Stereochemistry

- Some objects are not the same as their mirror images (technically, they have no plane of symmetry)
  - A right-hand glove is different than a left-hand glove
  - The property is commonly called “handedness”
- Organic molecules (including many drugs) have handedness that results from substitution patterns on sp^3 hybridized carbon

Enantiomers – Mirror Images

- Molecules exist as three-dimensional objects
- Some molecules are the same as their mirror image
- Some molecules are different than their mirror image
  - These are stereoisomers called enantiomers

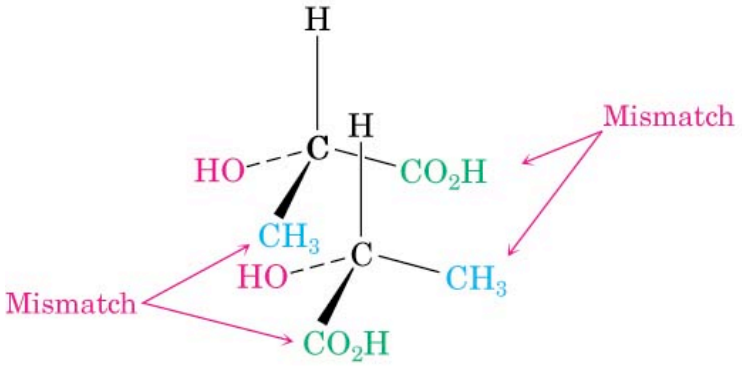
Why is this important?

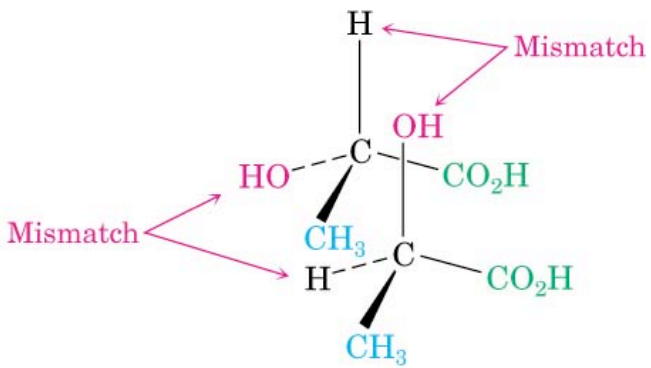
- Our bodies, for example, can only create and digest carbohydrates and amino acids of a certain stereochemistry
- All of our proteins that make up our hair, skin, organs, brain, and tissues, are composed of a single stereoisomer of amino acids
- Our bodies can make and digest starch (found in potatoes and bread)
- Our bodies cannot digest cellulose (found in wood and plant fibers), even though both are just polymers of glucose of different stereochemistry

Shown above: Only one stereoisomer of Ibuprofin has the correct three-dimensional shape to bind to the receptor, so only one isomer actively relieves pain.

Enantiomers and the Tetrahedral Carbon

- **Enantiomers** are molecules that are not the same as their mirror image
- They are the "same" if the positions of the atoms can coincide on a one-to-one basis (we test if they are *superimposable*, which is imaginary)
- This is illustrated by enantiomers of lactic acid



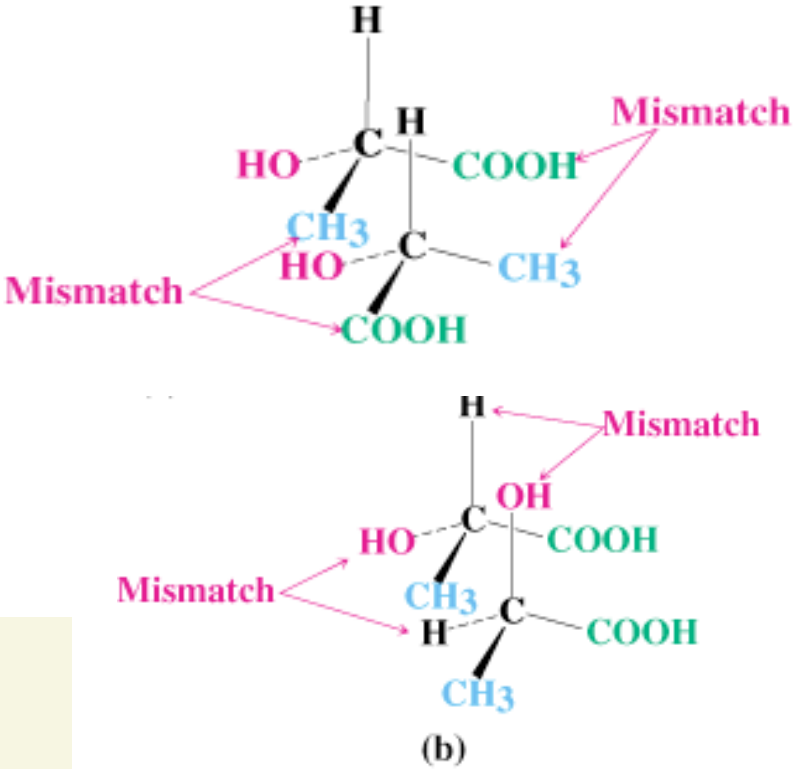


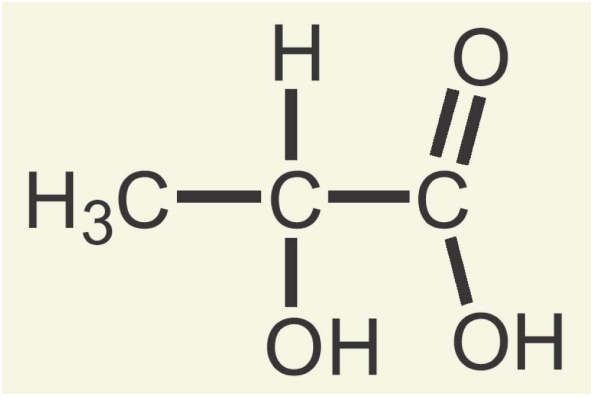
Examples of Enantiomers

- Molecules that have one carbon with 4 different substituents have a nonsuperimposable mirror image – enantiomer
- Build molecular models to see this

Mirror-image Forms of Lactic Acid

- When **H** and **OH** substituents match up, **COOH** and **CH_3** don't
- when **COOH** and **CH_3** coincide, **H** and **OH** don't





The Reason for Handedness: Chirality

- Molecules that are not superimposable with their mirror images are **chiral** (have handedness)
- A **plane of symmetry** divides an entire molecule into two pieces that are exact mirror images
- A molecule with a plane of symmetry is the same as its mirror image and is said to be **achiral**

Chirality

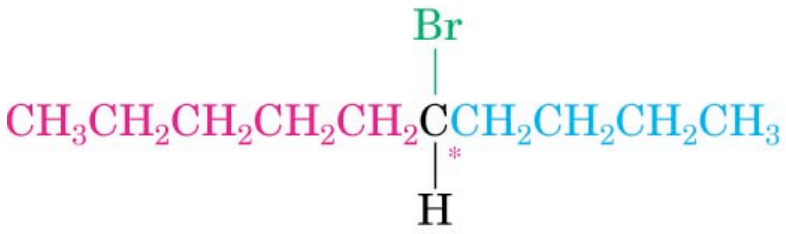
- If an object has a plane of symmetry it is necessarily the same as its mirror image
- The lack of a plane of symmetry is called “handedness”, **chirality**
- Hands, gloves are prime examples of chiral object
  - They have a “left” and a “right” version

Plane of Symmetry

- The plane has the same thing on both sides for the flask
- There is no mirror plane for a hand

Chirality Centers

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

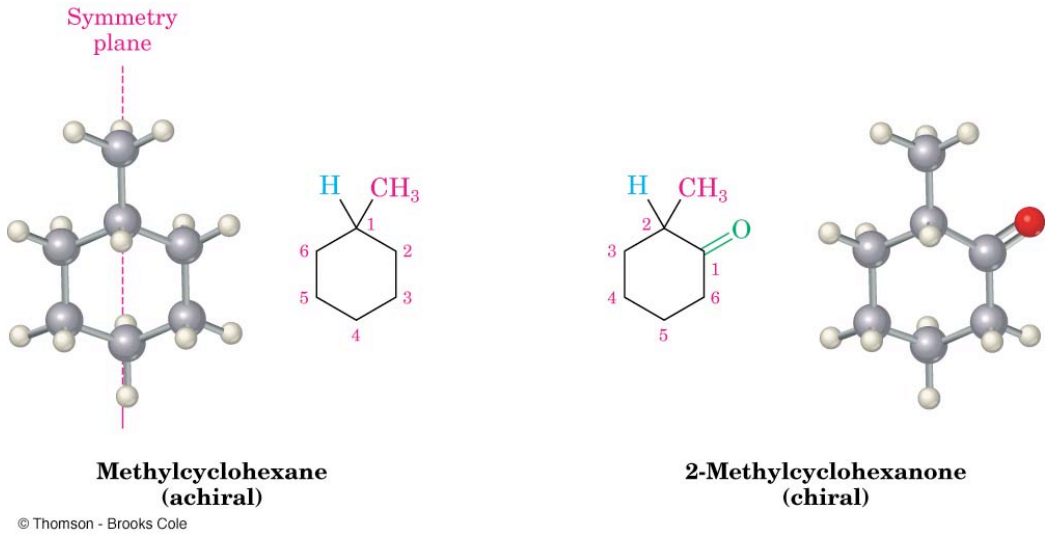


5-Bromodecane (chiral)

Substituents on carbon 5
—H
—Br
—$CH_2CH_2CH_2CH_3$ (butyl)
—$CH_2CH_2CH_2CH_2CH_3$ (pentyl)

Chirality Centers in Chiral Molecules

- Groups are considered “different” if there is anystructural variation (if the groups could not be superimposed if detached, they are different)
- In cyclic molecules, we compare by following in each direction in a ring



Methylcyclohexane (achiral)

2-Methylcyclohexanone (chiral)

Optical Activity

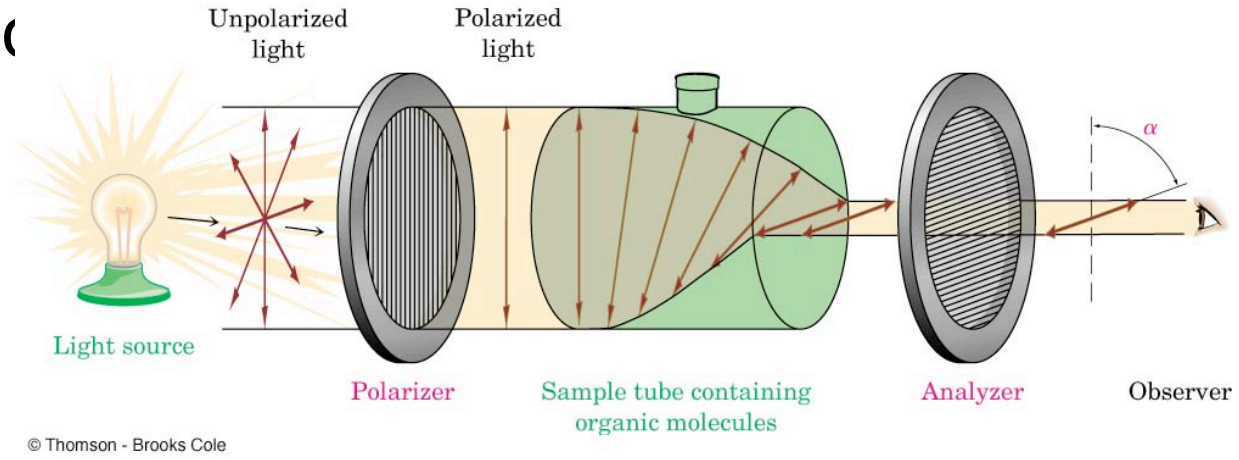
- Light restricted to pass through a plane is *plane-polarized*
- Plane-polarized light that passes through solutions of achiral compounds remains in that plane
- Solutions of chiral compounds rotate plane-polarized light and the molecules are said to be *optically active*
- Phenomenon discovered by Biot in the early 19th century

Optical Activity

- Light passes through a plane polarizer
- Plane polarized light is rotated in solutions of optically active compounds
- Measured with polarimeter
- Rotation, in degrees, is [α]
- Clockwise rotation is called **dextrorotatory**
- Anti-clockwise is **levorotatory**

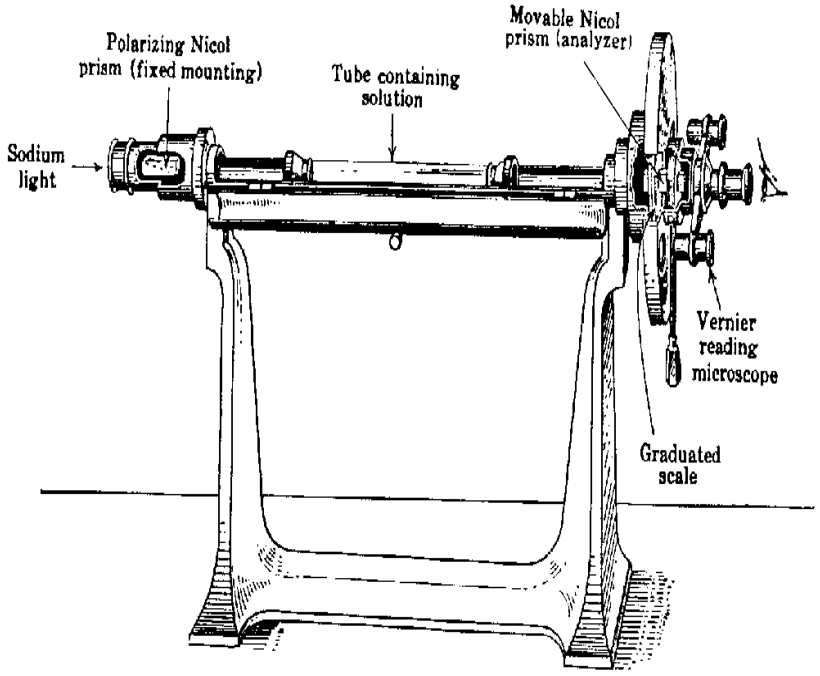
Measurement of Optical Rotation

- A *polarimeter* measures the rotation of plane-polarized that has passed through a solution
- The source passes through a *polarizer* and then is detected at a second polarizer
- The angle between the entrance and exit planes is the (



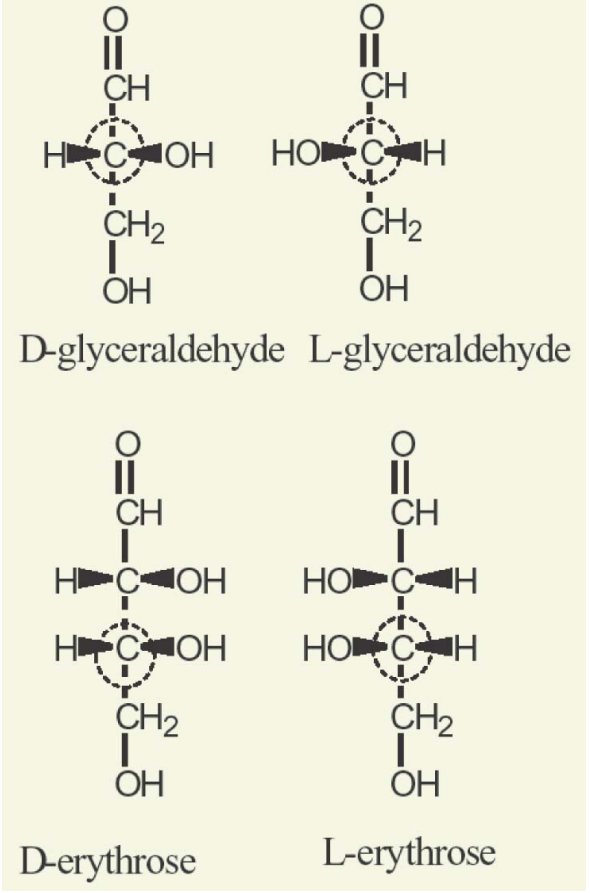
A Simple Polarimeter

- Measures extent of rotation of plane polarized light
- Operator lines up polarizing analyzer and measures angle between incoming and outgoing light



Relative 3-Dimensionl Structure

- The original method was a correlation system, classifying related molecules into “families” focused on carbohydrates
  - Correlate to D- and L-glyceraldehyde
  - D-erythrose is the mirror image of L-erythrose
- This does not apply in general

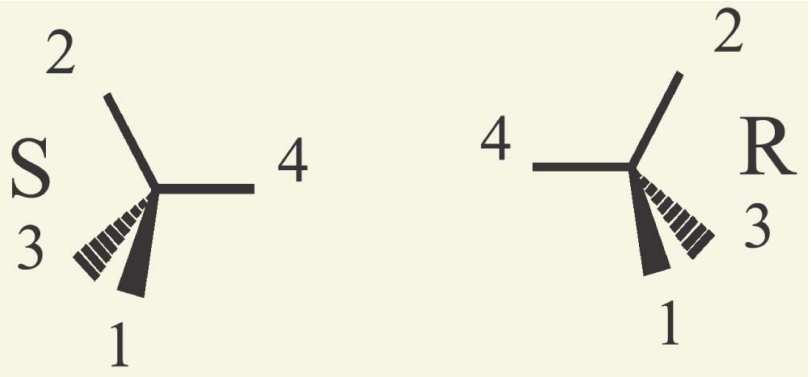


Sequence Rules for Specification of Configuration

- A general method applies to the configuration at each chirality center (instead of to the the whole molecule)
- The configuration is specified by the relative positions of all the groups with respect to each other at the chirality center
- The groups are ranked in an established priority sequence and compared
- The relationship of the groups in priority order in space determines the label applied to the configuration, according to a rule

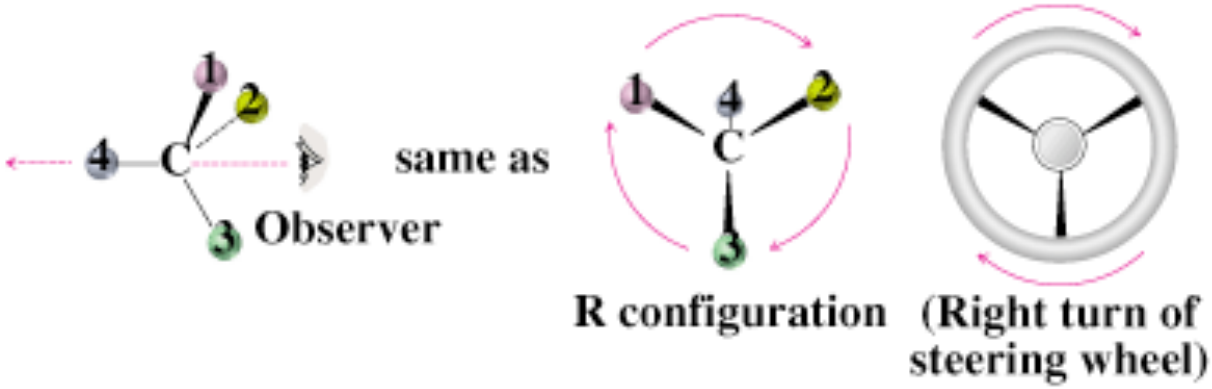
Sequence Rules (IUPAC)

- Assign each group priority according to the Cahn-Ingold-Prelog scheme With the lowest priority group pointing away, look at remaining 3 groups in a plane
- Clockwise is designated R (from Latin for “right”)
- Counterclockwise is designated S (from Latin word for “left”)



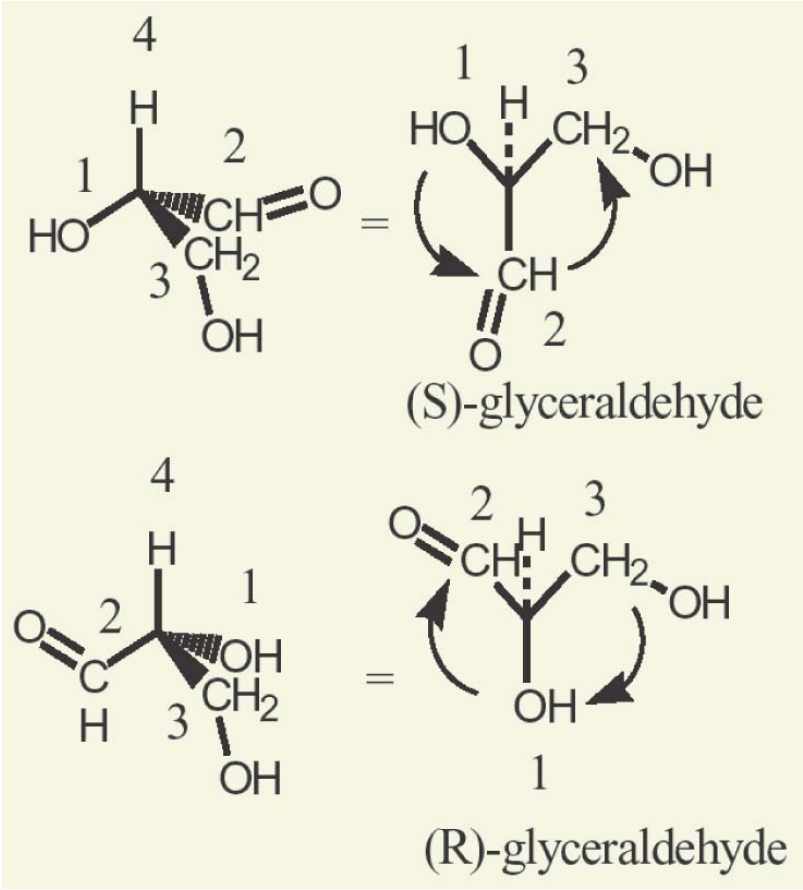
R-Configuration at Chirality Center

- Lowest priority group is pointed away and direction of higher 3 is clockwise, or right turn

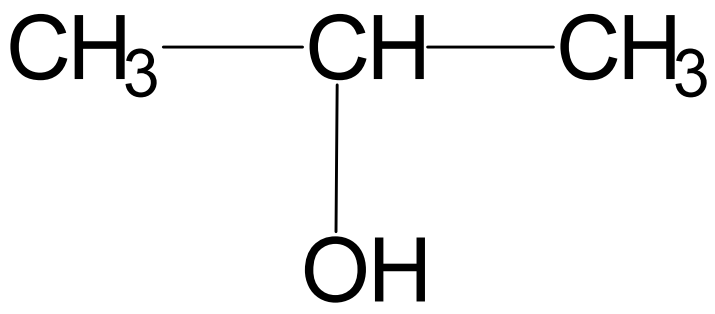


Examples of Applying Sequence Rules

- If lowest priority is back, clockwise is R and counterclockwise is S
  - R = Rectus
  - S = Sinister



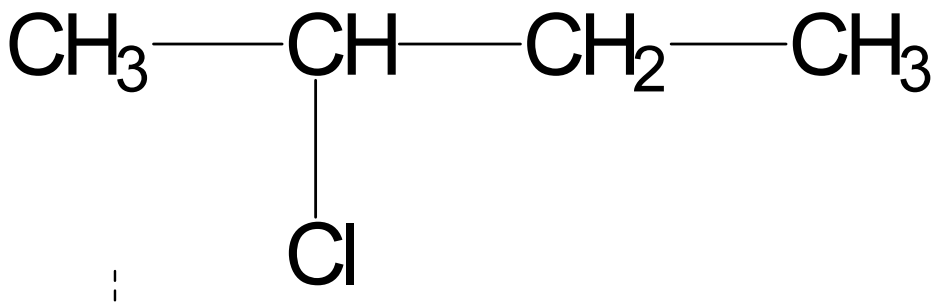
propan-2-ol

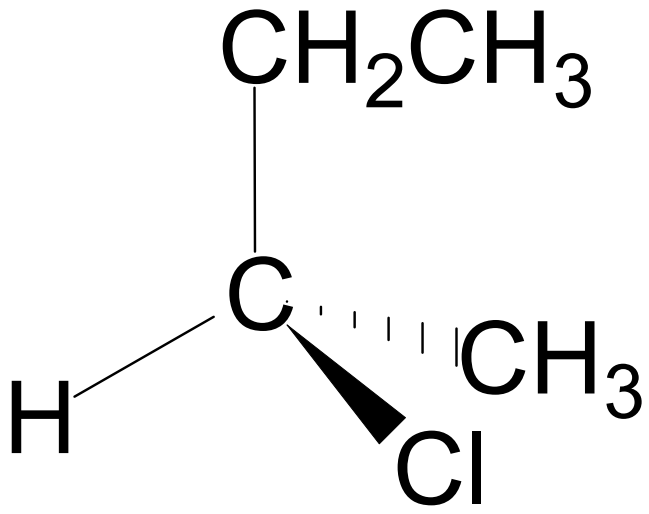


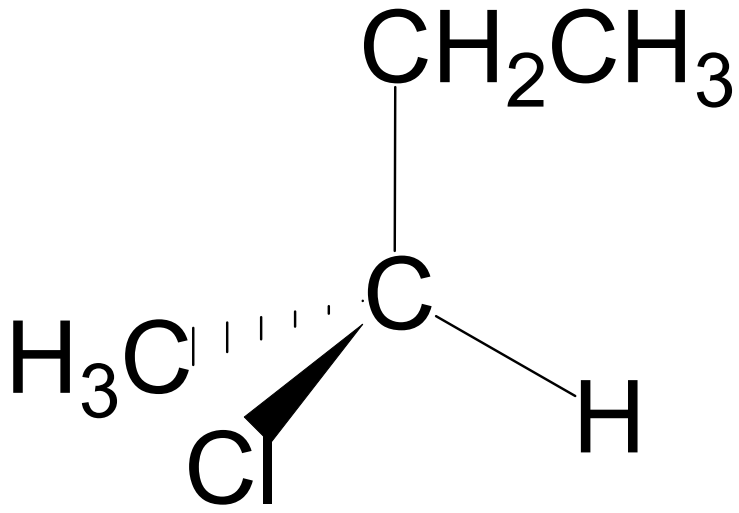
NOT OPTICALLY ACTIVE

Click here to go back to the optical isomerism task

2-chlorobutane







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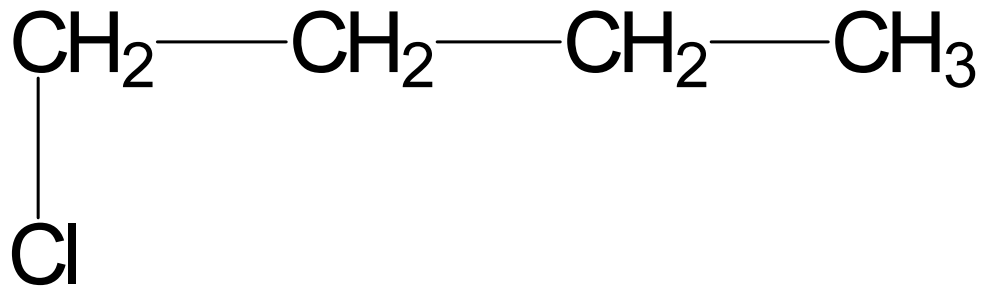
1-chlorobutane



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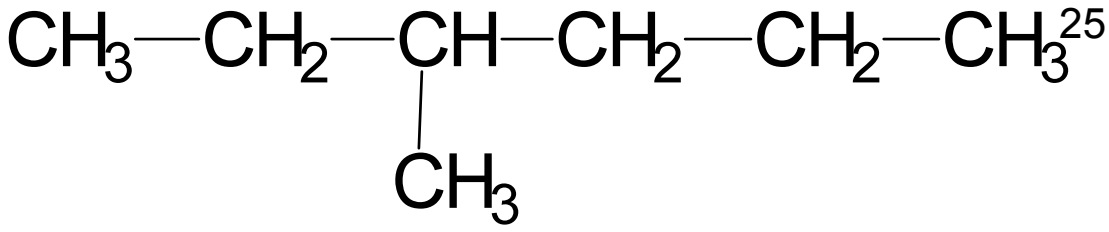
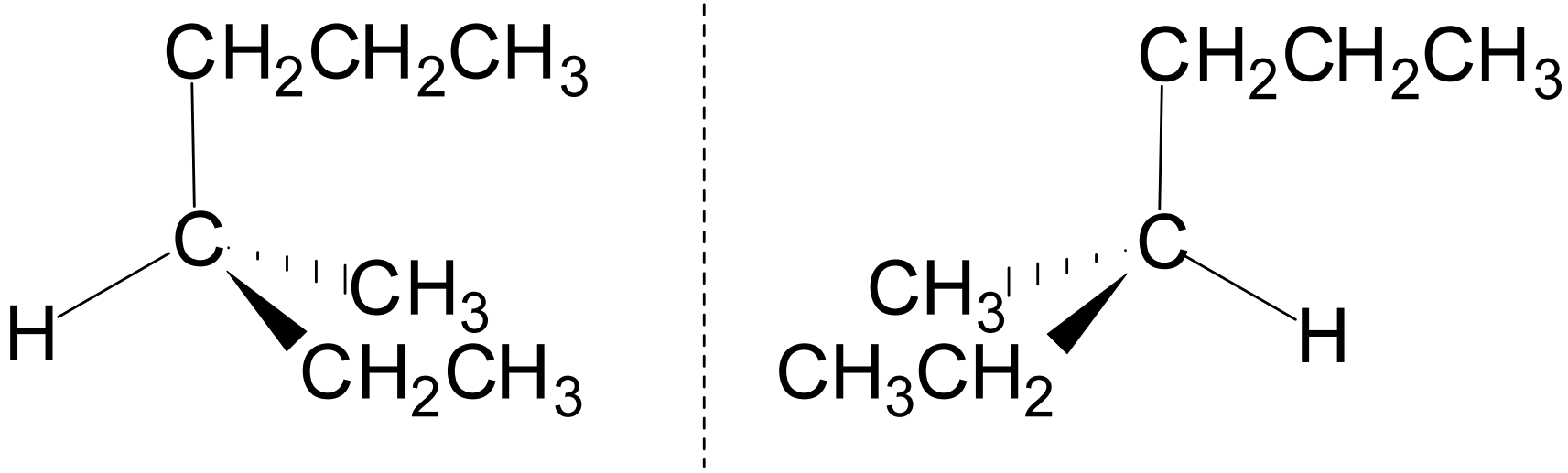
3-methylhexane 



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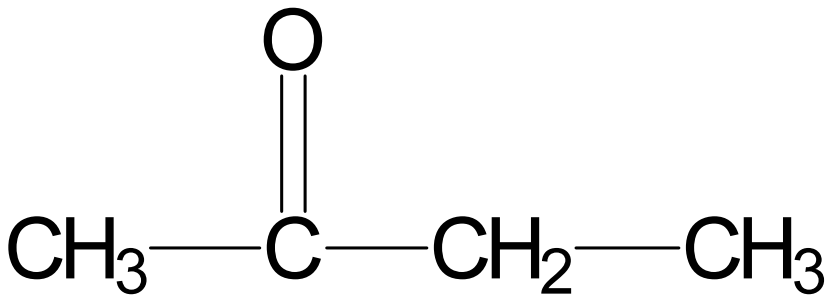
butanone



NOT OPTICALLY ACTIVE

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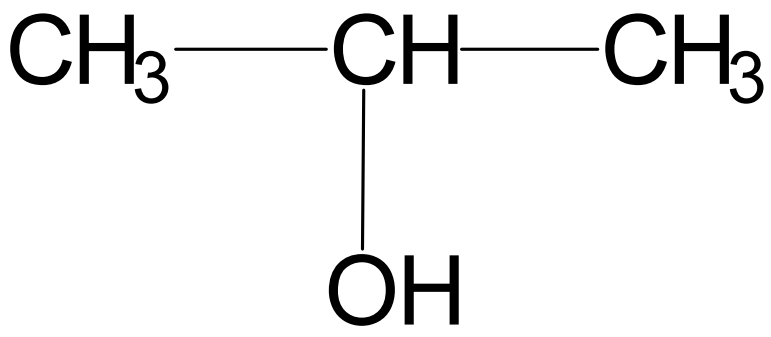
propan-2-ol



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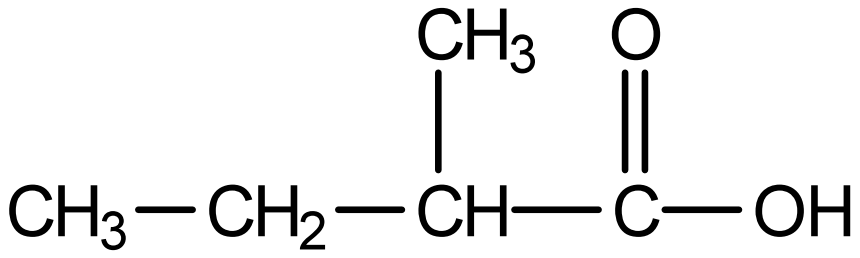
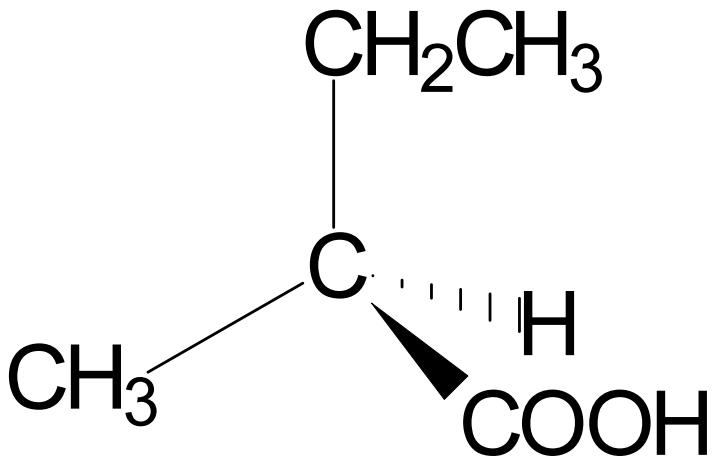
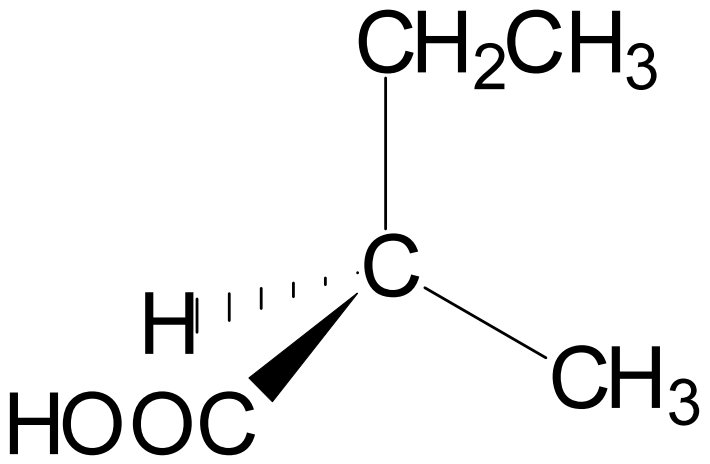
2-methylbutanoic acid







OPTICALLY ACTIVE

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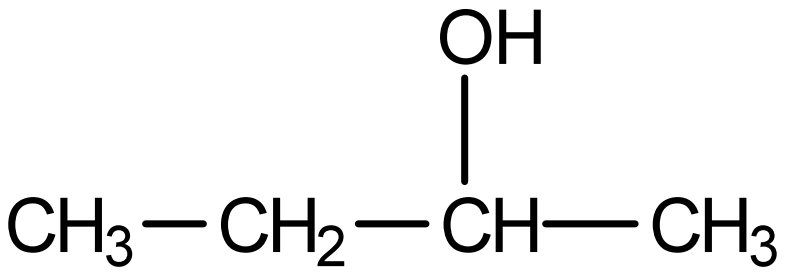
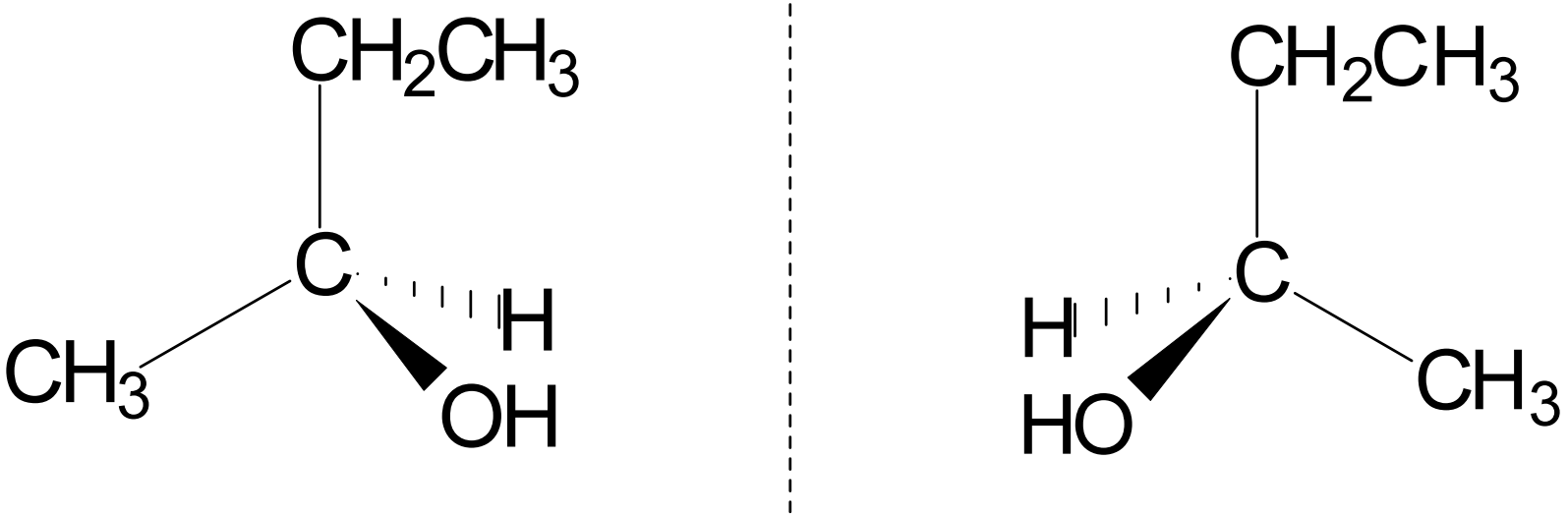
butan-2-ol





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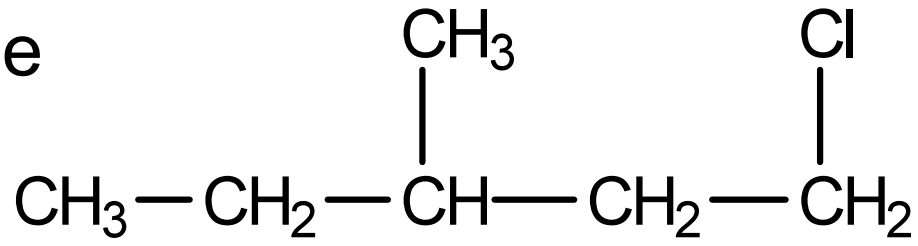
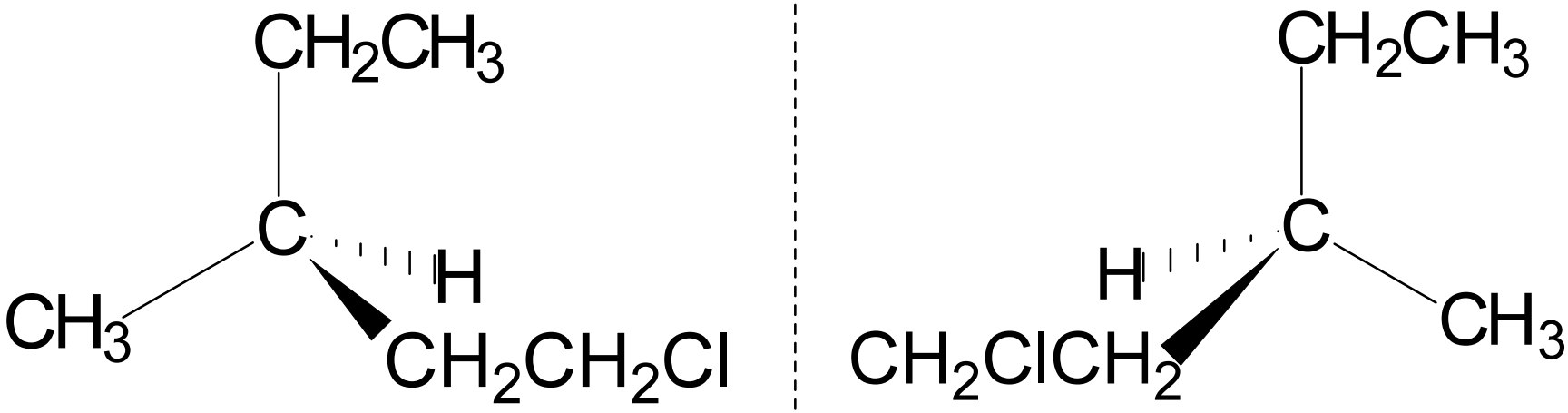
1-chloro-3-methylpentane





OPTICALLY ACTIVE

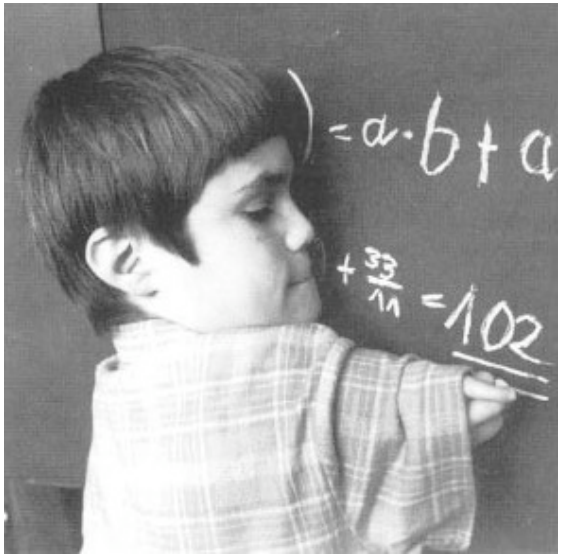
Click here to go back to the optical isomerism task

- Chiral molecules often react differently with other chiral molecules.
- This is like the idea that a right hand does not fit a left handed glove – the molecule must be the correct shape to fit the molecule it is reacting with.
- Many natural molecules are chiral and most natural reactions are affected by optical isomerism.

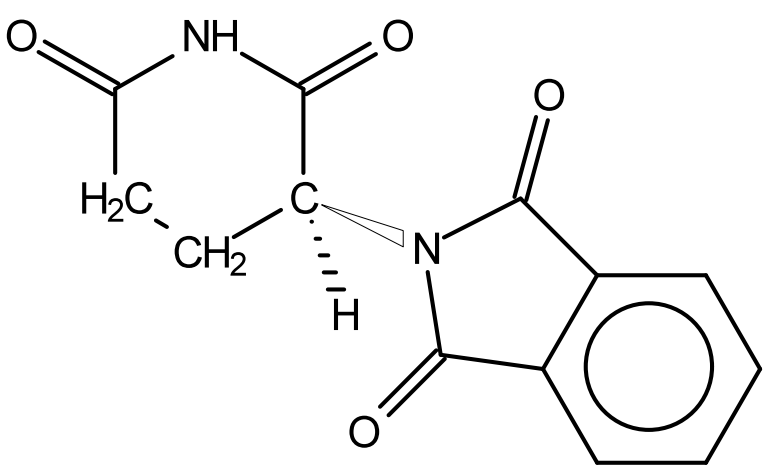
- For example, most amino acids (and so proteins) are chiral, along with many other molecules.
- In nature, only one optical isomer occurs (e.g. all natural amino acids are rotate polarised light to the left).

- Many drugs are optically active, with one enantiomer only having the beneficial effect.
- In the case of some drugs, the other enantiomer can even be harmful, e.g. thalidomide.

- In the 1960's thalidomide was given to pregnant women to reduce the effects of morning sickness.
- This led to many disabilities in babies and early deaths in many cases.

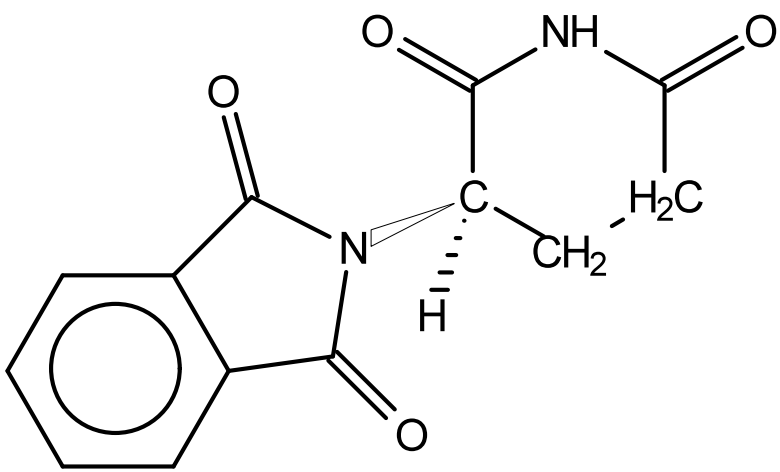


The photographs are both from 'Molecule of the Month' at Bristol University:
http://www.chm.bris.ac.uk/motm/thalidomide/start.html



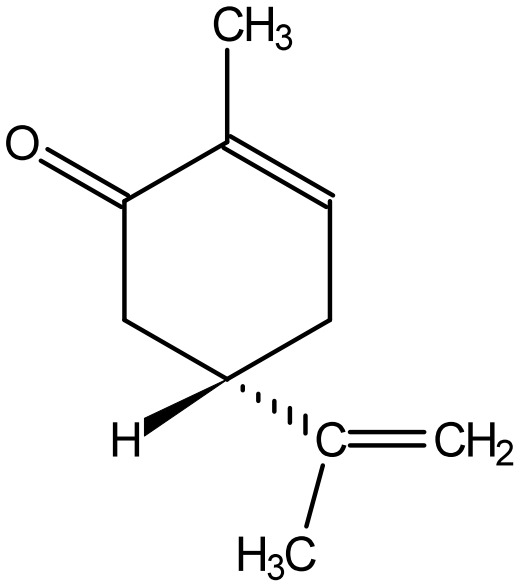
S thalidomide (effective drug)

The body racemises each enantiomer, so even pure S is dangerous as it converts to R in the body.

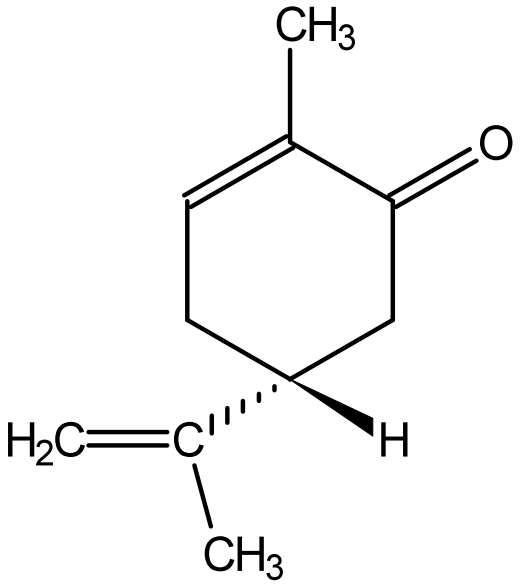


R thalidomide (dangerous drug)

- Thalidomide was banned worldwide when the effects were discovered.
- However, it is starting to be used again to treat leprosy and HIV.
- Its use is restricted though and patients have to have a pregnancy test first (women!) and use two forms of contraception (if sexually active).

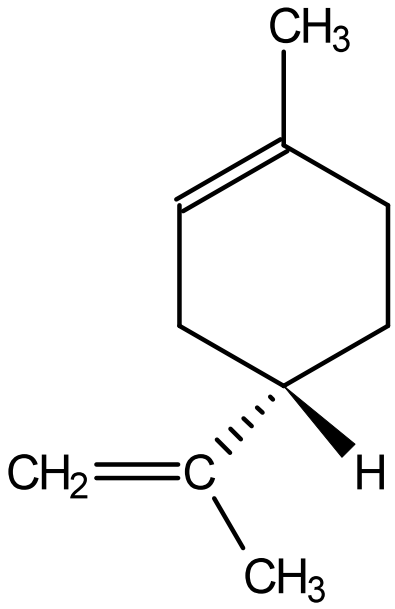


S carvone (caraway seed)

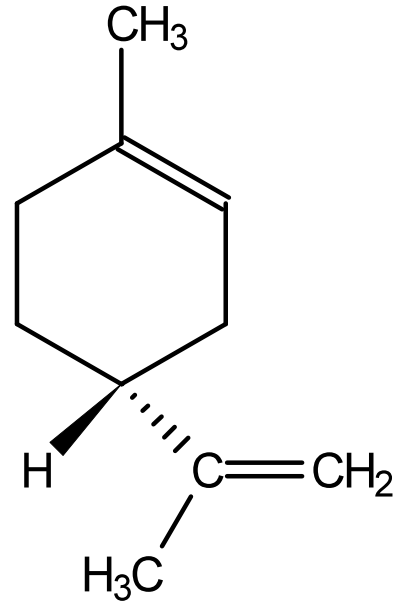


R carvone (spearmint)

Caraway Seed has a warm, pungent, slightly bitter flavour with aniseed overtones.



S limonene (lemons)



R limonene (oranges)