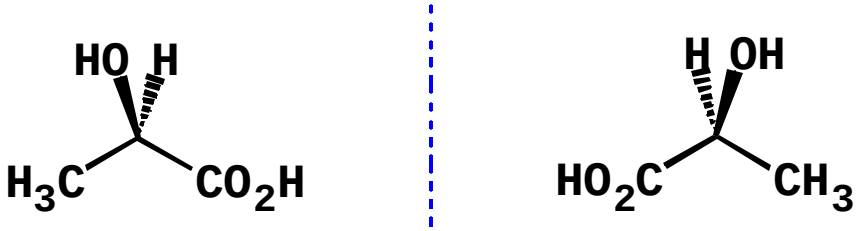
Chapter 9 – Stereochemistry*

stereochemistry = chemistry in 3D

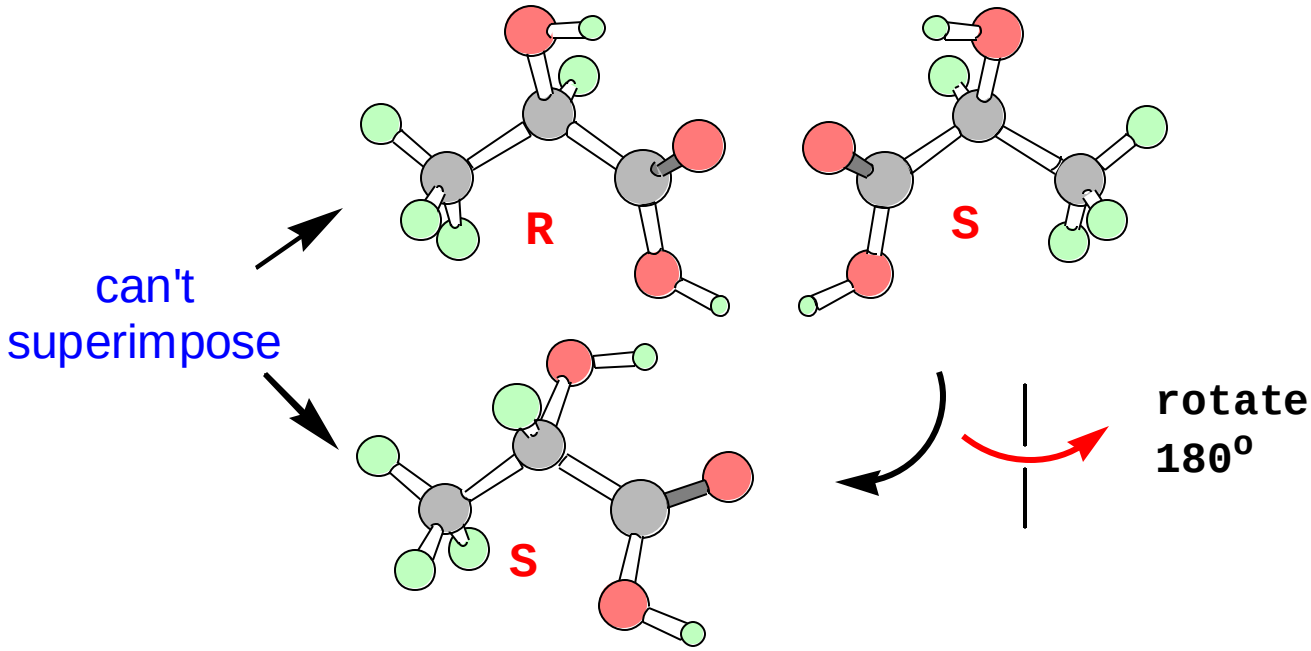
stereo isomers = isomers which differ only in their 3D structures; examples are cis & trans-2-butene and **enantiomers**

enantiomers = **non-superimposable** (different) mirror images; majority of chemical and physical properties are identical



(R)-(-)-lactic acid (S)-(+)-lactic acid

enantiomers



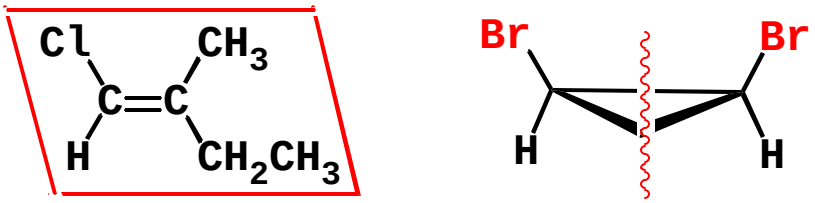
chiral = describes a molecule that is **different** from its mirror image; enantiomers are chiral

achiral = describes a molecule that is the **same** as its mirror image

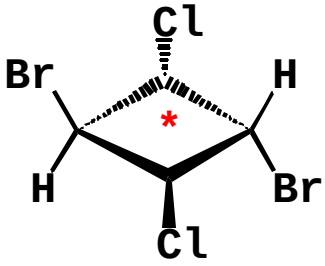
achiral molecules have either one or both of the following…

- → plane of symmetry
- → center of symmetry

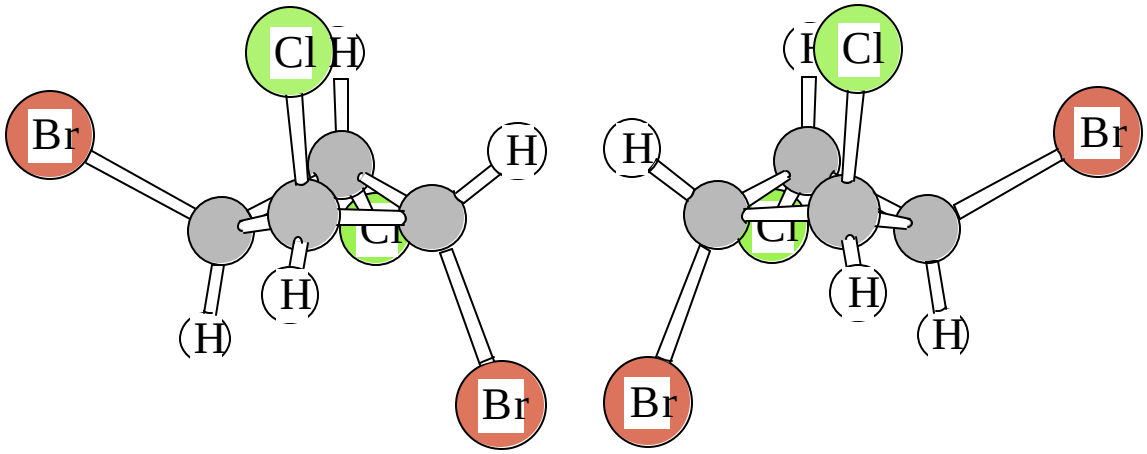
chiral molecule → (R)-lactic acid
achiral molecule → water



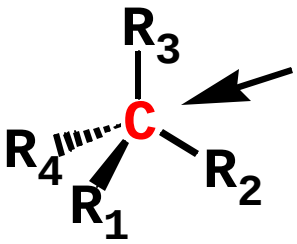
mirror planes of symmetry



* = center of symmetry in geographical middle of the molecule



chiral center (or stereo or stereogenic center) = an atom attached to 4 different atoms or groups;

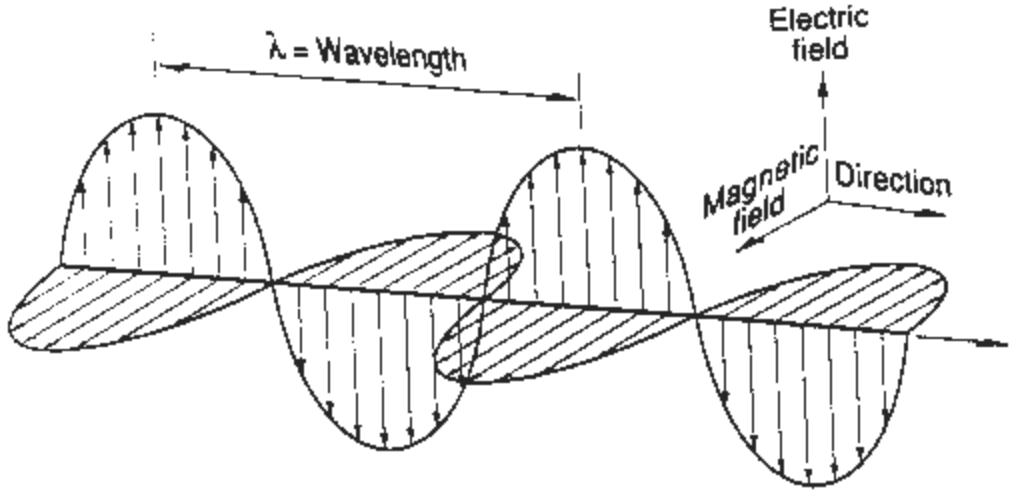


chiral center

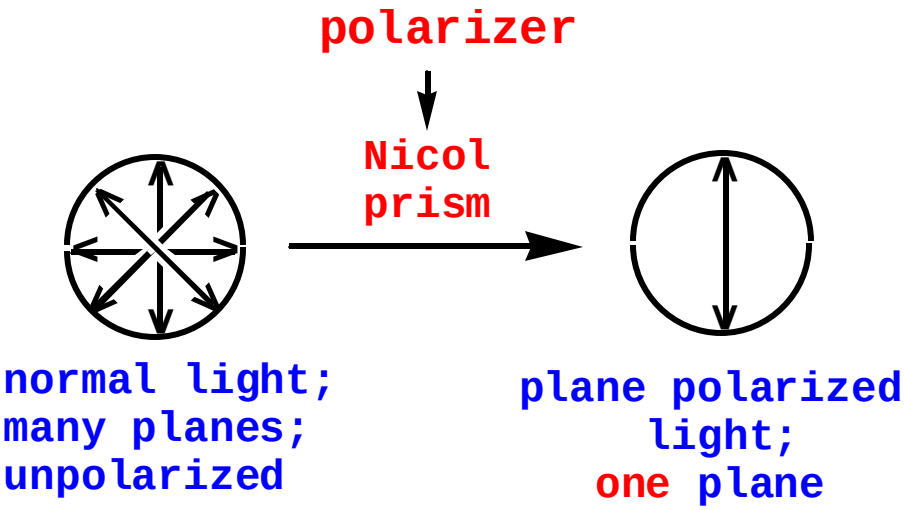
most chiral molecules contain chiral centers, but a molecule can be chiral and not contain a chiral center (how about 2,3-hexadiene?)…check this out

plane polarized light = light whose electric field amplitude vector oscillates in a single plane; the rotation of plane polarized light is about the only physical property that distinguishes enantiomers

Some characteristics of an electromagnetic wave…



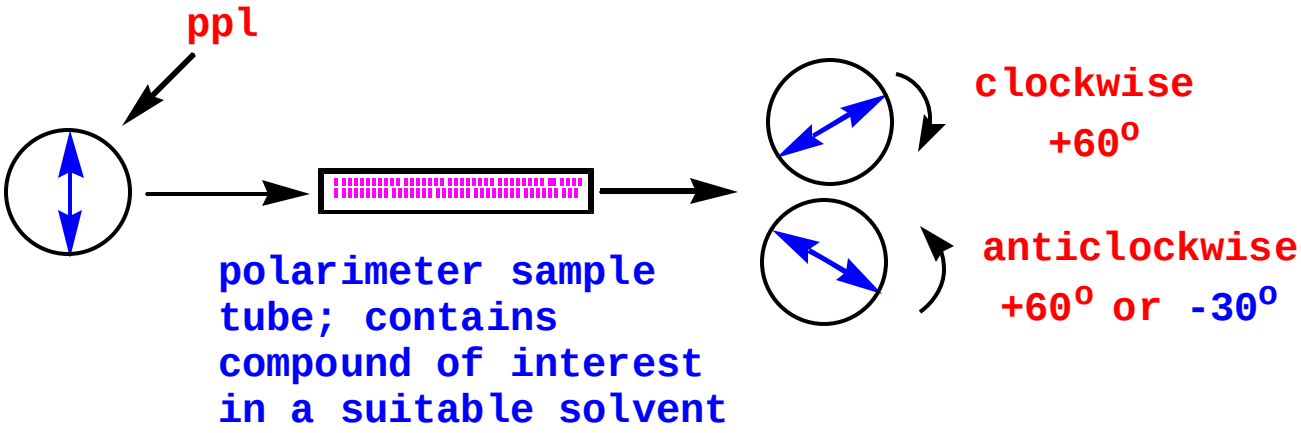
“Normal” unpolarized light consists of all possible orientations of the electromagnetic waves. A single wave can be obtained by passing normal light through a polarizer → this is plane polarized light.

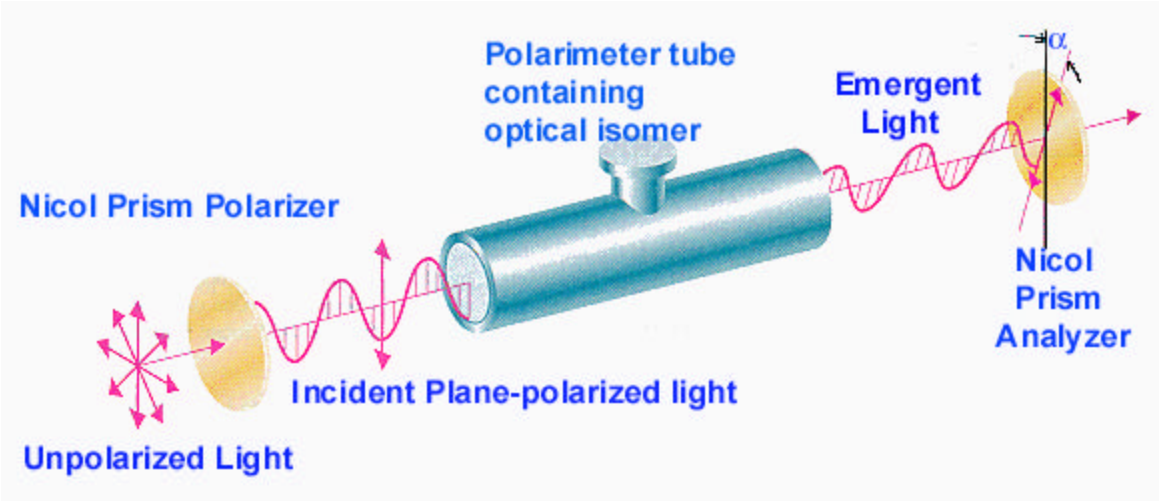


Chiral compounds rotate ppl →

polarimeter = instrument used to measure the amount (in °) by which materials rotate plane polarized light

Schematic diagrams of a polarimeter…

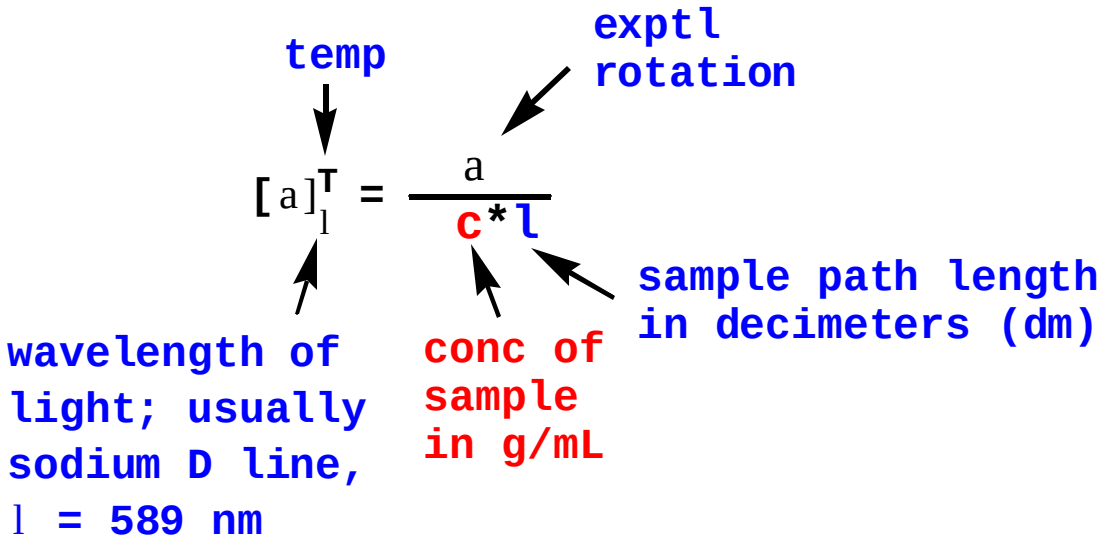




optical activity = a substance that rotates plane polarized light is **chiral** and said to be **"optically active"**

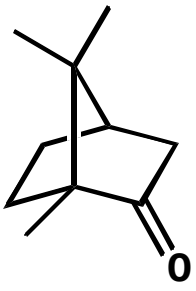
specific rotation, [a] = amount (degrees) that a substance rotates ppl expressed in a standard form; it accounts for variables such as concentration (c) and length (l) of the light path through the sample solution;

in the equation shown below, a is the measured rotation



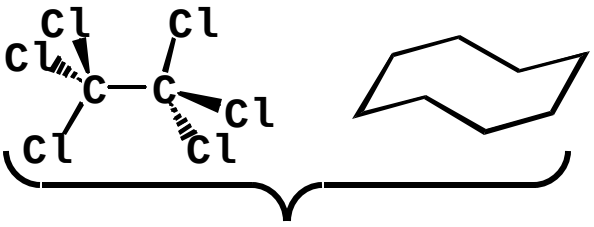
compound	$[a]_{D}^{20}$
camphor	-44.2°
nicotine	+163.2
sucrose	+66.4

Some camphor like compounds (similar odor)…



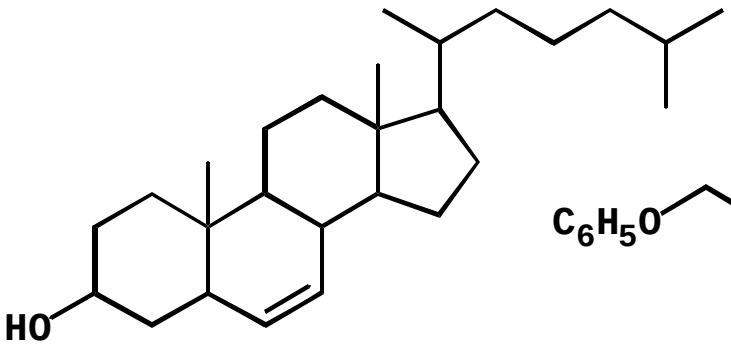
camphor

[a] = -44.2°



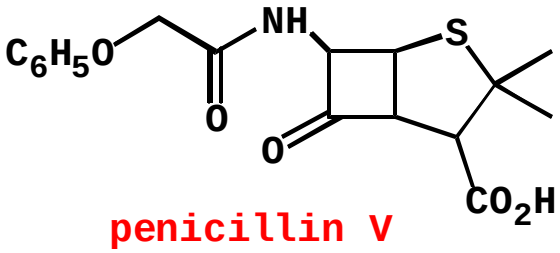
have camphor-like odor

Other optically active compounds…



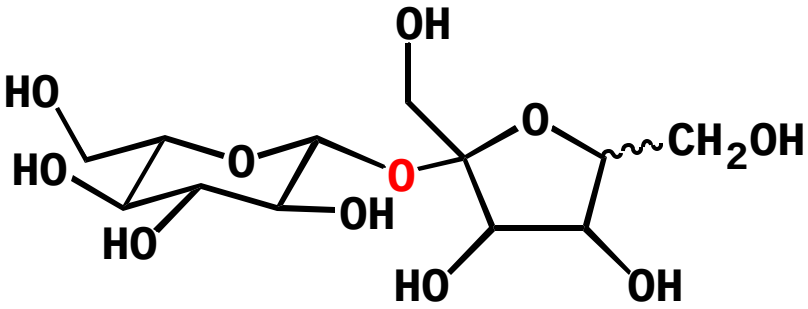
cholesterol

[a] = -31.5°



penicillin V

[a] = +223°



sucrose

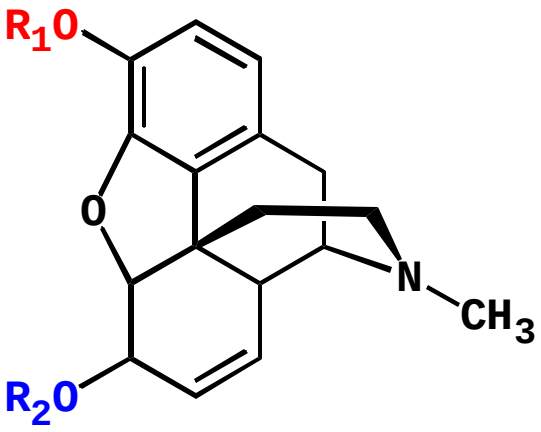
[a] = +66.4°

glucose

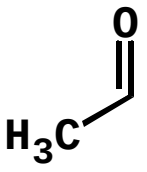
[a] = +53°

fructose

[a] = -92°



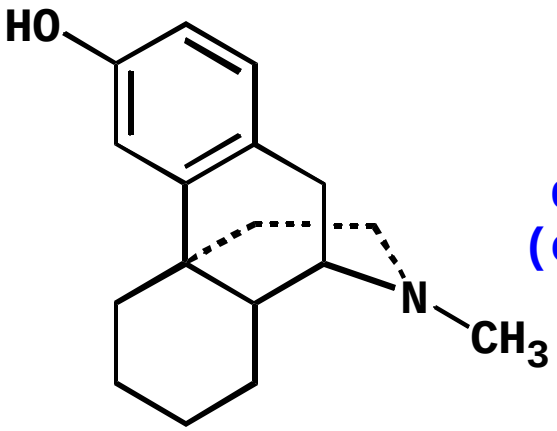
heroin: R_1 = R_2 =



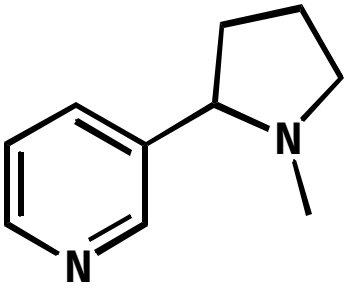
codeine: R_1 = CH_3, R_2 = H

morphine, R_1 = R_2 = H

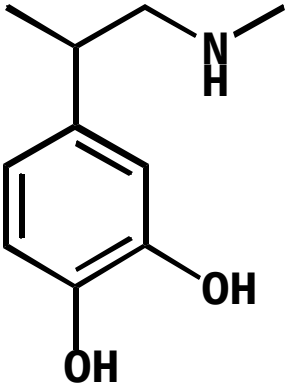
[a] = -132°



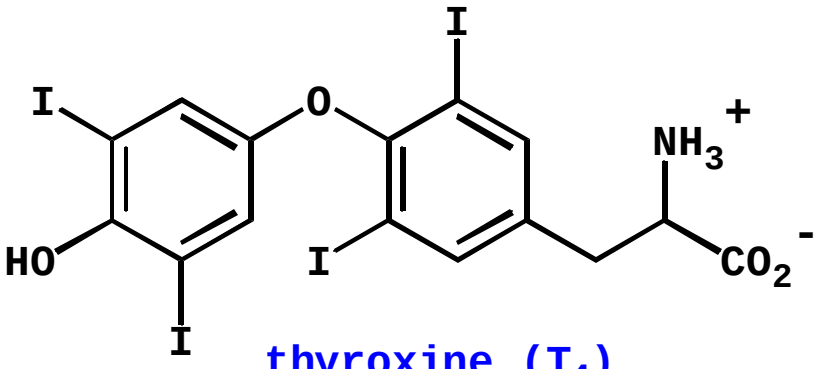
dextromethorphan (cough supressant)



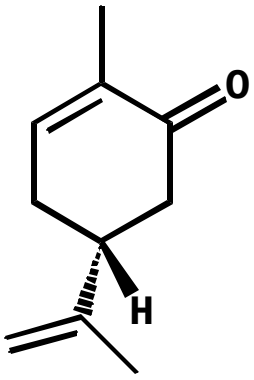
nicotine



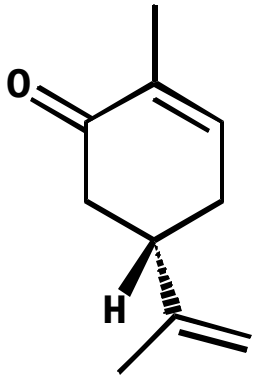
adrenaline



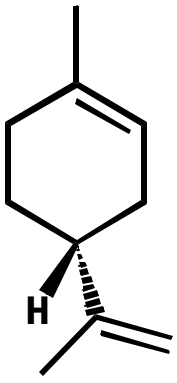
thyroxine (T_4)



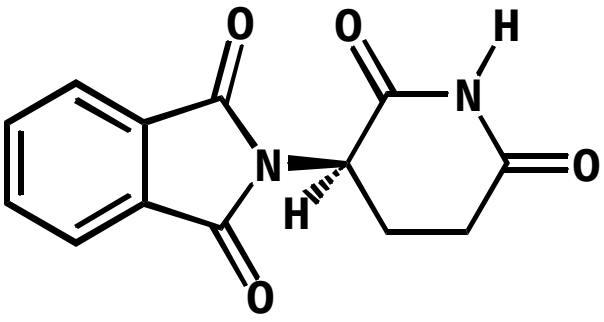
(-)-carvone
(spearmint)



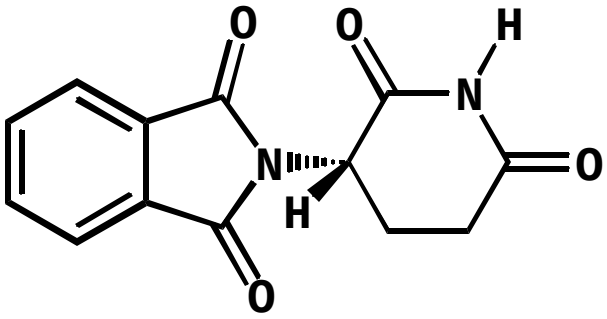
(+)-carvone
(caraway)



limonene
(lemon oil)



(R)-thalidomide (antidepressant)



(S)-thalidomide (mutagenic and antiabortive)

The thalidomide story and tragedy…..

Late 50’s, it was prescribed as an analgesic for morning sickness and used extensively in Europe and Canada despite strong warning that it not be used by pregnant women. FDA had not approved its use in U. S. at the time.

By 1961, it was recognized as the cause for numerous birth defects (~7-10,000 in 28 countries).

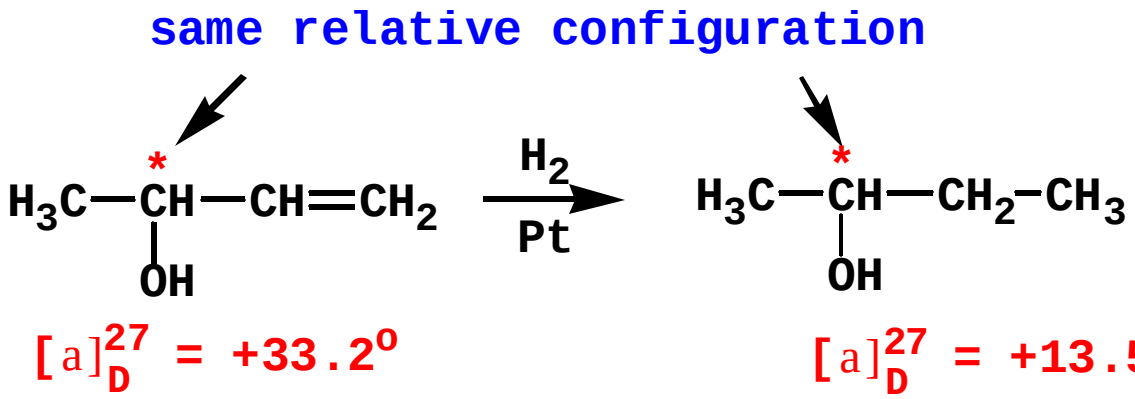
Presently is being evaluated for the treatment of

AIDS CANCER LEPROSY ARTHRITIS

Question: You have a solution of a molecule that is suspected to be chiral (should demonstrate optical activity) and find that the experimental rotation (a) is exactly 0°. What else could be done to demonstrate that the molecule actually is chiral? It is highly improbable that the specific rotation of a chiral molecule would be exactly 0°.

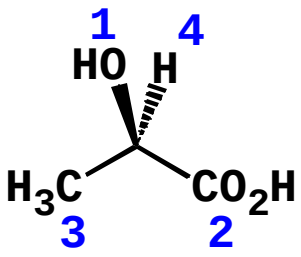
Absolute and relative configurations…

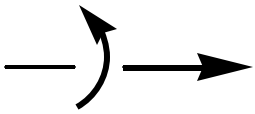
absolute configuration = the precise (true) 3D arrangement of atoms in a molecule

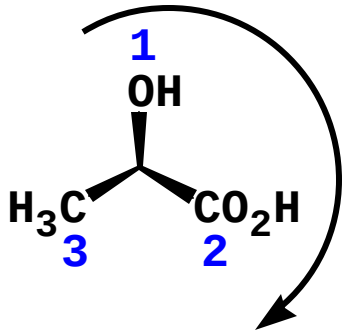


1951, X-ray experiments were developed to allow the determination of the **absolute configuration** of a molecule

Cahn-Ingold-Prelog R/S notation = specifies absolute configuration of a chiral center; there is **no** correspondence between R and + or S and –



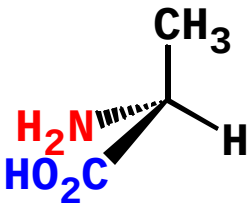




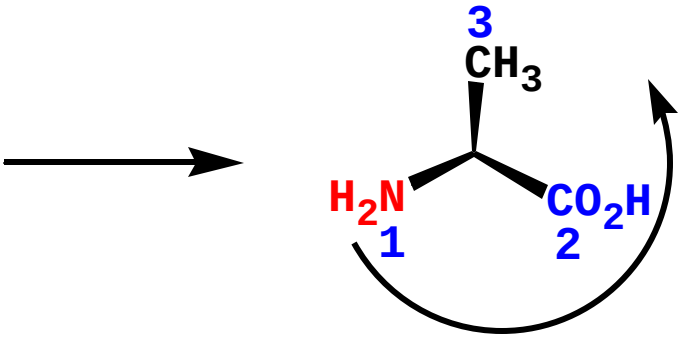
(R)-(-)-lactic acid

m.i. = (S)-(+)-lactic acid

clockwise = R



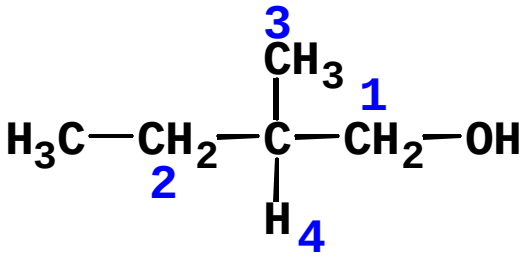
L-alanine

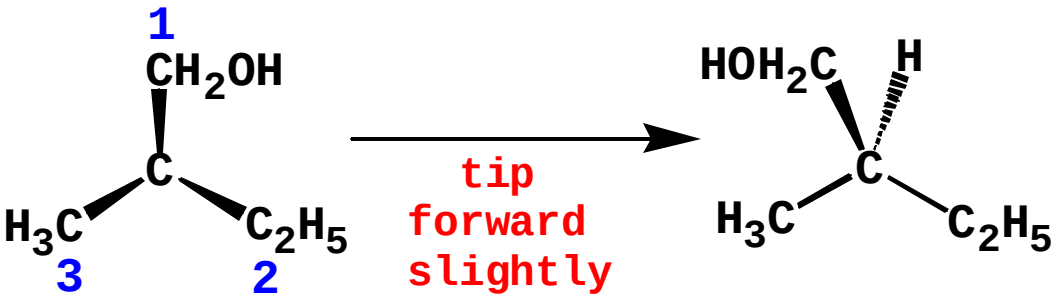


2-aminopropanoic acid

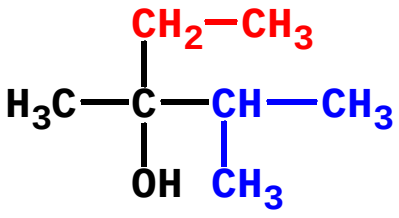
counter-clockwise = S

*Question: Draw a 3D structure for (R)-2-methyl-1-butanol

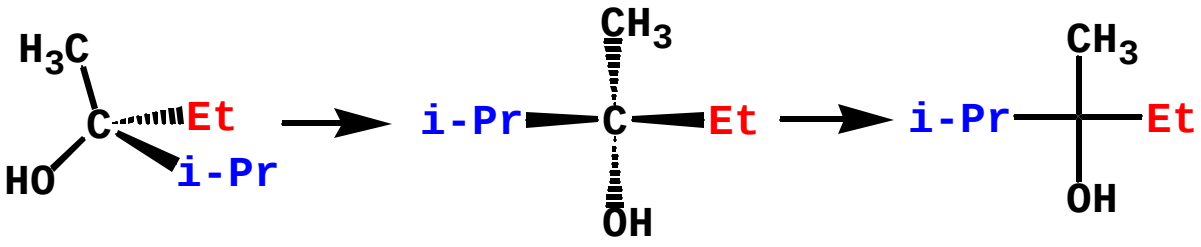




Fischer projections = Short-hand notation for displaying molecules with stereogenic centers. Horizontal bonds are out of paper toward viewer and vertical bonds are into the paper away from the viewer. Rotation of a Fischer projection by 90° has the effect of inverting the configuration (R -> S and *vice versa*). They ONLY can be rotated 180° about an axis perpendicular to the paper without altering the configuration. If the projection is rotated in a way that lifts some groups out of the paper, the absolute configuration will be reversed.

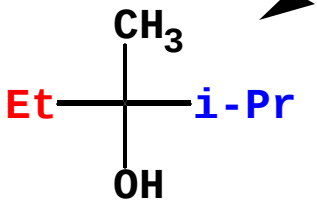


2,3-dimethyl-3-pentanol

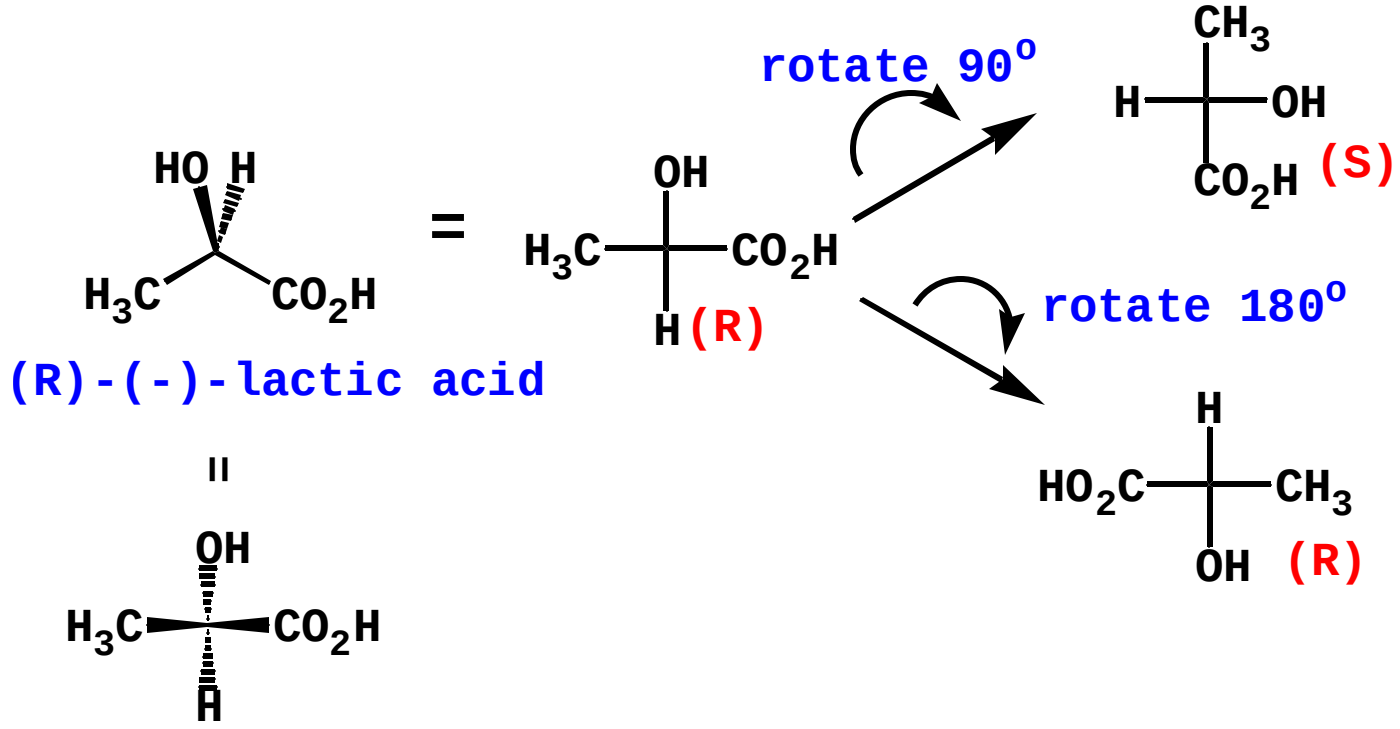


(R)

interchange i-Pr and Et

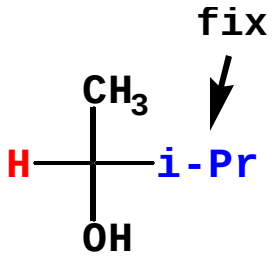


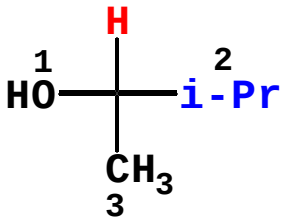
(S)



(R)-(-)-lactic acid

Note: if you interchange two of the groups attached to a chiral center, the molecule is converted into the mirror image. An odd number of interchanges gives the mirror image whereas an even number leaves the absolute configuration unchanged.



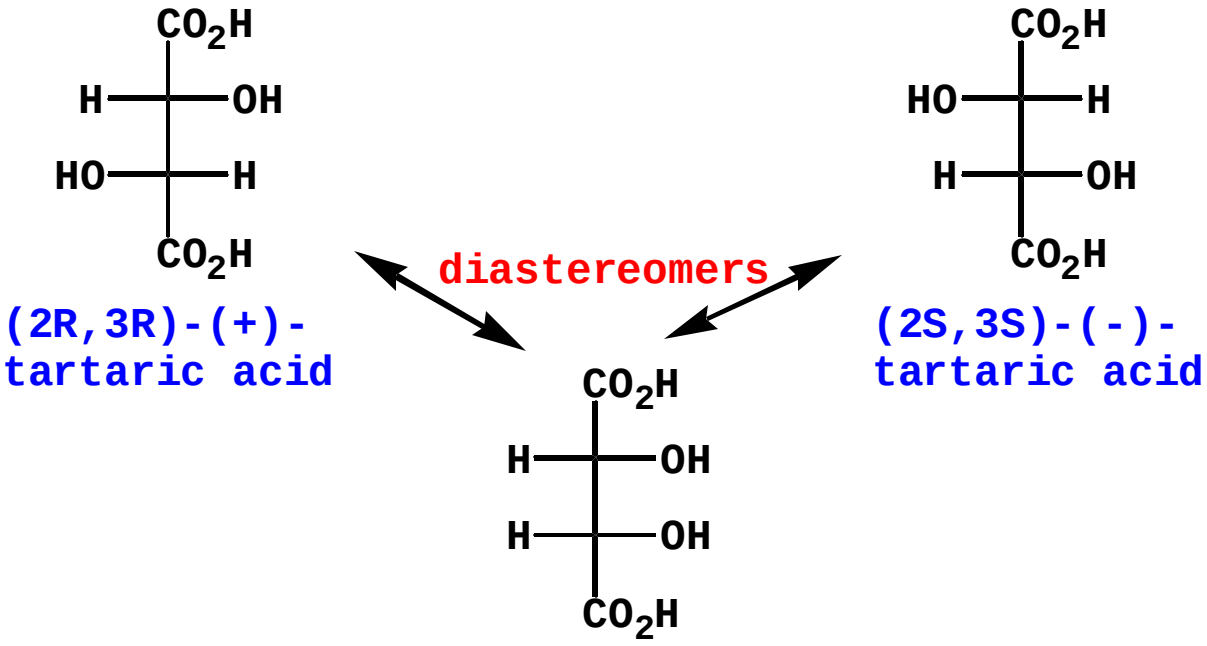


Absolute configuration can be determined from a Fischer projection.

1. **Move the lowest priority atom to the top (or bottom) without altering abs conf.**
2. **Fix one group and rotate other 3.**
3. **Look at the other 3 and determine clockwise or counter-clockwise.**
4. **1->2->3 = clockwise.**
5. **(R)-3-methyl-2-butanol**

diastereomers = stereoisomers that are **not** enantiomers; have **different** chemical and physical properties

***disastereomer example…**



meso isomer = an achiral molecule with 2 or more chiral centers and an internal plane of symmetry; the molecule is achiral

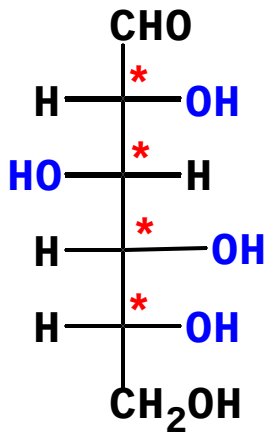
Note that the absolute configurations of the two chiral centers in meso-tartaric acid are opposite, **R and S**, and the molecule has an internal plane of symmetry

Properties of tartaric acids…

Stereo-isomer	Mp (°C)	$[a]_D^{20}$ (°)	r (gm/ml)	H_2O solubility (gm/100 ml)
(+)	168-170	+12	1.760	139
(-)	168-170	-12	1.760	139
meso	146-8	0	1.660	125
(+-)	206	0	1.788	20.6

	pK_a # 1	pK_a # 2
(+) or (-)	2.98	4.34
meso	3.23	4.82

# of stereoisomers = a molecule with n stereogenic centers (and for which a meso isomer isn't possible) will have 2^n stereoisomers



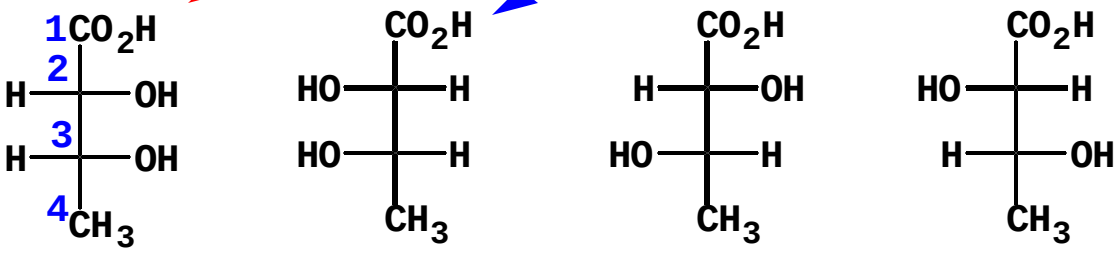
(+)-glucose

# of chiral centers = 4

total # of stereoisomers = $2^4 = 16$

*Chiral molecules with two stereogenic centers…

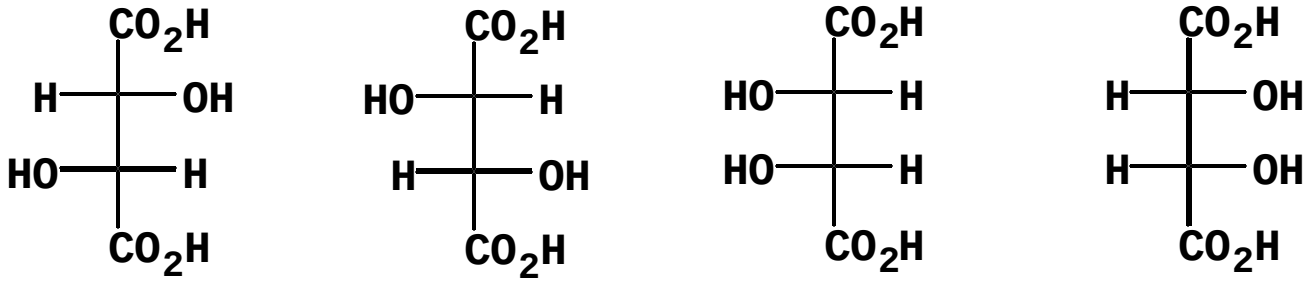
diastereomers



(2R,3R) (liquid) | (2S,3S) | (2R,3S) (solid) | (2S,3R)

various 2,3-dihydroxybutanoic acids

*Achiral molecules with two stereogenic centers…



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

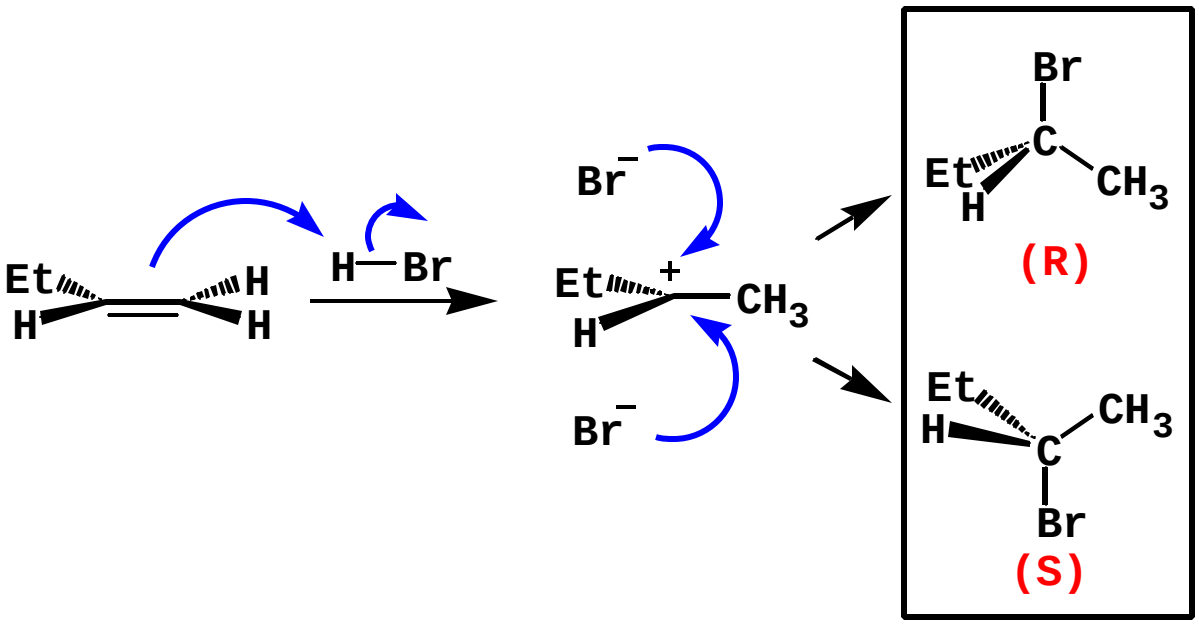
identical

meso isomer

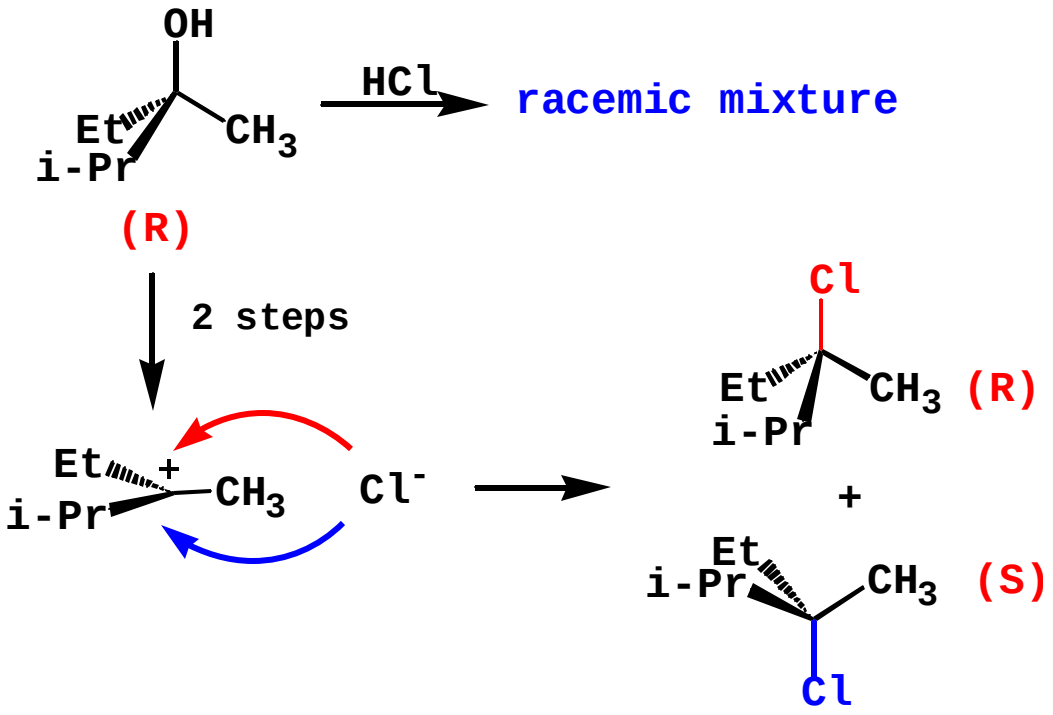
various tartaric acids

racemic mixture = 1:1 mixture of enantiomers; has no optical activity

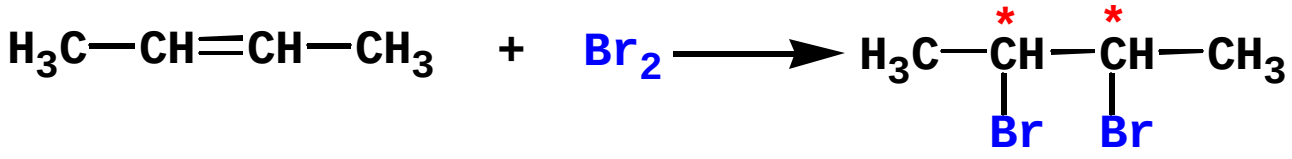
Stereochemistry of two reactions that produce chiral molecules…



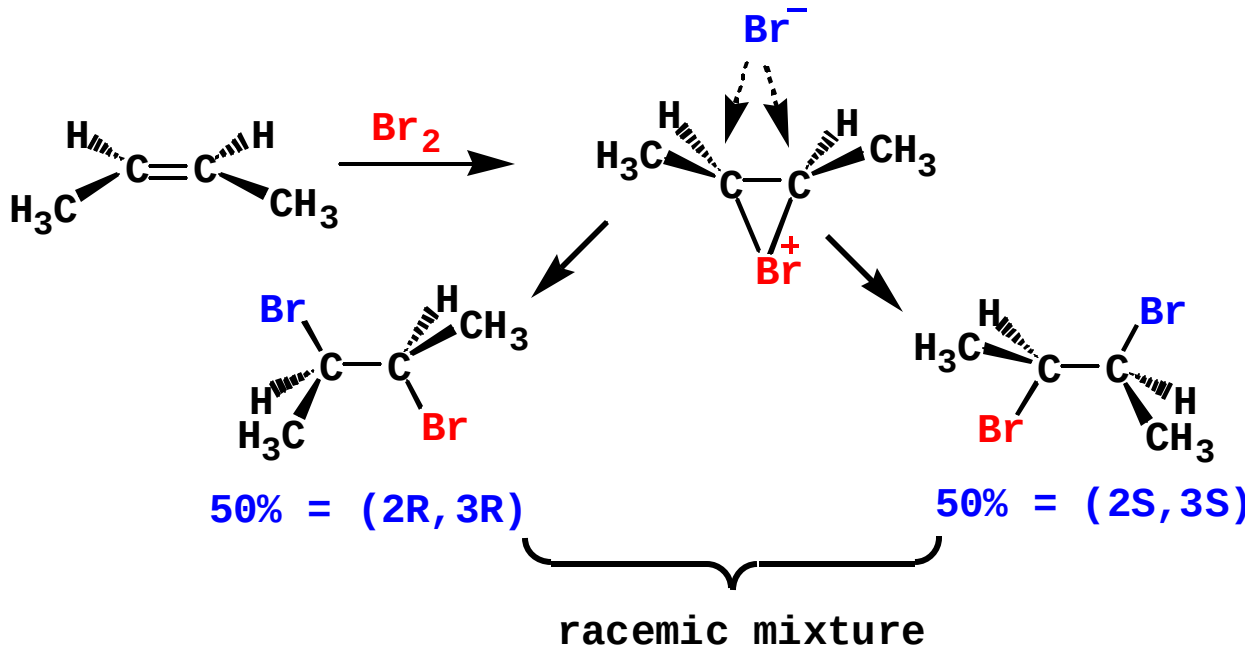
racemic mixture


OH
HCl
racemic mixture
Et
i-Pr
CH3
(R)
2 steps
Et
i-Pr
+
CH3
Cl-
Cl
Et
i-Pr
CH3
(R)
+
Et
i-Pr
CH3
(S)
Cl

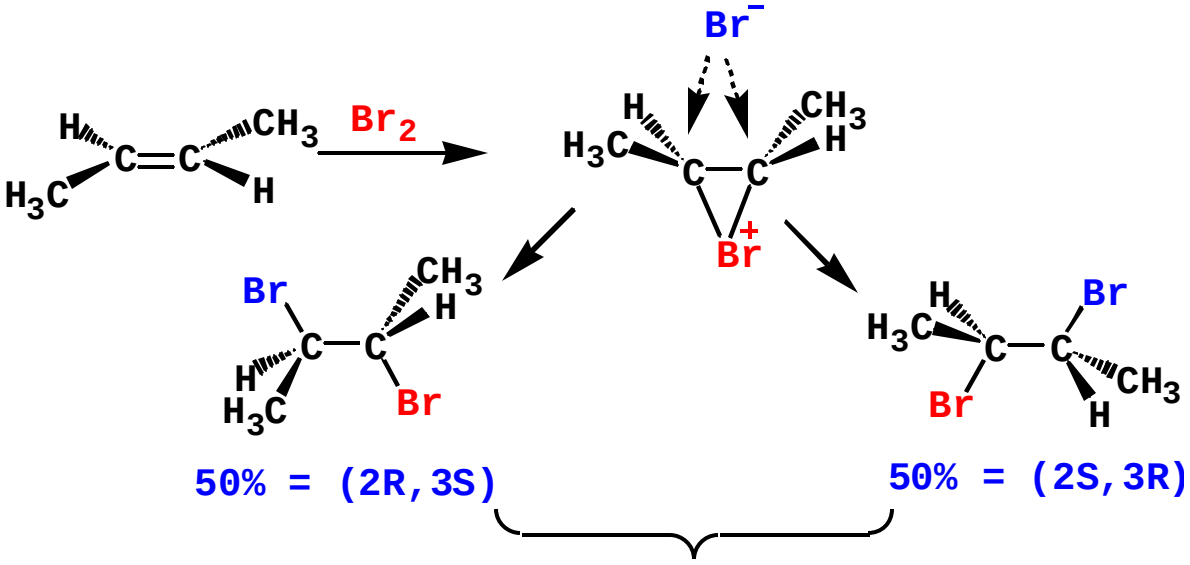
Reactions that produce diastereomers…



1) *cis*-alkene + anti-addition → racemic mixture……



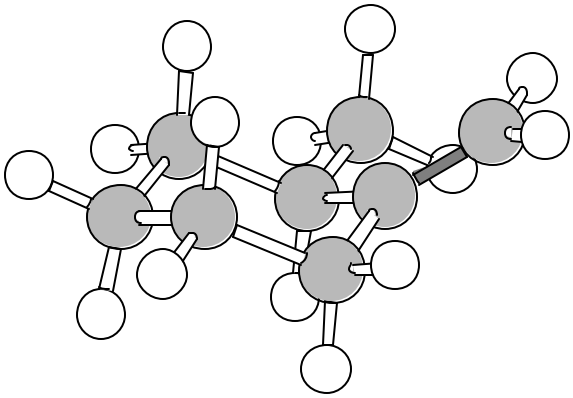
2) *trans*-alkene + anti-addition → meso isomer……

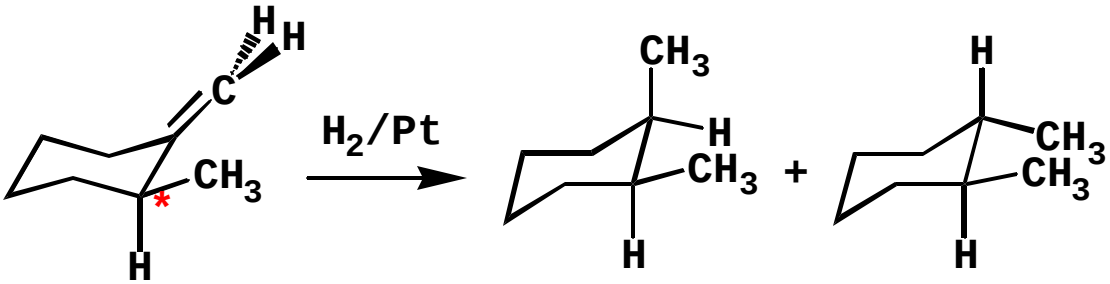


identical = meso isomers

Question: Determine the products from *cis* and *trans*-alkenes and syn-addition (eg $KMnO_4$).

unsymmetrical alkene → (top & bottom of C=C are different)





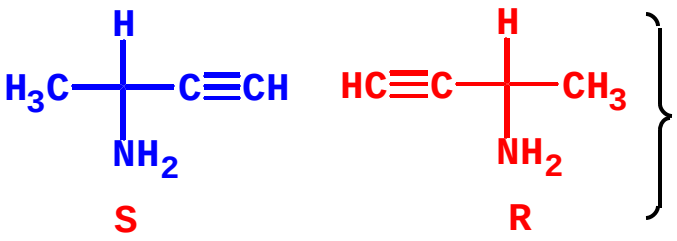
68% cis

32% trans

***Question:** **(+) & (-)-Carvone are enantiomers; one smells like spearmint and the other like caraway. Why do they smell differently?**

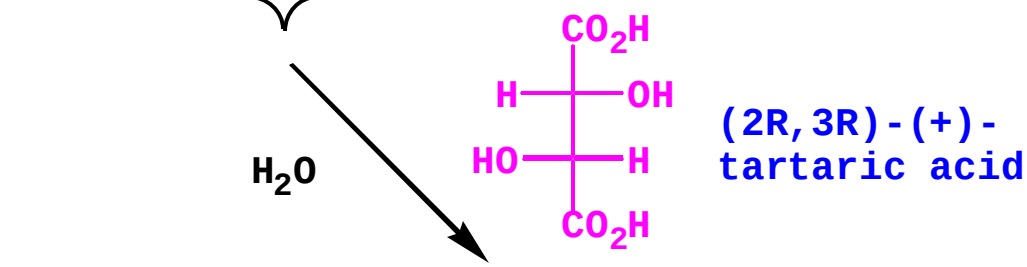
resolution = The process of separating enantiomers. It basically involves converting a racemic mixture (enantiomers) into disastereomers which have different physical properties and can be separated. For example, use a chiral amine (a base) to react with a racemic mixture of acids to form a mixture of diastereomeric salts (amine-H+ with anion of acid). The salts have, among other things, different solubilities, and can be separated by fractional crystallization. One could also use a chiral chromatography column for the direct separation of the racemic mixture.

Example: Amines can be resolved by enantiomerically pure carboxylic acids.

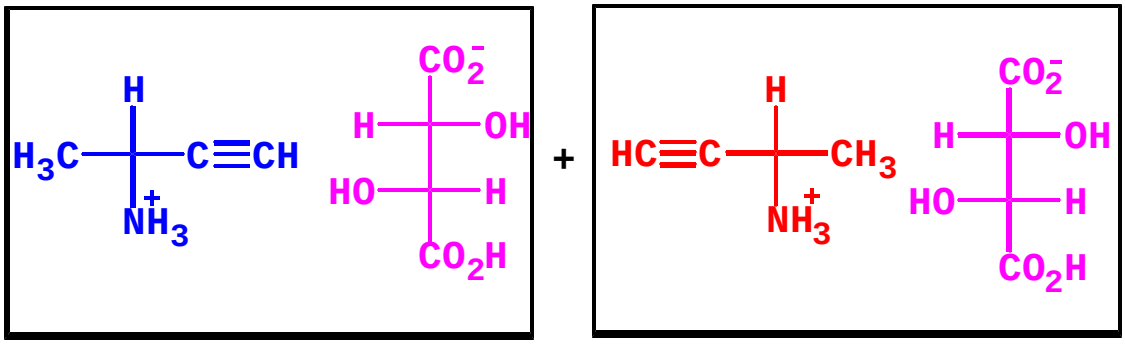


a racemic amine

[a] = 0°



(2R,3R)-(+)-
tartaric acid



tartrate salt of the
S-amine [S,R,R]
[a] = -24.4°

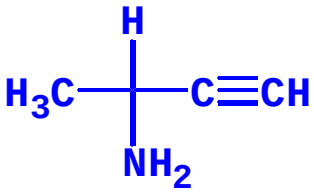
tartrate salt of the
R-amine [R,R,R]
[a] = +24.1°

careful fractional crystallization

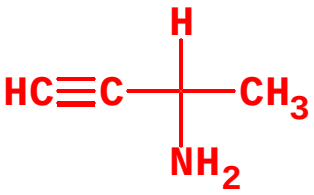
S,R,R-diastereomer
crystallizes = solid

R,R,R-diastereomer
remains in solution

K_2CO_3, H_2O

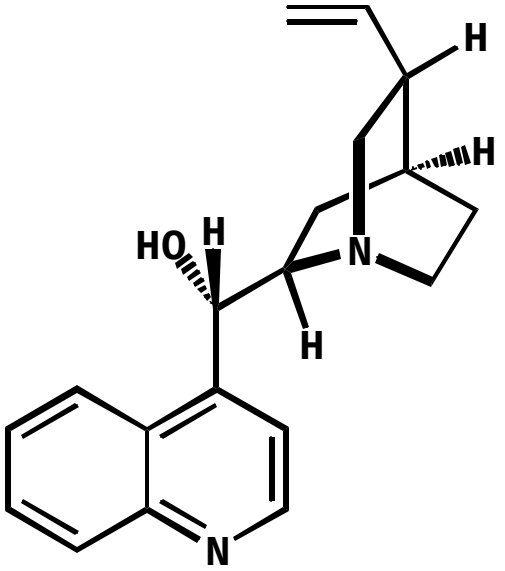


(S) [a] **= -52.7°,**
bp 82-4°

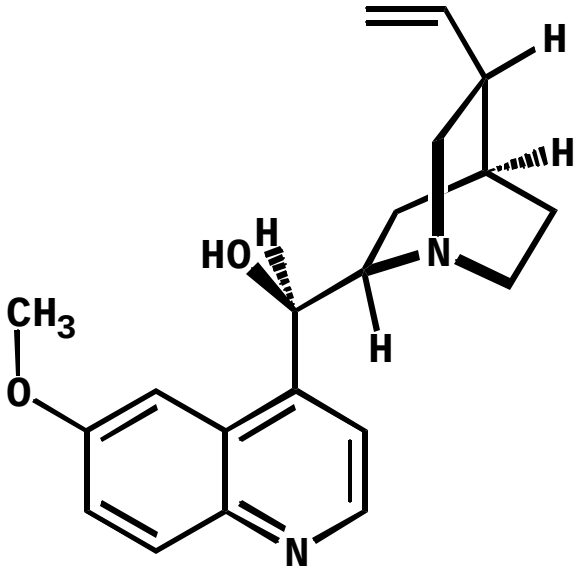


(R) [a] **= +53.2°,**
bp 82-4°

Similarly, acids can be resolved with enantiomerically pure bases…



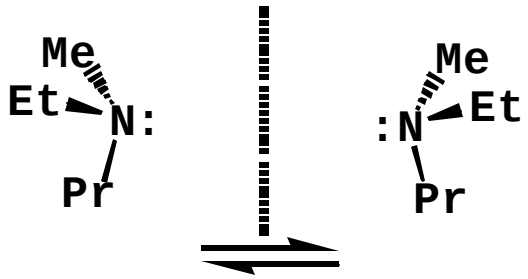
(+)-cinchonine
[a] = +228°



(-)-quinine
[a] = -165°

The above are chiral alkaloids from the bark of the cinchona, a genus of evergreen tree & bush found in some tropical regions. The genus was named after the Countess of Chinchon (wife of viceroy of Peru) who was cured of fever by an extract from the bark of a Peruvian tree. Quinine is more potent than cinchonine.

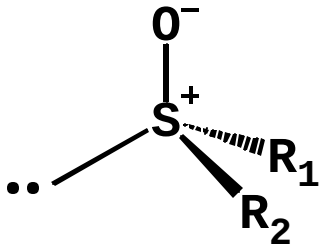
Other stereogenic centers…



this umbrella inversion also takes place in phosphines

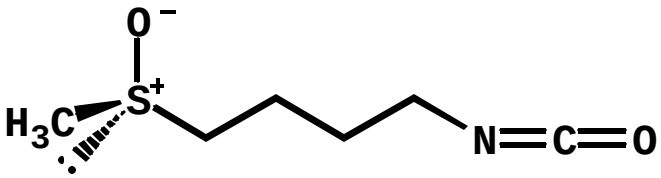
rapid equilibration

with sulfur the rate of inversion is slow.... enantiomers can be isolated



Broccoli contains sulforaphane…

It increases the activity of certain enzymes capable of degrading toxic/carcinogenic compounds.



Only (R)-stereoisomer is active and found in plants.

Problems: