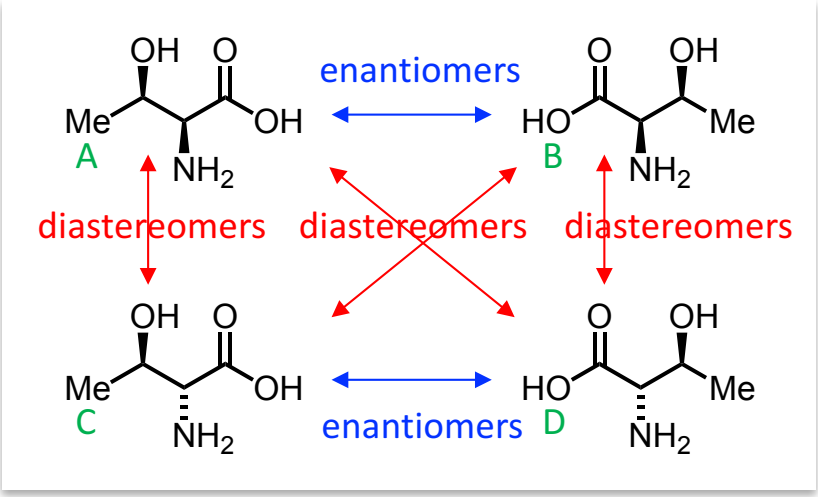
Introduction to Organic Chemistry

Handout 2 – Stereochemistry



http://burton.chem.ox.ac.uk/teaching.html

- *Organic Chemistry* J. Clayden, N. Greeves, S. Warren
- *Stereochemistry at a Glance* J. Eames & J. M. Peach
- *The majority of organic chemistry text books have good chapters on the topics covered by these lectures*

- *Eliel* Stereochemistry of Organic Compounds (advanced reference text)

- representations of formulae in organic chemistry

- skeletal representations are far less cluttered and as a result are much clearer than drawing all carbon and hydrogen atoms explicitly, they also give a much better representation of the likely bond angles and hence hybridisation states of the carbon atoms

- skeletal representations allow functional groups (sites of reactivity) to be clearly seen

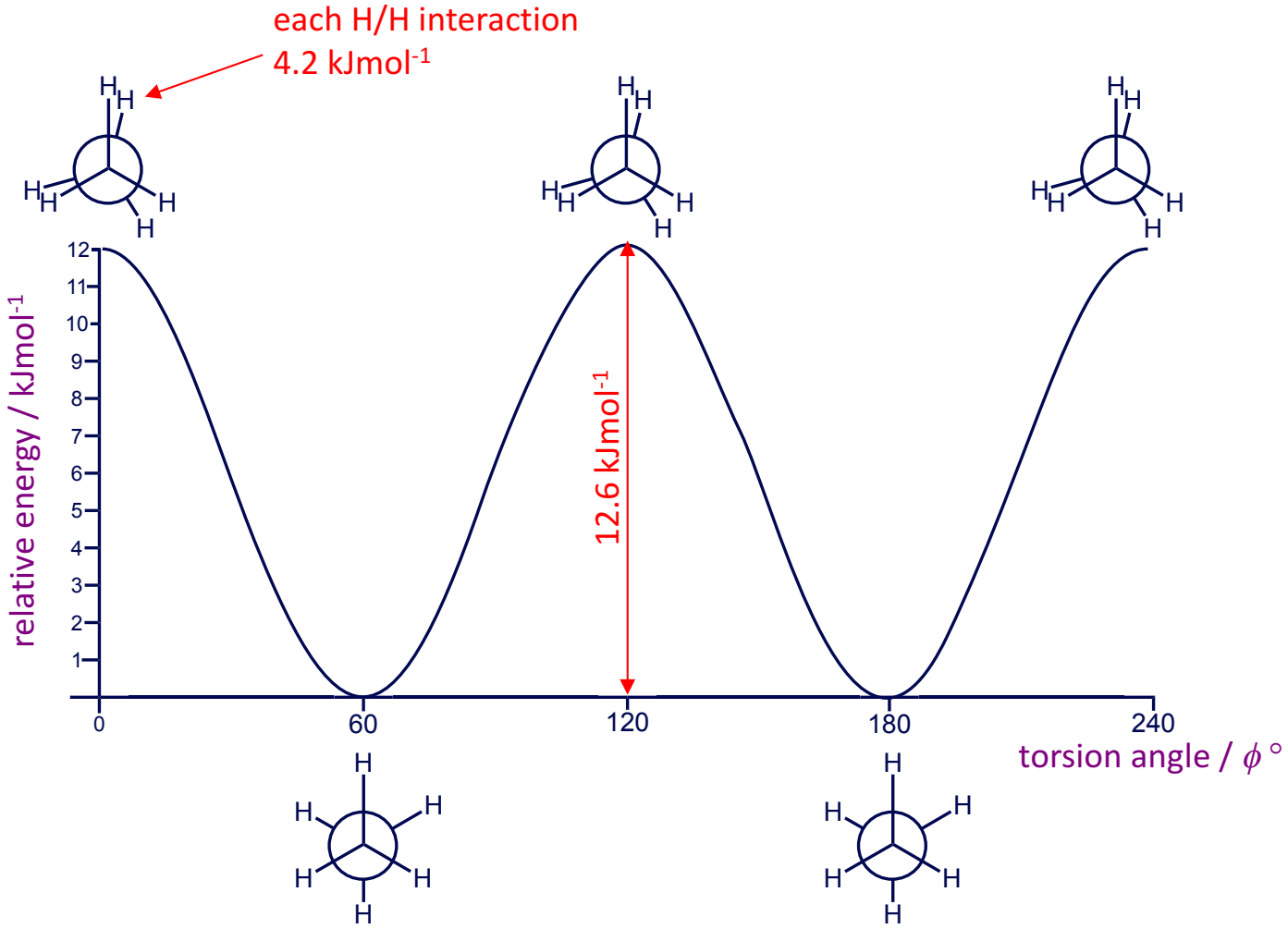
- guidelines for drawing skeletal structures

i) draw chains of atoms as zig-zags
ii) do not draw C atoms unless there is good reason to draw them
iii) do not draw C-H bonds unless there is good reason to draw then
iv) do not draw Hs attached to carbon atoms unless there is good reason to draw them
v) make drawings realistic

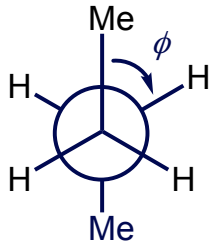
- representing structures in three dimensions

- a wedged bond  indicates the bond is projecting out in front of the plane of the paper
- a dashed bond  indicates the bond is projecting behind the plane of the paper
- a wavy bond  indicates one of two things: *either* unknown or unspecified stereochemistry *or* a mixture of two stereoisomers

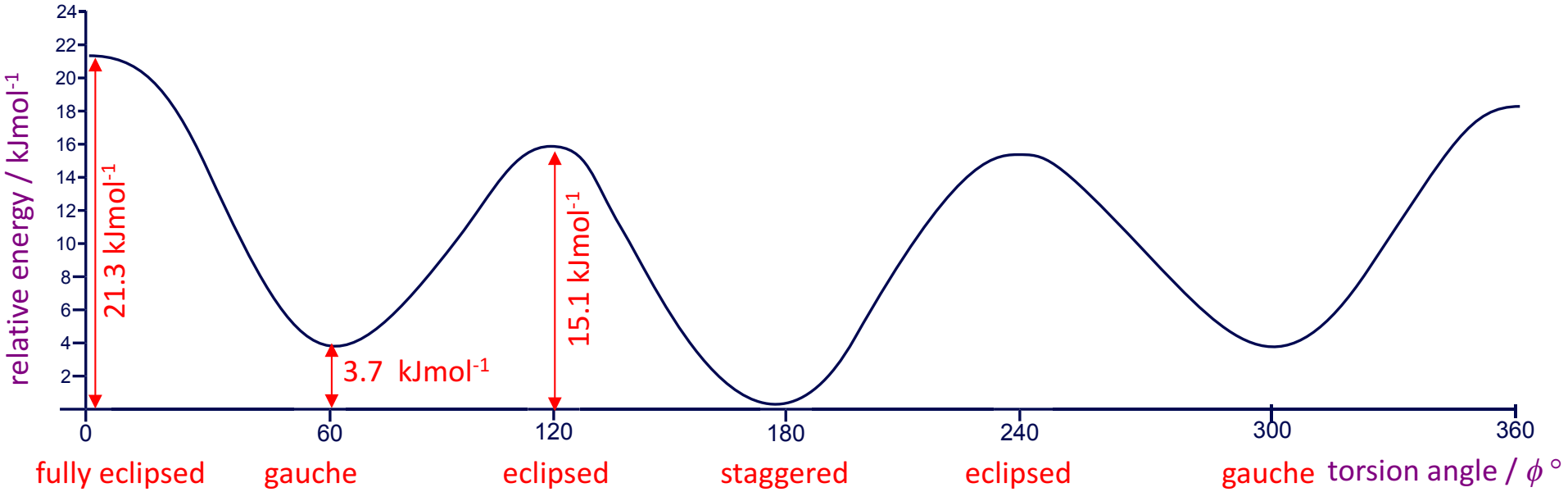
- **conformation** – any spatial arrangement of atoms of a molecules that can be achieved by rotation about single bonds
- virtually an infinite number of conformations
- generally only the most and least stable conformations are discussed
- C_2H_6 - ethane



- conformational analysis of butane is similar to that of ethane



ϕ is the torsion angle



- staggered conformations are energy minima
- eclipsed conformations are energy maxima
- lowest energy conformation has Me groups as far apart as possible
- highest energy conformation has Me groups eclipsing one another

STEREOCHEMISTRY – from the Greek stereós (στερεός) meaning solid

- **isomers** – non-identical molecules with the same molecular formula

- **constitution** of a molecule is defined by the sequence of bonds (atom connectivity) between atoms without reference to their directions in space – constitutional isomers have the same molecular formula but different connectivity

- **stereoisomers** – isomers with the same connectivity – i.e. A linked to B linked to C etc., but different disposition of atoms in space

stereoisomers cannot be interconverted by rotation about single bonds (more later)

- stereoisomers can be divided into two mutually exclusive classes – enantiomers and diastereoisomers (diastereomers)

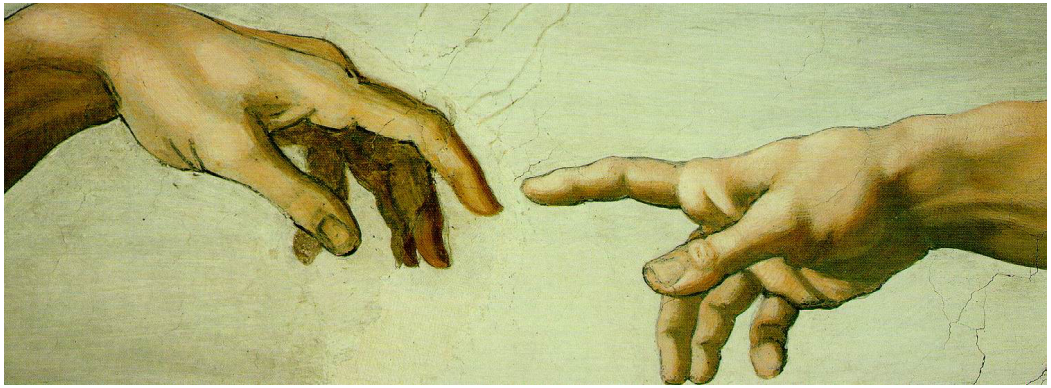
- **enantiomers** (from the Greek for opposite – énanti (έναντι) – are stereoisomers which are related as non-superimposable object and mirror image (non-identical molecules related as object and mirror image)

- molecules (and objects) which have a non-superimposable mirror image are called ***chiral*** (from the Greek for hand – *chéri* (χέρι))

- a carbon atom (or other atom) bearing four different substituents is termed a ***stereogenic centre*** or ***stereocentre*** – frequently termed a chiral centre

- compounds in which one or more carbon atoms have four non-identical substituents are the largest class of chiral molecules

- conversely a molecule (or object) is termed ***achiral*** if it is superimposable on its mirror image

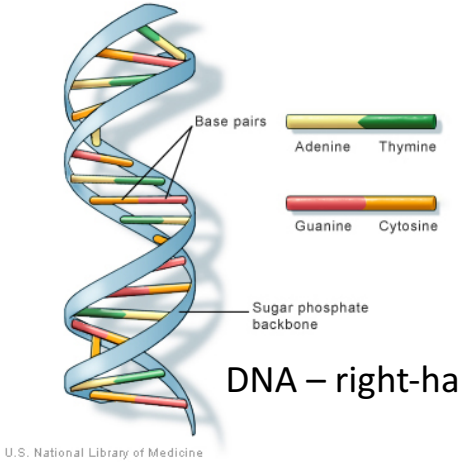


hands - chiral

screws – chiral – right-handed screw

golf clubs - chiral

snails – chiral –
usually right-handed helix

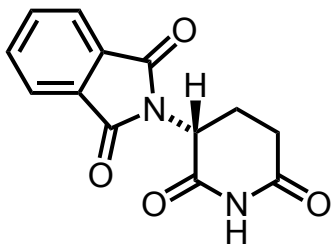


DNA – right-handed screw

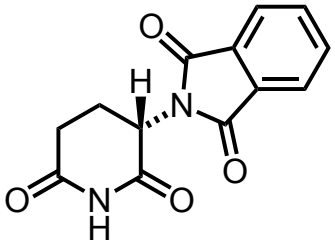
tennis rackets - achiral

left-handed snails are rarer

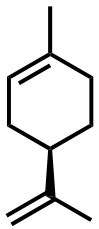
- enantiomers have the same physical and chemical properties in a non-chiral (*achiral*) environment – i.e. they are identical (in an achiral environment)
- enantiomers have *different* properties in a *chiral* environment e.g. an enzyme
- separated enantiomers rotate the plane of *plane polarised light* in equal but opposite directions – this is optical activity and the sample is said to be optically active
- optical activity was first demonstrated by Pasteur in 1848 and led to the idea of tetrahedral carbon
- Jean Baptiste Biot (1774-1862) first showed that some natural substances can rotate the plane of plane polarised light



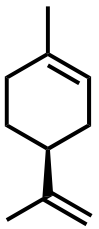
(+)-thalidomide, $[\alpha]_D^{21}$ = +63 (*c* 2.03, DMF)
sedative, hypnotic, stops morning sickness



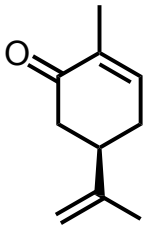
(–)-thalidomide, $[\alpha]_D^{21}$ = –63 (*c* 2.03, DMF)
teratogen, foetal damage, congenital malformation



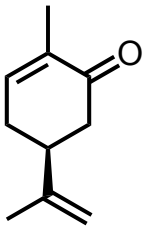
(+)-limonene
oranges



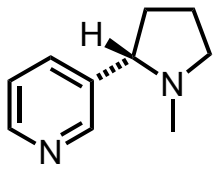
(–)-limonene
turpentine / lemon



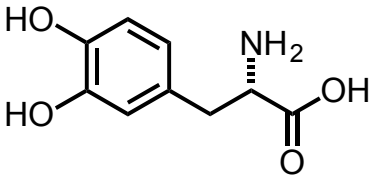
(–)-carvone
spearmint



(+)-carvone
caroway and dill

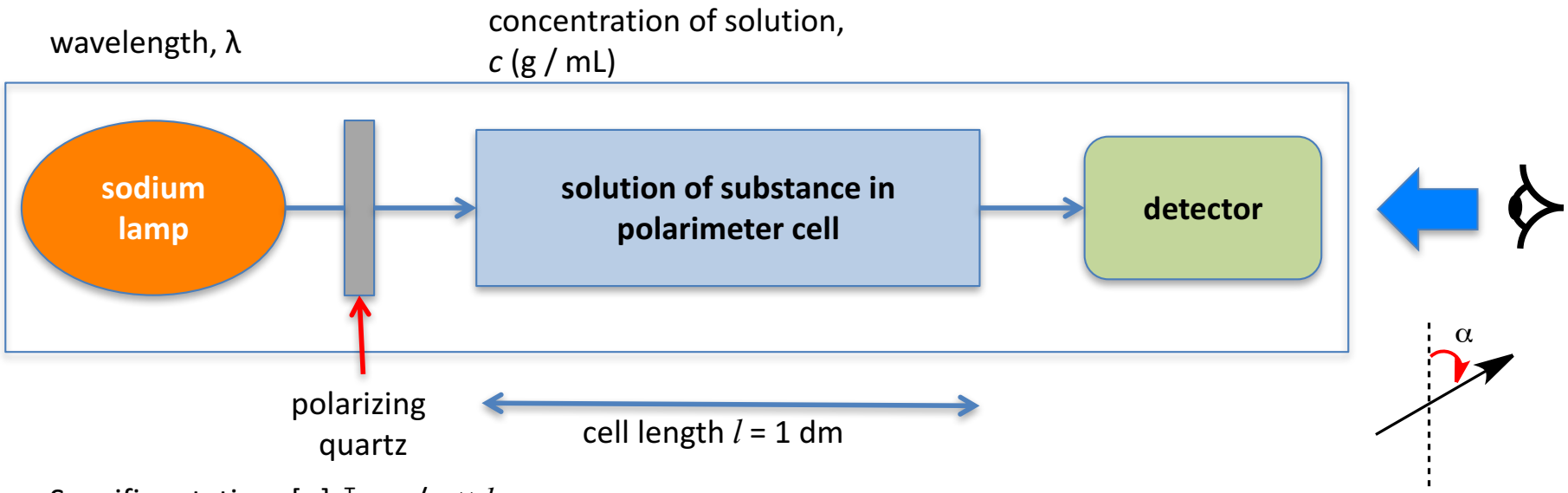


(*S*)-(–)-nicotine



L-DOPA

- optical rotation.
- schematic of a polarimeter



Specific rotation: $[\alpha]_D^T = \alpha / c \times l$

α = observed rotation

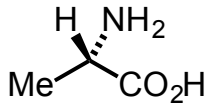
D = wavelength of sodium "D" line – 589 nm

c = concentration of solution in g / mL

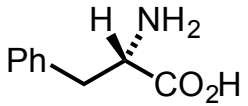
l = length of cell in dm (usually 1 dm)

T = temperature in °C

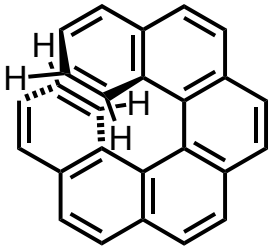
rotation to the right
dextrorotatory (+)
rotation to the left
levorotatory (-)



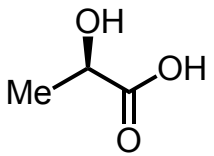
(S)-L-(+)-alanine
$[\alpha]_D$ = +14.7



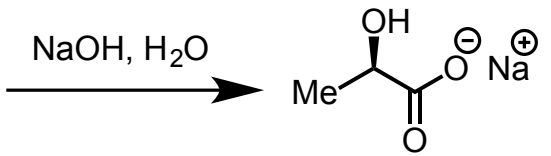
(S)-L-(–)-phenylalanine
$[\alpha]_D$ = –35.2



hexahelicene
$[\alpha]_D$ = +3640!



(*R*)-D-(-)-lactic acid
$[\alpha]_D$ = -3.8



(*R*)-sodium lactate
$[\alpha]_D$ = +13.5

- there is no simple connection between structure and specific rotation; however, single enantiomers always show equal and opposite rotation if the specific rotation is measured under identical conditions

- the magnitude of the specific rotation depends on the wavelength, the temperature, the concentration and the solvent, among other things

- a 1:1 mixture of *enantiomers* is termed a ***racemic mixture*** (or ***racemate***), a *racemic mixture* is optically inactive – does not rotate the plane of plane polarised light

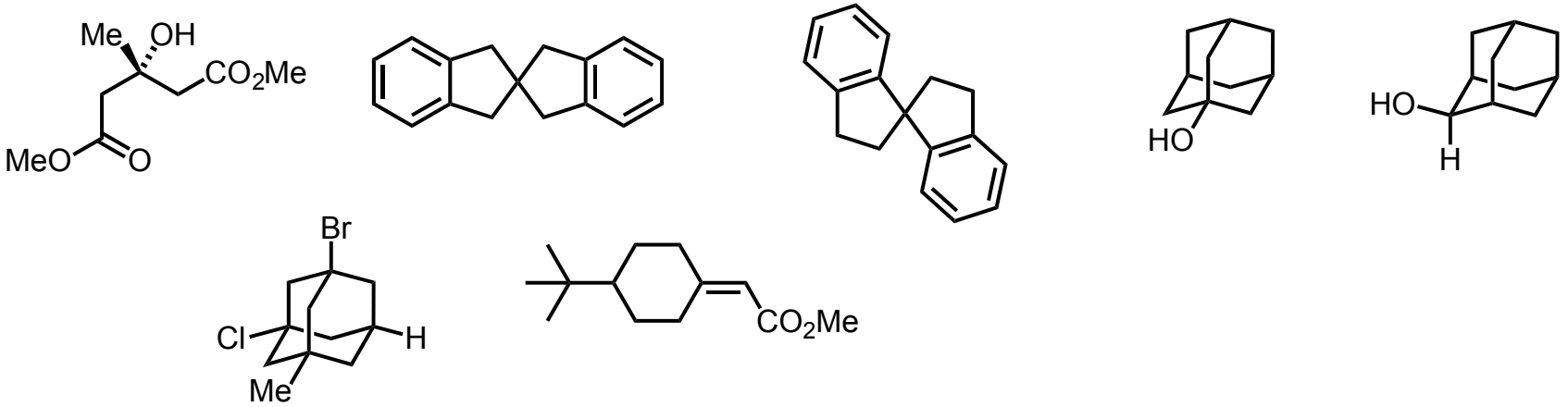
- *achiral* (non-chiral) molecules do *not* rotate the plane of plane polarised light and are optically inactive

- if a reaction is to produce an excess of one enantiomer over the other then the reaction must be conducted in a chiral, non-racemic environment e.g. in the presence of an enzyme or enantiomerically enriched reagent or catalyst

- *no* optically active material can be generated if all the staring material, reagents and conditions are either *achiral* or *racemic* i.e. optically inactive.
i.e. if a chiral compound is synthesised from achiral or racemic reactants, reagents and catalysts then it will be formed as a racemate

- *Note:* a sample of a chiral molecule may contain a single enantiomer or it may be a mixture of enantiomers, depending on how it was made

- which of the following molecules are chiral?



- **configuration** – the spatial arrangement of atoms that distinguishes stereoisomers

- tests for the presence of chirality

- if a molecule (or object) has a plane symmetry it **cannot be chiral**

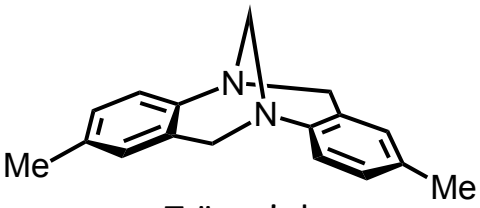
- the presence of a stereogenic centre, a.k.a a stereocentre (i.e. a carbon with four different substituents, often called a chiral centre), is a reliable test for chirality if the molecule has **only one** stereocentre

- molecules with more than one stereocentre can be achiral (more of this later)

- the only reliable test to determine if a molecule is chiral, is the test of non-superimposability of the mirror image with the object

- chiral molecules are not restricted to those having a carbon atom carrying four different substituents
- sulfoxides, sulfinamides, phosphines and phosphine oxides can all be chiral and are frequently configurationally stable at room temperature
- the central atom (P or S) can carry four different substituents one of which can be a lone pair of electrons

- generally amines that have three different groups on nitrogen cannot be resolved into separate enantiomers as very rapid pyramidal inversion occurs at room temperature



Tröger's base
a chiral molecule

- if the nitrogen substituents can be 'tied-back' to prevent pyramidal inversion then the amine may be resolved

- stereoisomers which are not related to each other as enantiomers are termed **diastereomers**
- all stereoisomers which are not related as non-superimposable object and mirror image are related as diastereomers

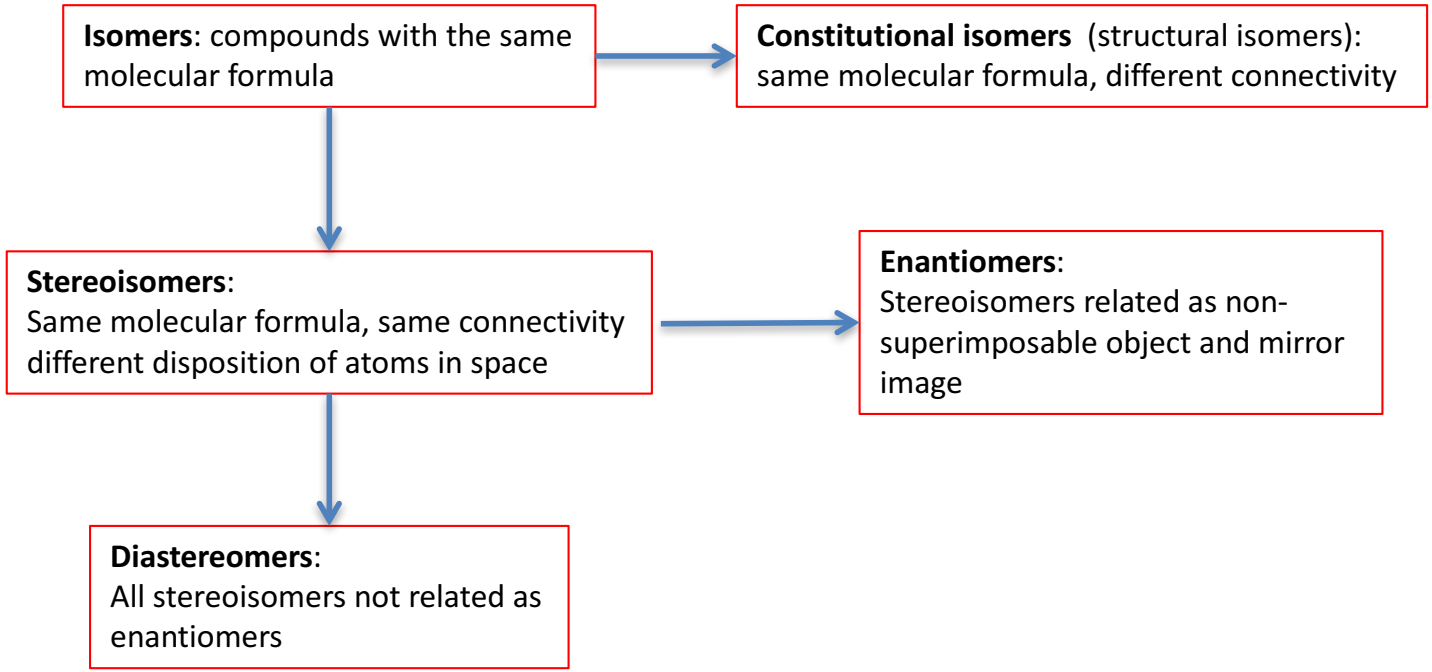
- *Note: it is the **relationships, enantiomeric and diastereomeric,** that are mutually exclusive*

i.e. two particular stereoisomers are ***either*** *enantiomers* or *diastereomers*; however, a molecule that is *enantiomeric* to one other molecule, may also be *diastereomeric* to other molecules

- diastereomers have different physical and chemical properties – different NMR spectra, IR spectra, melting point, boiling point etc. – they are ***different*** compounds

- remember enantiomers are related as non-superimposable object and mirror image and hence only have different properties in a chiral environment – they are identical in an achiral environment – more on this later

- flow chart of isomers



Cahn-Ingold-Prelog Sequence Rules

- it is important to be able to label the ***configuration*** of a *stereocentre* centre in much the same way as geometrical isomers of double bonds are termed ***cis*** and ***trans***

- *R* = Rectus (Latin for 'right') and *S* = Sinister (Latin for 'left') are used to label the configurations of *stereogenic* centres

- assign the priority of each atom directly attached to the stereocentre on the basis of atomic number – higher atomic number = higher priority

- if atoms directly attached to the stereocentre have the same atomic number move down each substituent one atom at a time until the *first* difference is reached, with higher atomic number always being the first point of difference

- same atomic number but different mass number – higher mass number takes priority e.g. T > D > H

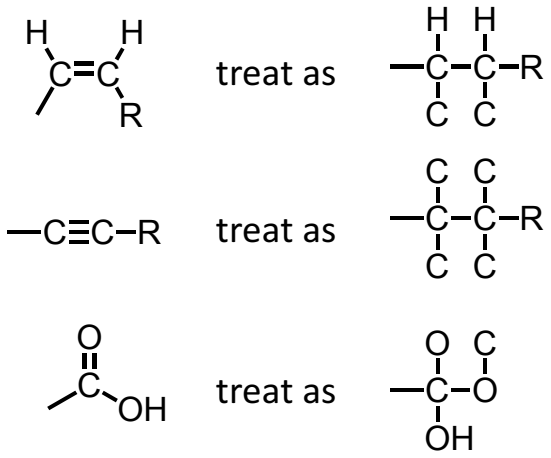
substituent	1st atom	2nd atom	priority

- draw molecule with the lowest priority substituent (priority d) at the rear

- a→b→c is clockwise the stereochemical descriptor is *R*
- a→b→c is anticlockwise the stereochemical descriptor is *S*

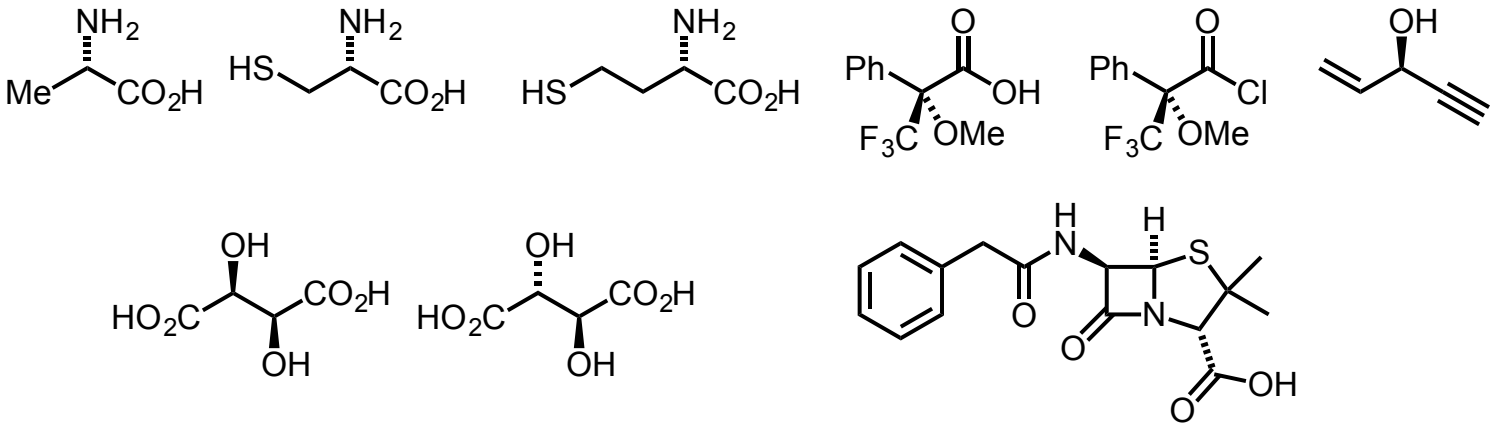
■ *Cahn-Ingold-Prelog Sequence Rules - continued*

Treat double and triple bonds as multiple single bonds:



substituent	treat as	1st atom	2nd atom	priority

■ assign *R* and *S* stereochemical descriptors to the following molecules



- *Cahn-Ingold-Prelog Sequence Rules - continued*
- the CIP rules can be extended to the assignment of double bond geometry.

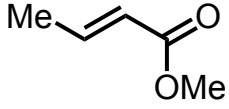
- look at one end of the double bond and decide which substituent has higher priority.

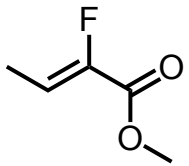
- look at the other end of the double bond and decide which substituent has higher priority.

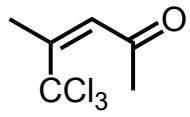
- double bond is (*Z*) if the the higher order substituents are on the same side of the double bond (**Zusammen** – together in German)

- double bond is (*E*) if the higher order substituents are on the opposite side of the double bond (**Entgegen** – opposite in German)

- assign (*E*) or (*Z*) to the following alkenes







- some useful stereochemical projections
- sawhorse projection – looking down the C–C bond with an angled projection

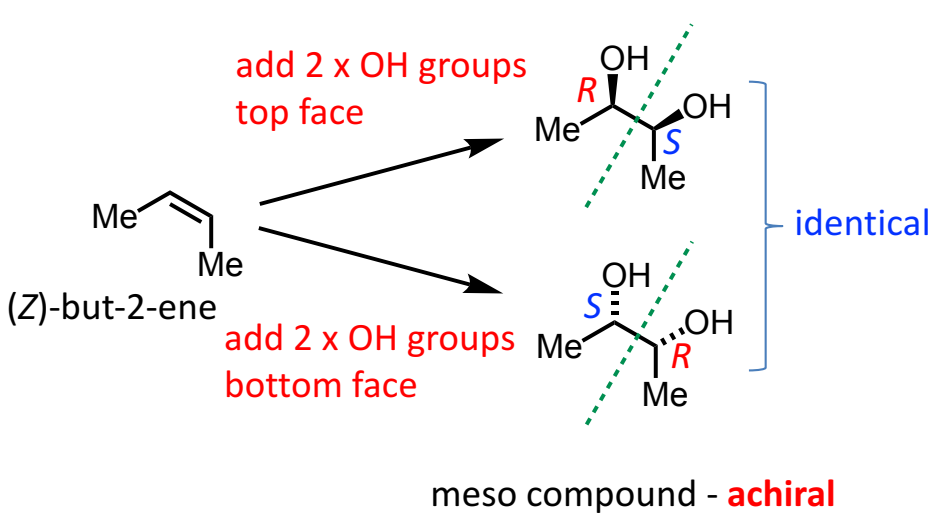
- Newman projection – looking down the C–C bond

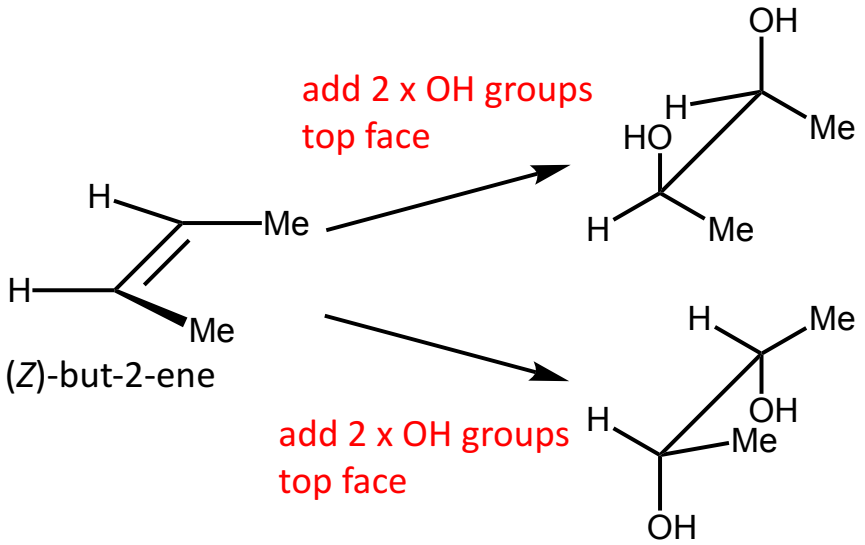
- Fisher projections are no longer a useful stereochemical projection but are historically important
e.g. tartaric acid

- molecules with two stereocentres – we will use the dihydroxylation of alkenes using osmium tetroxide as an example
- OsO_4 is a reagent that adds two 'OH' groups to the same face of an alkene – ***syn*** addition (mechanism in later course)

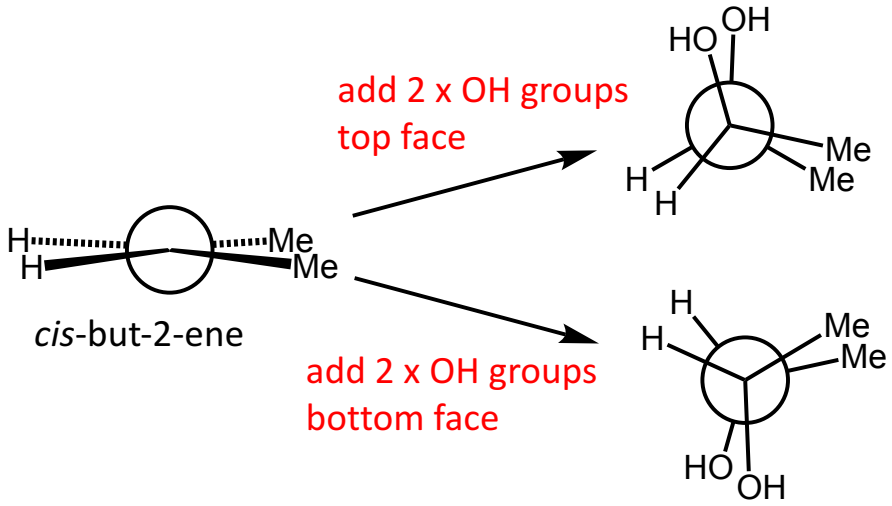
- three projections of the products formed from the ***syn***-addition of two OH groups to the top or bottom face of (*E*)-but-2-ene (*trans*-but-2-ene)
- the products formed from addition to either face of the alkene are different – they are stereoisomers – they are enantiomers
- *aside* - if two groups are added to the opposite faces of an alkene this is termed ***anti*** addition

- (*Z*)–but-2-ene





- three projections of the products formed from the ***syn***-addition of two OH groups to the top or bottom face of (*Z*)-but-2-ene (*cis*-but-2-ene)
- the products formed from addition to either face of the alkene are the same i.e. only one stereoisomer is formed
- this stereoisomer has a plane of symmetry and is thus achiral (not chiral and is optically inactive)
- this stereoisomer is termed a ***meso*** compound

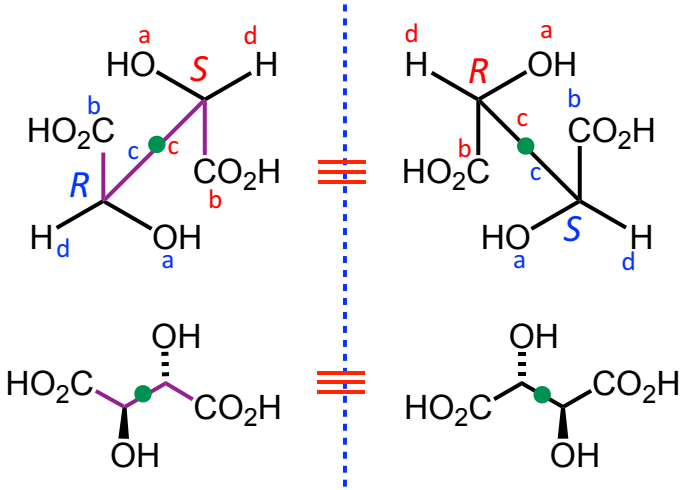


- there are therefore three stereoisomers of butane-2,3-diol

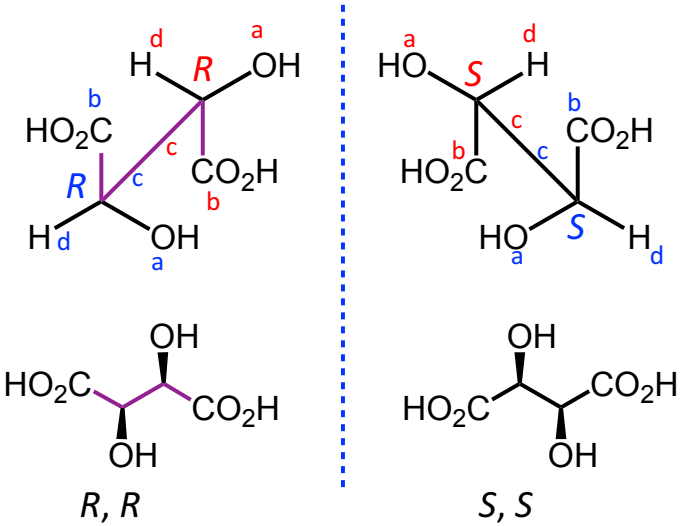
- a simple definition of a *meso* compound is a stereoisomer with two or more stereocentres but which is itself achiral

a fuller definition is that a ‘meso compound is an achiral member of a set of diastereomers that includes at least one chiral member’ *Elliel*

■ 2-stereogenic centres – tartaric acid – potential descriptor combinations *RR, SS, RS, SR*



object and mirror image are the same
(superimposable) achiral,
meso, form *SR* = *RS* = *meso*



R, R *S, S*

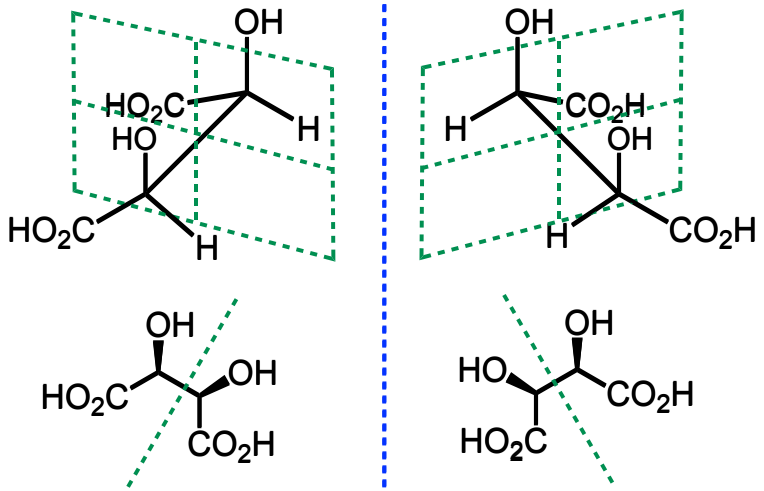
pair of enantiomers
(non-superimposable object and mirror image)

■ there are 3 steresiomers of tartaric acid, a pair of enantiomers, and the *meso*-form

■ as drawn the conformers of the meso compound have a centre of inversion *i* (•)

■ molecules (objects) with a centre of inversion cannot be chiral

■ redrawing in a different conformation reveals a plane of symmetry (σ, often easier to spot than *i*) indicating that this stereoisomer is achiral



■ if a molecule can gain access to a conformation which is non-superimposable on its mirror image then it will be **achiral**

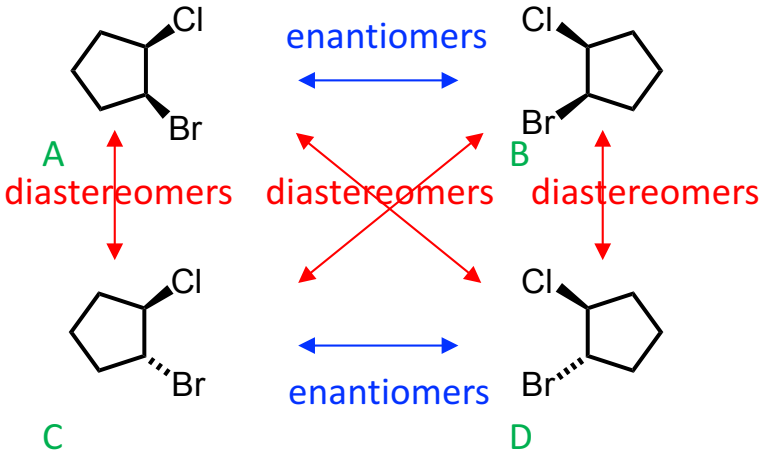
■ if a molecule can gain access to a conformation that has a plane of symmetry or centre of inversion (or more generally an improper axis of rotation S_n) then it will be **achiral**

■ 2-stereogenic centres - 1,2-dichlorocyclopropane – 3 stereoisomers

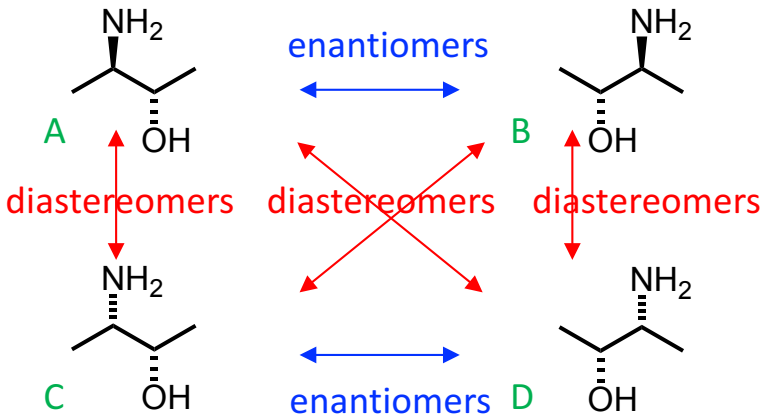
■ in compounds with 2 stereocentres, when the groups are not the same there are always 4 stereoisomers

■ if a compound has *n* stereogenic centres (or more generally stereogenic elements) then the maximum number of stereoisomers is 2^n

■ 2-stereogenic centres – 1-bromo-2-chlorocyclopentane
4 stereoisomers, 2 pairs of enantiomers

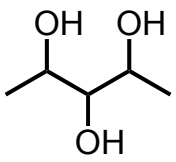


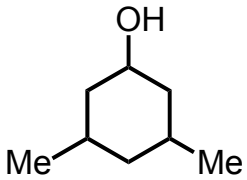
■ 2-stereogenic centres – 3-aminobutan-2-ol
4 stereoisomers, 2 pairs of enantiomers

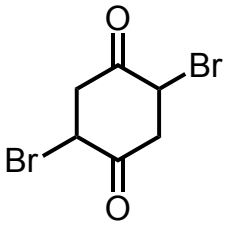


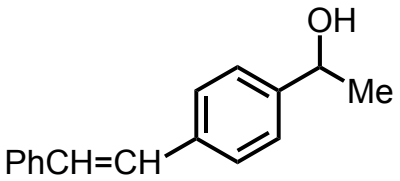
■ for molecules with multiple stereocentres all stereocentres must be inverted to convert one enantiomer into the opposite enantiomer

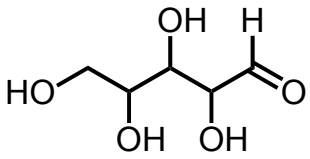
■ draw all the stereoisomers of the following compounds. What are the stereochemical relationships between the various pairs of stereoisomers? Which of the stereoisomers are chiral? Identify any *meso* compounds









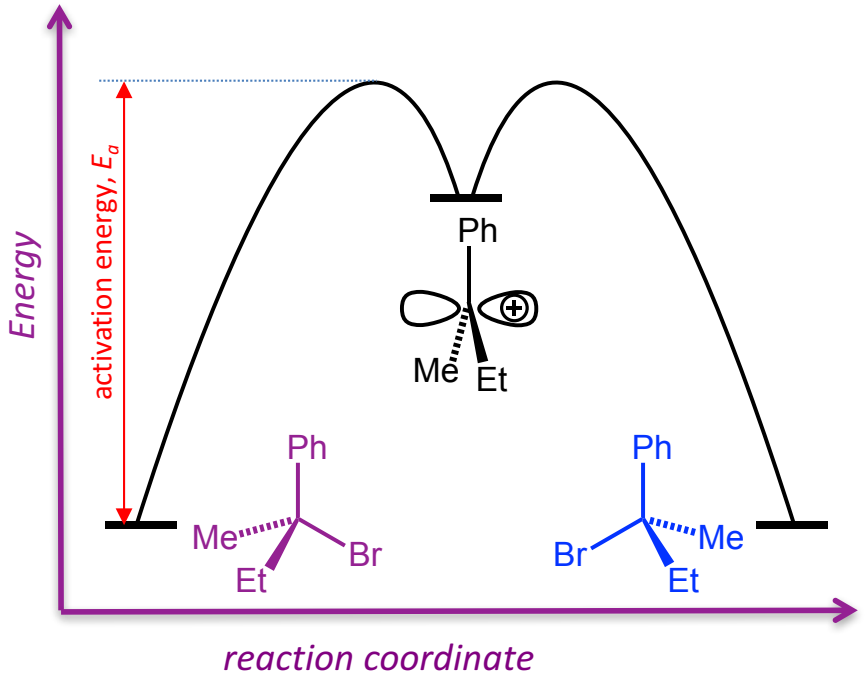


■ to investigate how many stereoisomers a compound has the following method may be useful:

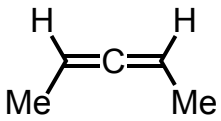
i) if a compound has *n* stereogenic centres (or more generally stereogenic elements) then the maximum number of stereoisomers will be 2^n – if you have more than 2^n you have made a mistake
ii) if the compound is acyclic draw it in zig-zag fashion
iii) identify the stereocentres
iv) decide how many diastereomers there are by putting substituents, with defined stereochemistry on the stereocentres
v) look for possible planes of symmetry (or centres of inversion) and hence decide which diastereomers are chiral – identify *meso* compounds – the presence of meso compounds reduces the number of stereoisomers
vi) draw the enantiomers of any chiral diastereomers by inverting *all* of the stereogenic centres - chiral steroisomers *always* come in pairs i.e. two enantiomers

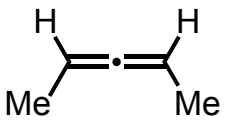
- **racemisation** – the conversion of one enantiomer (or an excess of one enantiomer) into a 1:1 mixture of enantiomers (a racemate or racemic mixture)
- e.g. S_N1 reaction (more of this in later courses)

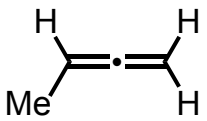
- on recombination, Br^- has equal probability of attacking either side of the carbocation leading to a racemic mixture

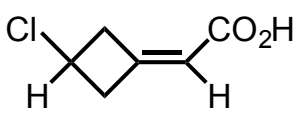


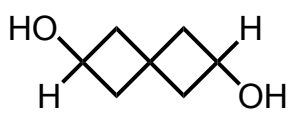
- so far we have mainly looked at 'central' chirality – we will now briefly look at planar, axial and helical chirality
- chirality is a molecular property (in fact a property of an object) so it is not necessary for a molecule to posses a stereocentre (chiral centre) in order to be chiral
- the necessary and sufficient condition for a molecule to be chiral is that it is non-superimposable on its mirror image (i.e. that it lacks an improper axis of rotation (S_n))
- allenes

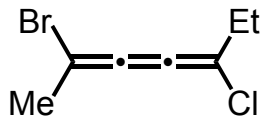












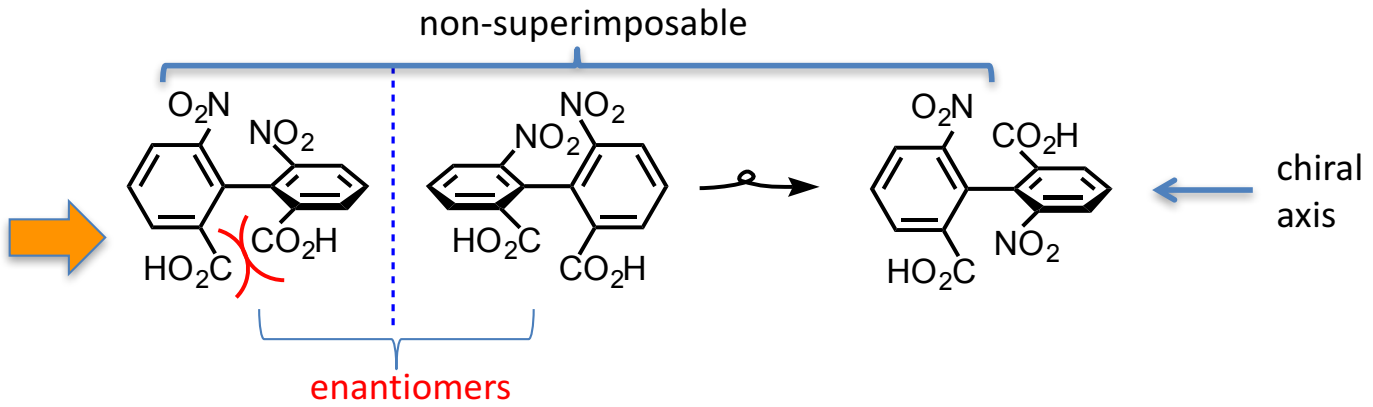
- which of the following molecules are chiral?

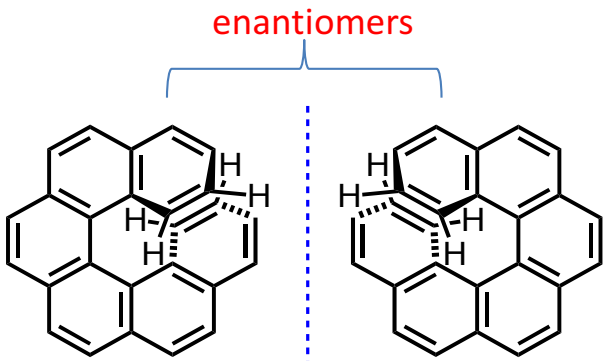
- atropisomers and axial chirality – biphenyls

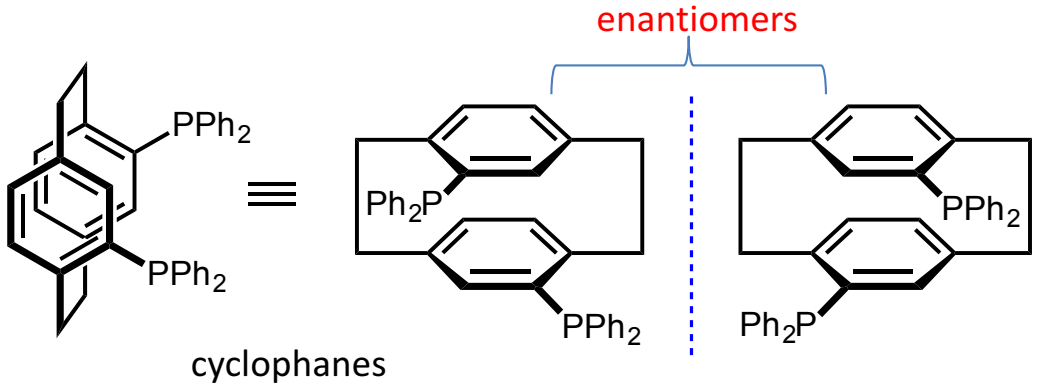
- atropisomers may be defined as stereoisomers resulting from restricted rotation about single bonds

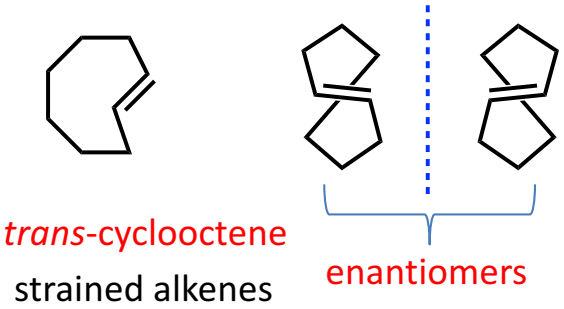
- the (arbitrary) definition of atropisomers is that they have a half life of at least 1000s at a given temperature (>90 kJ•mol^{-1} at 300 K) – the rotational barrier needs to be high enough that the separate isomeric species can be isolated

severe steric hindrance means rotation around the central C-C single bond only occurs at high temperature and this compound can be resolved

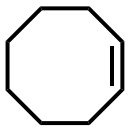








- *trans*-cyclooctene is stable to racemisation indefinitely at 20 °C (chiral)
- *cis*-cyclooctene is achiral

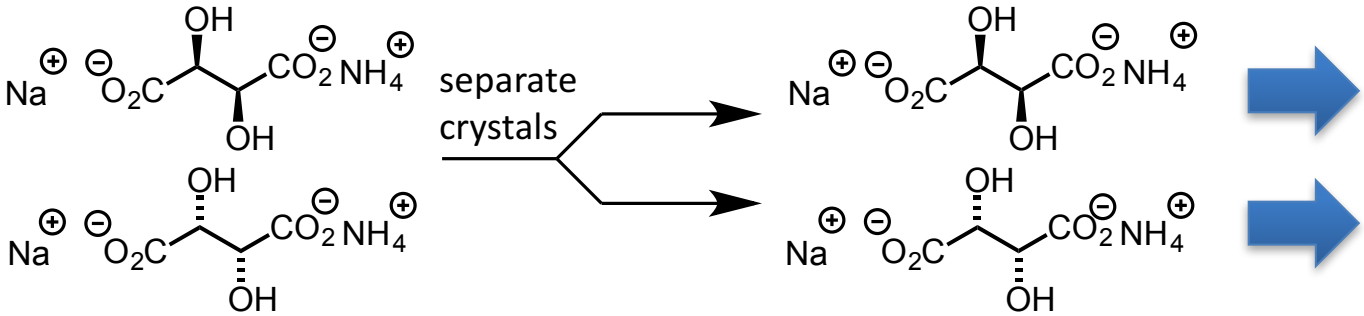


- **Resolution of Racemates** – separation of a 1:1 mixture of enantiomers i.e. (±) mixture, into pure (+) and (–) forms

- problem: enantiomers have identical physical properties therefore they are very difficult to separate

- if a racemate crystallises it can either crystallise so that each crystal contains both enantiomers (a racemic crystal) or such that each crystal is either (*R*) or (*S*) – this is termed a conglomerate and approximately 5-10% of chiral crystalline materials crystallise in this manner

- sodium ammonium tartrate crystallises as a conglomerate, which allowed Pasteur to separate the enantiomeric crystals by hand

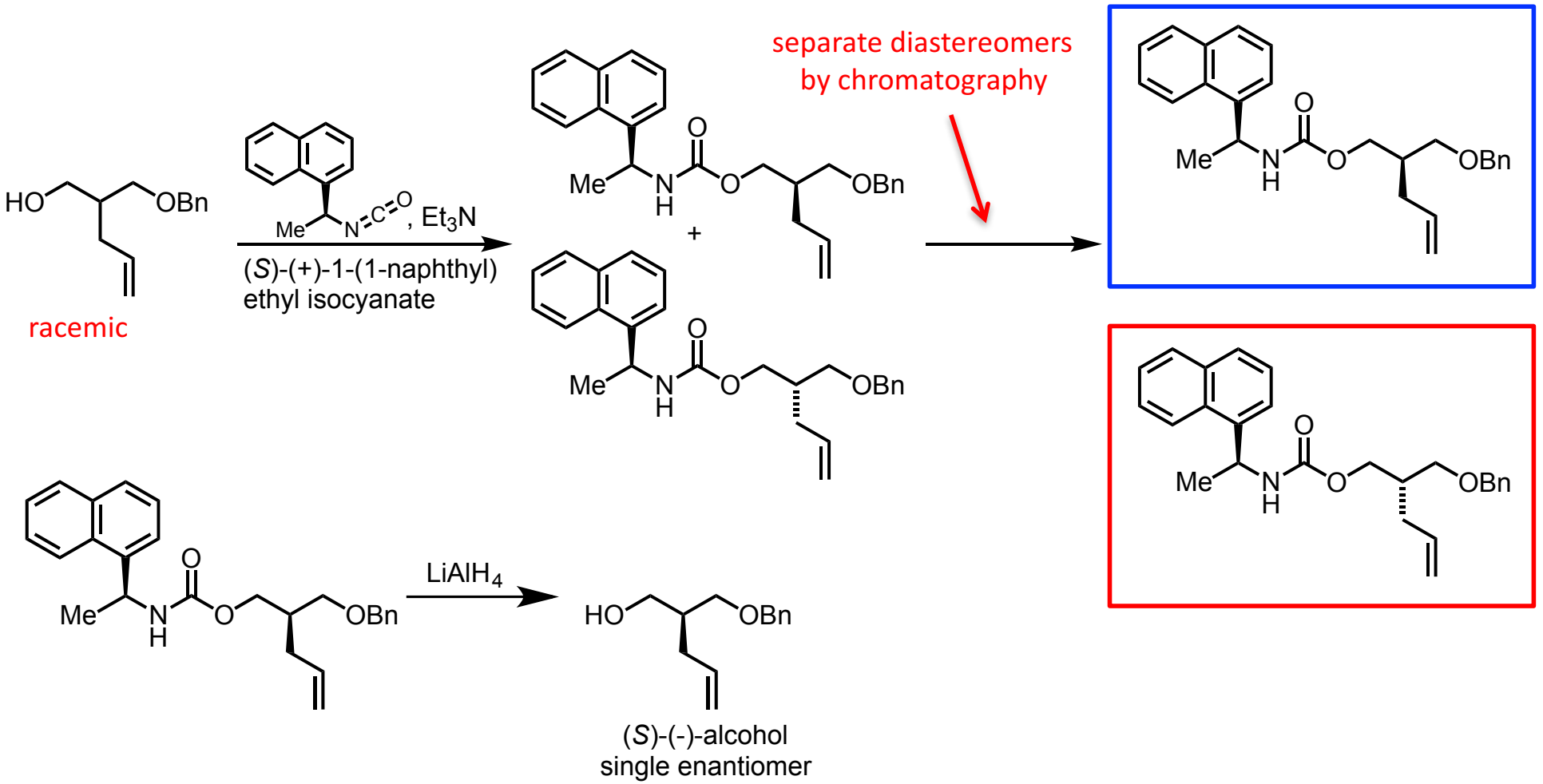


$[\alpha]_D^{20}$ = –12 (*c* = 20 in water)
(–)-tartaric acid - unnatural

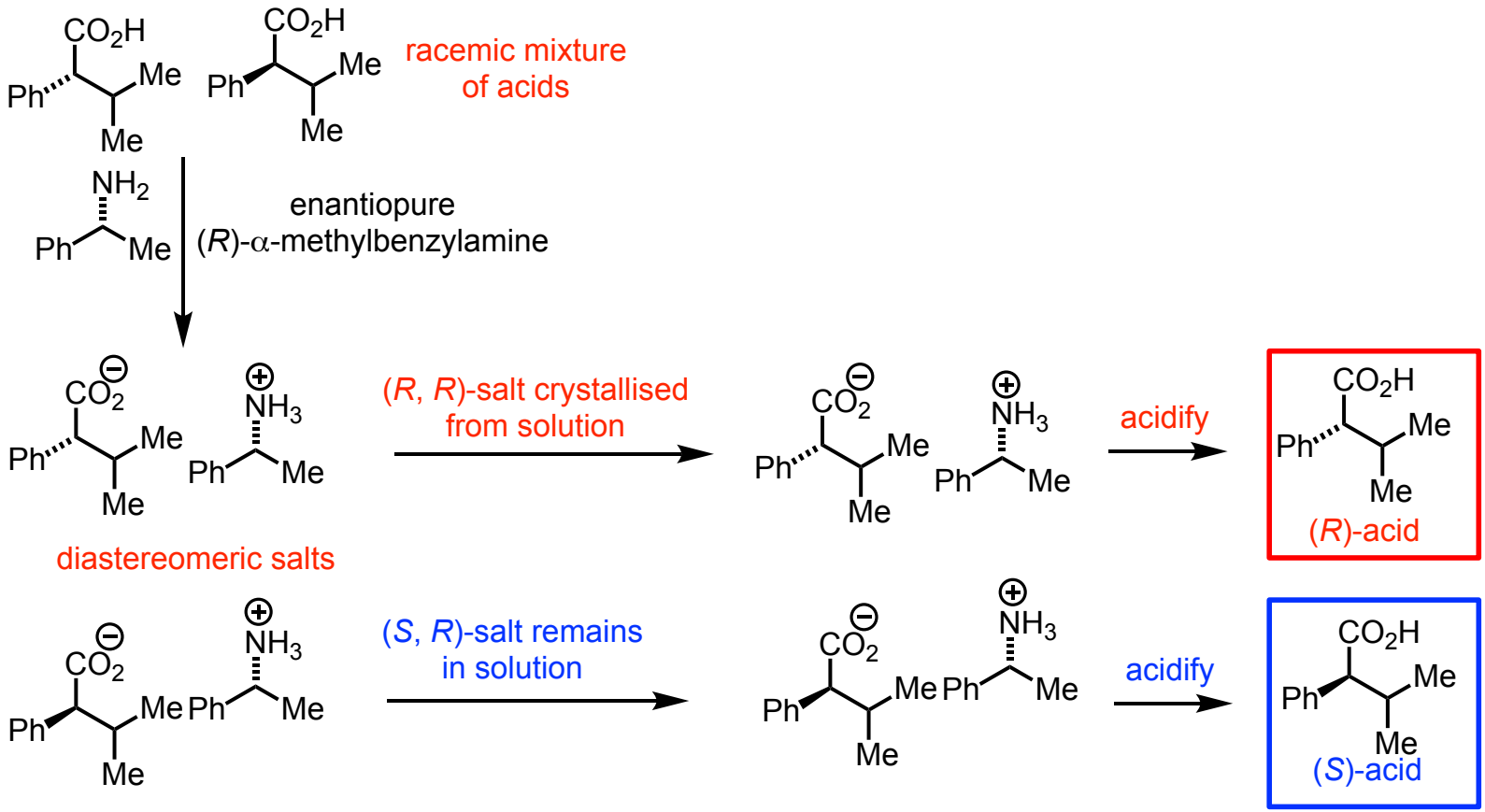
$[\alpha]_D^{20}$ = +12.4 (*c* = 20 in water)
(+)-tartaric acid - natural

- this is not a general solution to the separation of enantiomers as:
  - i) not all racemates are crystalline
  - ii) the majority of chiral crystalline materials are not conglomerates

- separating diastereomers – diastereomers are different molecules, and have different physical properties,
- we should therefore expect to be able to separate diastereomers by standard methods including: chromatography on silica, crystallisation, distillation etc.
- this property of diastereomers indirectly allows the separation of mixtures of enantiomers
- a racemic mixture is a 1:1 mixture of enantiomers
- if we react the racemic mixture with a single enantiomer of a reagent we will produce diastereomers which are (at least theoretically) separable



- it can be much more efficient to do a resolution by selective crystallisation of diastereomeric salts
- diastereomeric salts, much like diastereomers, have different physical properties including melting points and solubility and hence selective crystallisation is frequently possible



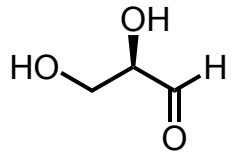
■ **absolute and relative configuration**

■ before 1951 we did not know the absolute configuration of any molecule i.e. we did not know what the actual 3-D arrangement of atoms was. For example we could not tell if (+)- tartaric acid was (*R, R*) or (*S*, *S*)

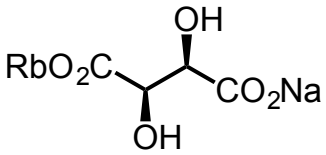
■ Rosenhoff had arbitrarily assigned the absolute configuration of D-(+)-glyceraldehyde as (*R*)

■ many compounds were assigned absolute configuration by tedious chemical degradation, if they were related to the assigned configuration of D-glyceraldehyde they were called D-compounds, regardless of the direction of optical rotation (if they were related to the enantiomer of D-glyceraldehyde they were called L-compounds)

■ in 1951 **Johannes Martin Bijvoet** (1892-1980) used X-ray crystallography to assign the absolute configuration to sodium rubidium (+)-tartrate tetrahydrate – Rosenhoff had guessed correctly.



D-(+)-glyceraldehyde



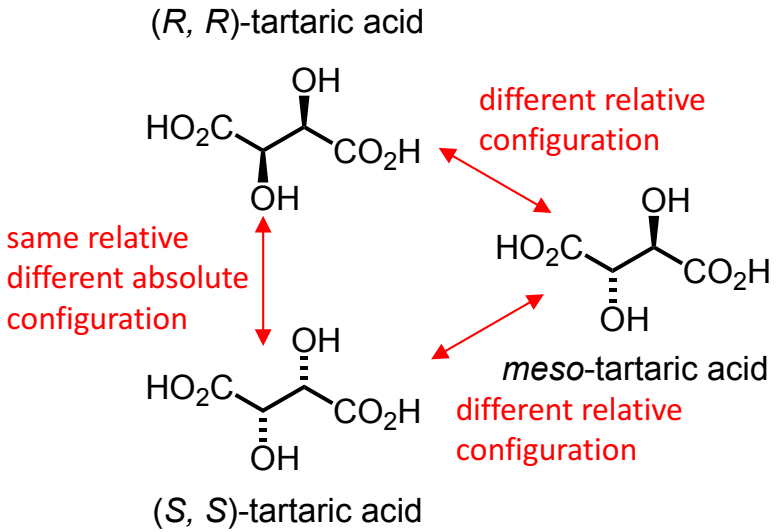
(+)-tartaric acid
sodium rubidium salt
(*R, R*)

absolute and relative configuration

■ absolute and relative configuration can therefore be defined as follows:
if we know which enantiomeric series a molecule is in we know its absolute configuration

if we only know its relative configuration we only know how the stereogenic centres within a molecule are related to one another

■ to put it another way:
"When the stereochemistry drawn on a molecule means 'this diastereomer' we say we are representing **relative configuration**; when it means 'this enantiomer of this diastereomer' we say we are representing its **absolute configuration**" *from Clayden, Greeves, Warren*

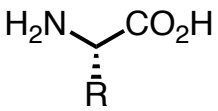


■ generation of chirality – the chiral pool
As stated previously *no* optically active material can be generated if all the staring material, reagents and conditions are either *achiral* or *racemic* i.e. optically inactive.

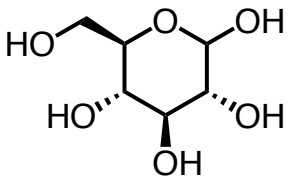
Ultimately to generate *non-racemic* material (material which is optically active) it is necessary to utilise molecules from the *chiral pool* i.e. from the vast array of *enantiopure* and *enantioenriched* molecules which occur in Nature

The Chiral Pool

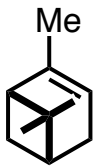
Amino acids



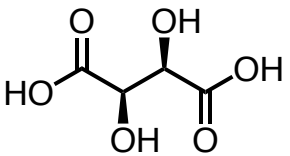
Sugars



Terpenes



Hydroxy acids etc.



Glossary of terms (working definitions)

achiral – not chiral *i.e.* molecule/object has a superimposable mirror image. If a molecule can gain access to a conformation which has a plane of symmetry (or centre of inversion) it will be *achiral*

chiral – molecules (and objects) which have a non-superimposable mirror image

chiral centre – see stereogenic centre

diastereomers – *stereoisomers* which are not related as *enantiomers*

enantioenriched – consisting of an excess of one *enantiomer*

enantiopure – consisting of a single *enantiomer*.

enantiomers - *stereoisomers* which are related as non-superimposable object and mirror image

epimer – *diastereomers* related by the difference in configuration at one *chiral centre*

meso compound - a *stereoisomer with two or more stereocentres but which is itself achiral (an achiral member of a set of diastereomers that includes at least one chiral member)*

optically active – rotates the plane of plane polarised light – can only occur with non-racemic samples

racemate or *racemic mixture* – 50:50 mixture of *enantiomers*; a *racemate* is *optically inactive*.

racemisation – the conversion of one *enantiomer* (or an excess of one *enantiomer*) into a 50:50 mixture of *enantiomers*

stereogenic centre (stereocentre) – an atom (generally carbon) with four *non-identical* substituents – also called a *chiral centre*

stereoisomers – isomers with the same connectivity – i.e. A linked to B linked to linked to C etc. but different disposition of atoms in space

name of group	formula	abbreviation
methyl	$-CH_3$	Me
ethyl	$-CH_2CH_3$	Et
propyl	$-CH_2CH_2CH_3$	Pr
butyl	$-CH_2CH_2CH_2CH_3$	Bu
phenyl	$-C_6H_5$	Ph
acyl	CH_3CO	Ac