1. Read the following paper on the synthesis of Irbesatan (Avapro®):


The aim of the paper was to avoid the use of DMF and column purification – cited as making the initial scheme commercially unviable. However the first step still involves the following bromination using DBDMH:

The greenest replacement according to the reagent guide is the use of halogenase enzymes. Why is this unlikely to be feasible for this reaction? With this in mind, please suggest an alternative bromination reagent and give your reasoning.

Answer should mention that halogenase enzymes – particularly bromination ones – are often found in aqueous systems and note that the starting material here is highly apolar and unlikely to be water soluble. Good answers could refer to the MSDS sheet and point out the lack of solubility data. NBS is likely to be suggested as an alternative due its noted inability to react directly with nitriles and aromatic rings without catalysts – though questions over solubility may remain. Any other well-justified answer can be accepted though.

2. Read the following paper on the synthesis of an intermediate of atorvastatin (Lipitor®, Sortis®):


Whilst the paper details some improvements, one key step still includes the following oxidation process using CrO₃ with sulphuric acid in acetone at 0 °C:

Using the reagent guide, please suggest an alternative reagent to use for this oxidation. Please provide your reasoning.
Answers should mainly focus on selectively oxidising the aldehyde group whilst leaving the nitrile and acetal groups untouched. Particular attention should be paid to strong nucleophiles and Lewis acids. Required solvents should also be considered. What should also be considered is whether or not the oxidation reagents can convert primary alcohols and aldehydes all the way to carboxylic acids.

E.g. Selective only to aldehyde: Sodium Tungstate

Unselective: MnO₂, MnO₄⁻, H₂O₂

Strong nucleophile: Pyridine

Solubility issues: IBX

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The views expressed in regards to education and training materials represent the aspiration of the CHEM21 consortium, although may not always be the view of each individual organisation.