Answers to end-of-chapter questions

1) The positions of the two labels in atropine are not suitable for drug metabolism studies. *N*-Demethylation is a common metabolic reaction and so the labelled *N*-methyl group would be quickly lost. The tritium label would also be quickly lost. It is positioned next to a carbonyl group and so it is slightly acidic. Proton-tritium exchange with water will result in loss of the tritium label from the molecule. Therefore, it is unlikely that either label will survive long enough in order to identify any metabolites of atropine.

2) A placebo is a preparation which does not have any physiological effect and is used in clinical trials to distinguish whether a drug has a real pharmacological effect or not. Frequently, there is a significant pharmacological effect when a patient takes a placebo. The patient believes the preparation will have a beneficial effect and this belief can be beneficial in itself. This is called the placebo effect. Clinical trials test one set of patients with the drug and another set of patients with the placebo to see whether there is any added benefit from taking the drug. Patients must have no idea whether they are receiving the drug or the placebo. Therefore, the placebo must be as similar as possible to the drug in its physical appearance, taste, and smell. It must also be administered in the same way.

3) In chemical development, the aim is to design a large-scale synthesis which is cheap and efficient, 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 (see also section 15.3.1).

4) Scale up is certainly part of the chemical development process, but it is only part of the process. Certain reactions may not be suitable for scale up due to the cost or toxicity of the chemicals used. This would require altering the conditions of particular reactions or changing the synthetic route altogether (see also section 15.3.1).

5) There is the problem with the first step of the reaction sequence - an electrophilic substitution of an aromatic ring. The carboxylic acid group of fexofenadine is electron withdrawing, whereas the methyl group of terfenadine is electron donating.
In the latter case, the Friedal Crafts acylation gives only the *para* product. Alkyl groups are electron donating and direct substitution to the *ortho/para* positions. 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.

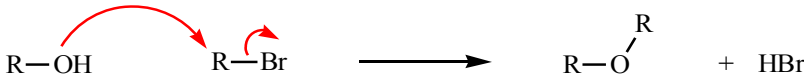
6) The reaction involves the removal of protecting groups to generate a dipeptide. The dipeptide exists as a zwitterion and is highly polar. As a result, it should be more soluble in water than in ethanol.

The protected dipeptide has the polar groups masked and is more hydrophobic. It will dissolve more easily in ethanol than in water.
If the reaction is carried out in ethanol, the starting material can be dissolved, but as soon as the dipeptide is formed, it is likely to precipitate from solution. This in itself is not a disadvantage, but the reaction involves a catalyst and precipitation of the product results in the catalyst becoming coated and inactive. As a result, the reaction stops and a poor yield is obtained.
If water is used, the product will not precipitate, but the starting material is poorly soluble and can coat the catalyst, again leading to a poor yield.
The answer to the problem is to use a solvent mixture of ethanol and water which is capable of dissolving both the protected dipeptide and the product.

7) 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.

8) 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, and 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.

9) 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.