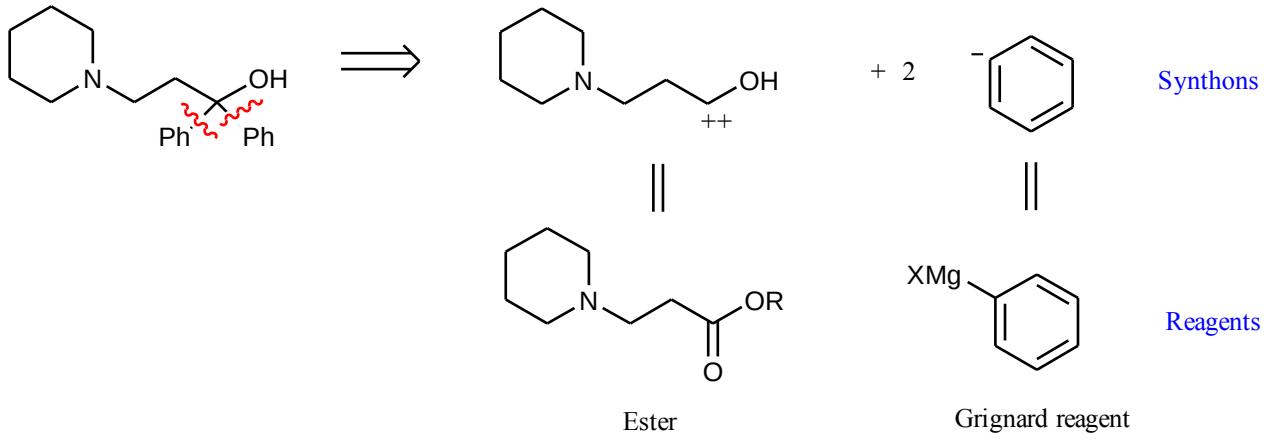
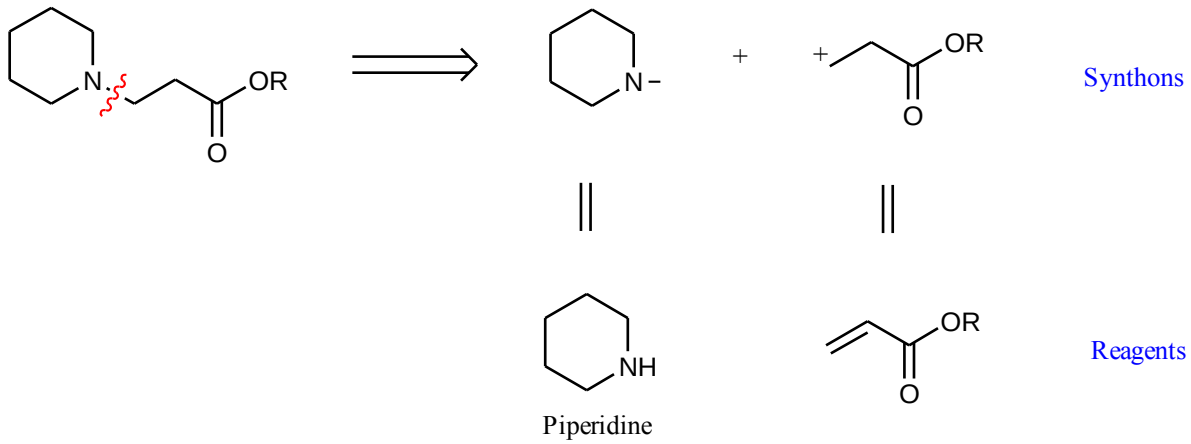
Chapter 3: Retrosynthesis

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

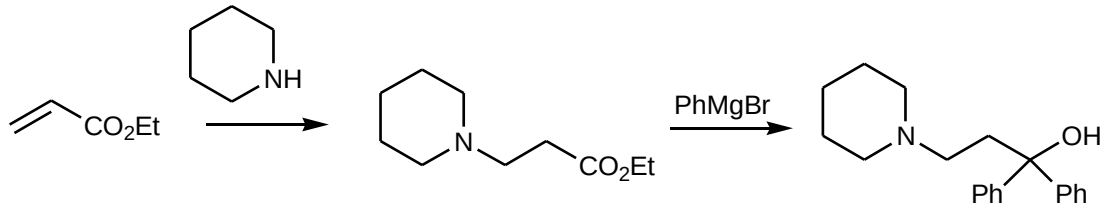
Answer
A key feature in the structure of pirindol is a tertiary alcohol with two identical substituents (the aromatic rings). This is the 'molecular signature' for a Grignard reaction with ester. Disconnecting the two substituents has the following key advantages.
*They disconnect a bond between an aromatic 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)

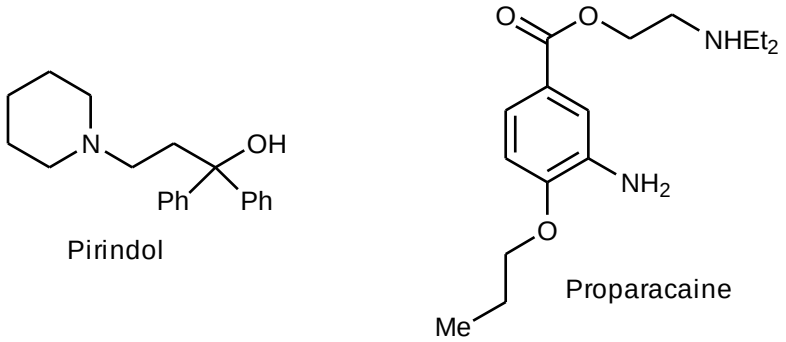


Both reagents are commercially available. The corresponding synthesis is as follows;



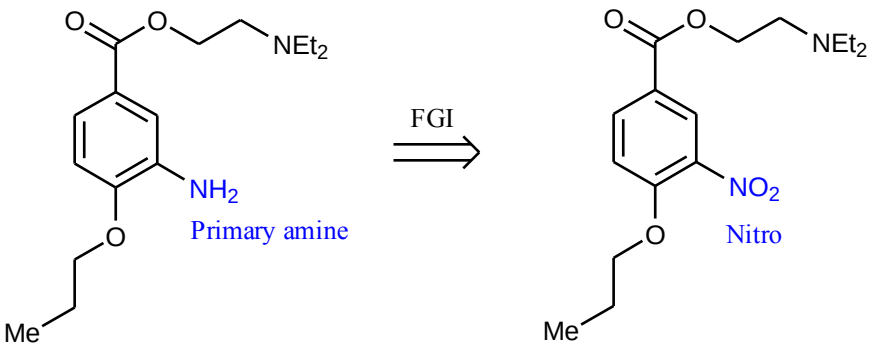
Question 3.2

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.

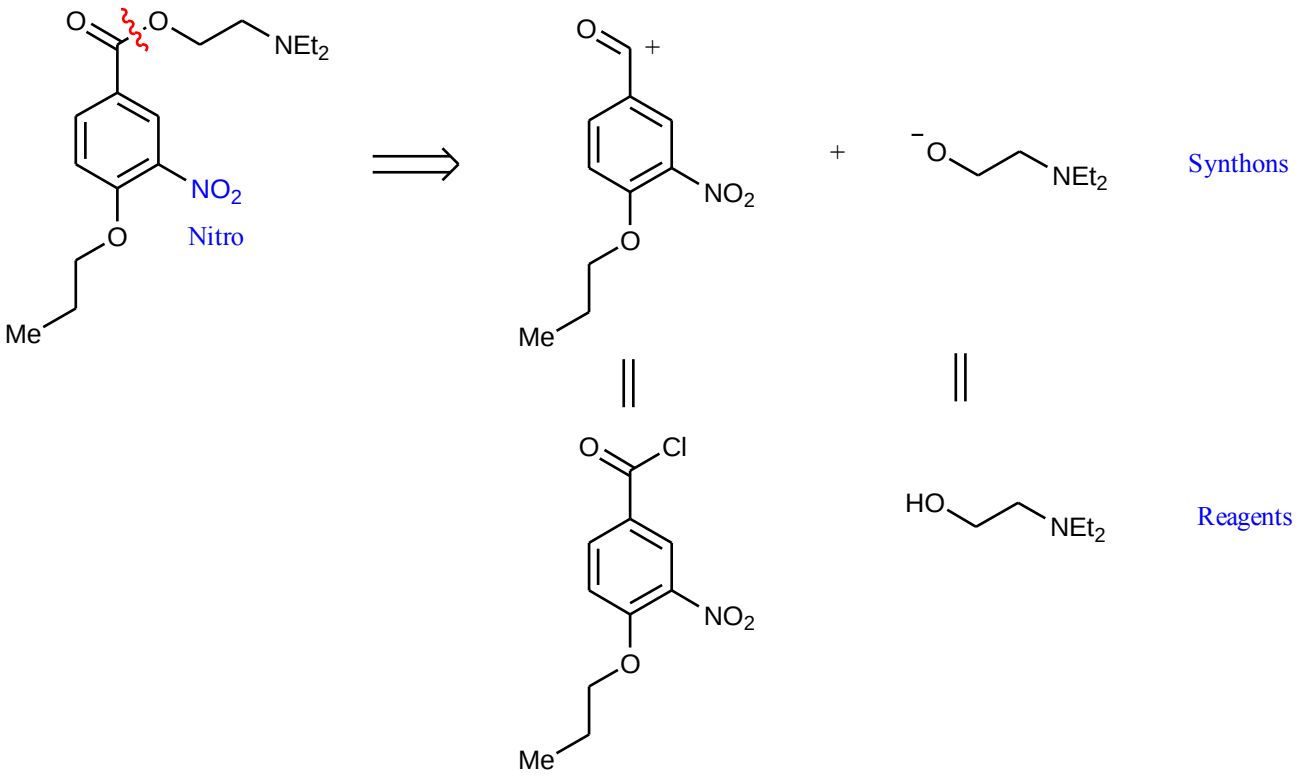


Answer

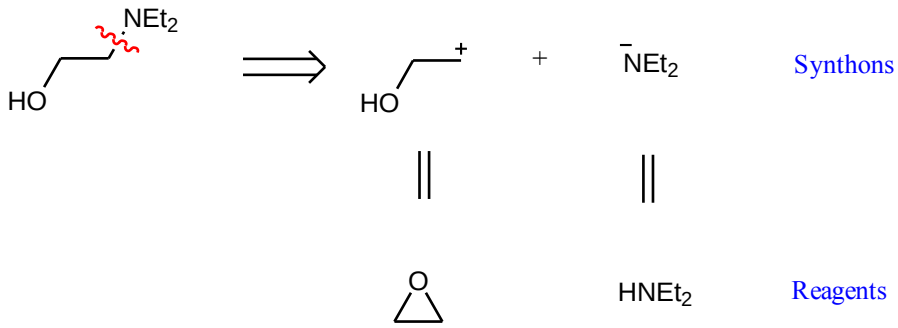
A key feature in the final product is the primary amine. This is a group that usually has to be protected during a synthesis since it is basic and nucleophilic. Therefore, it would be logical to introduce or reveal it as the final stage of the synthesis. This could involve the removal of a protecting 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).



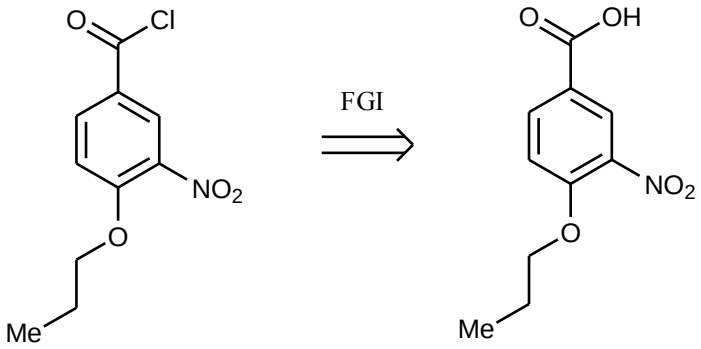
We now consider the nitro compound. A promising disconnection would be of the ester group which fits one of the criteria for a good disconnection since it involves a C-X bond where X is a heteroatom (O)
The reagents corresponding to the resulting synthons would be an acid chloride and an alcohol.



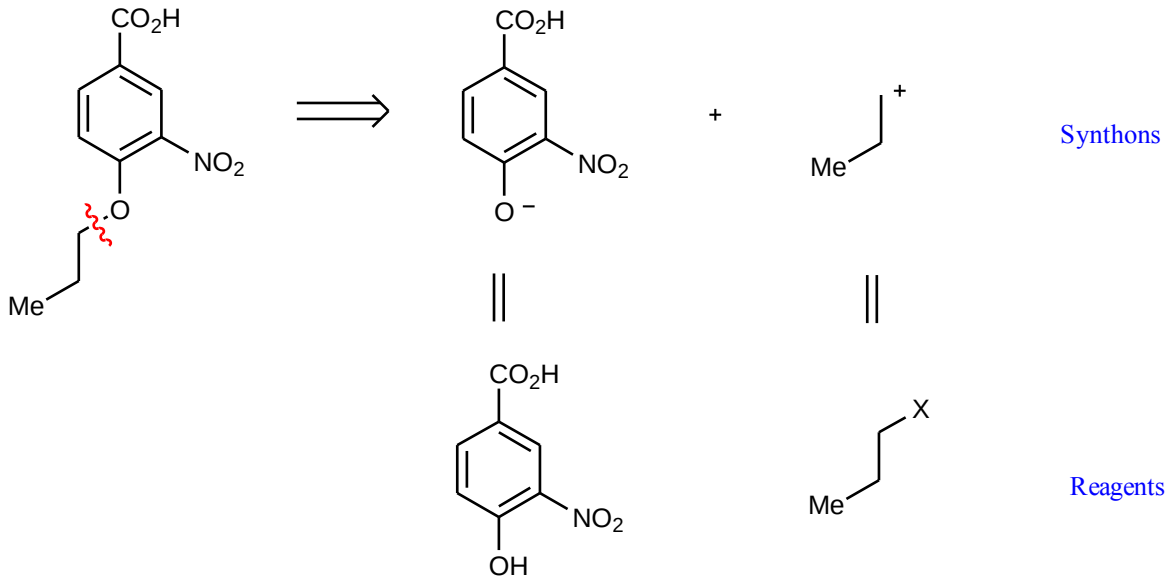
The amino alcohol could be obtained from an amine and an epoxide, both of which are commercially available.



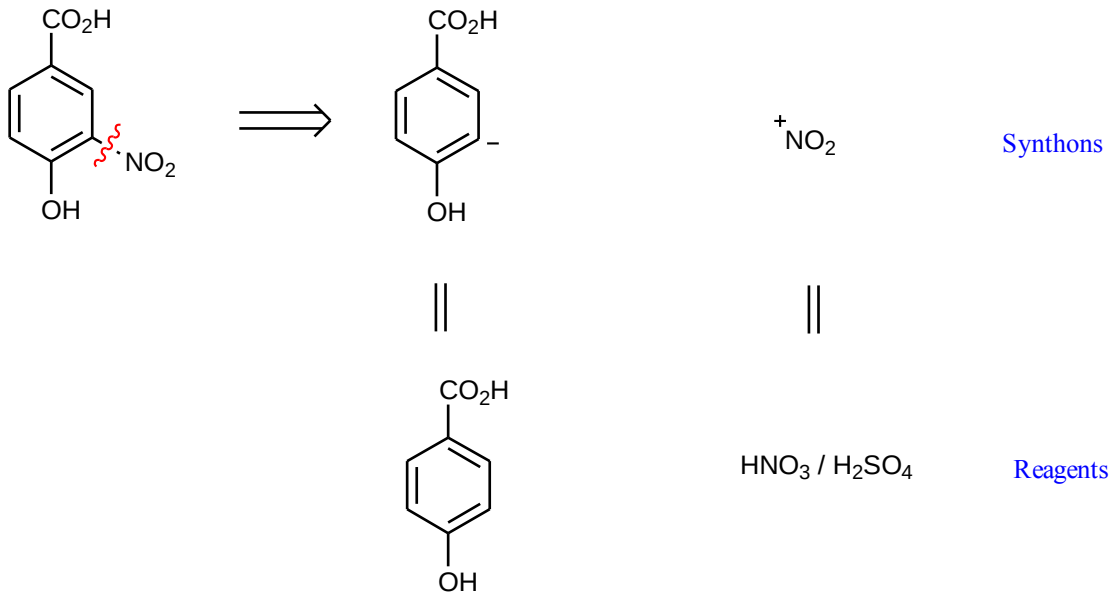
The acid chloride can be obtained from a carboxylic acid



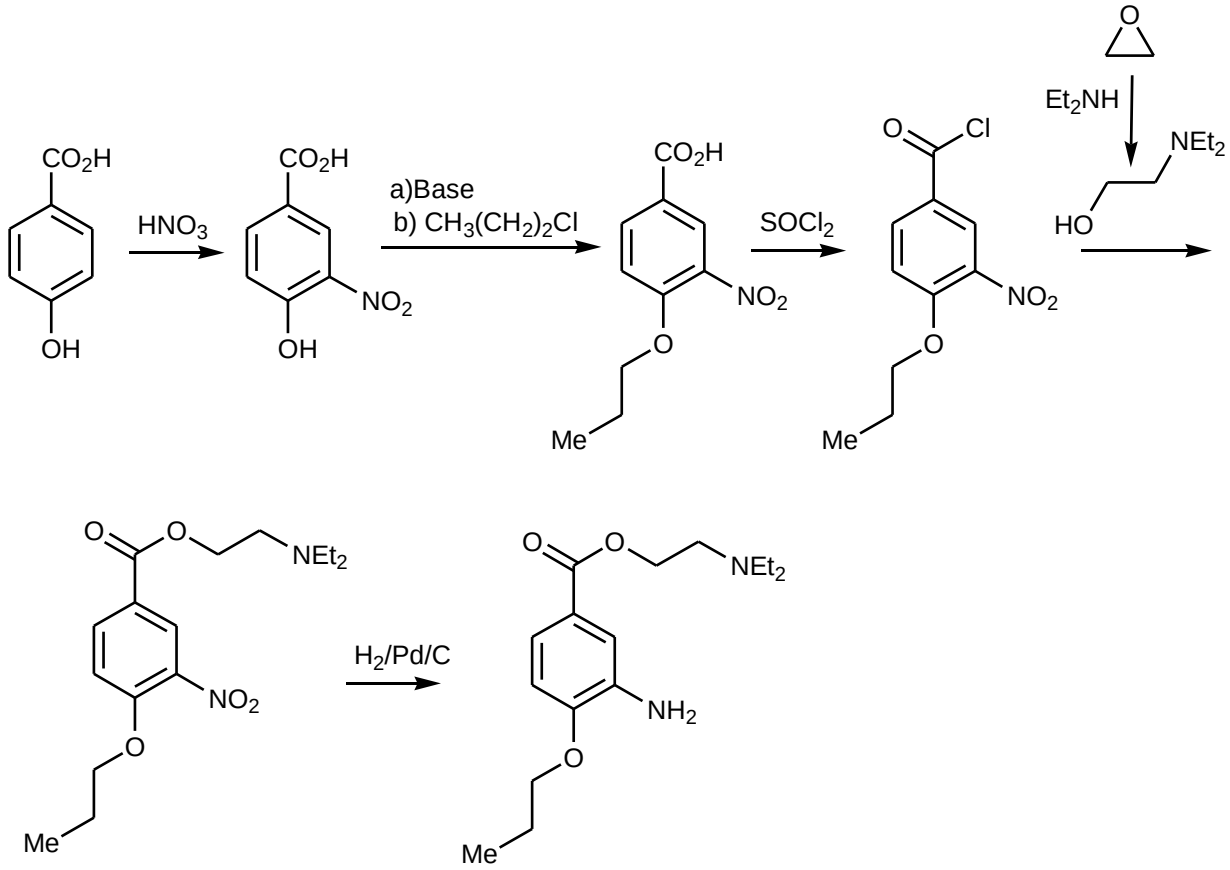
Another favoured disconnection is possible by disconnecting the C-O bond of the ether.



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

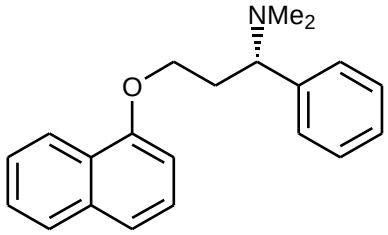


At each stage of the above retrosynthetic analysis, there are available reagents for the synthons or structures produced, and the reactions involving these reagents are feasible. The overall synthesis is the following -



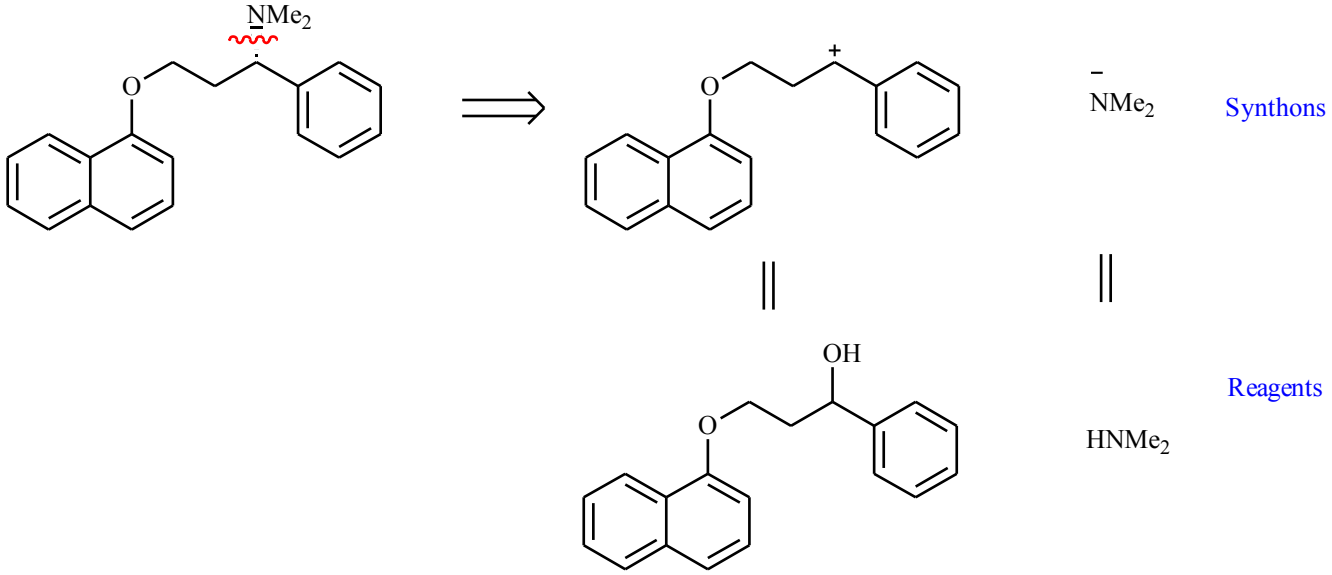
Note that the initial nitration is favoured since both substituents direct electrophilic substitution to the same position of the aromatic ring *(ortho* to the phenol and *meta* to the carboxylic acid).

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

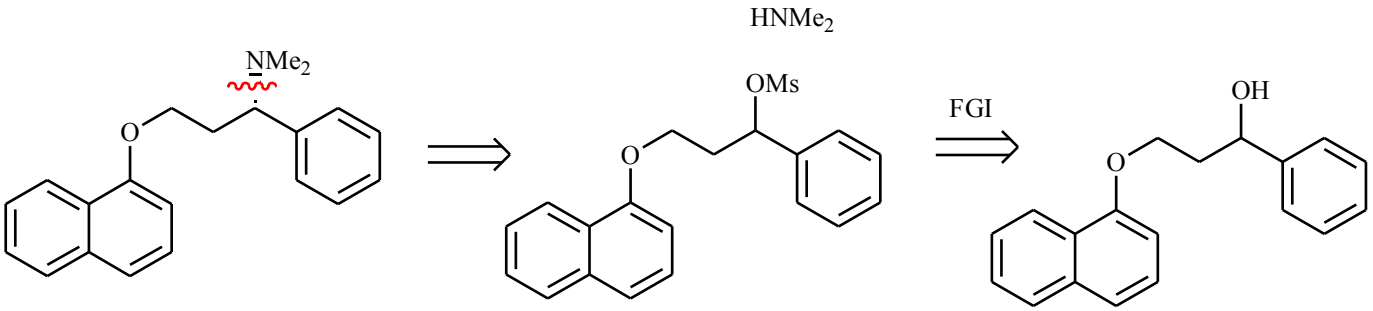


Dapoxetine

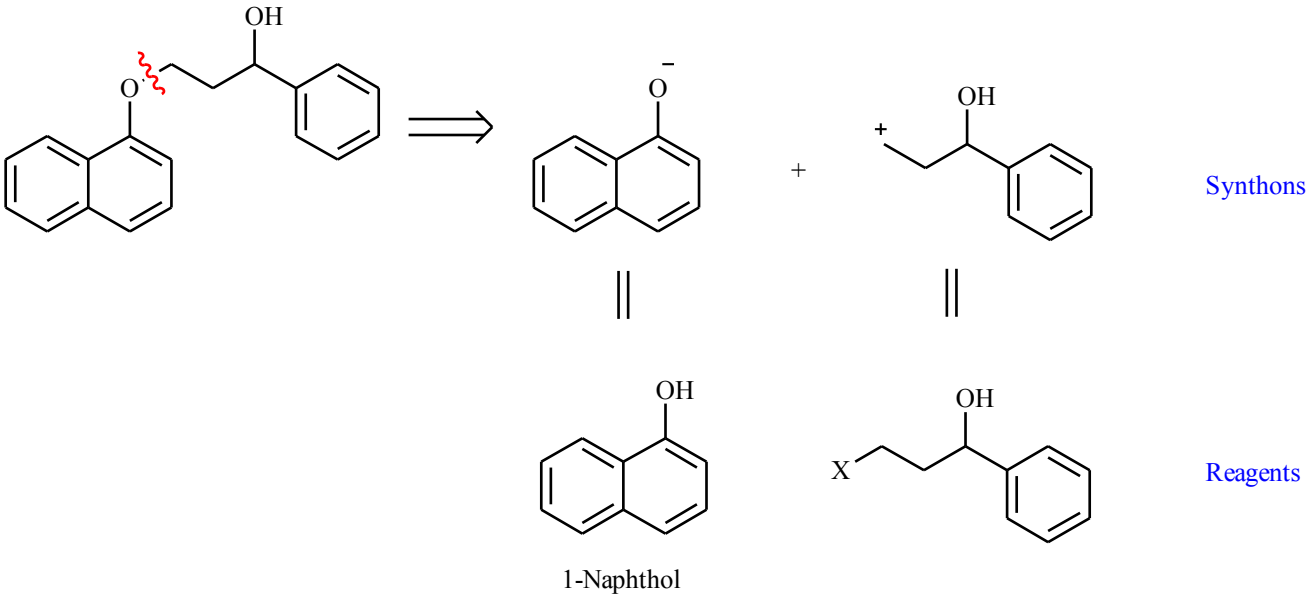
Answer
One possible approach is the following. A possible disconnection is the C-N bond.



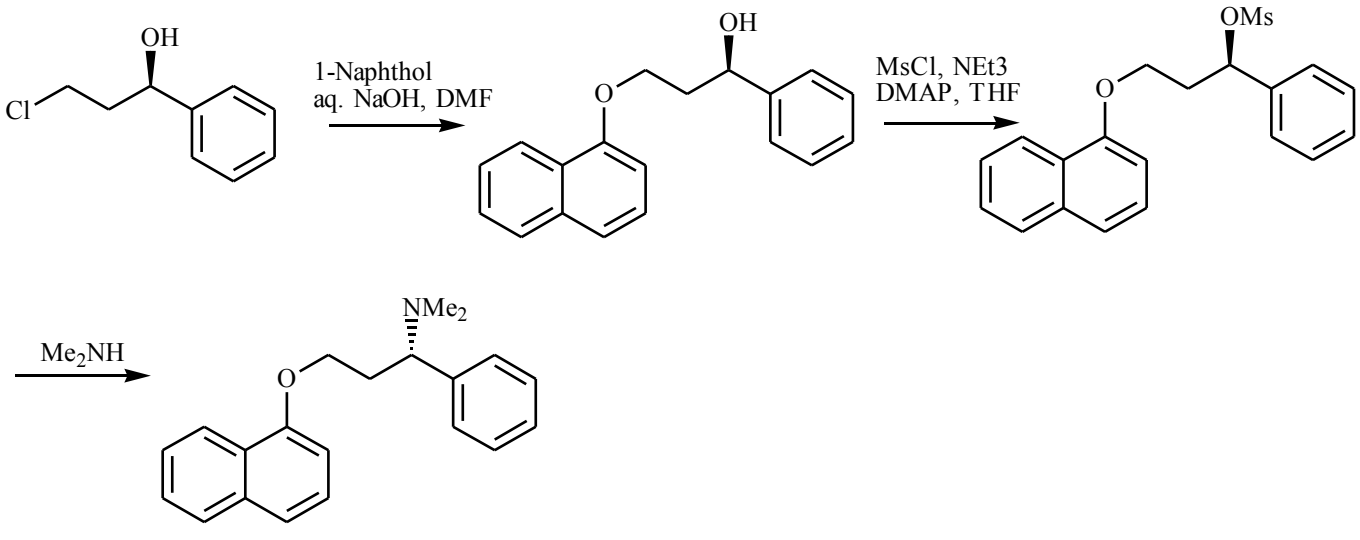
This is a favoured disconnection since a C-N bond is involved. The corresponding reagent for the synthon would be dimethylamine which is commercially available. The other synthon could correspond to an alcohol. Is the reaction between the alcohol and dimethylamine feasible? Would the amine be able to 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.

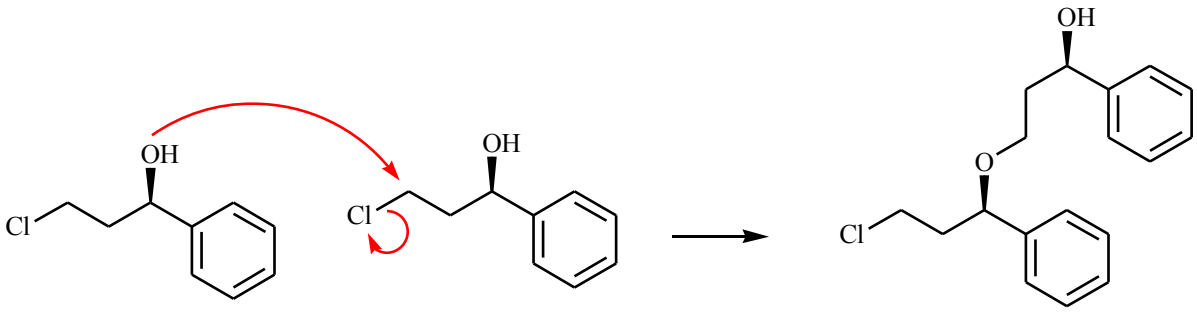


The synthon having the oxygen will have a natural negative charge. The corresponding reagent is 1-naphthol which is commercially available. The positively charged synthon corresponds to a reagent which will have a good leaving group at that position such as a halide, mesylate or tosylate. It makes sense 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.