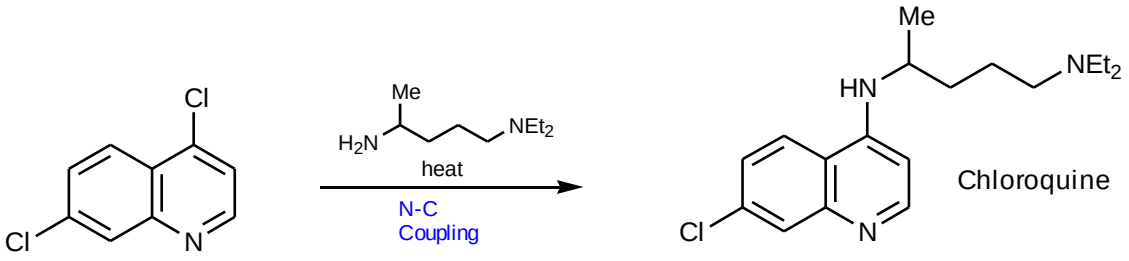
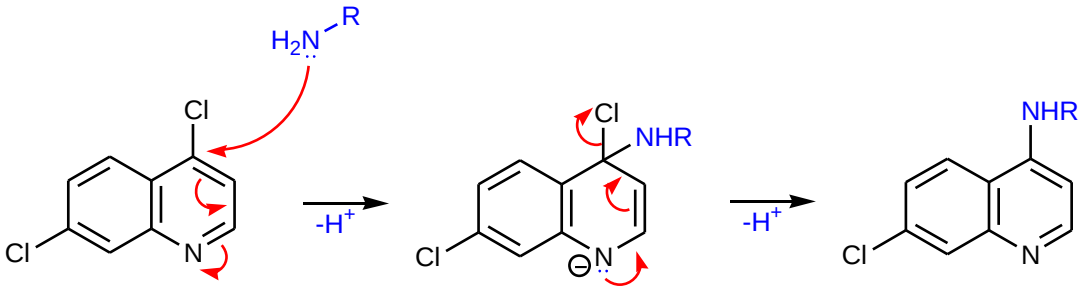
Chapter 2: Drug synthesis

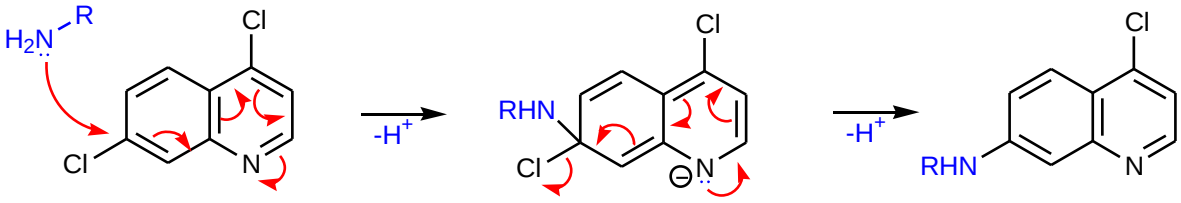
Question 2.1
Explain why the N-C coupling reaction used in the synthesis of the antimalarial agent **chloroquine** displaces one of the chlorine substituents in the bicyclic starting material rather than the other. What kind of selectivity is observed here?



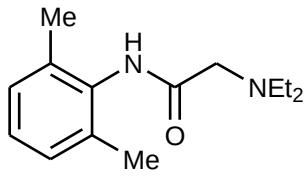
Answer
This is a chemoselective reaction. The nitrogen in the quinoline ring system is responsible for the chemoselectivity. The nitrogen atom is in the correct position to participate in the substitution mechanism as shown below. The negative charge of the intermediate can be placed on the electronegative nitrogen atom where it is more stable than if it was on a carbon atom.



It could be argued that the same stabilisation is possible if the amide reacted with the other chlorine. However, this would require disruption of the aromatic system in both of the bicyclic rings. In the mechanism above, the intermediate still contains an aromatic ring and should be more stable.

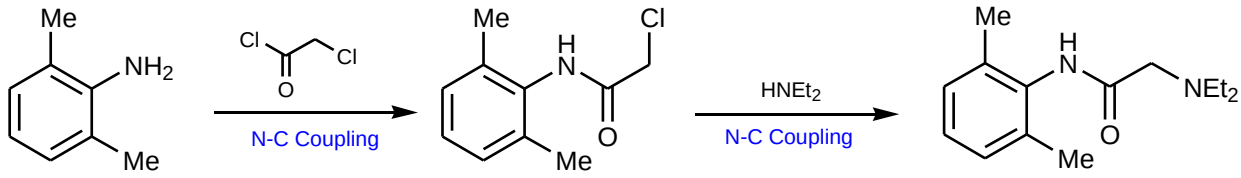


Question 2.2
Suggest how two consecutive coupling reactions could be used to synthesise the local anaesthetic **lidocaine.**



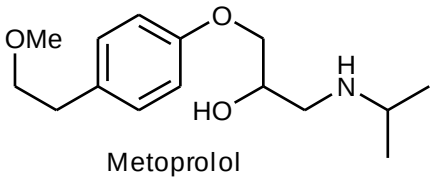
Lidocaine

Answer
Lidocaine can be synthesised from 2-6-dimethylaniline by two consecutive N-C couplings. The first coupling is a nucleophilic substitution of the amine with an acid chloride. The acid chloride is more reactive than the alkyl chloride and so chemoselectivity is possible. The second N-C coupling is a nucleophilic substitution of the alkyl chloride with diethylamine.



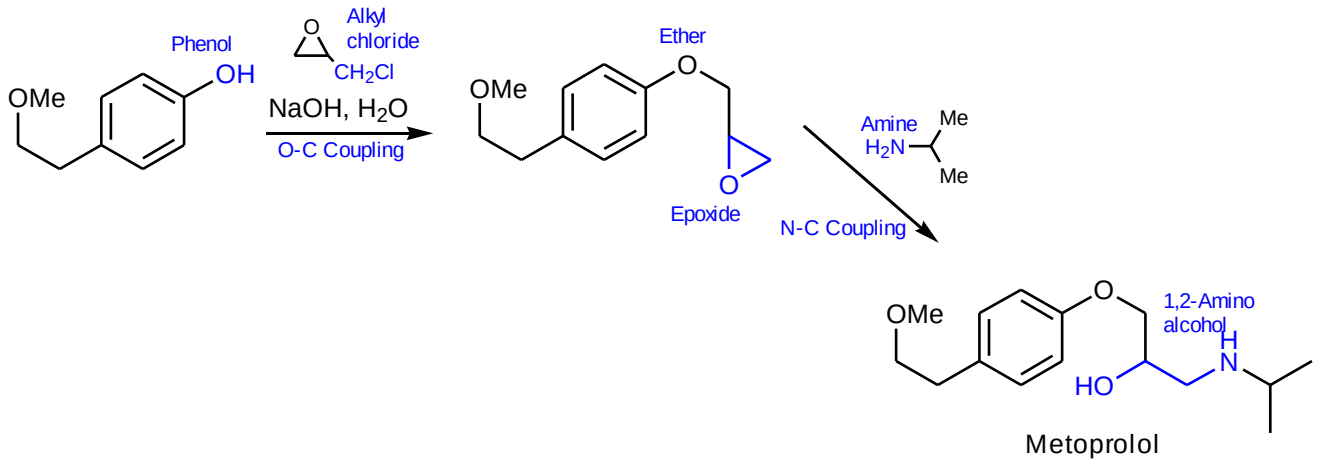
Lidocaine

Question 2.3
Suggest how 2 consecutive coupling reactions could be used to synthesise **metoprolol.**

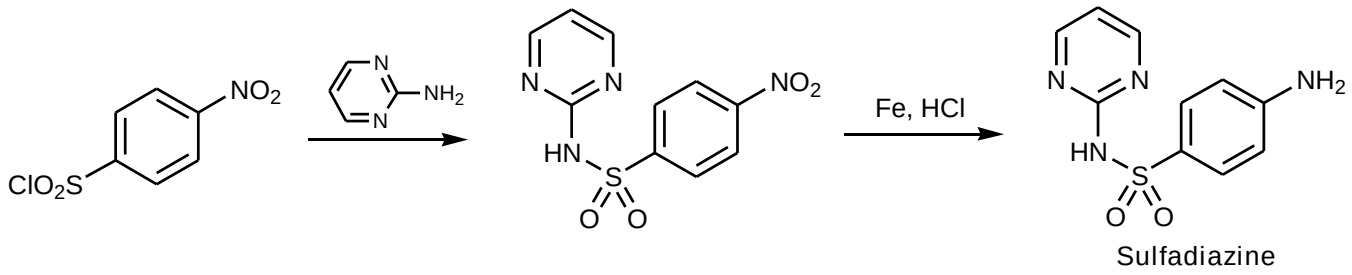


Metoprolol

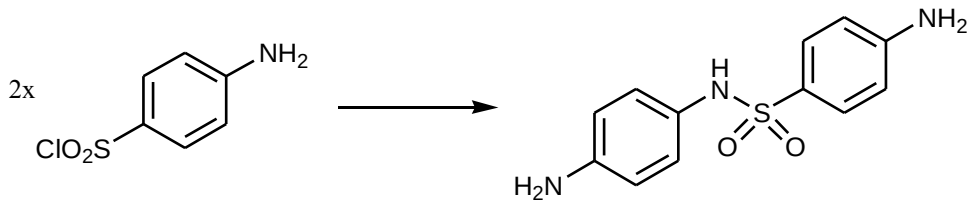
Answer
A similar synthesis to that used for the synthesis of propranolol can be used (compare Fig. 2.31 in Chapter 2). Note again the chemoselectivity in the first coupling reaction where the alkyl chloride is more reactive than the epoxide.



Question 2.4
The synthesis of the antibacterial agent **sulfadiazine** is shown below. Why is a nitro substituent used in the starting material instead of an amine?



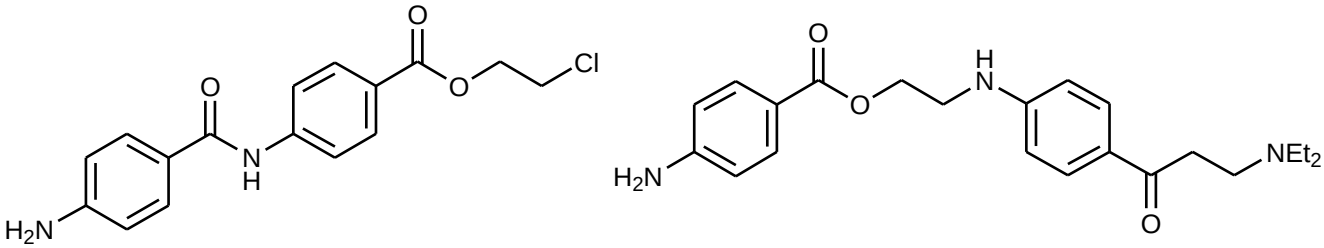
Answer
The nitro group is acting as a latent group for the amine group. If an amine group had been present from the beginning then a self condensation would have been possible resulting in an impurity and lowe yields of the desired product.



Question 2.5
In the synthesis of **procaine** shown in figure 2.41, the starting material contains a nitro group which is converted to an amino group at the final stage. Discuss whether the synthesis would have been successful if the reduction of the nitro group had been carried out at the beginning of the synthesis instead of the end.

Answer

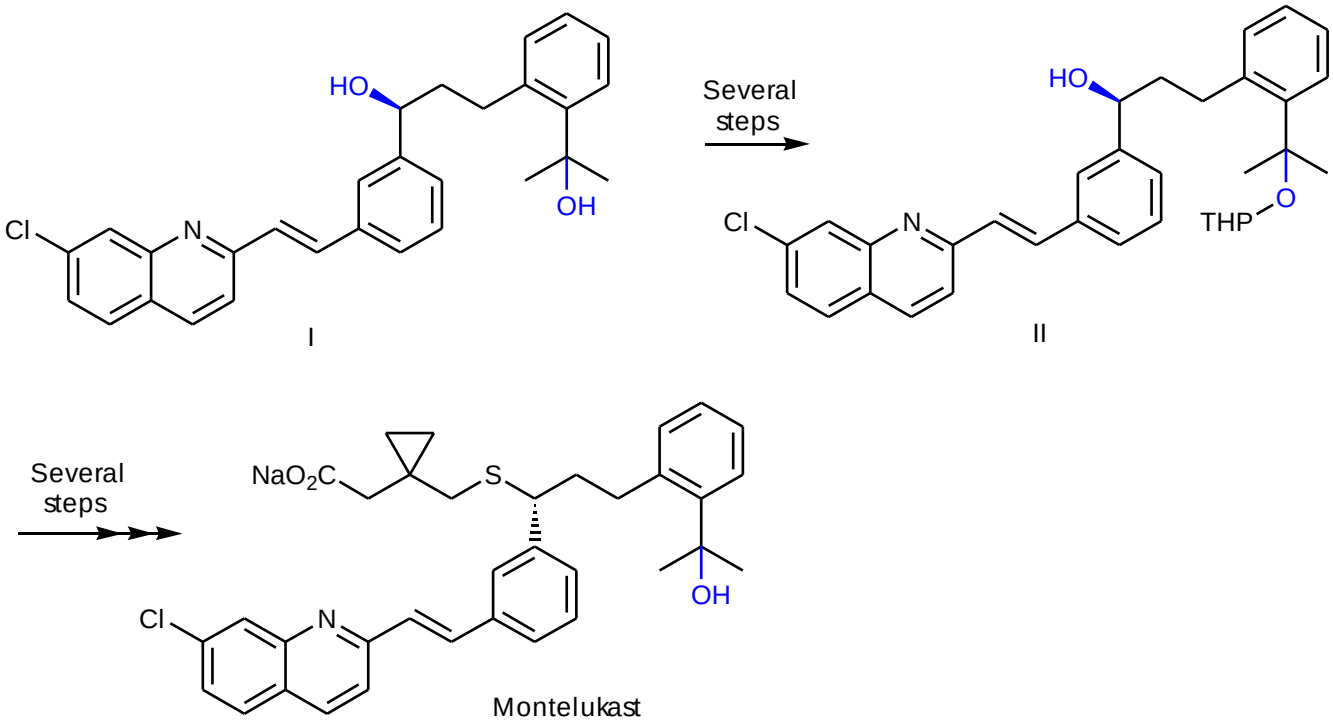
It is unlikely that the synthesis would have been as successful since the amine group could have acted as a nucleophile and competed with the reagents in both coupling reactions to give a number of alternative products. For example, the following might have been formed



Question 2.6
The two reactions shown in figure 2.25 involve an alcohol reacting with an acid chloride, instead of an amine. However, an amine nitrogen is more nucleophilic than an alcohol oxygen. Why do these reactions produce esters rather than amides?

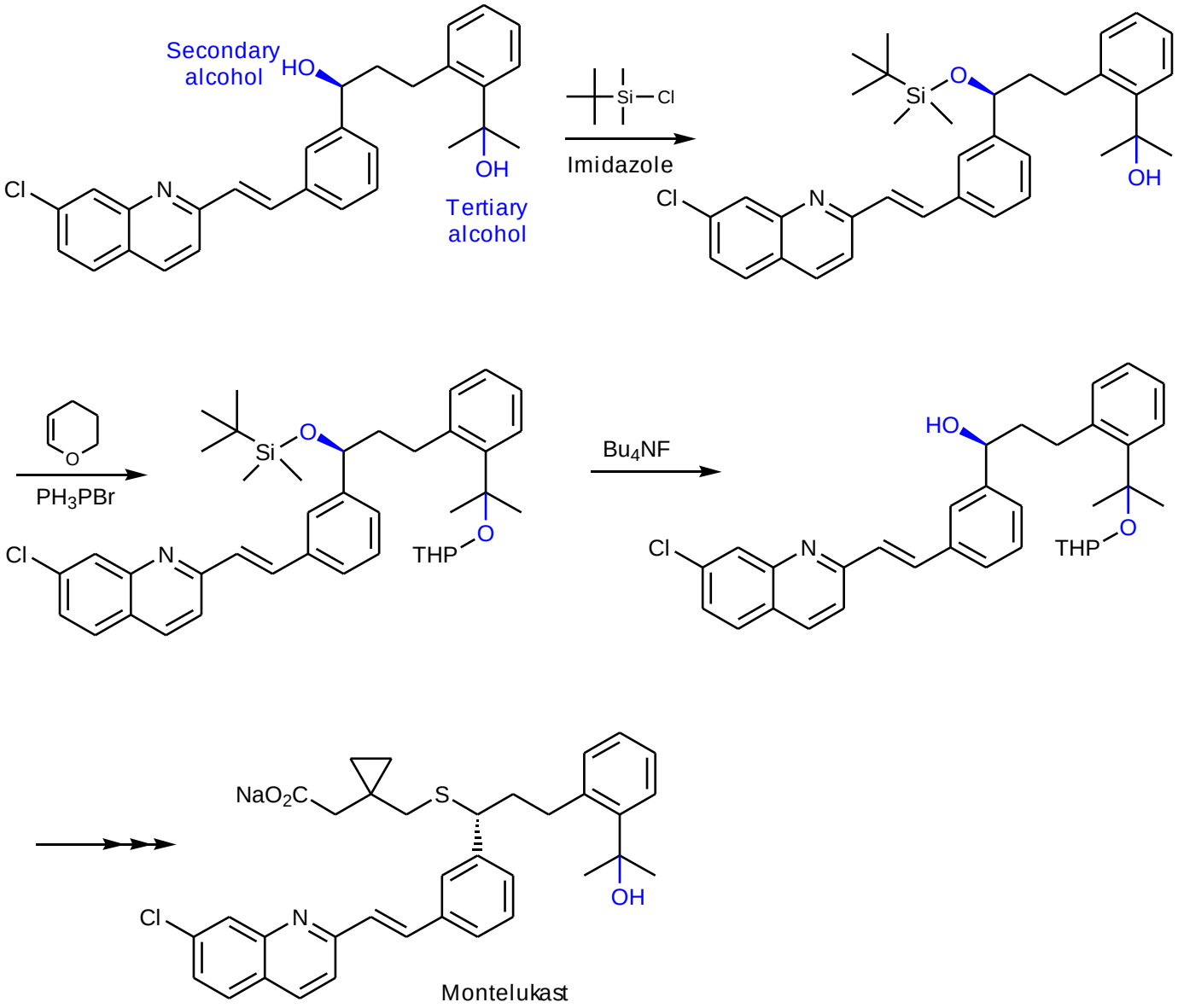
Answer
The first reaction is carried out under acid conditions in order to protonate the amine group as a hydrochloride salt. This means that the nitrogen atom has a positive charge and cannot competer with the alcohol as a nucleophile.
The presence of a base is usual when synthesising an ester from an alcohol and an acid chloride. The base serves to remove the OH proton from a reaction intermediate involved in ester formation. However, this does not explain why the alcohol reacts in preference to the amine. In this case, steric factors may be important. The amine is secondary with the nitrogen nitrogen is linked to a crowded quaternary centre. This may be acting as a steric shield and hindering the amine from acting as a nucleophile. In contrast, the alcohol is primary and is situated at the end of the chain. There is little steric hindance to it acting as a nucleophile.

Question 2.7
A synthesis of the anti-asthmatic agent **montelukast** involved an intermediate (I) containing two alcohol groups, and an intermediate (II) where one of the alcohol groups was protected. Suggest how intermediate (I) could be converted to intermediate II.



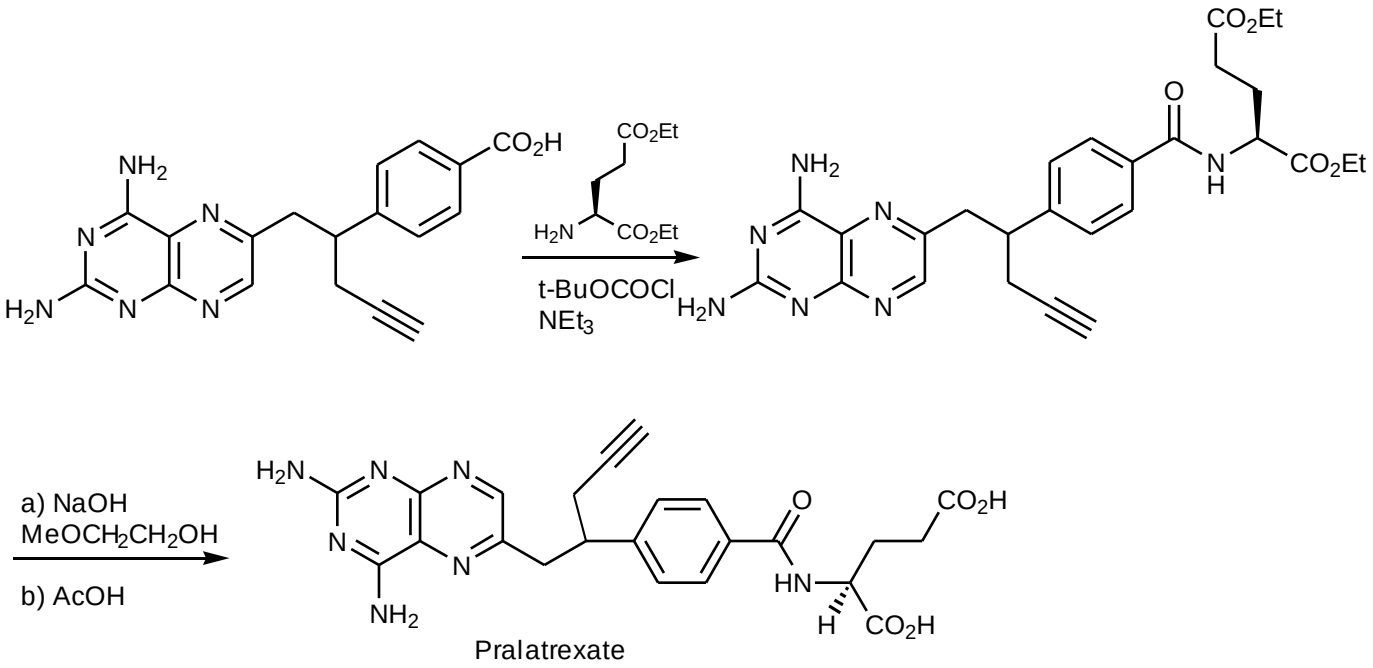
Answer

Chemoselectivity is possible between two similar functional groups if one of the functional groups is more accessible than the other, in which case the more exposed functional group will react more readily. In this example, the more exposed secondary alcohol can be protected selectively with the bulky *tertiary*-butyldimethylsilyl protecting group without reaction at the tertiary alcohol. The selectivity is enhanced by using a bulky silylating agent which differentiates more clearly between the two alcohol groups. The tertiary alcohol can then be protected with a tetrahydropyran group. It is then a case of removing the silyl protecting group selectively. This can be done using tetrabutylammonium fluoride (TBAF).



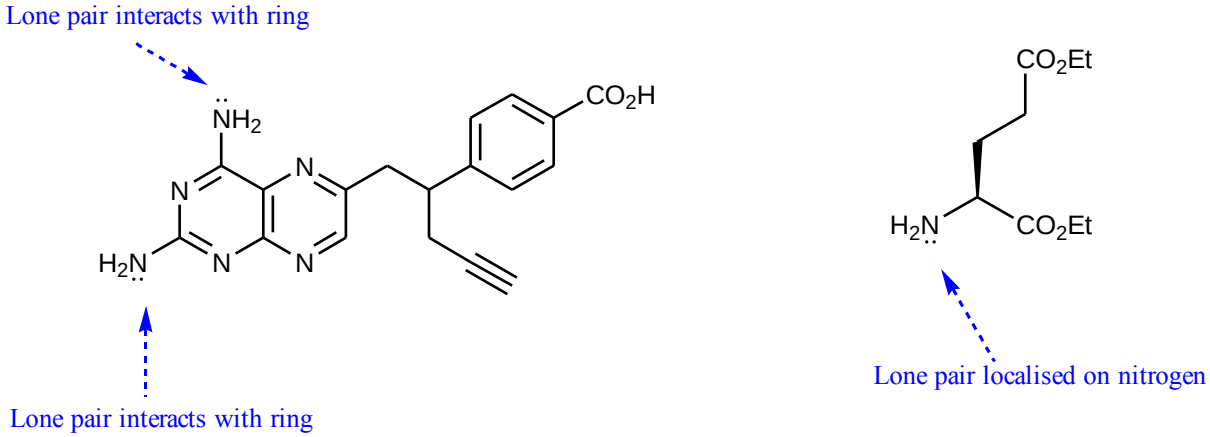
Question 2.8

Pralatrexate is an anticancer agent which can be synthesised as follows. The first stage is a coupling reaction between an amine and a carboxylic acid to give an amide. The amine groups in the bicyclic starting material are not protected, so why do they not react with the carboxylic acid in a self condensation reaction?

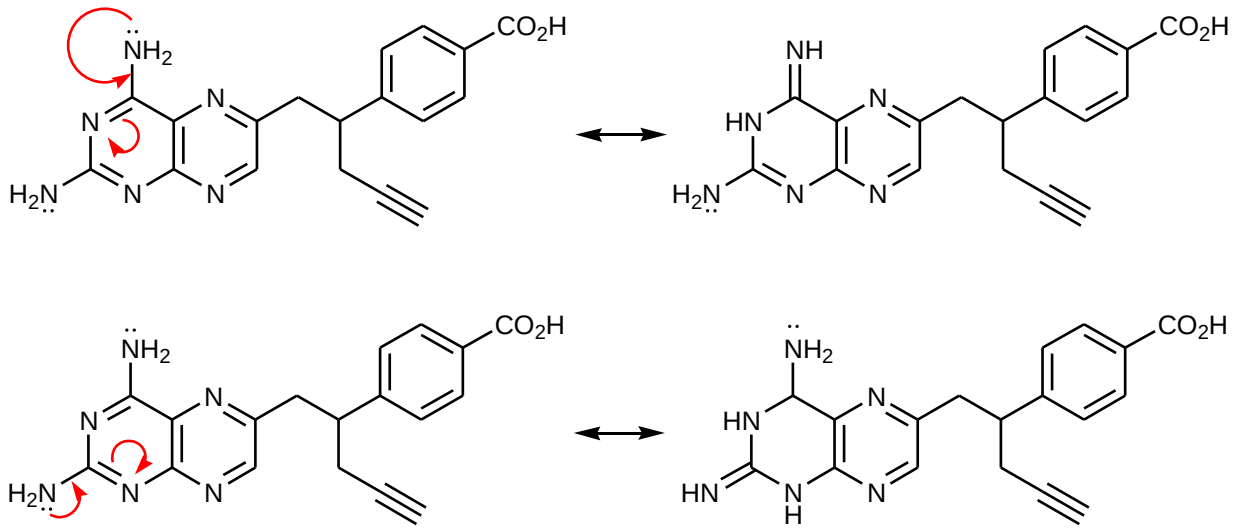


Answer

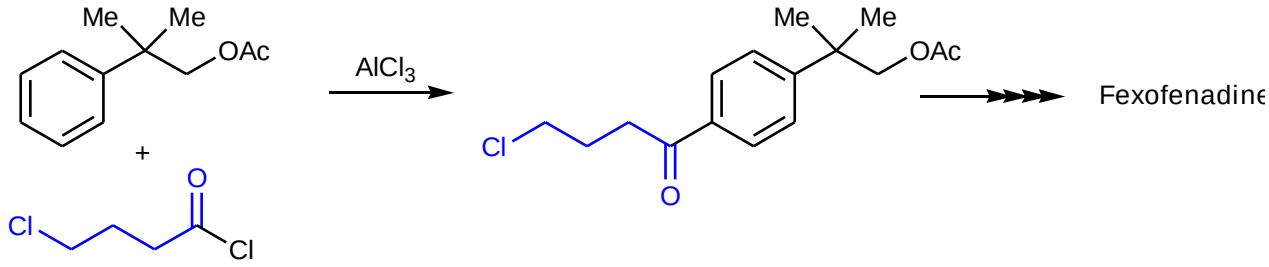
The amine groups that are present in the starting material are substituents of a heteroaromatic ring system. As a result, they are not very nucleophilic. This is because the lone pairs of the two amine nitrogen atoms can interact with the heteroaromatic ring through resonance. Therefore, both of these amine groups will be much less nucleophilic than the amine group present in the protected amino acid. The lone pair in this case is localised on the nitrogen atom and is much more available to form a bond.



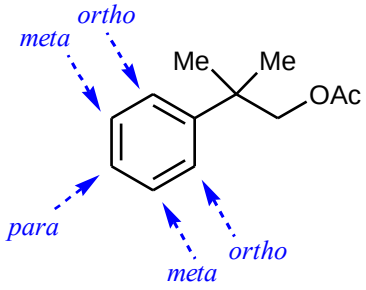
Examples of mechanisms by which the lone pair interacts with the ring.

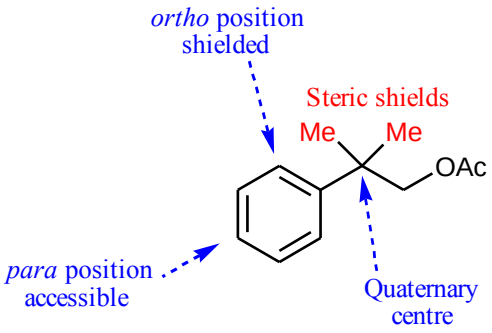


Question 2.9
The following reaction was carried out as one of the early stages in a synthesis of fexofenadine. There is a high regioselectivity for the *para* position over the *ortho* and *meta* positions. Explain the reasons for this selectivity. Identify any chemoselectivity observed in the reaction.



Answer
The reaction is a Friedel Crafts acylation of the aromatic ring with an acid chloride. The reaction is chemoselective since the acid chloride reacts rather than the alkyl chloride, since the acid chloride is more reactive.
There is a substituent already present on the aromatic ring which will affect the regioselectivity of the reaction. There is an ester group present on the side chain, but this is three bonds away from the aromatic ring and will have little influence. Therefore, the substituent will behave like an alkyl substituent in the way it influences the regioselectivity of the Friedel Crafts acylation. This means that it will activate the ring and direct the reaction to the ortho and para positions, rather than the meta position. However, very little ortho substitution takes place despite the fact that there are two ortho positions and only one para position. This is because of the quaternary centre linked directly to the aromatic ring. The two methyl groups act as steric chields and hinder reaction at the ortho positions.

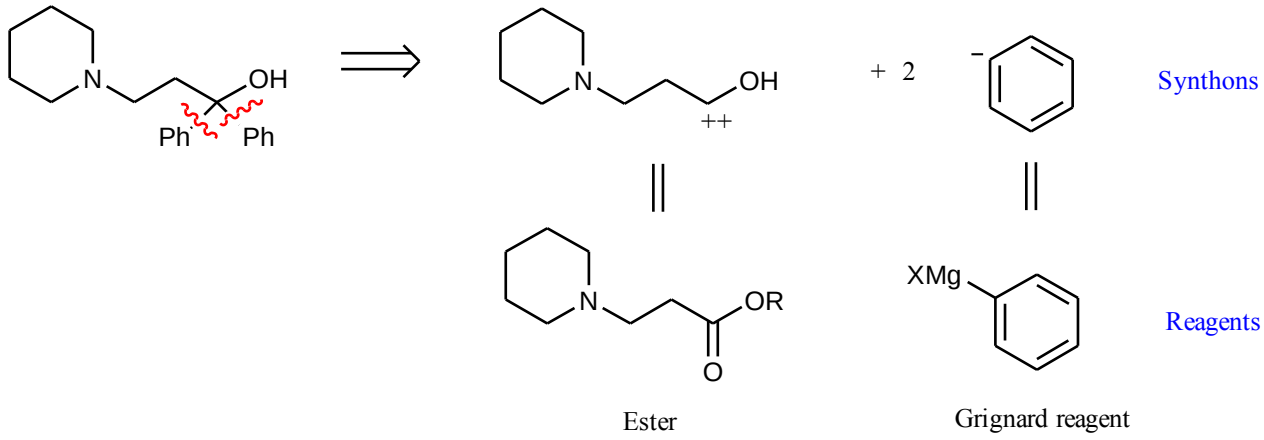




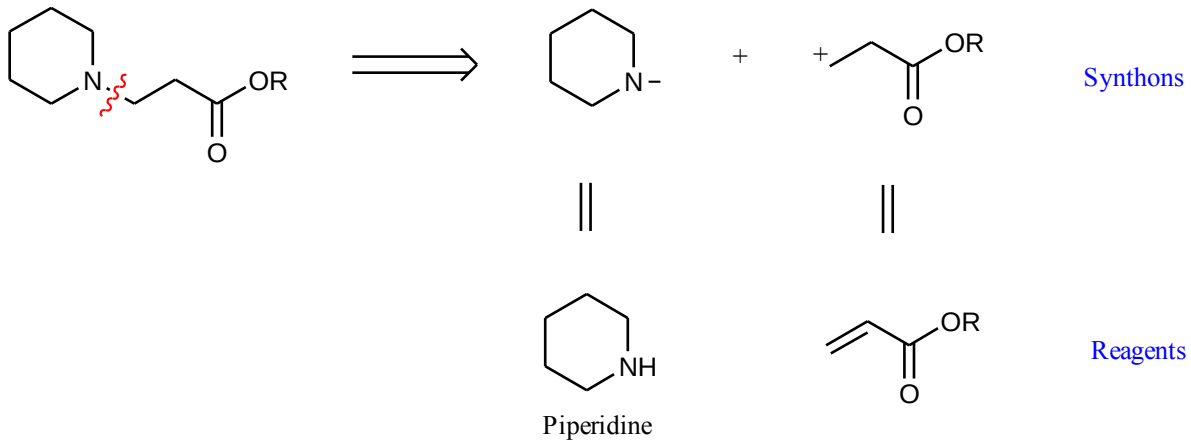
Chapter 3: Retrosynthesis

Question 3.1
1. Carry out a retrosynthetic analysis of the muscle relaxant **pirindol** and propose a possible synthesis.

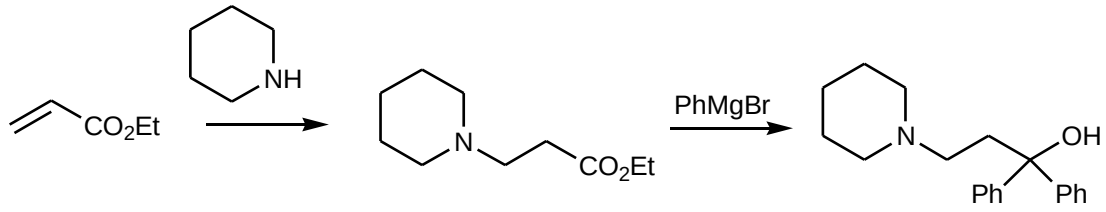
Answer
A key feature in the structure of pirindol is a tertiary alcohol with two identical substituents (the aromatic rings). This is the 'molecular signature' for a Grignard reaction with ester. Disconnecting the two substituents has the following key advantages.
*They disconnect a bond between an aromatic ring and a substituent
*The disconnection is at a branch point in the target structure. Such disconnections are more likely to result in simple synthons and reagents.



The Grignard reagent is commercially available. The ester contains a piperidine ring and is not commercially available. The following disconnection is likely to be useful since it involves the following key aspects.
* It disconnects a bond between a ring and a substituent
* It disconnects a C-X bond where X is a heteroatom (N)

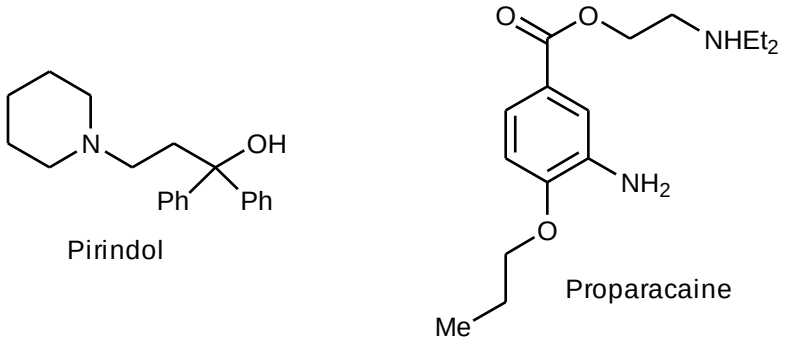


Both reagents are commercially available. The corresponding synthesis is as follows;



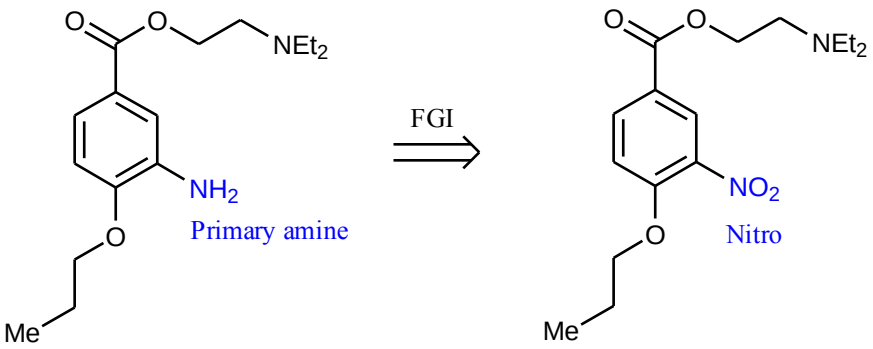
Question 3.2

Proparacaine (**proxymetacaine**) is a local anaesthetic that is used in ophthamology and is applied in eye drops. Carry out a retrosynthetic analysis of its structure and propose a possible synthesis.

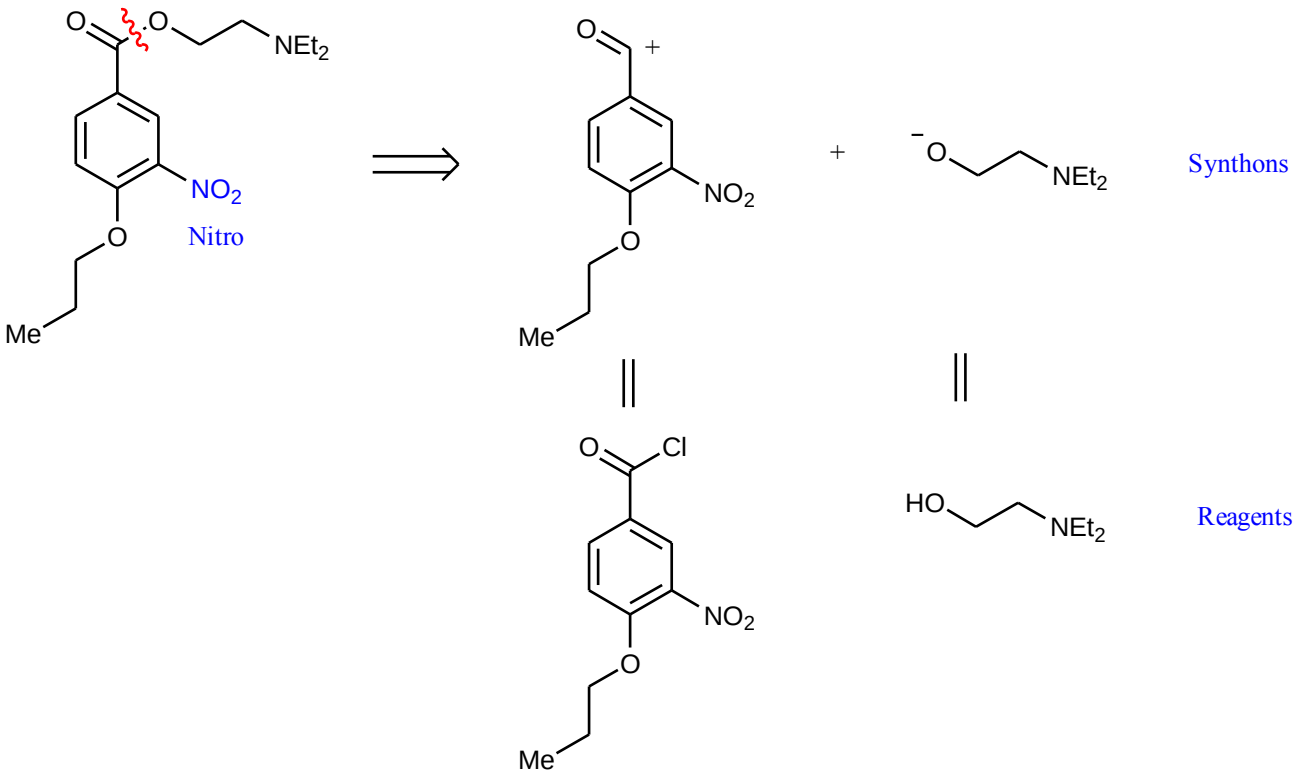


Answer

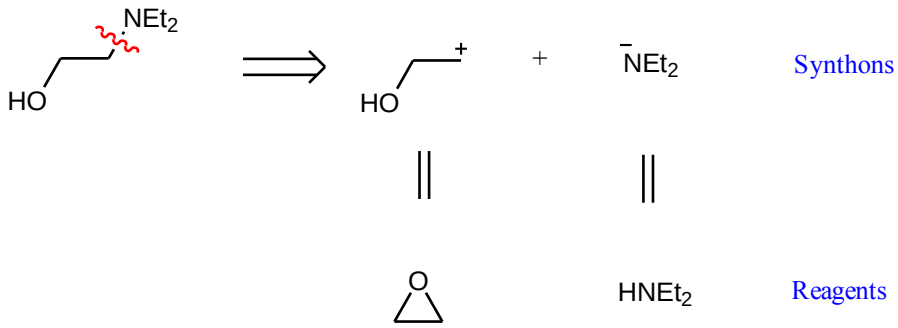
A key feature in the final product is the primary amine. This is a group that usually has to be protected during a synthesis since it is basic and nucleophilic. Therefore, it would be logical to introduce or reveal it as the final stage of the synthesis. This could involve the removal of a protecting group or the use of a latent group. A nitro group is commonly used as a latent group for a primary amine and so we will choose that approach. Therefore the first stage in the retrosynthesis is a functional group interconversion (FGI).



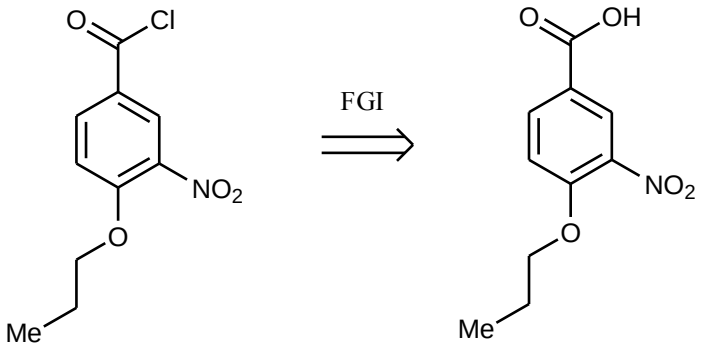
We now consider the nitro compound. A promising disconnection would be of the ester group which fits one of the criteria for a good disconnection since it involves a C-X bond where X is a heteroatom (O)
The reagents corresponding to the resulting synthons would be an acid chloride and an alcohol.



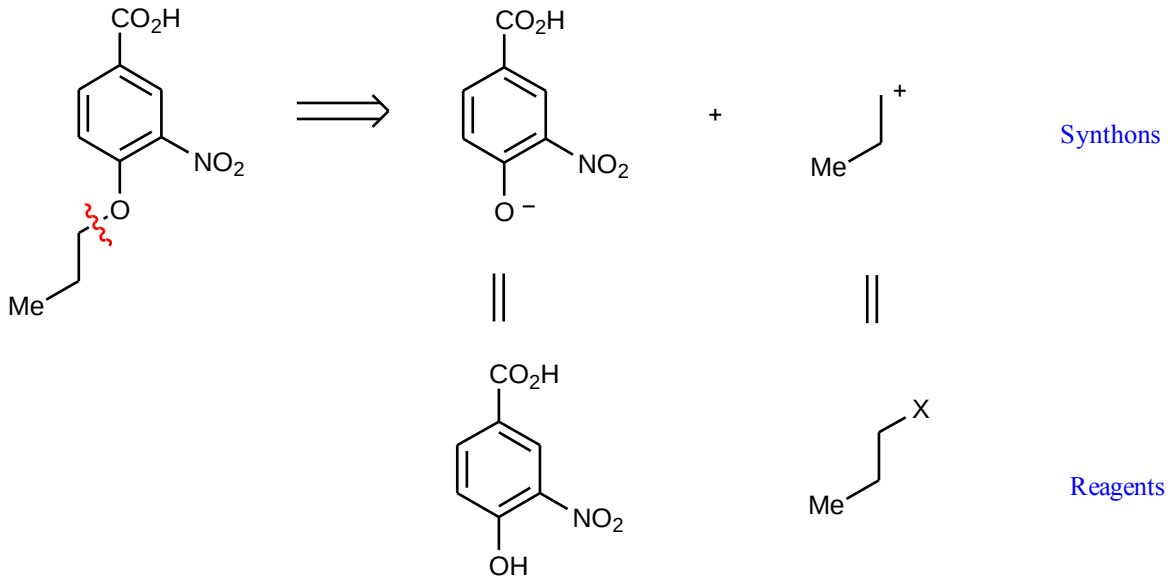
The amino alcohol could be obtained from an amine and an epoxide, both of which are commercially available.



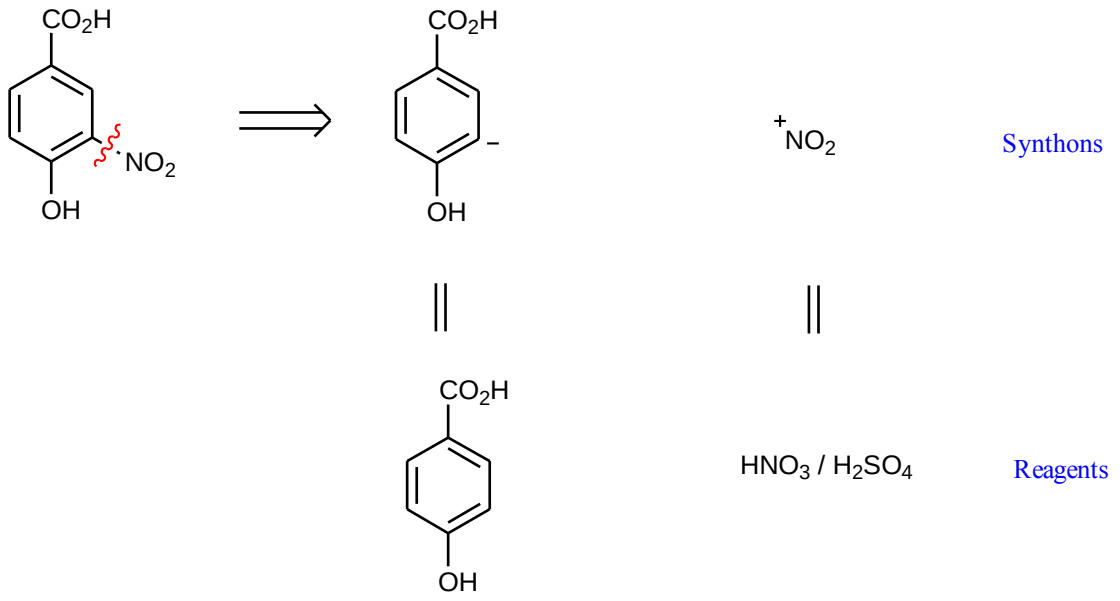
The acid chloride can be obtained from a carboxylic acid



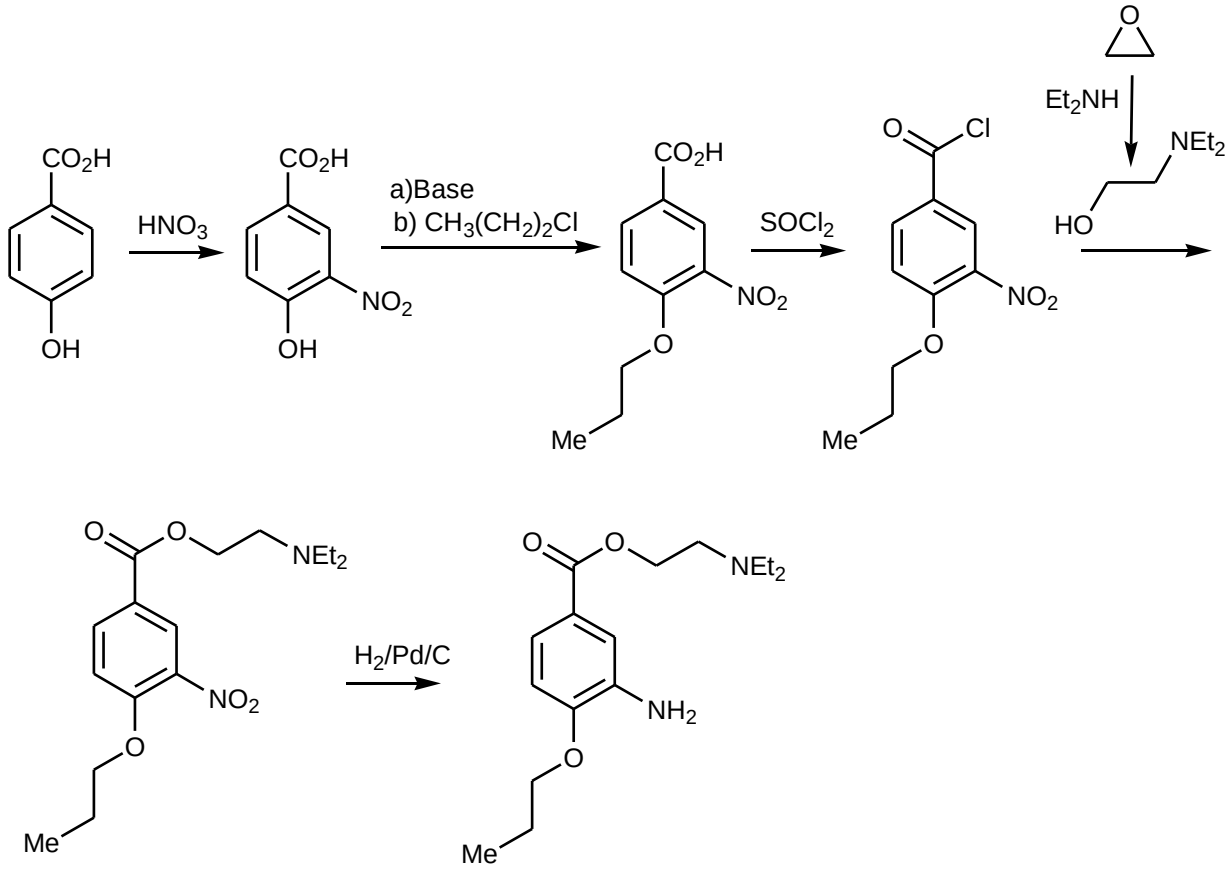
Another favoured disconnection is possible by disconnecting the C-O bond of the ether.



Finally, the bond to the nitro group can be disconnected to give a symmetrical aromatic structure that is commercially available.

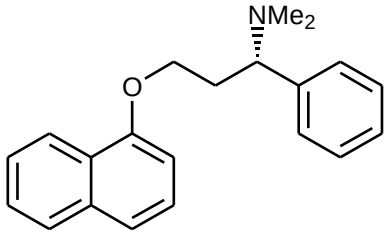


At each stage of the above retrosynthetic analysis, there are available reagents for the synthons or structures produced, and the reactions involving these reagents are feasible. The overall synthesis is the following -



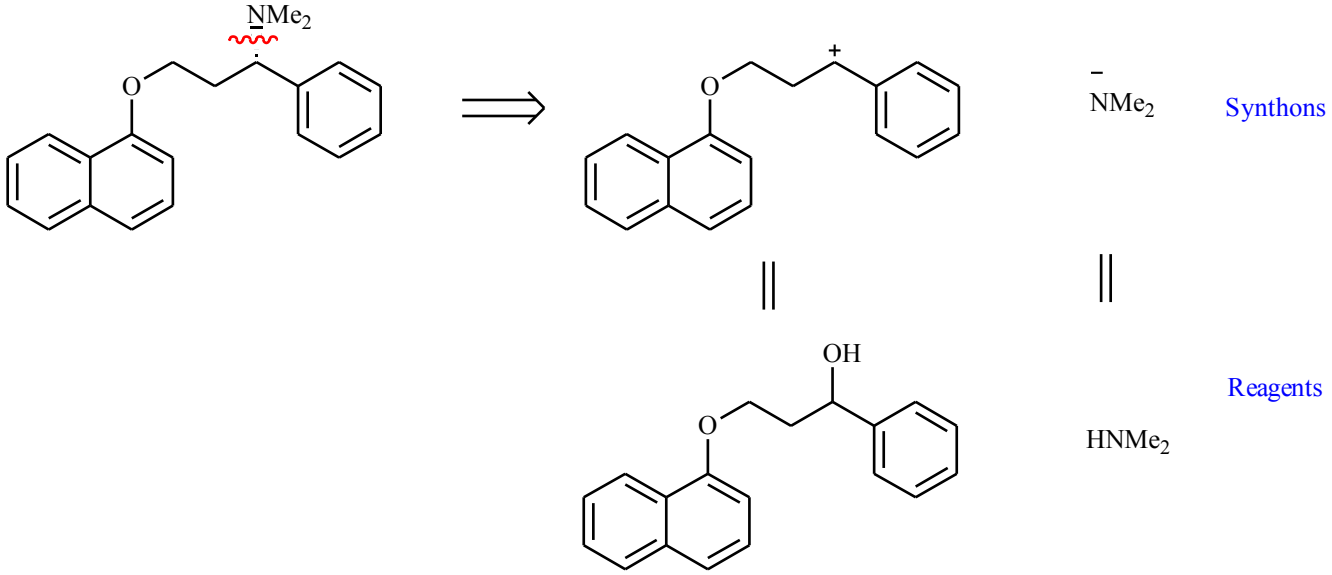
Note that the initial nitration is favoured since both substituents direct electrophilic substitution to the same position of the aromatic ring *(ortho* to the phenol and *meta* to the carboxylic acid).

Question 3.3
Carry out a retrosynthetic analysis of the antidepressant **dapoxetine** and propose a possible synthesis.

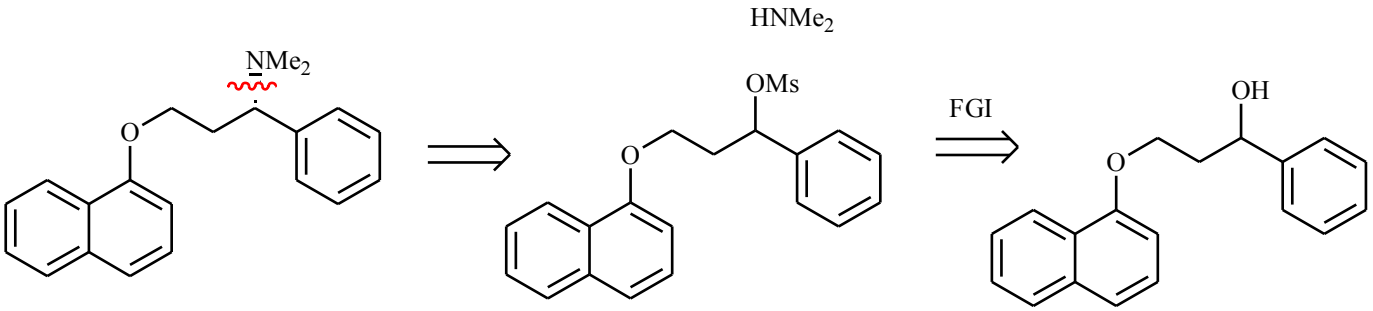


Dapoxetine

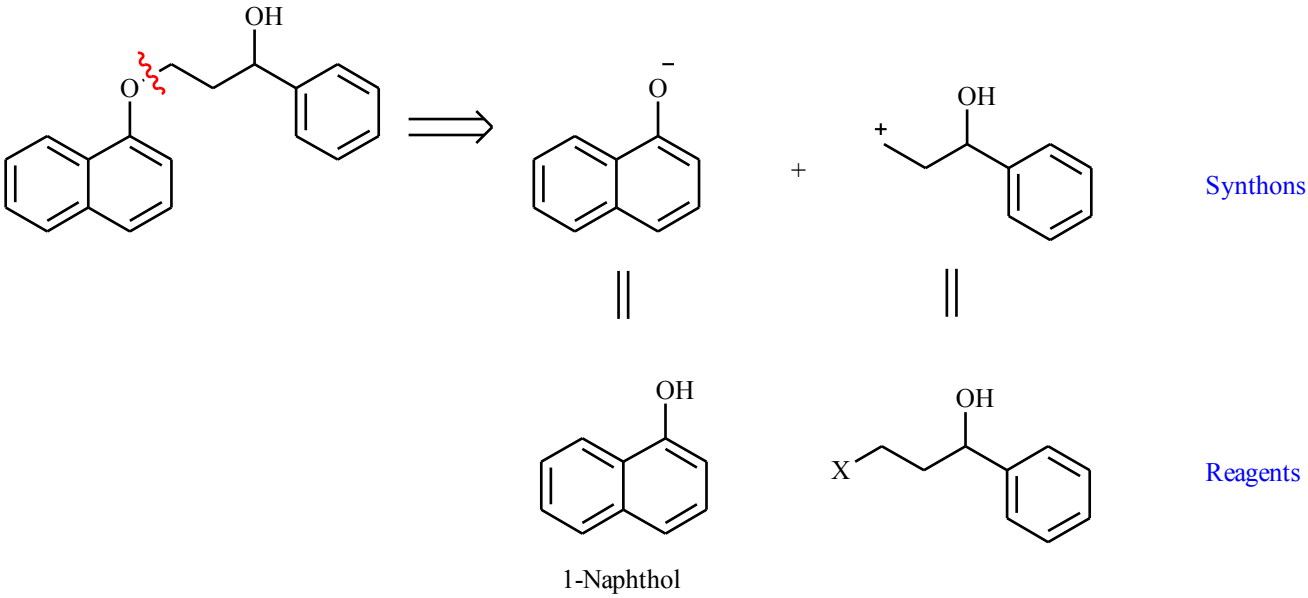
Answer
One possible approach is the following. A possible disconnection is the C-N bond.



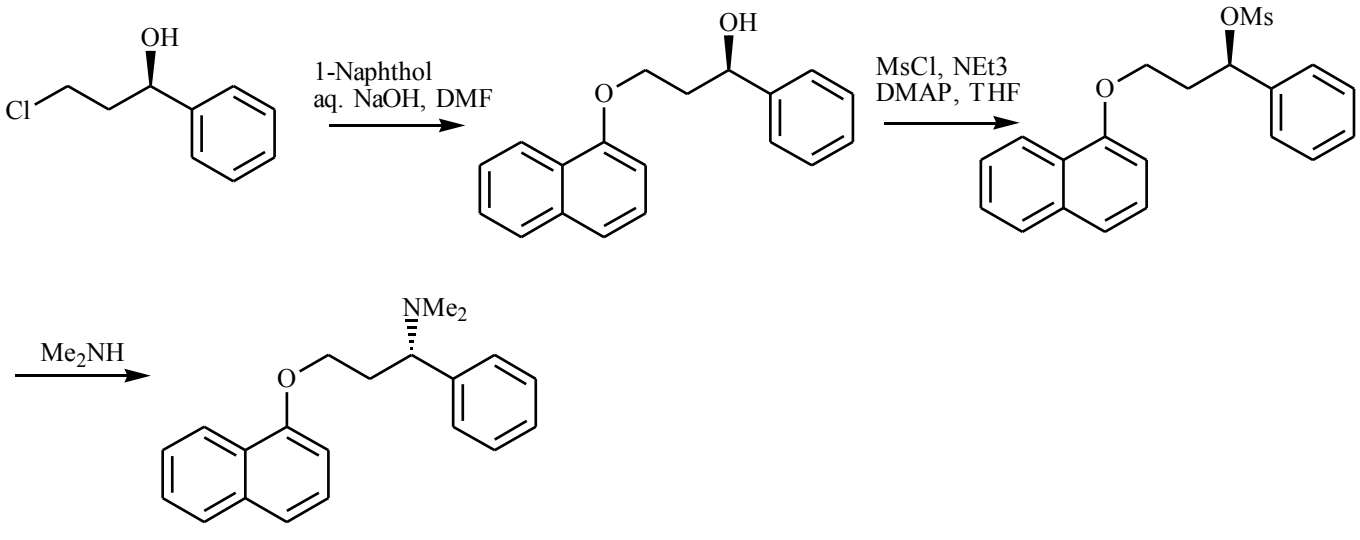
This is a favoured disconnection since a C-N bond is involved. The corresponding reagent for the synthon would be dimethylamine which is commercially available. The other synthon could correspond to an alcohol. Is the reaction between the alcohol and dimethylamine feasible? Would the amine be able to substitute the alcohol group? Alcohol groups are not particularly good leaving groups. However, an alcohol group can be easily converted to a mesylate of a tosylate. Therefore, we can modify the retrosynthesis to the following.



Disconnection the C-O bond of the ether group looks like a key disconnection since it disconnects a C-X bond, and is also in the heart of the molecule, rather than the periphery, such that it will lead to two similarly sized molecules as starting materials.

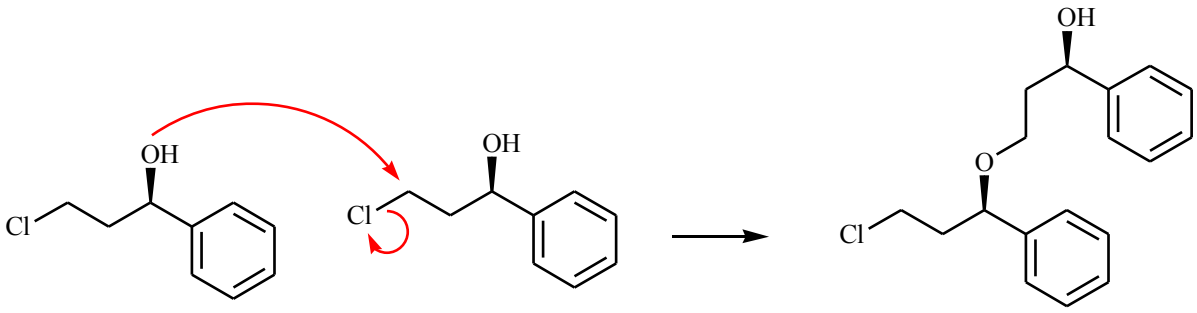


The synthon having the oxygen will have a natural negative charge. The corresponding reagent is 1-naphthol which is commercially available. The positively charged synthon corresponds to a reagent which will have a good leaving group at that position such as a halide, mesylate or tosylate. It makes sense to have a halogen since the mesylate or tosylate would have to be synthesised from a diol and it would be difficult to get chemoselectivity for one of the alcohol groups over the other. It is then a case of seeing whether which alkyl halide is commercially available.
The reaction scheme corresponding to the retrosynthesis is as follows.



Dapoxetine

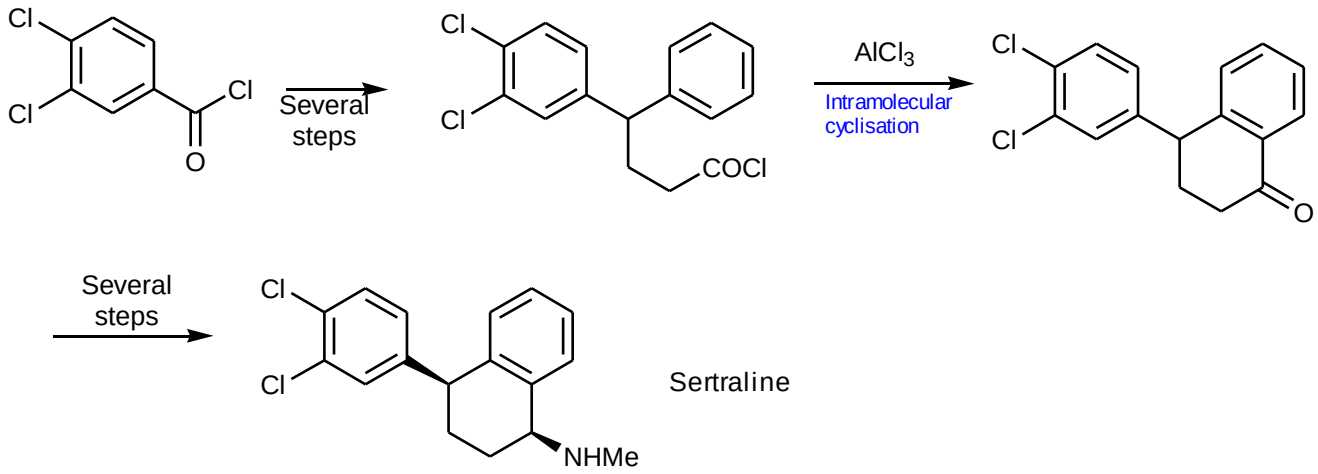
Note that the first stage involves the phenol group reacting with the alkyl halide. However, what is to stop two molecules of the alkyl chloride reacting together as follows?



This unwanted reaction can be prevented by carrying out the reaction in the presence of sodium hydroxide. This is a strong enough base to remove the proton from the phenol to form a phenoxide ion, but not strong enought to remove the proton from the alcohol to form an alkoxide ion. The phenoxide ion will prove a much stronger nucleophile than the uncharged alcohol group and so the reaction will favour the desired product.

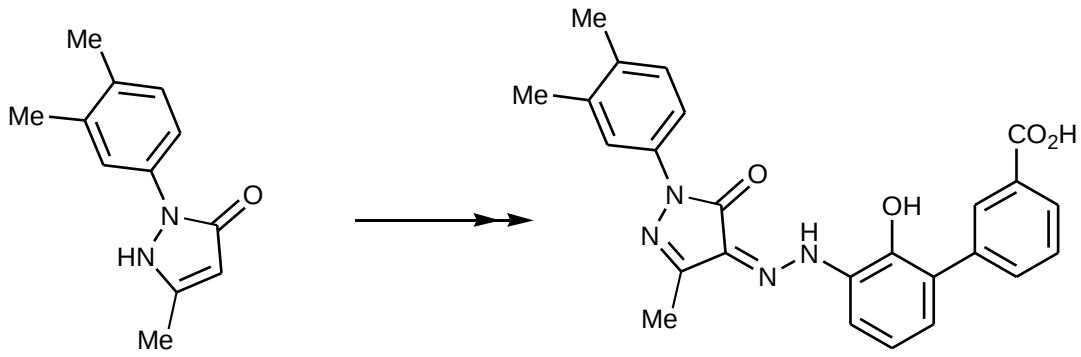
Chapter 4: Cyclic systems in drug synthesis

Question 4.1
In the synthesis of **sertraline** shown in Fig. 4.10, a Friedel Crafts acylation took place on one aromatic ring but not the other. Why?



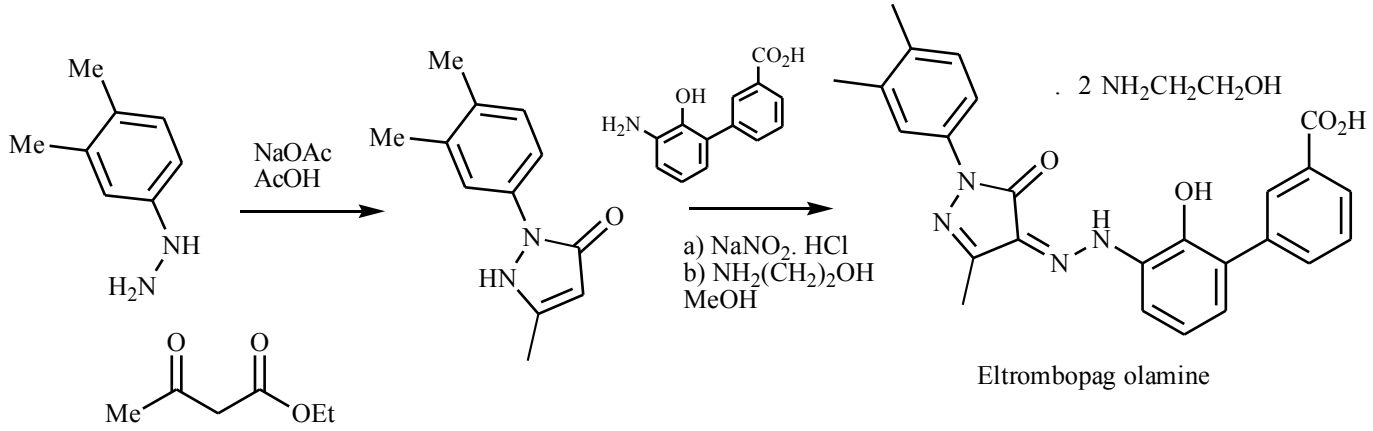
Answer
This is due to the different reactivies of the rings to electrophilic substitution. Chloro substituents have an elecron withdrawing effect on an aromatic ring making it less electron rich and less liable to undergo electrophilic substitutions such as the Friedel Crats acylation.

Question 4.2
Eltrombopag is a drug that was approved in 2008 for the treatment of patients having low platelet counts. It acts as an agonist at the receptor for the hormone **thrombopoietin.** The synthesis of the compound involves intermediate I. Suggest how this intermediate could be synthesised.



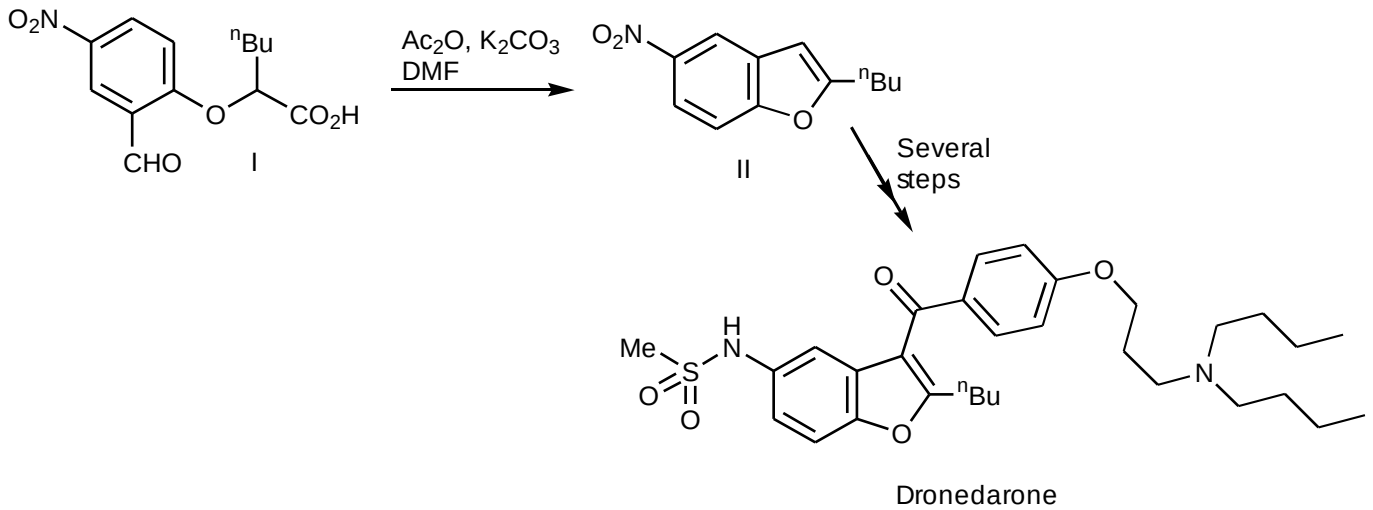
Answer

The intermediate contains a 5-membered heterocycle which could be formed by an intermolecular cyclisation involving a hydrazine and a β-keto ester. The hydrazine would act as a dual nucleophile and the β-keto ester as a dual electrophile.



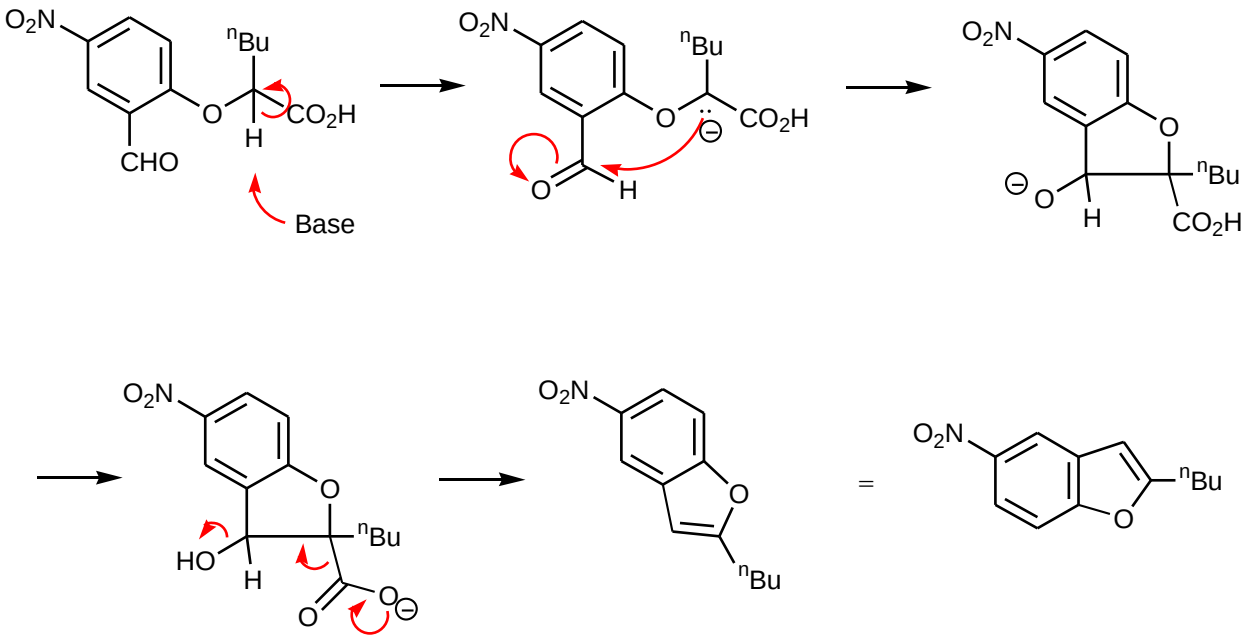
Eltrombopag olamine

Question 4.3
The following synthesis of a benzofuran (II) was involved in the synthesis of **dronedarone,** which is used in the treatment of cardiac arrythmias. Propose a mechanism by which the benzofuran intermediate is formed.



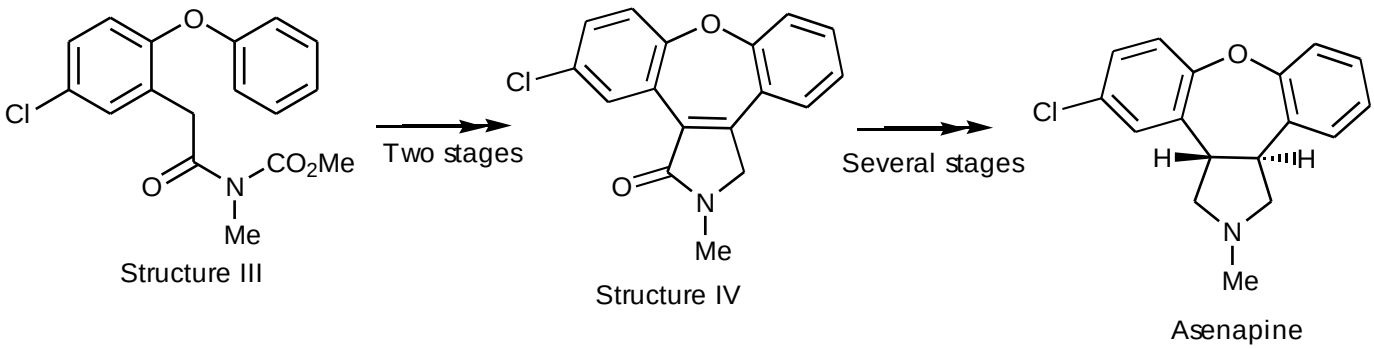
Dronedarone

Answer
One possible mechanism is the following



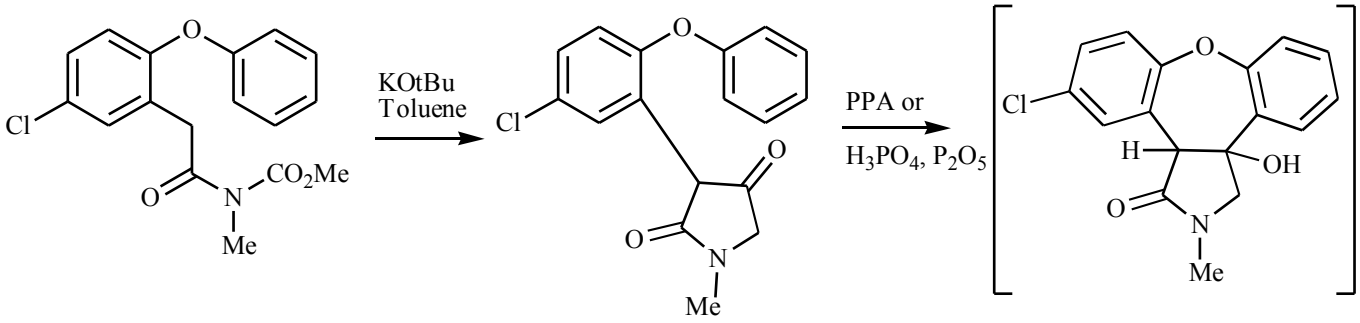
Question 4.4

Structure III was prepared as part of a synthesis to **asenapine,** which has been approved in the US as an atypical antipsychotic agent. Structure III was converted in two stages to the tetracyclic structure IV. Suggest how this might have been carried out.

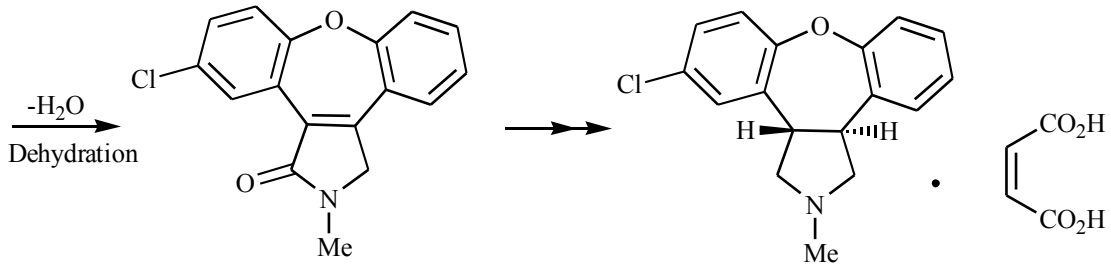


Answer

It involves a Diekmann like cyclisation to give an oxo lactam, which is then treated with acid to promote an intramolecular Friedal crafts reaction followed by a dehydration.



Oxo lactam

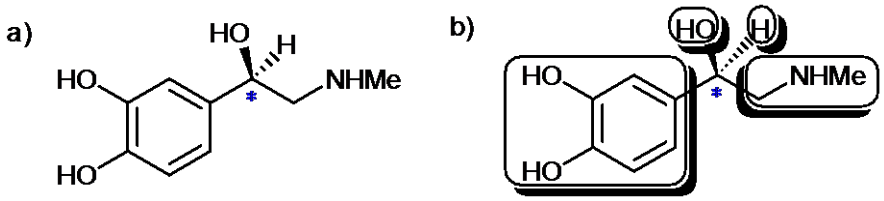


Asenapine maleate

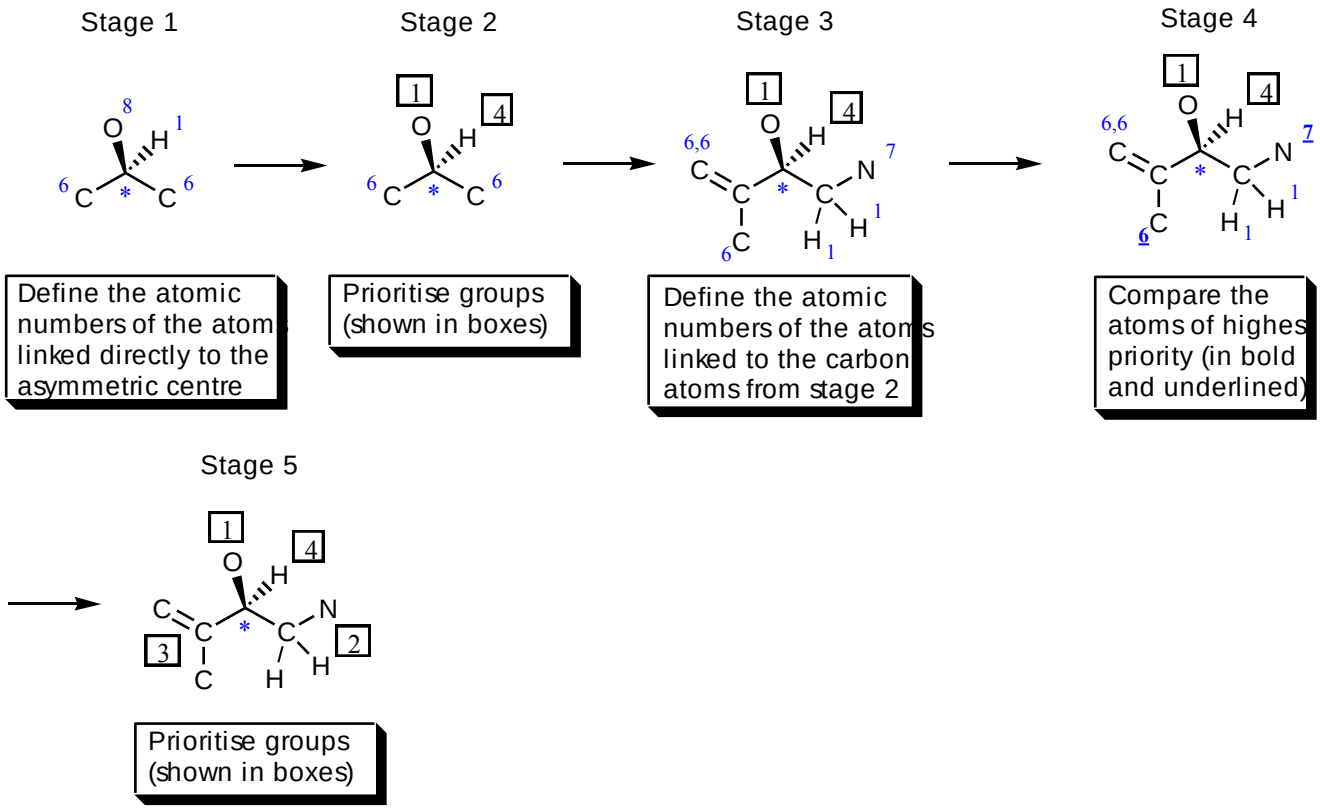
Chapter 5: The synthesis of chiral drugs

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.

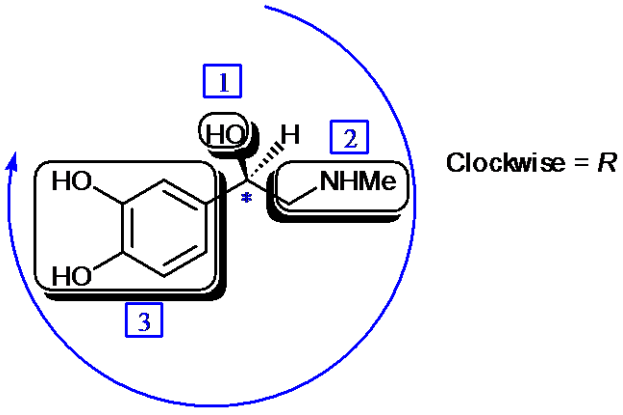
Answer
Assignment of the chiral centre in adrenaline
The four different substituents attached to the asymmetric centre of adrenaline are highlighted below.



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.

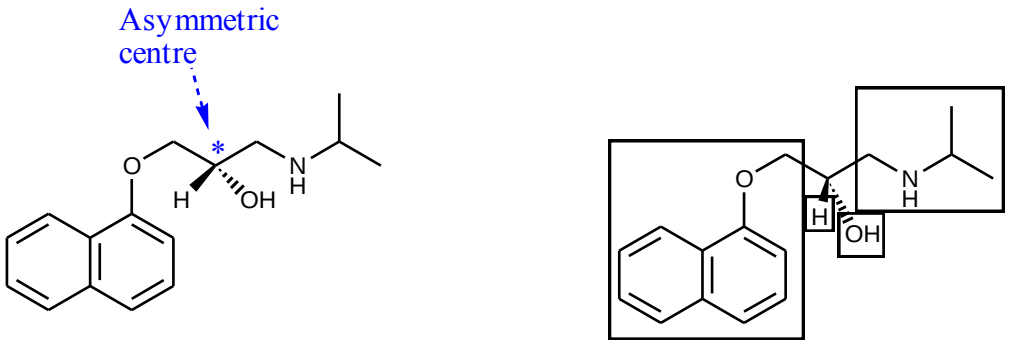


Having identified the priorities of the groups, the molecule is orientated such that the group of lowest priority is pointing backwards. If the remaining three groups are arranged clockwise from highest to lowest priority, then the centre is defined as *R*. If they are arranged anticlockwise, the centre 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*.

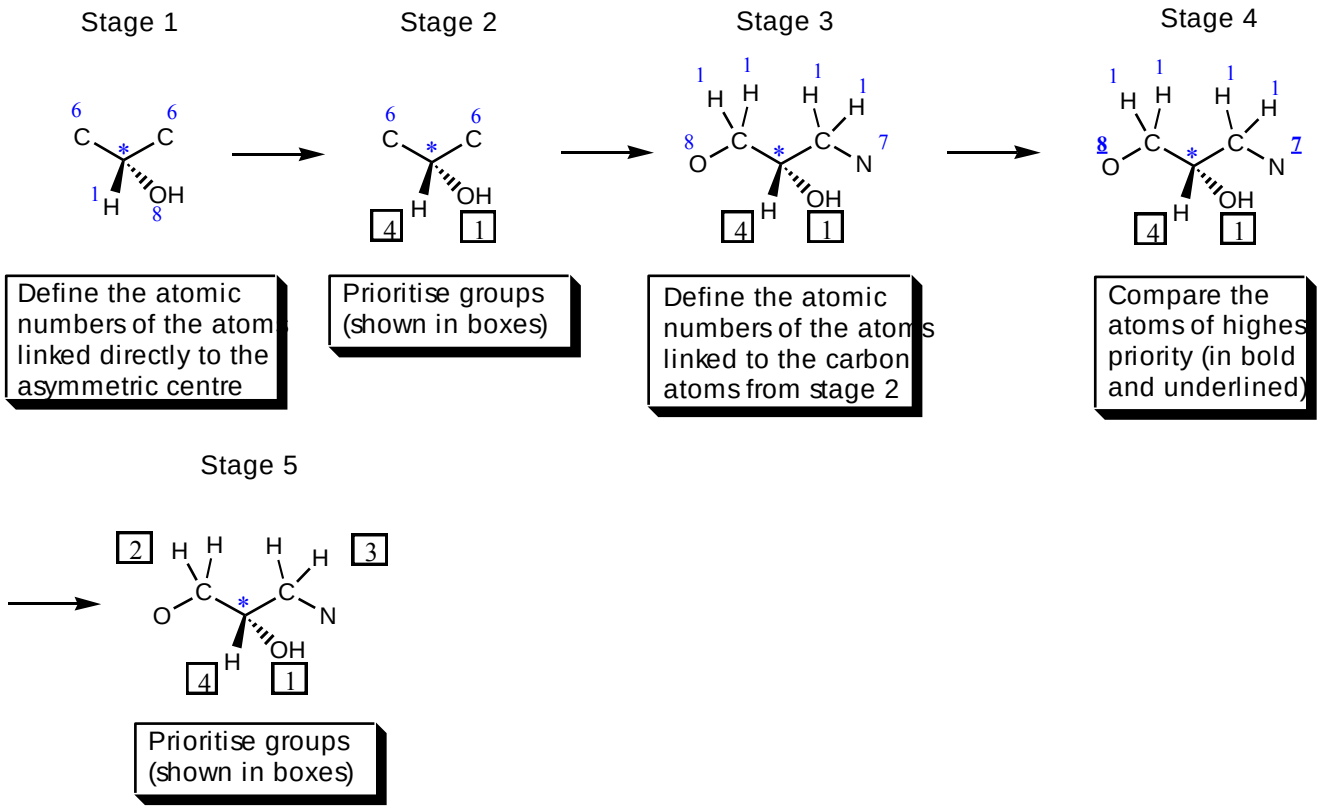


Assignment of the chiral centre in propranolol

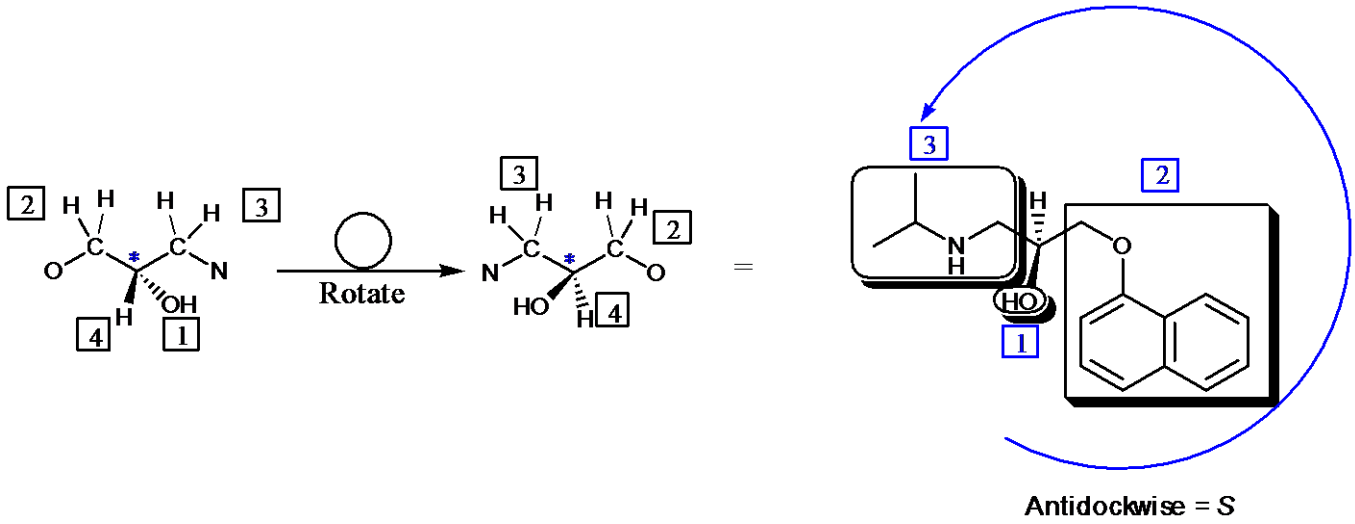
The four different substituents attached to the asymmetric centre of propranolol are highlighted below.



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.

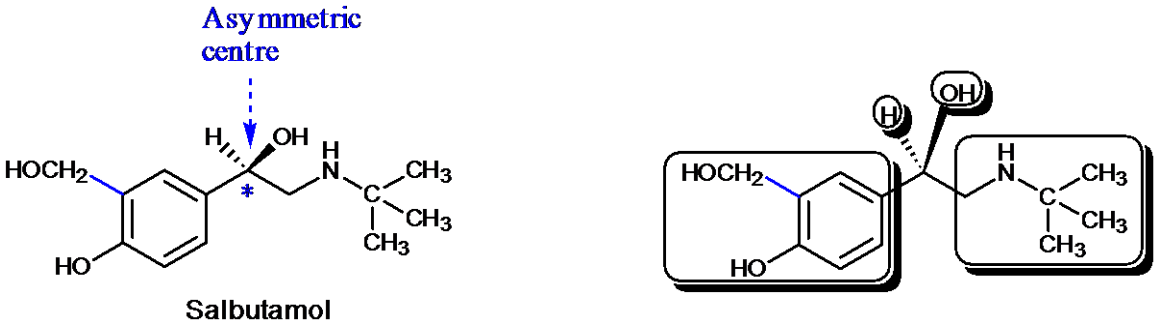


Having identified the priorities of the groups, the molecule is orientated such that the group of lowest priority is pointing backwards. If the remaining three groups are arranged clockwise from highest to lowest priority, then the centre is defined as *R*. If they are arranged anticlockwise, the centre 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*.

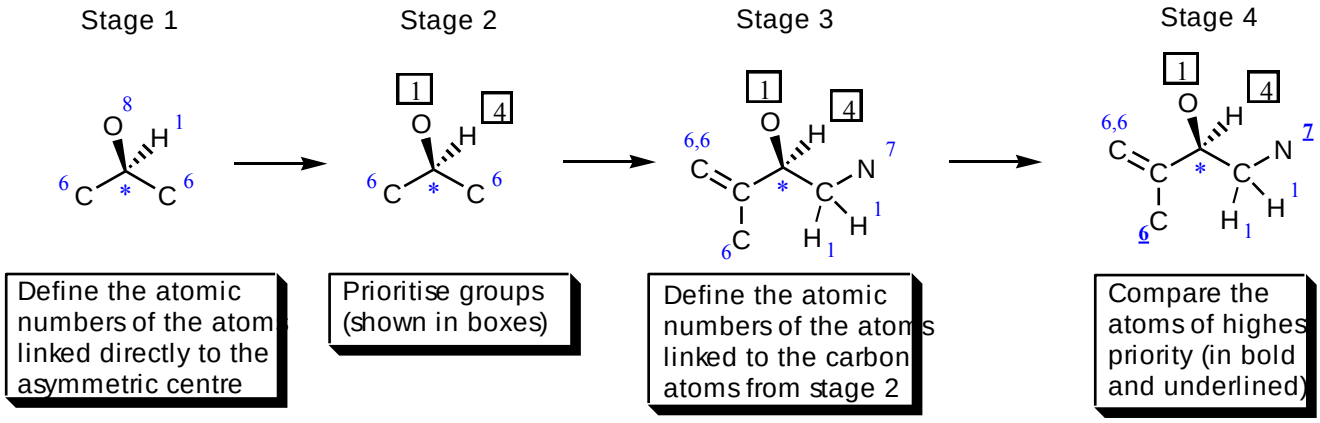


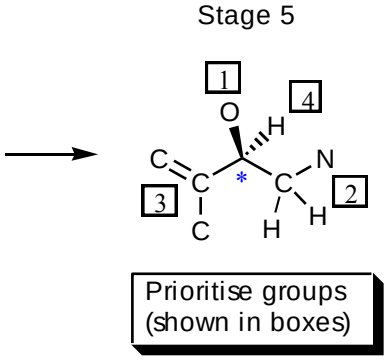
Assignment of the chiral centre in salbutamol

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

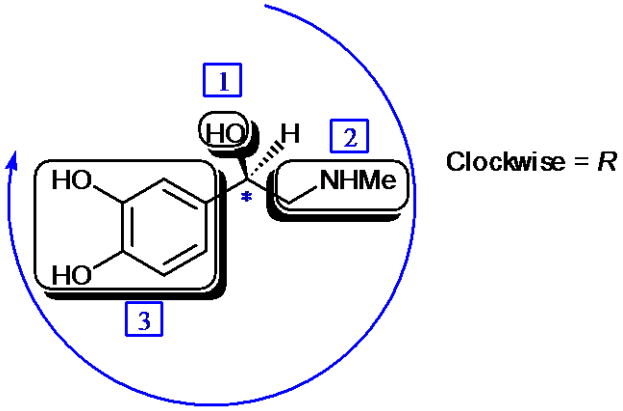


The prioritisation process is very similar to the one for adrenaline



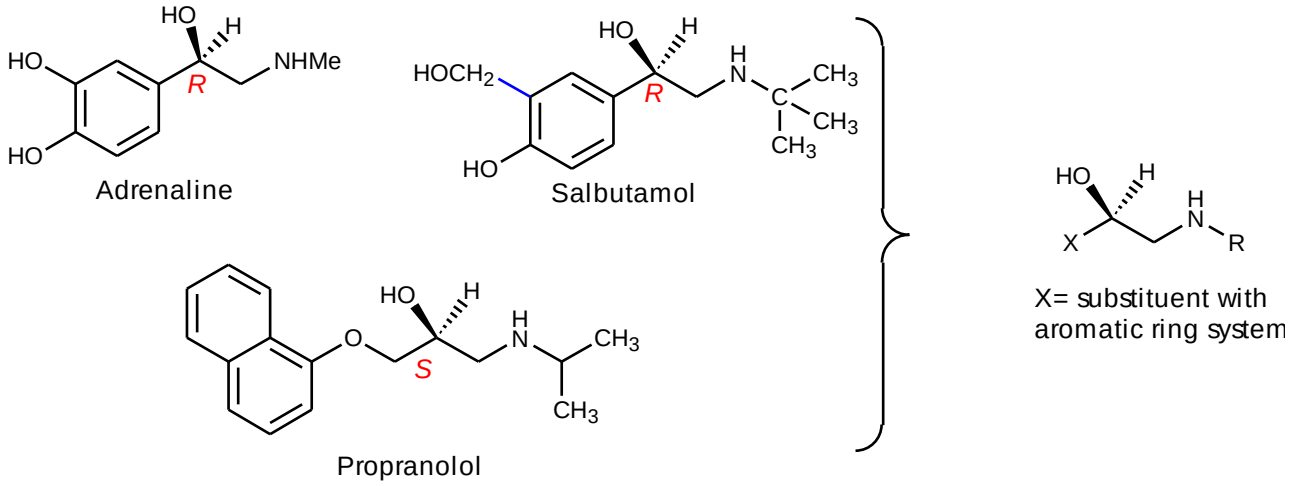


The asymmetric centre of salbutamol can be assigned as *R*.

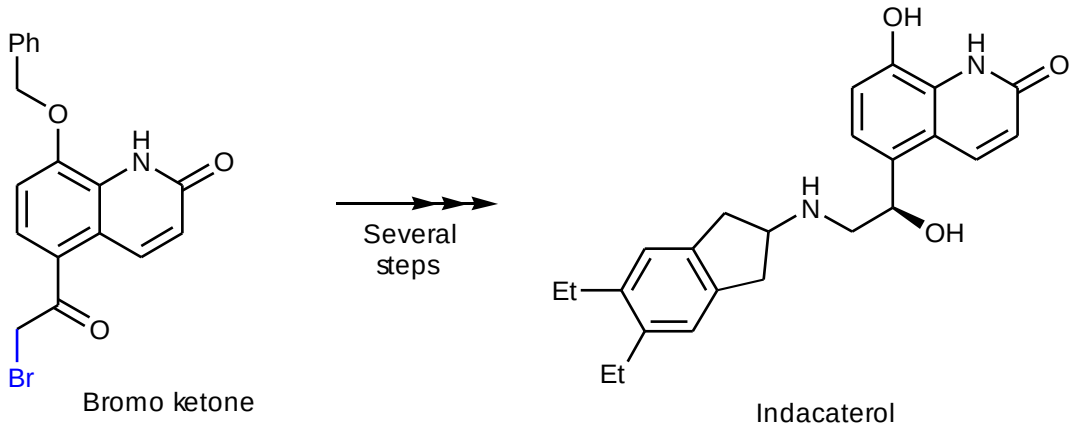


Question 5.2
Both salbutamol and adrenaline are adrenergic agonists having an asymmetric centre with the *R*-configuration. The adrenergic antagonist propranolol has an asymmetric centre that is in the S-configuration. Does this mean that antagonism is caused by different orientations of the groups at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

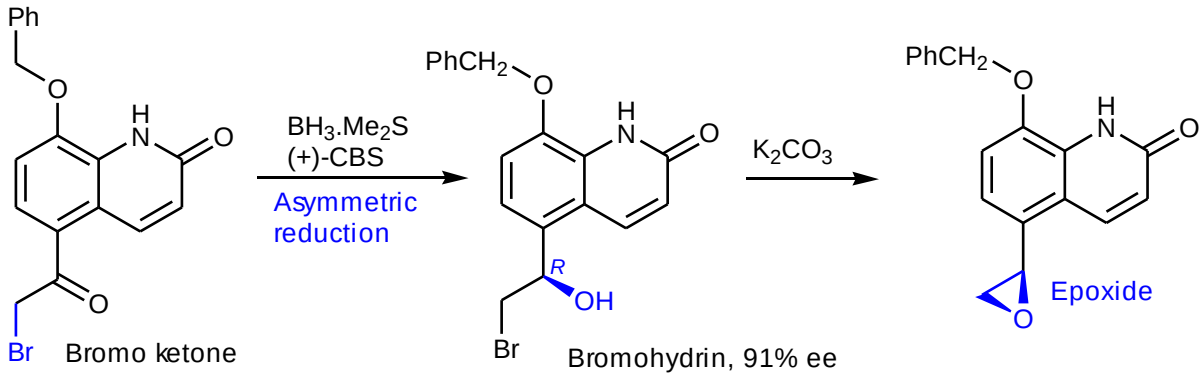


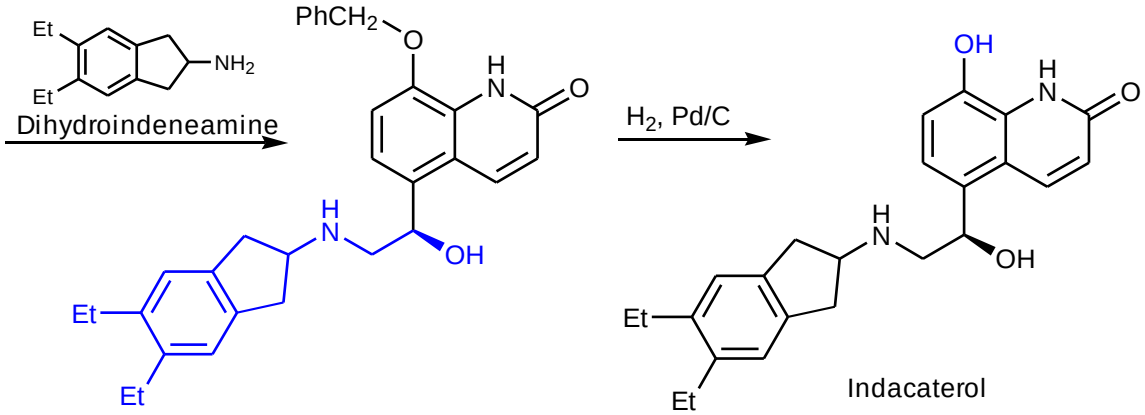
Bromo ketone

Indacaterol

Answer

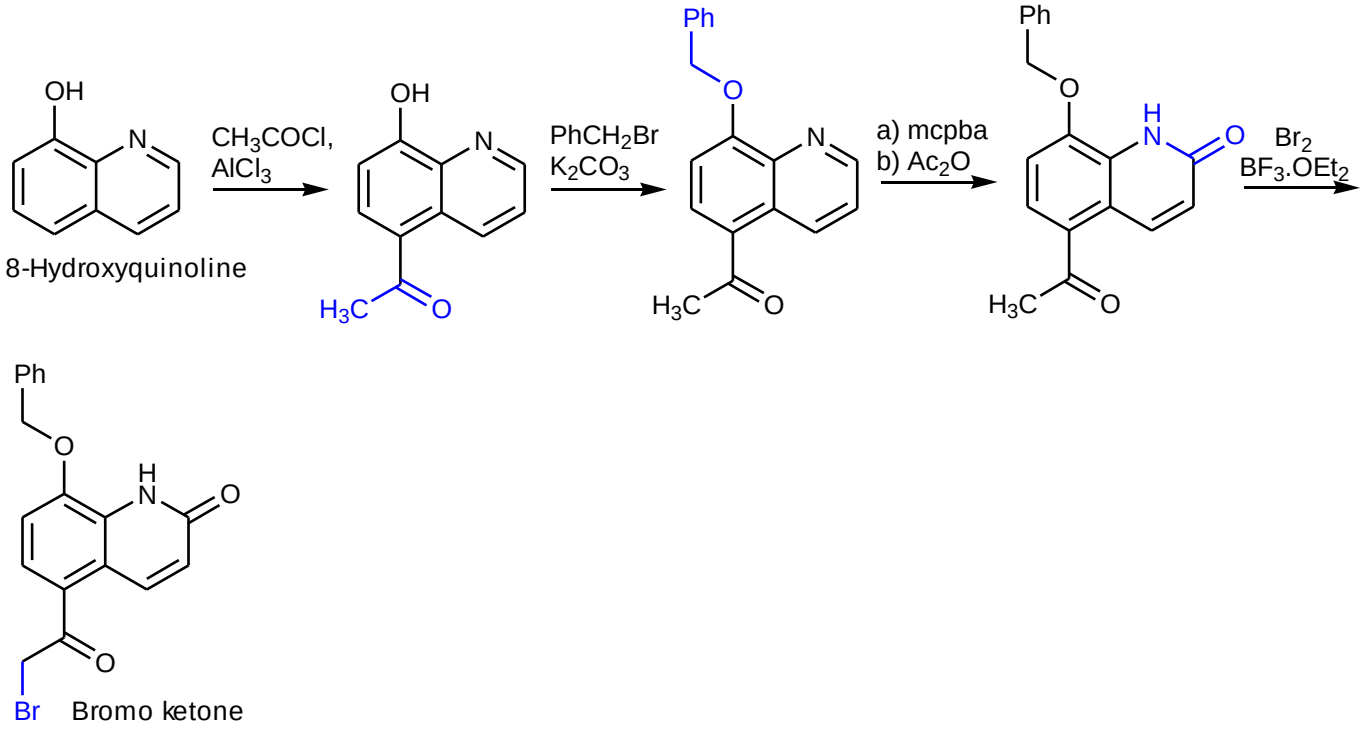
One possible approach that has been published is the following. The bromoketone is reduced with diborane in the presence of a chiral agent CBS (the Corey-Bikashi-Shibata reaction). The resulting bromohydrin is set up for the formation of an epoxide which was carried out with potassium carbonate. Reaction 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.



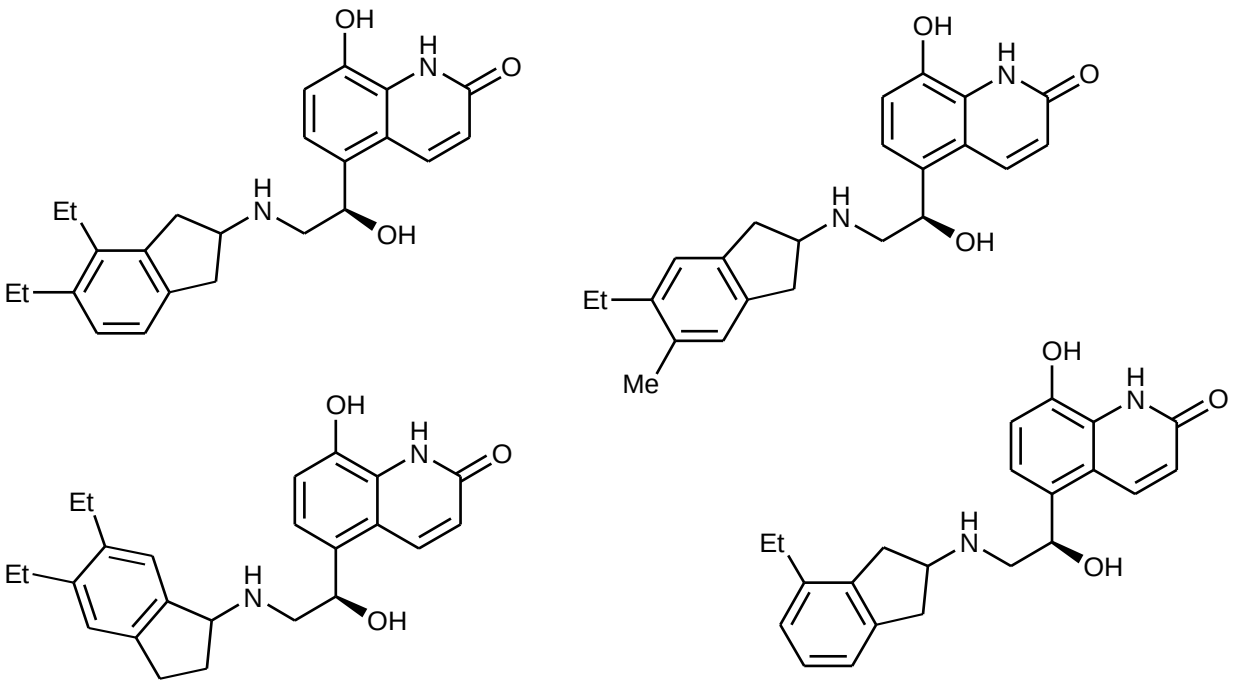


Indacaterol

The bromoketone intermediate itself was synthesised as follows;

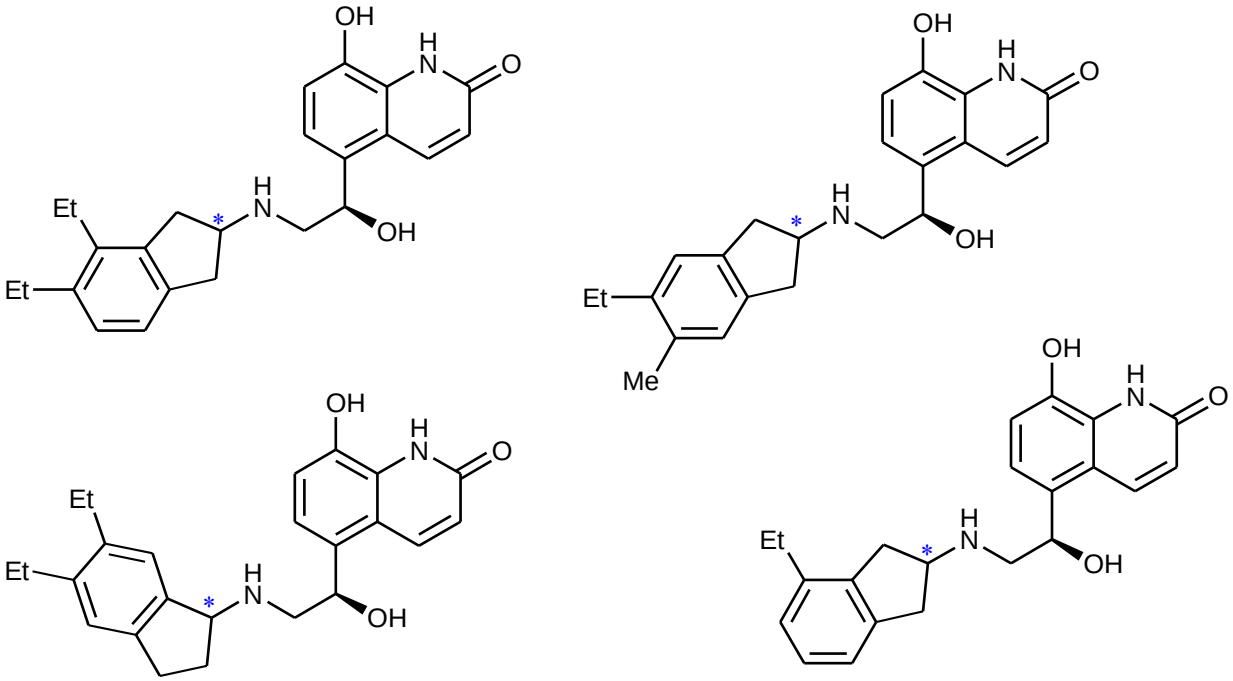


Question 5.4
Consider the following analogues of indacaterol. Can you foresee any added complications involved in the synthesis of these compounds? Describe a general strategy that can be applied to simplify the synthesis of chiral molecules.



Answer

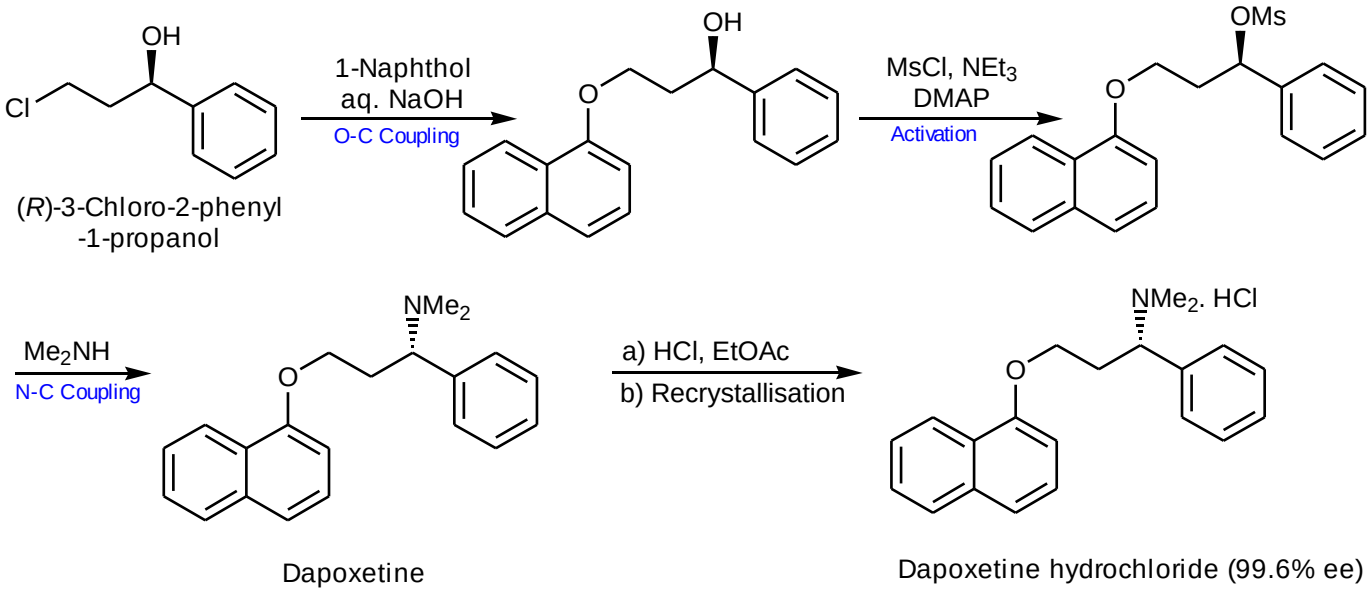
All of these analogues have an extra chiral centre as shown by the asterisks below.



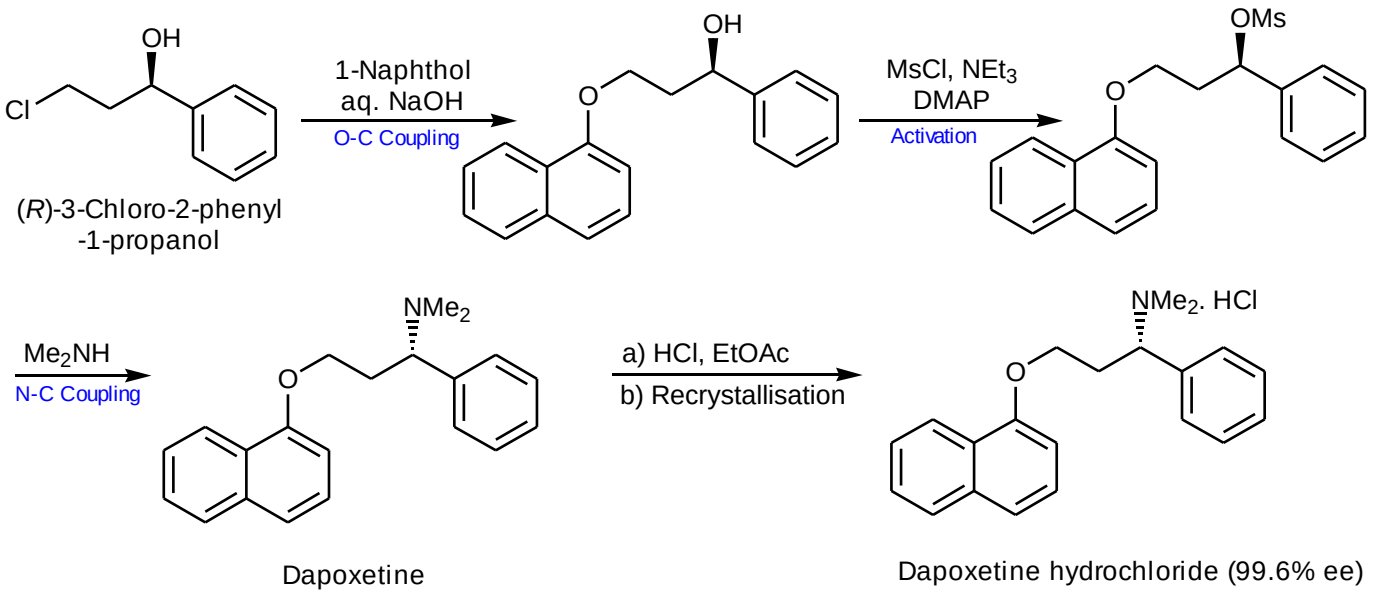
The dihydroindeneamines that would be needed for the synthesis are inherently chiral, and if a racemate of a particular dihydroindeneamine was used, the synthesis would result in two diastereoisomers having different properties. In order to avoid this, it would be

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.



Chapter 6: Combinatorial and parallel synthesis

Question 6.1
Identify three stages of the drug discovery, design, and development process where combinatorial chemistry or parallel synthesis is of importance.

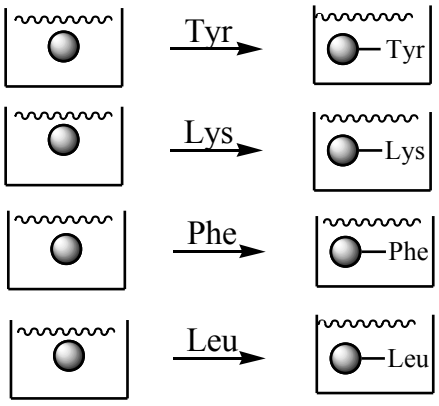
Answer
The identification of a lead compound; the generation of analogues for a study into structure-activity relationships; the generation of analogues aimed at optimising activity and other properties.

Question 6.1
A pharmaceutical laboratory wishes to synthesize all the possible dipeptides containing the amino acids tyrosine, lysine, phenylalanine, and leucine. Identify the number of possible dipeptides and explain how the lab would carry this out using combinatorial techniques.

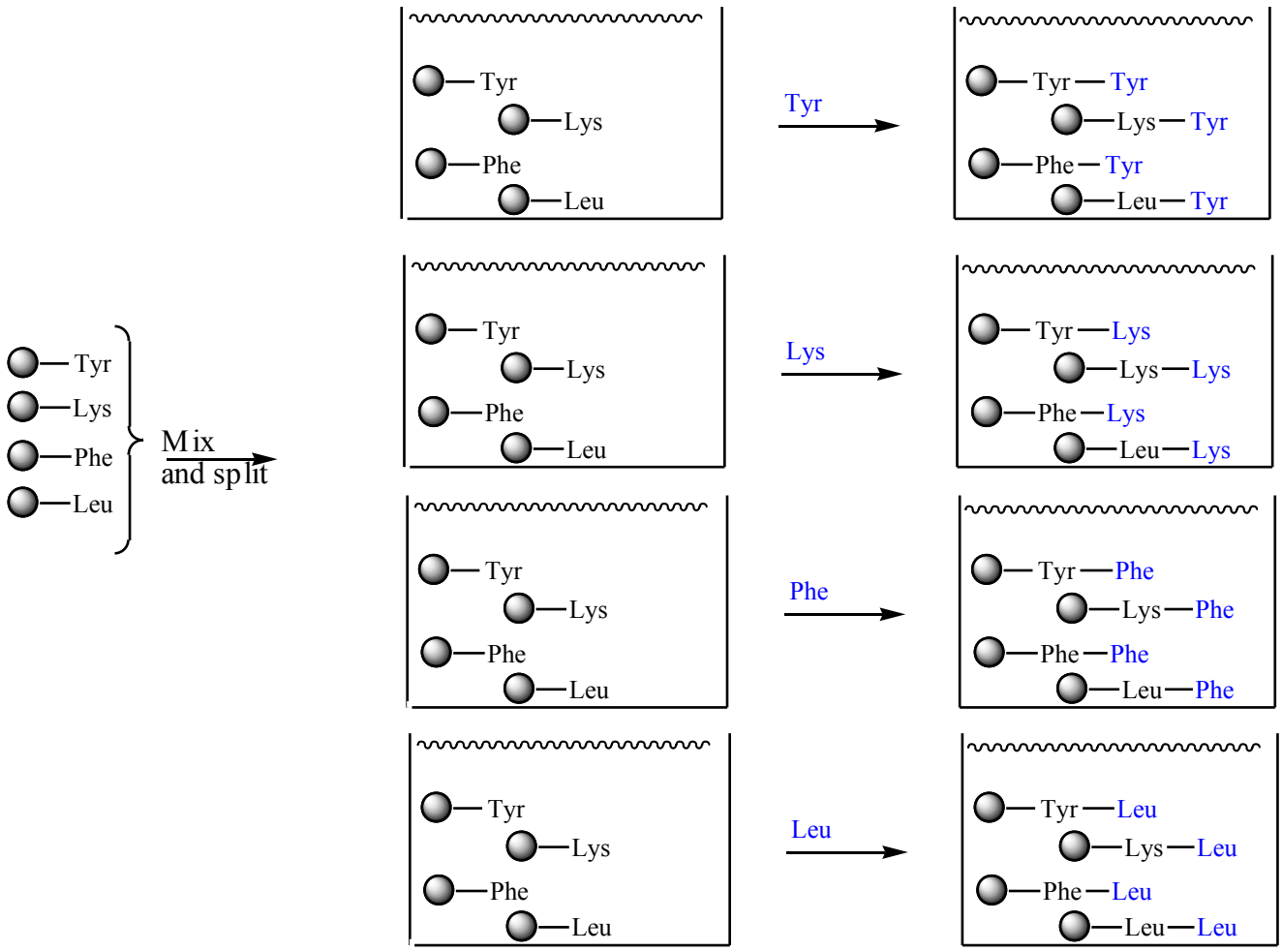
Answer
There are 16 possible dipeptides as follows
Tyr-Tyr; Tyr-Lys; Tyr-Phe; Tyr-Leu
Lys-Tyr; Lys-Lys; Lys-Phe; Lys-Leu
Phe-Tyr; Phe-Lys; Phe-Phe; Phe-Leu
Leu-Tyr; Leu-Lys; Leu-Phe; Leu-Leu

These could be synthesised by a parallel combinatorial synthesis where each dipeptide is made in a separate flask.
Alternatively, the 16 dipeptides could be generated by a mixed combinatorial synthesis using mix and split procedures. This would involve the following stages:

Add the four amino acids to resin in four separate reaction flasks.



Mix and split the beads amongst four separate reaction flasks. Each flask contains the same mixture. Add a different amino acid to each flask



All 16 peptides are now present in four separate reaction flasks. No two flasks contain the same dipeptide.
(Note that the peptide synthesis used would involve protection, coupling and deprotection stages, for example see figure 16.2))

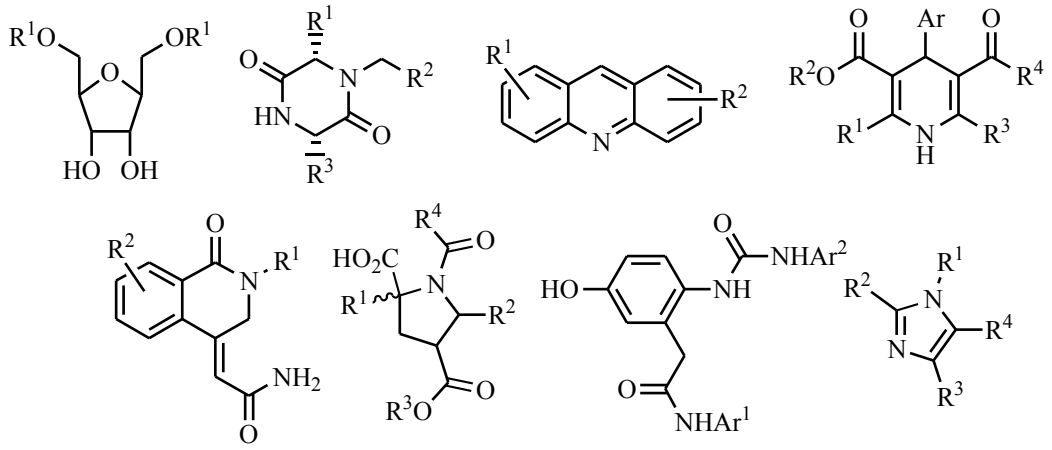
Question 6.3
What particular precautions have to be taken with the amino acids tyrosine and lysine in the above synthesis?

Answer
As stated in the previous question, normal procedures of peptide synthesis would be employed, involving protection, coupling and deprotection stages. Additional protection

strategies may be necessary for the amino acids tyrosine and lysine since these contain functional groups on their side chains. Tyrosine has a phenol group, while lysine has a primary amino group. Failure to protect these functional groups may lead to alternative reactions.

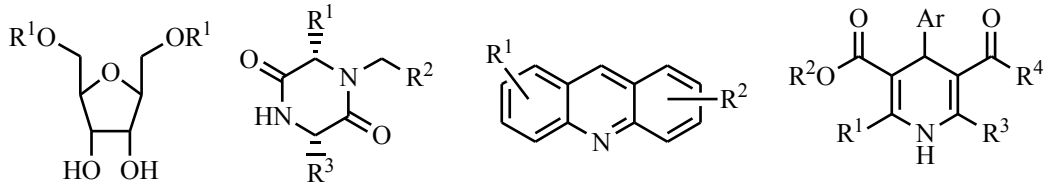
Question 6.4

Identify the advantages and disadvantages of the following structures as scaffolds.



Answer

In the following structures, it is assumed that the only variation allowed are the groups R^1-R^4.



I II III IV

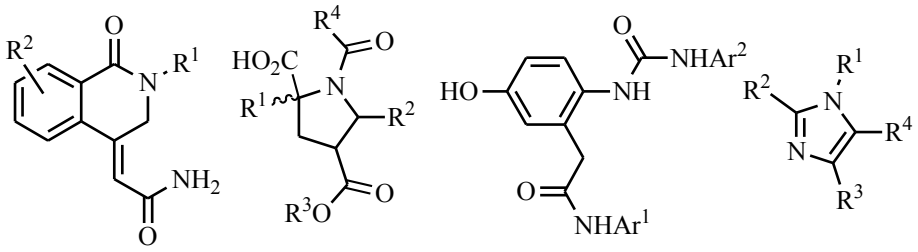
Structure I as illustrated is a poor scaffold since there is only limited variation allowed. There are two locations where variation can occur but the groups are identical. Moreover, the bottom half of the molecule is not varied at all. This is an example of a tadpole scaffold. If a synthesis could be devised that could lead to four different groups on all of the alcohol groups present in the structure, it would be a far better scaffold. However, distinguishing between four alcohol groups would not be easy.

Structure II is a good scaffold. The scaffold has a low molecular weight allowing flexibility in the sort of substituents that can be introduced. Three different substituents are allowed and they are not confined to one region of the molecule.

Structure III is not an ideal scaffold. Two different substituents are allowed at either end, and there are a variety of substituent positions allowed. However, the scaffold itself is

planar which places quite a restriction on the conformational space that can be explored round the molecule.

Structure IV is an excellent scaffold. It has a low molecular weight allowing a variety of substituents to be added. There are five variable substituents located right round the molecule, allowing an extensive search of the conformational space around it.



V VI VII VIII

Structure V is not ideal. There are only two variable positions and this limits the conformational space that can be explored. Moreover, the aromatic substituent must be in the plane of the aromatic ring.

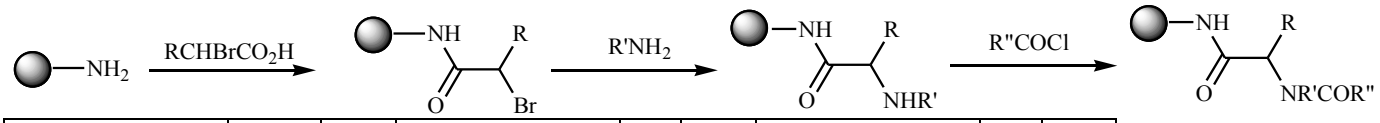
Structure VI is a good scaffold. The scaffold itself is small, and there are four variable positions evenly distributed around the molecule, allowing an extensive search of conformational space.

Structure VII is a poor scaffold. The molecule only has two variable positions. Both of these have to be aromatic rings and so the molecular weight of the molecule may be an issue.

Structure VIII is a good scaffold. The scaffold itself is small with a low molecular weight, and there are four variable substituents distributed round the ring.

Question 6.5
You wish to carry out the combinatorial synthesis shown in Fig. 6.40 using bar coding techniques rather than the conventional tagging scheme shown in the figure. You have nine molecules suitable for tagging purposes (A-I), seven bromo acids (B1-B7), seven amines (A1-A7), and seven acid chlorides (C1-C7). Construct a suitable coding system for the synthesis.

Answer



Bromoacid (R)	Tag	Code	Amine (R')	Tag	Code	Acid chloride (R")	Tag	Code
B1	A	100	A1	D	100	C1	G	100
B2	B	010	A2	E	010	C2	H	010
B3	C	001	A3	F	001	C3	I	001
B4	AB	110	A4	DE	110	C4	GH	110
B5	AC	101	A5	DF	101	C5	GI	101
B6	BC	011	A6	EF	011	C6	HI	011
B7	ABC	111	A7	DEF	111	C7	GHI	111

Question 6.6

Based on your coding scheme from Question 5, what product is present on the bead if the released tags resulted in the gas chromatograph shown in Fig. 6.41.

Answer

The code in figure 6.41 is 101, 110, 111

Based on the table above, this shows that the bromoacid used was B5, the amine used was A4, and the acid chloride used was C7

Chapter 10: Chemical and process development

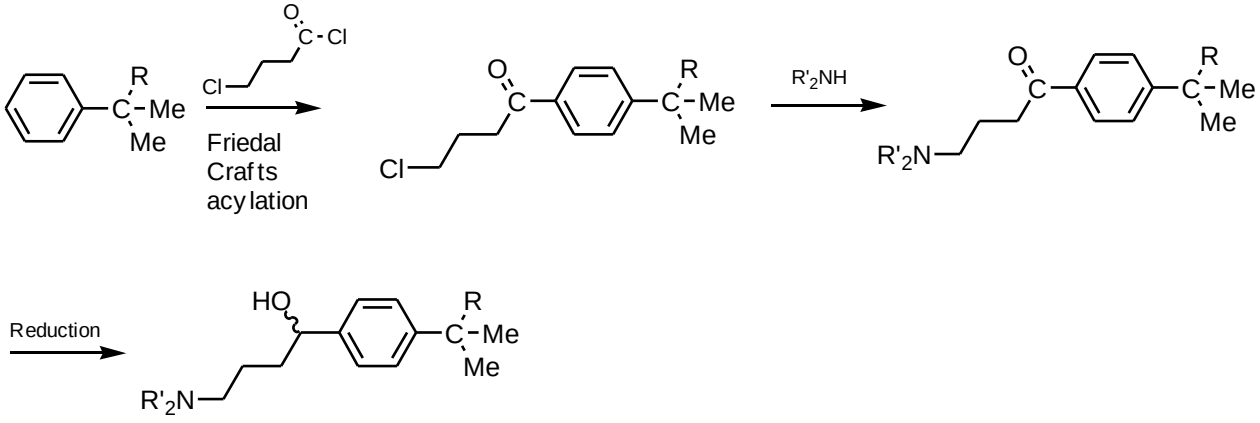
Question 10.1
Usually, a 'balancing act' of priorities is required during chemical development. Explain what this means.

Answer
In chemical development, the aim is to design a large scale synthesis which is cheap and fast, and which produces the final compound in high yield and high purity. However, it may not be possible to achieve all of these priorities. For example, high yield does not necessarily imply high purity, and a compromise between these two priorities may be necessary

Question 10.2
Discuss whether chemical development is simply a scale up exercise.

Answer
Scale up is certainly part of the chemical development process, but it is only part ot the process. Certain reactions may not be suitable for scale up due to the cost or toxicity of the chemical present. This would require altering the conditions of particular reactions or changing the synthetic route altogether

Question 10.3
The following synthetic route was used for the initial synthesis of fexofenadine (R=CO_2H) - an analogue of terfenadine (R=CH_3). The synthesis was suitable for the large-scale synthesis of terfenadine, but not for fexofenadine. Suggest why not. (Hint: consider the electronic effects of R)

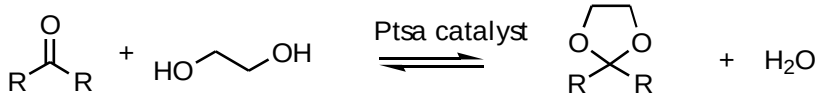


Answer
There is the problem with the first step of the reaction sequence - an electrophilic substitution of an aromatic ring. The carboxylic acid group in fexofenadine is electron withdrawing, whereas the methyl group in terfenadine is electron donating.
In the latter case, the Friedal Crafts acylation gives only the *para* product. Alkyl groups are electron donating and direct *ortho/para*. However, the alkyl group in terfenadine is branched and bulky, so it is unlikely that any *ortho* substitution will take place.

Turning to fexofenadine, the presence of the electron withdrawing carboxylic acid weakens the directing ability of the alkyl side chain. Consequently, both the *meta* and *para* products are obtained. these products have to be separated by chromatography which is inconvenient on large scale, especially at such an early stage of the synthesis.

Question 10.4

The following reaction was carried out with heating under reflux at 110^{o} C. However, the yield was higher when the condenser was set for distillation. Explain.



Answer

Water is produced in this reaction. If the condenser is set to reflux, the water remains in the reaction solution and the reaction proceeds to equilibrium.
If the condenser is set to distillation, water will be removed from the reaction solution. This removes one of the products of an equilibrium reaction and will pull the reaction through to completion.

Question 10.5

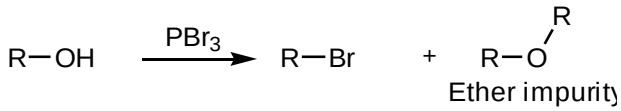
What considerations do you think have to be taken into account when choosing a solvent for scale up? Would you consider diethyl ether or benzene as a suitable solvent?

Answer

There are many considerations to be taken into account such as cost, commercial availability, purity, toxicity, volatility, flammability, flash point, ignition temperature, vapour density, solubility of the reagents and products in the chosen solvent, compatability of the solvent with the reaction attempted.
Diethyl ether should never be considered as a solvent for scale up. It is highly volatile and is flammable over a wide solvent/air range. It is heavier than air and can 'creep' along laboratory floors or benches. It can also be easily ignited by a spark or hot steam pipes.
Benzene should never be considered either since it is carcinogenic. Indeed, it is no longer used in small-scale preparations.

Question 10.6

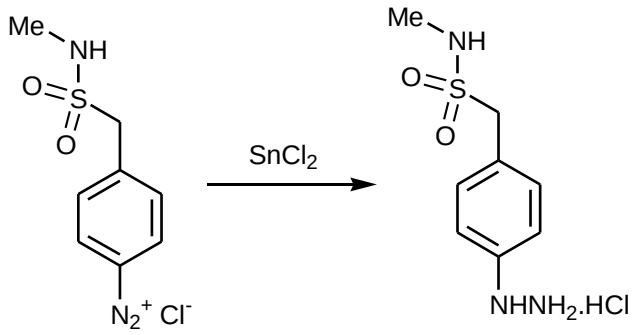
Phosphorus tribromide was added to an alcohol to give an alkyl bromide, but the product was contaminated with an ether impurity. Explain how this impurity might arise and how the reaction conditions could be altered to avoid the problem.



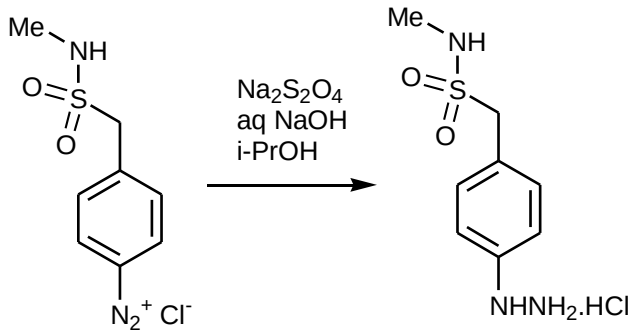
Answer
By adding phosphorus tribromide to the alcohol, the alkyl bromide will initially be formed in the presence of unreacted alcohol. As a result, the alcohol can react with the alkyl bromide to form the ether.

This can be avoided by adding the alcohol to the PBr_3 instead.

Question 10.7
Stannous chloride ($SnCl_2$) was used as a reducing agent in one of the early stages of a synthesis leading to sumatriptan. However, this was considered inappropriate for a large scale synthesis. Explain why and suggest an alternative reagent.



Answer
There are environmental concerns surrounding the use of stannous chloride ($SnCl_2$). It is toxic to aquatic organisms and could linger in soils and sediments. Sodium dithionite ($Na_2S_2O_4$) has fewer environmental problems and has an added advantage of being cheaper.

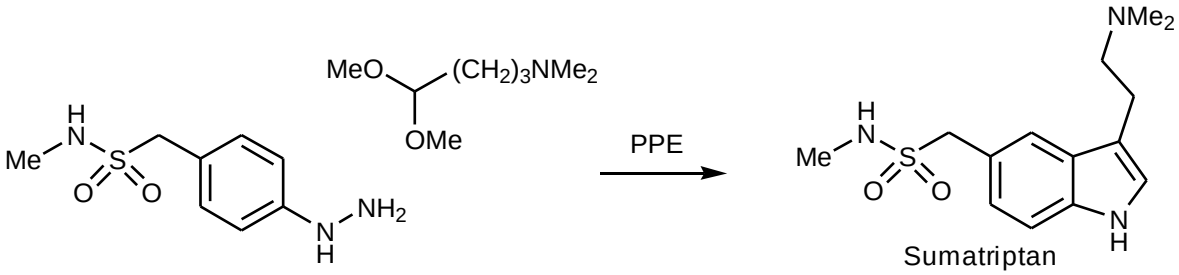


Question 10.8

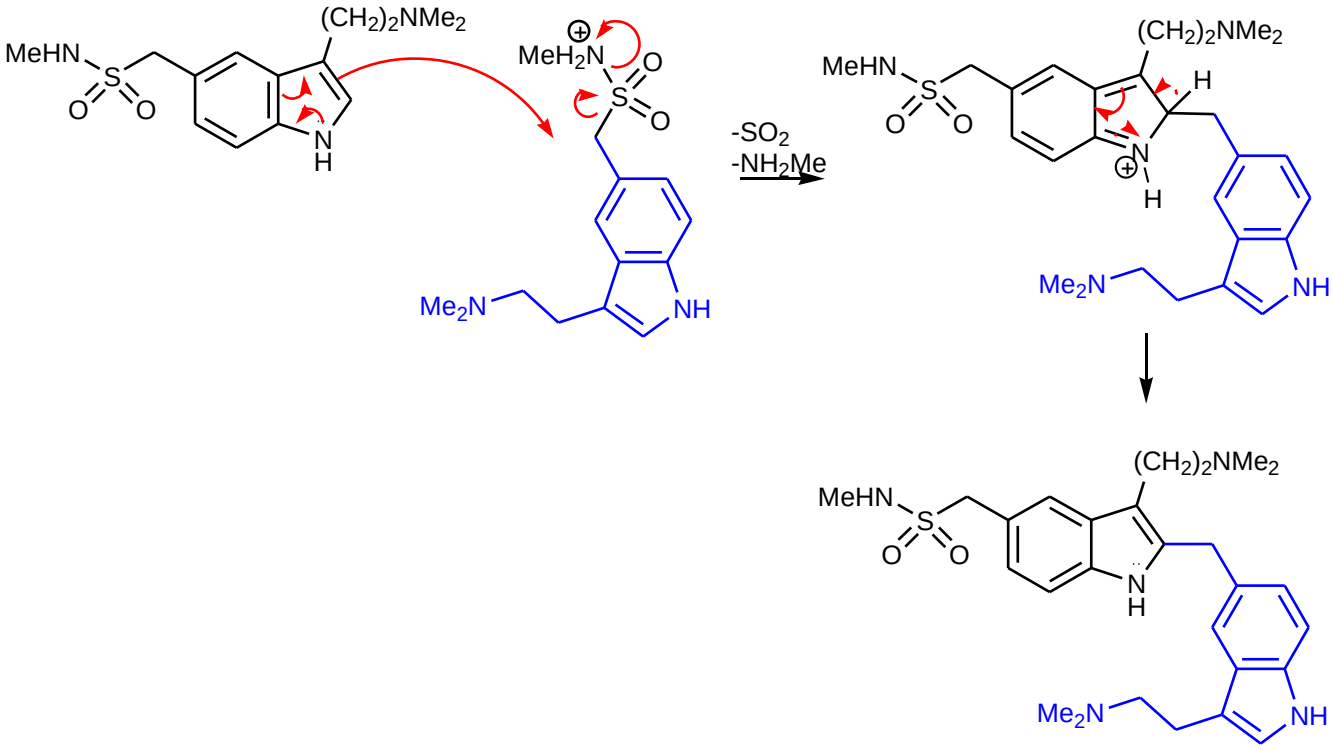
The Fischer Indole synthesis has been used to synthesise the antimigraine agent **sumatriptan** (see figure 10.27). Propose a mechanism by which the two impurities shown in figure 10.28 might have been formed, then suggest how the two ester groups used in figure 10.30 hinder the production of these impurities.

Answer

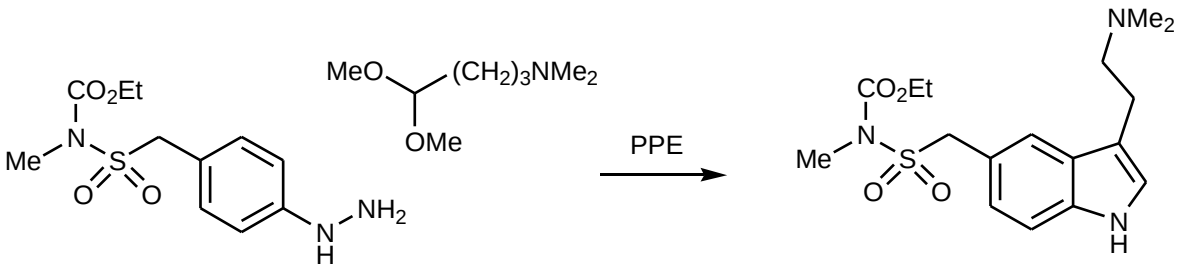
i) Impurity a) is formed when the following reaction is carried out.



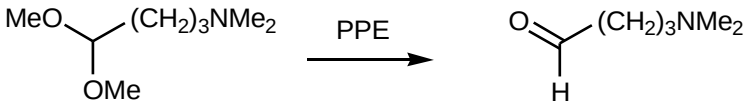
The impurity results from a further reaction where the above product undergoes an electrophilic substitution with a second molecule of product. Note that the amine group in the side chain of the second structure is protonated. This encourages the sulphonamide group to act as a leaving group.



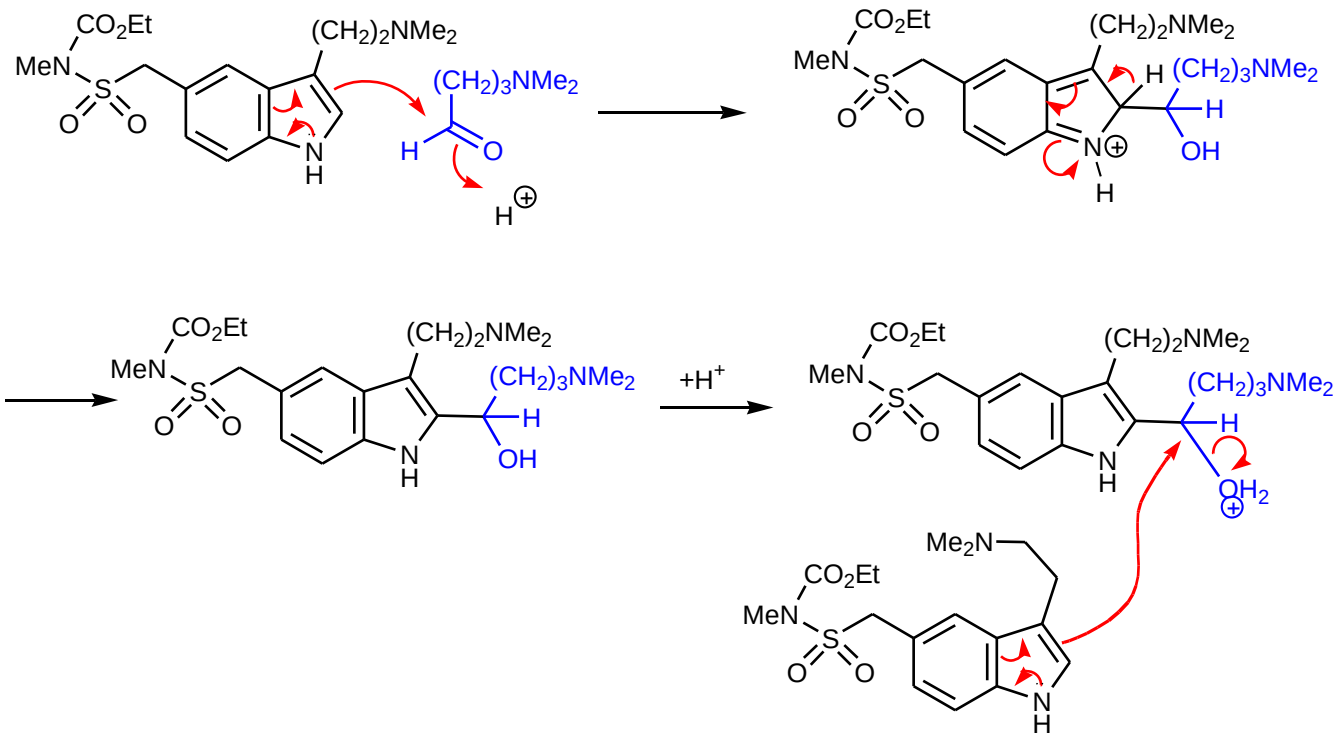
ii) The second impurity (b) is formed during the following reaction.

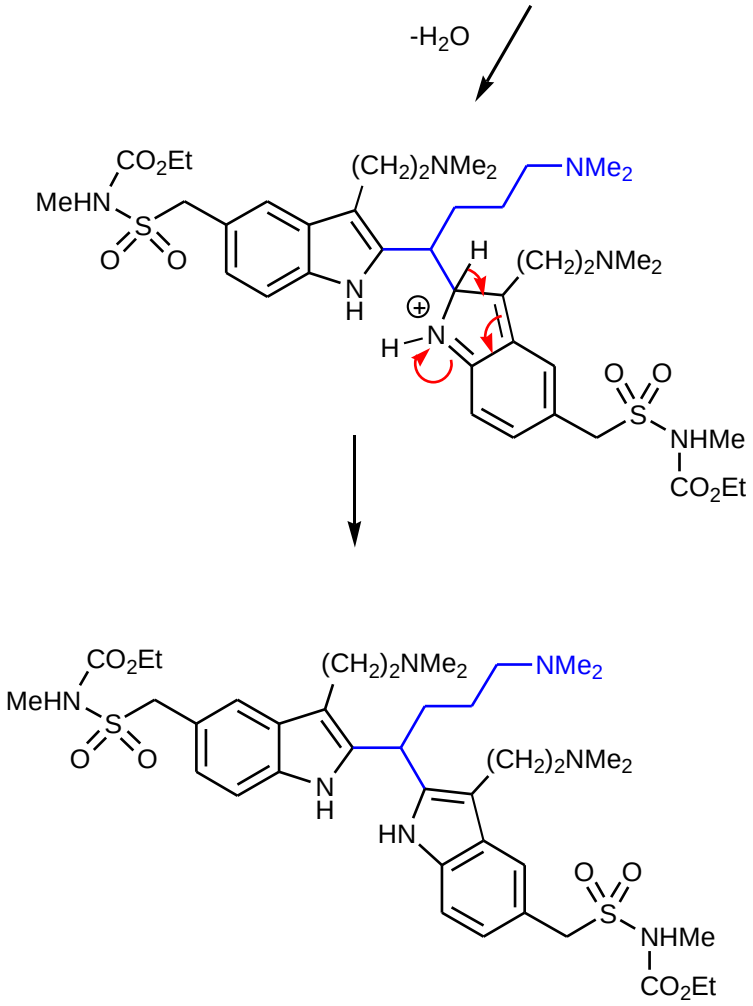


Under acidic conditions, the acetal is converted to an aldehyde which then reacts with the hydrazine to provide the indole.

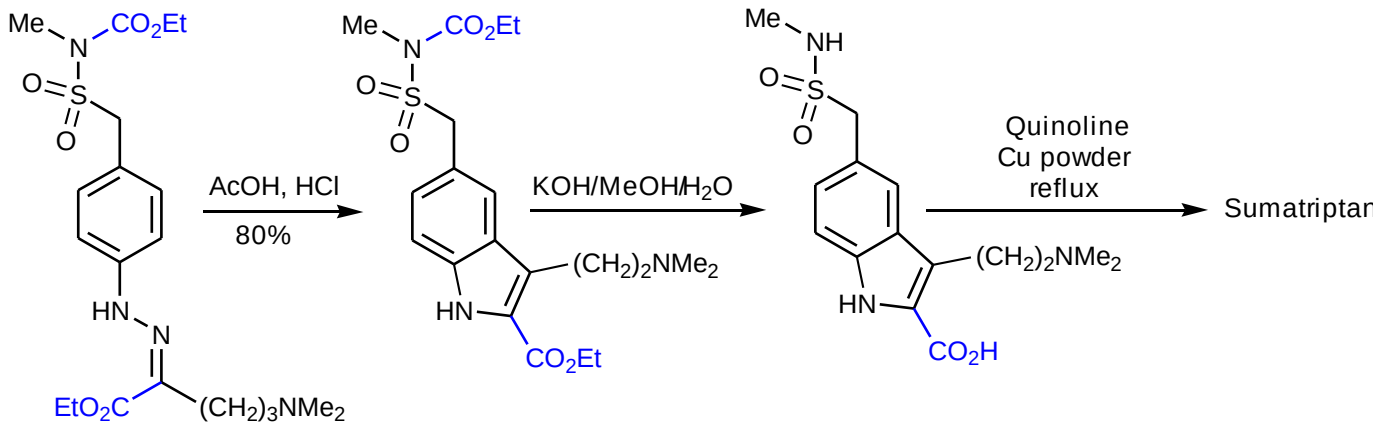


The side reaction involves some of the aldehyde reating with two molecules of product as follows.



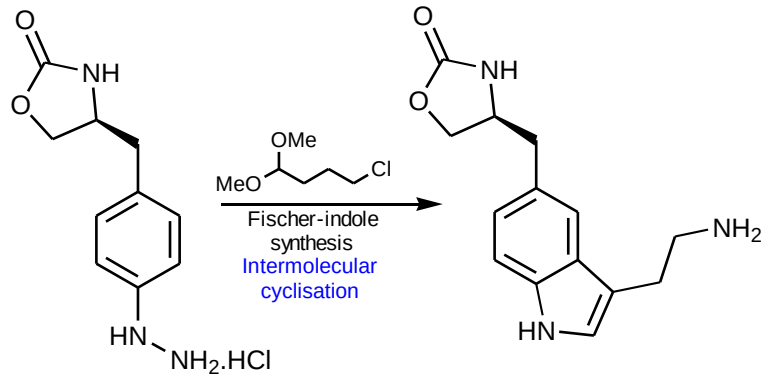


Both impurities were prevented by using a hydrazone which contained two ester groups shown in blue below. The ester group on the sulphonamide prevents the sulphonamide nitrogen from protonating. As a result, the sulphonamide can no longer act as a leaving group. The ester group on the hydrazone acts as a deactivating group in the final indole product and prevents the product undergoing electrophilic substitution at that position.

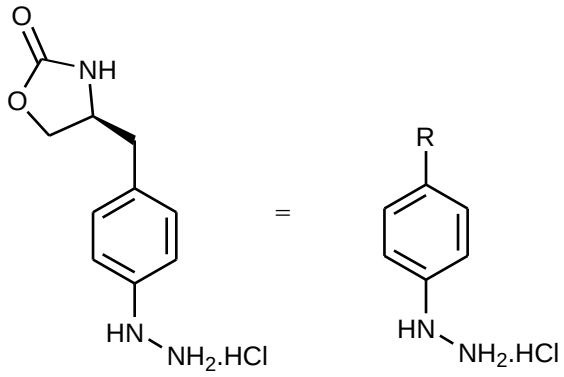


Question 10.9
Propose a mechanism by which the product from the Fischer-Indole synthesis shown in figure 10.43 is formed.

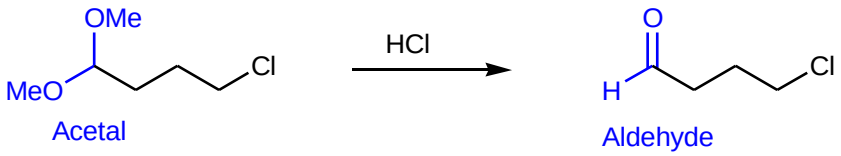
Answer
The relevant reaction in figure 10.43 is the following between a hydrazine hydrochloride and an acetal.



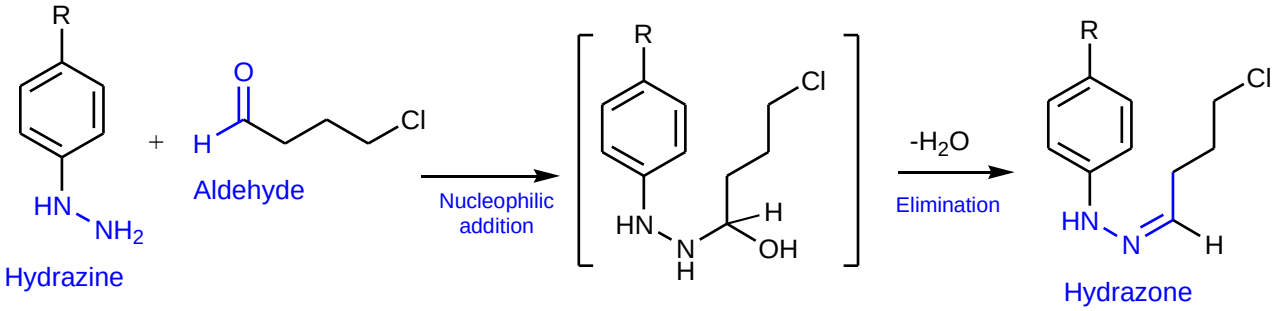
The hydrazine will be represented as follows since the aromatic substituent plays no role in the mechanism.



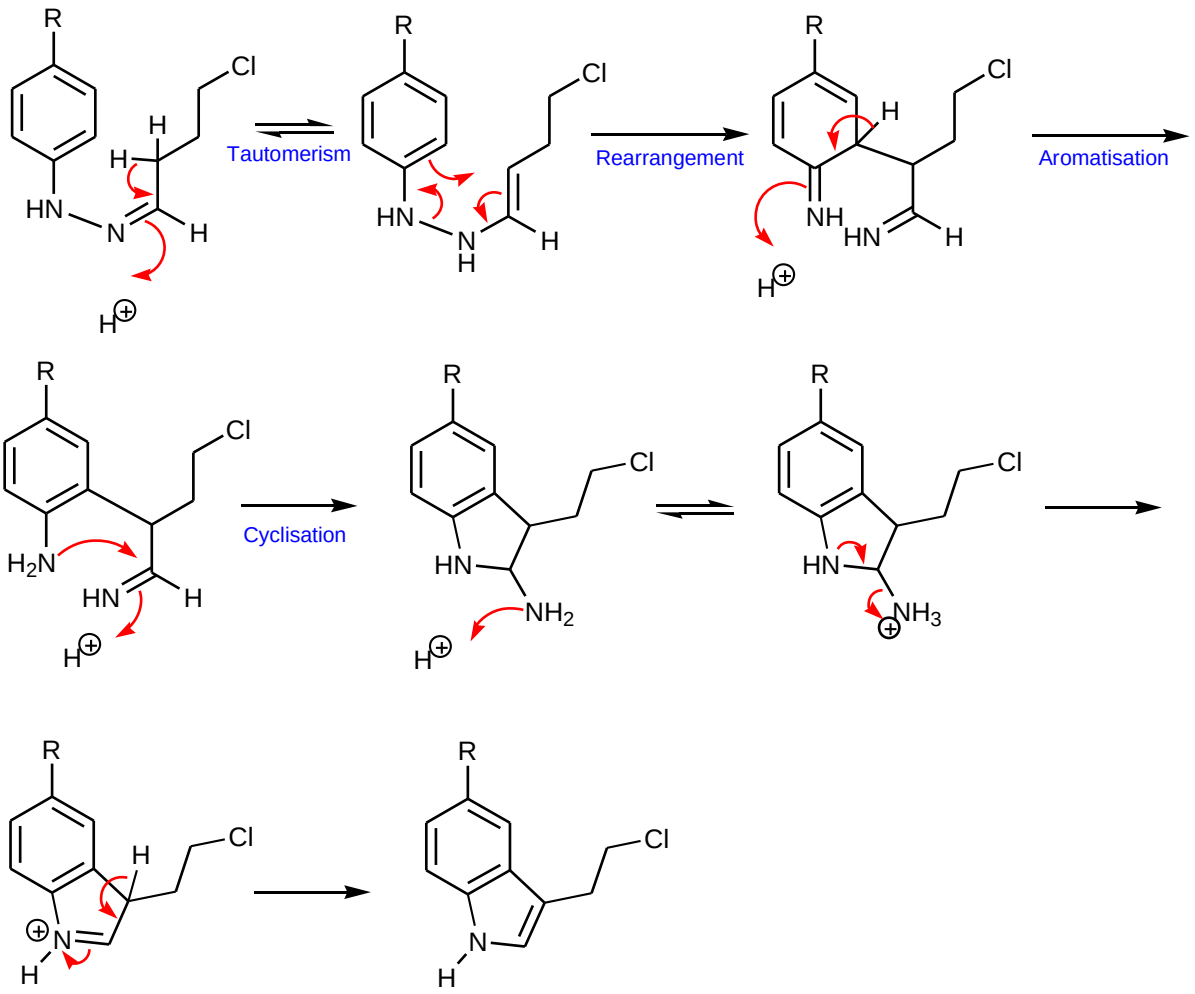
Under acidic conditions, the acetal is converted to an aldehyde.



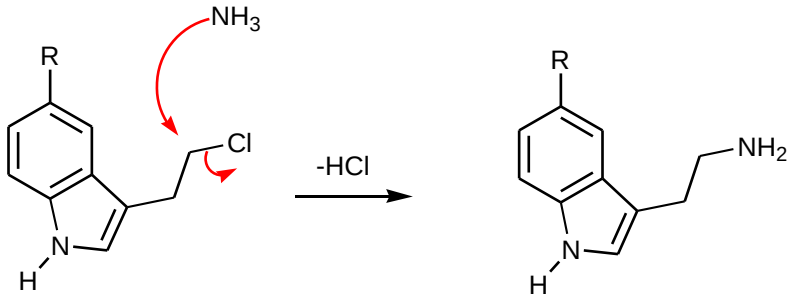
The hydrazine can now react with the aldehyde through nucleophilic addition and elimination of water to form a hydrazone.



The following mechanism for the cyclisation then ensues.



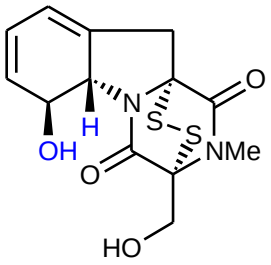
The indole ring has now been formed, In the process, ammonia has been released and can now act as a nucleophile to substitute the alkyl chloride and give the final product.



Case Study 4

Question CS4.1
Gliotoxin contains a hexadiene ring with an alcohol group present. Dehydration should result in a stable aromatic ring, yet this does not happen. Explain why this is the case.

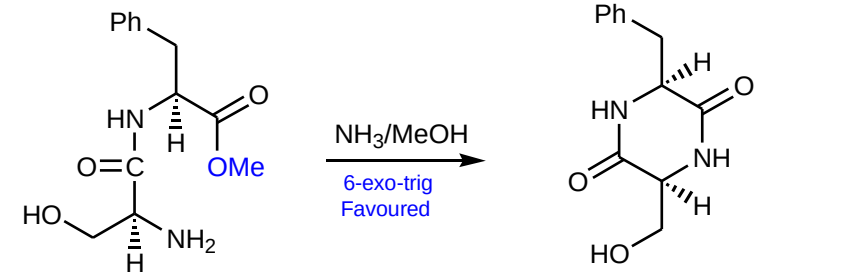
Answer
For a dehyration to occur, the OH and H coloured blue would have to be lost. However, both groups are pointing in the same direction and so this would rule out any possibility of a concerted E2 elimination mechanism.



Gliotoxin

Question CS4.2
Consider the intramolecular cyclisation reaction shown in figure CS4.3. Analyse the cyclisation using Baldwin's rules (section 4.11) and state whether it is favoured or not favoured.

Answer
The reaction is defined as 6-exo-trig, which is a favoured reaction.



L-Seryl-L-phenylalanine methyl ester

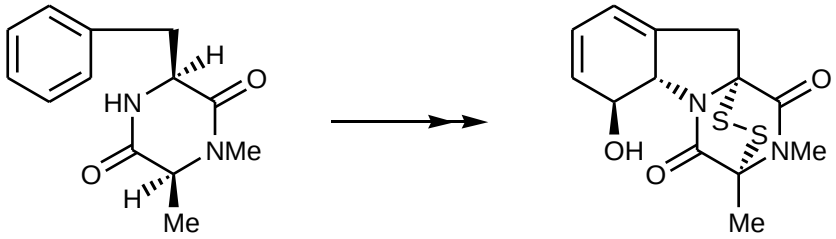
cyclo-(L-PhenylalanylL-seryl)

Question CS4.3
In section CS4.8, it was stated that the radiolabelled *N*-methylated cyclic dipeptide was not converted to gliotoxin. However, it was also stated that it was an 'unlikely' intermediate. Can you suggest why these results do not conclusively rule out this structure as a biosynthetic intermediate.

Answer
A couple of possible reasons could be the following;
*The radiolabelled structure failed to enter fungal cells.
*A multienzyme complex might be involved in the final stages of the biosynthesis. *N*-Methylation of *cyclo*-L-(phenylalanyl-L-seryl) might occur but the structure is immediately transferred to enzymes catalysing cyclisation and incorporation of the disulphide bridge. Such a multienzye complex might not recognise or accept externally administered *N*-methylated cyclic dipeptide.

Question CS4.4
Considering the successful biosynthesis of a gliotoxin analogue described in section CS4.12, can you identify any other analogues that might be successfully generated in this way? Which analogues would have the best chance of success?

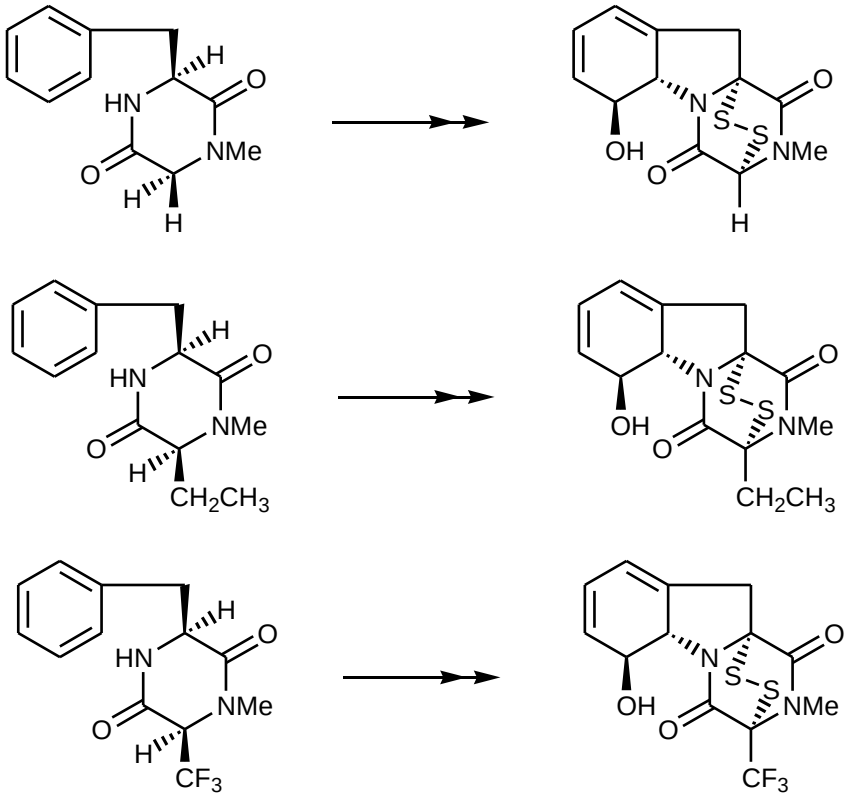
Answer
The successful analogue involved the use of alanine in the cyclic dipeptide, rather than serine in the 'southern' part of the molecule.



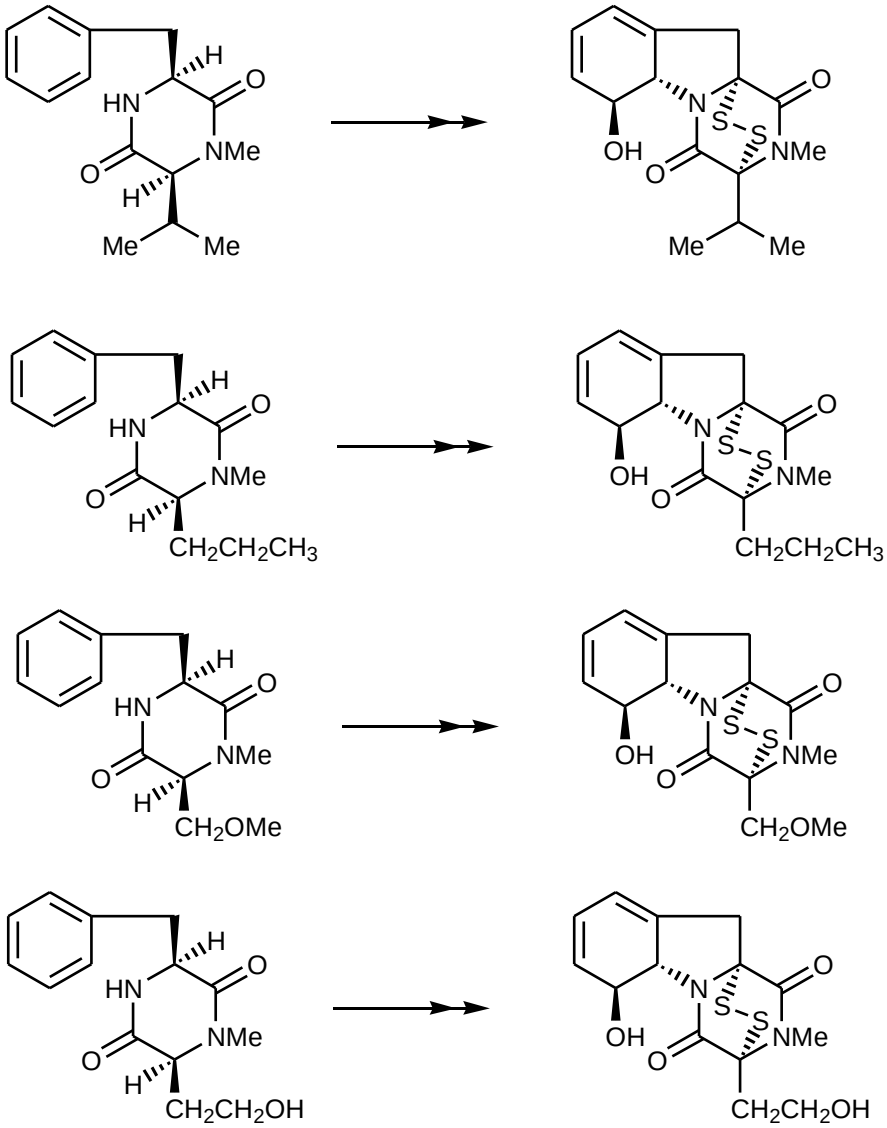
cyclo-(L-Alanyl-L-seryl)

Gliotoxin analogu

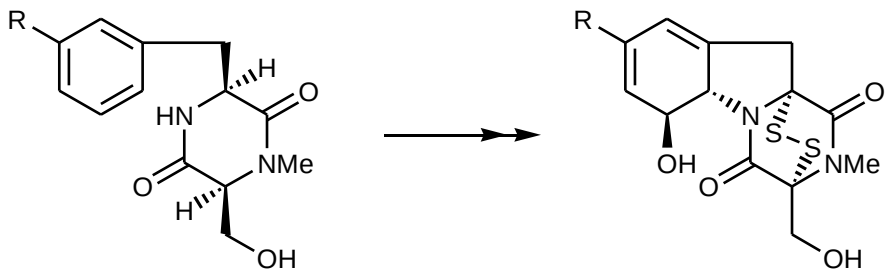
There are a huge number of natural and unnatural amino acids which could be tried instead of serine or alanine. The ones most likely to succeed are those that have side chains that are similar in size to the side chains of serine or alanine. Therefore, the following might be worth trying. The first of these would involve the natural amino acid glycine.



If these proved successful, one could try slightly longer or bulkier chains such as the following;

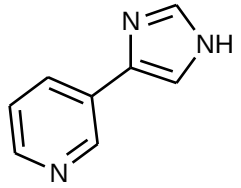


The first example of these would involve the amino acid valine. The last example, is where the hydroxyl group derived from serine has been 'extended' by one carbon unit. The success or otherwise of synthesising such analogues would provide indirect evidence of the steric restrictions imposed by the enzymes involved in the biosynthesis of gliotoxin in that region of the molecule.
It would also be of interest to see whether phenylalanine could be replaced with amino acids containing a substituted aromatic ring.

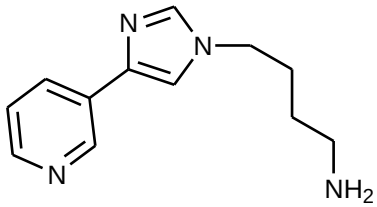


Chapter 13: Erythromycin and macrolide antibacterial agents

Question 13.1
Suggest a method of synthesising the primary amine (II) used in the synthesis of telithromycin (Fig. 13.8), starting from compound (I).

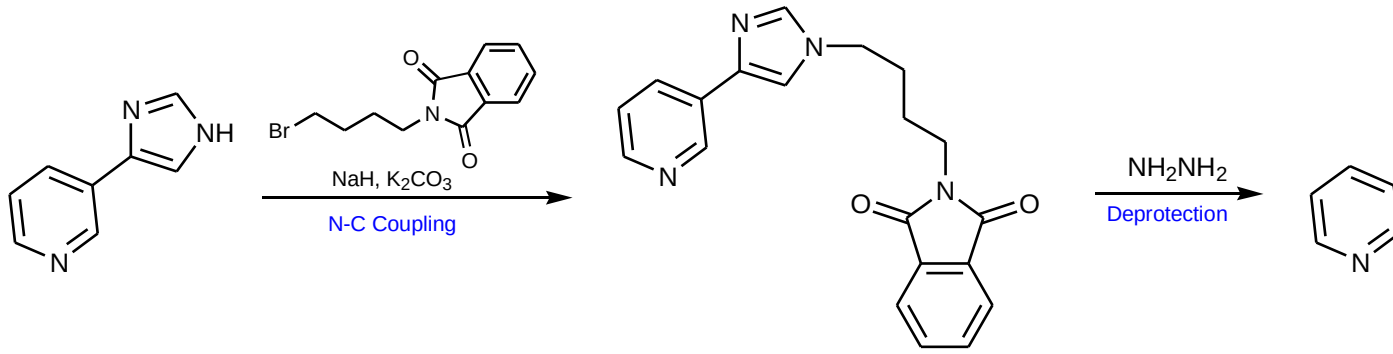


I



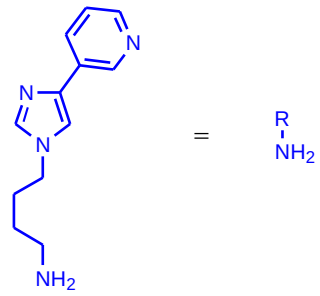
II

Answer
The synthesis could be carried out as follows. Note that it would be necessary to protect the primary amine group to prevent it reacting with the alkyl bromide. In this case, a phthalimide group has been used as the protecting group, but other protecting groups are equally possible.

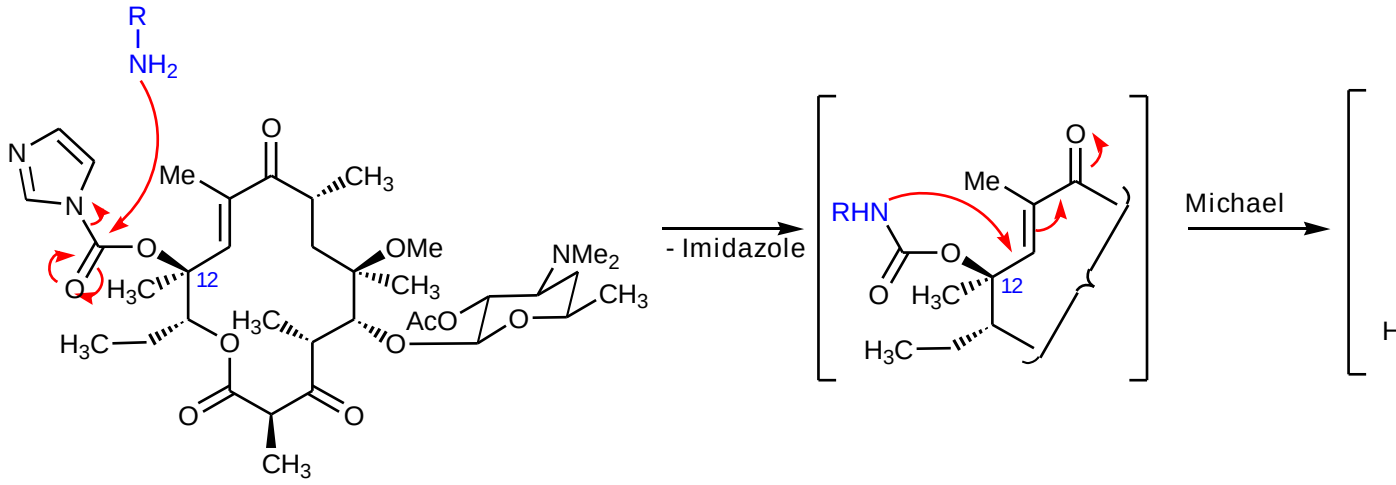


Question 13.2
Propose a mechanism by which telithromycin is formed in the reaction shown in Figure 13.8.

Answer
We shall simplify the primary amine as follows.



The mechanism could involve the primary amine reacting with the urethane group of the macrolide in a nucleophilic substitution reaction, with the imidazole ring acting as a leaving group. A cyclisation reaction then take place involving nitrogen atom of the inermediate urethane undergoing a Michael addition with the α,β-unsaturated ketone.



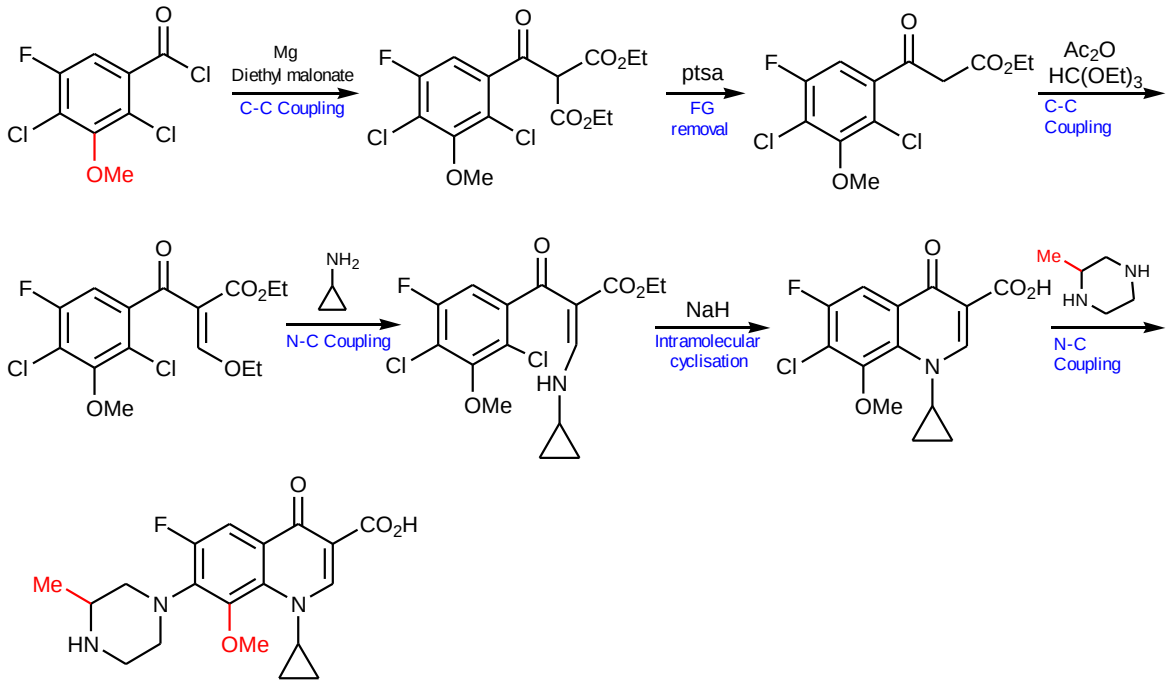
Chapter 14: Quinolones and fluoroquinolones

Question 14.1

Show how the synthesis used to produce **enrofloxacin** can be modified to produce **gatifloxacin** instead. What is the added complication in this synthesis and how significant it is likely to be?

Answer

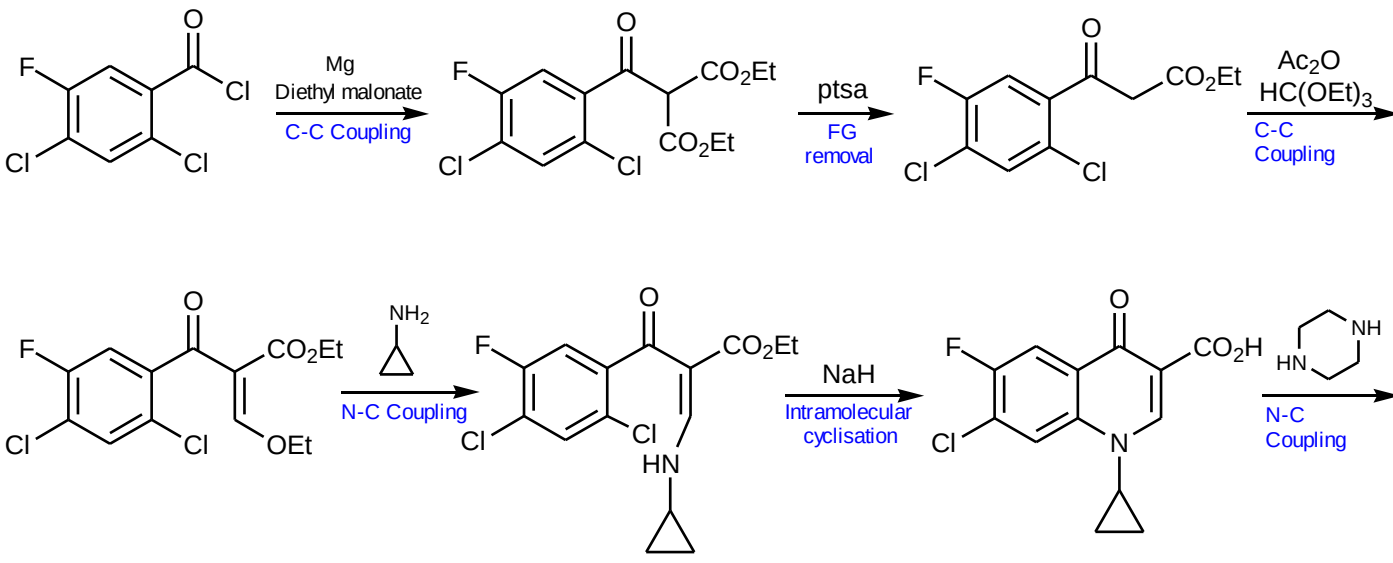
The synthesis for gatifloxacin requires a different acid chloride and a different piperazine (differences indicated in red).

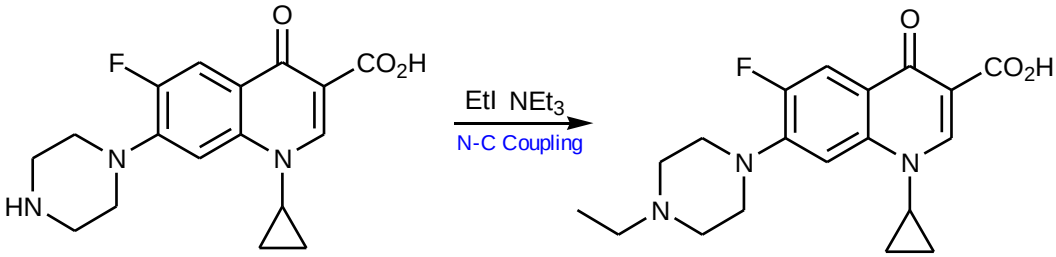


Gatifloxacin

The added complication is the methyl substituent on the piperazine ring. This introduces a chiral centre into the final structure and so this synthesis will produce a racemic mixture of the two enantiomers. Both enantiomers would have to be tested separately to see whether they had similar biological properties. If both enantiomers proved non toxic, the product could be marketed as the racemate. if it was necessary to use a single enantiomer, a resolution of the final product would have to be carried out. This would add significant expense and marketig the racemate would be preferable.

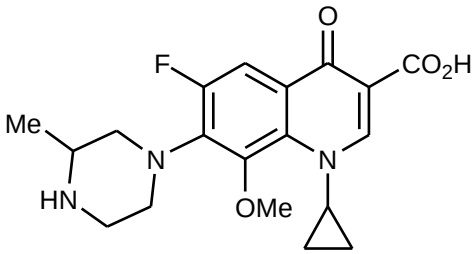
Another complication is the additional substituent present in the acid chloride. This may require a separate synthesis.





Ciprofloxacin

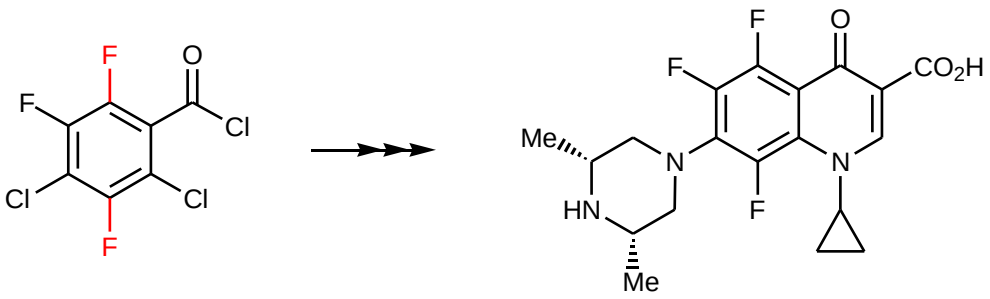
Enrofloxacin



Gatifloxacin

Question 14.2
What starting material would be needed in order to synthesise **orbifloxacin** if you wished to use the same strategy involved in synthesising **enrofloxacin?**

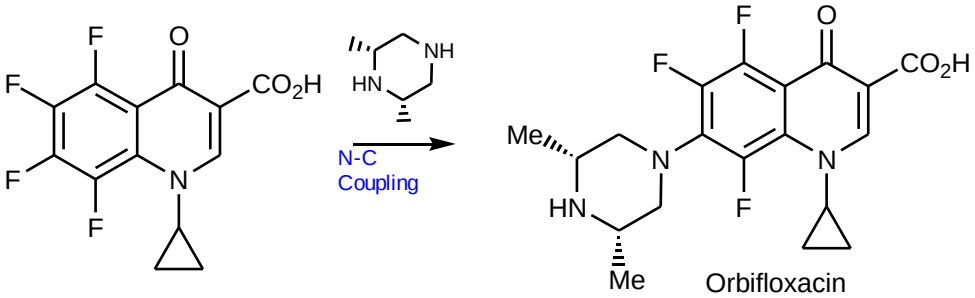
Answer



Orbifloxacin

Question 14.3

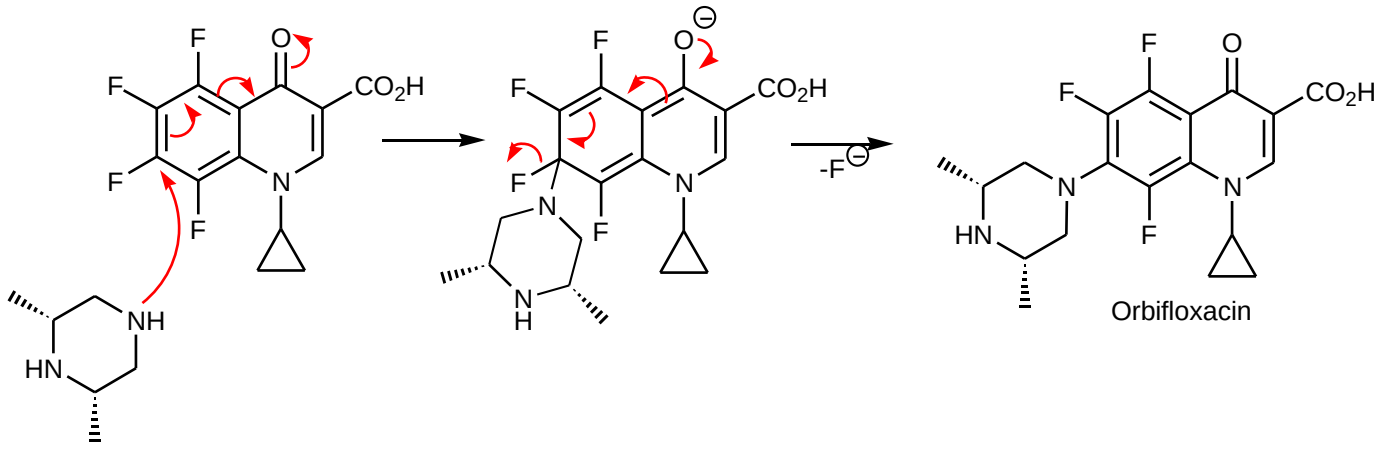
The final step of the synthesis leading to orbifloxacin involves an N-C coupling where a fluoro substituent is replaced at position 7. Why does the nucleophilic substitution occur selectively at this position and not at any of the other 3 positions bearing fluoro substituents?



Orbifloxacin

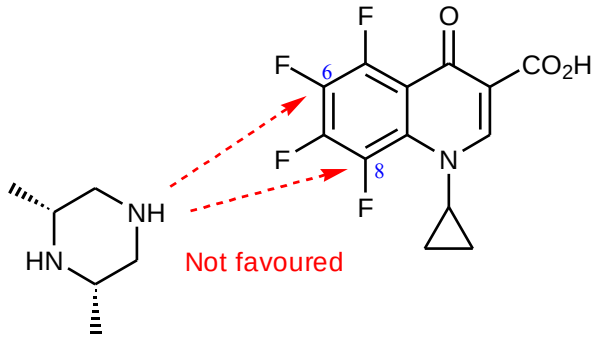
Answer

A mechanism can be drawn that involves the participation of the ketone group. This would assist the reaction by stabilising the negative charge in the intermediate.

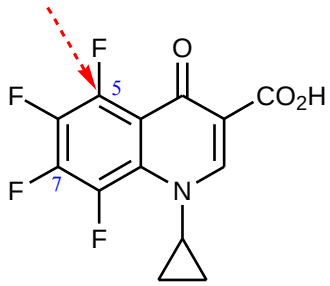


Orbifloxacin

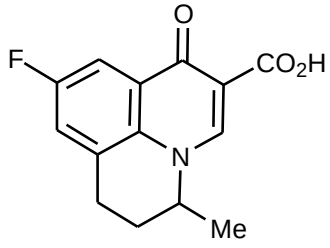
If the piperazine reacted at position 6 or 8, it would not be possible for the negative charge to end up on the oxygen atom, and so the negative charge is less stabilised.



Reaction at position 5 could result in an intermediate where the negative charge could be stabilised by being moved onto the oxygen atom. However, there are likely to be unfavourable steric interactions in the piperazine accessing that position compared to the more accessible 7-position.

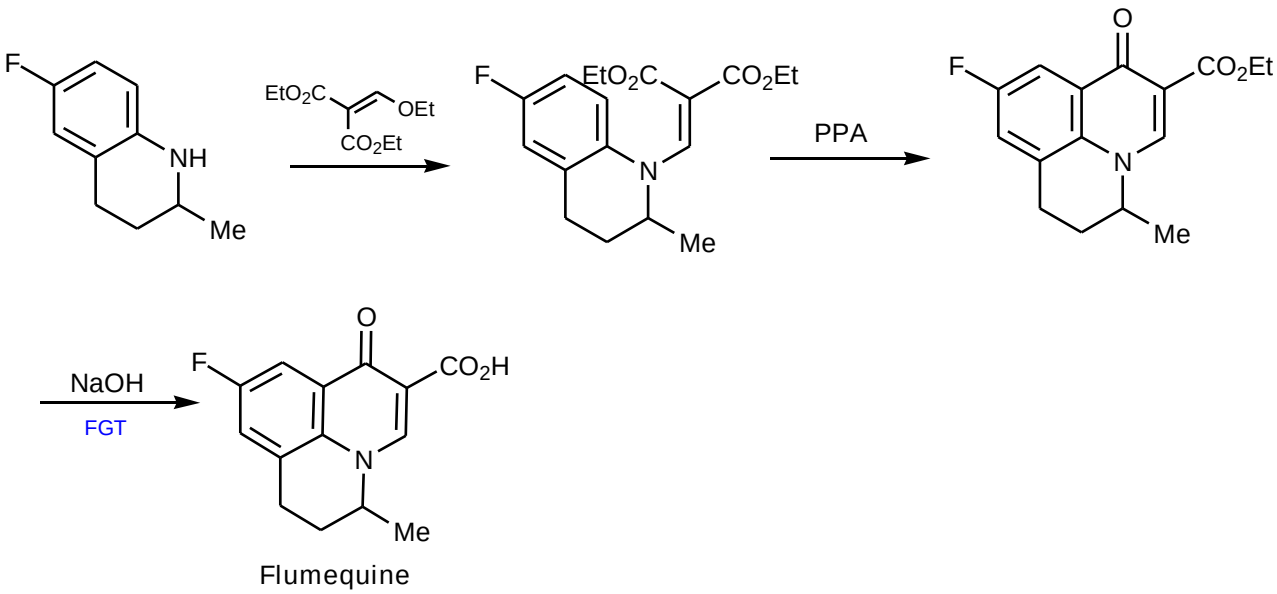


Question 14.4
Flumequine is a first-generation fluoroquinolone which has now been discontinued, although it is still used in veterinary medicine. Propose a possible synthesis.



Flumequine

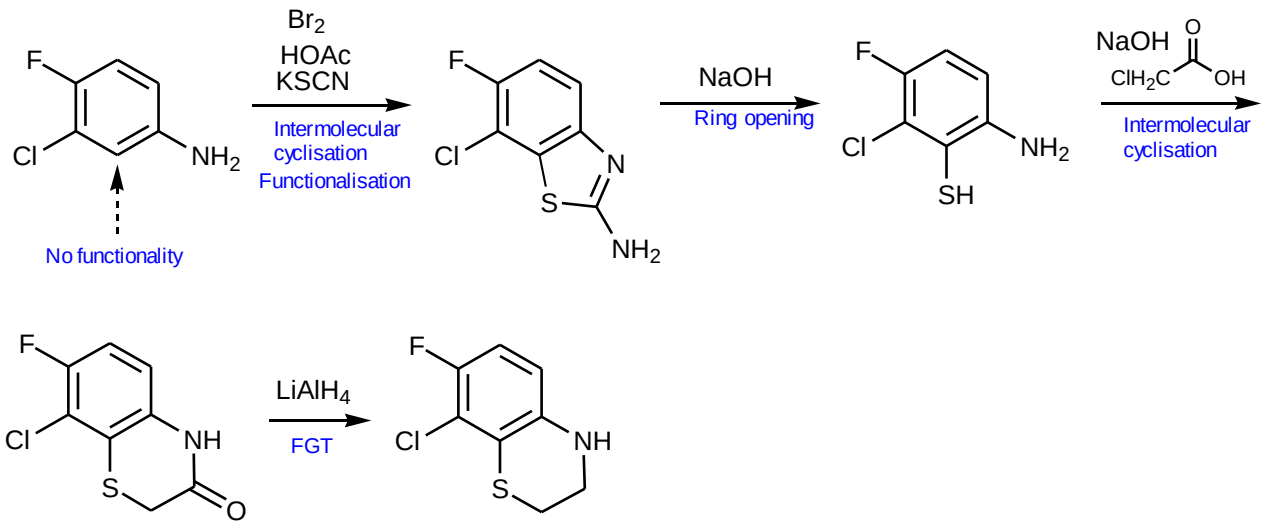
Answer
A possible synthesis is the following.



Flumequine

Question 14.5

Propose mechanisms for the two cyclisations shown in figure 14.21.



Answer

The key intermediates in the mechanism are likely to be the following structures (shown in brackets).