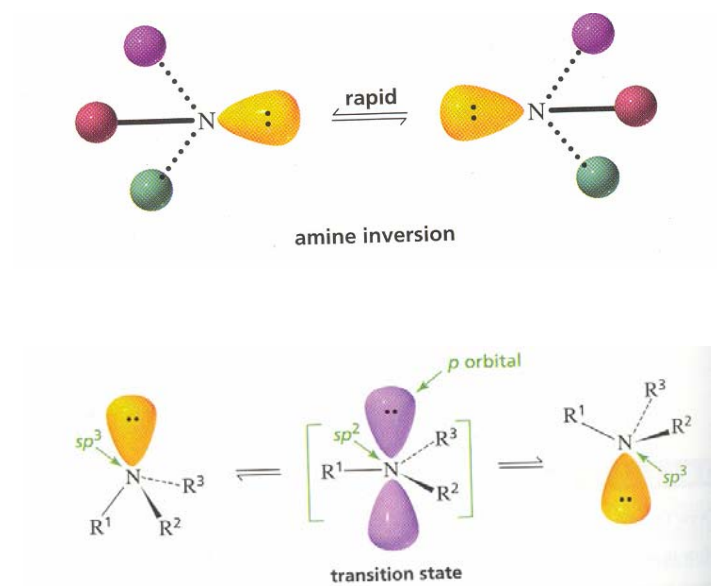


Nitrogen chirality center



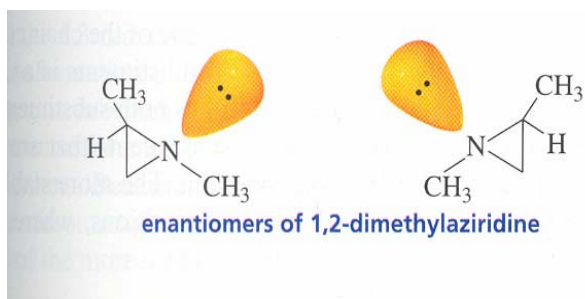
The inversion barrier is only 6 kcal/mol for R= alkyl

Ammonia: inverts 2×10^{11} times for second

Inversion is very fast and difficult to separate

Inversion becomes slow when

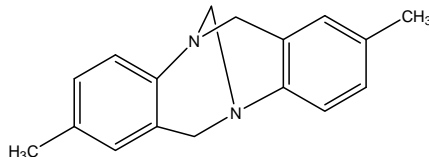
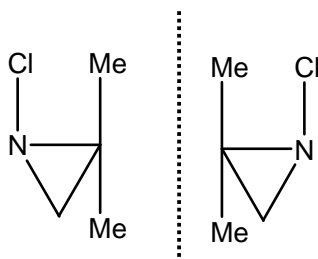
•N is in three-membered ring



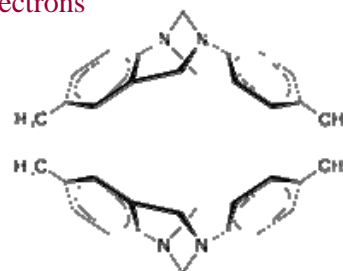
❖ N cannot achieve a 120° bond angle in a 3-membered ring

❖ The two enantiomers can be separated

•N-atom is connected to atom which has unshared lone pair of electrons

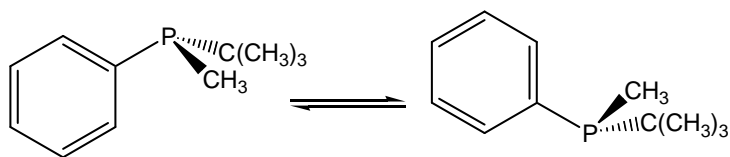


Tröger's base

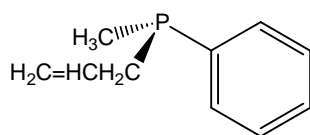


Nitrogen at bridgehead position,
Pyramidal inversion prevented, chiral

Phosphorus chirality center



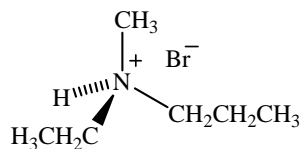
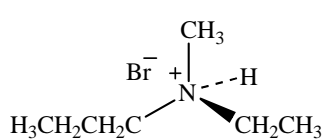
inversion barrier 32.7 kcal/mol



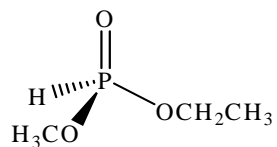
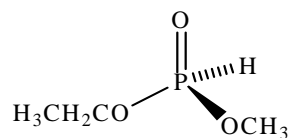
$[\alpha]_D = 16.8^\circ$

S-enantiomer

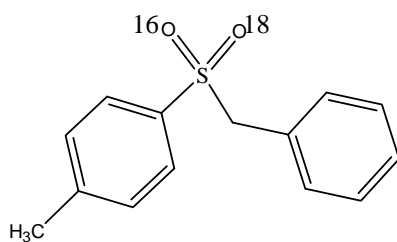
Nitrogen, Phosphorus, Sulfur attached to four different groups



a pair of enantiomers



a pair of enantiomers

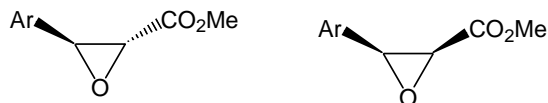


a pair of enantiomers

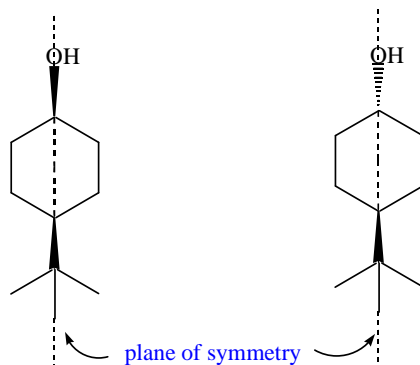
Diastereomers

- Diastereomers are stereoisomers that are not mirror images.
- Two diastereomers are different compounds and have different relative stereochemistry.

Diastereomers may be **chiral** (have no plane of symmetry):

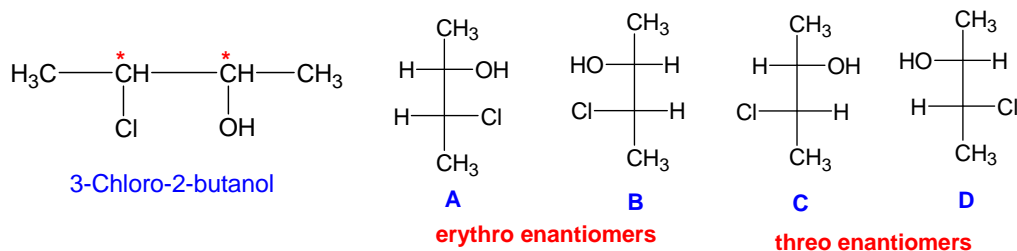


Diastereomers may be **achiral**



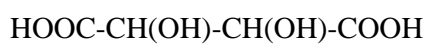
Relative Configurations in Compounds with Multiple Chiral Centers.

- The use of CIP nomenclature requires assignment of *R,S* descriptors for every center. The quicker way (older and a more ambiguous one) is by using **threo/erythro** nomenclature.
- Threo/erythro** It requires vertical projection of main chain.
- threo**-compounds are defined as those that have two groups of higher precedence on each carbon atom on the opposite sides of the chain.
- erythro** on the same side.

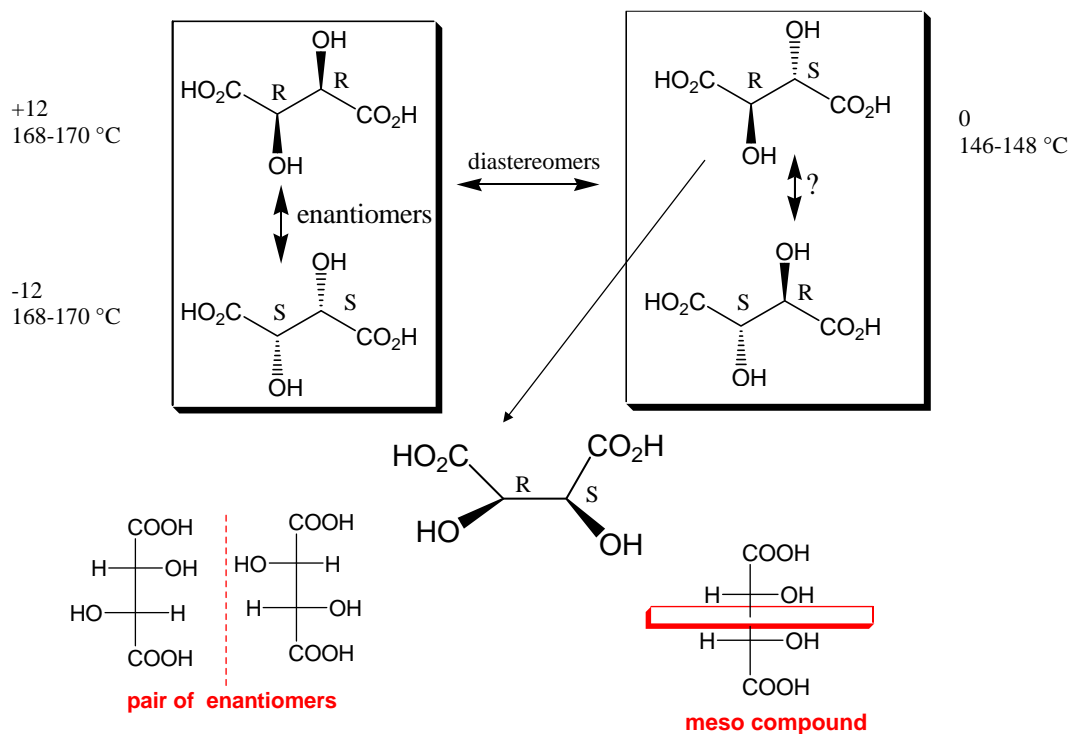


diastereomers {
A & C
A & D
B & C
B & D

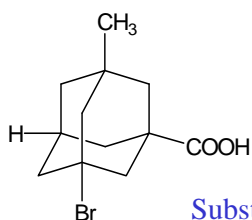
Tartaric acid



$2^2 = 4$ stereoisomers ?

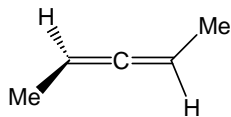
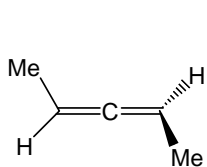


Compounds with **no** stereogenic centres

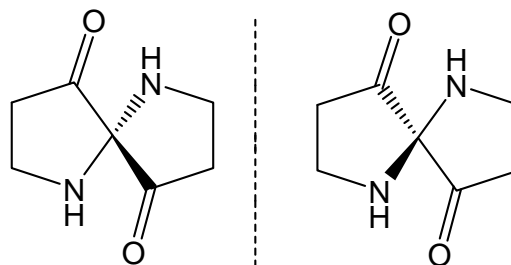
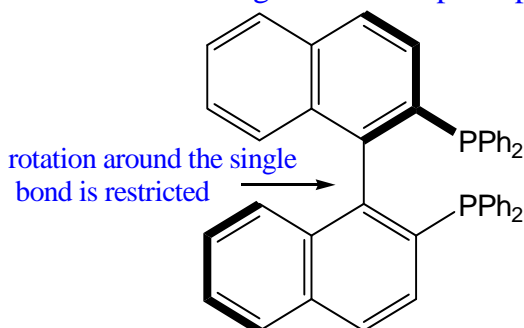
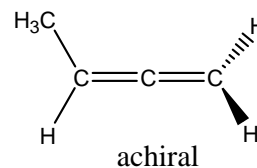


Substituted adamantane

The presence of chiral atom is neither a necessary nor a sufficient condition to be optically active

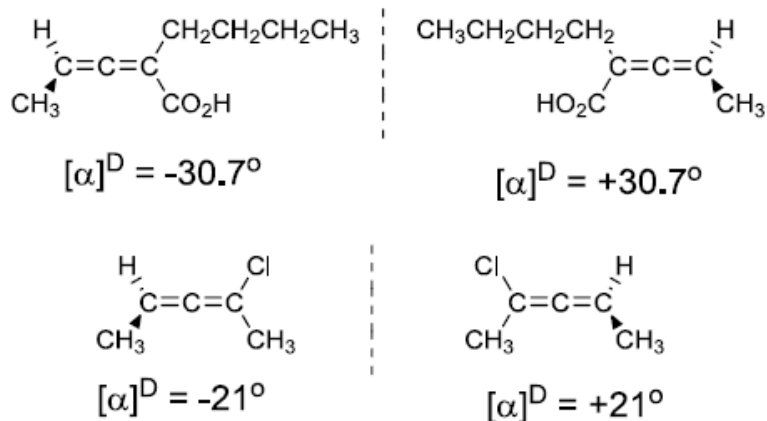


These mirror images are not superimposable - enantiomers



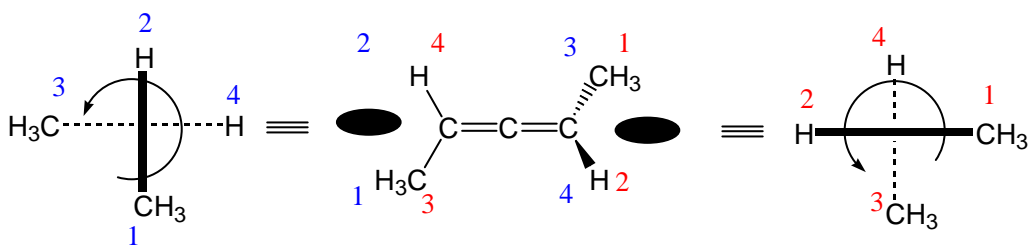
nonsuperimposable enantiomers

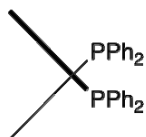
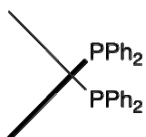
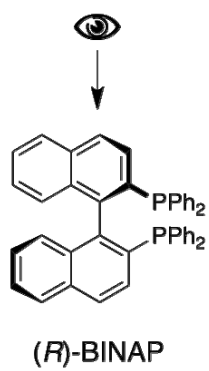
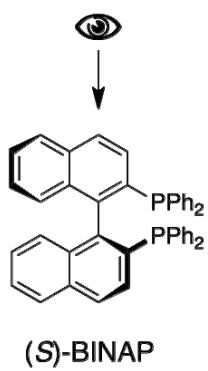
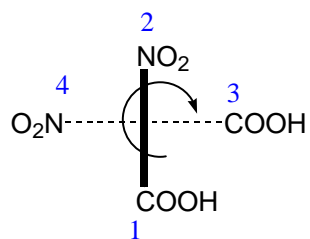
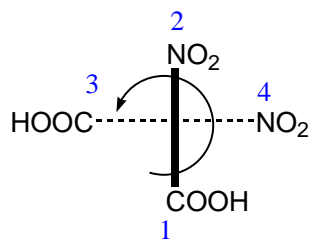
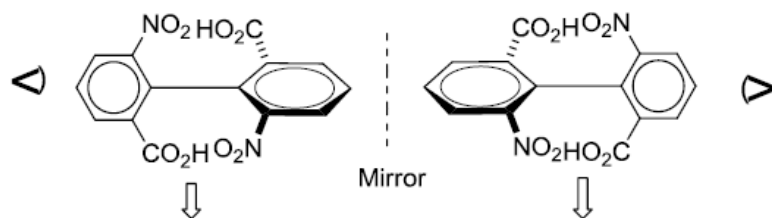
AXIAL CHIRALITY: HOW to ASSIGN configurations (R or S)?



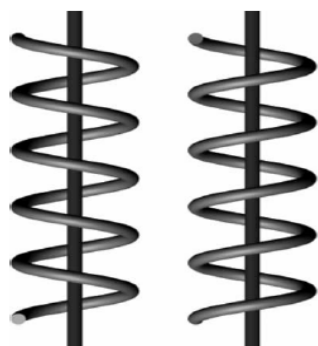
R_a or P (plus) and S_a or M (minus), subscript “a” refers to axial

- The CIP priority rules are used to assign priority to the end groups
- The near groups have a higher precedence over far groups
- The chiral axis is viewed end-on and the sense of configuration determined.

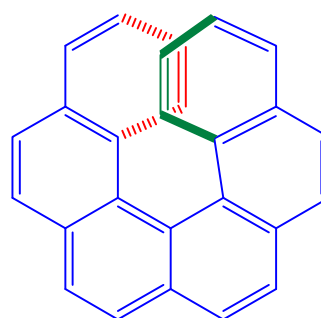
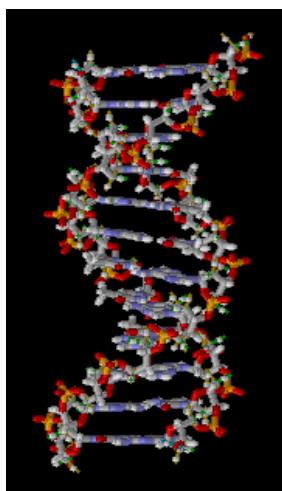




Helical and propellor Molecules



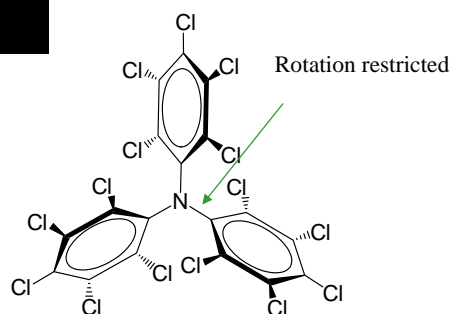
Left handed and Right Handed



Hexahelicene



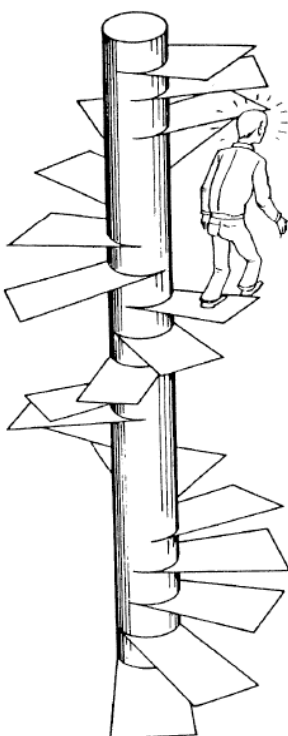
Propellor



perchlorotriphenylamine

Biological importance of chirality

- Chirality is a phenomenon
- Human body is structured
- Helical seashells are common
- Most plants show chirality in their supporting structures
- Most of the molecules in nature are chiral and usually occur in a given specific form
- All but one of the 20 amino acids are chiral
- Almost all natural sugars are chiral
- DNA itself has a helical structure
- Chiral molecules exhibit many ways, including the way they affect human beings



the universe

y wind around

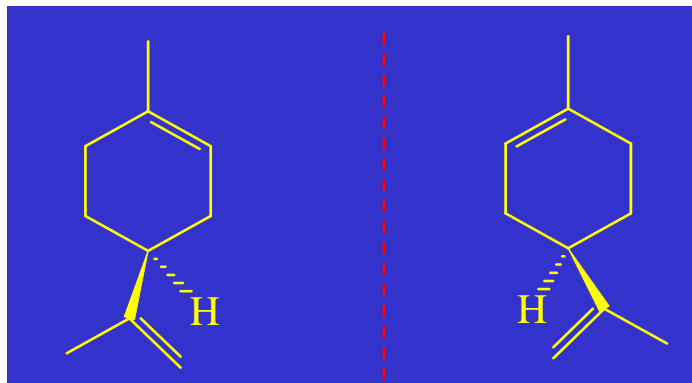
s and animals
al molecule

al and L-form

naturally



Why the smells of Orange and lemons are different?



(S)-(-) Limonene

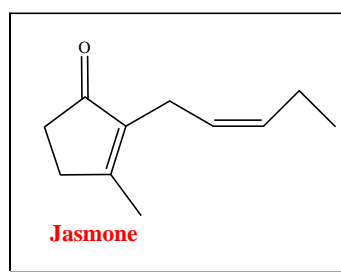
$[\alpha] = -123.0$
from lemons

(R)(+) Limonene

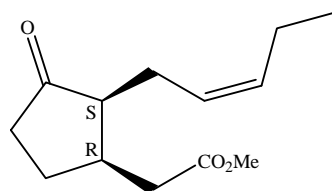
$[\alpha] = +123.0$
from oranges

Enantiomeric smell !!!

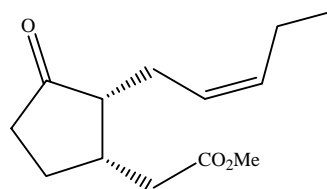
Perfumery compounds from jasmine



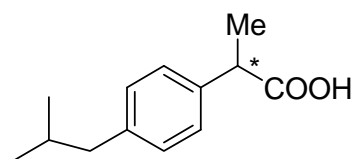
Cis-jasmone is the main compound in jasmone perfume



strong odour
(+)-Z-methyl epijasmonate

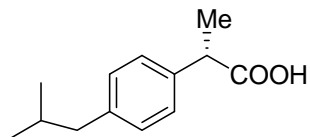


odourless
(-)-Z-methyl epijasmonate

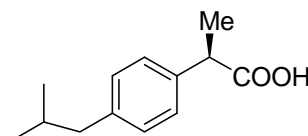


Ibuprofen

500 mg of one tablet contains only half of its as active drug

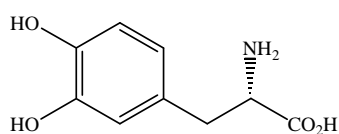


S is active

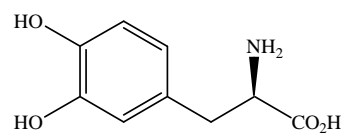


R is inactive

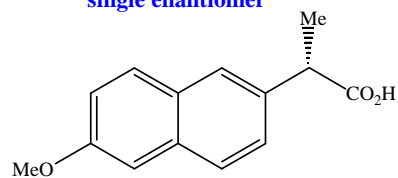
Drug for the treatment of Parkinson's disease
Only L-dopa can restore the nerve function.



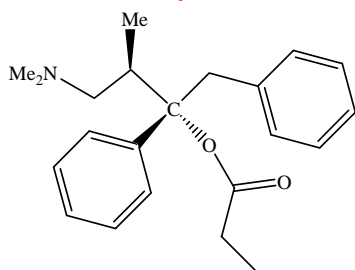
L-dopa
marketed as a
single enantiomer



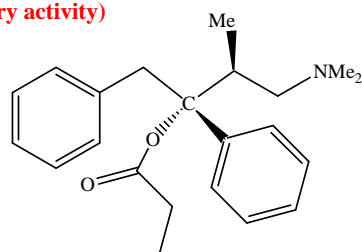
D-dopa
toxic



(S)-Naproxen
(only this has anti-inflammatory activity)



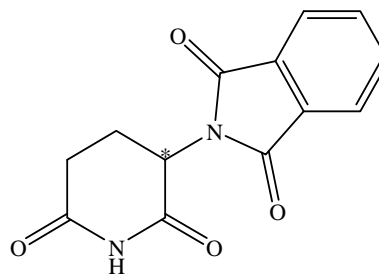
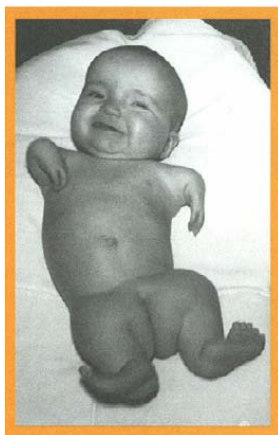
Darvon
(Pain killer)



Novrad
(anticough agent)

Thalidomide tragedy

- Missing or malformed limbs (bilateral)
- No ears or deafness
- Missing or extra fingers or toes
- Partial or total loss of sight
- Improper formation of the heart, kidney and other internal organs
- Improper formation of the anus and/or genitalia
- Cleft palate
- Flattening of the bridge of the nose

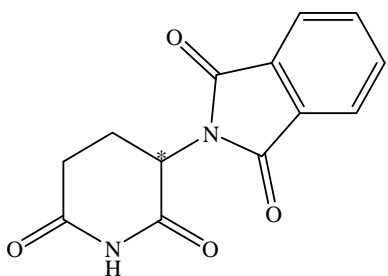


Thalidomide

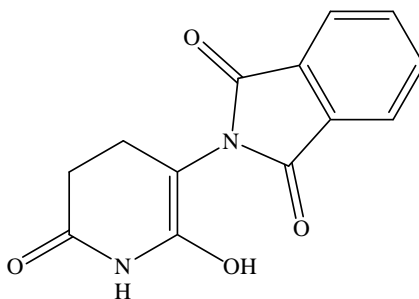
• **Drug sold in racemic mixture (approved in Canada & Europe but not in US)**

proclaimed as a "wonder drug" for insomnia, coughs, colds, headaches, pain killer and morning sickness for pregnant woman

- **dextrorotatory isomer → sedative**
- **levorotatory isomer → cause of birth defects**
- **even dextro isomers can cause mild defects because of in vivo racemization**



Thalidomide



(R)(+) Thalidomide

(S)(-) Thalidomide

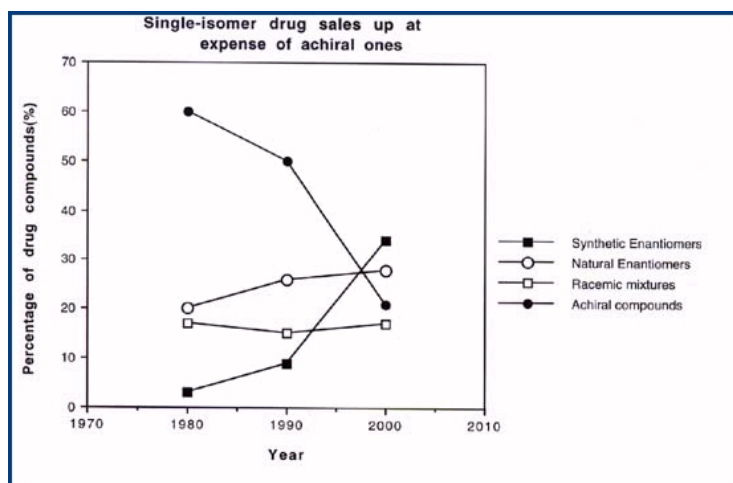


a sedative and hypnotic



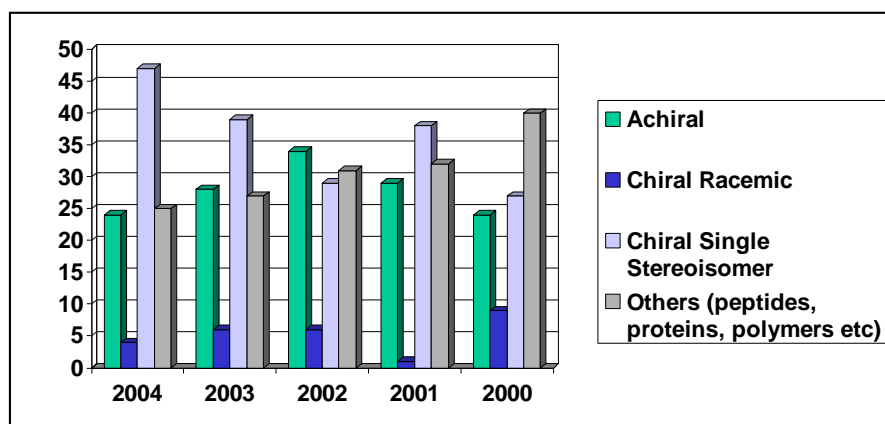
a teratogen

Why is drug chirality an important knowledge for future pharmacists?
The current trend in drug markets is a rapid increase of the sales of chiral drugs at the expense of the achiral ones.



- Chiral drugs, whether enantiomerically pure or as a racemic mixture, are expected to dominate drug markets in the near future.
- It is therefore important to understand how drug chirality affects its interaction with drug targets and the nature of forces responsible for those interactions.
- Proper nomenclature should be used in describing the drugs

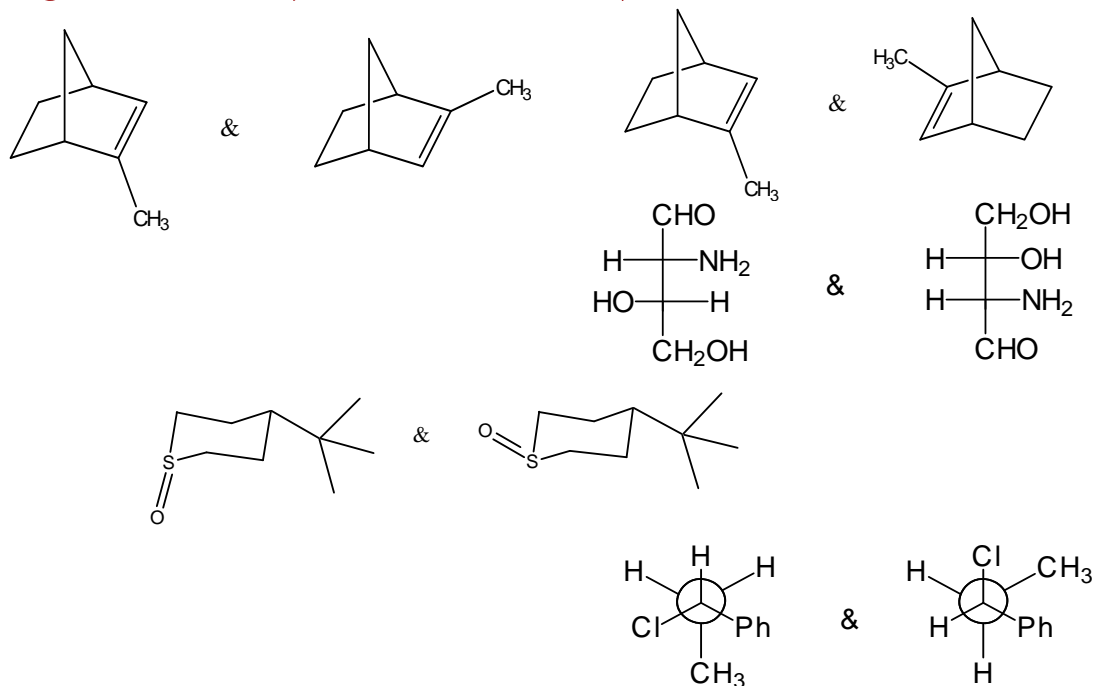
Recent Chiral Trends: USA



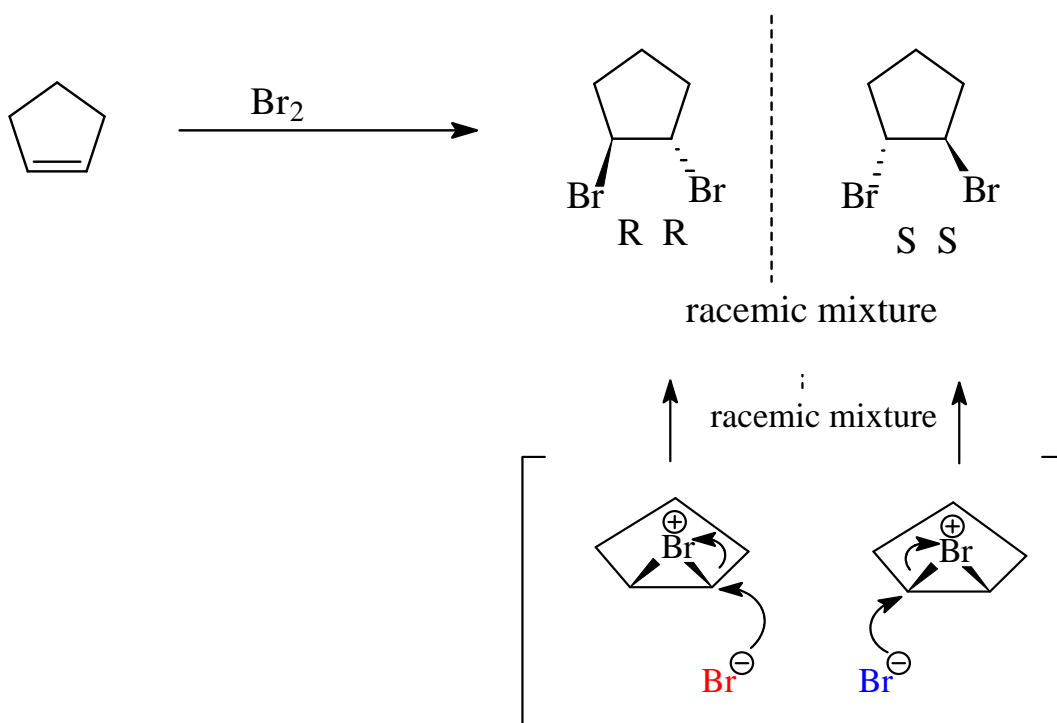
- “In 2006, 80% of small molecule drugs approved by the FDA were chiral and 75% were single enantiomers.”

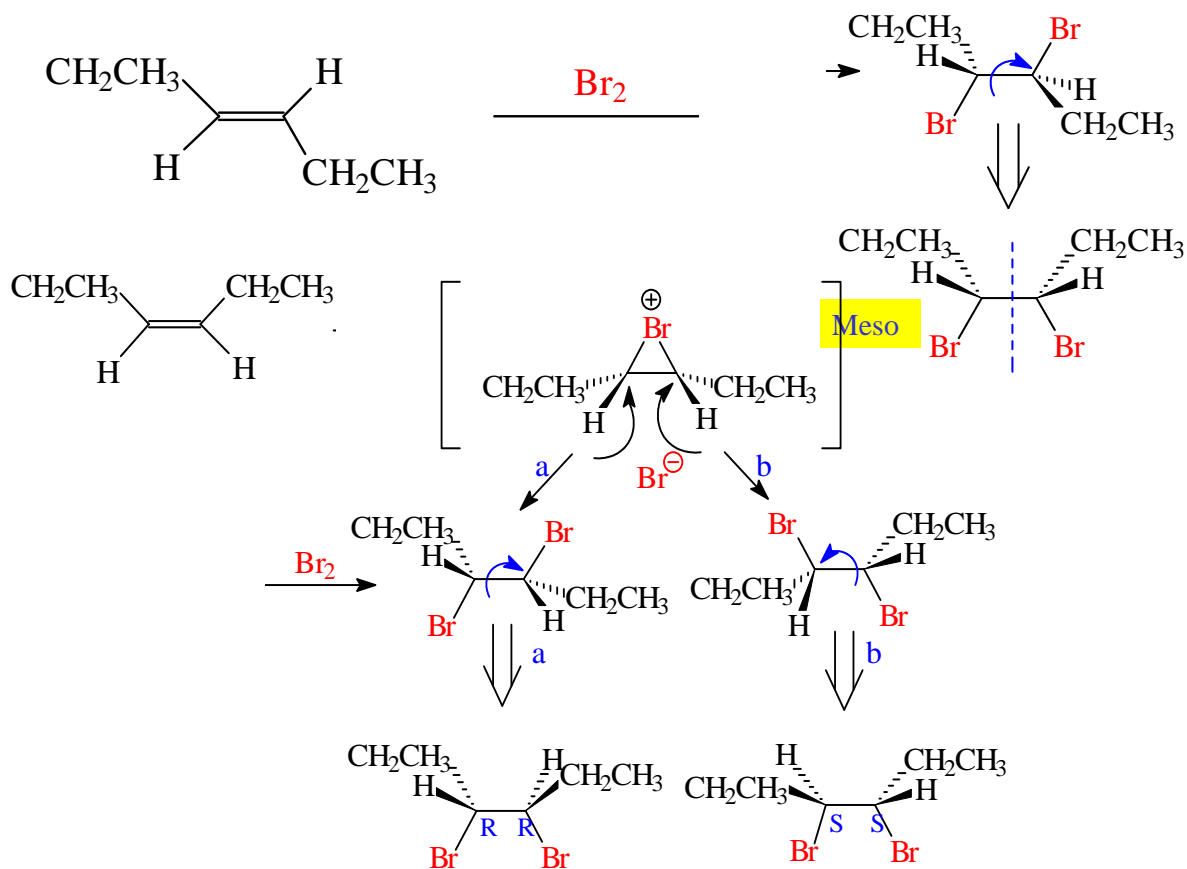
C&EN August 2007

Q. Identical, enantiomeric, or diastereomeric?

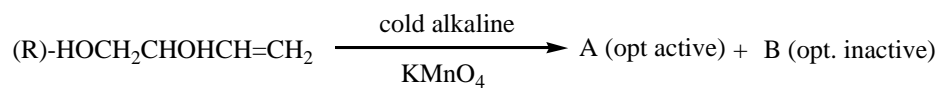


Bromine addition to alkenes

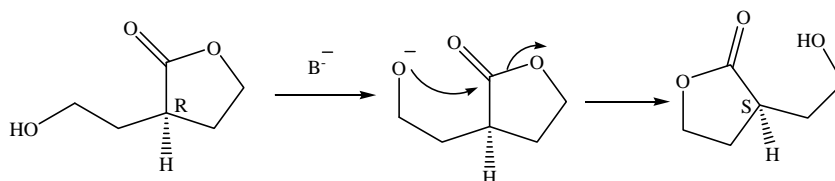




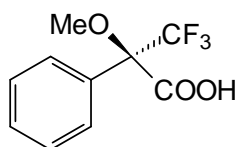
Q. Give structures (with R/S specification) of the products in the following reaction?



Q. The following compound racemises in base, why?



Q. Mosher's Acid



R or S ?

