Suggested solutions for Chapter 23

Several problems in this chapter ask you to suggest ways to carry out conversions of one molecule into another. We always give one possible answer and sometimes comment on alternatives but you should realise that there are usually many possible ‘right’ answers to questions of this sort. Make sure you understand the principle behind the question and, if your answer is very different from ours, check with someone with experience of synthesis.

**PROBLEM 1**
How would you convert this bromo-aldehyde chemoselectively into the two products shown?

![Chemical structures showing the transformation of a bromo-aldehyde into two products](image)

**Purpose of the problem**
A simple exercise in chemoselectivity and protection.

**Suggested solution**
You would like to add an organometallic reagent to go to the right and that's very simple as no protection is needed. A Grignard reagent will do the job.

\[
\begin{align*}
RBr & \xrightarrow{\text{Mg, Et}_2\text{O}} \text{RMgBr} & + \text{CHO} & \xrightarrow{?} \text{HO}\text{R} \\
\end{align*}
\]

The other product demands more care to avoid the reactions we have just done. The aldehyde needs to be protected, as an acetal, say, before
we make the Grignard reagent from the aryl bromide. Then we can add to RCHO, and deprotect with acid, and we have our product.

PROBLEM 2

How would you convert this lactone selectively into either the hydroxyacid or the unfunctionalised acid?

Purpose of the problem

Exploration of chemoselectivity.

Suggested solution

The conversion into the hydroxy-acid is just hydrolysis and can be carried out in aqueous base. Conversion into the unfunctionalized acid demands selective reduction of the C–O at the secondary benzylic centre. Possibilities include catalytic hydrogenolysis (p. 539 in the textbook) or HBr followed by C–Br reduction.

**PROBLEM 3**

Predict the products of Birch reduction of these aromatic compounds.

![Chemical structures](image)

**Purpose of the problem**

Exploring the principles of Birch reduction.

**Suggested solution**

In each case a unique product results if you draw a dianion intermediate placing the electron-withdrawing groups where they can stabilise the negative charges, and put the electron-donating groups on the alkenes, where they don’t destabilise the negative charges.

![Chemical reactions](image)

- See p. 542-543 in the textbook for explanation of why this approach works.

**PROBLEM 4**

How would you carry out these reactions? In some cases more than one step may be required.

![Chemical reactions](image)

**Purpose of the problem**

Reduction, selectivity, and protection in the same sequence.
The final product was used to make an analogue of thromboxane, a human blood clotting agent, by M. Hayashi and group, *Tetrahedron Lett.*, 1979, 3661.

**Suggested solution**

Every step is straightforward except the final reduction where a less reactive ester must be reduced in the presence of a more reactive ketone. Protection is the answer and an acetal is suitable.

PROBLEM 5

How would you convert this nitro compound into the two products shown? Explain the order of events with special regard for reduction steps.

**Purpose of the problem**

Reduction, selectivity, and protection in two related sequences.

**Suggested solution**

The nitro group must be reduced to an amino group and cyclised onto the ketone or the carboxylic acid. Reductive amination (p. 234-7 in the textbook) allows the amine to cyclise onto the more electrophilic ketone.

Forming the six-membered ring requires more control. Protection of the ketone (say as the acetal) before reduction will give the six-membered cyclic amide. Now the amide carbonyl must be reduced with
LiAlH₄ (p. 236 in the textbook) and the ketone deprotected. There are many good alternative answers to this problem.

**PROBLEM 6**

Why is this particular amine formed by reductive amination here?

Purpose of the problem

Extending the concept of reductive amination by combining it with deprotection and cyclisation.

Suggested solution

The two acetals will be hydrolysed at pH 5.5 to give the amine a choice between cyclisation to one or other of the two aldehydes.

Cyclisation to a five-membered ring is preferred to cyclisation to a (strained) four-membered ring so reductive amination occurs to the right and not to the left (as drawn). Cyanoborohydride is stable under the weakly acidic conditions and does not reduce the remaining aldehyde.

PROBLEM 7

Account for the chemoselectivity of the first reaction and the stereoselectivity of the second. A conformational drawing of the intermediate is essential.

Purpose of the problem

Extending chemoselectivity into more subtle distinctions and conformational analysis.

Suggested solution

The two ketones are different only because one is conjugated. Since acetal formation is a thermodynamically controlled reversible reaction, the one that is formed retains the enone as the stabilising effect of conjugation can be retained. A conformational diagram of the intermediate shows that there is inevitably one axial oxygen atom belonging to the acetal preventing the bottom face of the alkene from getting close to the catalyst. The axial methyl group is further away and more in the plane of the alkene. Hydrogen is delivered from the top face and the observed product results.