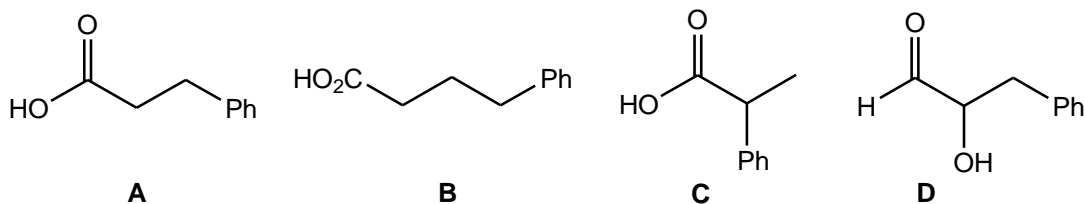

Isomerism and stereochemistry

Answers to worked examples

WE 18.1 Structural isomers (on p. 818 in *Chemistry*³)

For the following four compounds, **A–D**, identify which are chain isomers, which are position isomers and which are functional group isomers. (Ph stands for phenyl, C₆H₅–.)



Strategy

Determine the molecular formulae of these molecules:

1. To be structural isomers, these molecules must have the same molecular formulae.
2. To be position isomers, these molecules must have the same functional groups but at different positions.
3. To be functional group isomers, these molecules must have different functional groups.

Solution

1. Molecules **A**, **C** and **D** are structural isomers as they have the same molecular formulae (C₉H₁₀O₂). Molecule **B** is not a structural isomer since it has a different molecular formula (C₁₀H₁₂O₂).
2. Molecules **A** and **C** are positional isomers as they both contain the same functional groups [a carboxylic acid (-CO₂H) group and a phenyl (-Ph) group] but at different positions.

3. Molecule **D** is a functional group isomer of both molecules **A** and **B**, as it contains different functional groups (an alcohol and an aldehyde in **D** versus a carboxylic acid group in both **A** and **B**).

Answer

1. **A**, **C** and **D** are structural isomers – all have the molecular formula, C₉H₁₀O₂. **A** and **C** are position isomers (the Ph group is at different positions). **C** and **D** (and **A** and **D**) are functional group isomers (**C** is a carboxylic acid, **D** is an α -hydroxy-aldehyde).

WE 18.2 Using Newman projections (on p. 825 in *Chemistry*³)

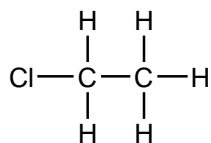
Use Newman projections to draw the eclipsed and staggered conformations of chloroethane. Explain which conformation you would expect to have the higher energy.

Strategy

1. Draw out the skeletal structure of chloroethane.
2. Draw out the staggered Newman projection of chloroethane; this is where all the C-H bonds and C-Cl bond are staggered.
3. Draw out the eclipsing Newman projection of chloroethane; this is where all the C-H bonds and the C-Cl bond are eclipsed.
4. Determine which Newman projection is more stable.

Solution

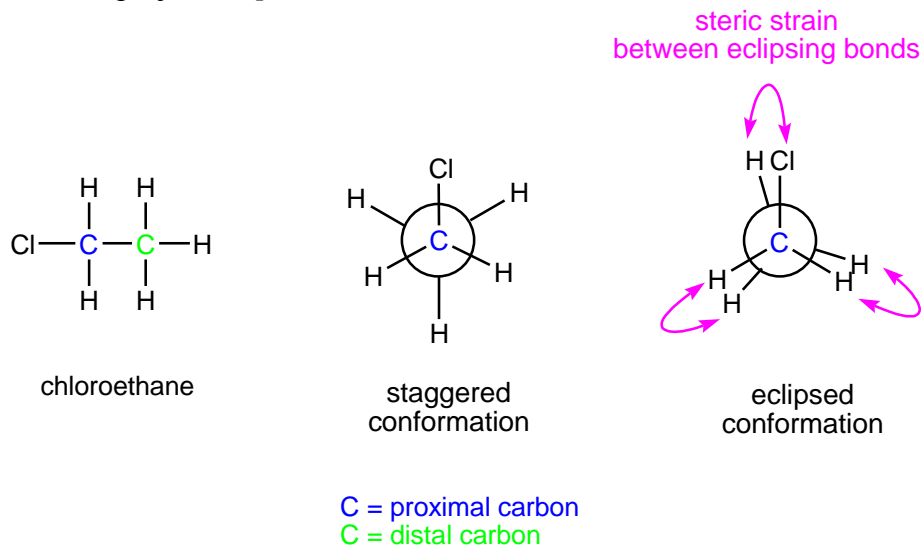
1. The condensed structure of chloroethane is:



chloroethane

2. The staggered Newman projection is where the three *distal* C-H bonds (on the back carbon atom) are **staggered** (by 120 degrees) with the three *proximal* bonds (two C-H bonds and the one C-Cl bond) on the front carbon atom. [Note: this *distal* carbon atom is not visible in this Newman projection.]

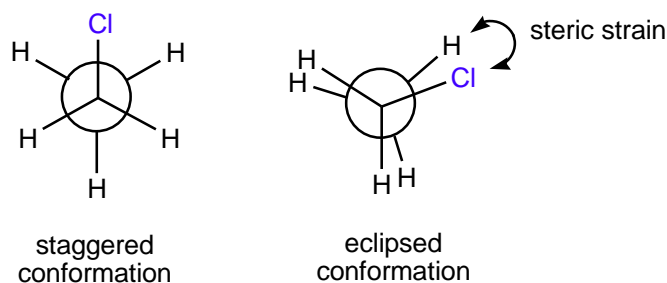
3. The eclipsing Newman projection is where the three *distal* C-H bonds (on the back carbon atom) are **eclipsed** with the three *proximal* bonds (two C-H bonds and the one C-Cl bond) on the front carbon atom. [Note: this *distal* carbon atom is not visible in this Newman projection.]



4. The staggered projection is more stable than the eclipsed projection as there is significantly less steric congestion between the *distal* and *proximal* bonds. Staggered projections are in energy *minima* and eclipsing projections are in energy *maxima*. Stable conformers are generally those which have their large groups staggered and positioned furthest away from each other.

Answer

The eclipsed conformation is higher in energy than the staggered conformation because there is steric strain between the chlorine atom and a neighbouring hydrogen atom, and two further H-, H- eclipsions.



WE 18.3 E/Z nomenclature (on p. 836 in *Chemistry*³)

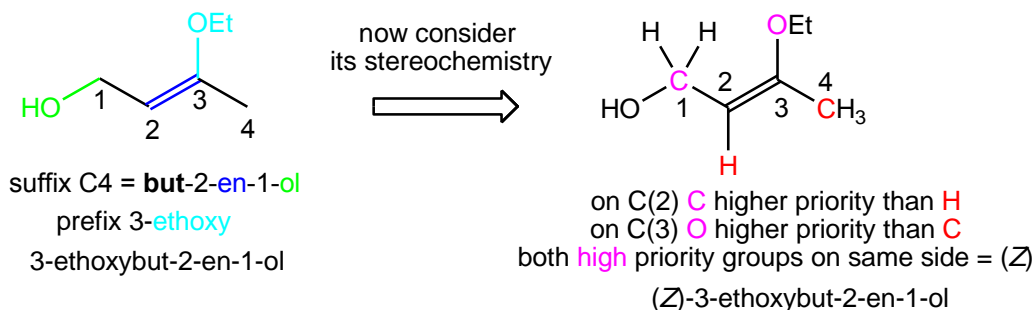
Draw a skeletal structure for (Z)-3-ethoxybut-2-en-1-ol.

Strategy

1. Draw out the longest continuous carbon chain as a *zig-zag* structure and remember to number the carbon atoms.
2. Draw out its double bond at its designated position.
3. A (*Z*)-isomer is where both high priority substituents are on the *same side* of the double bond, and an (*E*)-isomer is where the high priority substituents are on *opposite sides* of the double bond. The priorities are determined using the Cahn-Ingold-Prelog rules (See p. 839 in *Chemistry*³).
4. Identify the substituents from their suffix, and place them along this carbon chain at their designated positions.
5. Check that this structure is correct!

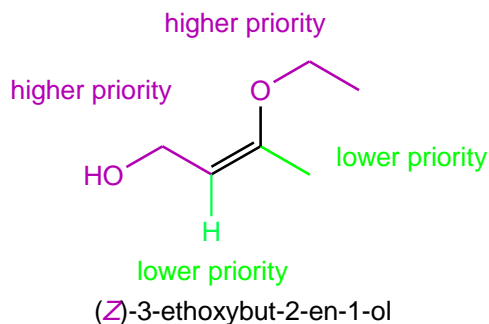
Solution

1. The longest number of continuous carbon atoms is four [(*Z*)-3-ethoxy**but**-2-en-1-ol]. Draw out this carbon chain in a *zig-zag* arrangement.
2. The suffix of this molecule is -ol [(*Z*)-3-ethoxybut-2-en-1-**ol**]; it is therefore an alcohol. This molecule also contains a double bond [(*Z*)-3-ethoxybut-2-**en**-1-ol], and this is positioned at carbon 2 (\rightarrow 3).
3. The double bond has (*Z*)-stereochemistry.
4. There is an ethoxy (-OEt) group at carbon-3.



5. Check that the structure is correct by re-naming it! This structure is (Z)-3-ethoxybut-2-en-1-ol.

Answer



WE 18.4 Enantiomers and enantiomeric excess (on p. 844 in *Chemistry*³)

What is the observed specific optical rotation of a mixture containing 25% (–)-nicotine and 75% (+)-nicotine?

Strategy

1. Work out which is the major enantiomer.
2. Work out the % optical purity of this sample.
3. Work out its relative composition (divide by 100 to give a ratio out of 1).
4. Multiply the relative composition by its known specific rotation (for the major enantiomer). This will ensure that you have the correct sign. (+)-Nicotine has a specific rotation of +166.

Solution

1. The major enantiomer is (+)-nicotine.
2. The % optical purity of this **enriched** (+)-nicotine sample is 75% - 25% = 50%.
3. The relative composition of this sample is 50 ÷ 100 = 0.5
4. The specific rotation of this optically enriched sample of (+)-nicotine is 0.5 × +166 = +83.

Answer

$$\text{enantiomeric excess, ee (\%)} = 75\% - 25\% = 50\%$$

$$50 = \frac{\text{observed } [\alpha]_{\text{D}}}{[\alpha]_{\text{D}} \text{ of pure enantiomer}} \times 100 = \frac{\text{observed } [\alpha]_{\text{D}}}{+166} \times 100$$

$$\text{observed } [\alpha]_{\text{D}} = \frac{50 \times 166}{100} = +83$$

WE 18.5 *R/S* nomenclature (on p. 846 in *Chemistry*³)

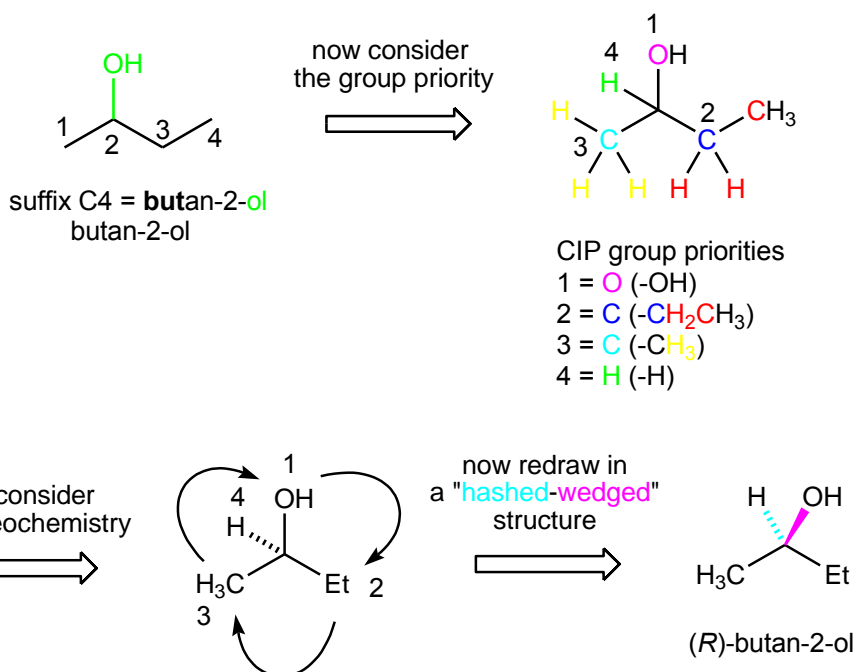
Draw a hashed-wedged line structure of (*R*)-butan-2-ol.

Strategy

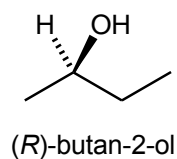
1. Draw out the longest continuous carbon chain as a *zig-zag* structure and remember to number the carbon atoms.
2. Identify any substituents from their suffix, and place them along this carbon chain at their designated positions.
3. Draw out the stereochemistry. This can be worked out using the Cahn-Ingold-Prelog rules (See p. 839 in *Chemistry*³).
4. Check that this structure is correct!
5. Draw out the hashed-wedged line structure of this molecule.

Solution

1. The longest number of continuous carbon atoms is four [(*R*)-**butan-2-ol**]. Draw out this carbon chain in a *zig-zag* arrangement.
2. The suffix of this molecule is -ol [(*R*)-**butan-2-ol**]; it is therefore an alcohol.
3. The chiral centre at carbon-2- has (*R*)-stereochemistry. A (*R*)-configuration is where the three highest priority groups (1, 2 and 3) on a particular conformation can be rotated clockwise (1→2→3), whilst the lowest priority group, 4, is at the rear of this conformer.

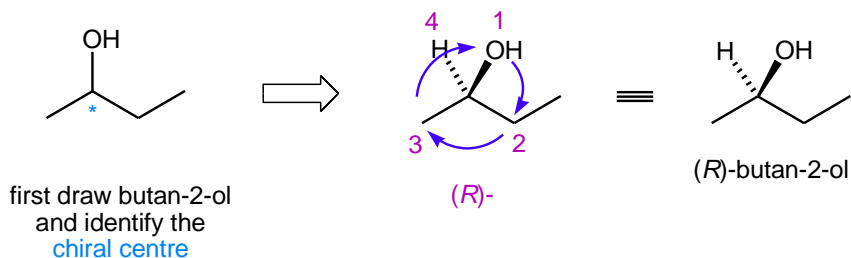


- Check that the structure is correct by re-naming it! This structure is (*Z*)-3-ethoxybut-2-en-1-ol.
- The hashed-wedged line structure of this molecule is:



Answer

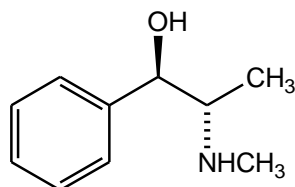
Draw in hashed-wedged notation and then rank the groups (1→4) directly attached to the chiral centre and apply the CIP rule:



WE 18.6 Enantiomers and diastereomers (on p. 853 in *Chemistry*³)

Ephedrine is a naturally occurring compound that is used to treat asthma.

- (a) Assign a configuration to each of the chiral centres in ephedrine.



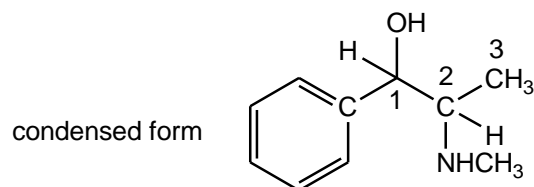
ephedrine

Strategy

1. Identify the two chiral centres in ephedrine, and label them.
2. Redraw this molecule in its condensed form.
3. Work out the configuration for both chiral centres. It is easier to consider one centre at a time. The (*R/S*)-stereochemistry is assigned using the Cahn-Ingold-Prelog rules (See p. 839 in *Chemistry*³).
4. Check that your assignments are correct.

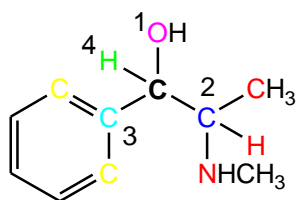
Solution

1. The longest continuous carbon chain (of propan-1-ol) has been numbered (1, 2 and 3) for ease. There are two chiral centres at carbons-1 and -2.
2. The condensed form of this molecule is:

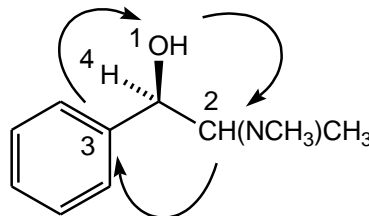
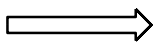


3. The configurations at carbons-1 and -2 are (*R*)- and (*S*)-, respectively.

Group priorities at carbon-1



assign
configuration



clockwise rotation = (*R*)-

CIP group priorities

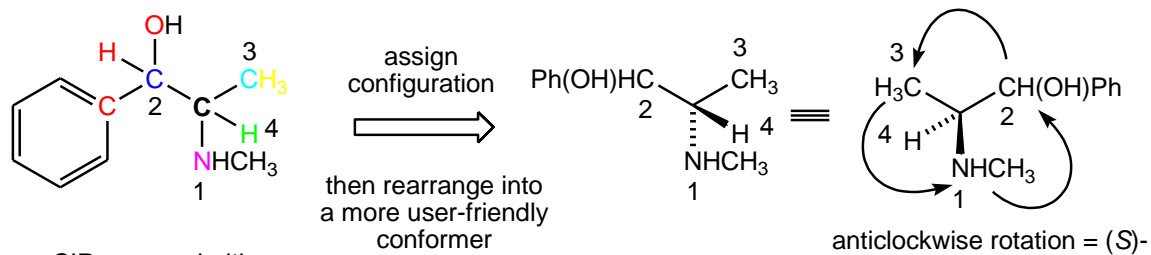
1 = ○ (-OH)

2 = ○ (-CH(NHCH₃)CH₃)

3 = ○ (-C-C(=O); Ph)

4 = ○ (-H)

Group priorities at carbon-2



CIP group priorities

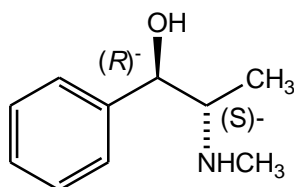
1 = N (-NHCH₃)

2 = C (-CH(OH)Ph)

3 = C (-CH₃)

4 = H (-H)

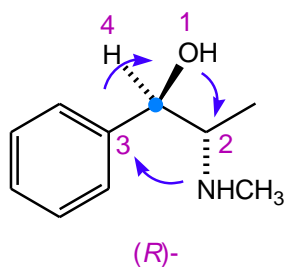
4. Check that the structure is correct by naming it! This structure is (1*R*,2*S*)-2-(methylamino)-1-phenylpropan-1-ol (ephedrine).



(1*R*,2*S*)-2-(methylamino)-1-phenylpropan-1-ol
ephedrine

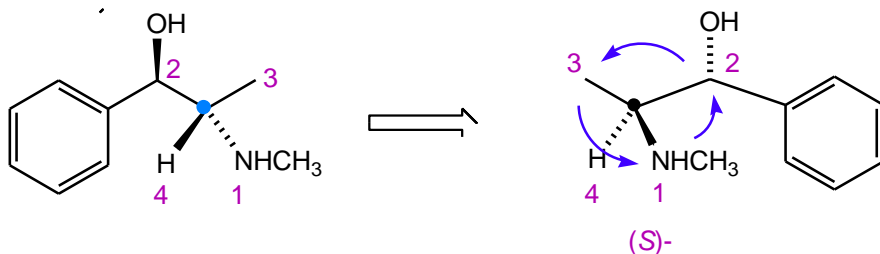
Answer

Chiral centre on the left-hand side

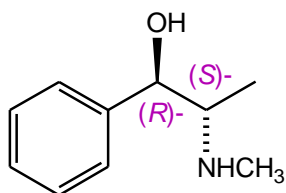


Chiral centre on the right-hand side

Rotate so that the group of lowest priority is pointing away from you



The configurations are:



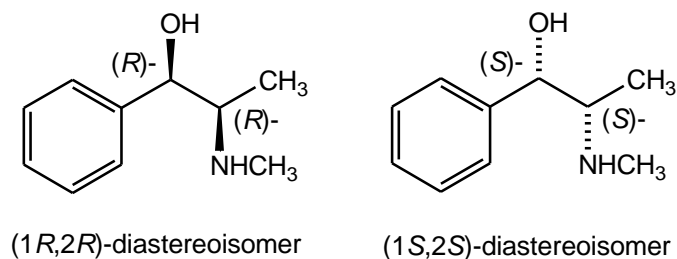
(b) Draw the structure of a diastereoisomer of ephedrine.

Strategy

1. Draw out a non-superimposable non-mirror images of (1*R*,2*S*)-ephedrine.

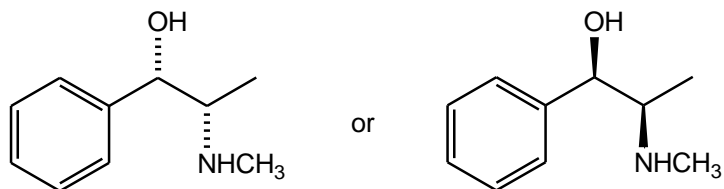
Solution

1. Two non-superimposable non-mirror images (diastereoisomers) of ephedrine can be drawn. These are the (1*R*,2*R*)- and (1*S*,2*S*)-diastereoisomers. The remaining stereoisomer (1*S*,2*R*)- is the enantiomer of (1*R*,2*S*)-ephedrine.



Answers

diastereomers of ephedrine



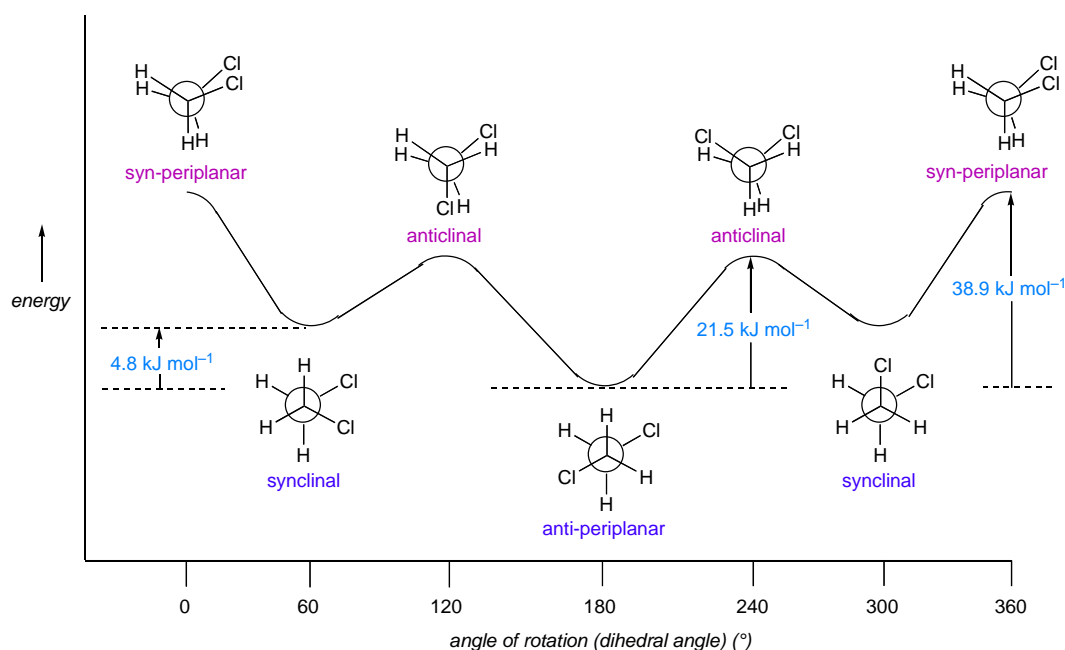
Answers to end of chapter questions (on p. 858 in *Chemistry*³)

1. The synclinal conformation of 1,2-dichloroethane is 4.8 kJ mol^{-1} higher in energy than the anti-periplanar conformation. The two energy barriers for rotation about the C–C bond in 1,2-dichloroethane are 21.5 kJ mol^{-1} and 38.9 kJ mol^{-1} higher than the energy of the anti-periplanar conformation

- (a) Sketch a graph of energy versus angle of rotation about the C–C bond (dihedral angle) for 1,2-dichloroethane.

Strategy

1. Draw out the most stable Newman projection of 1,2-dichloroethane.
2. Rotate clockwise the proximal (front) carbon atom of this projection (from part 1) by 60° and consider its relative energy.
3. Repeat this 60° clockwise rotation until a full revolution (180°) has been achieved.
4. Sketch the change in energy versus the *relative* angle of rotation. For ease, set the most stable projection as having 180° ; this is its dihedral angle.
5. Label each anti-periplanar, anticlinal, syn-periplanar and synclinal projections.

Solution

(b) What conformation of 1,2-dichloroethane has the highest energy?

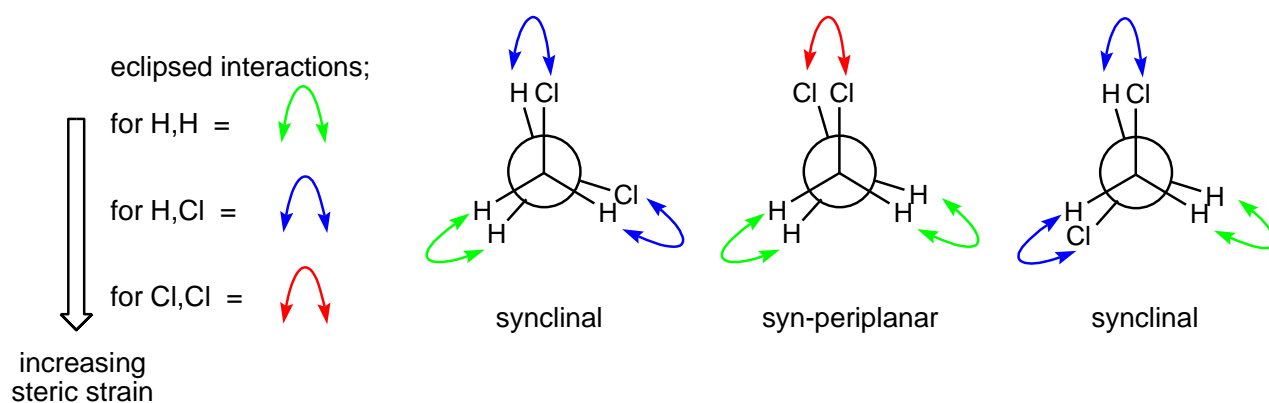
Strategy

Eclipsed conformers are higher in energy than staggered conformers. Draw out the three possible eclipsed projections of 1,2-dichloroethane, and consider which projection has the greatest eclipsing interactions.

Solution

Of the three eclipsing interactions, there are two identical synclinal projections and a single syn-periplanar projection. These synclinal projections contain two C-Cl/C-H and one C-H/C-H eclipsing interactions. The remaining syn-periplanar projection contains two C-H/C-H and one C-Cl/C-Cl eclipsing interactions; this C-Cl/C-Cl eclipsing interaction is by far the most unfavoured. Therefore, the syn-periplanar conformer of 1,2-dichloroethane has the highest energy.

Eclipsing interactions for 1,2-dichloroethane



Answer

The syn-periplanar conformation of 1,2-dichloroethane has the highest energy.

2. The following questions relate to *meso*-butane-2,3-diol.

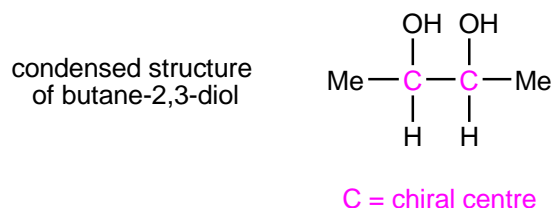
(a) Draw sawhorse and Newman projections of the syn-periplanar conformation of *meso*-butane-2,3-diol.

Strategy

1. Draw the condensed structure of butane-2,3-diol and remember to label its chiral centres.
2. It will be easier to first draw out the Sawhorse projection of *meso*-butane-2,3-diol as this is an eclipsing projection. It is worthy of note, for a molecule to be *meso*-, it must have at least two chiral centres and contain either a plane or point of symmetry. If you can orient your conformer so there is an internal mirror plane, this will automatically give the required syn-periplanar conformer.
3. Draw out the Newman projection of *meso*-butane-2,3-diol. It is worth remembering that a syn-periplanar conformer is an eclipsing conformer, where the same groups on both the proximal and distal carbon atoms (of its Newman projection) are in a *syn*-and eclipsing arrangement.

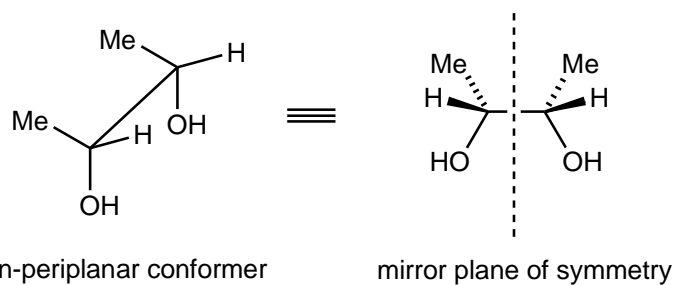
Solution

1. The condensed structure of butane-2,3-diol and the chiral centres are shown below:



2. The sawhorse projection of *meso*-butane-2,3-diol is shown below. If drawn correctly, all three different groups (OH, Me and H) will be syn-periplanar.

sawhorse projection of *meso*-butane-2,3-diol

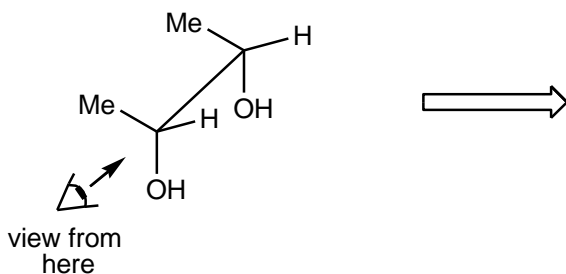


3. The syn-periplanar Newman projection can be drawn by looking down the central C(2)-C(3) bond.

Sawhorse projection of *meso*-butane-2,3-diol

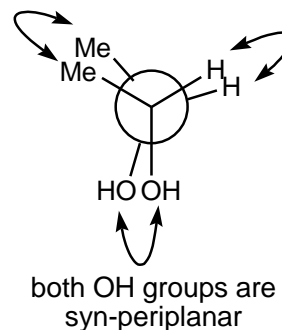
Newman projection of *meso*-butane-2,3-diol

syn-periplanar conformer

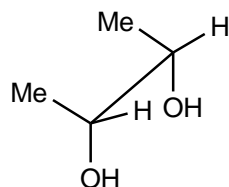


both Me groups are syn-periplanar

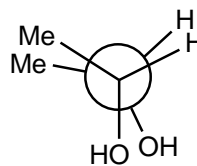
both H atoms are syn-periplanar



Answer



Sawhorse projection



Newman projection

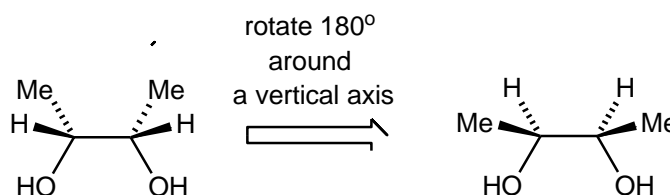
(b) Assign (*R*)- or (*S*)-configuration to each of the chiral centres in *meso*-butane-2,3-diol.

Strategy

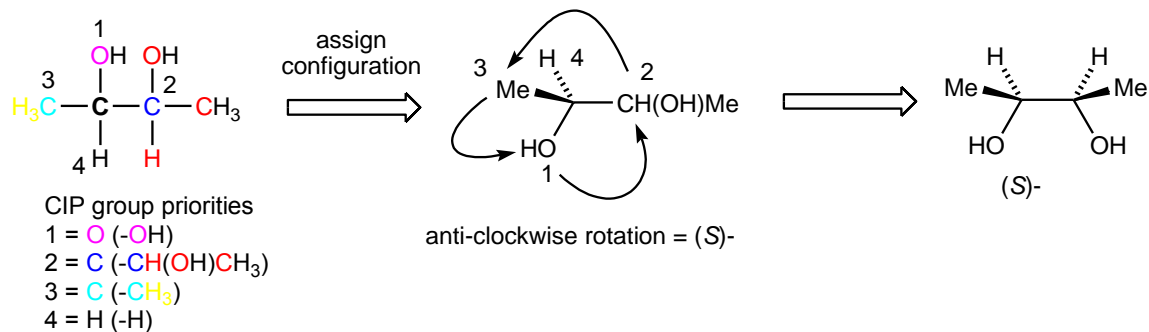
Assign the configurations of this molecule using the Cahn-Ingold-Prelog rules (See p. 839 in *Chemistry*³). For ease, use a conformer where the lowest priority groups on both chiral centres are facing away from you.

Solution

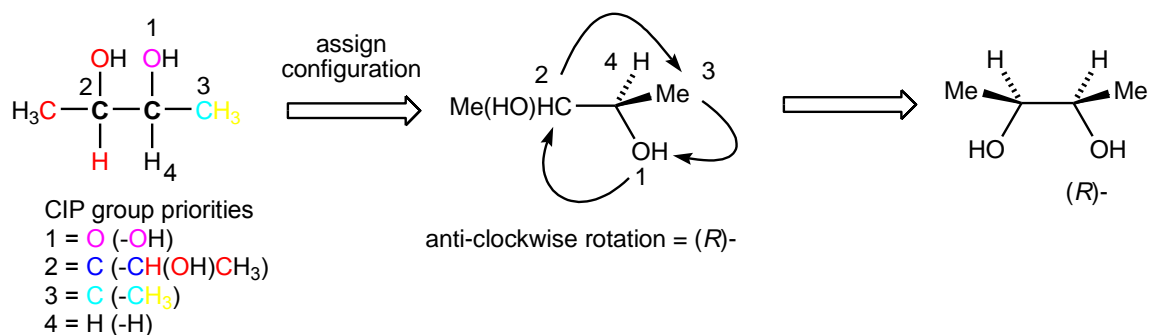
Rotate the sawhorse projection in 2(a), by 180° using a vertical axis, gives the more user-friendly sawhorse projection for determining these configurations.



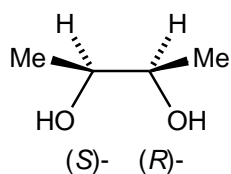
Assigning the configuration for the chiral centre on the left-hand side of this molecule using the Cahn-Ingold-Prelog rules:



Assigning the configuration for the chiral centre on the right-hand side of this molecule using the Cahn-Ingold-Prelog rules:

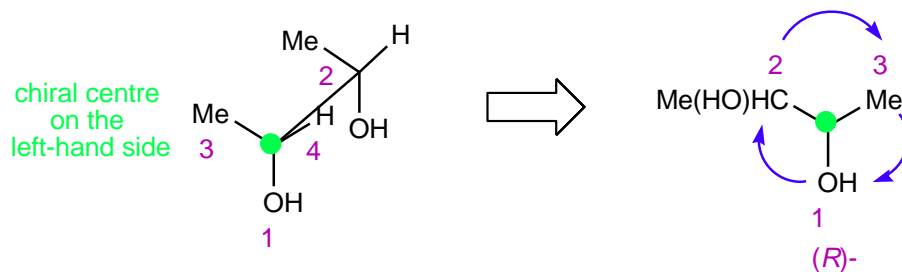


The overall configurations for *meso*-butane-2,3-diol are given below:

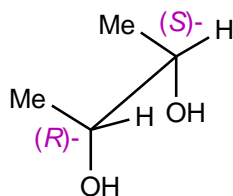
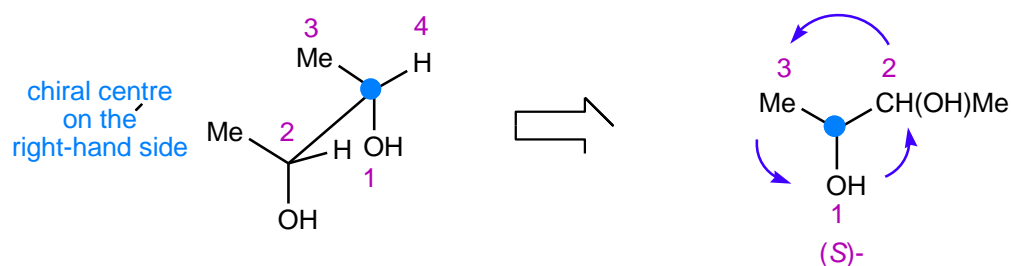


Answer

Rotate molecule so that the lowest priority group (H) is facing away from you



Rotate molecule so that the lowest priority group (H) is facing away from you



- (c) Draw a Fischer projection of *meso*-butane-2,3-diol and use this to explain why this is a *meso*-compound.

Strategy

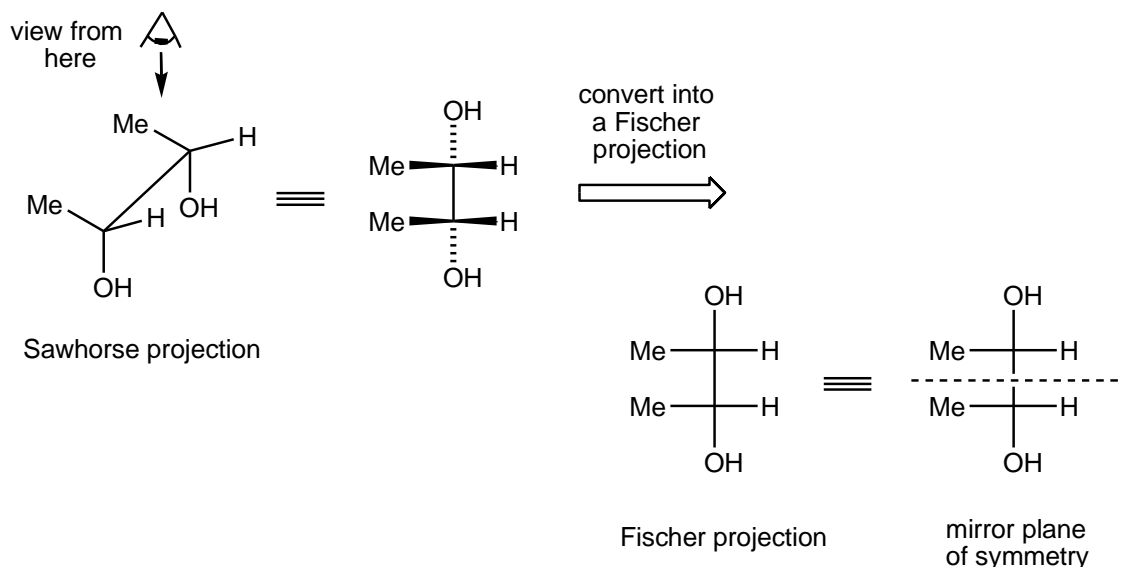
For a molecule to be *meso*-, it must contain two or more chiral centres and contain either a plane or point of symmetry. A Fischer projection is simply a 2D representation of a 3D sawhorse projection.

Solution

Butane-2,3-diol contains two chiral centres.

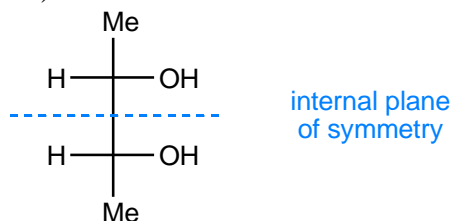
The sawhorse projection in part 2a can be converted into a Fischer projection by simply drawing its vertical projection as shown below. As this Fischer projection has a plane of symmetry (or a horizontal mirror plane) passing through the middle of its C(2)-C(3) bond, and contains two chiral centres, it is *meso*-. In addition, *meso*-butane-2,3-diol is not chiral as its mirror image is superimposable.

meso-butane 2,3 diol



Answer

This is a *meso*-compound because it contains two chiral centres and has an internal plane of symmetry (and so is achiral).



(d) Draw a Fischer projection of a diastereoisomer of *meso*-butane-2,3-diol.

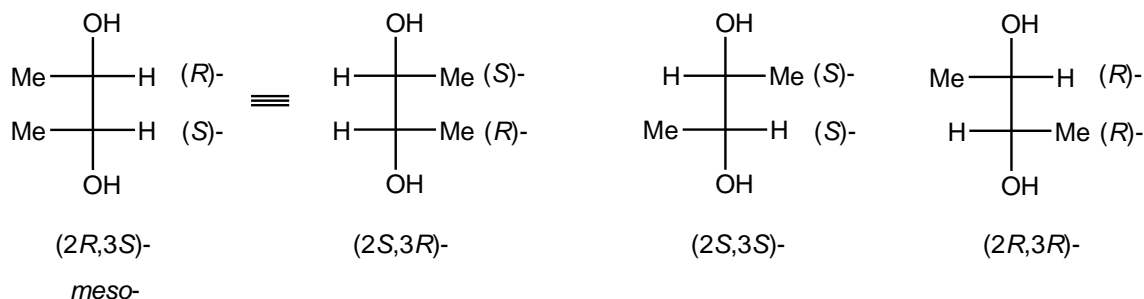
Strategy

Draw out the two non-superimposable non-mirror images of *meso*-butane-2,3-diol.

Solution

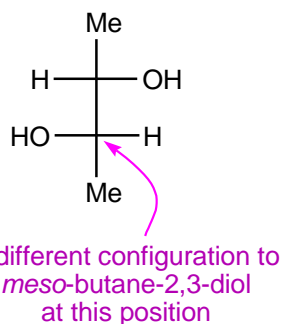
Two non-superimposable non-mirror images (diastereoisomers) of *meso*-butane-2,3-diol can be drawn. These are the (2*S*,3*S*)- and (2*R*,3*R*)-diastereoisomers. The remaining projection (2*S*,3*R*)- is identical to its original (2*R*,3*S*)- by 180° rotation.

Fischer projections of butane-2,3-diol



Answer

A diastereoisomer of *meso*-butane-2,3-diol has a different configuration at one of the chiral centres.



3. The citric acid cycle (Krebs cycle) is a series of reactions in the body involved in the oxidation of fats, proteins, and carbohydrates to form carbon dioxide and water (p.955 in *Chemistry*³). One step in the citric acid cycle is the addition of water to fumaric acid to make malic acid.

(a) Does the alkene double bond in fumaric acid have the (*E*)- or (*Z*)-configuration?

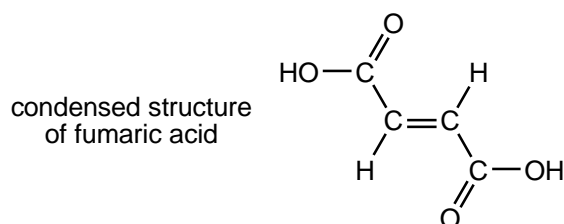
Strategy

1. Draw out the condensed structure of fumaric acid to include all H-atoms.
2. For molecules containing a single stereoisomeric double (C=C) bond. Its (*Z*)-isomer is where both high priority substituents are on the *same side* of the double bond, whereas, its (*E*)-isomer is when these high priority substituents are on *opposite sides*

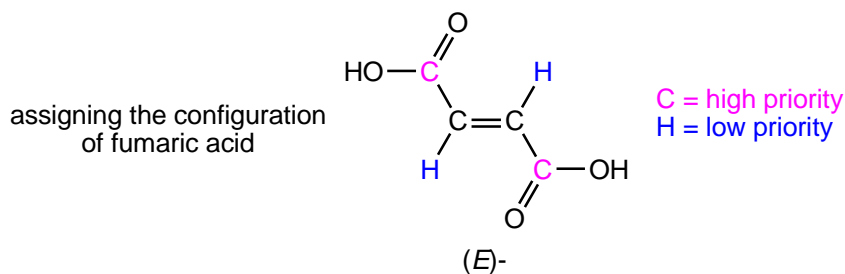
of the double bond. These priorities are determined using the Cahn-Ingold-Prelog rules (see p. 839 in *Chemistry*³).

Solution

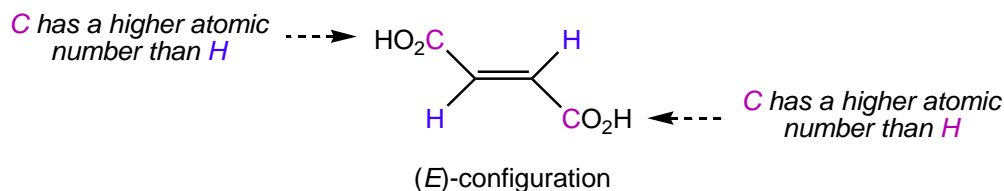
1. The condensed structure of fumaric acid is shown below:



2. For this double bond, assign the priority of its substituents using the Cahn-Ingold-Prelog rules (See p. 839 in *Chemistry*³); the carbon atom (C) of the carboxylic acid group has higher priority than the H-atom. This alkene has (*E*)-configuration as both high priority substituents are on *opposite sides* of this double bond.



Answer



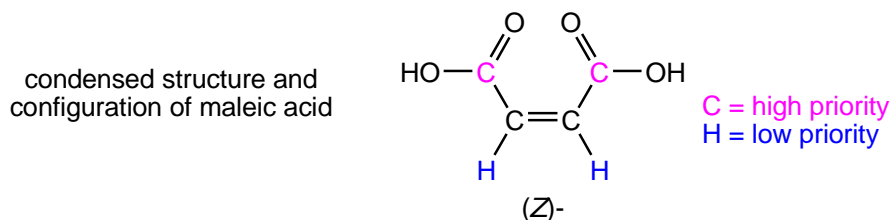
- (b) Maleic acid is a configurational isomer of fumaric acid. Draw the structure of maleic acid.

Strategy

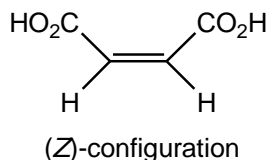
The only configuration in fumaric acid is its (*E*)-double (C=C) bond. As maleic acid is a configurational isomer, it must be the same condensed structure as fumaric acid (butenedioic acid) but a different alkene configuration. Fumaric acid is the (*E*)-isomer of butenedioic acid.

Solution

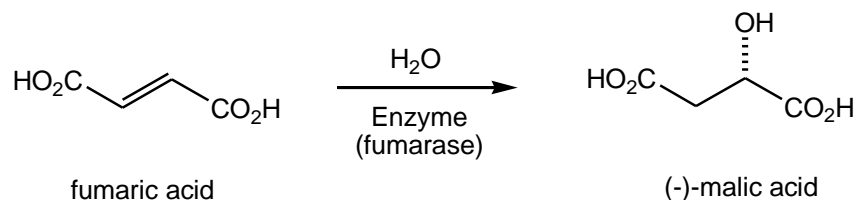
Maleic acid is the (*Z*)-isomer of butenedioic acid.



Answer



- (c) Explain why the conversion of fumaric acid to (–)-malic acid is an example of an enantioselective reaction.



Strategy

For a reaction to be enantioselective, an unequal mixture of enantiomers must be formed. A common example involves the conversion of an achiral starting material to an enantiomerically enriched product.

Solution

This reaction involves the selective formation of one enantiomer (–)-(*S*)-malic acid; its mirror image, (+)-(*R*)-malic acid, is not preferred. As there are **two** potential products { (–)-(*S*)- and (+)-(*R*)-malic acids } which can be formed; this reaction is **selective** as only

one of these **two** products are formed. This reaction is not **specific**. A specific reaction is where only **one** product can be formed.

Answer

This is an enantioselective reaction because (–)-malic acid is formed in preference to (+)-malic acid.

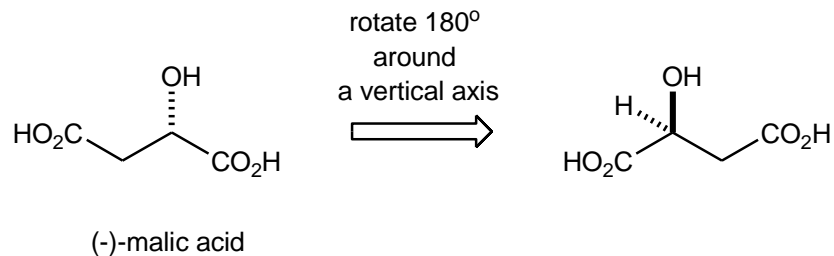
(d) Assign the (*R*)- or (*S*)-configuration to the chiral centre in (–)-malic acid.

Strategy

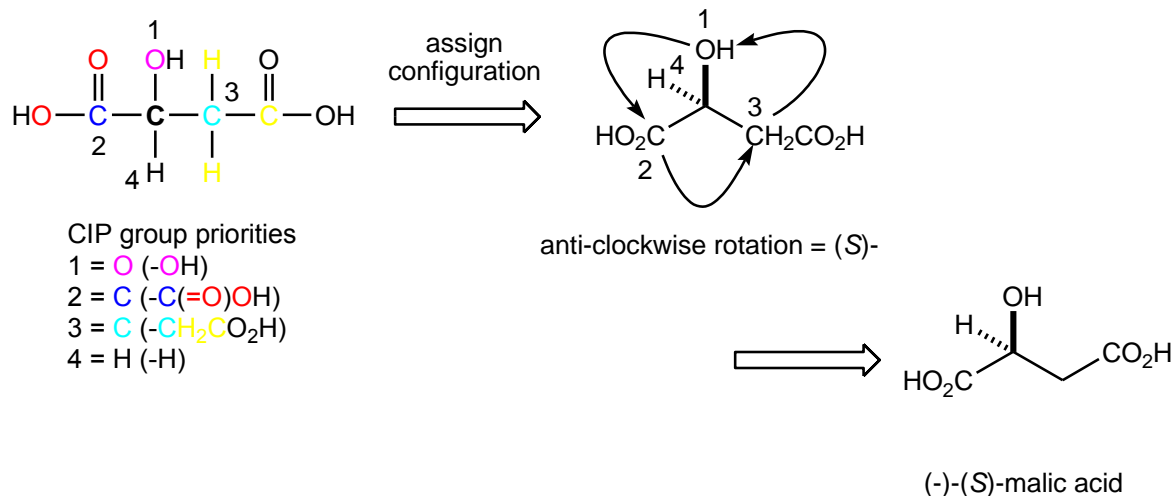
Assign the configuration of this molecule using the Cahn-Ingold-Prelog rules (See p. 839 in *Chemistry*³). For ease, use a conformer in which the lowest priority group on the chiral centre is facing away from you.

Solution

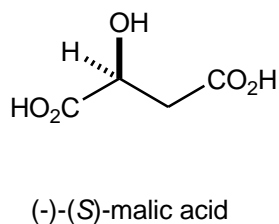
Rotate the projection in 2(c), by 180° using a vertical axis, gives the more user-friendly sawhorse projection for determining this configuration.



Assigning the configuration for this chiral centre using the Cahn-Ingold-Prelog rules:

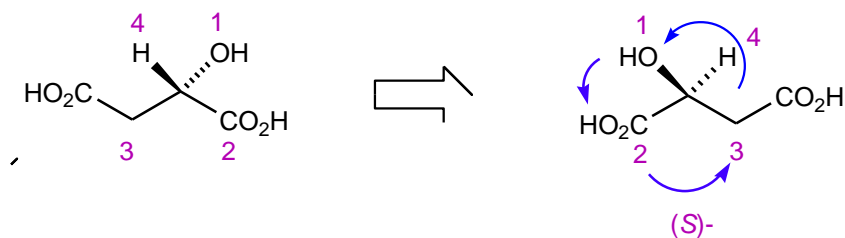


The configuration for (-)-malic acid is (S)- as shown below:

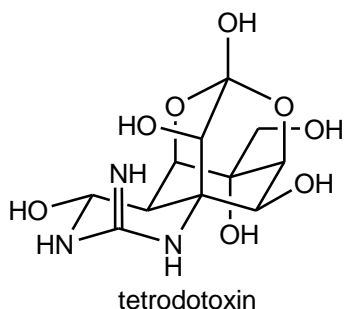


Answer

Rotate molecule so that the lowest priority group (H) is facing away from you

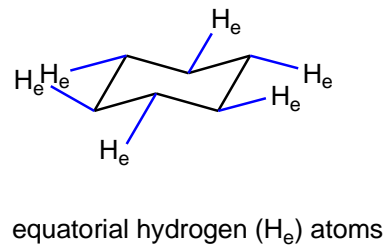
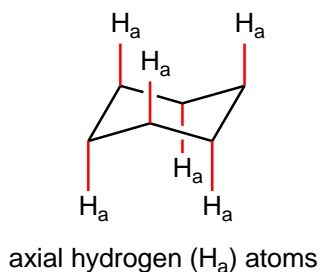
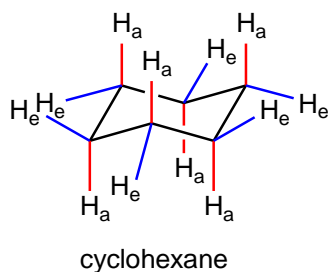


4. Tetrodotoxin is a potent poison that is found in the puffer fish. It is estimated to be more than 10 000 times deadlier than cyanide ions. The structure of tetrodotoxin contains a group of interconnected 6-membered rings. Which of the bonds on the cyclohexane ring of tetrodotoxin are in an axial position and which are in an equatorial position?



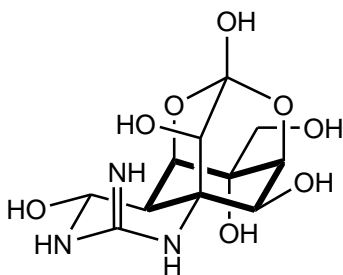
Strategy

1. Pick out the cyclohexane ring.
2. Highlight the equatorial and axial positions on this cyclohexane ring. This has been illustrated below for cyclohexane.



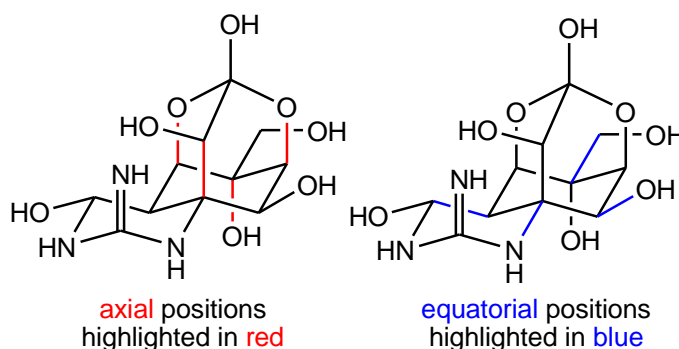
Solution

1. Of the four potential six-membered rings, there is only one cyclohexane ring. The remaining three rings are heterocyclic.

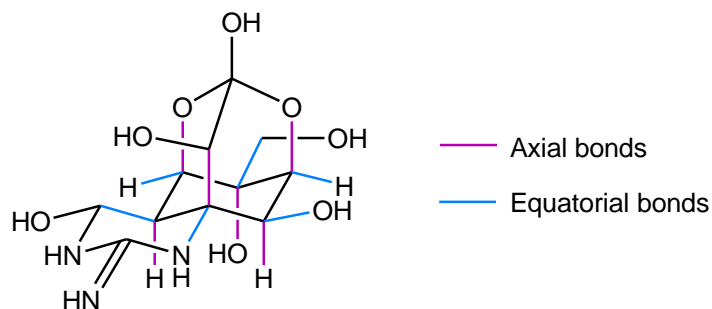


cyclohexane core

2. On this cyclohexane ring, the **axial** positions are “**vertical**” and the **equatorial** positions point away (by 19 degrees) from the equator of the ring.

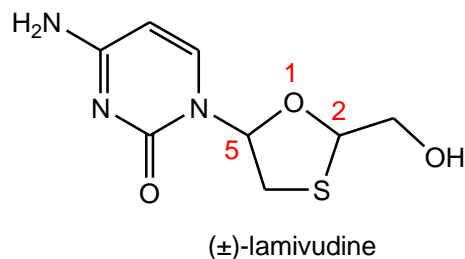


Answer



5. Lamivudine (Epivir) is used for the treatment of HIV (Aids) and is an example of a class of drugs called nucleoside reverse transcriptase inhibitors. These inhibitors stop HIV

from infecting cells in the body. Only the (–)-enantiomer of lamivudine is registered for the treatment of HIV because it is more active and less toxic than either the (+)-enantiomer or the racemate. In the (–)-enantiomer, the chiral centre at position-2 has the (*R*)-configuration and the chiral centre at position-5 has the (*S*)-configuration. Draw the structure of (–)-lamivudine using hashed–wedged line notation.

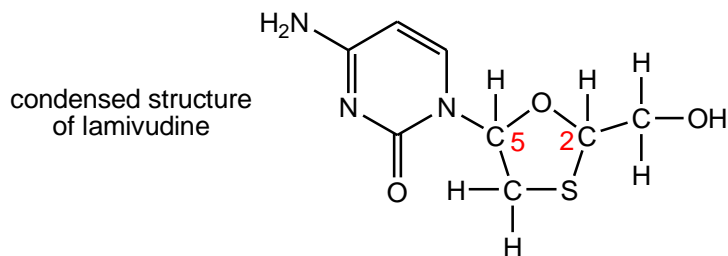


Strategy

1. Redraw this molecule in a condensed form.
2. Arbitrarily assign both chiral centres in (±)-lamivudine using the Cahn-Ingold-Prelog rules (See p. 839 in *Chemistry*³). It will be easier if you consider one chiral centre at time.
3. Pick out the correct diastereoisomer (*2R,5S*)-.
4. Draw out this diastereoisomer using hashed-wedged line notation.

Solution

1. The condensed structure of lamivudine is shown below:

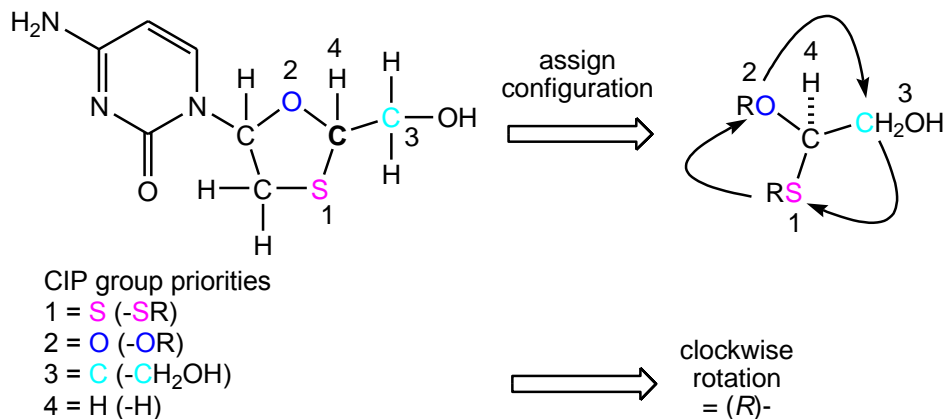


2. Arbitrarily assign the configurations of this molecule using the Cahn-Ingold-Prelog rules. For ease, use a conformer in which the lowest priority groups on both chiral centres are facing away from you.

Assign the configuration for the chiral centre at **carbon-2** using the Cahn-Ingold-Prelog rules: the chiral centre at carbon-2 has (*R*)-stereochemistry. A (*R*)-configuration is where the three highest priority groups (1, 2 and 3) on a particular

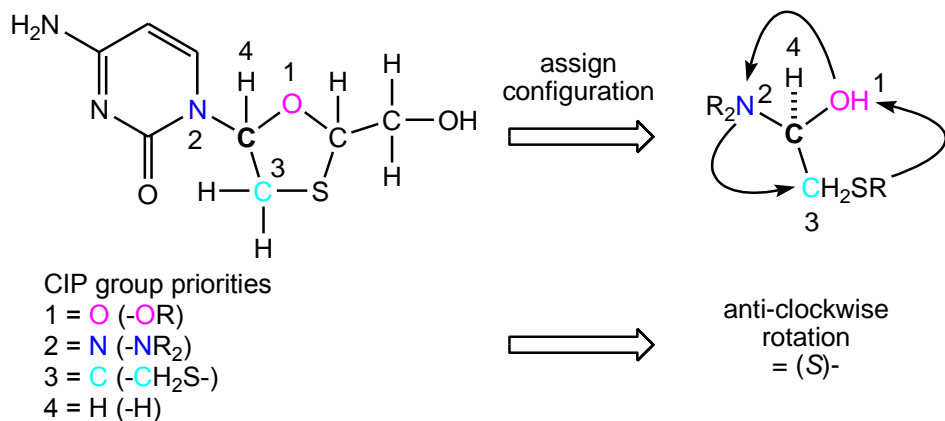
conformation can be rotated clockwise (1→2→3), whilst the lowest priority group, 4, is at the rear of this conformer.

Assigning the configuration at C(2)

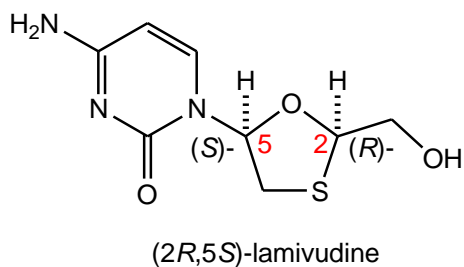


Assign the configuration for the chiral centre at **carbon-5** using the Cahn-Ingold-Prelog rules: the chiral centre at carbon-2 has (*S*)-stereochemistry. A (*S*)-configuration is where the three highest priority groups (1, 2 and 3) on a particular conformation can be rotated anticlockwise (1→2→3), whilst the lowest priority group, 4, is at the rear of this conformer.

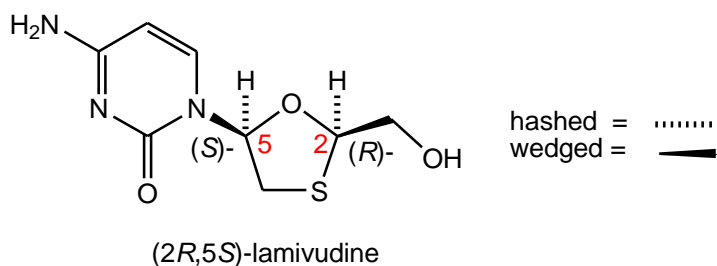
Assigning the configuration at C(5)



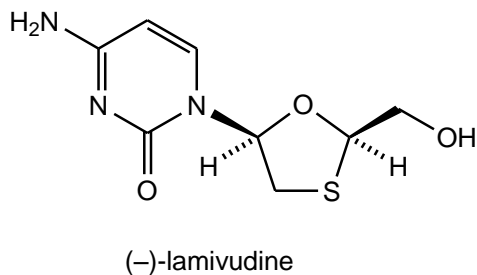
3. The required (*2R,5S*)-diastereoisomer is shown below.



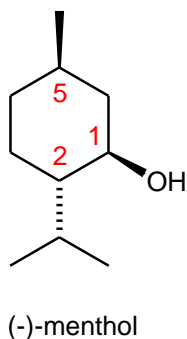
4. The hashed-wedged structure of (2*R*,5*S*)-lamivudine is shown below.



Answer



6. The following questions relate to (-)-menthol, a naturally occurring compound isolated from peppermint oil.



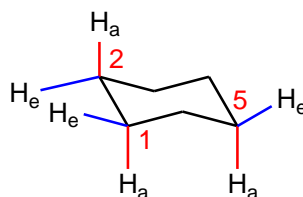
(a) Draw the preferred chair conformation of (-)-menthol.

Strategy

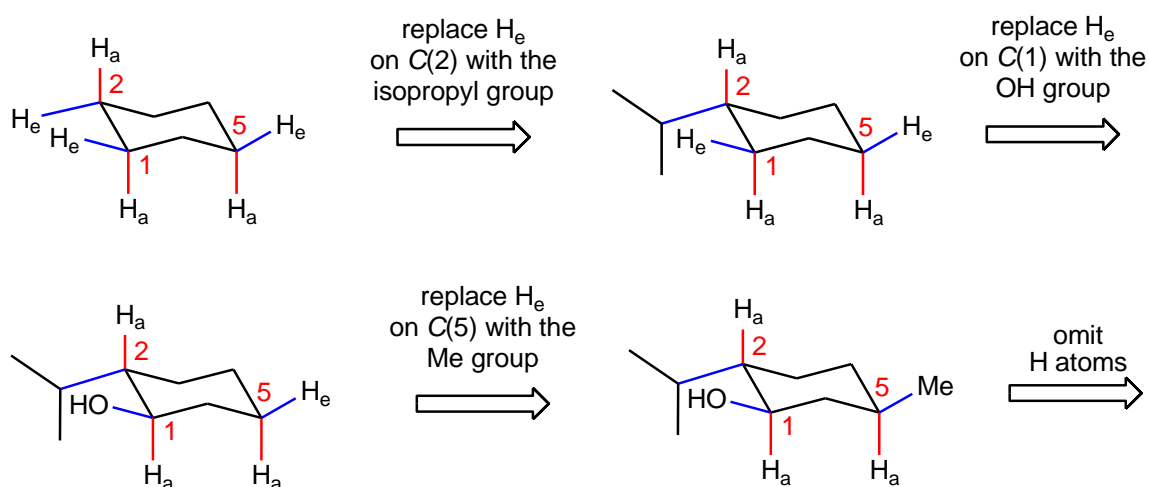
1. Draw a chair conformer for cyclohexane, and then draw out the axial and equatorial positions at carbons-1, -2 and -5.
2. Insert the substituents (at carbons-1, -2 and -5) in (-)-menthol onto this cyclohexane template. [Place the largest (isopropyl) group in the less steric demanding equatorial position.]

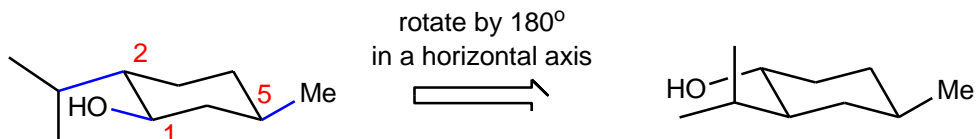
Solution

1. The axial and equatorial positions at carbons-1, -2 and -5 for cyclohexane are illustrated below.



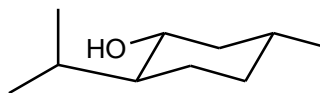
2. Replace the less steric demanding equatorial H_e atom with the largest isopropyl group at carbon-2. As the neighbouring OH group at carbon-1 is on the opposite sides of this molecule (*anti*-stereochemistry between carbons 1 and 2), replacing the H_e atom at carbon-1 with this OH group will give the correct stereochemical relationship between these substituents. The remaining Me group at carbon-5 is on the same face as this OH group, and therefore will be in an equatorial position.





Answer

all three substituents
are equatorial



(b) Assign (*R*)- or (*S*)-configuration to each of the chiral centres in (–)-menthol.

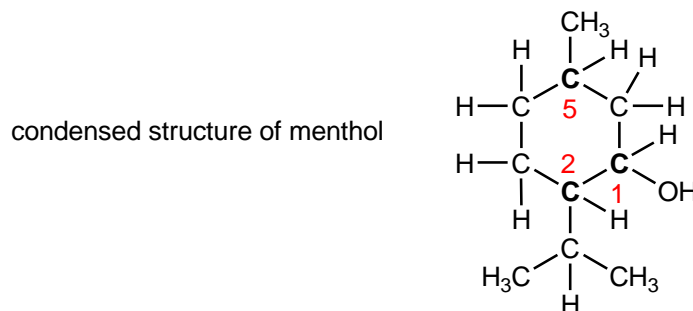
Strategy

Assign the configurations of this molecule using the Cahn-Ingold-Prelog rules (See p. 839 in *Chemistry*³). For ease, assign each configuration separately and use a conformer in which the lowest priority group on each chiral centre is facing away from you.

1. Redraw (–)-menthol in a condensed form.
2. Assign all three chiral centres in (–)-menthol using the Cahn-Ingold-Prelog rules. It will be easier if you consider one chiral centre at time.

Solution

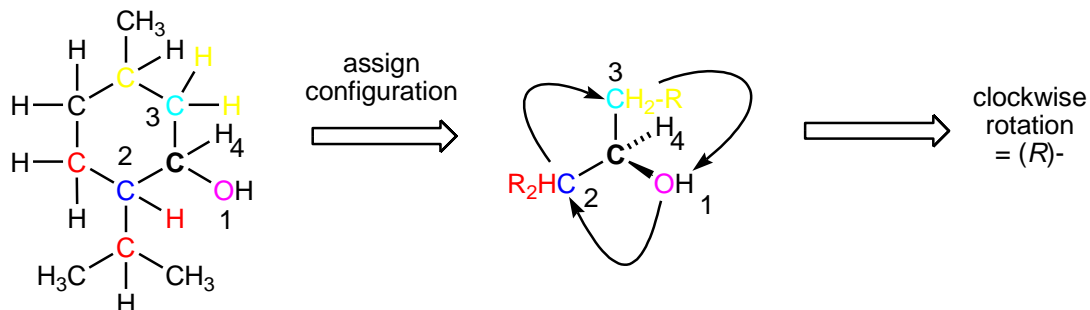
1. The condensed structure of menthol and the three chiral centres are shown below.



2. Assign the configurations of (–)-menthol using the Cahn-Ingold-Prelog rules. For ease, when assigning each chiral centre use a conformer in which the lowest priority group is facing away from you.

Assign the configuration for the chiral centre at **carbon-1** using the Cahn-Ingold-Prelog rules: the chiral centre at carbon-1 has (*R*)-stereochemistry. A (*R*)-configuration is where the three highest priority groups (1, 2 and 3) on a particular conformation can be rotated clockwise (1→2→3), whilst the lowest priority group, 4, is at the rear of this conformer.

Assigning the configuration at C(1)



CIP group priorities

1 = O (-OH)

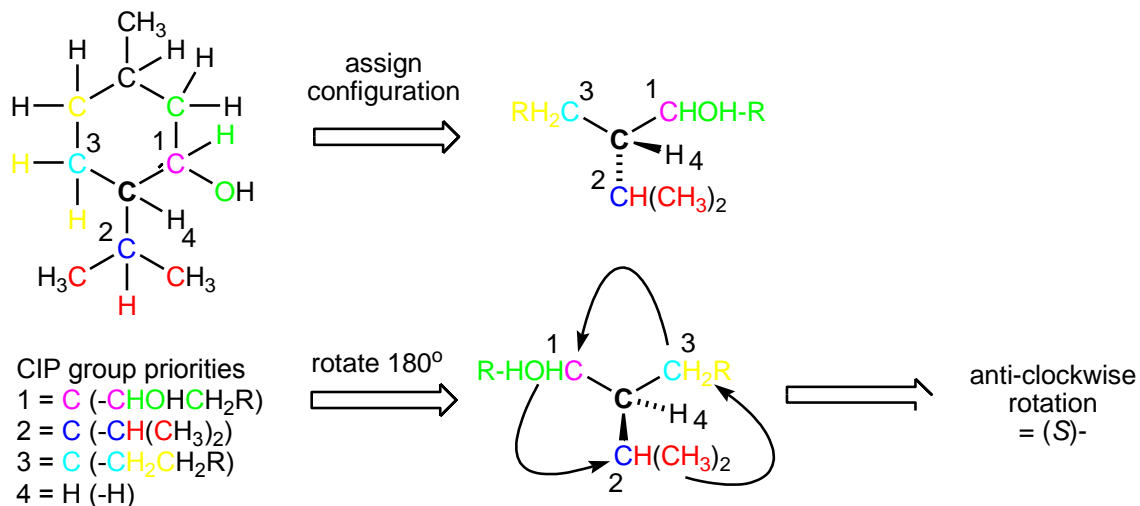
2 = C (-C(CH₂CH₃)₂(CH₂-)H)

3 = C (-CH₂CHCH₃-)

4 = H (-H)

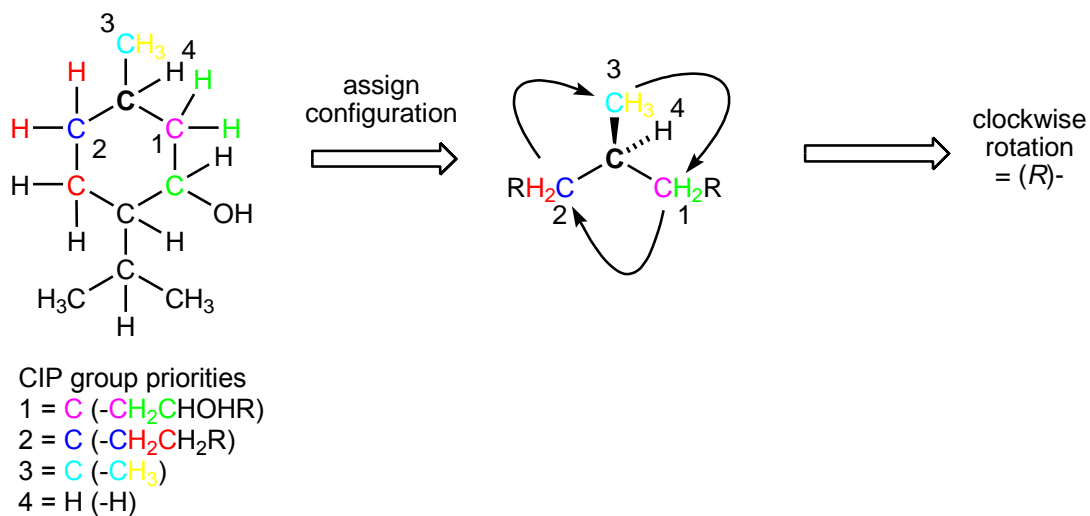
Assign the configuration for the chiral centre at **carbon-2** using the Cahn-Ingold-Prelog rules: the chiral centre at carbon-2 has (*S*)-stereochemistry. A (*S*)-configuration is where the three highest priority groups (1, 2 and 3) on a particular conformation can be rotated anti-clockwise (1→2→3), whilst the lowest priority group, 4, is at the rear of this conformer.

Assigning the configuration at C(2)



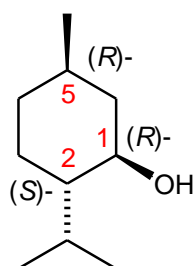
Assign the configuration for the chiral centre at **carbon-5** using the Cahn-Ingold-Prelog rules: the chiral centre at carbon-5 has (*R*)-stereochemistry.

Assigning the configuration at C(5)



The three configurations of (-)-menthol are:

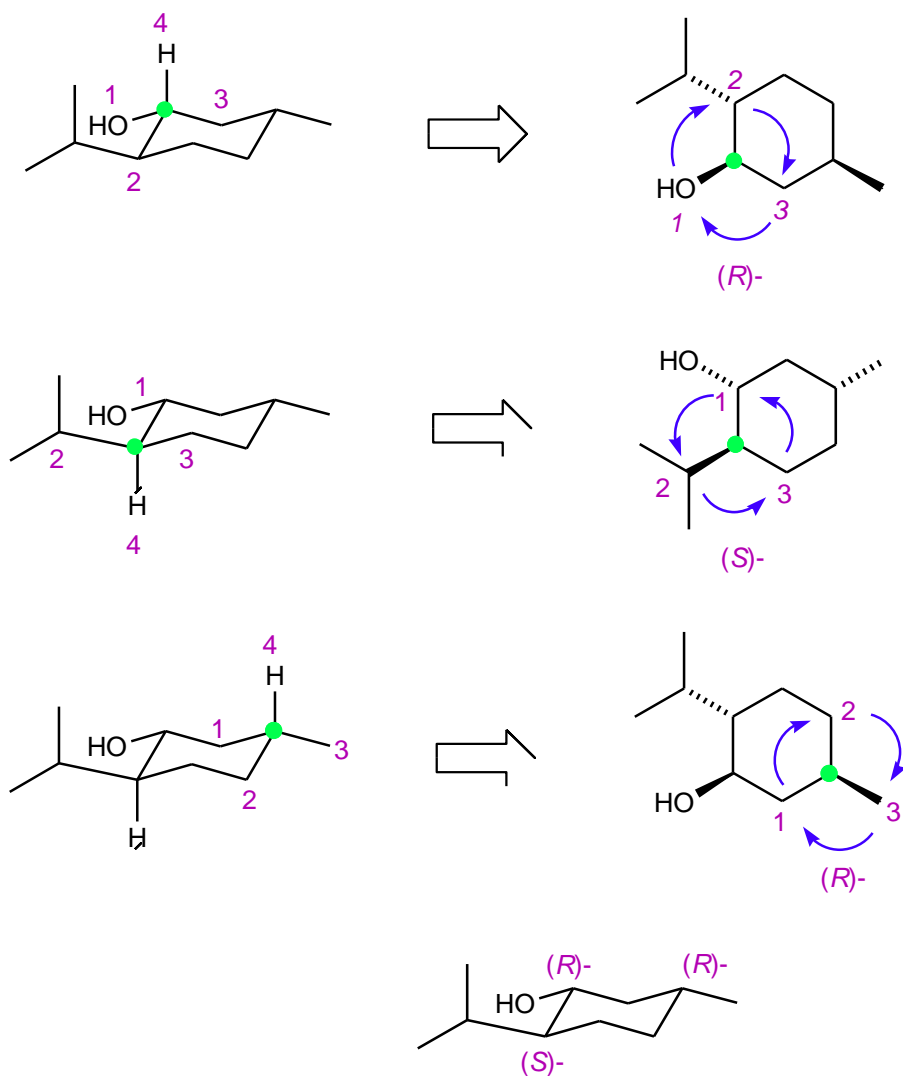
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(-)-(1*R*,2*S*,5*R*)-menthol

Answer

Rotate molecule so that the lowest priority group (H) is facing away from you



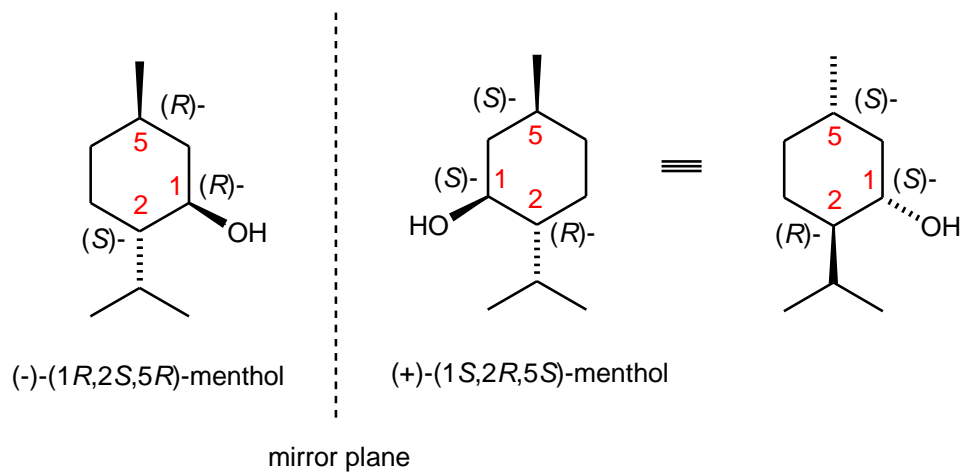
(c) Draw the enantiomer of (-)-menthol.

Strategy

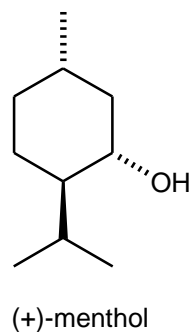
Draw out the non-superimposable mirror image of (-)-menthol.

Solution

Two non-superimposable mirror images (enantiomers) of menthol can be drawn. These are the (-)-(1*R*,2*S*,5*R*)- and (+)-(1*S*,2*R*,5*S*)-enantiomers.



Answer



(d) Draw a diastereoisomer of (-)-menthol.

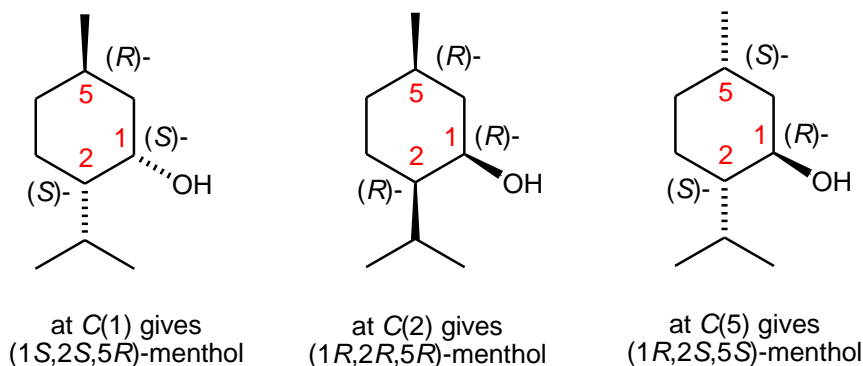
Strategy

Draw out the non-superimposable non-mirror images of (-)-menthol.

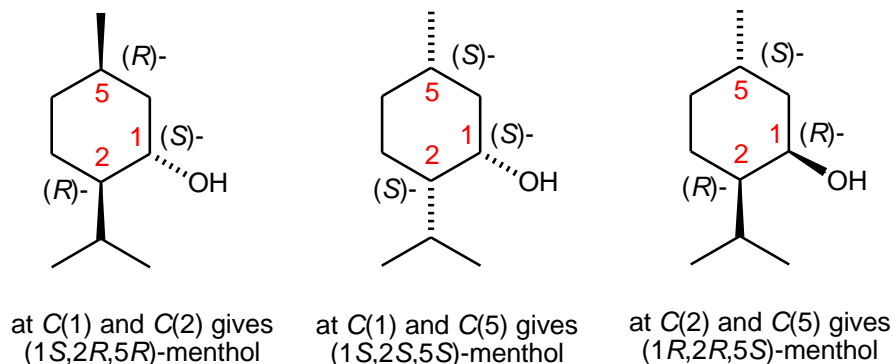
Solution

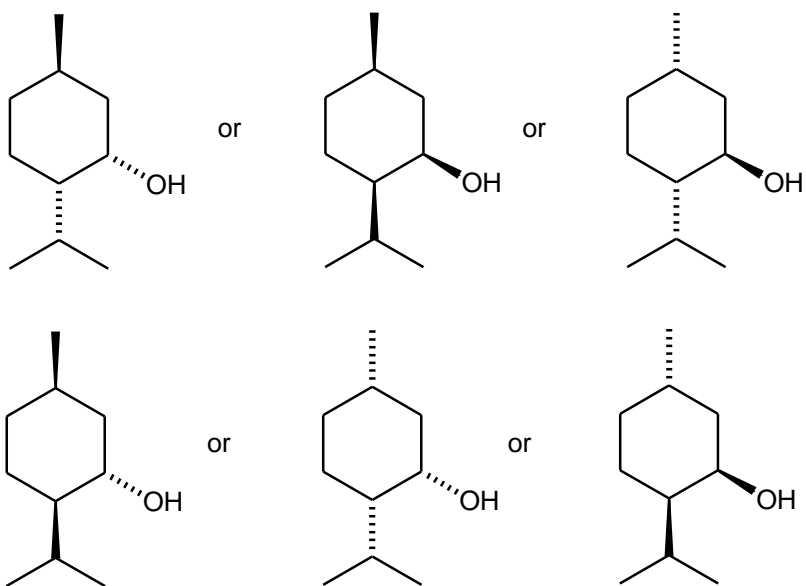
Six non-superimposable non-mirror images (diastereoisomers) of (-)-menthol can be drawn. These diastereoisomers, (1*S*,2*S*,5*R*)-, (1*R*,2*R*,5*R*)-, (1*R*,2*S*,5*S*)-, (1*S*,2*R*,5*R*)-, (1*S*,2*S*,5*S*)- and (1*R*,2*R*,5*S*)- are shown below. The first three of these can be drawn by inverting a single chiral centre of (-)-(1*R*,2*S*,5*R*)-menthol, and the last three can be drawn by inverting two chiral centres of (-)-(1*R*,2*S*,5*R*)-menthol. Interestingly, changing all three chiral centres of (-)-(1*R*,2*S*,5*R*)-menthol gives its enantiomer, (+)-(1*S*,2*R*,5*S*)-menthol.

Changing a single chiral centre of (-)-menthol



Changing two chiral centres of (-)-menthol

Answer



Solutions provided by J. Eames (j.eames@hull.ac.uk)