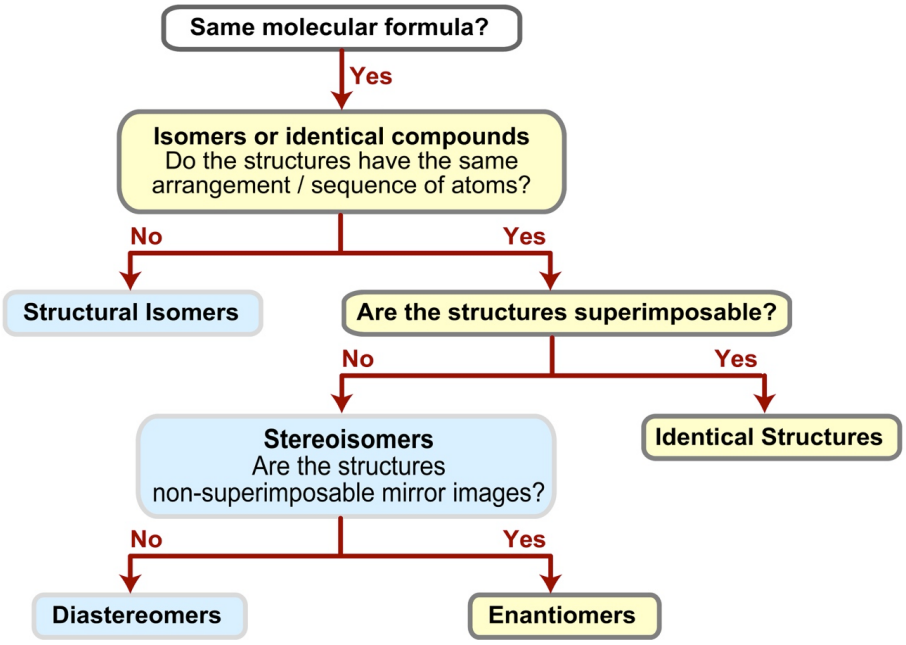
Recall:



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

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.

Labelling Stereocentres

R/S Nomenclature:

R and S designation of stereoisomers

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

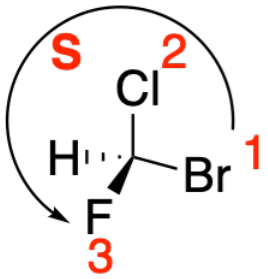
Labelling a stereogenic center as R or S:

- 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:

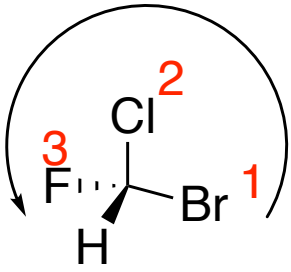


Place lowest priority to the back

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?



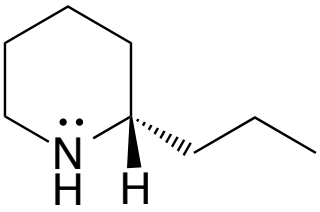
Counting 1, 2, 3 gives clockwise, BUT the smallest group is pointing forward, so the configuration is opposite of what you get if the smallest group is back

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

Example

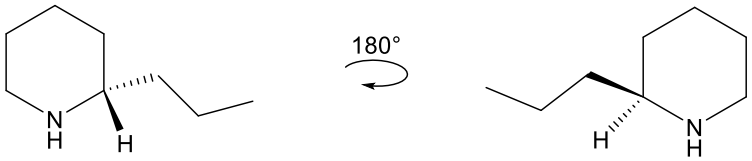
CONIINE, Poison hemlock, potent neurotoxin, killed Socrates

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

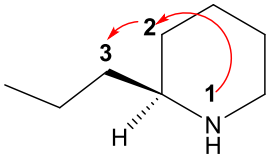


Assigning Configuration:

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

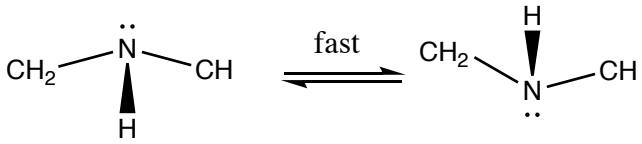


2) Assign priority to the remaining substituents. Then count 1,2,3.

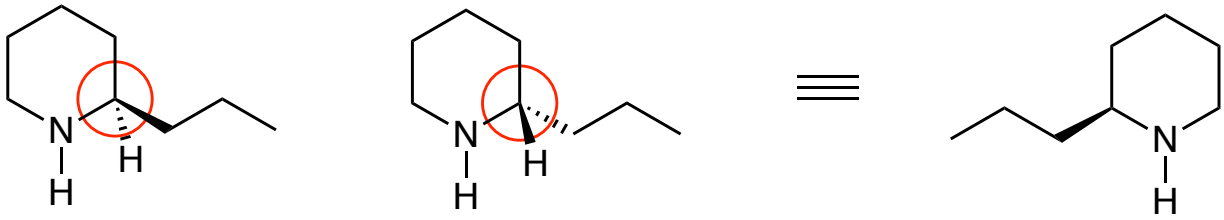


Counterclockwise **S enantiomer**

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

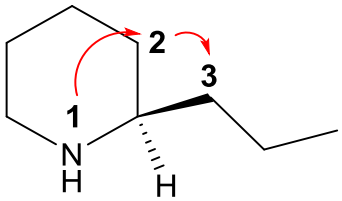


R - enantiomer of coniine
Non-toxic
invert EVERY stereocenter

S - enantiomer of coniine - highly toxic - natural

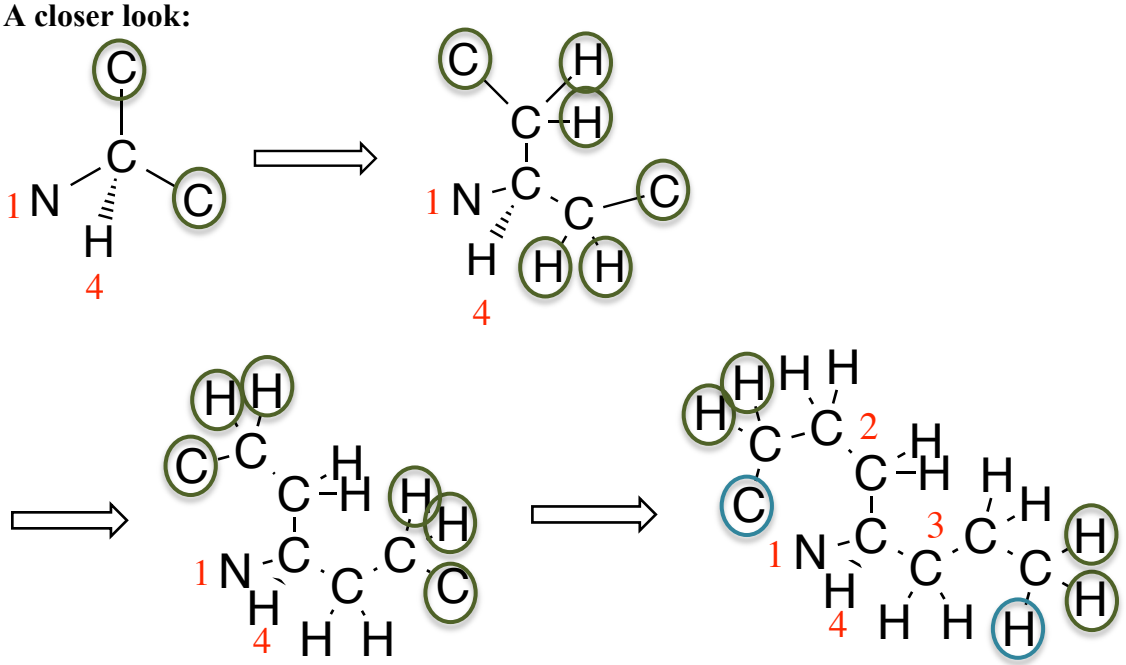
Example of determining priority of groups in enantiomer on natural coniine

- 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.



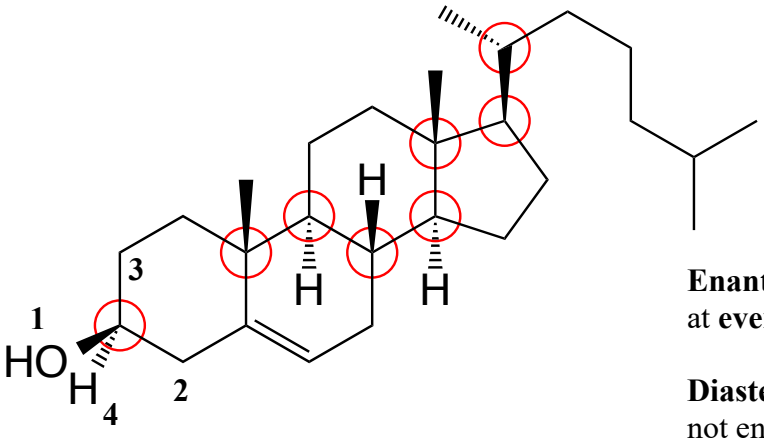
Clockwise R enantiomer

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.

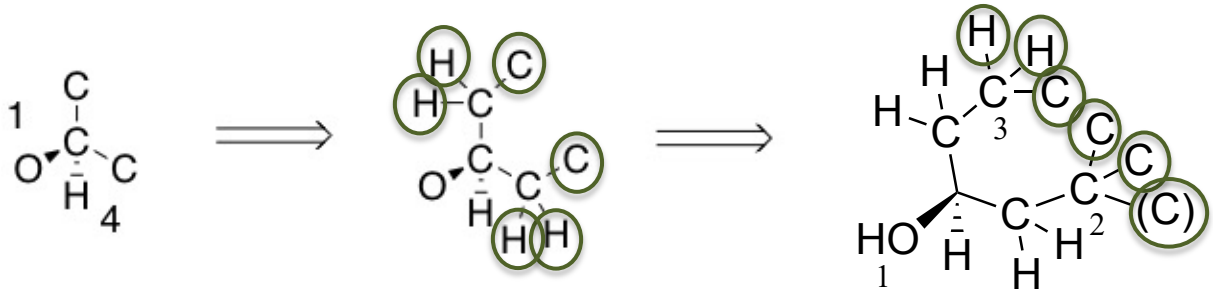
Cholesterol - A steroid with 8 stereogenic centers (red circles)



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:

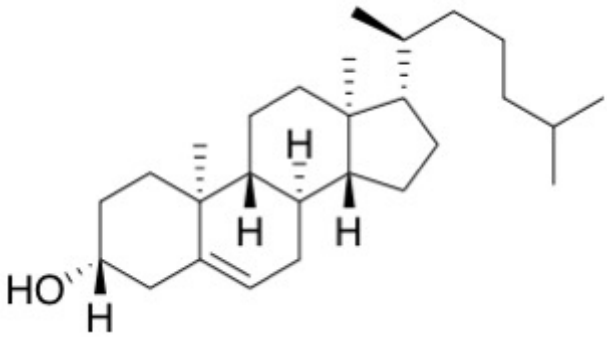
1 Cholesterol (the bioactive natural product)

1 enantiomer of cholesterol

254 are diastereomers of cholesterol

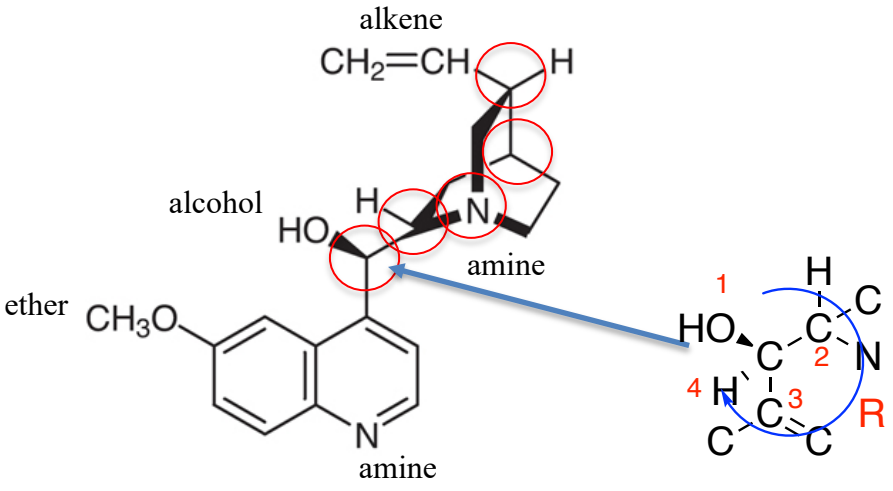
Enantiomer of cholesterol:

To make the enantiomer of cholesterol, invert every stereogenic center



Quinine:

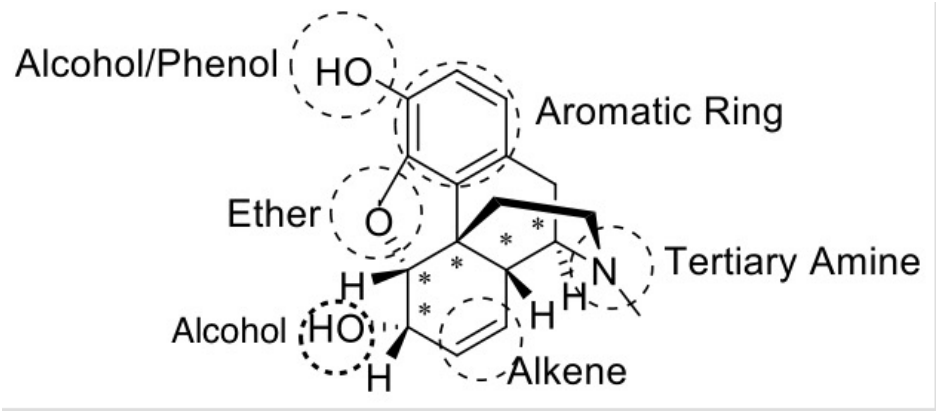
- An anti-malarial agent found in cinchona trees in South America
- Was brought to Spain by Jesuit missionaries in 1632 but was used by native populations long before
- Has 5 chiral centers (labeled in red)
- Here nitrogen is all tied back and **is** a stereogenic center, but typically it is not
- $2^5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

Morphine:

- Is an alkaloid, meaning it contains nitrogen, can be isolated from a plant (or bacteria) and is considered a natural product.
- From Morpheus, Greek god of sleep
- Opium: Sap from the seed pod of opium poppy (*Papaver somniferum*)
    - (poppy sleep-carrying)
- ~10% of opium is morphine
- Morphine is used as an analgesic
- Heroin (diacetylmorphine) is even more potent (and more addictive)



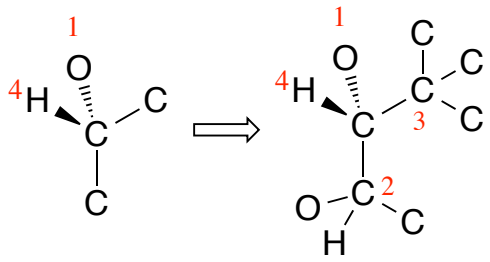
- 5 stereogenic centers in morphine (represented by *) – Nitrogen NOT a stereogenic centre because the methyl group can move up or down
    - $2^5 = 32$ stereoisomers possible, where:
    - 1 morphine (itself)
    - 1 enantiomer
    - 30 diastereoisomers

Mithridates VI (135-63 BC)

- Poisoned slaves and attempted to cure them using mixtures of different plants
- Favorite mixture was Theriac, which contained morphine

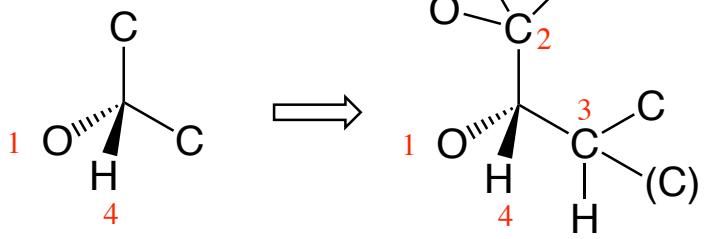
Examples of Configuration in Stereocenters of Morphine

Configuration at the **ether** stereocenter:

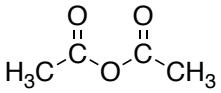


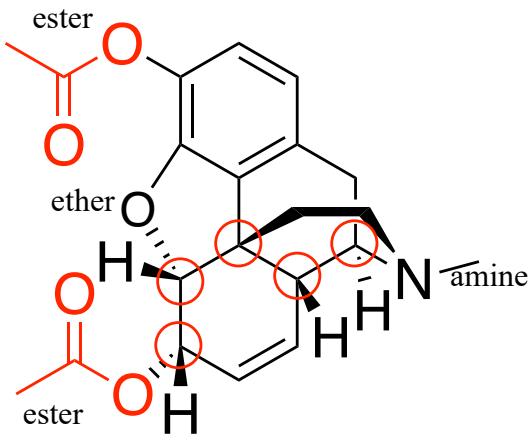
- Cannot assign 2, 3 at first try
- At the second atoms in the chain, there is a difference. The alcohol carbon is attached to one oxygen, one carbon, and one hydrogen. It has a higher priority than the other carbon which is attached to three carbons.
- Count 1, 2, 3: Counterclockwise
- This center is *R* and not *S* because the lowest priority group (the hydrogen) is pointing toward the front, not to the back.

Configuration at the **alcohol** stereocenter:



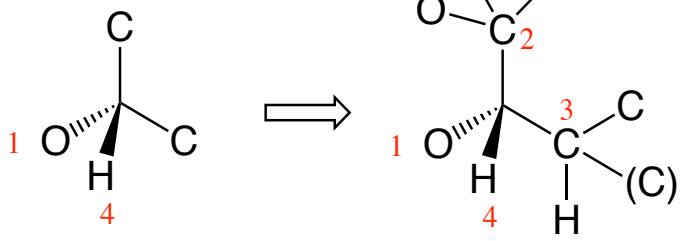
- Cannot assign 2, 3 at first try
- At the second atoms in the chain, the eth carbon is attached to one oxygen, one carl and one hydrogen. It has a higher priority the alkene carbon which is attached to tw carbons and one hydrogen
- Count 1, 2, 3: Clockwise
- This center is *S* and not *R* because the lo priority group (the hydrogen) is pointing toward the front, not the back

If you substitute CH_3COO for the two alcohol residues in morphine by reacting with acetic anhydride (), you then create **HEROIN.**



1000x stronger as analgesic and more addictive than morphine

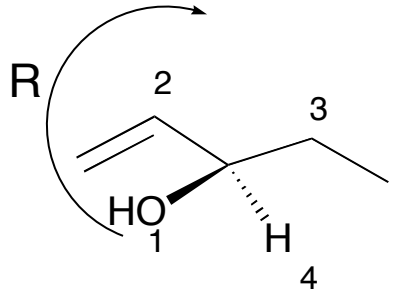
Configuration at the **C** attached to ester stereocenter:



- Cannot assign 2, 3 at first try
- At the second atoms in the chain, the eth carbon is attached to one oxygen, one carl and one hydrogen. It has a higher priority the alkene carbon which is attached to tw carbons and one hydrogen
- Count 1, 2, 3: Clockwise
- This center is *S* and not *R* because the lo priority group (the hydrogen) is pointing toward the front, not the back

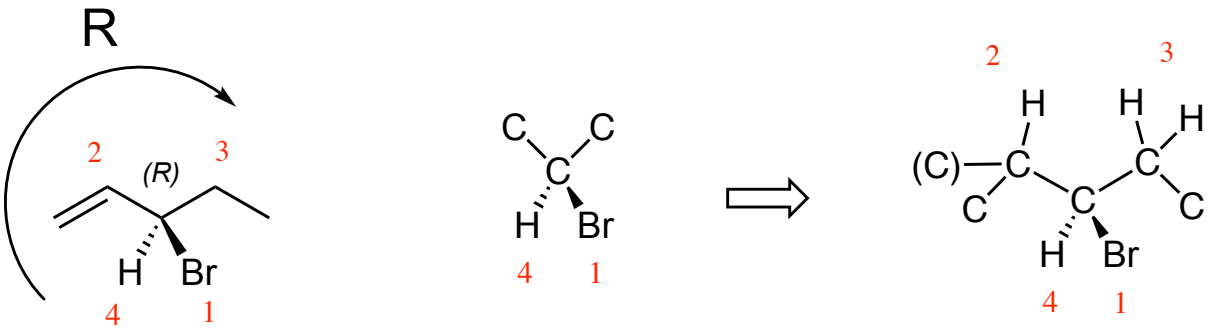
Chiral Centers:

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:



Example:

Achiral

meso compound - has stereogenic centers, but has a mirror plane of symmetry, so is achiral