Selective Problem & Solution of Retrosynthesis

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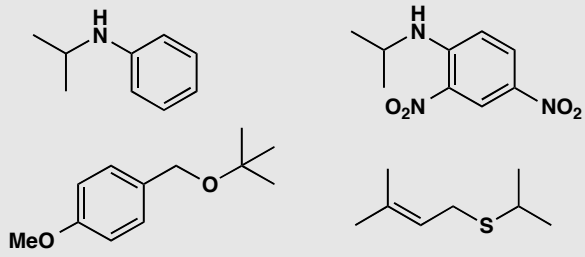
PROBLEM 1

How would you make these four compounds? Give your disconnections, explain why you chose them and then give reagents for the synthesis.

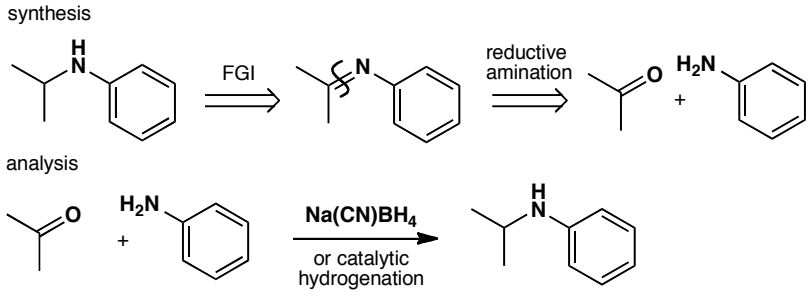


Purpose of the problem

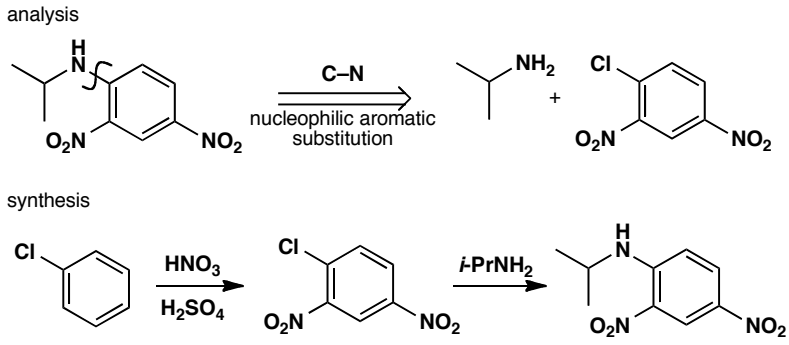
Exercises in basic one-group C–X disconnections.

Suggested solution

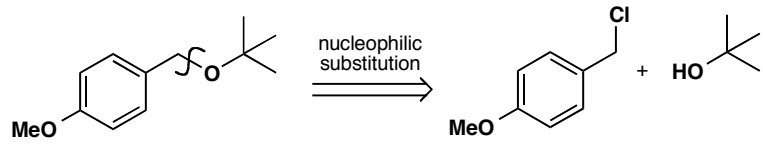
We wish to disconnect one of the C–N bonds and prefer the one not to the benzene ring as we aim to use reductive amination (p. 234) as the best way to make amines.



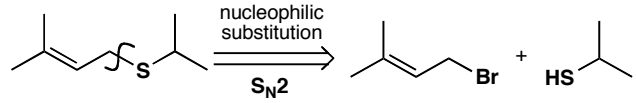
However the second aromatic amine can be made a different way. The two nitro groups promote nucleophilic aromatic substitution (p. 514) and the compound can be made by the addition-elimination mechanism from the dinitro chloro compound that can be made by direct nitration.



For the ether we again have a choice from two C–O disconnections. We prefer not to add the *t*-butyl group by S_N2 (though we could by S_N1) and disconnect on the other side. The synthesis is trivial: we just mix the two reagents with base or make the anion from the alcohol first.

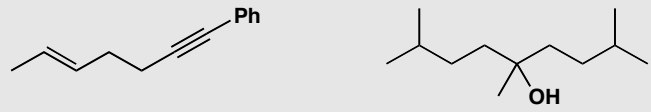


For the sulfide we shall want to use an S_N2 reaction and there is a slight preference for the disconnection we show as the allylic halide is very reactive. You would not be wrong if you had chosen the alternative C–S bond. This time only a weak base will be needed as the SH group is much more acidic than the OH group.



PROBLEM 2

How would you make these compounds? Give your disconnections, explain why you chose them and then give reagents for the synthesis.

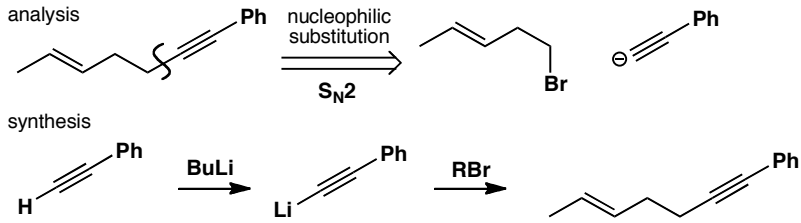


Purpose of the problem

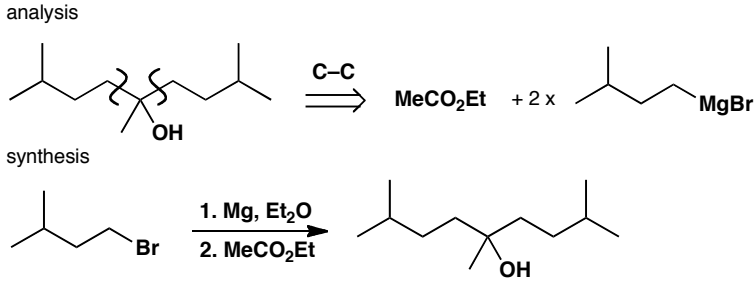
Exercises in basic one-group C–C disconnections.

Suggested solution

There are obviously more choices when you use C–C disconnections, but choose wisely! We suggest a solution, but you may have thought of others. The first compound is an alkyne and disconnection next to the alkyne (but not on the side of the benzene ring) makes a simple synthesis.

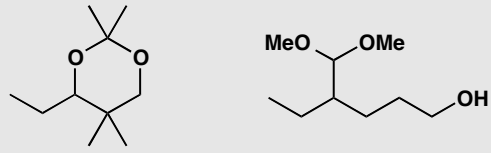


The alcohol has some symmetry: you will want to use Grignard or organolithium chemistry (chapter 9) and you could disconnect one or two of the identical groups using a ketone or an ester as the electrophile. The double disconnection leads to a shorter synthesis.



PROBLEM 3

Suggest ways to make these two compounds. Show your disconnections and make sure you number the functional group relationships.

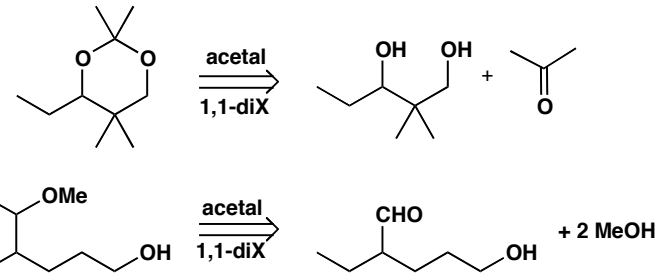


Purpose of the problem

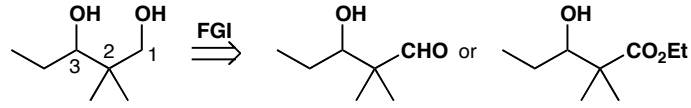
First steps in using two functional groups to design a synthesis.

Suggested solution

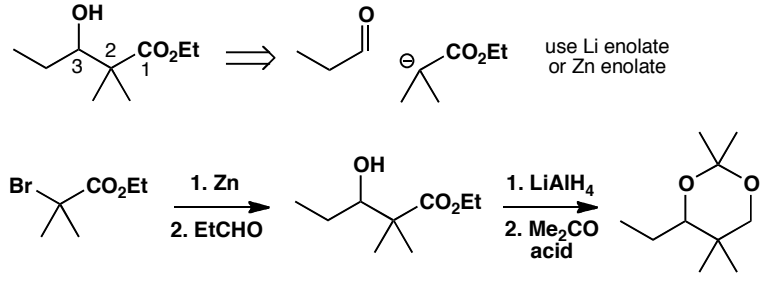
Both compounds have two oxygens singly bonded to the same carbon atom: they are acetals so they come from a carbonyl compound. Disconnecting the acetals helps us see what we are really trying to make.



The diol has a 1,3-relationship between the two alcohols so we need aldol or Claisen ester chemistry (chapter 26). One alcohol will have to be changed into a carbonyl group, perhaps an aldehyde or ester. Since we shall reduce all carbonyl groups to alcohols, it doesn't really matter whether we have aldehydes, ketones, or esters.

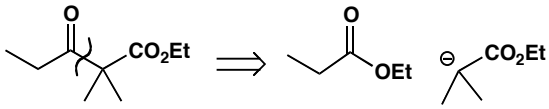


We prefer to make the disconnection between C2 and C3 to cut the molecule more or less in half and simplify the problem. There are various ways to do this—either the lithium or the zinc enolate would do, and below we show the use of zinc in a Reformatsky reaction.

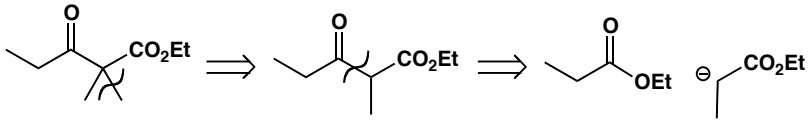


If the keto-ester is used as a starting material it can be made by the same strategy (disconnection A) or alternatively (disconnection B) by first removing just one methyl group to reveal a symmetrical keto-ester made by a Claisen ester condensation.

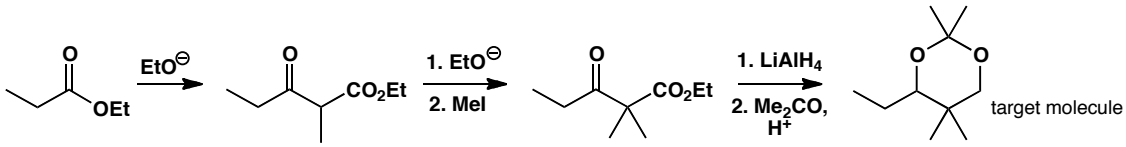
Disconnection A



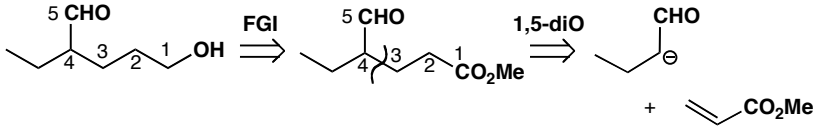
Disconnection B



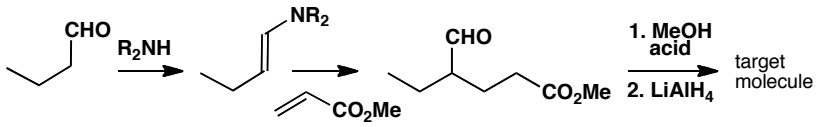
The advantage of disconnection B is that the synthesis involves a simple self-condensation of ethyl propionate. Methylation of the resulting keto-ester followed by reduction to the diol and acetal formation gives the target molecule.



The other compound has a 1,5-relationship between the two functional groups and will need some sort of conjugate addition of an enolate (chapter 25). This time we want to reduce only one of the two carbonyl groups so we must make sure they are different. We already have an aldehyde so we choose an ester for the other one.

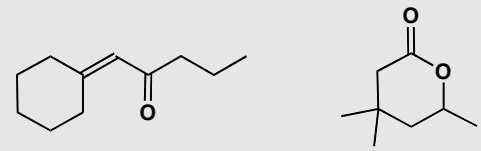


We must use a specific enol equivalent for the aldehyde enolate to avoid self-condensation: an enamine or a silyl enol ether would be fine. Since we must reduce the ester in the presence of the aldehyde, it makes sense to put the acetal in before we do this.



PROBLEM 4

Propose syntheses of these two compounds, explaining your choice of reagents and how any selectivity is achieved.

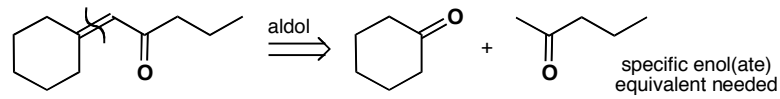


Purpose of the problem

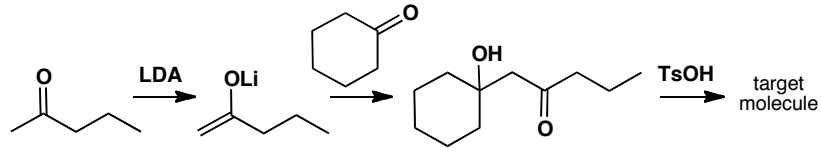
First steps in designing syntheses in which selectivity is required.

Suggested solution

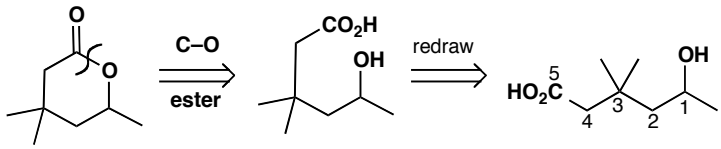
The first compound is an α,β-unsaturated carbonyl compound and this is one of the most important functional group combinations for you to recognise in planning syntheses. It is the product of an aldol reaction so simply disconnect the alkene and write a new carbonyl group at the far end of the old one. Don't lose any carbon atoms!



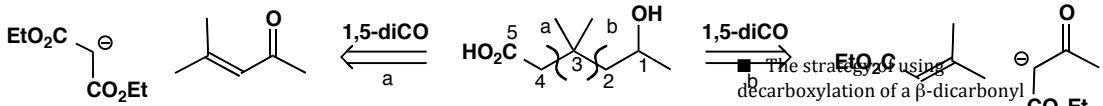
We need a crossed aldol reaction between two ketones so we also need chemoselectivity. We have to make one enol(ate) from an unsymmetrical ketone so we need regioselectivity as well. The obvious solution is to use a lithium enolate, a silyl enol ether, or a β-ketoester. Here is one solution.



The second compound contains another common functional group: a lactone or cyclic ester. We should first disconnect the structural C–O bond to see the carbon skeleton.

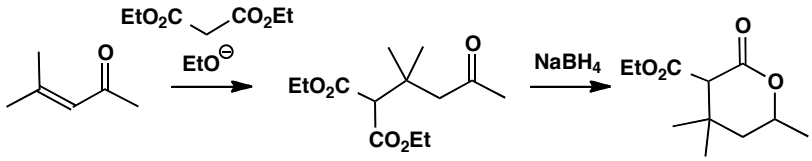


We discover that we have a 1,5-relationship between the functional groups and so we shall need conjugate addition. We must change the alcohol into a ketone, and the acid group to an ester. Notice that there are two reasonable disconnections and that we have added an ester group to each potential enolate as the way of making a specific enolate.



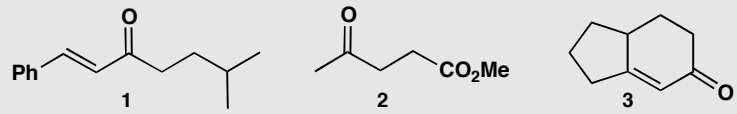
■ The strategy of using decarboxylation of a β-dicarbonyl compound is described on p. 597 of the textbook.

One possibility is to add malonate to the unsaturated ketone, which is an aldol dimer of acetone and readily available. We can reduce the ketone, expecting cyclisation to be spontaneous, and decarboxylate to give our target molecule.

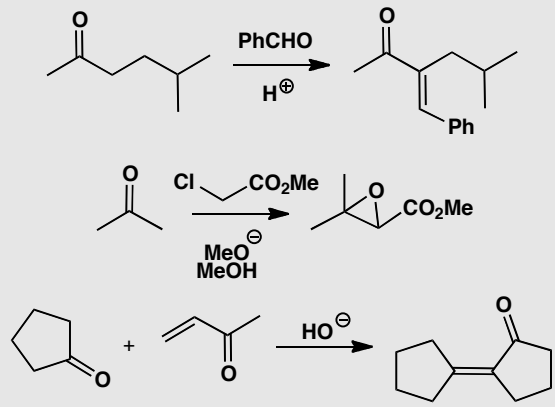


PROBLEM 5

The reactions to be discussed in this problem were planned to give syntheses of these three molecules.



In the event each reaction gave a different product from what was expected, as shown below. What went wrong? Suggest syntheses that would give the target molecules above.

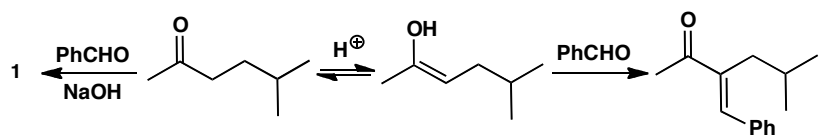


Purpose of the problem

Finding out what might go wrong is an important part of planning a synthesis.

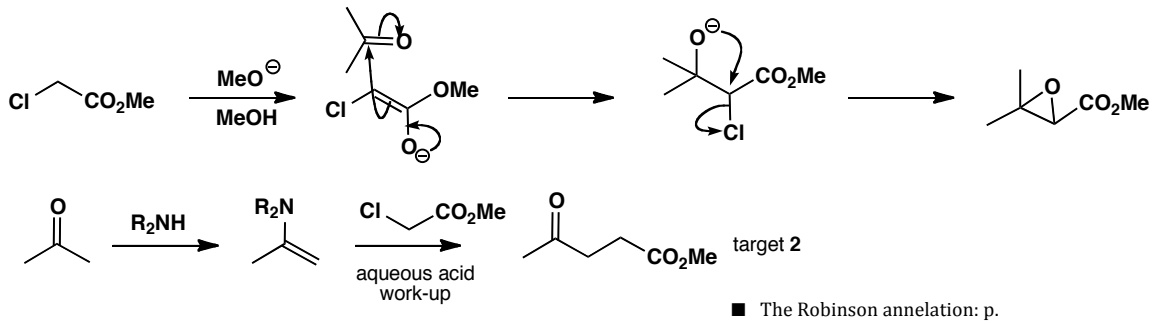
Suggested solution

The aldol reaction planned for target molecule **1** looks all right but enol formation has occurred on the wrong side. This is not surprising in acid solution, so use base instead.



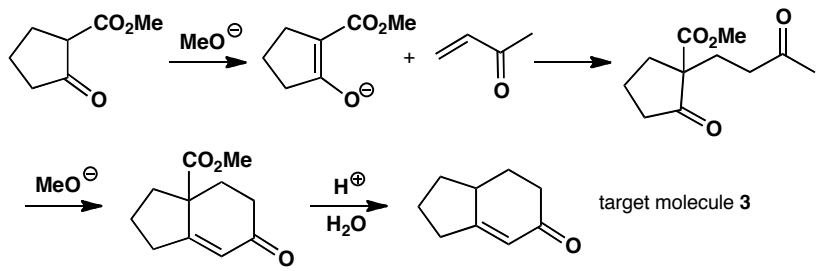
In the second case, alkylation of the enolate of the ketone was planned but evidently it is easier to form the enolate of the chloro-ester.

The reaction that occurred is the Darzens condensation. To avoid this problem use a specific enolate of the ketone such as an enamine or a β-ketoester.



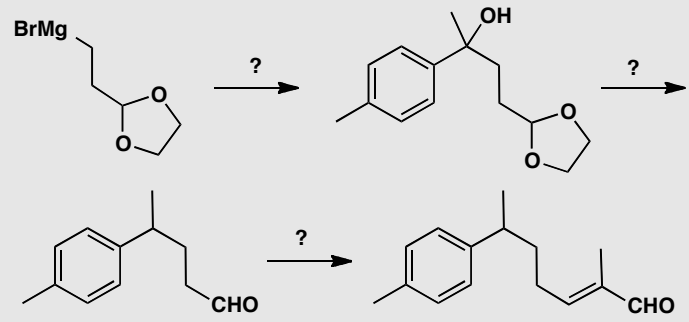
■ The Robinson annelation: p. 638 of the textbook.

In the third case, the cyclopentanone has self-condensed and ignored the enone. The answer again is to use a specific enolate, such as the easily made β-keto-ester below. The six-membered ring is then easily formed by intramolecular aldol reaction. These two reactions together make a Robinson annelation. Finally the CO_2Me group must be removed by hydrolysis and decarboxylation.



PROBLEM 6

The natural product nuciferal was synthesised by the route summarised here.



(a) Suggest a synthesis of the starting material.

(b) Suggest reagents for each step.

(c) Draw the retrosynthetic analysis giving the disconnections that you consider the planners may have used and label them suitably.

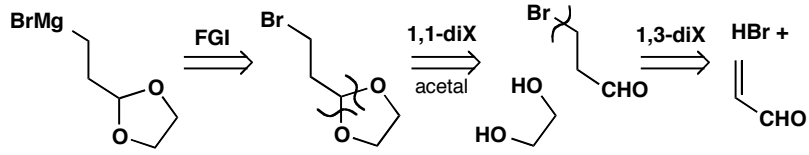
(d) Which synthon does the starting material represent?

Purpose of the problem

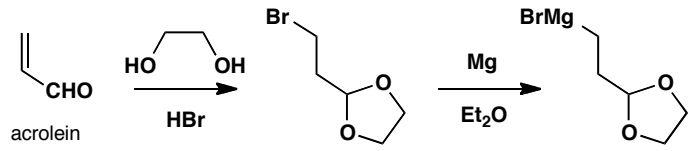
Practice at an important skill—learning from published syntheses—as well as a popular style of exam question.

Suggested solution

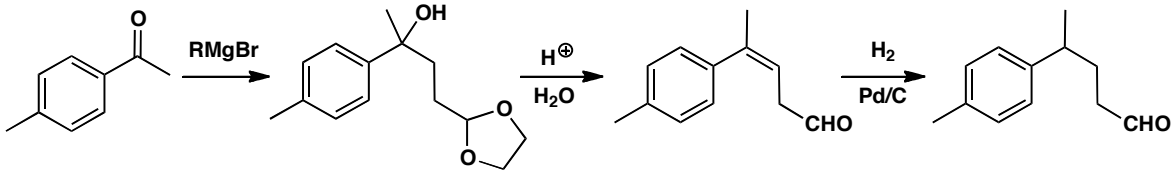
(a) Grignard reagents are made from the corresponding halide and the rest of the analysis used simple C–X disconnections.



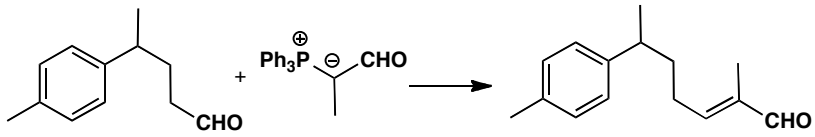
It turns out that the addition of HBr to the unsaturated aldehyde (trivially known as acrolein) and the protection as an acetal can be carried out in a single step as both are acid-catalysed.



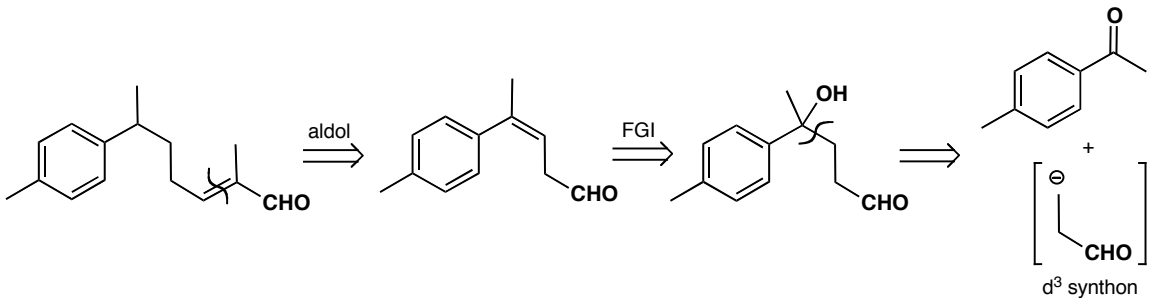
(b) The Grignard has obviously been added to a ketone to give the tertiary alcohol, but how do we replace OH by H? One way is direct catalytic hydrogenation but an easier way is to eliminate the tertiary (and benzylic) alcohol and hydrogenate the alkene. The acid used for dehydration will also remove the acetal.



The last step is an aldol reaction between two aldehydes. The easiest way to do this is by a Wittig reaction but a specific enol of propanal would also be fine.

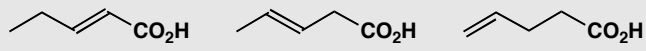


(c) and (d) The retrosynthetic analysis is straightforward except for the last step. It is not obvious what reagent to use for the synthon in brackets. But you already know what was used: a Grignard reagent with a protected aldehyde, i.e. a d^3 reagent. This is needed because the 1,4 relationship between OH and CHO requires *umpolung* (p. 720).



PROBLEM 7

Show how the relationship between the alkene and the carboxylic acid influences your suggestions for a synthesis of these three compounds.

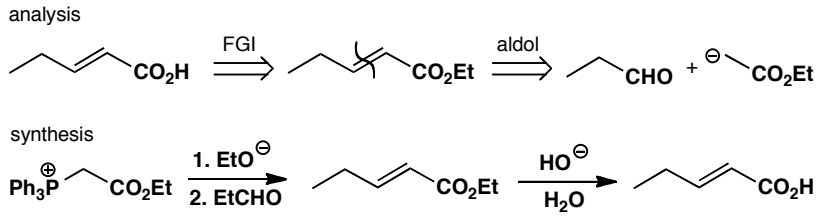


Purpose of the problem

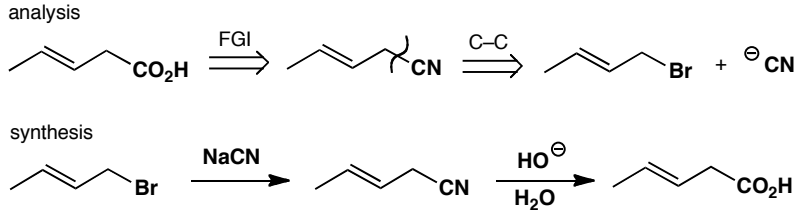
An exploration of the importance of functional group relationships.

Suggested solution

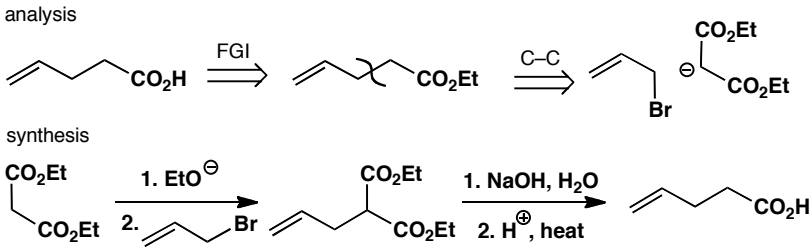
The first is an α,β-unsaturated carbonyl compound and can best be made by an aldol reaction using some sort of specific enol equivalent for the acid part. A Wittig reagent, a malonate, or a silyl enol ether look the best.



The second synthesis is difficult because the alkene can easily slip into conjugation with the carbonyl group. Perhaps the easiest strategy is to use cyanide ion as synthetic equivalent of $^{-}CO_2H$ since then the electrophile is an allylic halide. Other alternative routes could include alkyne reduction.

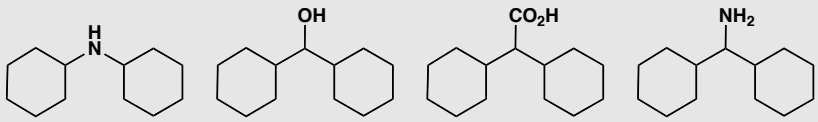


The third is best approached by alkylation of a malonate with allyl bromide itself followed by hydrolysis and decarboxylation.



PROBLEM 8

How would you make these compounds?

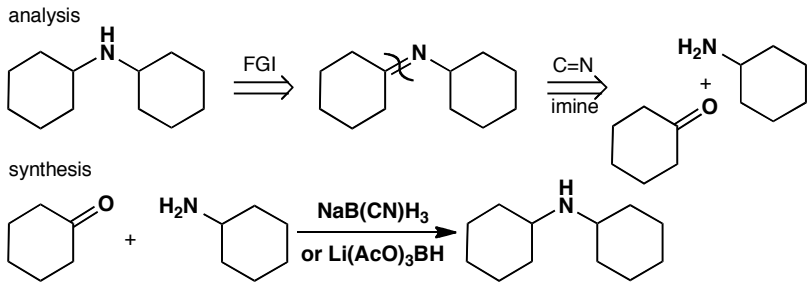


Purpose of the problem

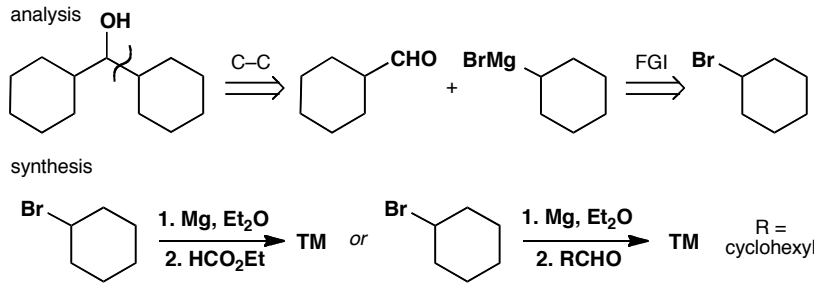
A reminder of reductive amination and that simple syntheses of apparently related compounds may require very different chemistry.

Suggested solution

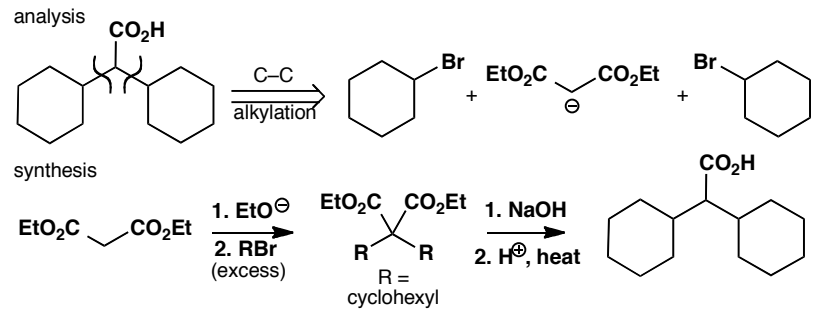
The secondary amine is best made by reductive amination via the imine (not usually isolated).



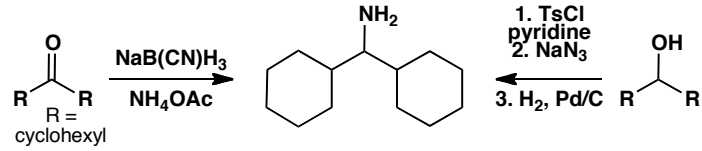
The secondary alcohol can be made by some sort of Grignard chemistry. Cyclohexyl Grignard could be added twice to ethyl formate or once to the cyclohexane aldehyde.



The carboxylic acid could be made by double alkylation of malonate or some other specific enol equivalent.

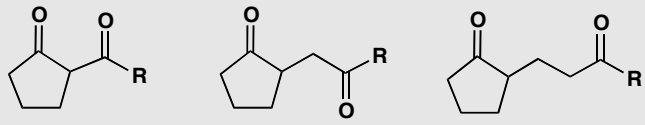


Finally the primary amine could be made by reductive amination of a ketone that could in turn be made by oxidation of the secondary alcohol we have already made. Among many alternatives is the displacement of the tosylate of the same alcohol with azide ion and reduction of the azide.



PROBLEM 9

Show how the relationship between the two carbonyl groups influences your choice of disconnection when you design a synthesis for each of these ketones.

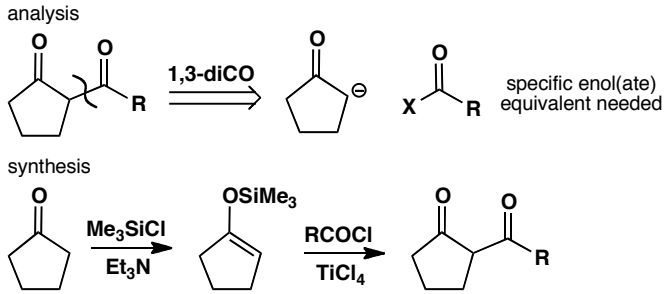


Purpose of the problem

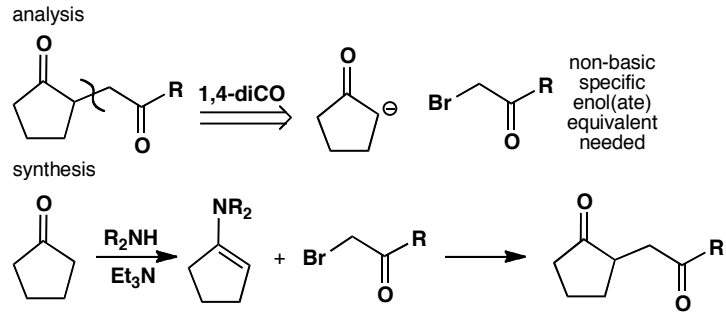
An exercise in counting to reinforce the way that odd and even relationships affect the choice of a synthetic route.

Suggested solution

The three diketones have 1,3-, 1,4-, and 1,5-dicarbonyl relationships. In each case the obvious disconnection is of the bond joining the ring to the chain. But the chemistry is very different in each case. The 1,3-diketone can be made by acylation of a specific enolate. An enamine or a silyl enol ether is a good choice.



The same disconnection on the 1,4-diketone leads to different chemistry (alkylation of an enolate) and requires an enamine as the specific enol.



The 1,5-diketone requires conjugate addition of the same enolate and we suggest a different specific enolate equivalent though other would be just as good. This time the specific enol equivalent is needed to stop self-condensation of the cyclopentanone.