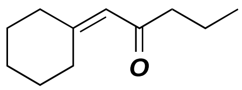
Retrosynthetic Analysis 2

Some common examples are being discussed here.

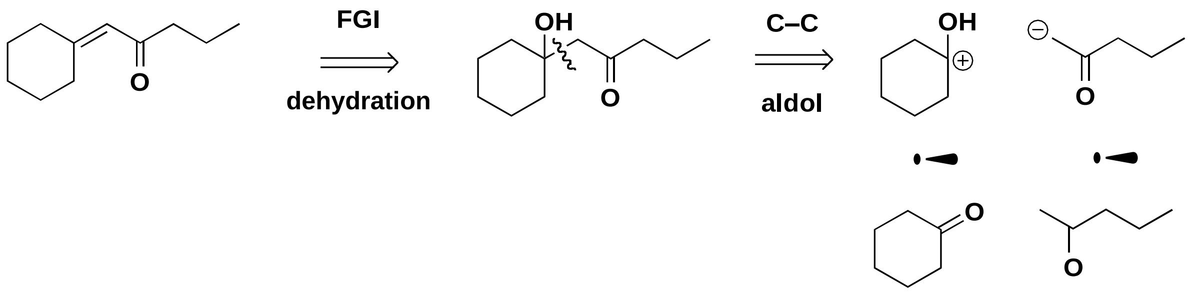
Case 1.

Propose a retrosynthetic analysis of the following two compounds. Your answer should include both the synthons, showing your thinking, and the reagents that would be employed in the actual synthesis.

Compound A

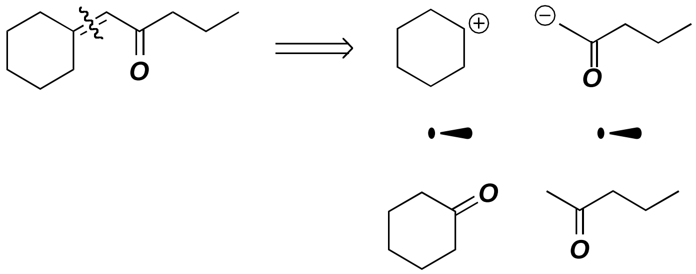


Answer:

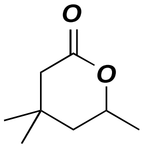


Remember that a conjugated double bond can easily be prepared by dehydration, thus we can perform an FGI to give the aldol product. The 1,3-diO relationship should make spotting the disconnection very easy. Of course, in the forward direction the reaction is not quite that simple; we have two carbonyl groups so we must selectively form the correct enolate but this should be possible by low temperature lithium enolate formation prior to the addition of cyclohexanone.

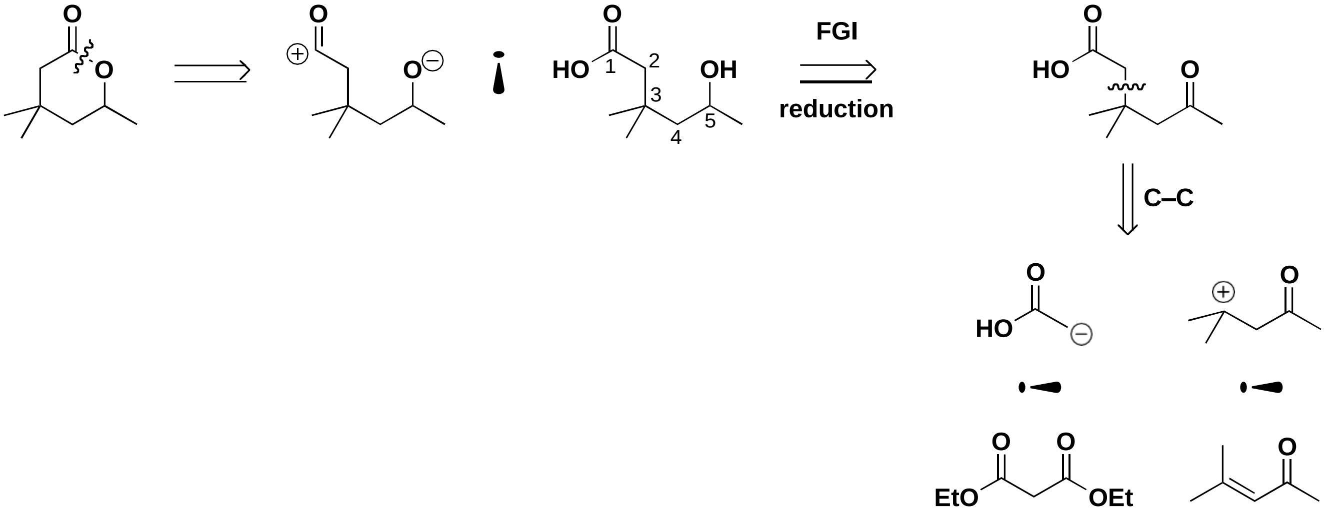
The aldol condensation is such a common reaction that it is perfectly acceptable to do the following disconnection:



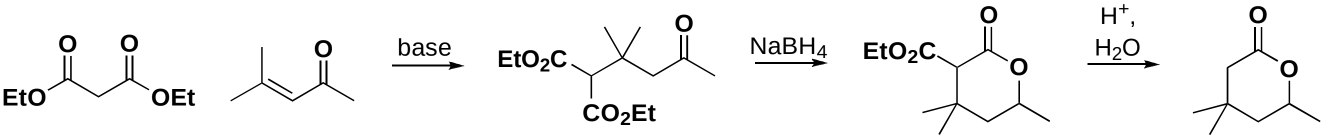
Compound B



Answer

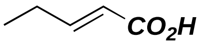


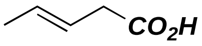
The first disconnection should be relatively simple, break the C–O bond to give the acid and alcohol. The next stage might be slightly tougher…your best bet is to look at the relationship between the two functional groups; it is 1,5. This can be formed *via* a conjugate addition of an enolate. To do this we need two carbonyl groups so next move is a FGI to form the dicarbonyl. Two possible disconnections are now possible depending on which enolate we add to which activated alkene. The one I have drawn is simpler, diethyl malonate is commercially available as is the enone (or it can be prepared by the self-condensation of acetone). Additionally, conjugate addition of malonates prefers 1,4 to 1,2 addition, which can be an issue with simple carbonyls. Chemoselectivity in the reduction step is not an issue; $NaBH_4$ does not reduce esters.

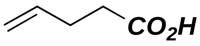


Case 2.

Give the retrosynthetic analysis for the following three compounds. Pay special attention to the relationship between the functional groups.

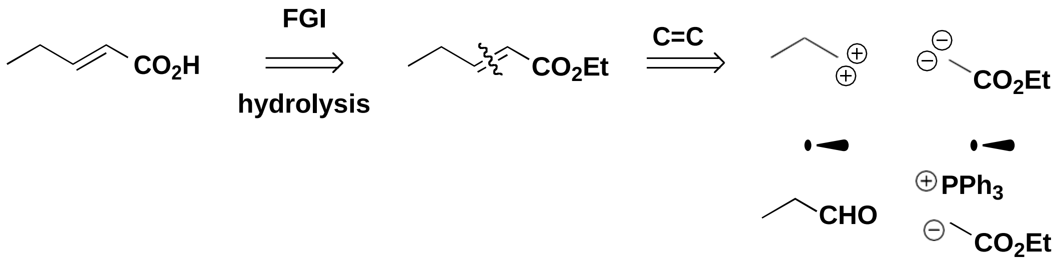




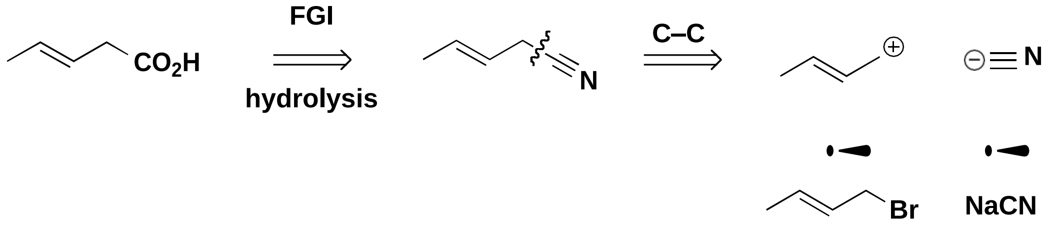


Answers:

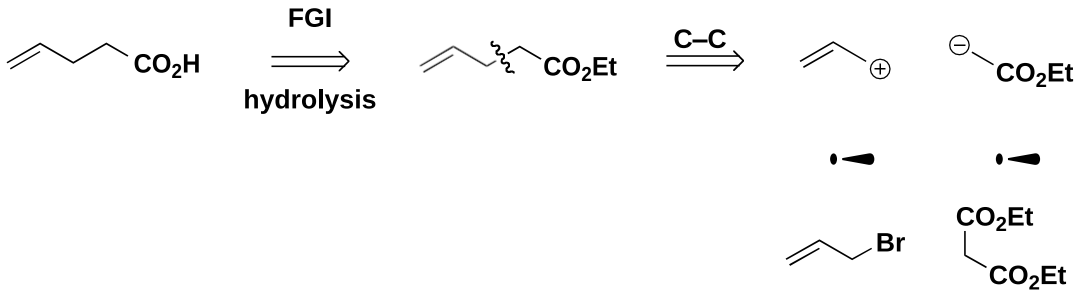
The first is the easiest; it is an !,″-unsaturated compound so we are looking at either aldol condensation or a simple Wittig reaction. Sometimes you will see double bond disconnections drawn with a double charge synthon…I'm not convinced it helps but if it allows you to rationalise what is going on more readily then use it!



The second is probably the hardest; there is no simple enolate disconnections so we have to look slightly further a field. Whilst we can go *via* an alkyne, the best route probably involves FGI to a nitrile and then simple C–C bond formation by a substitution with a cyanide anion.

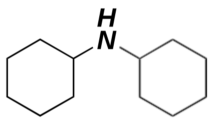


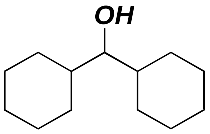
Alkylation of an enolate offers the most rapid approach to the third structure. Not much needs to be said about this one.

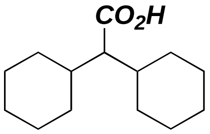


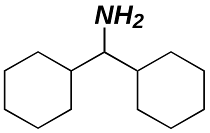
Case 3.

How would you make these compounds?



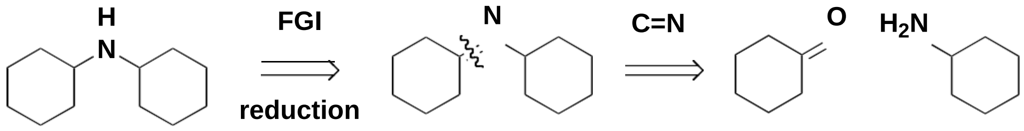




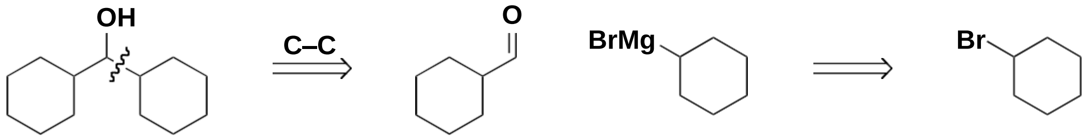


Answers

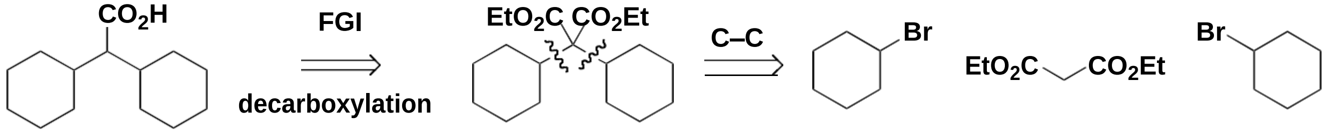
The first is simply a case of reduction amination. We cannot form an amide so it has to proceed by the imine.



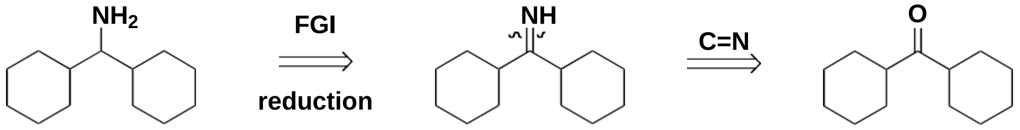
The next isn't much harder…we have an alcohol, this should yell Grignard addition to a carbonyl and hence the disconnections are:

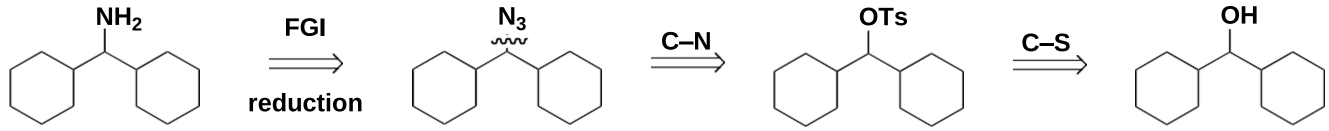


This one is potentially a little harder…but not much. The best route to the acid is *via* alkylation of diethyl malonate. The latter is easily enolised, will only undergo two additions, is fairly robust yet will readily undergo decarboxylation.



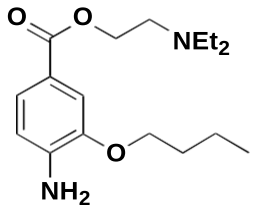
The final compound is a primary amine. This could either be prepared by reductive amination of the appropriate ketone (made from oxidation of the secondary alcohol made earlier) or by substitution of an appropriately derivatised secondary alcohol (tosylation of the secondary amine) with azide followed by reduction.



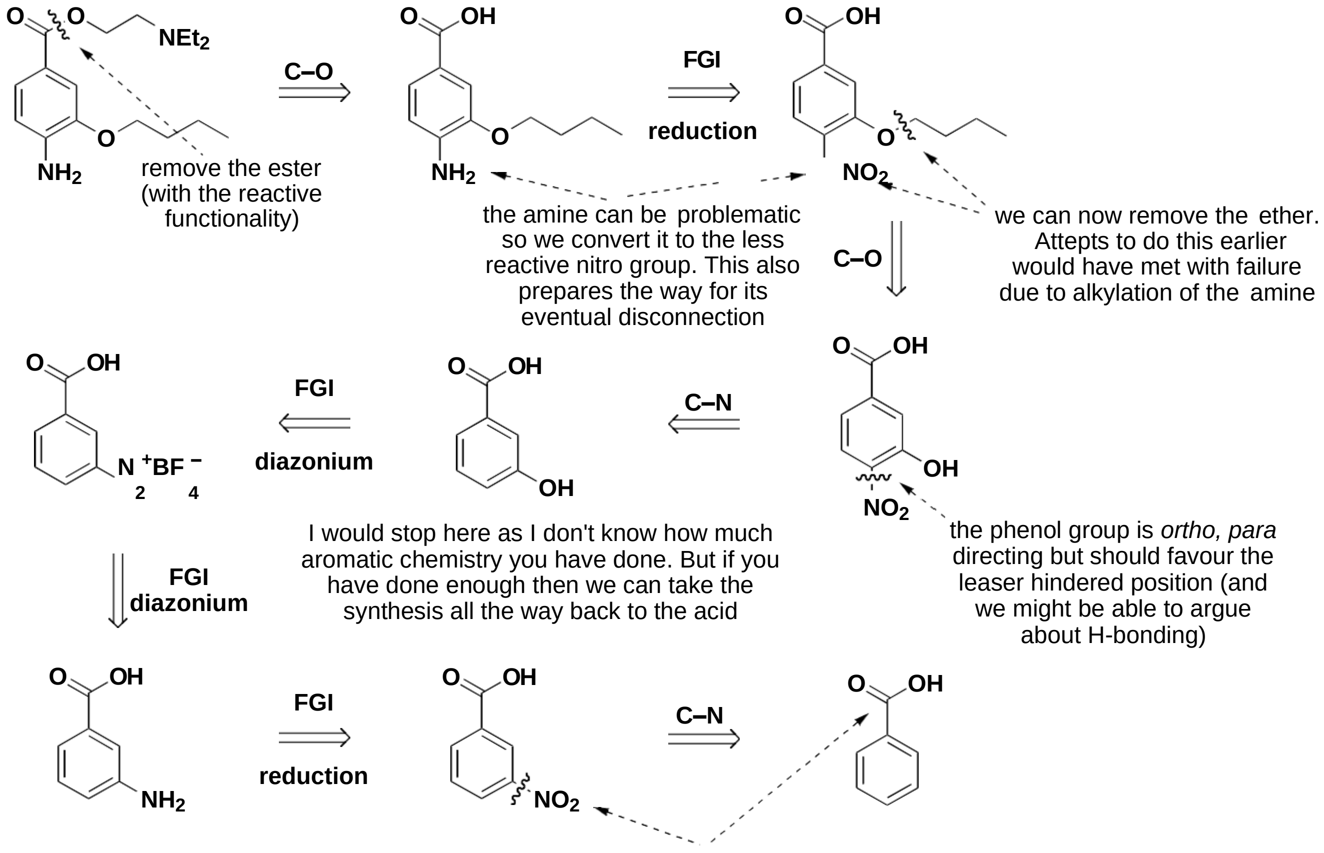


Case 4.

Perform the retrosynthetic analysis of the following compound. Remember, your planned synthesis must be synthetically possible and shouldn't suffer from regio- or chemoselectivity issues.



Answer



remove the ester (with the reactive functionality)

the amine can be problematic so we convert it to the less reactive nitro group. This also prepares the way for its eventual disconnection

we can now remove the ether. Attepts to do this earlier would have met with failure due to alkylation of the amine

I would stop here as I don't know how much aromatic chemistry you have done. But if you have done enough then we can take the synthesis all the way back to the acid

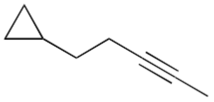
the phenol group is *ortho, para* directing but should favour the leaser hindered position (and we might be able to argue about H-bonding)

remember, the acid is electron withdrawing so is *meta* directing

Case 5.

(a)

How would you synthesise



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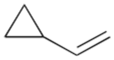

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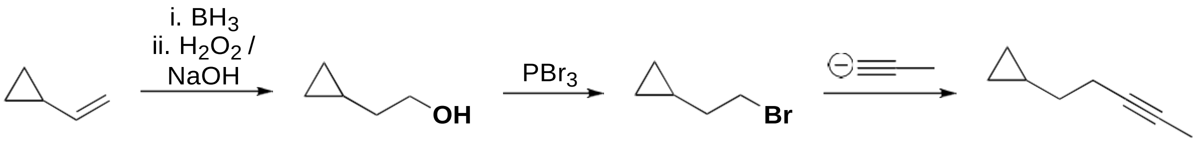
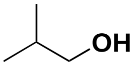


Remember, we need to get anti-Markovnikof addition of the hydroxyl group so we use hydroboration / oxidation.

(b)

How would you synthesise



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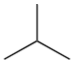

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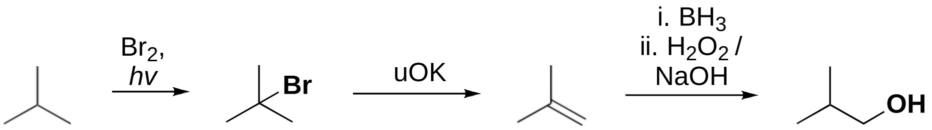
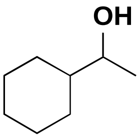


The key to this one is functionalisation of the hydrocarbon. This is achieved by radical bromination, then its plain sailing.

(c)

How would you synthesise



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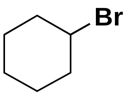

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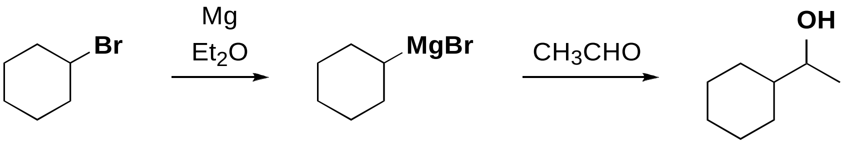
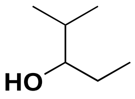


Lets be honest, if you can’t do this one then you’re in trouble!

(d)

How would you synthesise



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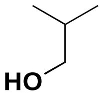

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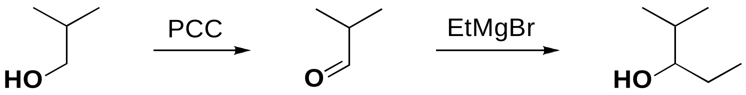
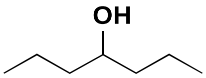


Likewise, this one is not that taxing but hopefully gets you thinking about functional group interconversions.

(e)

How would you synthesise



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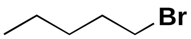

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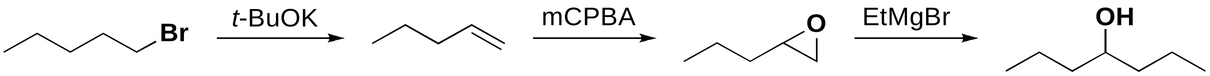
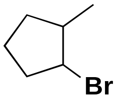


This one is quite hard. But again, it is all about FGI and recognising where the original carbons are. I recommend number you carbons and then trying to identify relationships between functional groups and this numbering.

(f)

How would you synthesise



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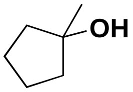

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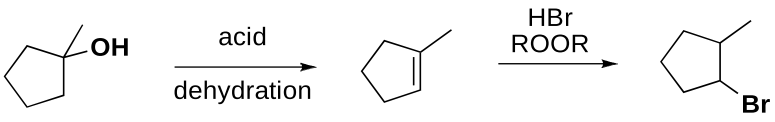
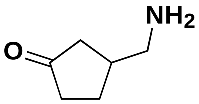


Quick, but not necessarily straightforward; the more reactions you know the easier this becomes. Here we require *anti*-Markovnikov addition of the HBr. Therefore, we add peroxide to allow a radical reaction.

(g)

How would you synthesise



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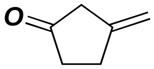

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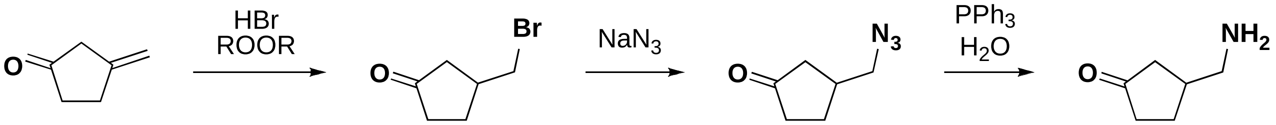
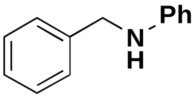


Again, need *anti*-Markovnikov so use radical bromination. The add nitrogen *via* the azide. Of course, there are other answers (hydroboration , oxidation and reductive amination??)

(h)

How would you synthesise



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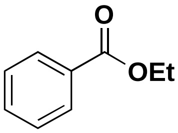

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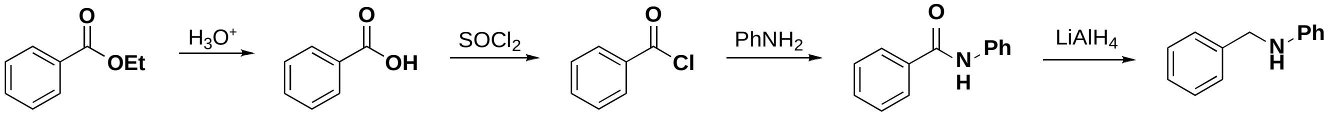
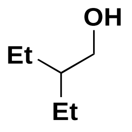


Hopefully, this one doesn't cause too many problems.

(i)

How would you synthesise



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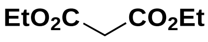

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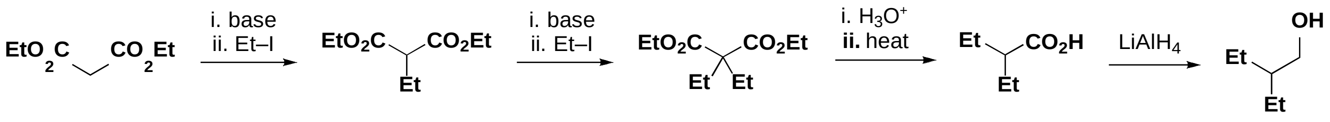
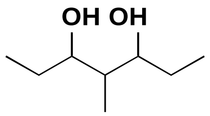


This one is all about recognising which functional groups are required and how they can be interconverted.

(j)

How would you synthesise



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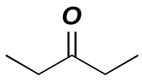

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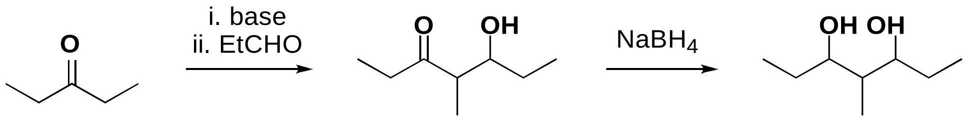
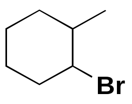


Don’t get fooled by how similar molecules may appear. Count the atoms, look for real relationships. In this case we have a 1,3-diol derived from a ketone; start thinking about an aldol reaction right away.

(k)

How would you synthesise



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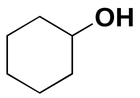

Answer: