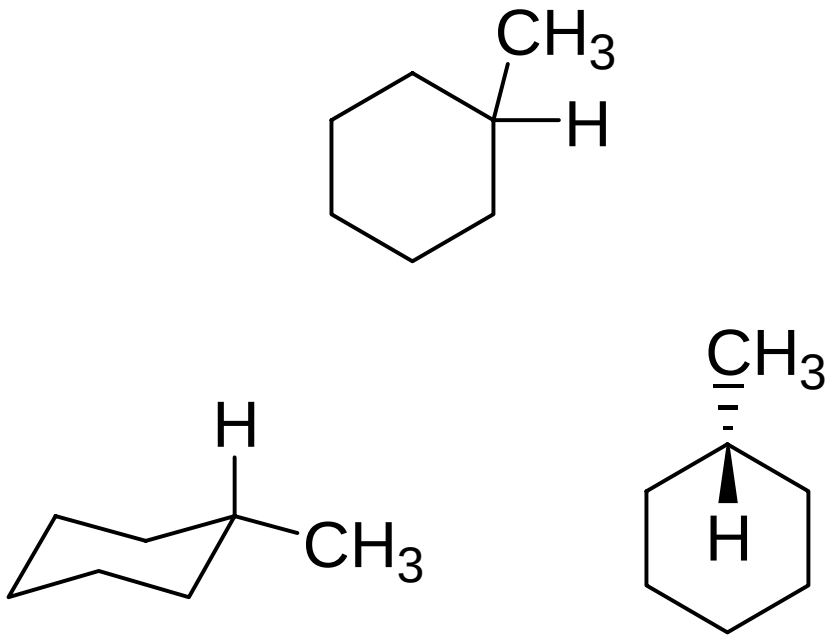






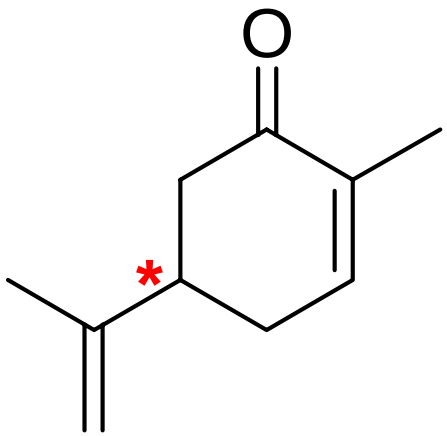


Practice :

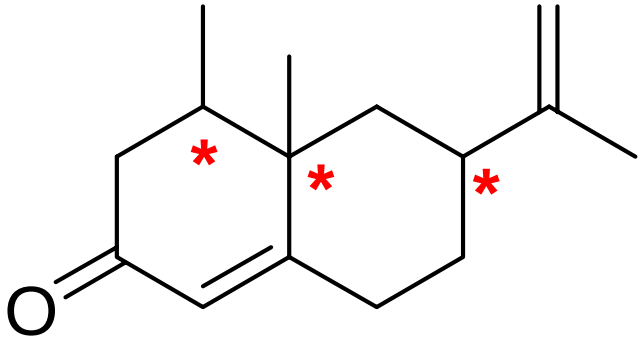


plane of symmetry

Practice :



Carvone
(spearmint oil)

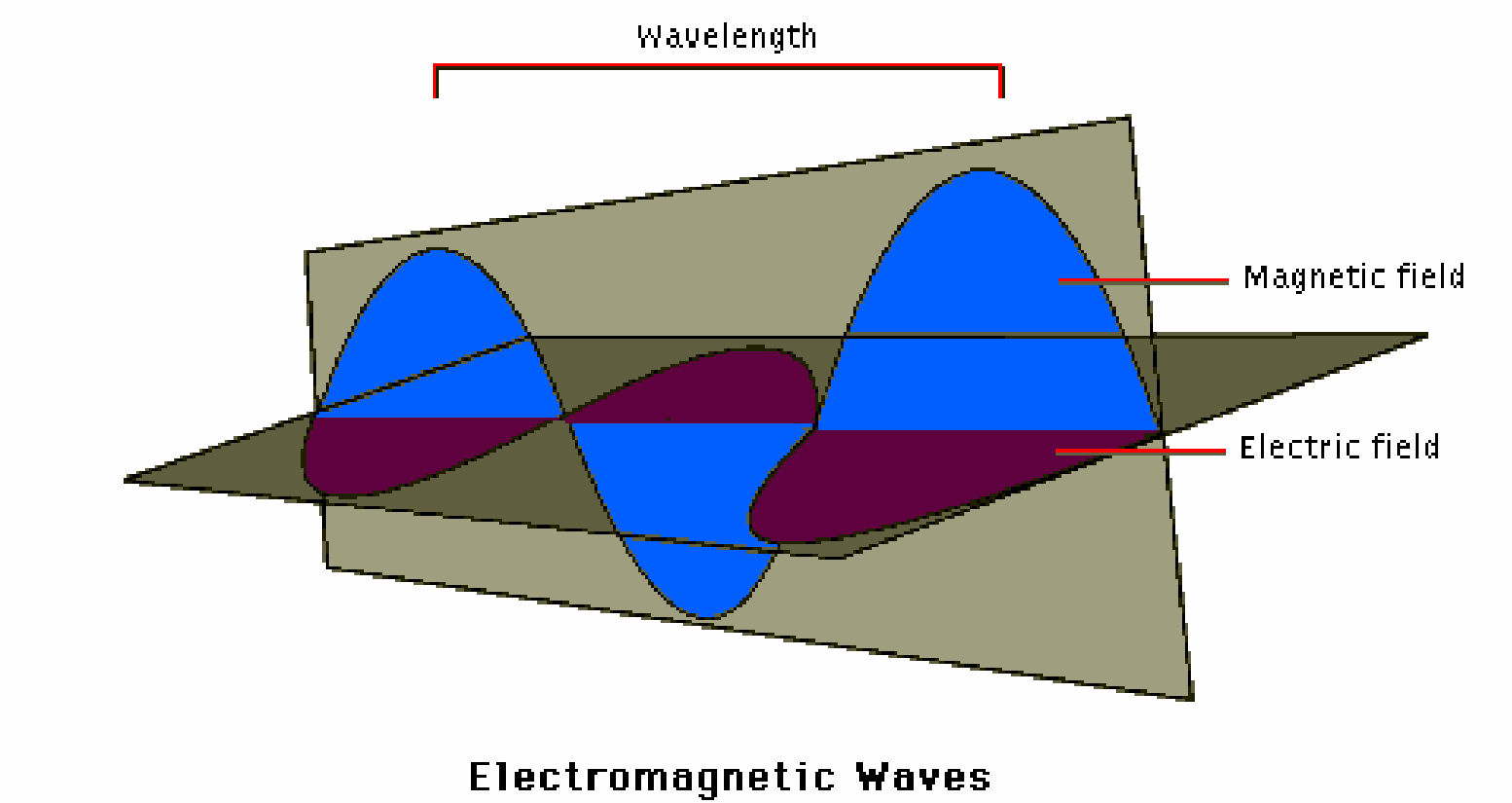


Nootkatone
(grapefruit oil)

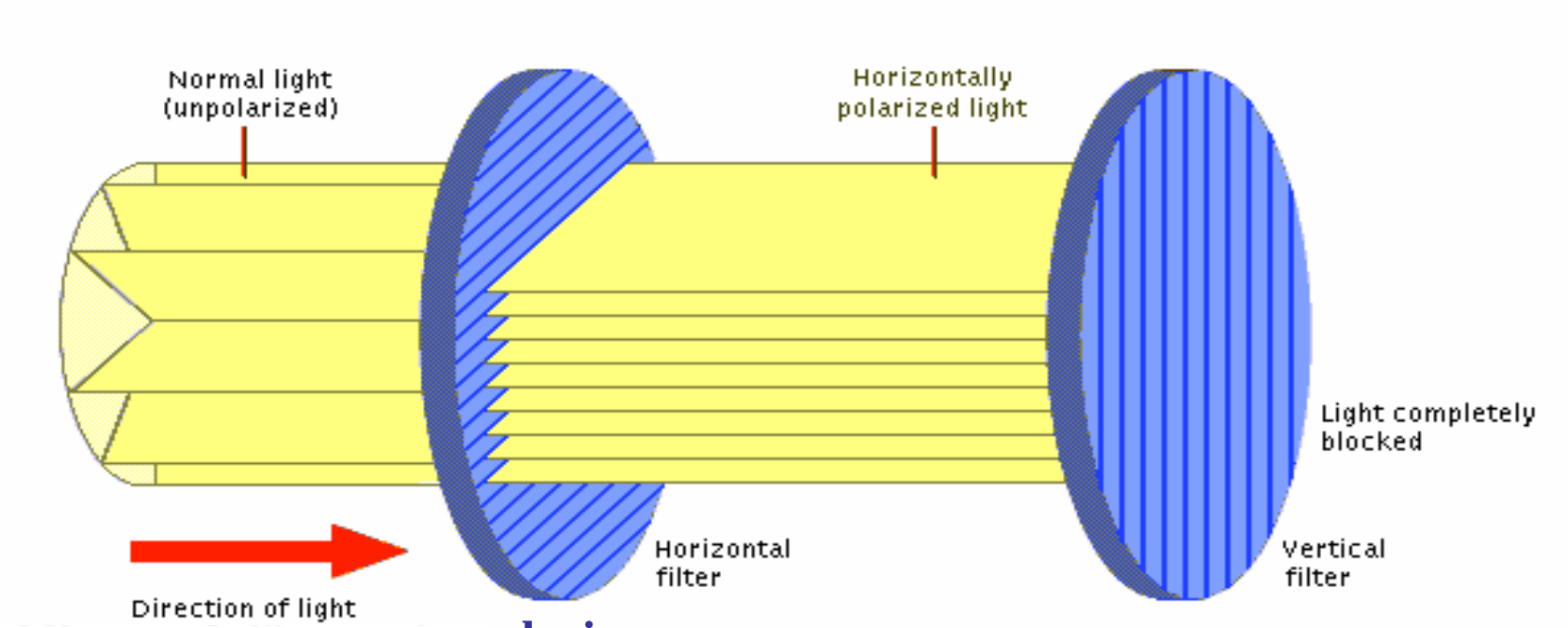
9.3 Optical Activity

19th C, J. B. Biot

Ordinary light: electromagnetic waves that oscillate in an infinite number of planes at right angle to the direction of light travel

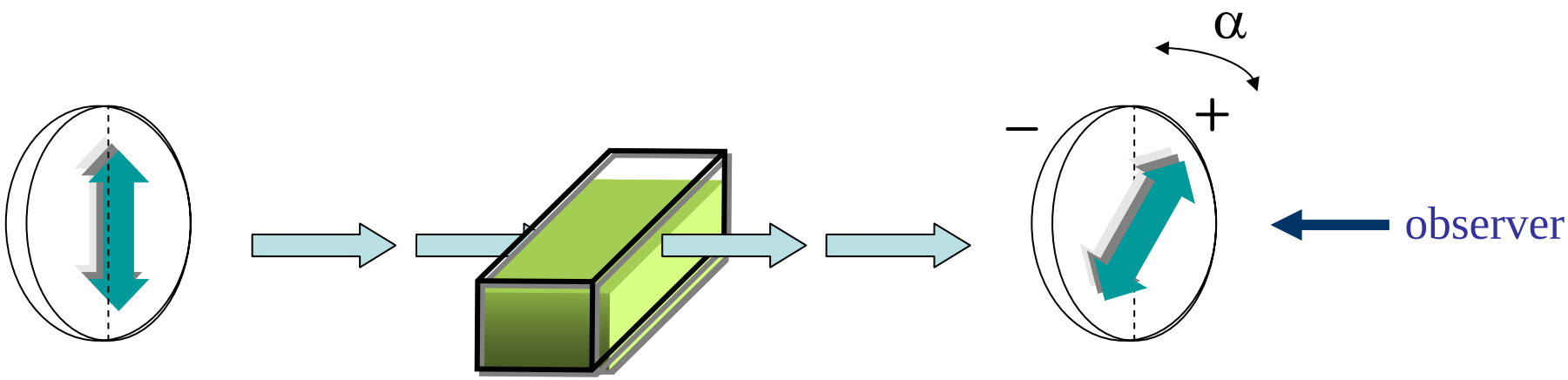


Plane-polarized light: oscillates in a single plane



polarizer

Polarimeter: optically active molecules rotate the plane of polarization of plane-polarized light



sample tube containing organic molecule

extent of rotation: α
directions of rotation: *d*, *l* or (+), (-)

levorotatory: counterclockwise rotation, *l*, (-)
dextrorotatory: clockwise rotation, *d*, (+)

The amount of rotation depends on the number of optically active molecules (sample concentration and sample path length) and the wavelength of the light used.

Specific rotation, $[\alpha]_D$: meaningful, comparable

- path length: l = 1 dm (10 cm)
- concentration: C = g / mL
- light: sodium D line (589 nm)

$$[\alpha]_D = \frac{\text{observed rotation },\alpha \text{ (degree)}}{\text{pathlength, } l \text{ (dm) x concentration, C (g/mL)}} = \frac{\alpha}{l \times C}$$

Specific rotation is a physical constant characteristic of a given optically active compound

- enantiomers have opposite sign but same value of specific rotations

(+) lactic acid, $[\alpha]_D$ = + 3.82; (-) lactic acid, $[\alpha]_D$ = - 3.82

	$[\alpha]_D$		$[\alpha]_D$
Penicillin V	+ 233°	Cholesterol	-31.5°
Sucrose	+ 66.47°	Morphine	-132°
Camphor	+ 44.26°	Acetic acid	0°
Monosodium glutamate	+ 25.5°	Benzene	0°

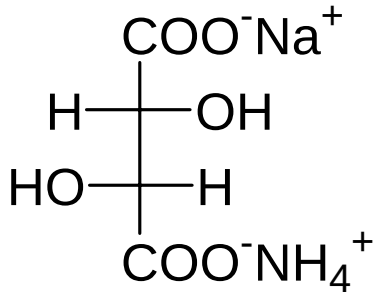
- the values and sighs of specific rotations depend on the types of compounds ; in general, unpredictable

9.4 Pasteur's Discovery of Enantiomers

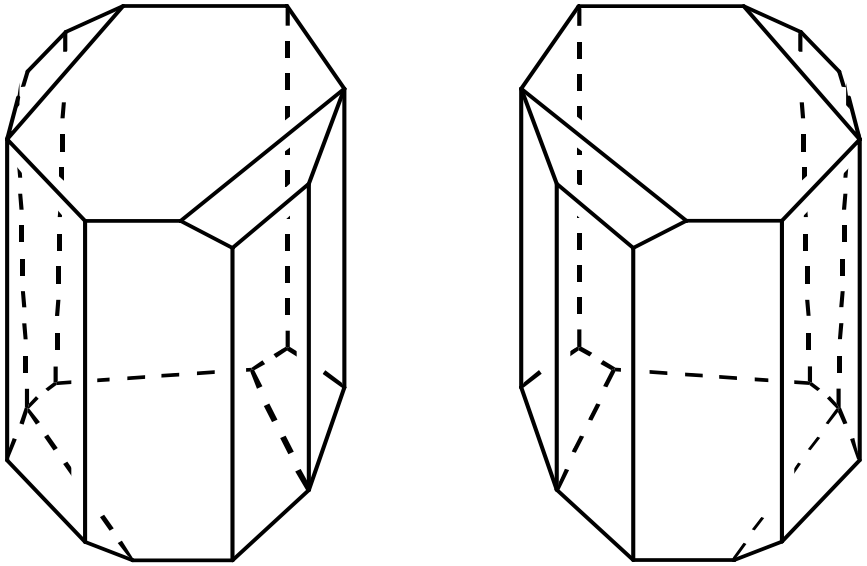
1849, Louis Pasteur

- discovered the phenomenon of enantiomerism

- separated two distinct kinds of crystals from racemic sodium ammonium tartrate
; two kinds of crystals were mirror images



Sodium ammonium tartrate



But, generally, two enantiomers are not separable by simple crystallization.

9.5 Sequence Rules for Specification of Configuration

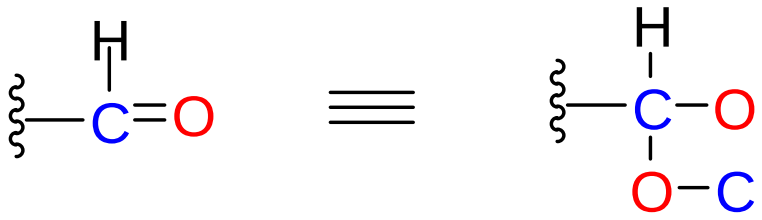
Configuration: three-dimensional arrangement of atoms at a chiral center

Sequence Rule (Cahn-Ingold-Prelog rule): priority of substituents

Rule 1 assign the priorities according to atomic number ; highest atomic number is ranked first

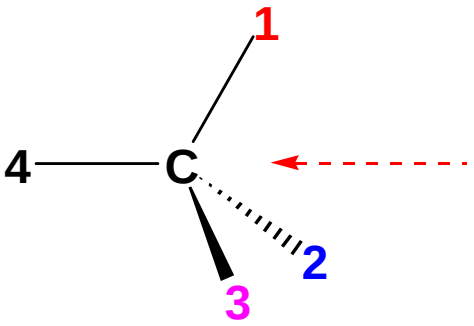
Rule 2 If a decision can't be reached by ranking the first atoms in the substituents, look at the second, third, or fourth atoms away from the carbon until the first difference is found.

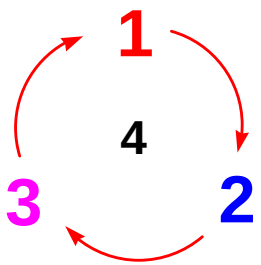
Rule 3 Multiple-bonded atoms are equivalent to the same number of single-bonded atoms.



Assignment of configuration: priority (1 > 2> 3> 4)

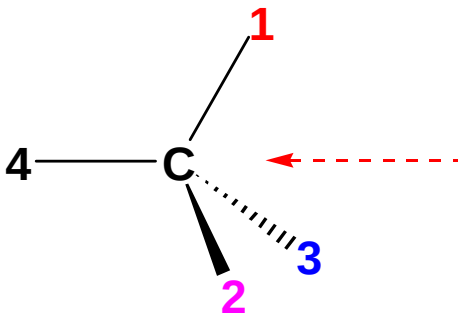
R (Latin *lectus*, "right"): S (Latin *sinister*, "left")

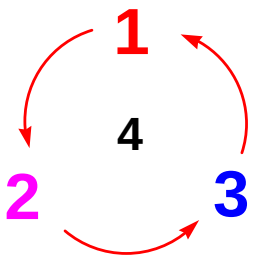




clockwise (right turn)

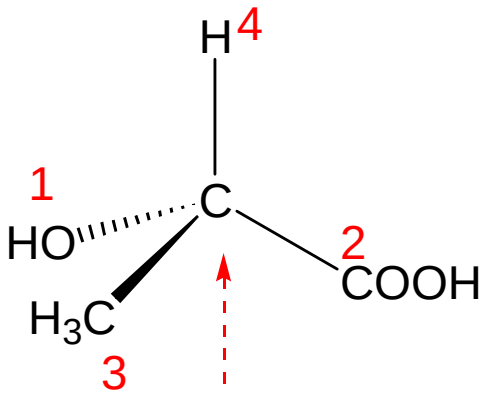
***R* configuration**

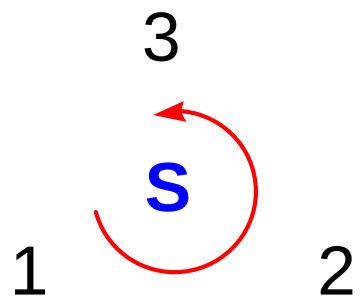




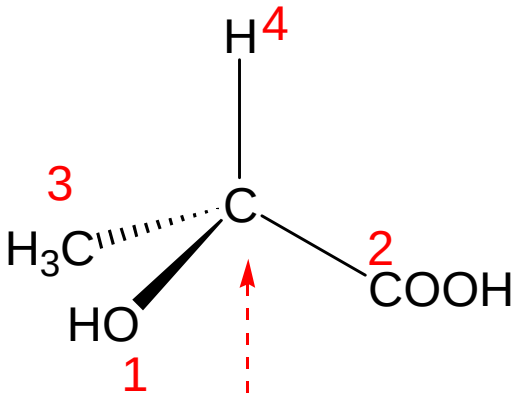
counterclockwise (left turn)

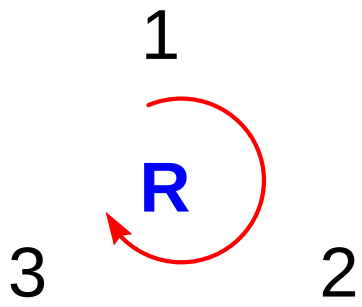
***S* configuration**



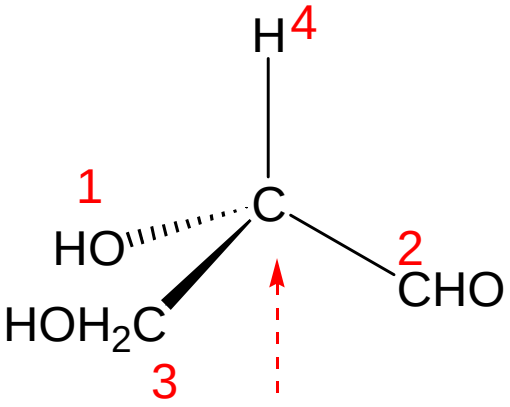


(*S*)-(+)-Lactic acid



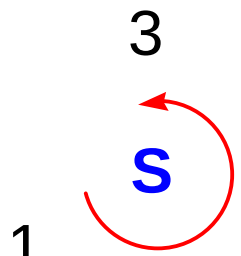


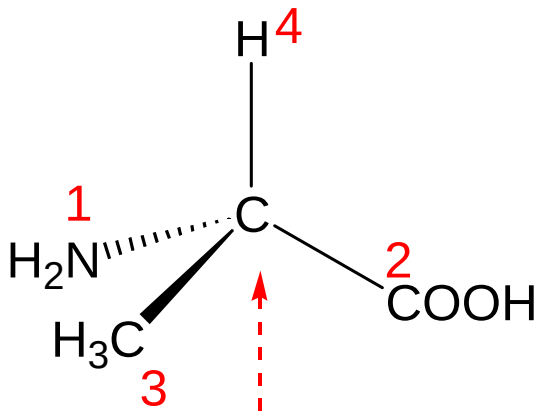
(*R*)-(-)-Lactic acid



(*S*)-(-)-Glyceraldehyde

$[\alpha]_D = -8.7^o$





(*S*)-(+)-Alanine

$[\alpha]_D = +8.5^o$

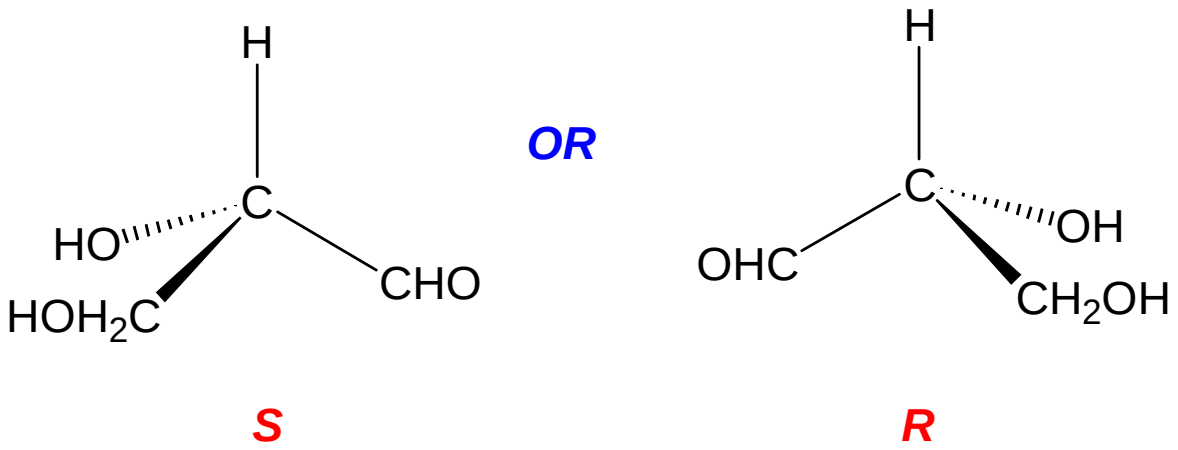
Note that the sign of optical rotation, (+) or (-), is not related to the R, S designation.

There is no simple correlation between R, S configuration and direction or magnitude of optical rotation.

How do we know that our assignments of *R*, *S* configuration are correct in an absolute, rather than a relative, sense?

Absolute configuration: relationship between R/S to (+)/(-)

Glyceraldehyde optical rotation measured by polarimeter: (-)



S ***R***

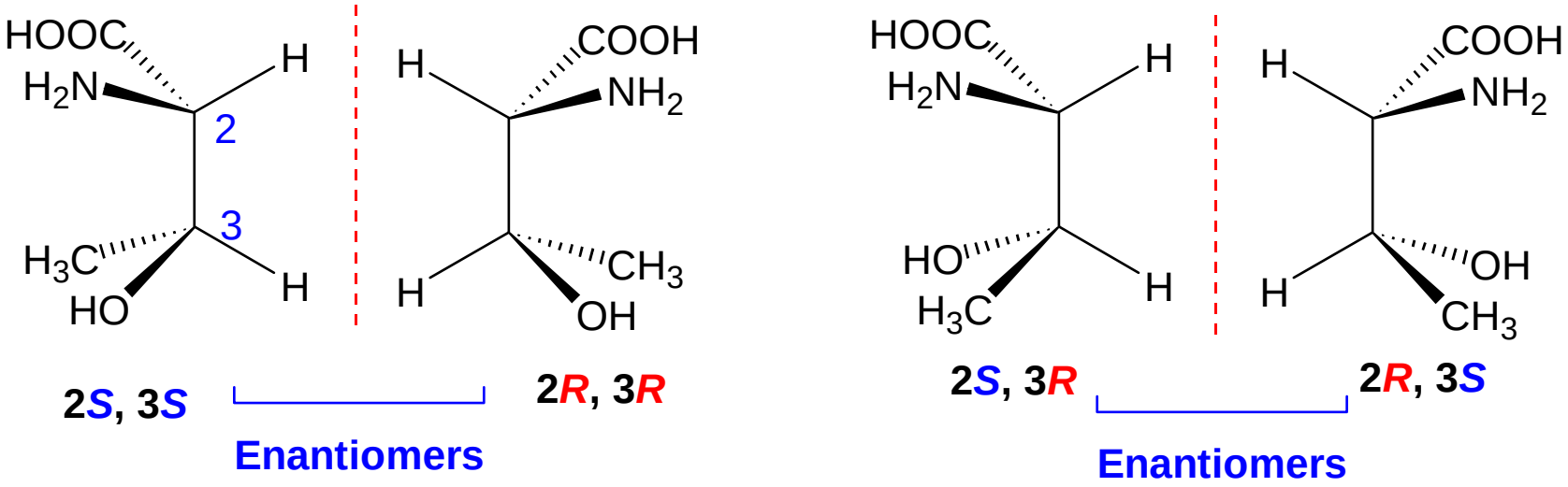
1951, J. M. Bijvoet; used X-ray crystallographic method (determine the absolute spatial arrangement of atoms in a molecule)

9.6 Diastereomers

; for molecules with more than one chiral centers

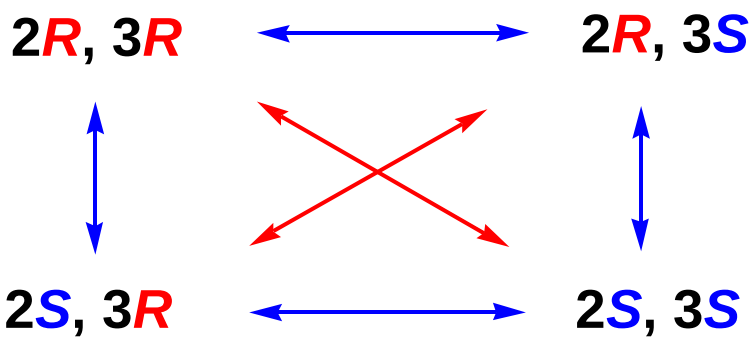
Diastereomer: stereoisomers but not enantiomers

2-Amino-3-hydroxybutanoic acid (Threonine)



2*S*, 3*S* — **2*R*, 3*R*** : **Enantiomers**

2*S*, 3*R* — **2*R*, 3*S*** : **Enantiomers**



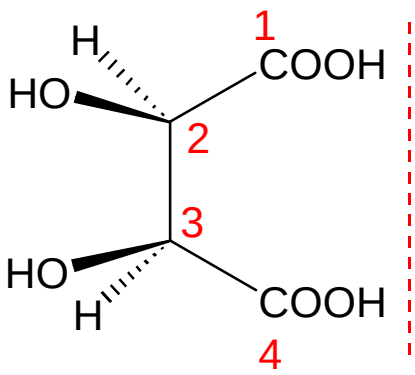
diastereomeric relationship

enantiomeric relationship

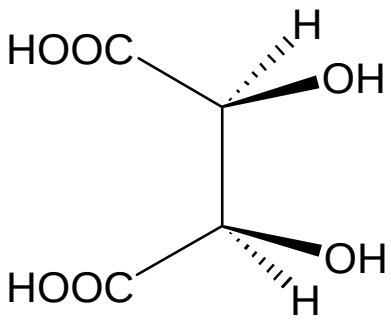
9.7 Meso Compounds

Tartaric acid: four stereo isomers possible

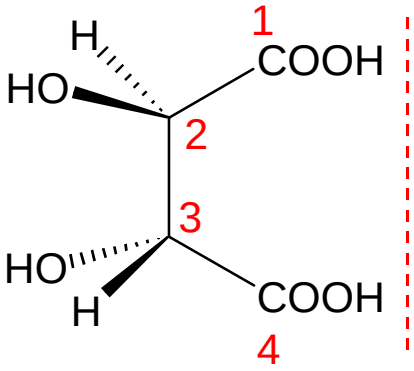
Tartaric acid



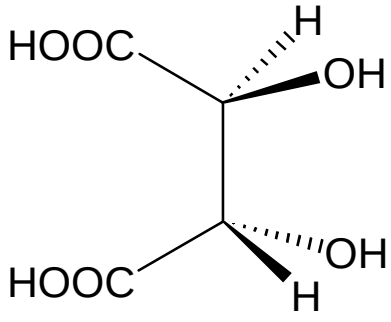
2R*, 3*S



2S*, 3*R



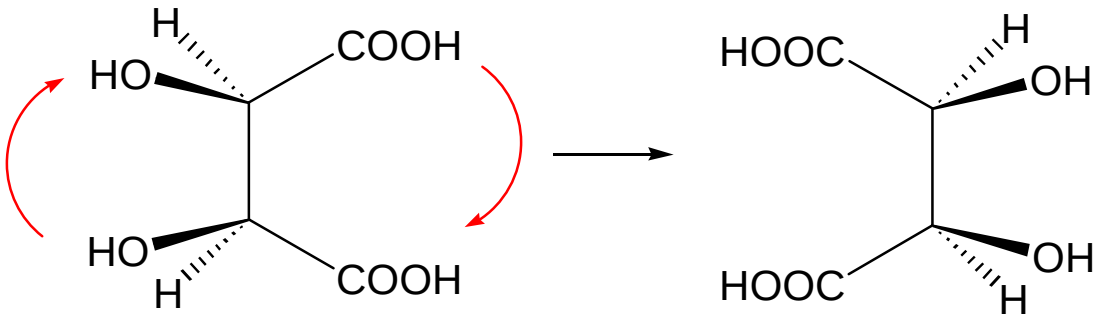
2R*, 3*R



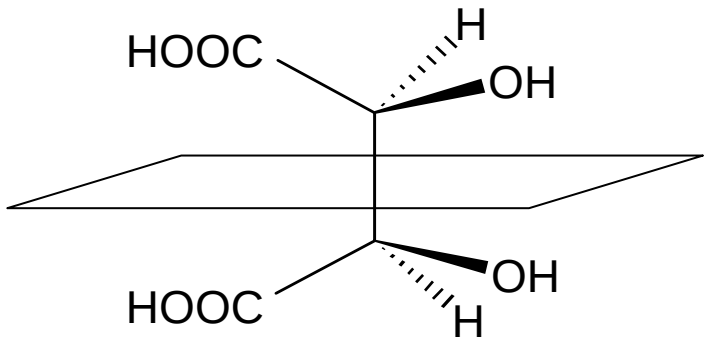
2S*, 3*S

Enantiomers

2*R*, 3*S* and 2*S*, 3*R*: plane of symmetry

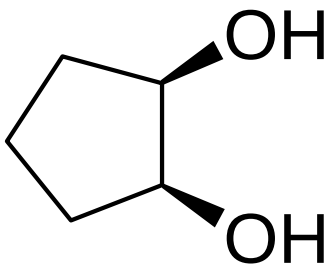


2*R*, 3*S* **Identical** **2*S*, 3*R***

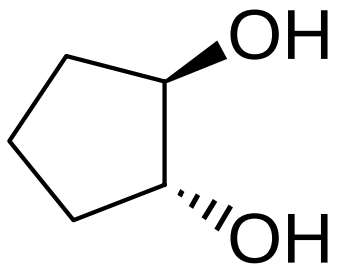


Meso compound: contain chiral centers but achiral due to plane of symmetry

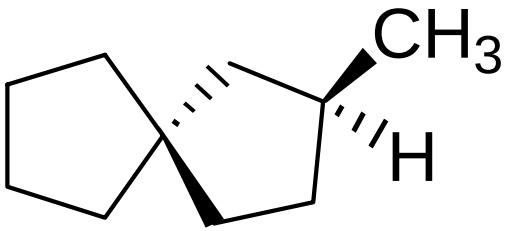
Meso compound ?

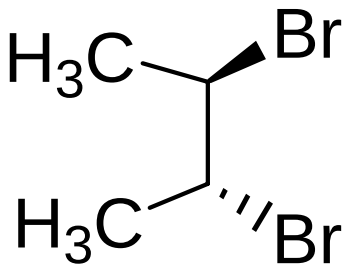


plane of symmetry



C_2 symmetry

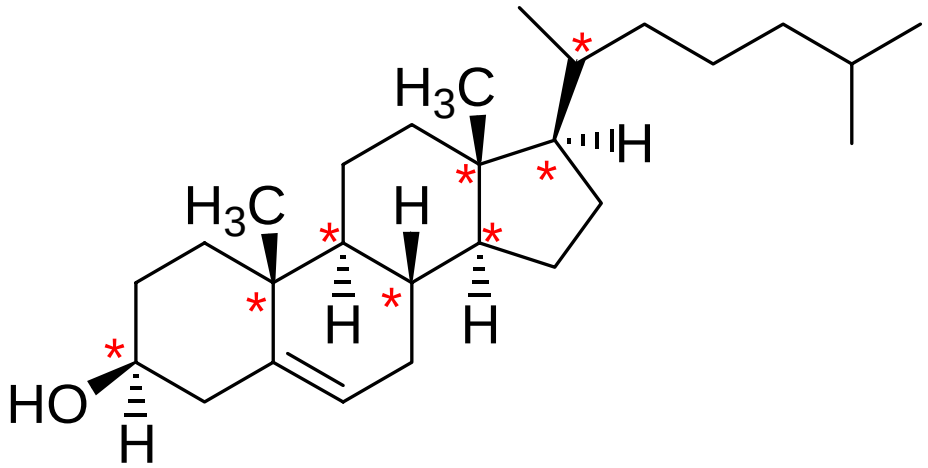




9.8 Molecules with More Than Two Chiral Centers

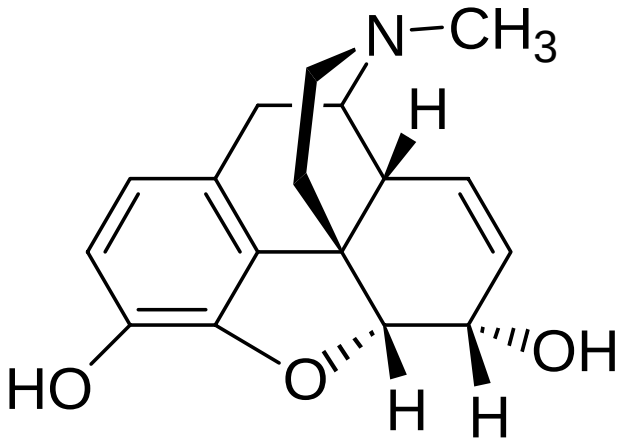
• n chiral centers → 2^n stereoisomers and 2^{n-1} pairs of enantiomers

• cholesterol: 8 stereogenic centers → 2^8 = 256 stereoisomers possible but only **one** is produced in nature.



Cholesterol

How many stereoisomers of morphine are possible?



Morphine

9.9 Physical Properties of Stereoisomers

Some Properties of Stereoisomers of Tartaric acids

Stereoisomers	**m.p. (°C)**	**$[\alpha]_D$ (degrees)**	**Density (g/cm^3)**	**Solubility at 20°C (g/100 mL H_2O)**
(+)	168-170	+12	1.7598	139.0
(-)	168-170	-12	1.7598	139.0
Meso	146-148	0	1.6660	125.0

9.10 Racemic Mixtures and Their Resolution

Racemic mixture or **Racemate**: (±) or *d*,*l*

- a 50:50 mixture of two enantiomers
- zero optical rotation: cancel out

Seperation of Enantiomers

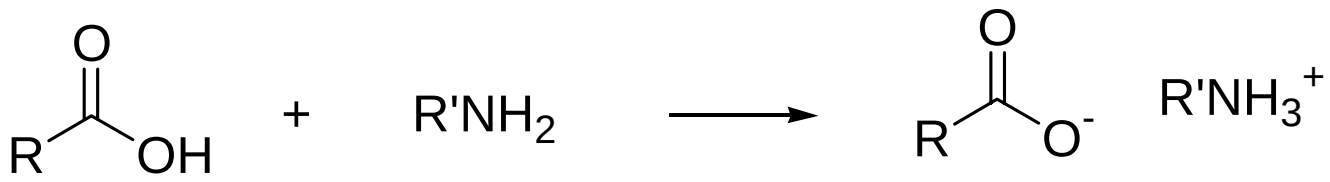
Enantiomers; same physical, chemical properties
same rate of reaction with achiral reactants

Diastereomers; different physical, chemical properties

Resolution: separation of two enantiomers

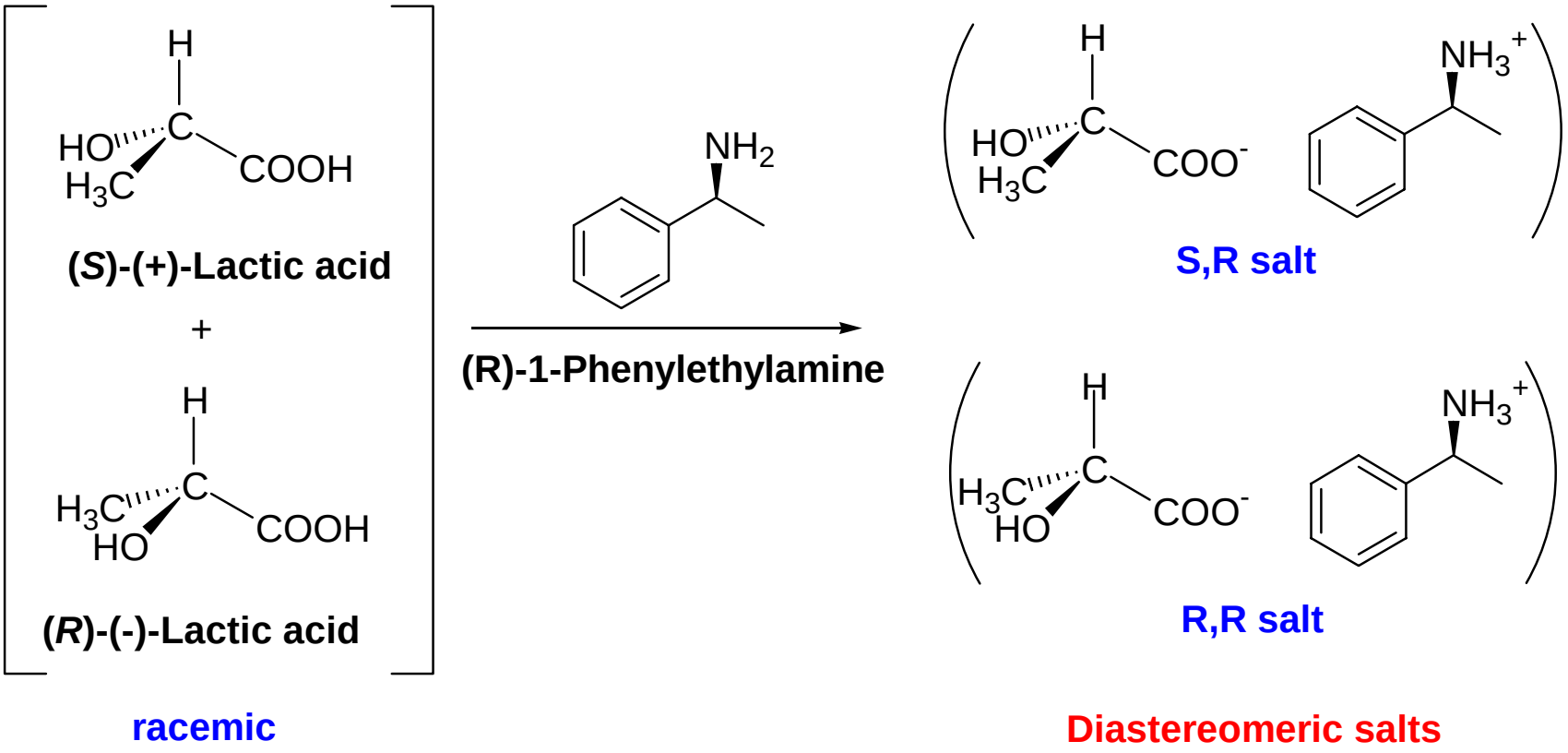
; the most common method of resolution uses diastereomeric ammonium salts

; uses an acid-base reaction between racemic mixtures of chiral carboxylic acids and an amine



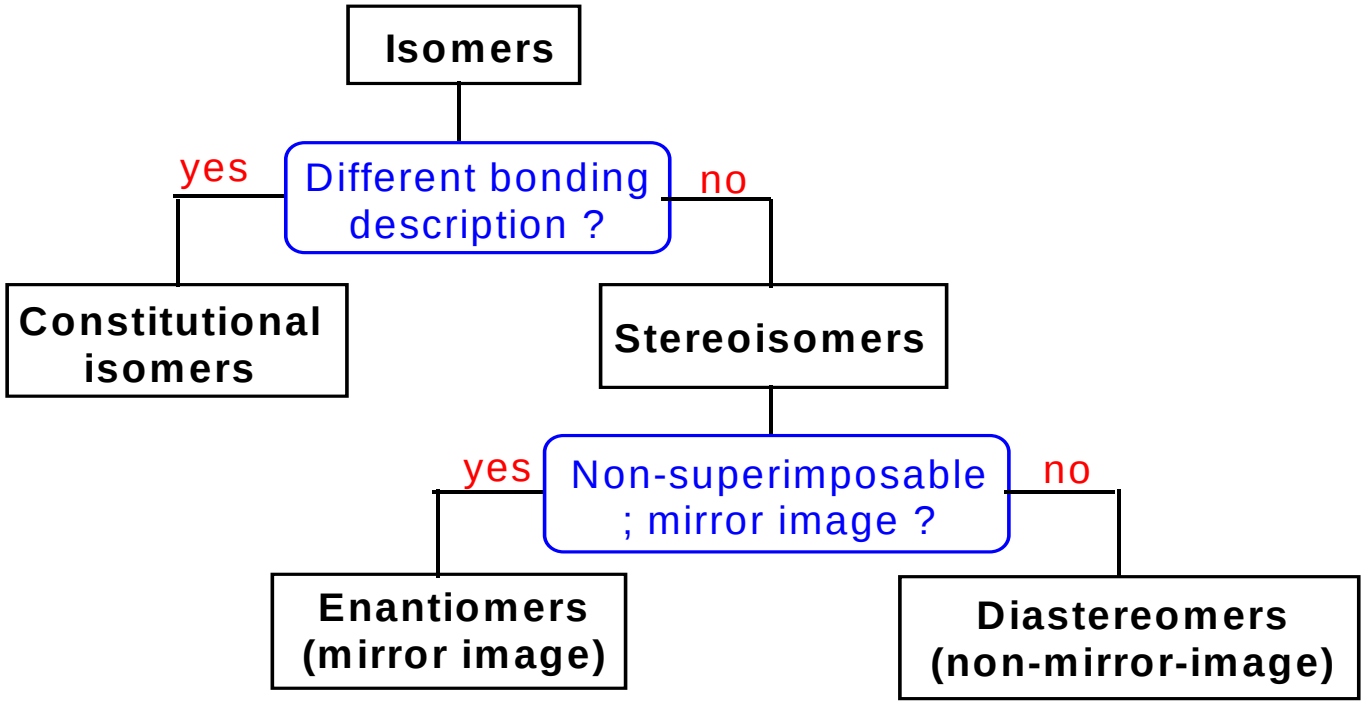
ammonium salt

Diastereomeric salts → selective crystallization



Once separated, acidification of the two diastereomeric salts with strong acid gives pure enantiomers and recover the chiral amine.

9.11 A Brief Review of Isomerism

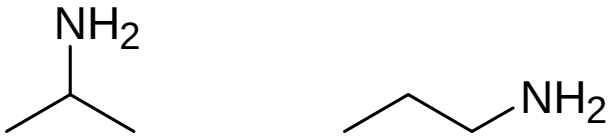


Constitutional isomers

different carbon skeletons

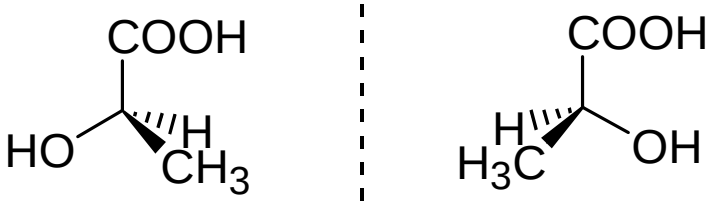
different functional groups

different position of functional groups



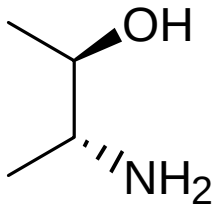
Stereoisomers

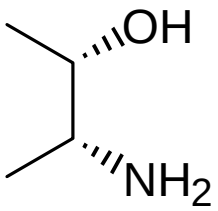
enantiomers



diastereomers

configurational diastereomers

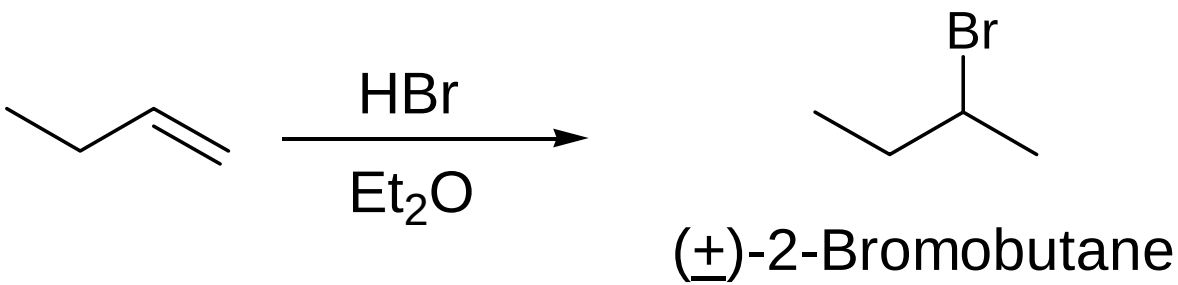




cis-trans isomers

9.12 Stereochemistry of Reactions: Addition of HBr to Alkenes

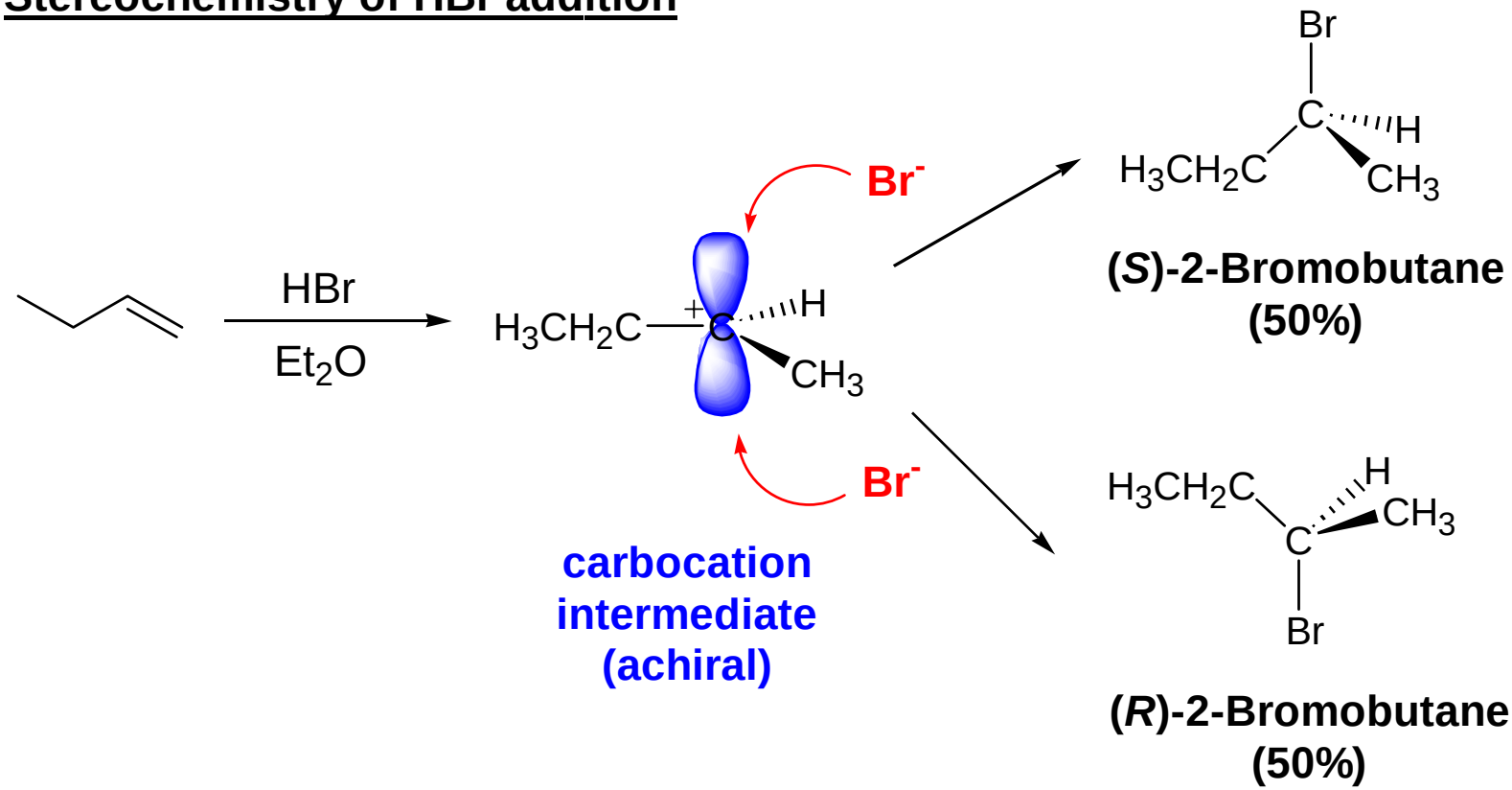
Most of the biochemical reactions that take place in the body and many organic reactions in the laboratory yield products with chiral centers.



(±)-2-Bromobutane

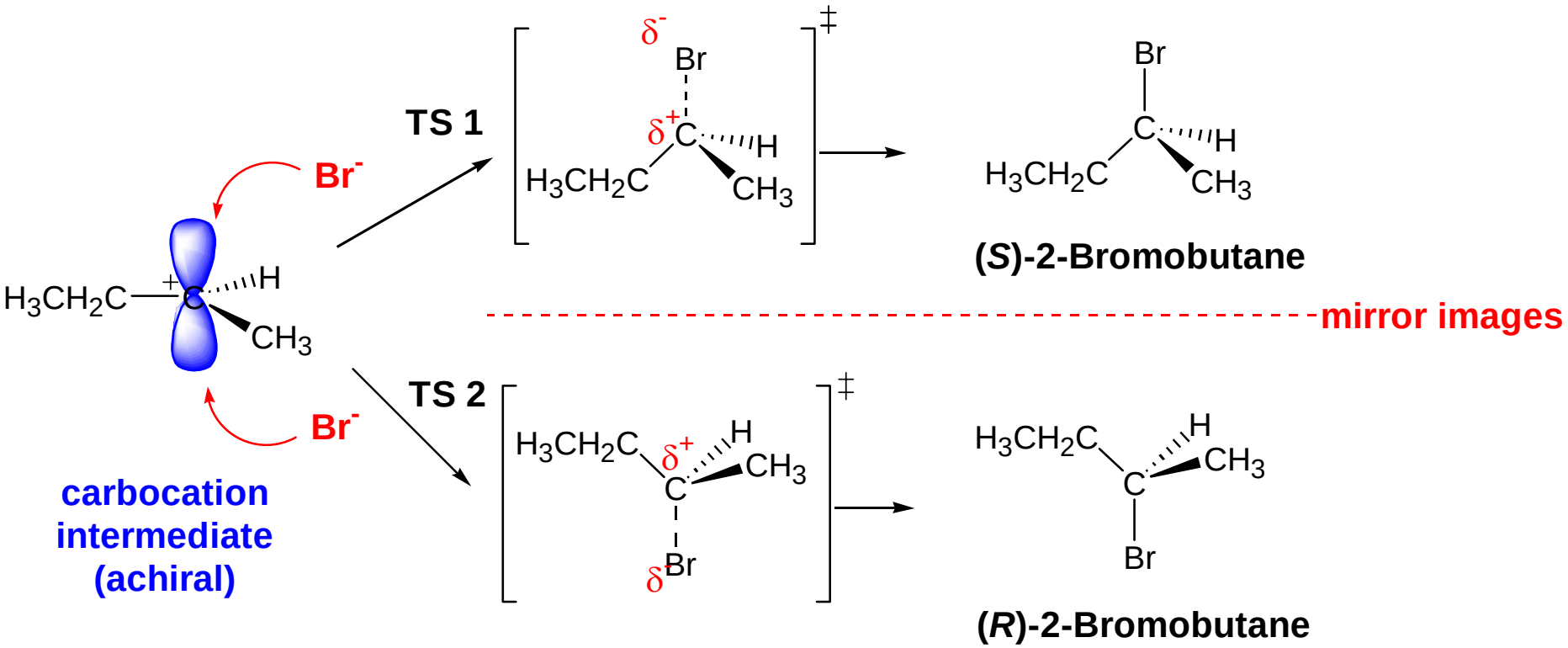
racemic, chiral

Stereochemistry of HBr addition



The achiral carbocation intermediate is planar and reacts equally from top and bottom faces.

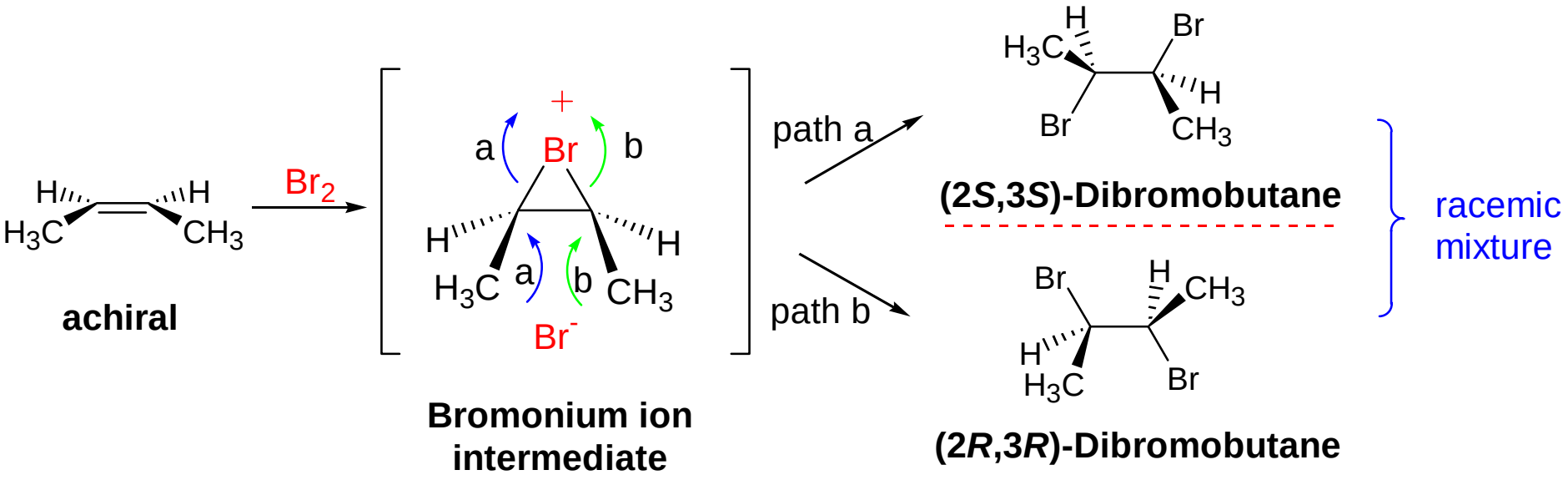
Mirror image transition states



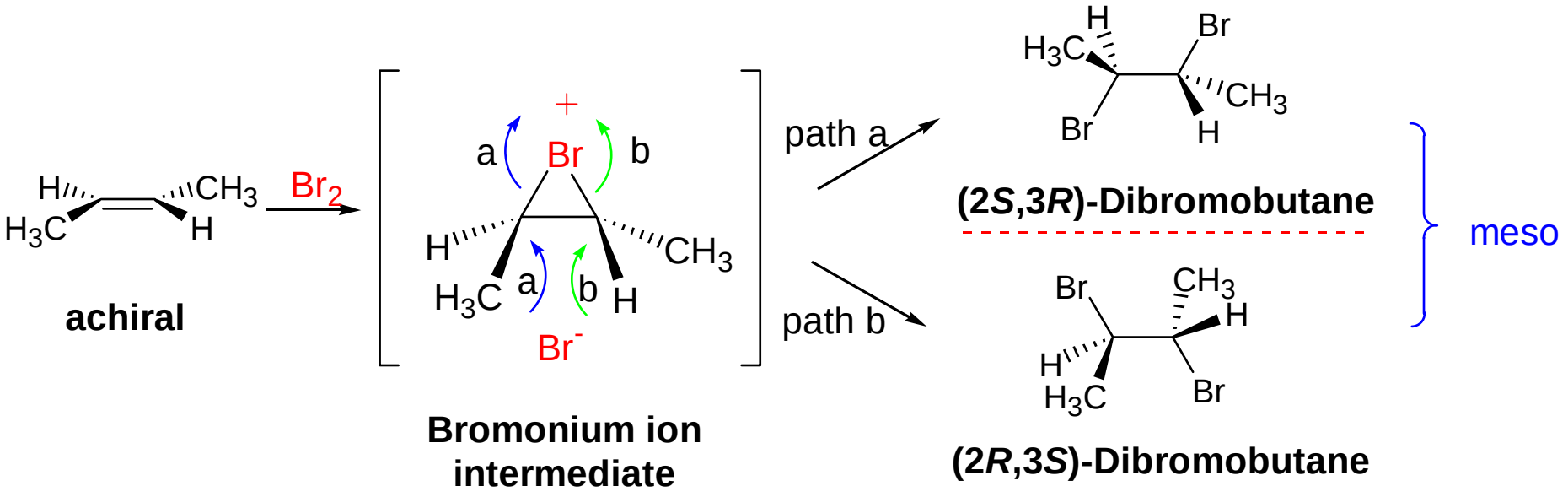
9.13 Stereochemistry of Reactions: Addition of Br_2 to Alkenes

Two chiral centers are generated.

addition Br_2 to (*cis*)-2-butene



addition Br_2 to (*trans*)-2-butene



Reactions between two optically inactive (achiral) partners always leads to an optically inactive product- either racemic or meso.

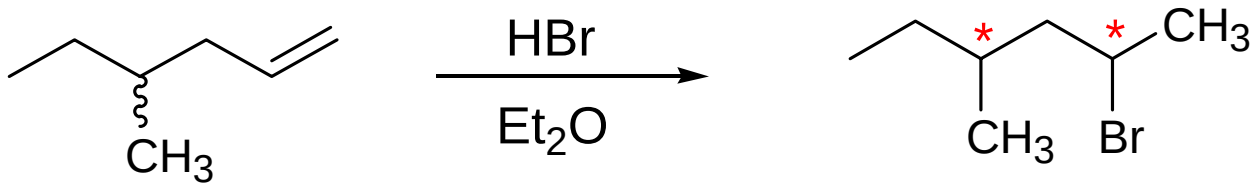
Optical activity can't come from nowhere; optically active products can't be produced from optically inactive reactants.

Then, how does Nature evolve to a chiral world ?

9.14 Stereochemistry of Reactions: Addition of HBr to a Chiral Alkene

- reactions of chiral molecules

chiral, racemic

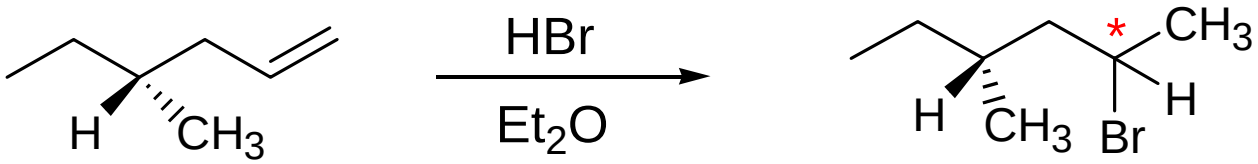


4-Methyl-1-hexene

(racemic)

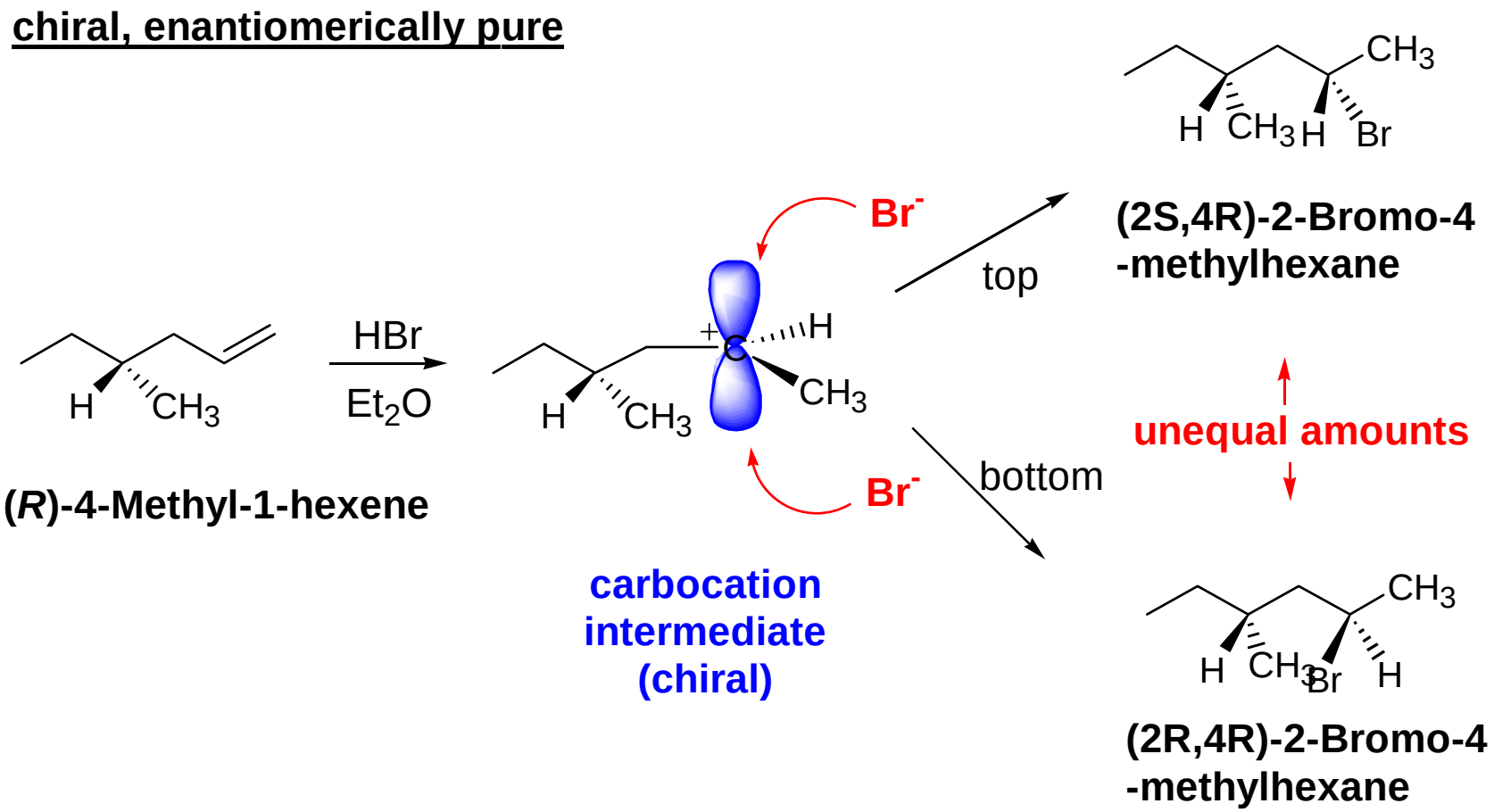
2-Bromo-4-methylhexane

chiral, enantiomerically pure



(*R*)-4-Methyl-1-hexene **2-Bromo-4-methylhexane**

The carbocation with a chiral center does not have a plane of symmetry; it is chiral because of the chiral center.



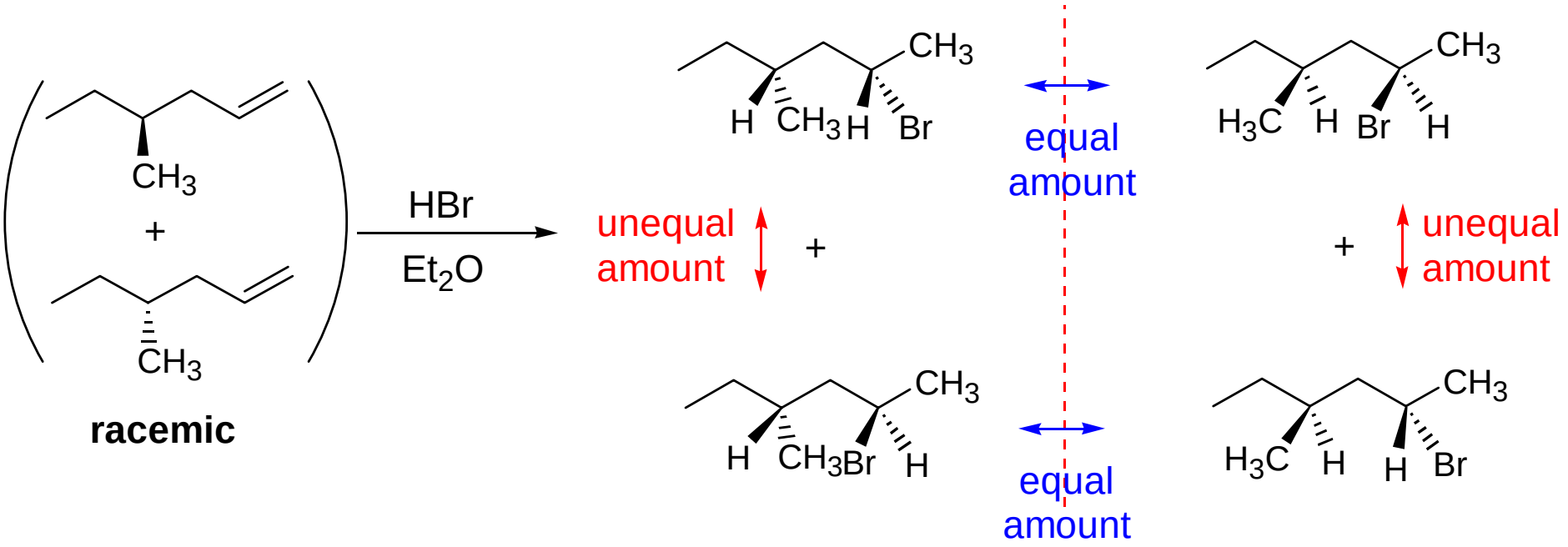
One of the two faces is likely, for steric reasons, to be a bit more accessible than the other face, leading to a mixture of two diastereomeric products in unequal amounts.

Reaction of a chiral reactant with an achiral reactant leads to unequal amounts of diastereomeric products.

If the chiral reactant is optically active because only one enantiomer is used, then the products are also optically active.

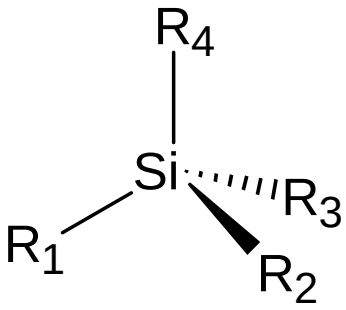
A racemic reactant produces racemic mixtures of unequal amounts of two diastereomers.

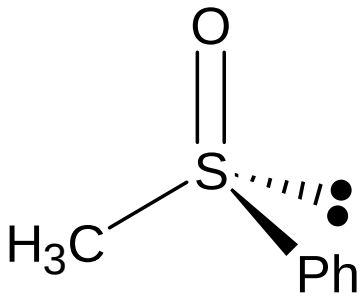
chiral, racemic

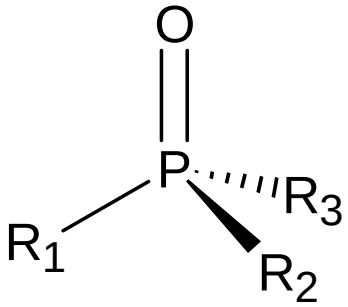


9.15 Chirality at Atoms Other Than Carbon

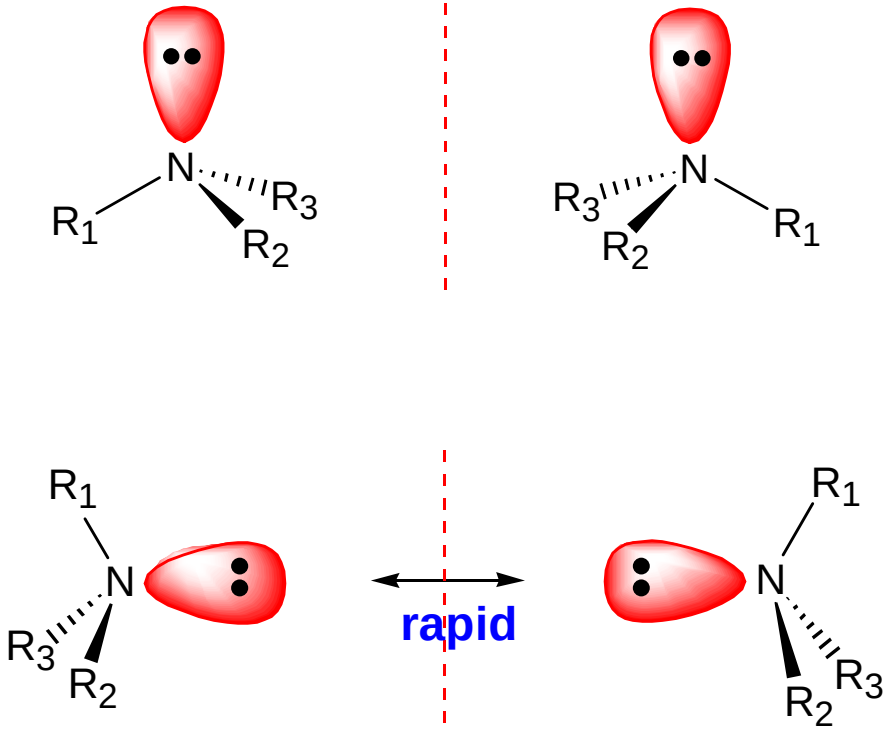
• tetrahedral atoms other than carbon can also be chiral centers: Si, N, P, S...





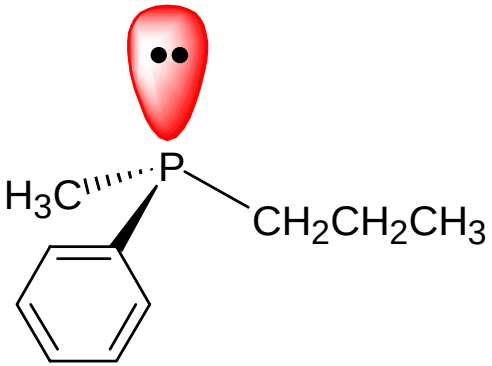


Trisubstituted amines have a chiral center, but undergo a rapid umbrella-like inversion that interconverts enantiomers. Therefore, it's not chiral except special cases.



Trisubstituted phosphines: undergo slower inversion

- stable cgiral phosphines can be isolated

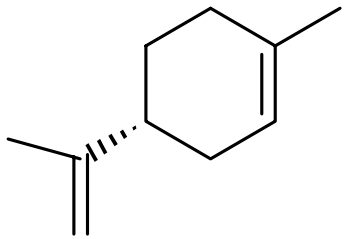


(R)-Methylpropylphosphine
(configurationally stable)

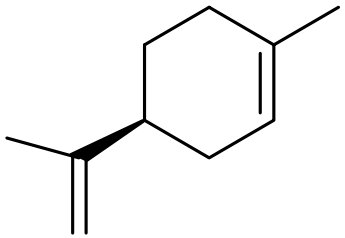
- configurationally stable for several hours at 100°C

9.16 Chirality in Nature

Although the different enantiomers of a chiral molecule have the same physical properties, they usually have different biological properties.

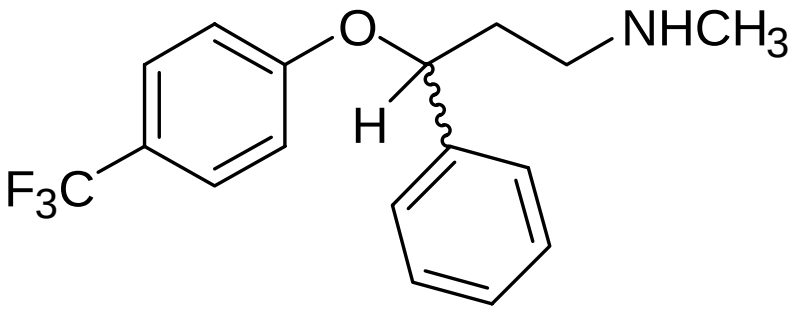


(+)-Limonene
(in oranges)

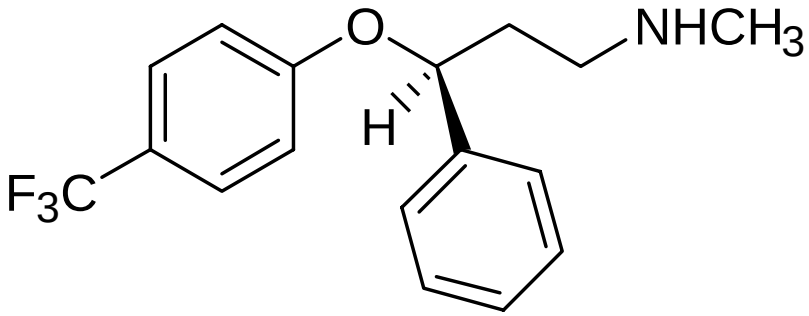


(-)-Limonene
(in lemons)

• Chiral Drugs:



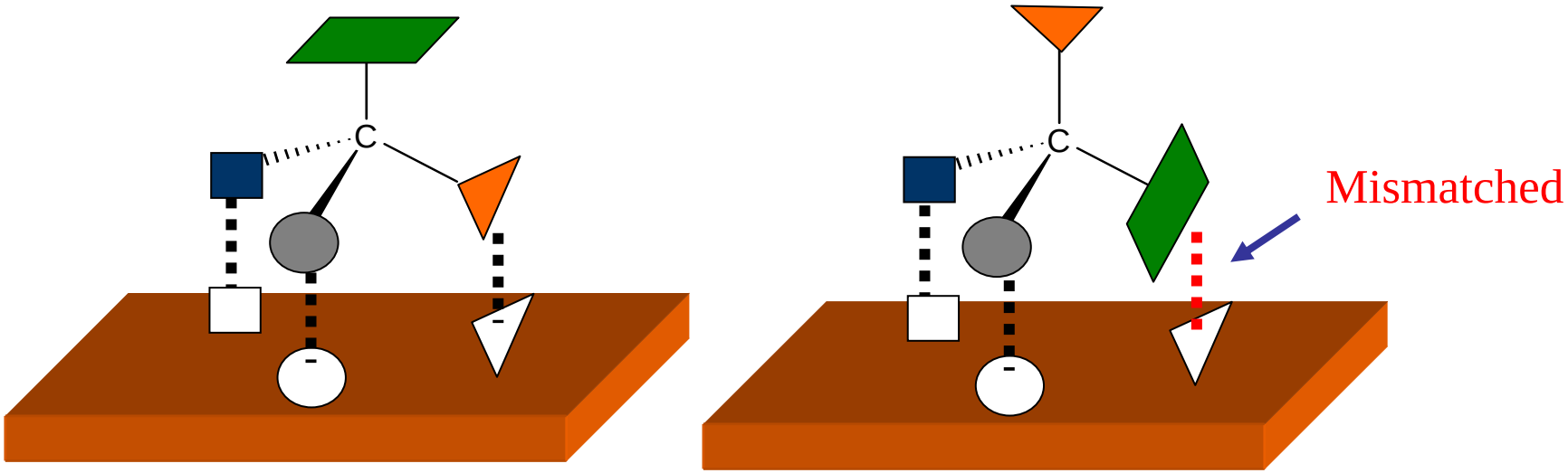
racemic
(±)-Fluoxetine
(antidepressant)



(S)-Fluoxetine
(prevent migraine)

Why do different stereoisomers have different biological properties?

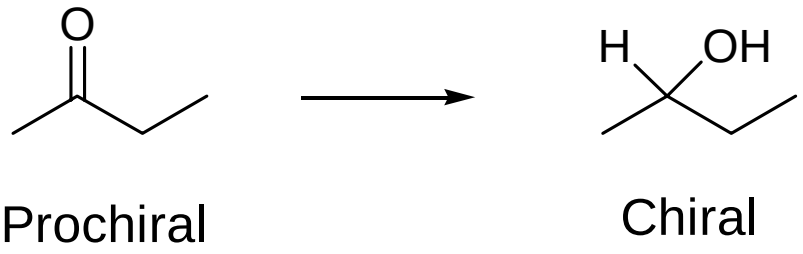
A chiral molecule must fit into a **chiral receptor** at some target site to exert its biological action.

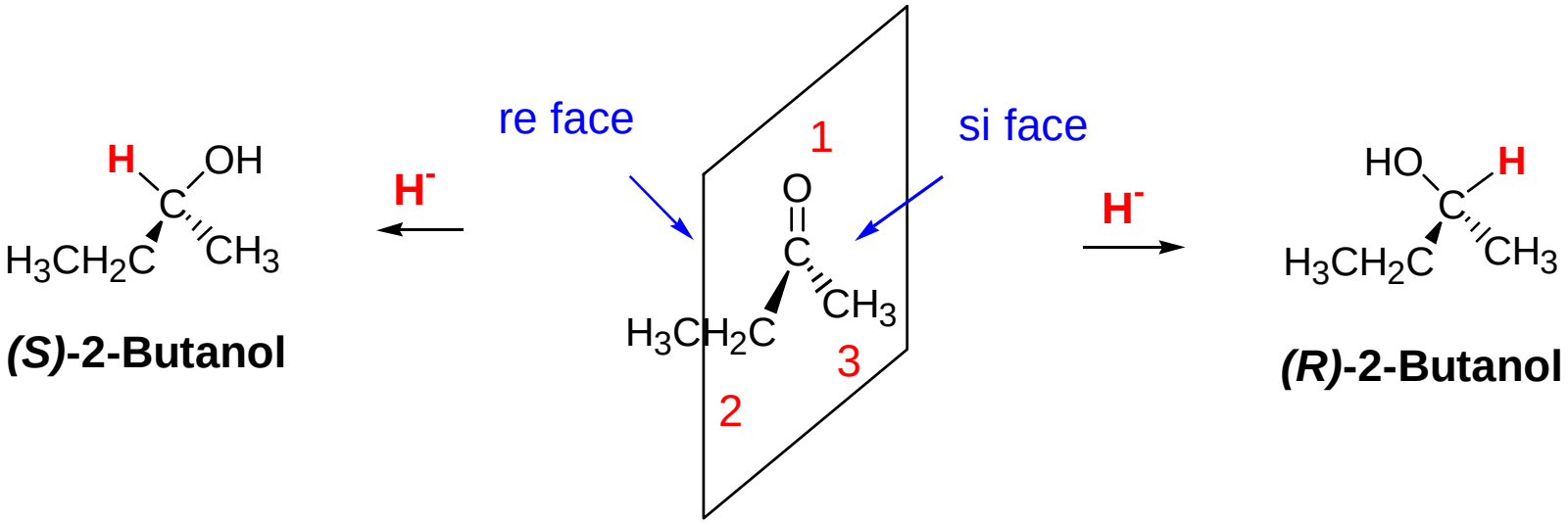


9.17 Prochirality

Prochiral: A molecule is said to prochiral if can be converted from achiral to chiral in a single chemical step.

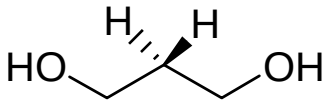
Prochirality face: sp^2

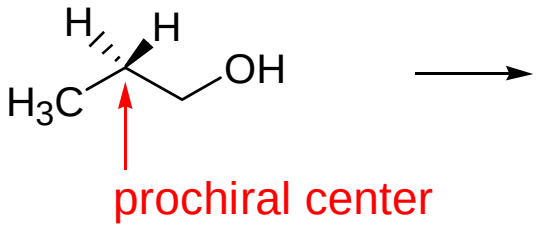


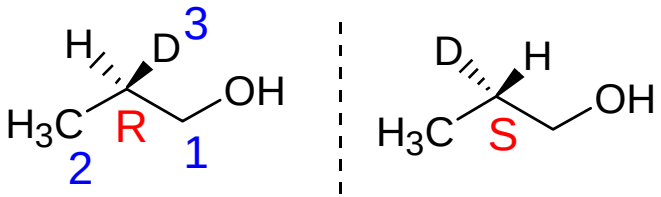


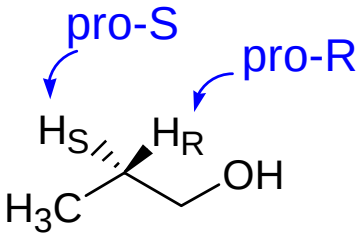
Prochirality center: sp^3

pro-R / pro-S; assign higher priority to one of the two
-> if R then pro-R; if S then pro-S

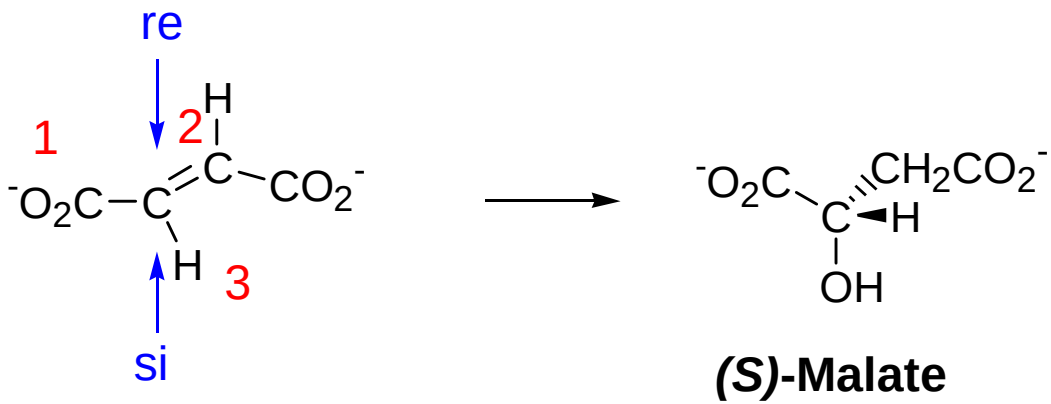




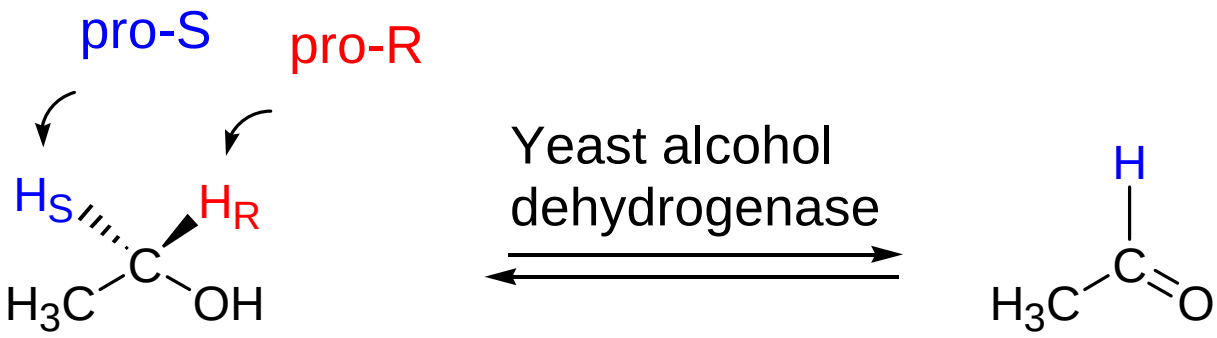




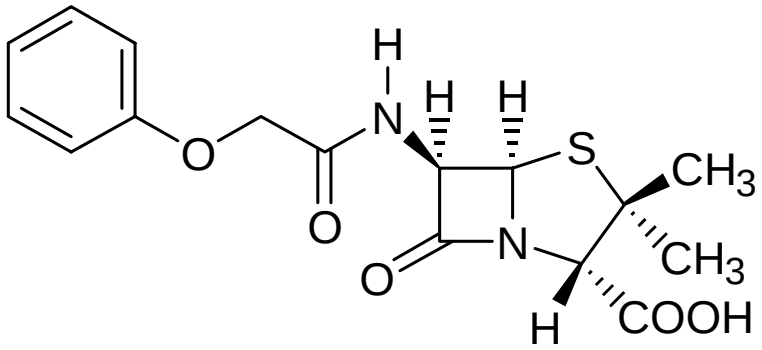
Biological Prochiral



***(S)*-Malate**

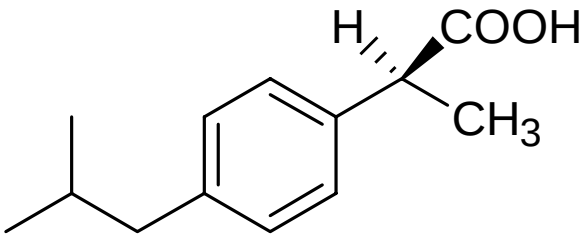


Natural drugs



Penicillin V

Synthetic drugs



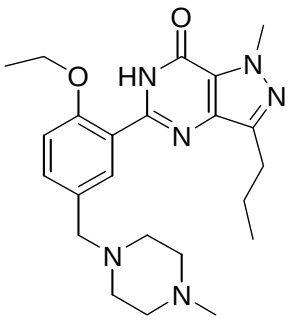
(S)-Ibuprofen
(an active analgesic agent)

R enantiomer is inactive

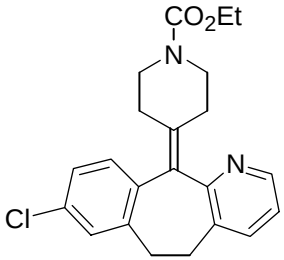
enantioselective synthesis: prepare only a single enantiomer rather racemic mixture

- no waste of the other enantiomer
- wrong enantiomer in racemic mixture can have side effects

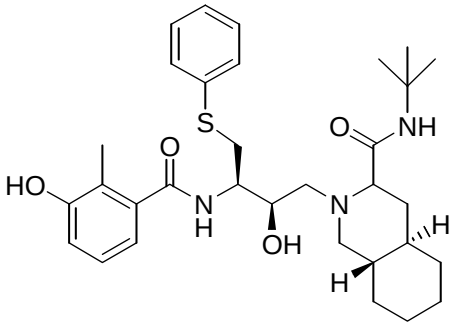
Selected Medications of 20th Century



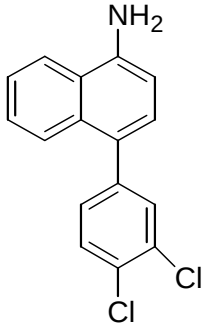
Viagra
(treatment of impotence)



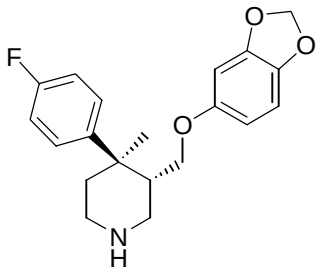
Claritin
(antihistamine,
i.e. antiallergic)



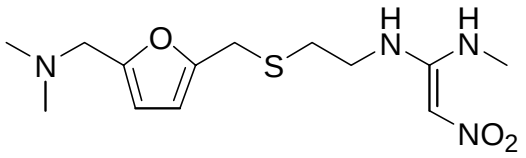
Viracept
(treatment of AIDS)



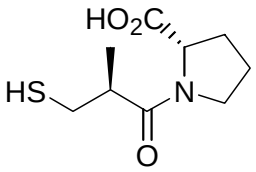
Zoloft
(psychotherapeutic)



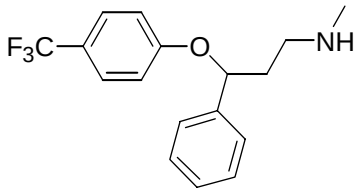
Paxil
(psychotherapeutic)



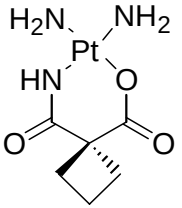
Zantac
(treatment of ulcer)



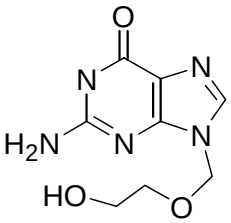
Captopril
(treatment of hypertension)



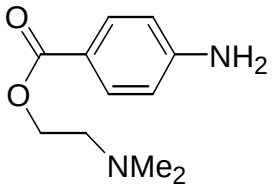
Prozac
(antidepressant)



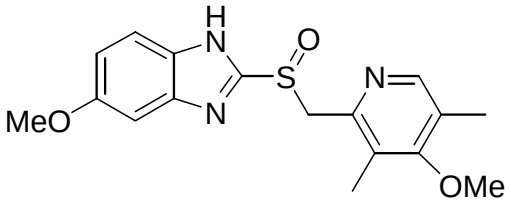
Carboplatin
(treatment of ovarian cancer)



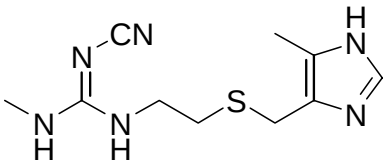
Acyclovir
(antiviral)



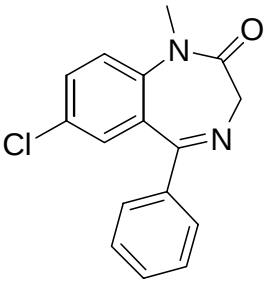
Novocain
(local anesthetic)



Prilosec
(antispasmodic)

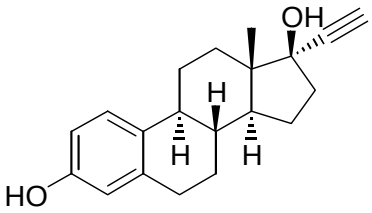


Tagamet
(treatment of ulcer)

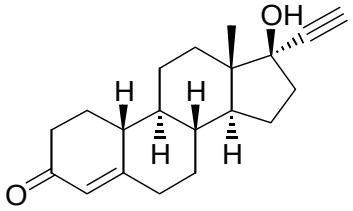


Valium
(tranquilizer)

Selected Medications of 20th Century

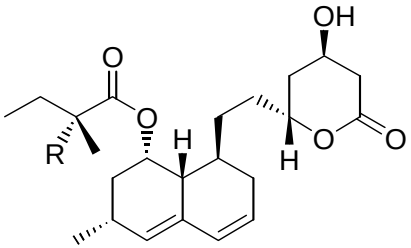


17-ethynylstradiol

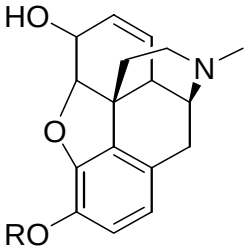


norethindrone

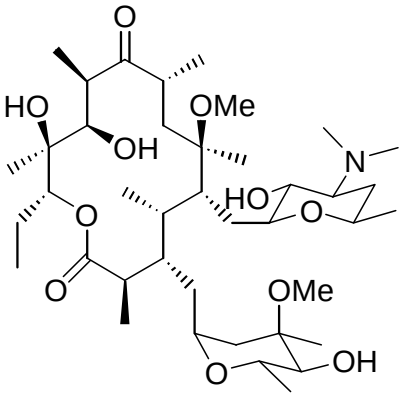
(the "Pill"; contraceptive)



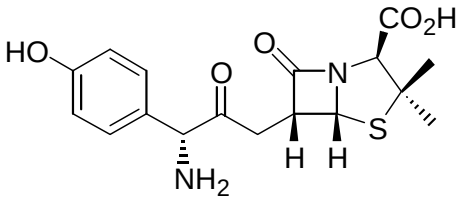
R= H Mevacor
R=Me Zocor
(treatment of high cholesterol)



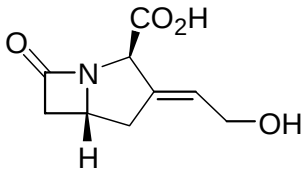
R= H Morphine
R= Me Cocaine
(pain killer)



Clarithromycin
(antibacterial)



Ampicillin
(antibiotic)



Clavulanic acid
(β-lactamase inhibitor)

Augmentin
(antibiotic)