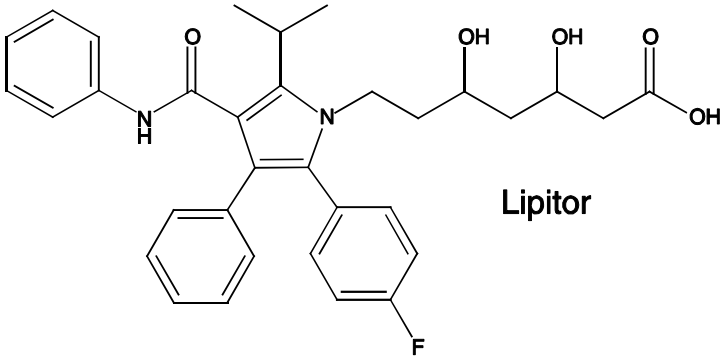
4. This question is about the synthesis of top-selling drug Lipitor®

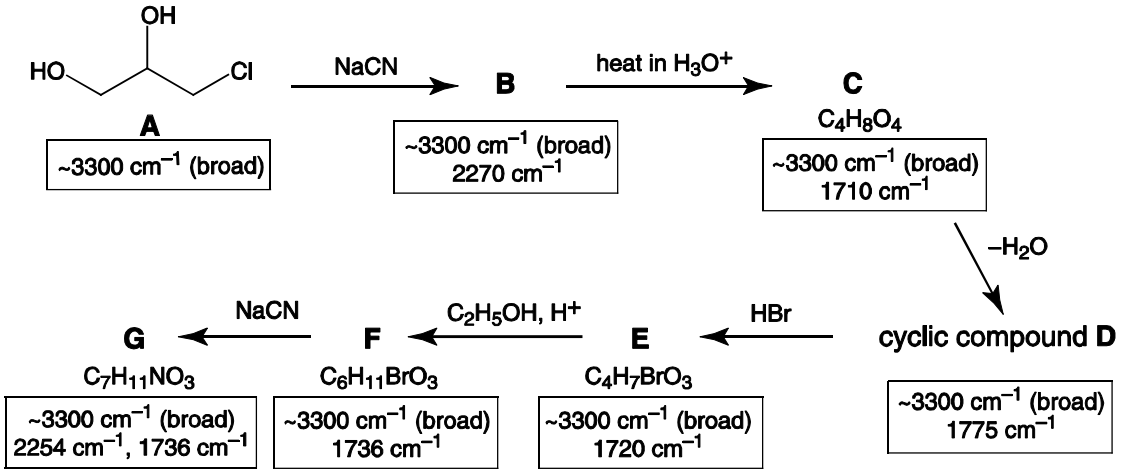


Lipitor

With annual sales worth billions of pounds, for many years Pfizer's cholesterol-lowering drug Lipitor has been the best-selling pharmaceutical in the world. The first steps of a multi-stage synthesis of Lipitor are shown below.

Given in the boxes are the most characteristic IR stretching frequencies of the intermediates in the synthesis. No stretches due to any C–C or C–H bonds are included; stretching frequencies due to single bonds other than bonds to hydrogen do not show up in the range listed. You are not expected to know these stretching frequencies, but through careful reasoning, you should be able to use them to help work out the structures of the unknowns.

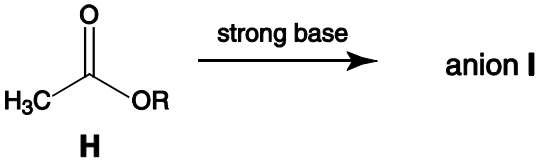
Note that not all the by-products are shown in the reaction schemes.



(a) Give the structures for the compounds **B** to **G** and, over the course of the whole question, complete the table of IR absorptions found in compounds **A** to **M**.

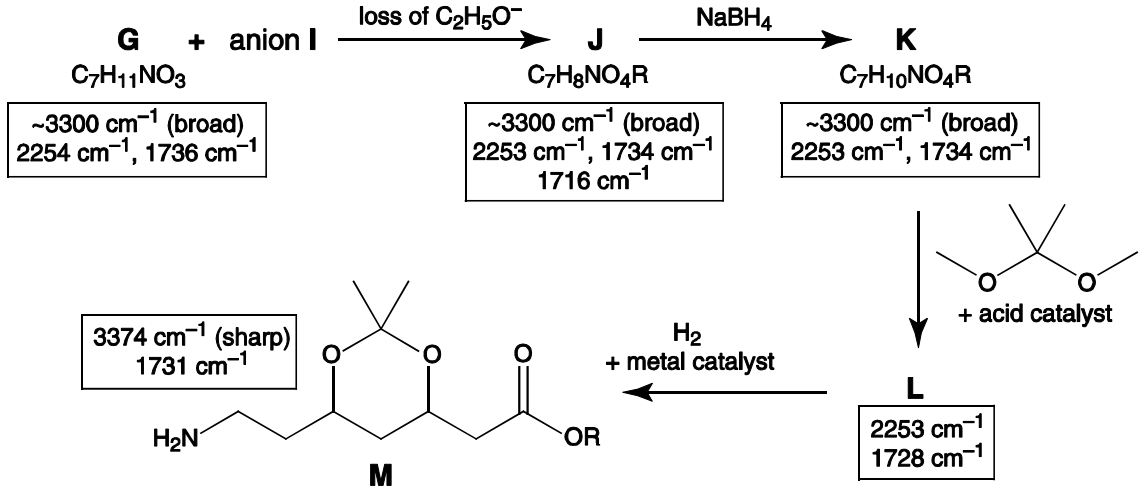
absorption / cm^{-1}	~ 3300 (broad)	?	2250-2275	?	1700-1740
bond	?	C=O in a small ring	?	N–H	?

Ester **H** is deprotonated by strong bases to give the reactive carbon nucleophile, anion **I**. The R group in the structure is an alkyl chain which remains unchanged throughout the entire synthesis.



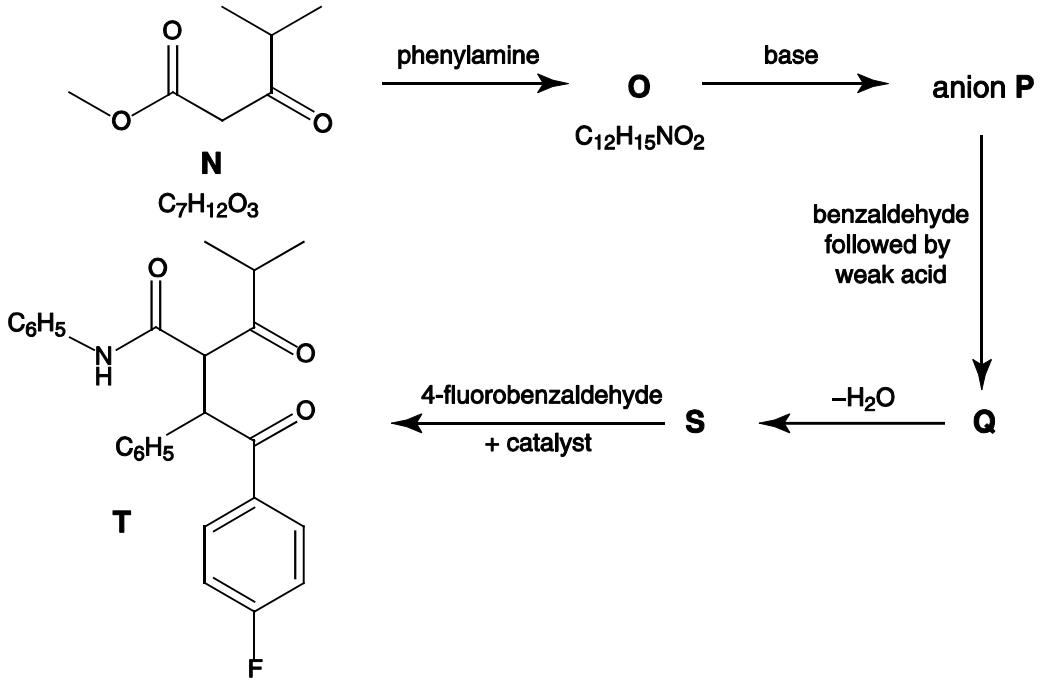
(b) Draw the structure for the anion **I**.

The synthesis continues as shown below:



(c) Give the structures for the compounds **J**, **K** and **L**.

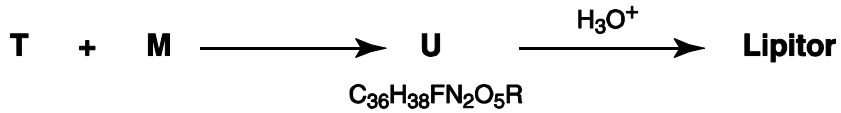
In a separate branch of the synthesis, **N** reacts with phenylamine to give compound **O**. This may be deprotonated in base to give another carbon nucleophile, anion **P**. Anion **P** reacts with benzaldehyde to give **Q** ; **Q** then dehydrates to give compound **S**. **S** reacts with fluorobenzaldehyde in the presence of a catalyst to give compound **T**.



(d) Give the structures of phenylamine and 4-fluorobenzaldehyde.

(e) Suggest structures for **O**, anion **P**, and compounds **Q** and **S**.

In the final stage of the synthesis, **T** and **M** are brought together to give compound **U** which on hydrolysis in aqueous acid gives the target, the drug Lipitor.



(f) Suggest a structure for compound **U**.