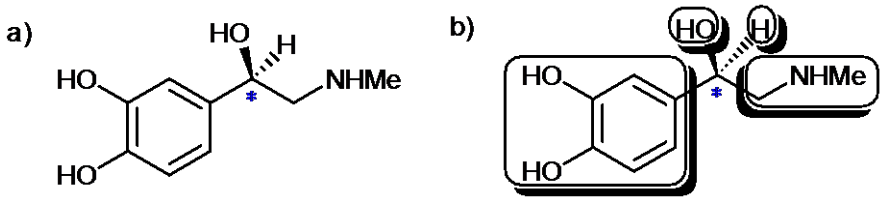
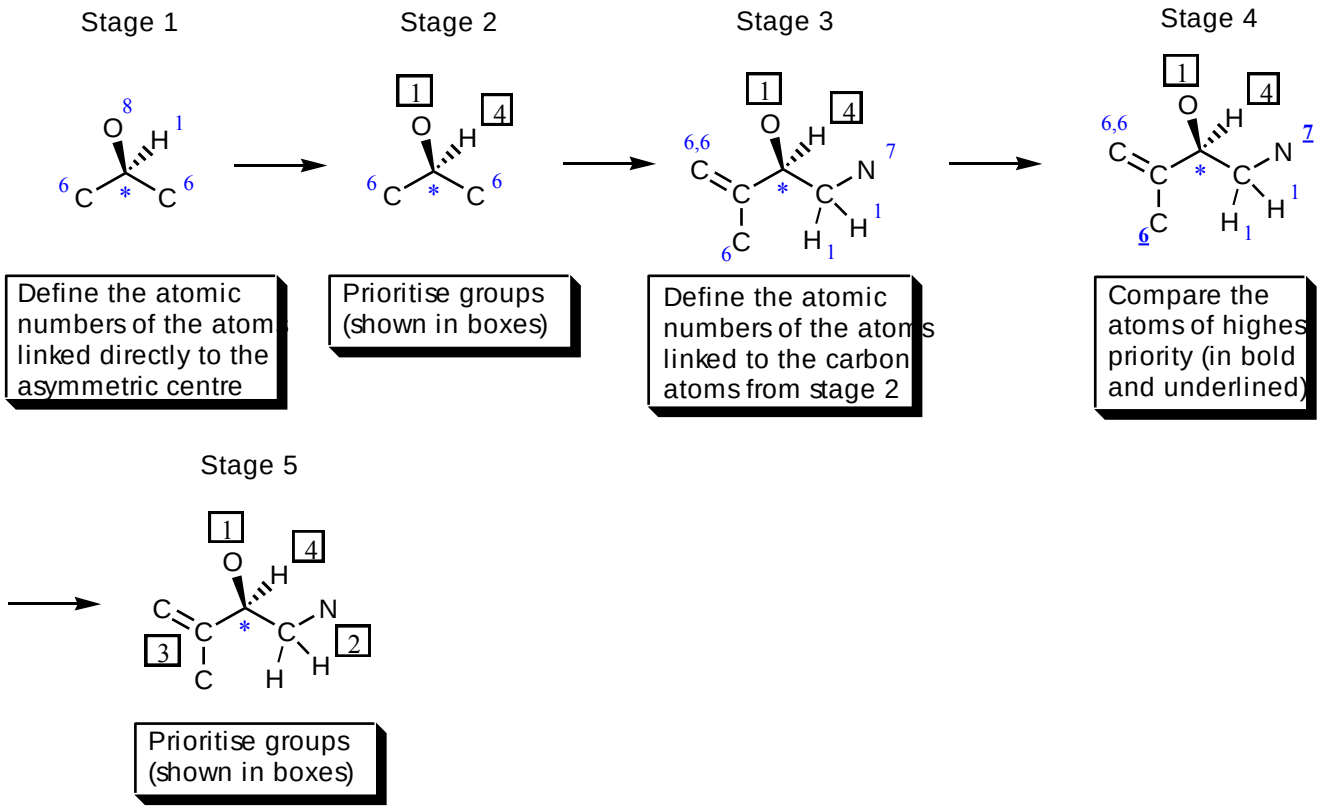
# Chapter 5: The synthesis of chiral drugs

**Question 5.1**
**Propranolol** is a beta blocker that acts as an antagonist at adrenergic receptors, whereas **salbutamol** is an anti-asthmatic agent that acts as an adrenergic agonist. The asymmetric centres present in the active enantiomers of propranolol and salbutamol are *S* and *R* respectively, whereas the asymmetric centre in the naturally occurring hormone **adrenaline** is *R*. Show how these assignments were worked out.

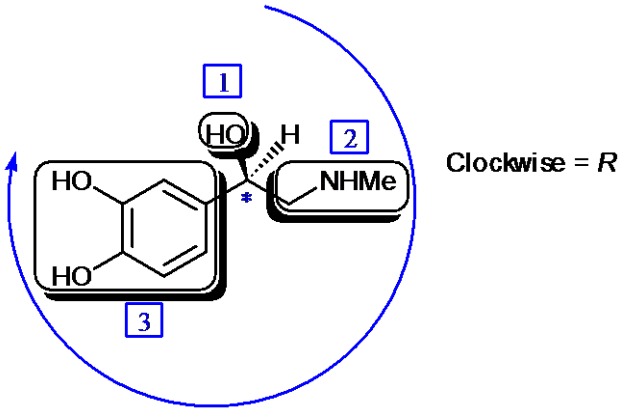
**Answer**
Assignment of the chiral centre in adrenaline
The four different substituents attached to the asymmetric centre of adrenaline are highlighted below.




The first step in the prioritisation process is to identify the atoms directly linked to the asymmetric centre and assign their atomic numbers (stage 1). Next, the atoms are prioritised with respect to their atomic numbers (stage 2). Oxygen has the highest atomic number and so it takes priority 1. Hydrogen has the smallest atomic number and so it takes priority 4. However, we have two identical carbon atoms and so we cannot distinguish between them at this stage. We now have to identify the atom of highest priority attached to each of the carbon atoms (stage 3). Therefore, the atoms linked to the carbon atoms have to be identified and assigned atomic numbers. One of the carbons is an aromatic carbon and so there are another two carbons linked to it. However, the rules state that any atom linked by a double bond can be counted twice. Therefore, there are a nominal three carbons attached. The other carbon has a nitrogen and two hydrogens attached. In the final stage (stage 4), we compare the atoms of highest priority in each of the groups. In this case, we are comparing nitrogen with carbon. Nitrogen has the higher atomic number and so the group containing nitrogen takes priority. Note that it is not a case of 'adding up' the atomic numbers of the atoms concerned in each group. Therefore, priorities are *not* based on how large a particular group is. For example, the aromatic ring in adrenaline is larger than the $CH_2NHMe$ group, but takes a lower priority as a result of the prioritisation process.

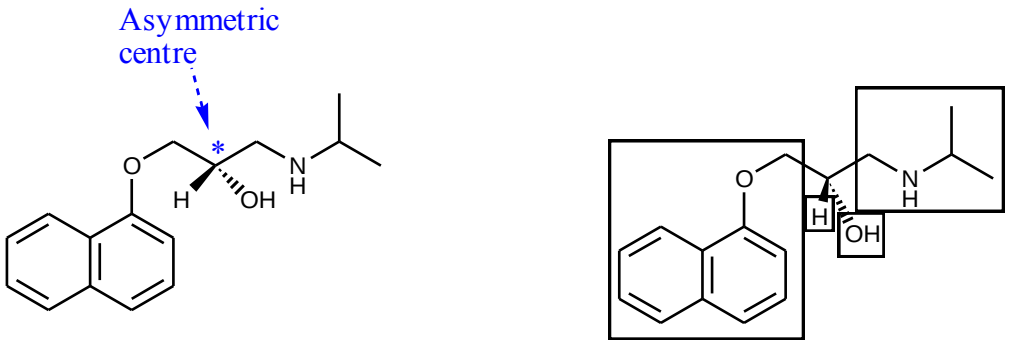



Having identified the priorities of the groups, the molecule is orientated such that the group of lowest priority is pointing backwards. If the remaining three groups are arranged clockwise from highest to lowest priority, then the centre is defined as *R*. If they are arranged anticlockwise, the centre is defined as *S*. In our example, the group of lowest priority is already pointing backwards (note the hatched wedge bond). The priority groups (1-2-3) are arranged in a clockwise fashion and so the asymmetric centre of adrenaline can be assigned as *R*.

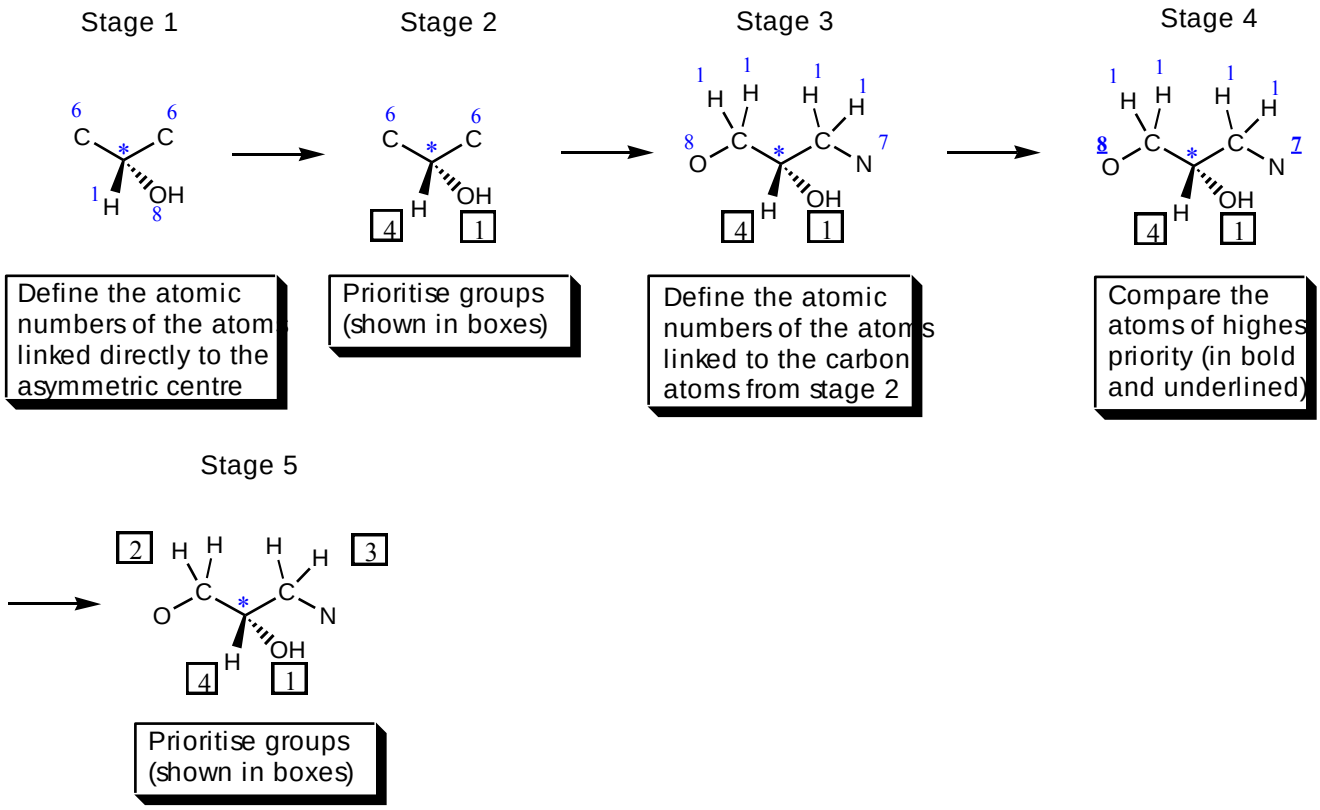



Assignment of the chiral centre in propranolol

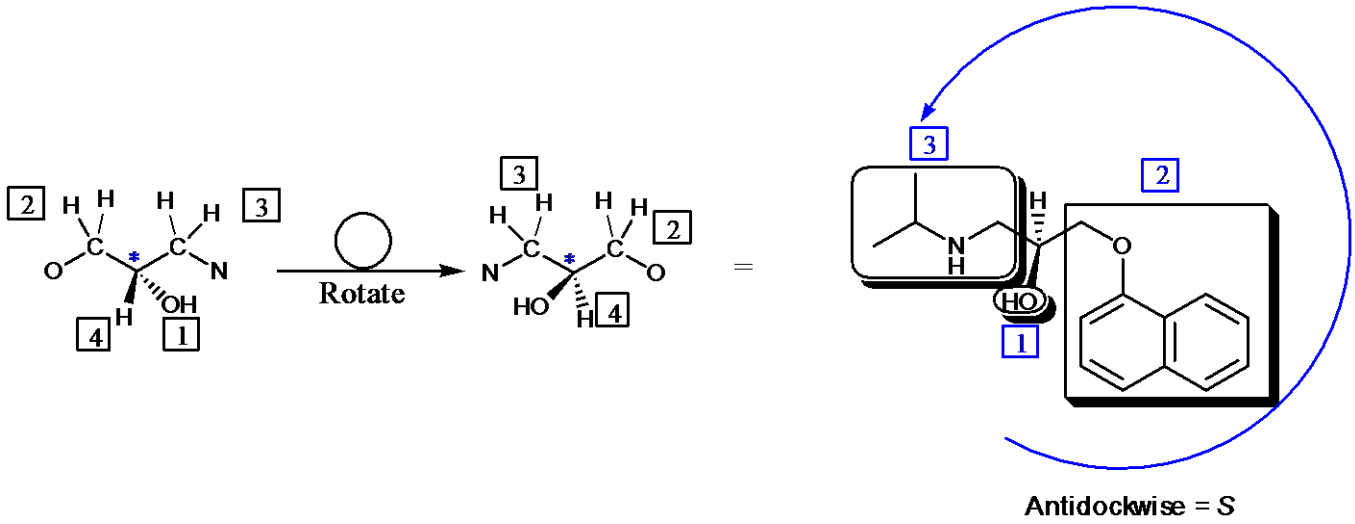
The four different substituents attached to the asymmetric centre of propranolol are highlighted below.




The first step in the prioritisation process is to identify the atoms directly linked to the asymmetric centre and assign their atomic numbers (stage 1). Next, the atoms are prioritised with respect to their atomic numbers (stage 2). Oxygen has the highest atomic number and so it takes priority 1. Hydrogen has the smallest atomic number and so it takes priority 4. However, we have two identical carbon atoms and so we cannot distinguish between them at this stage. We now have to identify the atom of highest priority attached to each of the carbon atoms (stage 3). Therefore, the atoms linked to the carbon atoms have to be identified and assigned atomic numbers. One of the carbons is an aromatic carbon and so there are another two carbons linked to it. However, the rules state that any atom linked by a double bond can be counted twice. Therefore, there are a nominal three carbons attached. The other carbon has a nitrogen and two hydrogens attached. In the final stage (stage 4), we compare the atoms of highest priority in each of the groups. In this case, we are comparing nitrogen with carbon. Nitrogen has the higher atomic number and so the group containing nitrogen takes priority. Note that it is not a case of 'adding up' the atomic numbers of the atoms concerned in each group. Therefore, priorities are *not* based on how large a particular group is. For example, the aromatic ring in adrenaline is larger than the $CH_2NHMe$ group, but takes a lower priority as a result of the prioritisation process.

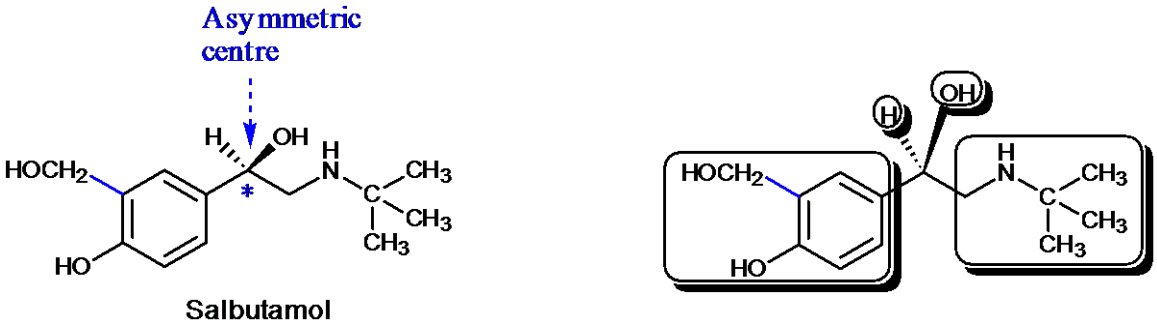



Having identified the priorities of the groups, the molecule is orientated such that the group of lowest priority is pointing backwards. If the remaining three groups are arranged clockwise from highest to lowest priority, then the centre is defined as *R*. If they are arranged anticlockwise, the centre is defined as *S*. In our example, the group of lowest priority is pointing forwards and so the structure has to be rotated. The priority groups (1-2-3) are arranged in a clockwise fashion and so the asymmetric centre of propranolol can be assigned as *R*.

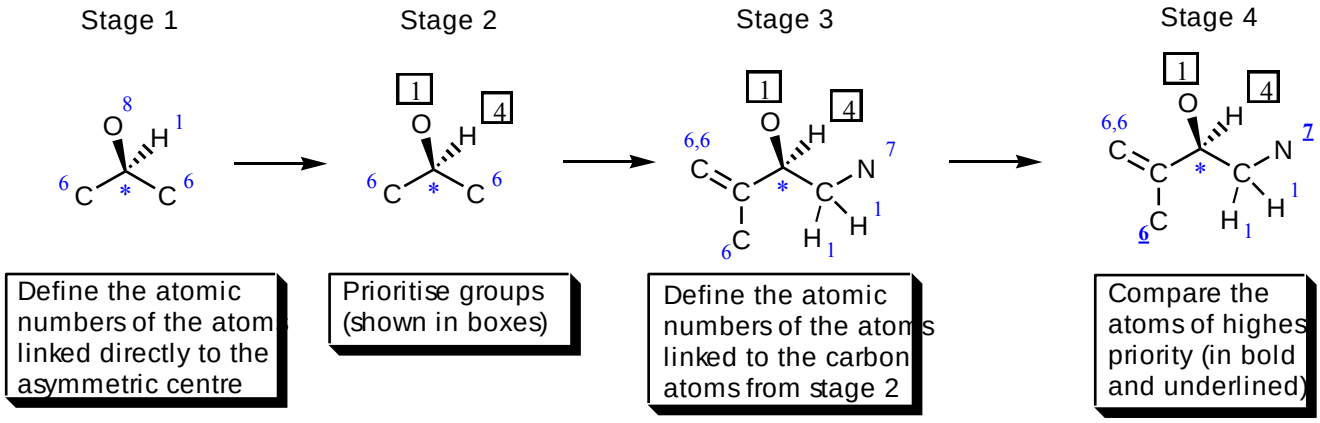


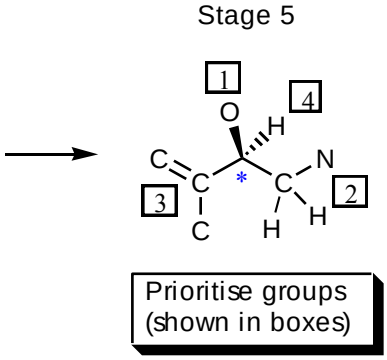
Assignment of the chiral centre in salbutamol

The four different substituents attached to the asymmetric centre salbutamol are highlighted below.

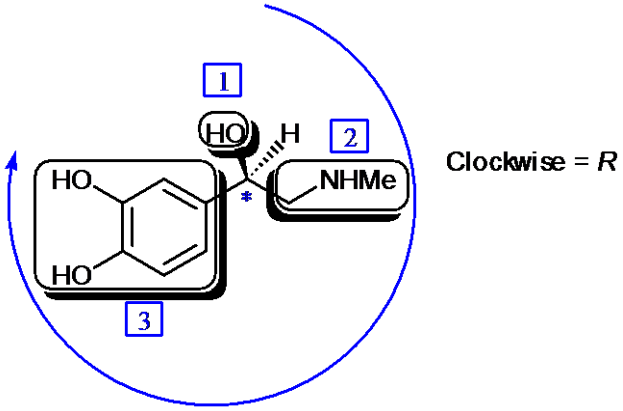



The prioritisation process is very similar to the one for adrenaline



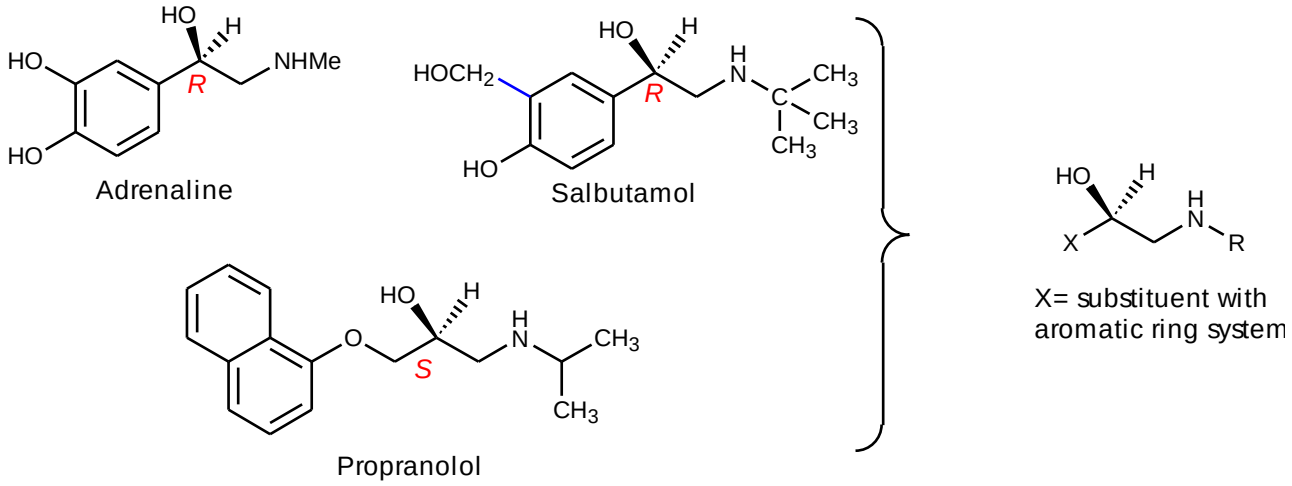




The asymmetric centre of salbutamol can be assigned as *R*.

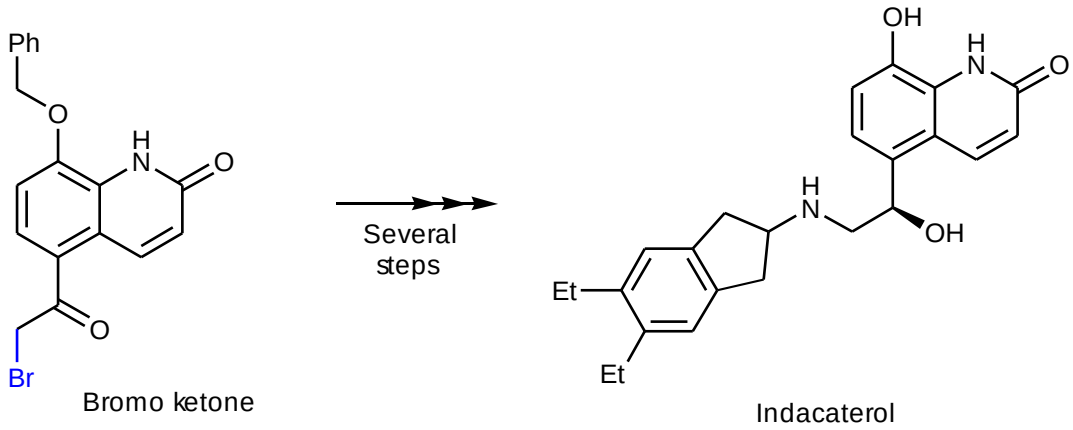



**Question 5.2**
Both salbutamol and adrenaline are adrenergic agonists having an asymmetric centre with the *R*-configuration. The adrenergic antagonist propranolol has an asymmetric centre that is in the S-configuration. Does this mean that antagonism is caused by different orientations of the groups at the asymmetric centre?

**Answer**
No. Propranolol can be drawn in a different way to show that the orientations of OH, H, the groups contain nitrogen and the group containing the aromatic ring are the same for all three structures. The different assignments (*R* and *S*) are a consequence of the rules involved in prioritising groups. The presence of the extra oxygen in salbutamol affects the priorities of the various groups




**Question 5.3**
**Indacaterol** is a β-adrenergic agonist approved in Europe as Onbrez, and is used for the treatment of asthma and other related diseases. Suggest an asymmetric synthesis that could be used to prepare indacaterol from the bromo ketone structure shown below.

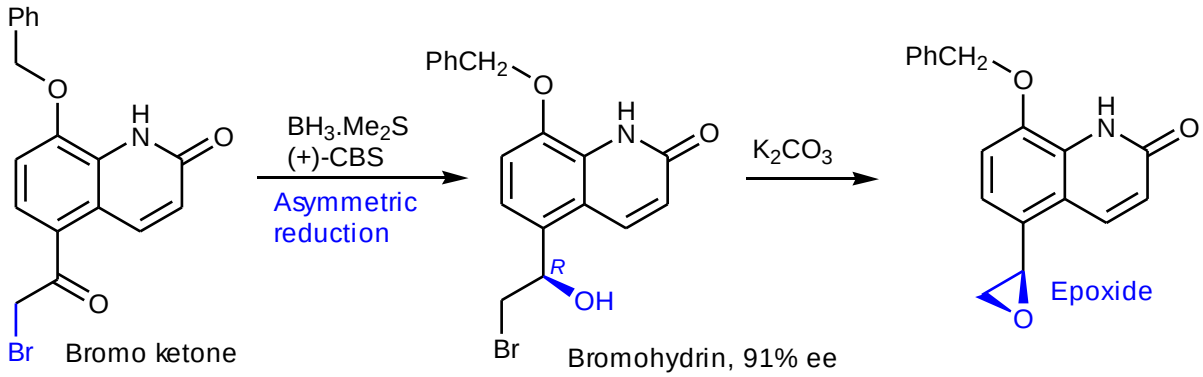


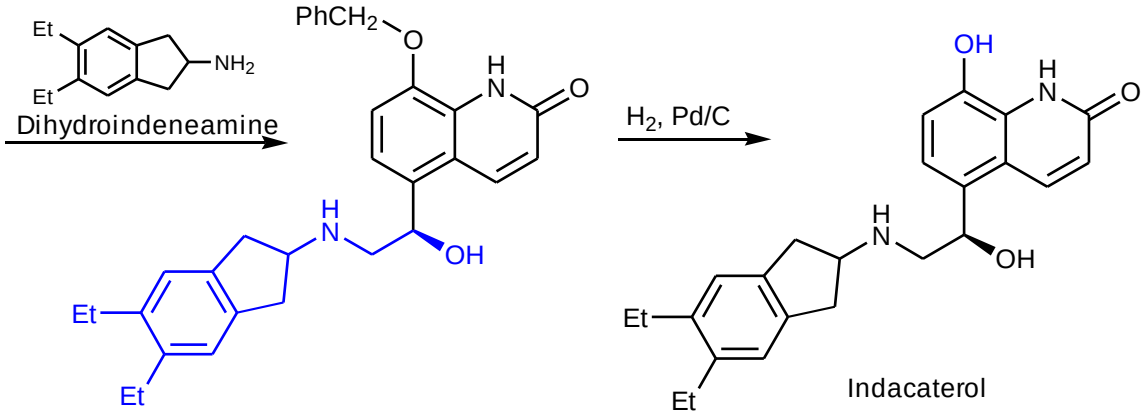

Bromo ketone

Indacaterol

**Answer**

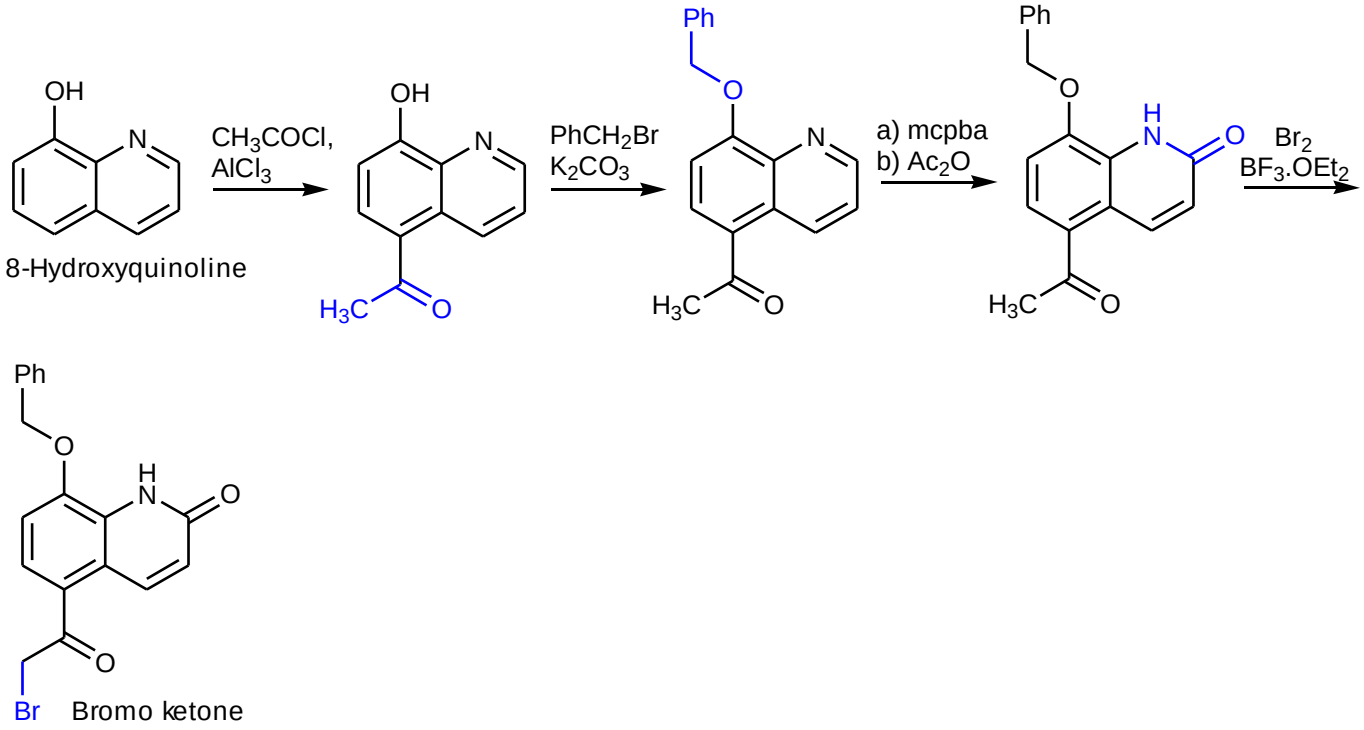
One possible approach that has been published is the following. The bromoketone is reduced with diborane in the presence of a chiral agent CBS (the Corey-Bikashi-Shibata reaction). The resulting bromohydrin is set up for the formation of an epoxide which was carried out with potassium carbonate. Reaction of the epoxide with a dihydroindeneamine resulted in a regioselective addition of the amine to the less substituted carbon of the epoxide and restored the required alcohol group with the correct absolute configuration. A final deprotection step then generated indacaterol.



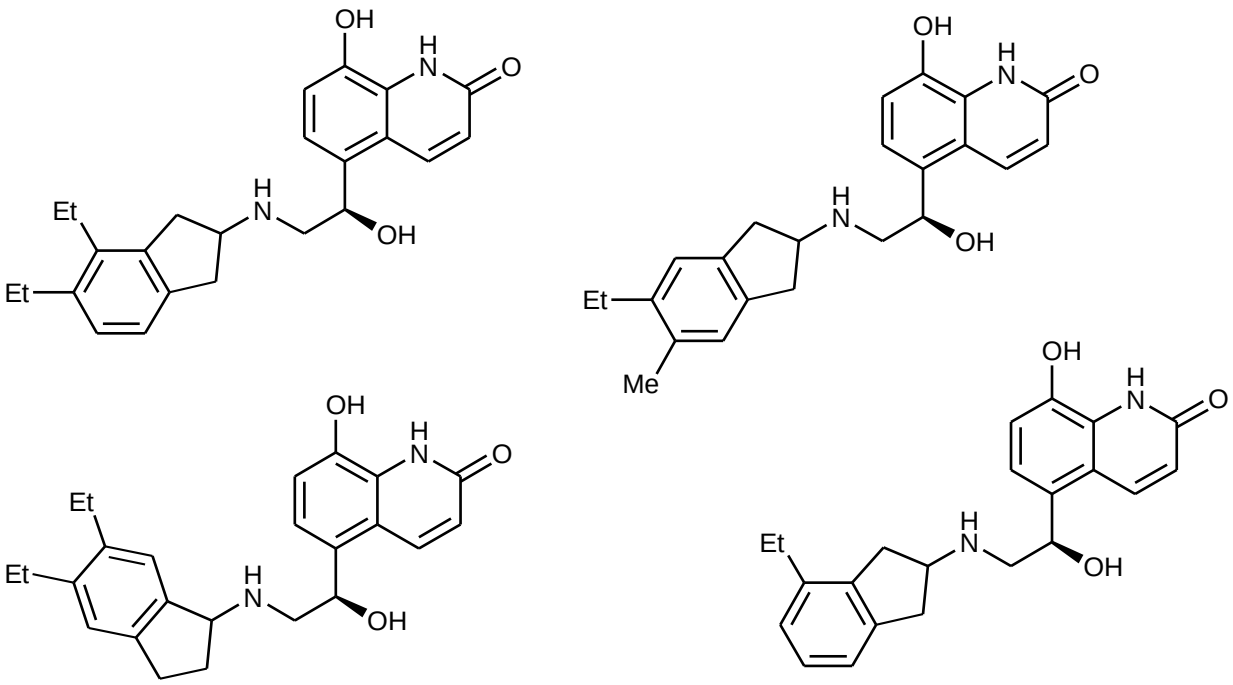




Indacaterol

The bromoketone intermediate itself was synthesised as follows;

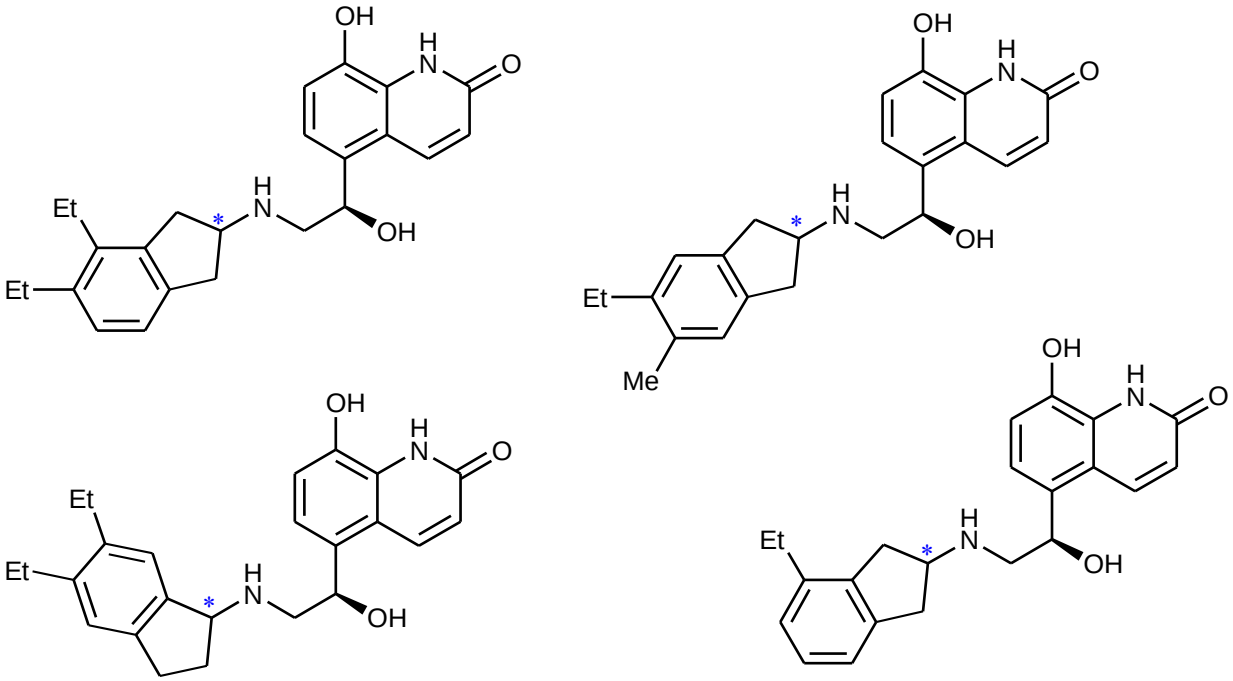



**Question 5.4**
Consider the following analogues of indacaterol. Can you foresee any added complications involved in the synthesis of these compounds? Describe a general strategy that can be applied to simplify the synthesis of chiral molecules.




**Answer**

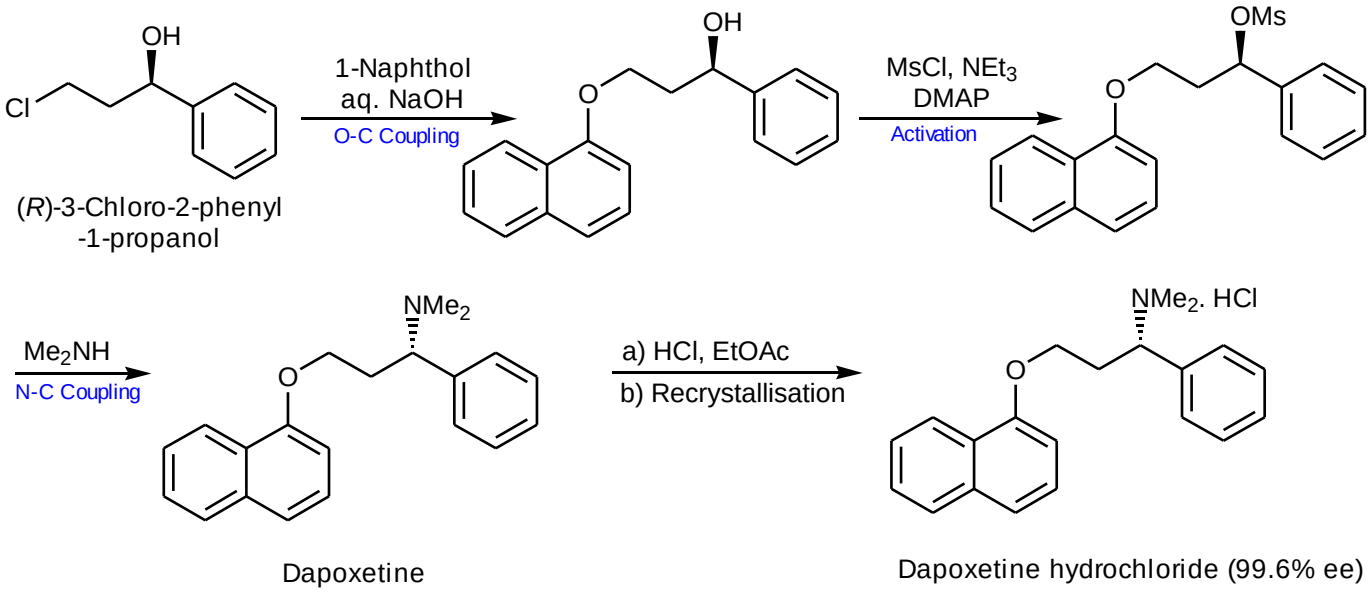
All of these analogues have an extra chiral centre as shown by the asterisks below.




The dihydroindeneamines that would be needed for the synthesis are inherently chiral, and if a racemate of a particular dihydroindeneamine was used, the synthesis would result in two diastereoisomers having different properties. In order to avoid this, it would be

necessary to separate the two diastereoisomers at the end of the synthesis, or use a single enantiomer of the dihydroindeneamine.
A general strategy to simplify drug synthesis is to use symmetrical starting materials to avoid (or reduce) the number of chiral centres that will be present in the final structure. Using symmetrical dihydroindenamines such as the one involved in the synthesis of indacaterol would avoid the problems of an extra chiral centre.

**Question 5.5**
Consider the first stage in the synthesis of **dapoxetine** (Box 5.6). Describe any chemoselectivity that is present and explain why it occurs.




**Answer**
There are two examples of chemoselectivity.
*The Cl is displaced by 1-naphthol and not the OH. The chloride ion is a better leaving group than the hydroxide ion.
*Secondly, the phenol present in 1-naphthol acts as the nucleophile and not the alcohol that is present in the alkyl chloride itself. Under the basic conditions used (NaOH), the phenol is ionised to form a phenoxide ion which is a stronger nucleophile than the OH group of an alcohol. A much stronger base would be required to remove the proton from an alcohol group in order to form an alkoxide ion.