**PROBLEM 1**
The aldehyde and the ketone below are self-condensed with aqueous NaOH so that an unsaturated carbonyl compound is the product in both cases. Give a structure for each product and explain why you think this product is formed.

![Chemical structures](image)

**Purpose of the problem**
Drawing mechanisms for the simplest of aldols: self-condensation of aldehydes and ketones.

**Suggested solution**
In both cases only one compound can form an enolate and only one compound—the same one—can be the electrophile. This is very obvious with the aldehyde

![Mechanisms](image)

With the ketone, there is a question of regioselectivity in enolate formation, but the aldol product can lose water only if the enolate from the methyl group is the nucleophile. If we draw both enolates and combine them with the ketone in an aldol reaction, it is clear that one can dehydrate as it has two enolisable H atoms but the other cannot dehydrate as it has no H atoms on the vital carbon atom (in grey). The mechanism is the same as the one with the aldehyde and the elimination in both cases is by the E1cB mechanism.

See p. 399 and p. 616 in the textbook for the E1cB mechanism.
PROBLEM 2
Propose mechanisms for the 'aldol' and dehydration steps in the termite defence compound presented on p. 623 in the textbook.

Purpose of the problem
Revision of elimination reactions and the mechanism for 'an aldol that can’t go wrong.'

Suggested solution
The nitro group is twice as electron-withdrawing as a carbonyl group so it will readily form an 'enolate.' It cannot self condense as nucleophilic attack rarely occurs on nitro groups so it attacks the aldehyde instead. Notice that the alkoxide product is basic enough to deprotonate another molecule of nitromethane so the reaction is catalytic in base.

The elimination step involves acylation of the hydroxyl group and an E1cB elimination again driven by the 'enolate' of the nitro group. Note that pyridine, a weak base, is strong enough.
PROBLEM 3
How would you synthesise the following compounds?

![Chemical structure]

Purpose of the problem
Application of the aldol reaction to make unsaturated carbonyl compounds.

Suggested solution
Just find the conjugated alkene and so find the hidden carbonyl group. In the first case, cyclohexanone provides two enols to react with benzaldehyde. The phenyl rings in the product lie trans to the carbonyl group so that they can be planar.

In the second case, more options are available. Our solution suggests using a Wittig reaction for the first as we need the enolate of acetaldehyde (p. 628 in the textbook), and malonic acid for the second (p. 630 in the textbook). There are many alternatives such as using an aldol reaction for the first step, but with an excess of acetaldehyde, to compensate for self-condensation.
**PROBLEM 4**

How would you use a silyl enol ether to make this aldol product? Why is it necessary to use this particular intermediate? What would be the products be if the two carbonyl compounds were mixed and treated with base?

![Chemical structures](image)

**Purpose of the problem**

Exploring control, and the lack of it, in different styles of aldol reaction.

**Suggested solution**

This is about the most difficult type of aldol reaction: two slightly different aldehydes, both enolisable, both capable of self-condensation. The only solution is to couple the silyl enol ether of one aldehyde with the other aldehyde using a Lewis acid as catalyst. This gives the aldol itself that can be dehydrated to the enal.

![Chemical reactions and structures](image)

Without this control, each aldehyde would self-condense and would condense with the other aldehyde giving four products in unpredictable amounts. One of the cross-condensation products is, of course, the enal we are trying to make.
**PROBLEM 5**

In what way does this reaction resemble an aldol reaction? Comment on the choice of base. How can the same product be made without using phosphorus chemistry?

![Chemical reaction diagram]

**Purpose of the problem**

Showing that there are reactions closely related to the aldol reaction that give similar products.

**Suggested solution**

The formation of an alkene and the loss of phosphorus are typical of a Wittig reaction but the formation of an unsaturated carbonyl compound using an enolate is very like an aldol reaction. The phosphonate ester reagent is also like a 1,3-dicarbonyl compound, with P replacing C. The very weak base used shows how stable the enolate must be. The enolate attacks the aldehyde, perhaps to form an intermediate oxyanion.

![Mechanism diagram]

There is no doubt that the next intermediate is formed. It is a stable four-membered ring (phosphorus likes 90° bond angles). Finally phosphorus captures oxygen (the P–O bond is very strong) eliminating the alkene in its preferred trans stereochemistry.

![Further reactions]

The final product could also be made by the aldol condensation of a silyl enol ether and the same aldehyde. The silyl enol ether is the less substituted possibility so it will have to be made via the lithium enolate. The product will be the aldol itself and this can be dehydrated to the enone with TsOH.
PROBLEM 6
Suggest a mechanism for this attempted aldol reaction. How could the aldol product be made?

Purpose of the problem
A demonstration of one way that aldol reactions with formaldehyde may fail.

Suggested solution
The aldol reaction appears to have taken place and then the ketone has been reduced. The only possible reducing agent is more formaldehyde and the reduction takes place by the Cannizarro reaction (p. 620 in the textbook). The aldol can be successful if a weaker base such as Na₂CO₃ is used as the Cannizarro requires a dianion intermediate.
**PROBLEM 7**

The synthesis of six-membered ketones by intramolecular Claisen condensation was described in the chapter where we pointed out that it doesn’t matter which way round the cyclisation happens as the product is the same.

![Chemical structure](image)

Strangely enough, five-membered heterocyclic ketones can be made by a similar sequence. The starting material is not symmetrical and two cyclized products are possible. Draw structures for these products and explain why it is unimportant which is formed.

![Chemical structure](image)

**Purpose of the problem**

To make sure you understand how extra ester groups can solve apparently complex acylation problems.

**Suggested solution**

The cyclisation can occur in two different ways to give two different products as either ester can form an enolate that attacks the other in an intramolecular acylation. We should draw the two products.
Though these compounds are different, each gives the same ketone after hydrolysis and decarboxylation as the ketone carbonyl group is on the same position in the ring in both compounds.

**PROBLEM 8**

Attempted acylation at carbon often fails. What would be the actual products of these attempted acylations and how would you successfully make the target molecules?

**Purpose of the problem**

Revision of simple enolate reactions (chapter 20) and encouragement to clear thinking about what happens when you put carbonyl compounds in basic solutions.

**Suggested solution**

In the first case we want the aldehyde to form an enolate and then attack the ester. The first part is all right: the aldehyde will form an enolate more readily than the ester. But under these equilibrating conditions, the small amount of enolate that is formed will react faster with the aldehyde than with the less electrophilic ester. The aldehyde will self-condense in an aldol reaction.

To make the required compound we shall need to convert the aldehyde into a specific enol equivalent. There are various alternatives of which the best are an enamine or a silyl enol ether. Esters fail to acylate either and an acid chloride should be used instead. Don’t forget the Lewis acid if you use the silyl enol ether.
The enolate formation in the second example is a separate step and will work well because the two carbonyl groups cooperate in forming a stable enolate and NaOMe is quite strong enough to convert the diketone entirely into the enolate. The problem is the acylation step. With a sodium enolate and a reactive acylating agent such as PhCOCl, a charge-controlled (hard/hard) interaction will occur at the oxygen atom to give an enol ester.

The escape route from this problem suggested in the chapter (p. 648) was to use a lithium or magnesium enolate. Magnesium is chelated by the two oxygen atoms of the stable enolate and blocks attack there so that C-acylation occurs even with acid chlorides.
PROBLEM 9

Acylation of the phenolic ketone gives compound A, which is converted into an isomeric compound B in base. Cyclization of B gives the product shown. Suggest mechanisms for the reactions and structures for A and B.

Purpose of the problem

Predicting products of acylation reactions. This is always more difficult than just drawing mechanisms but here you might work backwards from the final product as well as forwards.

Suggested solution

The starting material is C₈H₈O₂ so A has an extra C₇H₄O. This looks like the addition of PhCOCl with the loss of HCl. The most obvious reaction is acylation of the phenolic oxygen rather than enolate formation as OH is much more acidic than CH and pyridine is a weak base. This phenol is unusually acidic as the carbonyl group helps to stabilise the anion. Compound A is simply the benzoate ester of the phenol. Treatment with KOH isomerises A to B and this is the heart of the problem. An intramolecular acylation of the only possible enolate can be catalysed by KOH even though it produces only a little enol as cyclisation to form a six-membered ring is so easy.

The final step is acid-catalysed and clearly involves the attack of the phenolic OH group on one of the ketones. This intramolecular reaction much prefers to form a six-membered ring rather than a strained four-membered ring, and dehydration gives an aromatic ring—two electrons each from the double bonds and two from a lone pair on oxygen making six in all. Drawing the delocalisation may help you to see this.
PROBLEM 10
How could these compounds be made using the acylation of an enol or enolate as a key step?

Purpose of the problem
Practice in using acylation at carbon to make compounds.

Suggested solution
The first problem has two possible solutions by direct acylation, labelled A and B in the diagram. A would have to be controlled as the straight chain ester could self-condense. B needs no control as only the ketone can enolize. Diethyl carbonate (EtO)₂CO is more electrophilic than a ketone and only the wanted product can enolize again and form a stable enolate under the reaction conditions. However, route B adds only one carbon atom.

Route A can be realised with either a lithium enolate or a silyl enol ether, as explained on p. 649, using an acid chloride as the electrophile.
Route B requires the synthesis of the ketone starting material and this could be done by Grignard methods (chapter 9) or by acylation of an organo-copper compound with an acid chloride. Acylation with diethyl carbonate requires no special control.

PROBLEM 11

Suggest how the following reactions might be made to work. You will probably have to select a specific enol equivalent.

Purpose of the problem

Making reactions work is an important part of organic chemistry.

Suggested solution

The first reaction is a standard acylation of an aldehyde creating a quaternary centre. You might have used a silyl enol ether but an enamine, such as one made from a cyclic secondary amine, is probably better.
The second example might just go with simple base (MeO⁻) catalysis as the conjugated ketone enolate is much more stable than the enolate of the ester. However, it's probably safer to use a lithium enolate (or a silyl enol ether—though you'd then have to use an acid chloride as the electrophile).

PROBLEM 12
Base-catalysed reaction between these two esters allows the isolation of a product A in 82% yield.

The NMR spectrum of this product shows that two species are present. Both show two 3H triplets at about δH = 1 and two 2H quartets at about δH = 3 ppm. One has a very low field proton and an ABX system at 2.1–2.9 with J_AB 16 Hz, J_AX 8 Hz, and J BX 4 Hz. The other has a 2H singlet at 2.28 and two protons at 5.44 and 8.86 coupled with J 13 Hz. One of these protons exchanges with D₂O. Any attempt to separate the mixture (for example by distillation or chromatography) gives the same mixture. Both compounds, or the mixture, on treatment with ethanol in acid solution give the same product B.

Compound B has IR 1740 cm⁻¹, δH 1.15-1.25 (four t, each 3H), 2.52 (2H, ABX system J_AB 16 Hz), 3.04 (1H, X of ABX split into a further doublet by J 5 Hz), and 4.6 (1H, d, J 5 Hz). What are the structures of A and B?

Purpose of the problem
Revision of enol structure by NMR and a further exploration of what happens to acylation products.
Suggested solution

Only the diester can form an enolate and ethyl formate (HCO₂Et—it is half an ester and half an aldehyde) is much more electrophilic than the diester. We should expect the diester to be acylated by ethyl formate.

The compound A₁ fits the formula for A and the ¹H NMR spectrum of the compound with the low field signal (assigned to the CHO proton). This structure would also show an ABX system in its ¹H NMR spectrum. But what is the other compound (A₂)? It is obviously in equilibrium with A₁ and it lacks both the aldehyde proton and the ABX system and it sounds like an enol. Compound A₁ is chiral so the CH₂ group appears as an ABX system but A₂ is not chiral so the CH₂ group is a singlet. Here are the structures with their NMR assignments. In both cases the 3H triplets and 2H quartets are ethyl groups.

Treatment with acidic ethanol simply makes the acetal from the aldehyde group of A₁. Since A₁ and A₂ are in equilibrium, all A₂ is eventually converted into A₁ and then into B. Compound B is again chiral so the ABX system reappears with further coupling of X with the acetal proton. There are now four triplets and four quartets from the four ethyl groups.