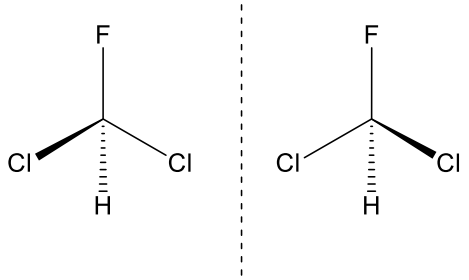
CHEM 261 Winter 2025 February 13, 2025

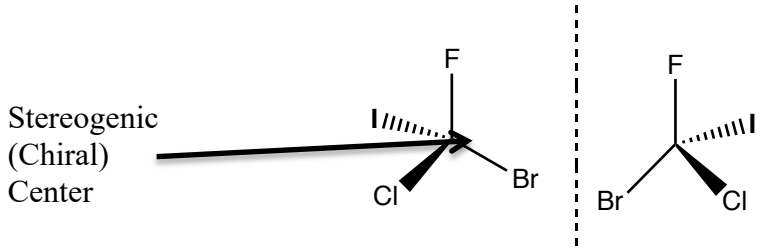
Introduction to Stereochemistry and Chirality (terminologies)

Chiral object or molecule: has a non-superimposable mirror image
Achiral object: not chiral, has a superimposable mirror image

Tetrahedral carbon with 4 different groups are said to be **CHIRAL** and are said to contain a **STEREOGENIC (CHIRAL) CENTER**



Achiral, identical – have a plane of symmetry



mirror

Non-superimposable

1850 - Louis Pasteur (1822-1895) separated the "right-handed" and "left-handed" forms of tartaric acid crystals (from wine)

1876 - J. van't Hoff and Le Bel proposed that differences are due to tetrahedral geometry of carbon
- Kolbe did not receive van't Hoff's idea very well

1901 - J. van't Hoff was the first recipient of the Nobel Prize in Chemistry

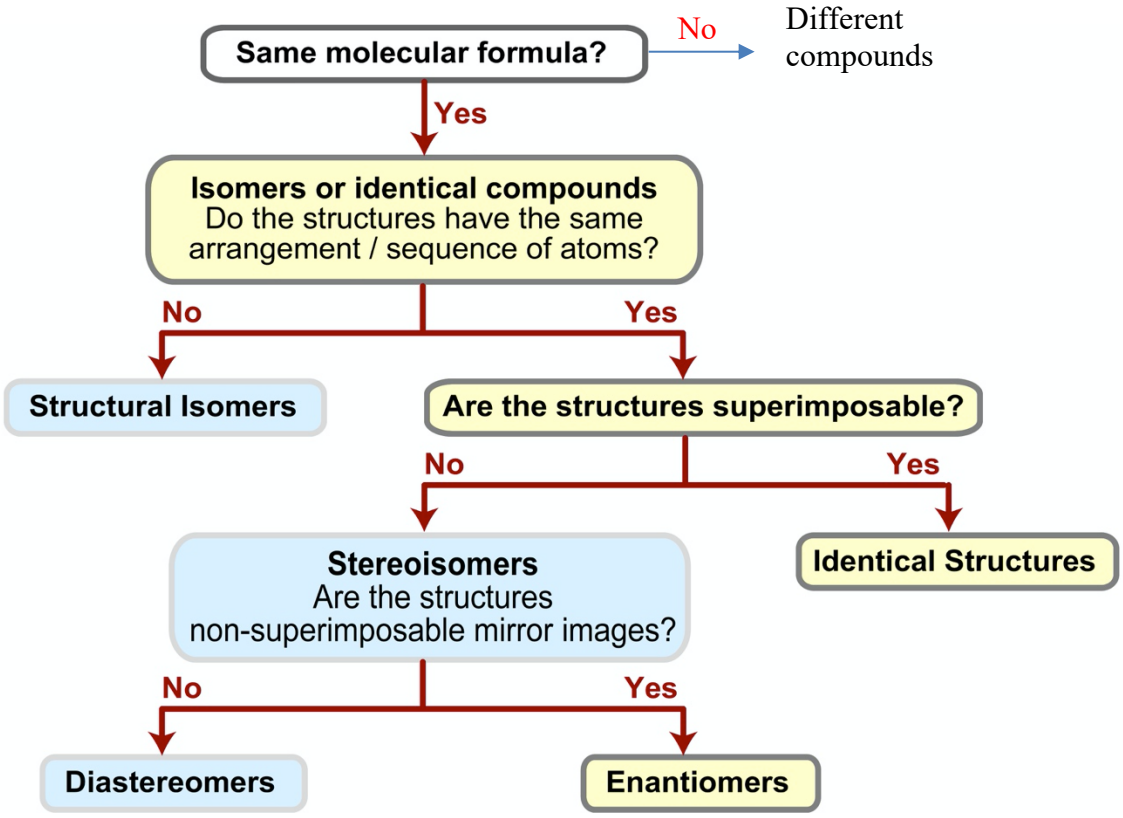
Resolution – separation of enantiomers

Enantiomers: molecules that are stereoisomers and are non-superimposable mirror images of each other. Opposite stereochemistry at every chiral center. Physical properties of enantiomers are the same, as far as they are measured in an achiral environment. A chiral agent of molecule is necessary to distinguish them.

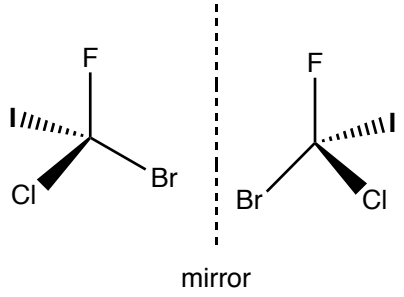
Diastereomers: all stereoisomers that are not enantiomers

Enantiomers	**Diastereomers**
Same physical properties (i.e., m.p, b.p, etc.)	Different chemical properties
Bend polarized light differently	
Hard to separate	Easier to separate
Mirror images	Not mirror images
Non-superimposable	Non-superimposable

How to Determine Relationships Among Structures



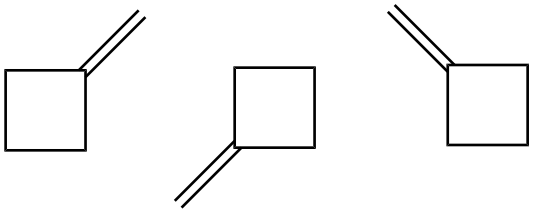
Example 1:



1) Same molecular formula? Yes
2) Same arrangement of atoms? Yes
3) Superimposable? No
4) Non-superimposable mirror images? Yes

NON-SUPERIMPOSABLE → Enantiomers

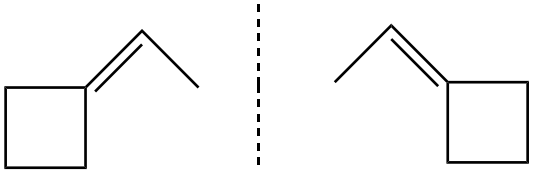
Example 2:



1. Same molecular formula? Yes
2. Same arrangement of atoms? Yes
3. Superimposable? Yes

Identical structures, superimposable, achiral

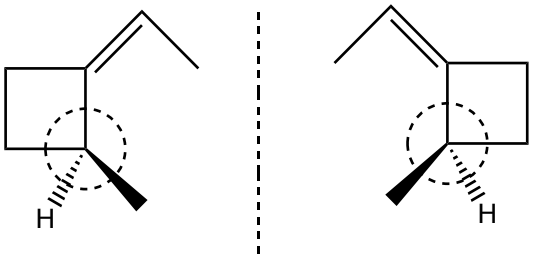
Example 3:



1. Same molecular formula? Yes
2. Same arrangement of atoms? Yes
3. Superimposable? Yes

- achiral
- no stereogenic center

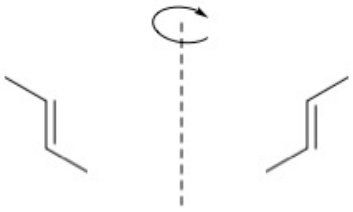
Same, identical compound



1. Same molecular formula? Yes
2. Same arrangement of atoms? Yes
3. Superimposable? No
4. Non-superimposable mirror images? Yes

- enantiomers
- dashed circle is stereogenic center carbon atom

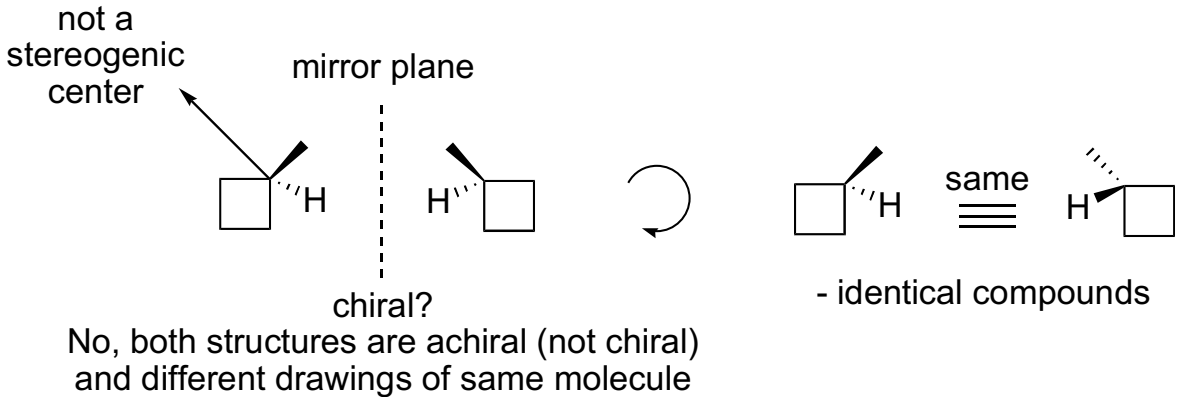
Example 4:



trans-2-butene is achiral

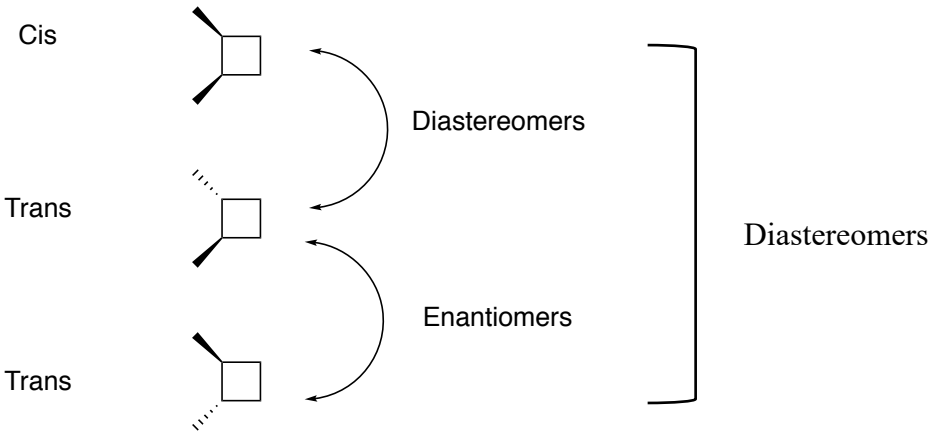
These two mirror images
are superimposable
as seen by a simple rotation

Examples of determining chirality within molecules



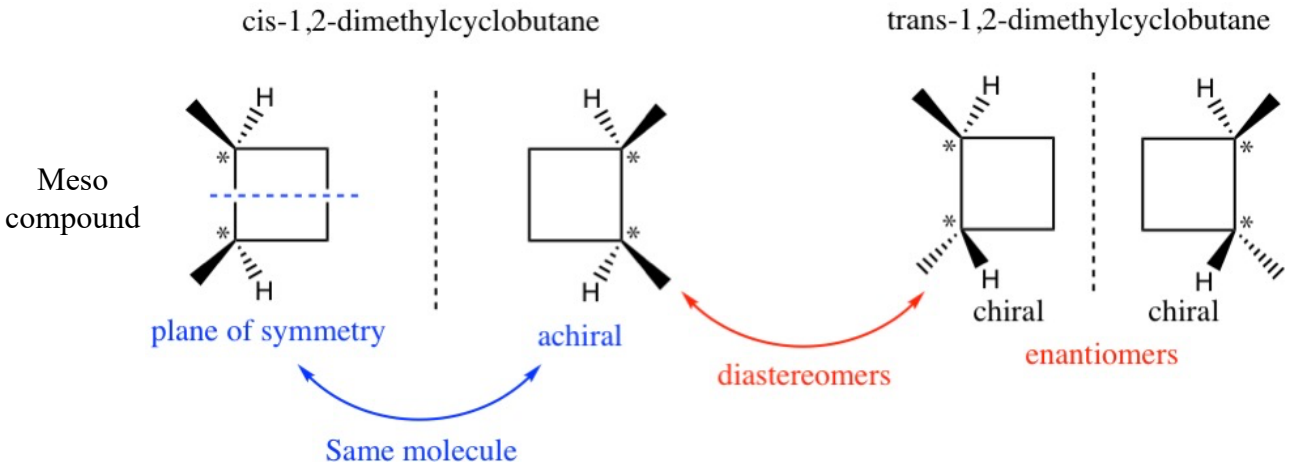
No, both structures are achiral (not chiral)
and different drawings of same molecule

Example:



Enantiomers have opposite stereochemistry at **every** stereocenter (chiral center)

Diastereomers are all stereoisomers that are not enantiomers



* *indicates a chiral center*

Diastereomers have different physical properties (e.g. mp, bp, etc), and can be separated. Stereogenic centers can exist in a molecule but if there is a plane of symmetry, it renders the whole molecule achiral.

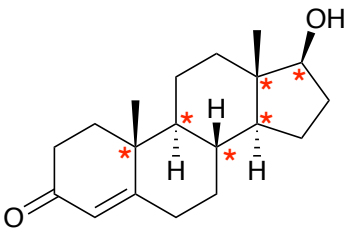
Note: a chiral center (or stereogenic center) exists if *4 different groups* are attached to the carbon in question

If there is plane of symmetry within a molecule, then the molecule is **achiral** (not chiral)

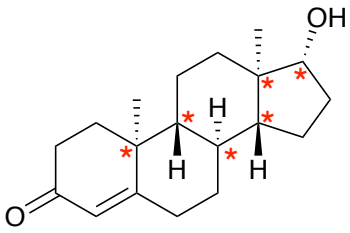
Meso compounds – molecules containing chiral (stereogenic) centers but has a plane of symmetry, therefore they are achiral

More Example:

Testosterone



* - indicates stereogenic centres

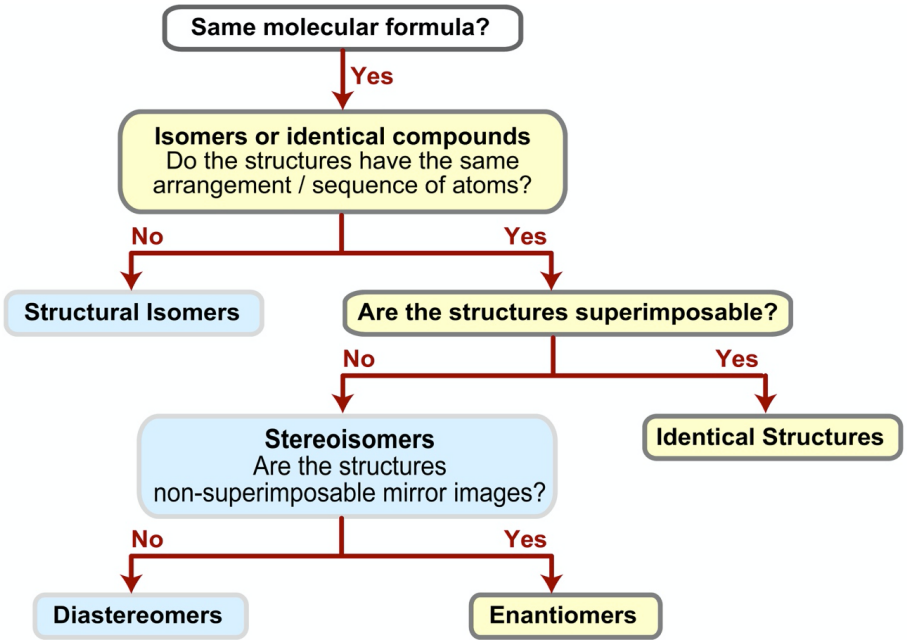


* - indicates stereogenic centres

If only some (not all) stereogenic centers are inverted, then a diastereomer of testosterone is produced

Number of Stereoisomers Calculation
Formula = 2^n, where n = number of stereogenic centres
Example: Testosterone has six stereogenic centres, n=6
$2^n = 2^6 = 64$ stereoisomers (1 is testosterone, 1 enantiomer of testosterone, 62 diastereomers)

Recall:



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Labelling Stereocentres

R/S Nomenclature:

R and S designation of stereoisomers

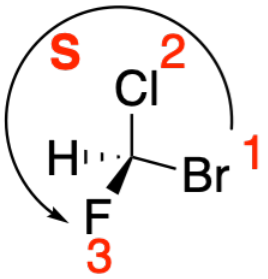
- R = Rectus (right-handed, clockwise)
- S = Sinister (left-handed, counterclockwise)

Labelling a stereogenic center as R or S:

- Identify all stereogenic centers (i.e. 4 different substituents)
- Look at atomic number of atoms attached to the stereogenic center
- Assign priority based on atomic number. If you cannot decide, go to the next set of atoms.
- Number from highest to lowest priority, then with the lowest priority group pointing back, count 1, 2, 3:
    - Clockwise → R configuration
    - Counterclockwise → S configuration

Each stereogenic center in a molecule is analyzed separately

Example:

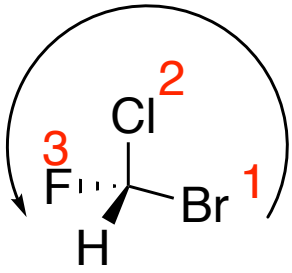


Place lowest priority to the back

1,2,3 --> clockwise = "R"
1,2,3 --> counterclockwise = "S"

Bromine has the highest atomic number (35), followed by chlorine (17), then fluorine (9), and lastly hydrogen (1).

What if the lowest priority group is pointing forward?



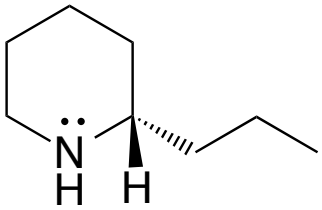
Counting 1, 2, 3 gives clockwise, BUT the smallest group is pointing forward, so the configuration is opposite of what you get if the smallest group is back

In this case, the configuration of the stereogenic center is "***R***"

Example

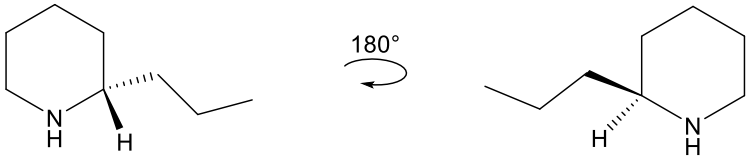
CONIINE, Poison hemlock, potent neurotoxin, killed Socrates

Stereogenic center (chiral centers or asymmetric centers) is circled in red

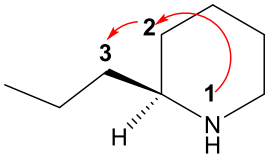


Assigning Configuration:

1) Move the lowest priority atom to the back (i.e., H)

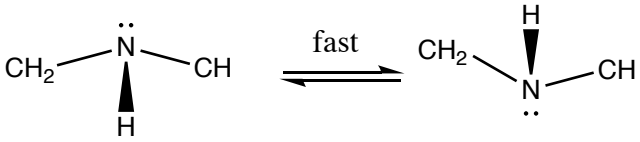


2) Assign priority to the remaining substituents. Then count 1,2,3.

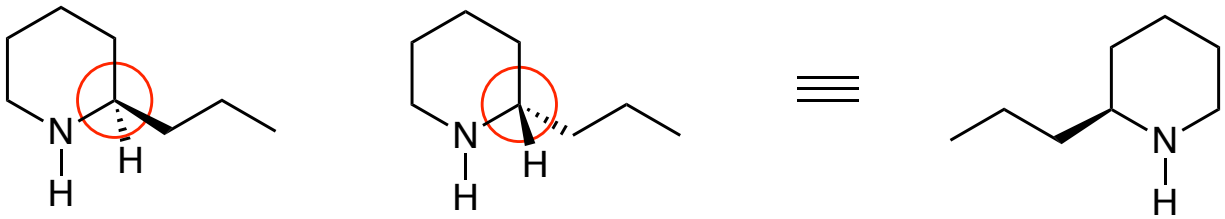


Counterclockwise **S enantiomer**

The nitrogen is nominally a stereogenic center since it has 4 different substituents, however it inverts rapidly, and so is not considered stereogenic. (unless all 3 groups are linked/held back by a ring)



To draw the enantiomer of coniine, invert the geometry at the stereocenter

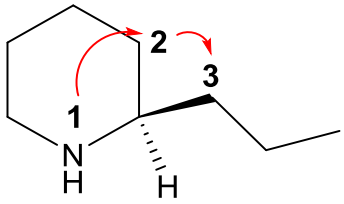


R - enantiomer of coniine
Non-toxic
invert EVERY stereocenter

S - enantiomer of coniine - highly toxic - natural

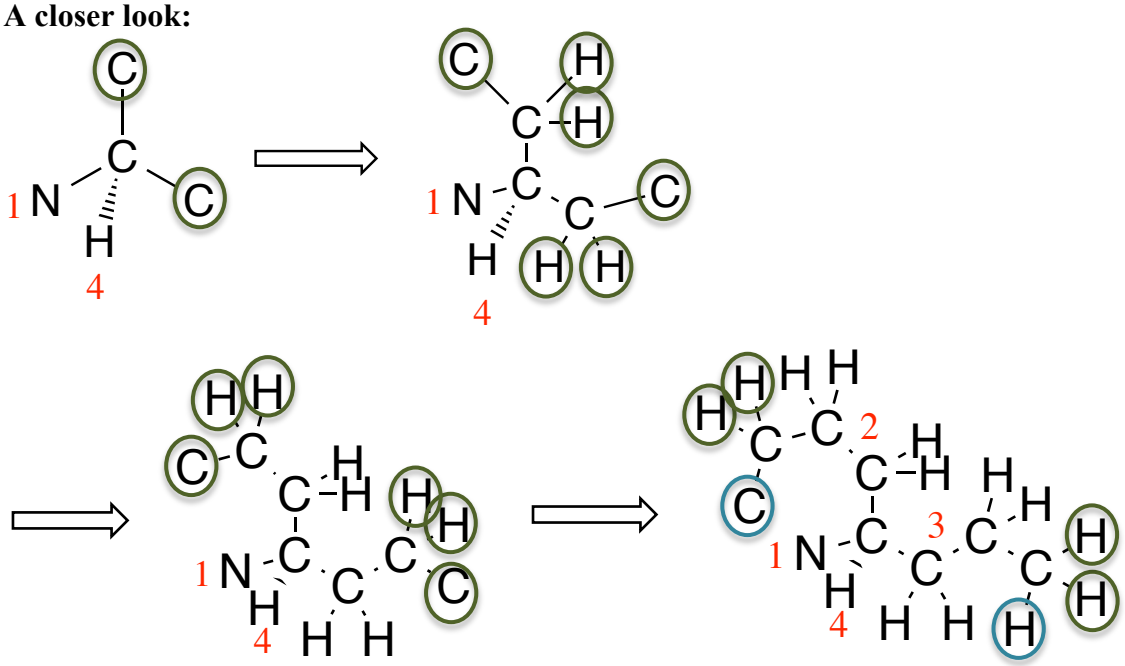
Example of determining priority of groups in enantiomer on natural coniine

- We can assign highest priority to the N and lowest to the H, but cannot immediately tell which carbon attached to the stereocenter is of higher/lower priority. When this is the case, we look at the next substituents in the chain.



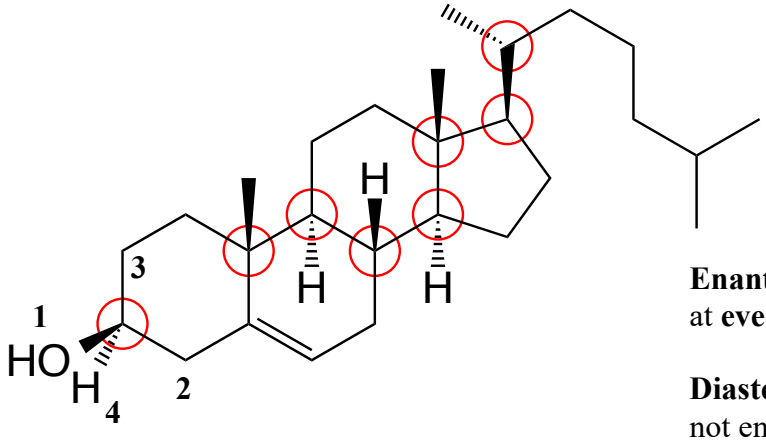
Clockwise **R enantiomer**

A closer look:



- We cannot tell at the second attached carbon, so we move on to the third.
- We still cannot tell at the third, so we move on to the fourth.
- At the fourth carbon we can see a difference. The carbon that is part of the propyl group ends in a CH_3 so it is bonded to three H, and the other carbon is bonded to two H and one C. The propyl group gets lower priority (3) and the other group gets higher priority (2).
- Counting 1,2,3 → clockwise is *R*. This is the *R* enantiomer.

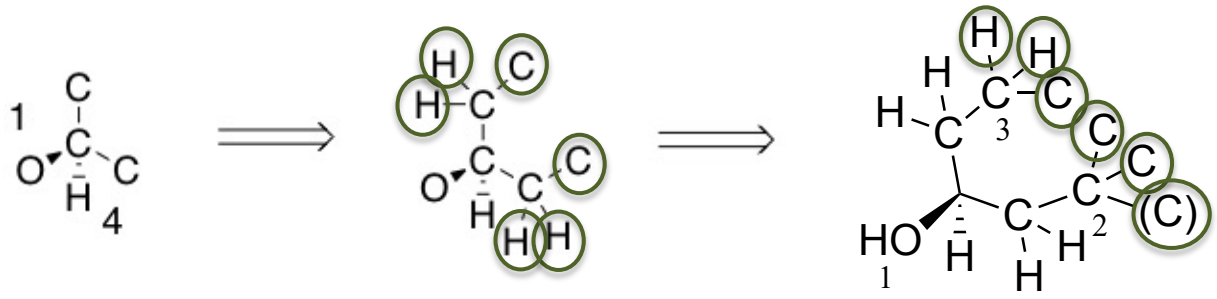
Cholesterol - A steroid with 8 stereogenic centers (red circles)



Enantiomers have opposite stereochemistry at **every** stereocenter (chiral center)

Diastereomers are all stereoisomers that are not enantiomers

Stereochemistry of carbon bearing the hydroxyl is **S**



Carbon in brackets represents the carbon-carbon double bond.

4

Stereoisomer calculation:
If only some (not all) stereogenic centers are inverted, then a diastereomer of cholesterol is produced.

8 stereocenters identified in cholesterol:

2^n = number of stereoisomers, where n = number of stereogenic centers

$2^n = 2^8 = 256$ stereoisomers, which are divided into three kinds below:

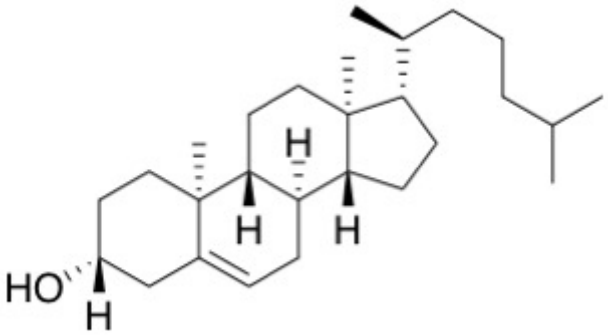
1 Cholesterol (the bioactive natural product)

1 enantiomer of cholesterol

254 are diastereomers of cholesterol

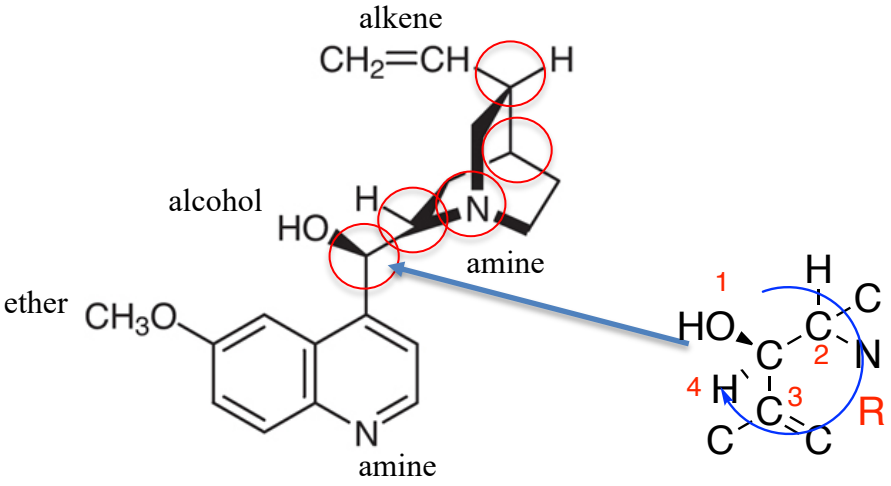
Enantiomer of cholesterol:

To make the enantiomer of cholesterol, invert every stereogenic center



Quinine:

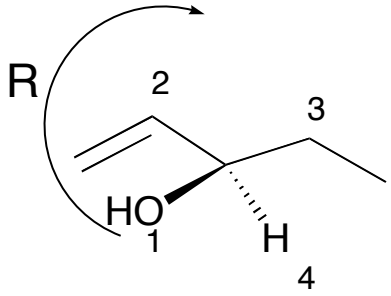
- An anti-malarial agent found in cinchona trees in South America
- Was brought to Spain by Jesuit missionaries in 1632 but was used by native populations long before
- Has 5 chiral centers (labeled in red)
- Here nitrogen is all tied back and **is** a stereogenic center, but typically it is not
- $2^5 = 32$ stereoisomers
    - 1 is quinine (itself)
    - 1 is the enantiomer
    - 30 are diastereomers



C attached to N will gain the 2nd priority because N has higher atomic number

Stereogenic (Chiral) Centres:

Example: 3-hydroxy-pent-1-ene



Carbon double bounded to another carbon is equivalent to a carbon bound to two carbons when considering priority

Example: