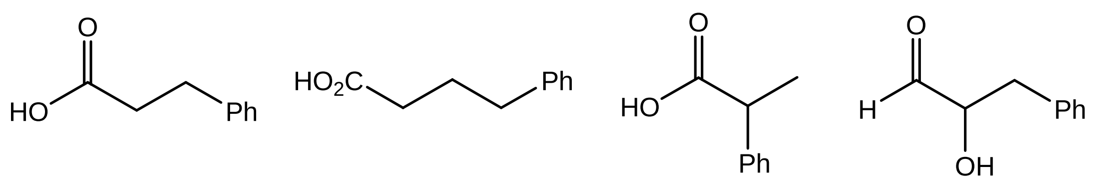
10

Isomerism and stereochemistry

Answers to worked examples

WE 10.1 Structural isomers (on p. 452 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, C_6H_5–.)



A **B** **C** **D**

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 ($C_9H_{10}O_2$). Molecule **B** is not a structural isomer since it has a different molecular formula ($C_{10}H_{12}O_2$).

2. Molecules **A** and **C** are positional isomers as they both contain the same functional groups [a carboxylic acid (-CO_2H) 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**).

<u>Answer</u>

1. **A**, **C** and **D** are structural isomers – all have the molecular formula, $C_9H_{10}O_2$. **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 10.3 *E*/*Z* nomenclature (on p. 470 in *Chemistry*^{3})

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

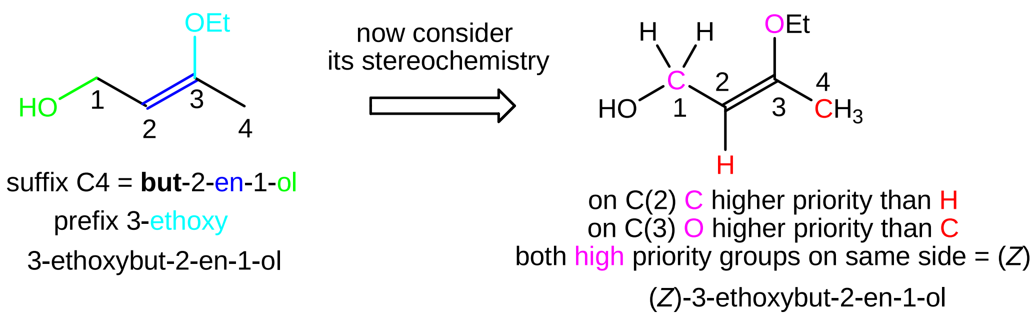
<u>Strategy</u>

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. 480 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!

<u>Solution</u>

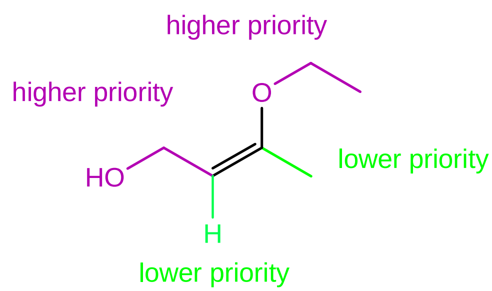
1. The longest number of continuous carbon atoms is four [(*Z*)-3-ethoxy**but**-2-en-1-ol]. Draw out this carbon chain in a *zig-zag* arrangement.

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** (→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.

<u>Answer</u>



(*Z*)-3-ethoxybut-2-en-1-ol

WE 10.5 *R*/*S* nomenclature (on p. 482 in *Chemistry*[3])

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

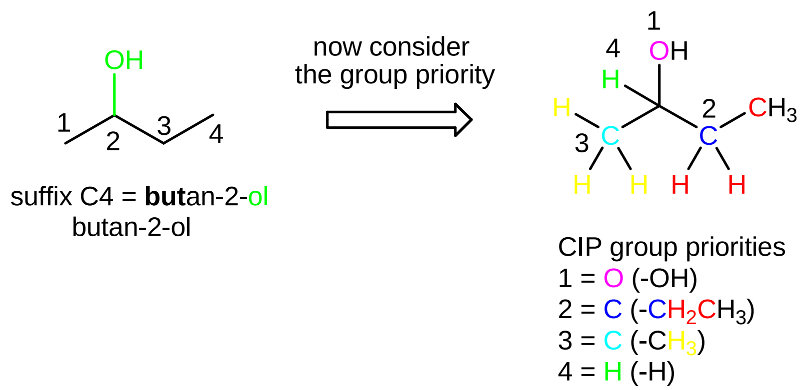
<u>Strategy</u>

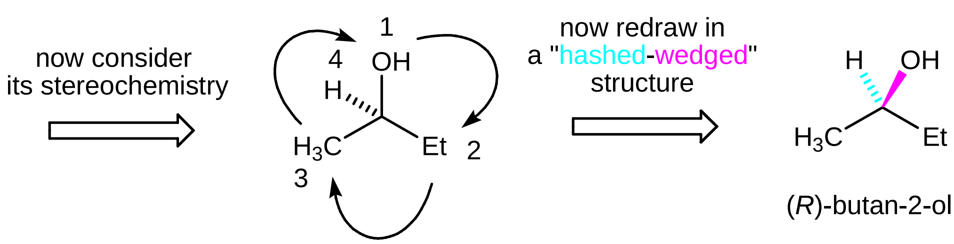
1. Draw out the longest continuous carbon chain as a *zig-zag* structure and remember to number the carbon atoms.
2. Identify any substituents from their suffix, and place them along this carbon chain at their designated positions.

3. Draw out the stereochemistry. This can be worked out using the Cahn-Ingold-Prelog rules (See p. 480 in *Chemistry*[3]).
4. Check that this structure is correct!
5. Draw out the hashed-wedged line structure of this molecule.

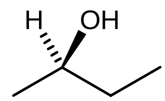
Solution

1. The longest number of continuous carbon atoms is four [(*R*)-**but**an-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.





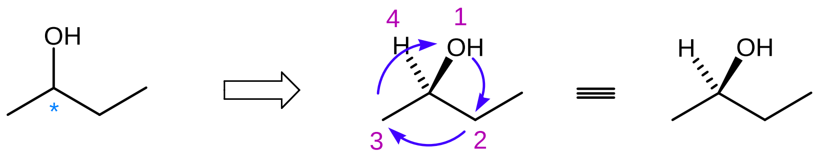
4. Check that the structure is correct by re-naming it! This structure is (*Z*)-3-ethoxybut-2-en-1-ol.
5. The hashed-wedged line structure of this molecule is:



(*R*)-butan-2-ol

<u>Answer</u>

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



first draw butan-2-ol and identify the chiral centre

(*R*)-

(*R*)-butan-2-ol

Answers to end of chapter questions (on p. 493 in *Chemistry*^{3})

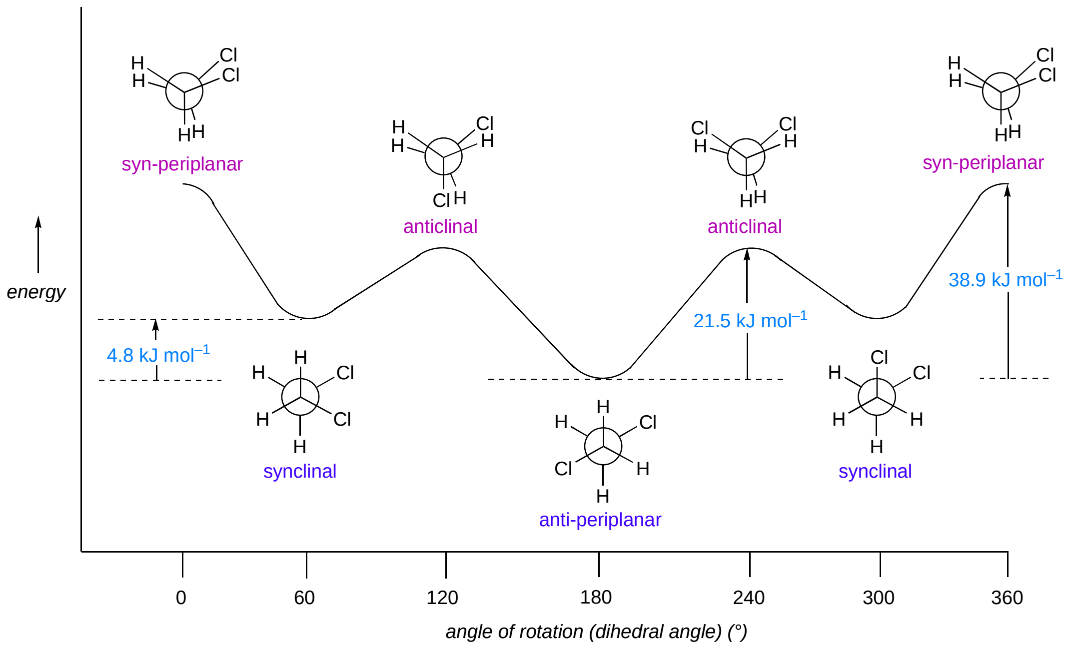
1. The synclinal conformation of 1,2-dichloroethane is 4.8 kJ mol^{-1} higher in energy than the anti-periplanar conformation. The two energy barriers for rotation about the C–C bond in 1,2-dichloroethane are 21.5 kJ mol^{-1} and 38.9 kJ mol^{-1} higher than the energy of the anti-periplanar conformation

(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^o and consider its relative energy.
3. Repeat this 60^o clockwise rotation until a full revolution (180^o) has been achieved.
4. Sketch the change in energy versus the *relative* angle of rotation. For ease, set the most stable projection has having 180^o; 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?

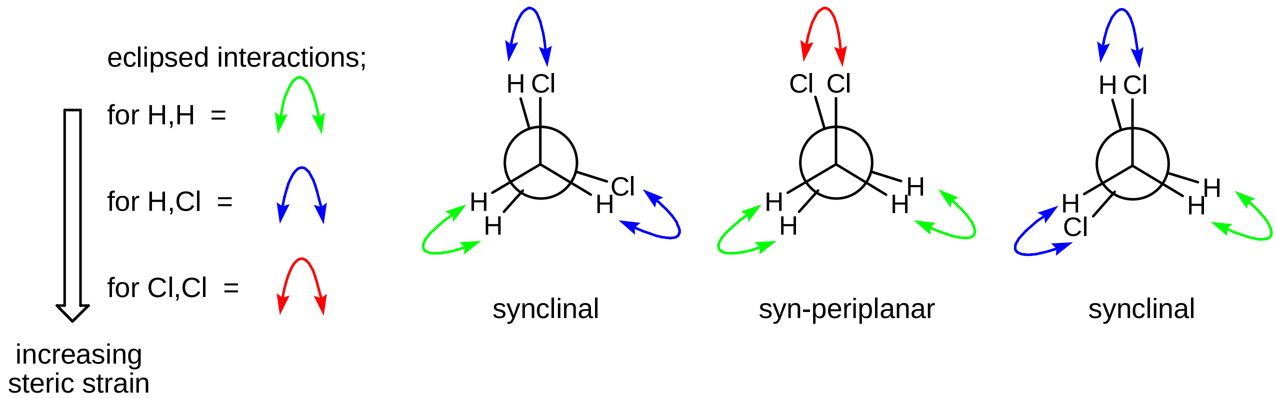
<u>Strategy</u>

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.

<u>Solution</u>

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



<u>Answer</u>

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

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.956 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?

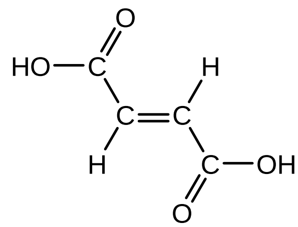
<u>Strategy</u>

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. 480 in *Chemistry*[3]).

<u>Solution</u>

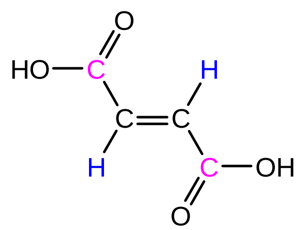
1. The condensed structure of fumaric acid is shown below:

condensed structure of fumaric acid



2. For this double bond, assign the priority of its substituents using the Cahn-Ingold-Prelog rules (See p. 480 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.

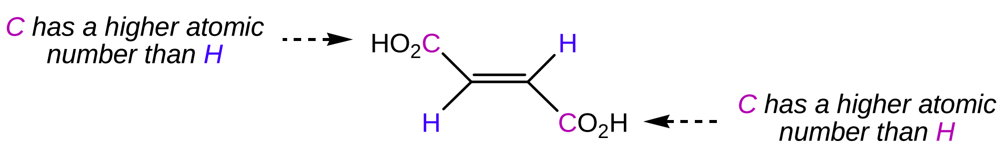
assigning the configuration of fumaric acid



C = high priority
H = low priority

(*E*)-

<u>Answer</u>



(*E*)-configuration

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

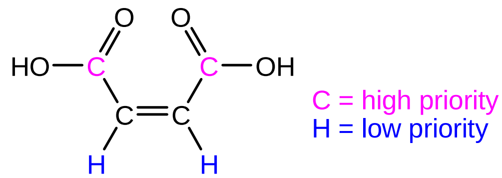
<u>Strategy</u>

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.

<u>Solution</u>

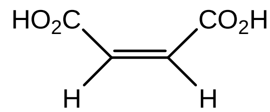
Maleic acid is the (*Z*)-isomer of butenedioic acid.

condensed structure and configuration of maleic acid



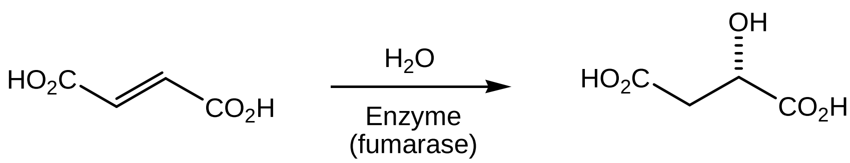
(*Z*)-

Answer



(*Z*)-configuration

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



fumaric acid (-)-malic acid

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.

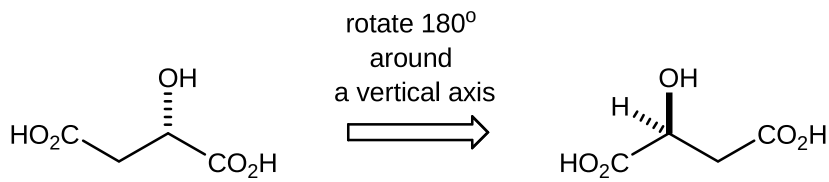
(d) Assign the (*R*)- or (*S*)-configuration to the chiral centre in (–)-malic acid.

Strategy

Assign the configuration of this molecule using the Cahn-Ingold-Prelog rules (See p. 480 in *Chemistry*[3]). For ease, use a conformer in which the lowest priority group on the chiral centre is facing away from you.

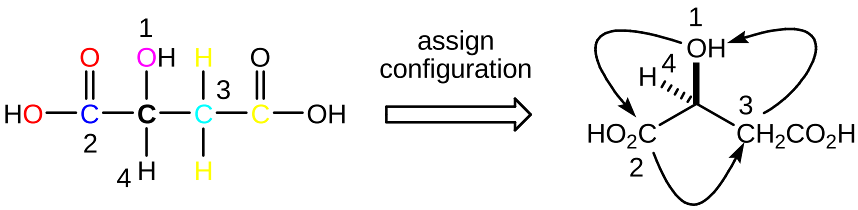
Solution

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



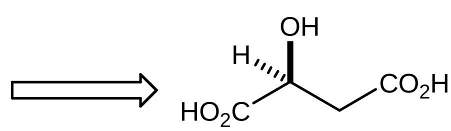
(-)-malic acid

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



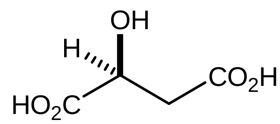
CIP group priorities
1 = O (-OH)
2 = C (-C(=O)OH)
3 = C ($-CH_2CO_2H$)
4 = H (-H)

anti-clockwise rotation = (*S*)-



(-)-(*S*)-malic acid

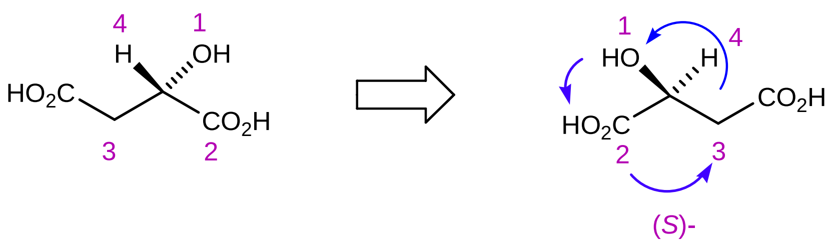
The configuration for (–)-malic acid is (*S*)- as shown below:



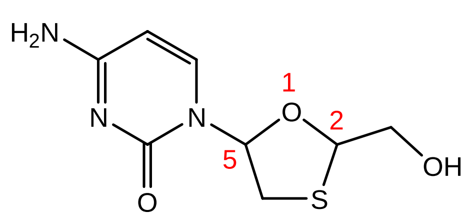
(-)-(*S*)-malic acid

Answer

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



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.



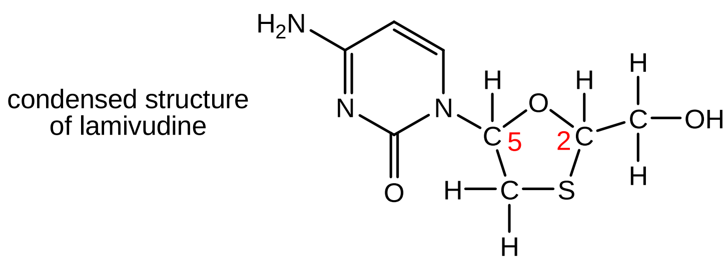
(±)-lamivudine

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. 480 in *Chemistry*[3]). It will be easier if you consider one chiral centre at time.
3. Pick out the correct diastereoisomer (2*R*,5*S*)-.
4. Draw out this diastereoisomer using hashed-wedged line notation.

Solution

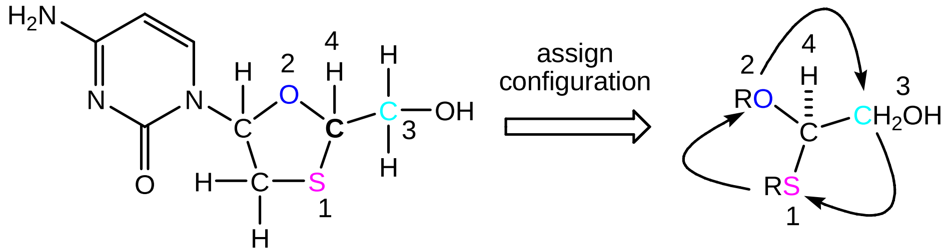
1. The condensed structure of lamivudine is shown below:



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)

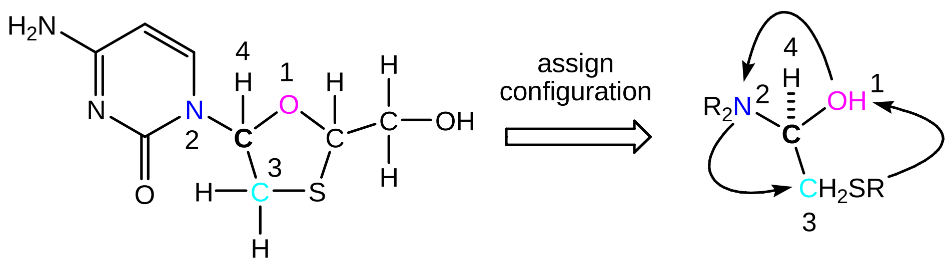


CIP group priorities
1 = S (-SR)
2 = O (-OR)
3 = C (-CH_2OH)
4 = H (-H)

clockwise rotation = (*R*)-

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.

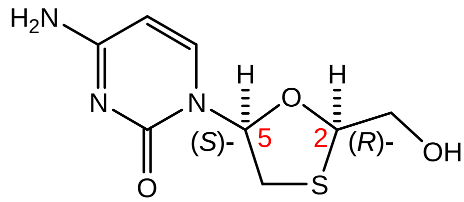
Assigning the configuration at *C*(5)



CIP group priorities
1 = O (-OR)
2 = N (-NR_2)
3 = C (-CH_2S-)
4 = H (-H)

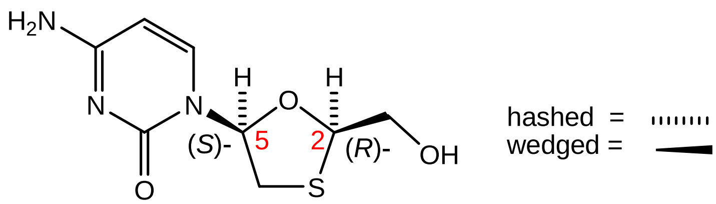
anti-clockwise rotation = (*S*)-

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



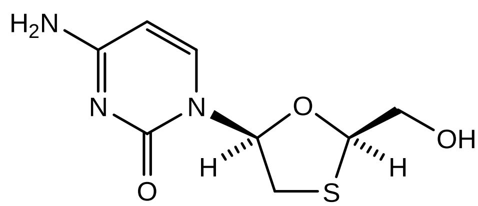
(2*R*,5*S*)-lamivudine

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



(2*R*,5*S*)-lamivudine

Answer



(–)-lamivudine

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