Designing Organic Syntheses

A Programmed Introduction to the Synthon Approach

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CONTENTS

WHAT DO YOU NEED TO KNOW BEFORE YOU START?

Though the programme may introduce you to some new reactions, its main aim is to euggest an analytical approach to the design of syntheses. You therefore need to have a reasonable grounding in organic chemistry so that you are familiar with most basic organic reactions and can draw out their mechanisms. If you are a third year univeraity student, a graduate, or someone with experiencc of organic chemistry in practice you will probably be able to work straight through the programme to learn the approach and not need to learn any new material. If you are a second year university student or someone with a limited knowledge of organic reactions you may find you need to learn some reactions as you go along. I have given references to these books to help you:

'The Carbonyl Programme':
"Chemistry of the Carbonyl Group, A Programmed Approach to Organic Reaction Mechanisms", Stuart Warren, Wiley 1974. This programme leads up to the present one.

'Fleming':
"Selected Organic Syntheses", Ian Fleming, Wiley 1973. Synthesis from the other side: notable examples of organic syntheses carefully explained in detail.

'Tedder':
"Basic Organic Chemistry", J. M. Tedder, A. Nechvatal, and others, Wiley, 5 volumes 1966-1976. A complete textbook of organic chemistry. Explains all the reactions used in the programme and describes many syntheses in detail.

'Norman':
"Principles of Organic Synthesis", R. 0. C. Norman, Methuen, 1968: A taxtbook of organic chemistry from the point of view of synthesis. An excellent source book for all the reactions used in this programme.

Whoever you are, you will certainly find discussion with your fellow students one way to get the most out of the programme and you may well find it is a good idea to work on the more difficult problems together. The review problems, revision problems, and problems without worked solutions are ideal for this. In some cases I have given references to the original literature so that you can find out more details of the various possible approaches for yourself if you want to. It isn't necessary to look up any of these references as you work through the programme.

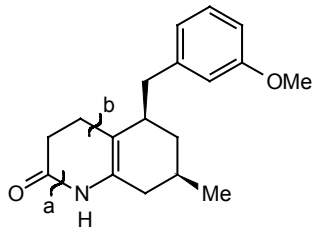
HOW TO USE THE PROGRAMME

The point of programmed learning is that you learn at your own pace and that you yourself check on your own progress. I shall give you information and ideas in chunks called frames, each numbered and separated by a black line. Most frames contain a question, sometimes followed by a comment or clue, and always by the answer. You must WRITE DOWN on a piece of paper your answer to each question. You'll find that you discover as you do so whether you really see what is being explained or not. If you simply say to yourself 'Oh, I can do that, I don't need to write it down', and look at the answers, you're missing the opportunity to check on your own progress as well as probably deceiving yourself.

When you are ready to start, cover the first page with a card and pull it down to reveal the first frame. Read and act on that frame, then reveal frame 2 and so on. If you are unfamiliar with the disconnection approach, I suggest you read the introduction 'Wby bother with disconnections' so that you can see what I'm driving at. Otherwise the first sections of the programme may seem rather pointless.

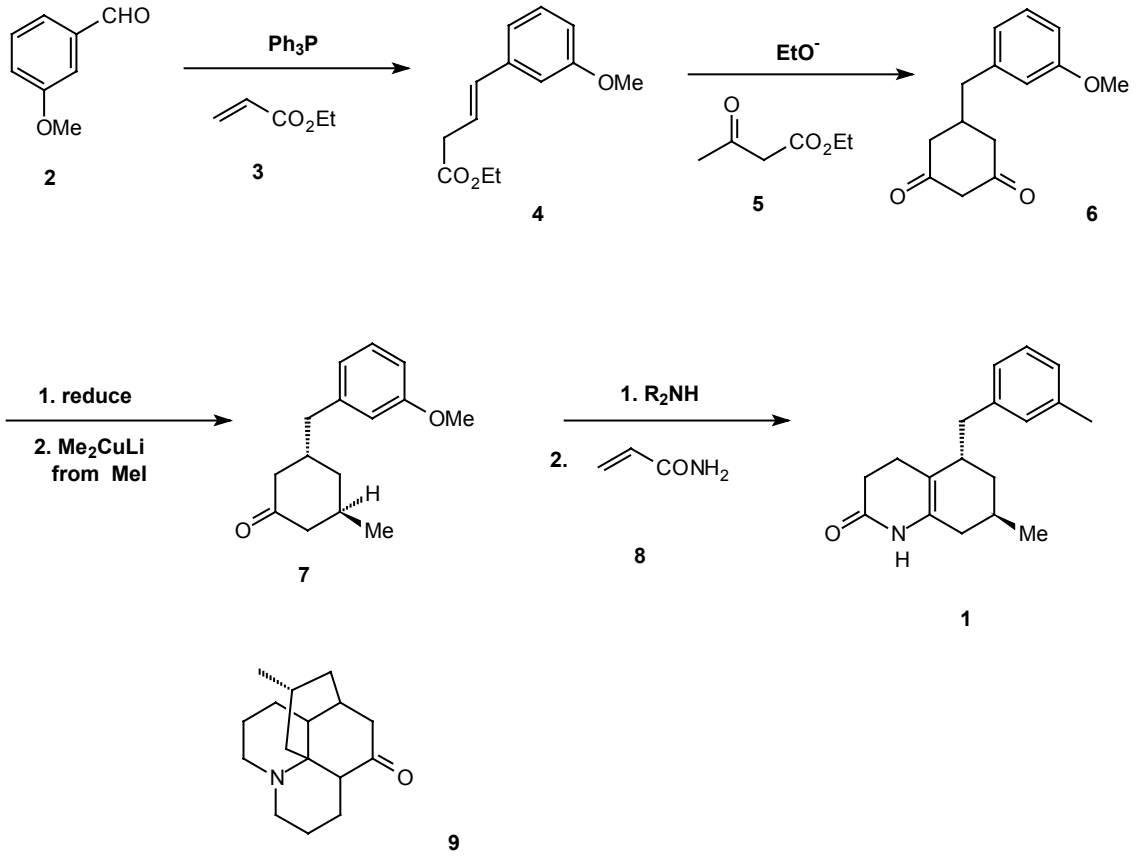
WHY BOTHER WITH DISCONNECTIONS?

The aim of this programme is that you should learn how to design an organic synthesis for yourself. Supposing you wanted to make this compound:

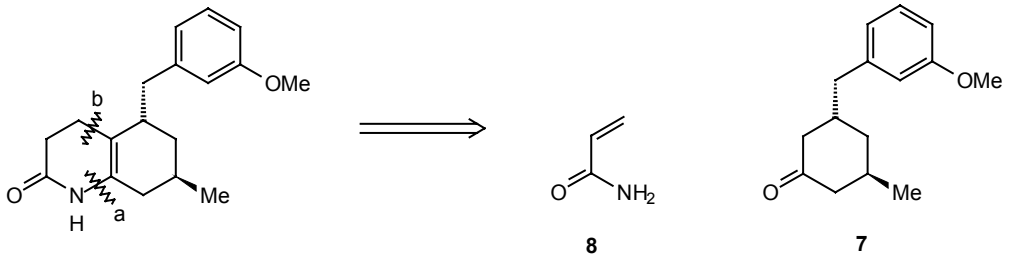


(1)

You would find that it had already been made by the route outlined on the chart on the next page. You could then buy the starting materials (compounds 2, 3, 5, 8, and **MeI**) and set to work. But supposing 1 had never been synthesised. How would you design a synthesis for it? You don't know the starting materials - all you know is the structure of the molecule you want - the TARGET MOLECULE. Obviously you have to start with this structure and work backwards. The key to the problem is the FUNCTIONAL GROUPS in the target molecule, in this case the nitrogen atom, the carbonyl group, the double bond and the benzene ring with its methoxyl group. You should learn from the programme that for most functional groups there are one or more good DISCONNECTIONS - that is imaginary processes, the reverse of real chemical reactions, which break a bond in the target molecule to give us the structure of a new compound from which the target molecule can be made.



Here the first disconnection (**a**) was of a **C-N** bond, the second (**b**) of a **C-C** bond taking us back to compounds (7) and (8):



These are in fact standard disconnections which you will meet in sections **G** and **C** of the programme. The first part of the programme (Sections **B** to **H**) shows you how to use disconnections and which disconnections are good ones. The second part shows you how to choose between alternative series of disconnections to get good synthetic schemes.

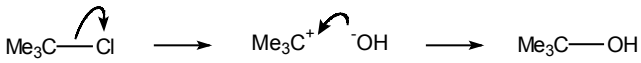
When you have finished the programme you should be able to design syntheses for molecules of the complexity of (1). Given this problem, you might not come up with the solution shown in the chart because there is no single "right answer" to a synthesis problem - any given molecule may well be made successfully by several different routes. In practice each of your proposals would have to be tested in the lab., and your overall scheme modified as a result. There were in fact several changes of plan in the synthesis of (1) and you can read more about the details in Stork's article in Pure and Applied Chemistry, (1968, 17, 383) where you will see that he used (1) as an intermediate in the synthesis of the alkaloid lycopodine (9). That is a target molecule beyond the scope of this programme, but organic chemists plan such syntheses using the same principles as you will learn here. You must first start at the beginning and learn in Section **A** how to use simple disconnections.

GLOSSARY

Disconnection: An analytical operation, which breaks a bond and converts a molecule into a possible starting material. The reverse of a chemical reaction. Symbol ⇒ and a curved line drawn through the bond being broken. Called a dislocation by some people.
FGI: Functional Group Interconversion: The operation of writing one functional group for another so that disconnection becomes possible. Again the reverse of a chemical reaction. Symbol ⇒ with FGI written over it.
Reagent: A compound which reacts to give an intermediate in the planned synthesis or to give the target molecule itself. The synthetic equivalent of a synthon.
Synthetic Equivalent: A reagent carrying out the function of a synthon which cannot itself be used, often because it is too unstable.
Synthon: A generalised fragment, usually an ion, produced by a disconnection. (Some people also use synthon for a synthetic equivalent).
Target Molecule: The molecule whose synthesis is being planned. Usually written **TM** and identified by the frame number.

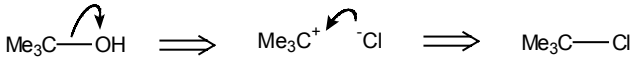
A. INTRODUCTION TO DISCONNECTIONS

1. You know that you can make t-butyl alcohol by hydrolysing t-butyl chloride:

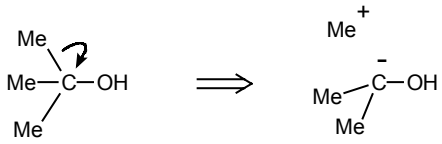


Draw the mechanism of the imaginary reverse reaction, the formation of t-butyl chloride from the alcohol.

2.



This then is the disconnection corresponding to the reaction. It is the thinking device we use to help us work out a synthesis of t-butyl alcohol. We could of course have broken any other bond in the target molecule such as:



Why is this less satisfactory than the disconnection at the start of this frame?

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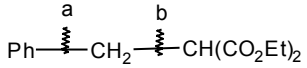
3. Because the intermodiates **Me^+** and **Me_2COH^-** are pretty unlikely species and they would have to be intermediates in the real reaction too! We have already found the first way to recognise a good disconnection: it has a reasonable mechanism. Choose a disconnection for this molecule, target molecule 3 (TM 3) breaking bond **a** or **b**. Draw the arrow and the intermediates.

TM 3



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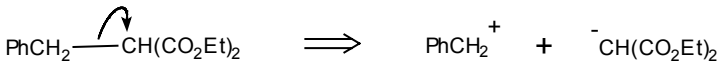
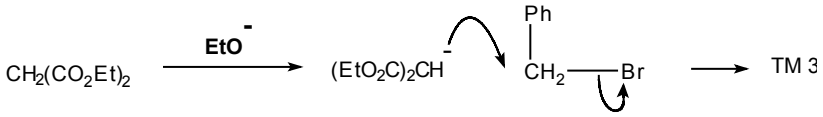
4. The best one is **b**:



since it gives a good cation and a good anion. You have probably noticed the sign (⇒) we use for disconnections. This reminds us that we are drawing the reverse of the real reaction. Our synthesis of TM 3 is then a normal malonate reaction:



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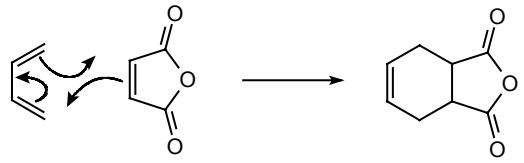
5. Another class of reaction where you can see at once that the disconnection is the reverse of the reaction is Pericyclic Reactions. An example would be the Diels-Alder reaction between butadiene and maleic anhydride. Draw the mechanism and the product.

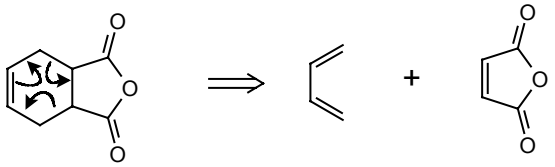
6.

TM 6

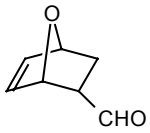


Now draw the disconnection (with mechanism) on the product, TM 6.

7.

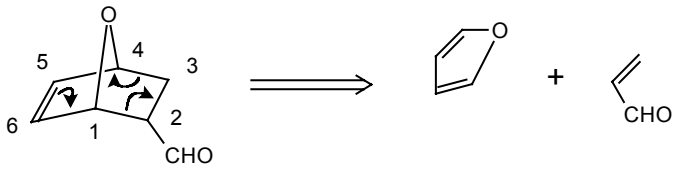


The double bond in the six-membered ring showed us where to start the disconnection. Can you see a similar disconnection for TM 7?



TM 7

8.



All you had to do was to find the six-membered ring (numbered) containing the double bond and draw the arrows.

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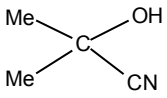
9. So we shall be using disconnections corresponding to ionic and pericyclic reactions, and we shall be looking all the time for a good mechanism to guide us. You should now see what a disconnection means and be ready for the next stage. In the next few chapters we

shall study some important one group disconnections - reliable disconnections we can use almost any time we see one particular functional group in a target molecule.

B. ONE GROUP DISCONNECTIONS

1. DISCONNECTIONS OF SIMPLE ALCOHOLS

10. Simply by looking for a food mechanism, you should be able to suggest a good disconnection for this alcohol:



TM 10

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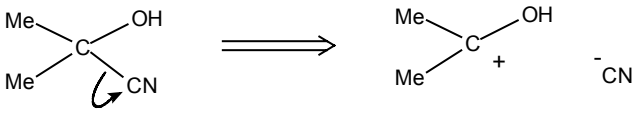
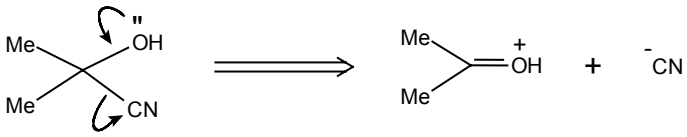
11. How about



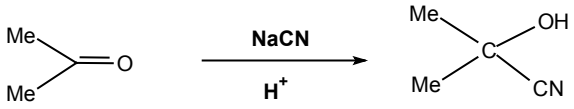
Cyanide is a good anion, and the cation is stabilised by a lone pair of electrons on oxygen. Draw the disconnection again using the lone pair.

12.

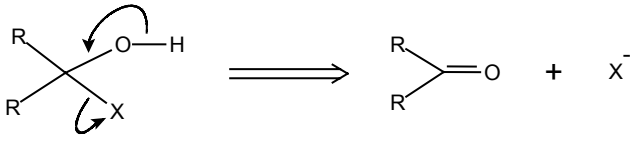


What is the real reaction which is the reverse of this disconnection?

13.

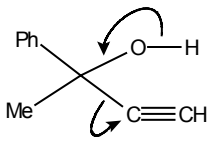


You probably saw the reaction before you saw the disconnection! All simple can be disconnected in this way. We simply choose the most stable anion of the substituents and disconnect to a carbonyl compound:



Suggest a disconnection for TM I3:

TM 13



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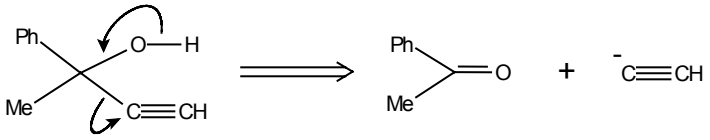
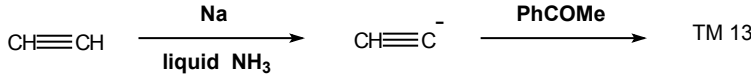
14. The acetylene anion HC≡C$^-$ is the most stable so:

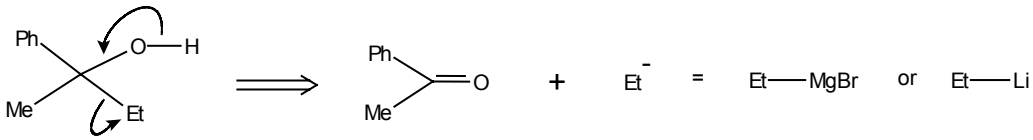


What is the real reaction?

15.

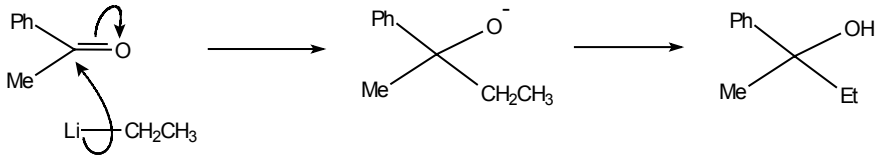


More usually, none of the substituents gives a stable anion and so we use the synthetic equivalent of the anion - the Grignard reagent or alkyl lithium. - We refer to "**Et**$^-$" as a SYNTHON for which **EtMgBr** is the synthetic equivalent.

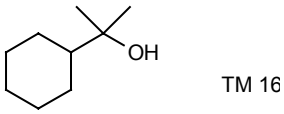


Dtaw the real reaction, the reverse of this disconnection, using **EtLi** with the mechanism.

16.



You can see how the alkyl-lithium acts as the synthon $\mathbf{CH_3CH_2^-}$ since the carbon-lithium bond breaks so that the electrons go with the carbon atom. Suggest a disconnection for TM 16.



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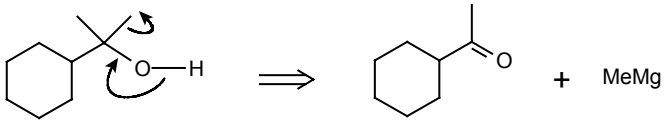
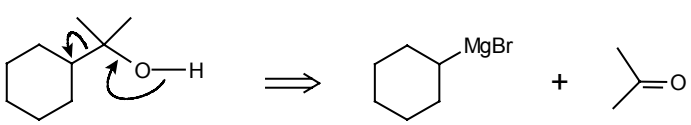
17. There are two possibilities:
a)



b)



Both have reasonable mechanisms, but we prefer (b) because it introduces more simplification. Route (a) simply chops off one carbon atom and leaves us with a new target almost as difficult to make as TM 16. Route (b) however breaks the molecule into two more equal pieces -acetone and cyclohexyl bromide.

We now have two criteria for a good disconnection: we look for (a) a good mechanism and (b) the greatest simplification.

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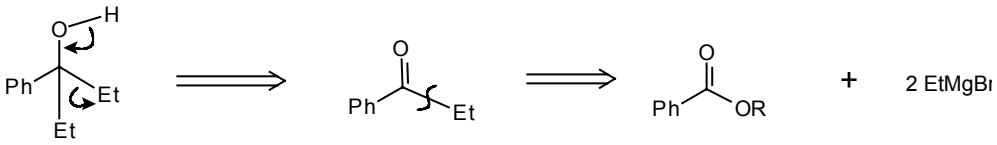
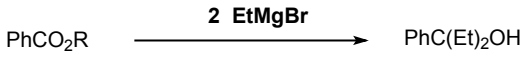
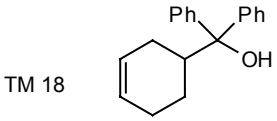
l8. An alternative approach to this problem, providing two of the groups on the tertiary alcohol are the same, is to remove both in a single disconnection going back to an ester and two mols of the Grignard reagent:



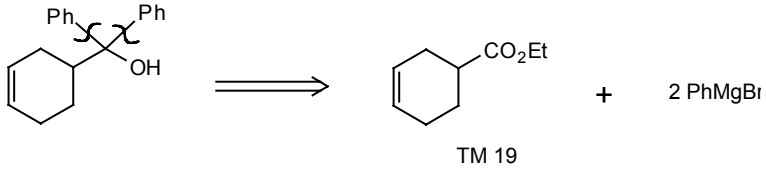
and the reaction is



How would you make TM 18?



19.



Can you continue one stage further back from TM 19?

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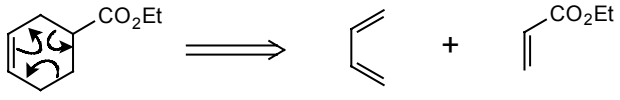
20. TM 19 has a double bond in a six-membered ring and we can use the Diels-Alder disconnection (frames 5-8).



Note that the Diels-Alder reaction works best when there is an electron-withdrawing group (here **CO_2Et**) on the olefinic component.

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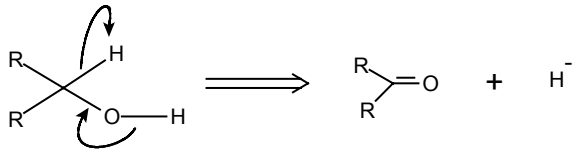
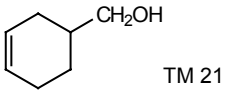
21. If one of the groups in the alcohol carbon atom is **H**, then another disconnection is:



The synthetic equivalents of the synthon $\mathbf{H^-}$ are the hydride donors sodium borohydride **$NaBH_4$**, and lithium aluminium hydride **$LiAlH_4$**. How might you make TM 21 using this disconnection?



TM 21

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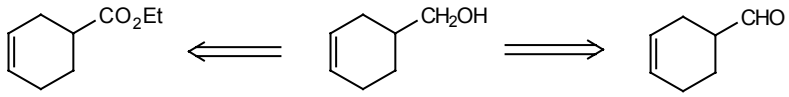
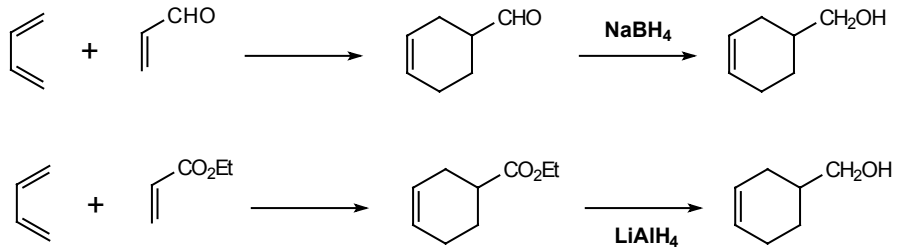
22. Remove either one or both hydrogen atoms:



either starting material can again be made by a Diels-Alder reaction.

The complete syntheses are then:



Note that **$NaBH_4$** reduces aldehydes (and ketones) but not esters while **$LiAlH_4$** reduces just about all carbonyl compounds. Neither reagent reduces an isolated deuble bond.

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2. COMPOUNDS DERIVED FROM ALCOHOLS

23. Have you noticed that the disconnections involving $\mathbf{H^-}$ are simply redox reactions and do not alter the carbon skeleton of the molecule? They are not then really disconnections at all but Functional Group Interconversions or **FGI** for short.

Alcohols are key functional groups in synthesis because their synthesis can be planned by an important disconnection and because they can be converted into a whole family of other functional groups. List three types of molecule you might make from an alcohol by FGI.

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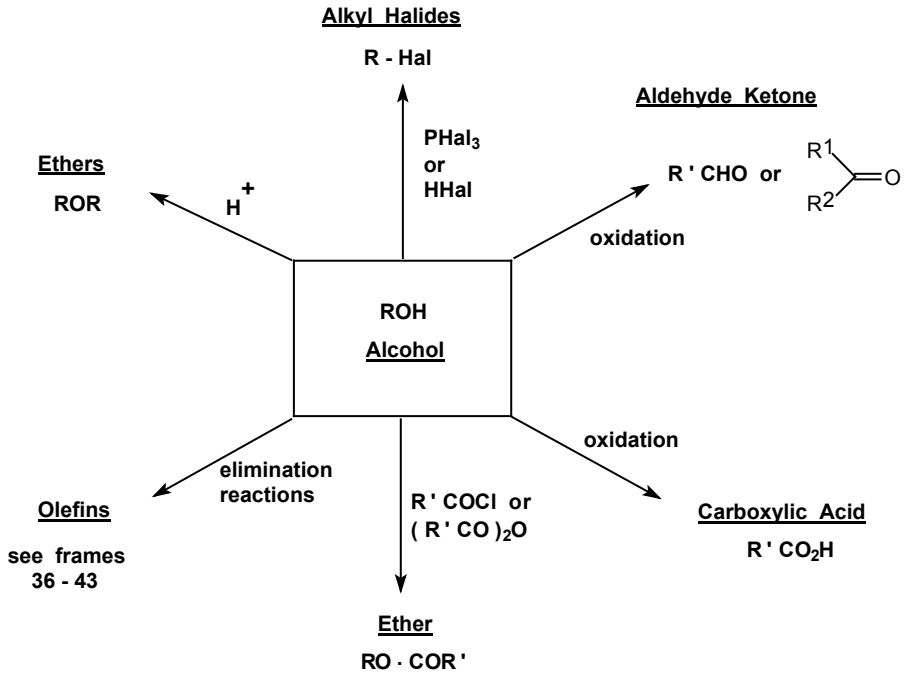
24. You might have chosen any from this chart: (there are others)



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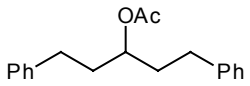
25. These FGI's are mostly straightforward, and the synthesis of any of these compounds is often best analysed by first going back to the alcohol and then disconnecting that. How would you make TM 25?



TM 25

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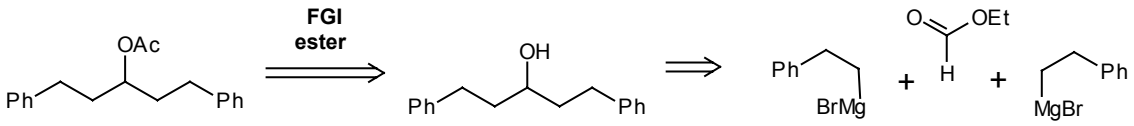
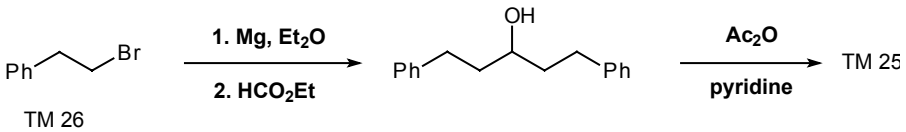
26. Analysis:

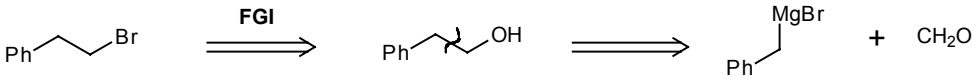


Synthesis:

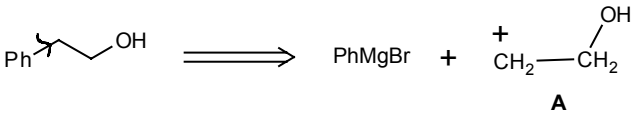


---

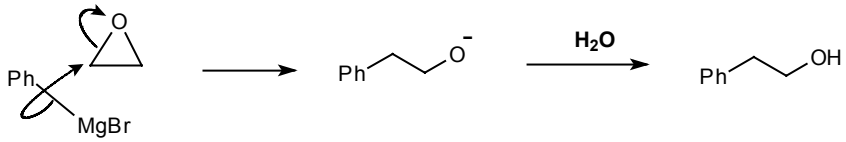
27. But let us analyse the synthesis of the halide (TM 26) a bit more. The obvious way to make it is:



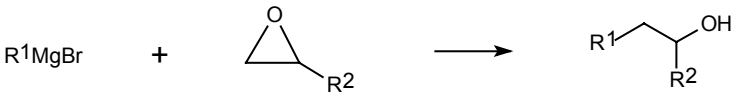
Unfortunately this route gives only a 40% yield (J. Amer. Cham. Soc., 1951, 73, 3237) in the Grignard reaction, largely because benzyl Grignard reagents easily give radicals which polymerise. In any case, it's poor tactics to chop off carbon atoms one at a time, and a better disconnection would be:



The reagent for synthon **A** is an epoxide so that the reaction becomes:



This reaction works well with monosubstituted epoxides:



but is unreliable if there are more substituents as you will see.

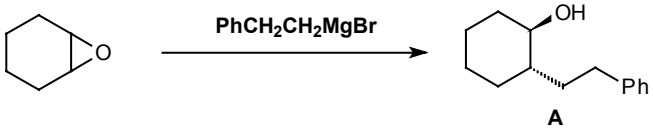
---

3. REVIEW PROBLEMS

28. From time to time during the programme, I shall break off from introducing new ideas and help you consolidate what you've already learnt with some review problems. These are meant to be realistic problems showing why synthesis is important and should let you try out your growing skills. You can either do the review problems as you meet them or come back later and use them as revision material or combine both methods by doing one or two now and the rest later. These remarks apply to all the review problems and I won't repeat them each time.

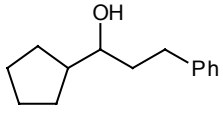
---

29. Review Problem 1: In 1936, Robinson carried out this reaction, hoping to get the alcohol **A**:



He got an alcohol all right, but it clearly wasn't **A**, and he thought it might be TM 29.

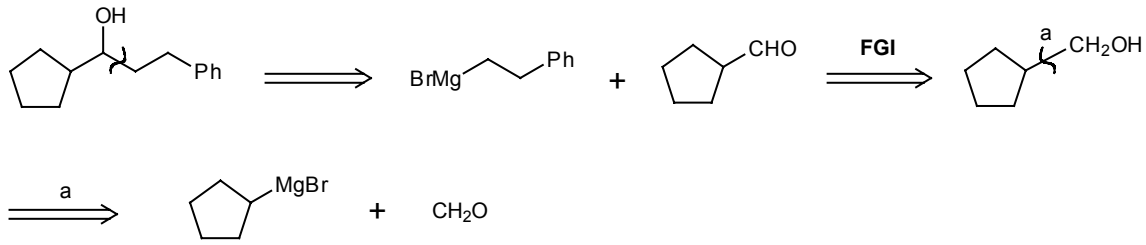
TM 29



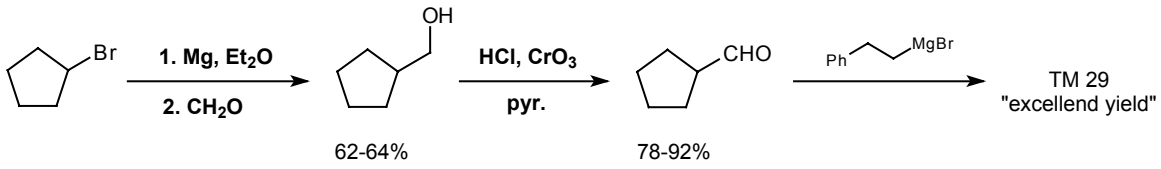
He therefore wanted to synthesise TM 29 to check. Even with modern spectroscopic methods the quickest way to check the identity of a compound will often be to synthesise it by an unambiguous route and compare the n.m.r. and fingerprint i.r. spectra. How then would you make TM 29?

---

30. Analysis: the obvious disconnection takes us back to the halide used by Robinson, the one we synthesised in frame 27:



This time the one-carbon disconnection **a** is all right because the Grignard reagent is from a normal alkyl halide and does not polymerise.
Synthesis:



TM 29, made by this route, did indeed turn out to be identical with the compound Robinson had made, and you might like to work out how it was formed. The reaction is discussed in Norman, p.501. The synthesis is described in J. Amer. Chem. Soc., 1926, 48, 1080; Tetrahedron Letters, 1975, 2647, and Robinson's original paper J. Cham. Soc., 1936, 80.

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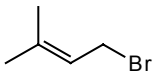
31. Review Problem 2: This allyl bromide is an important intermediate in the synthesis of terpenes (including many flavouring and perfumery compounds), as the five carbon fragment occurs widely in nature. How would you make it?



TM 31

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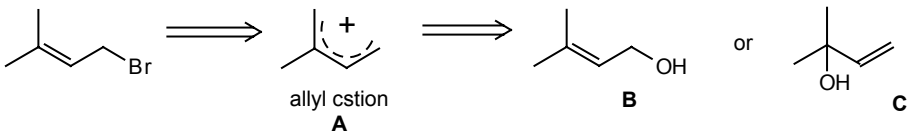
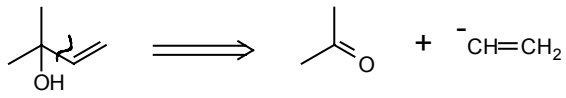
32. Analysis: did you consider both possible allylic alcohols as precursors?



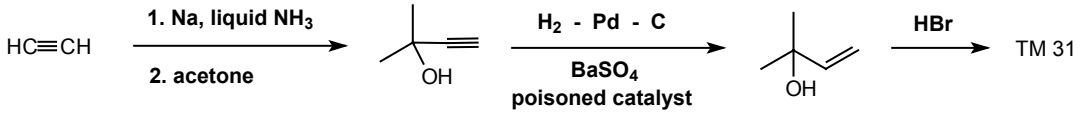
Both give TM 31 on treatment with **HBr** as the cation **A** reacts preferentially with $\mathbf{Br^-}$ at the **less** substituted carbon atom to give the **more** substituted double bond. Think again.

---

33. Analysis: you could make **32B** by using a vinyl Grignard reagent and formaldehyde but it is easier to go via **32C** and use the acetylide ion (frames 14-15) as a reagent for the synthon $^{-}$**CH=CH$_2$**:



Synthesis: partial reduction of the acetylene gives the olefin:



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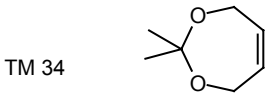
34. Review Problem 3: This odd-looking molecule (TM 34) was used by Corey as an intermediate in the synthesis of maytansine, an antitumour compound.

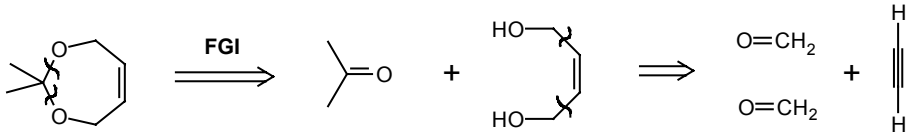


How would you make it? Don't be deceived by its oddness - identify the functional group and you will see what to do first.

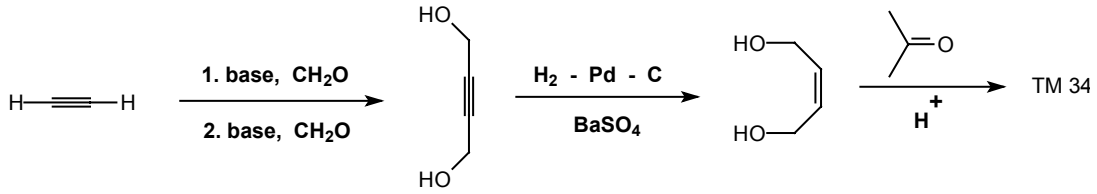
---

35. Analysis: the functional group is an acetal derived from alcohols and a carbonyl compound.

The diol must have a cis double bond so we can use the acetylene trick again here.



Synthesis (Tetrahedron Letters, 1975, 2643):



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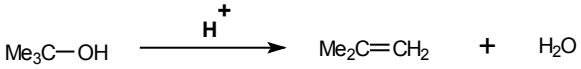
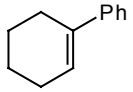
4. DISCONNECTIONS OF SIMPLE OLEFINS

36. Olefins are a little more complicated to analyse than alcohols. They can be made by the dehydration of alcohols:



So the FGI stage in designing an olefin synthesis is to add water across the double bond. How would you synthesise TM 36?

TM 36 

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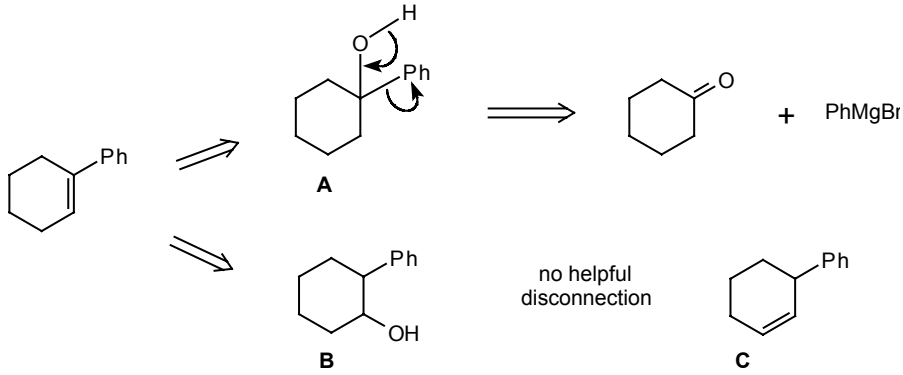
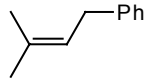
37. You should have two possible alcohols as the next step back, choosing one of these because it gives a useful disconnection while the other does not.

---

38. Analysis:



We must also consider whether the dehydration reaction might be ambiguous. Thus **A** can give only TM 36 on dehydration but **B** might give **C** as well. How would you make TM 38?

TM 38 

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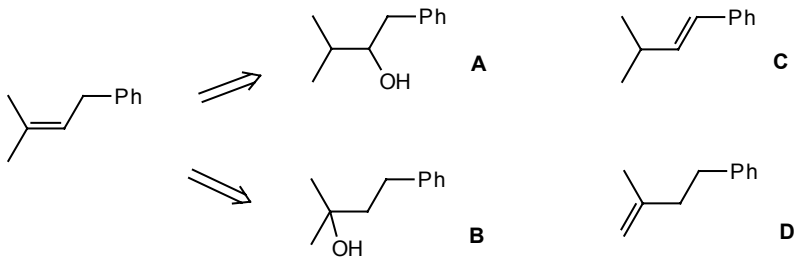
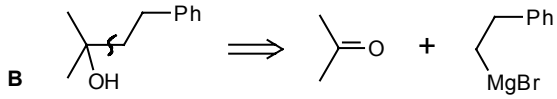
39. The alternatives are:



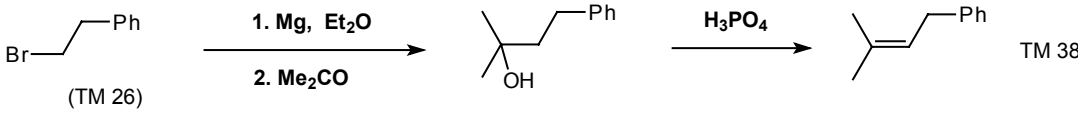
Dehydration of **A** could also give **C**, the conjugated olefin, but dehydration of **B** will give only TM 38 and none of the less substituted **D**. Now finish off the analysis and write out the synthesis.

---

40. Analysis:



Synthesis:



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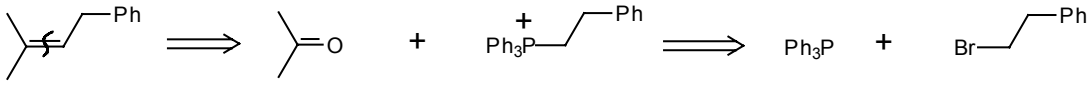
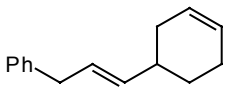
41. An alternative route to olefins is by an immediate disconnection of the double bond. This corresponds to the Wittig reaction:



If you are unfamiliar with the Wittig reaction see Norman p.297-299 or Tedder, Part 3, p.233-6.

The advantages of this route are that it is very short and that the double bond must go where we want it. Otherwise it is very like the route in frame 40 and actually uses the same starting materials. How might you make TM 41?

TM 41



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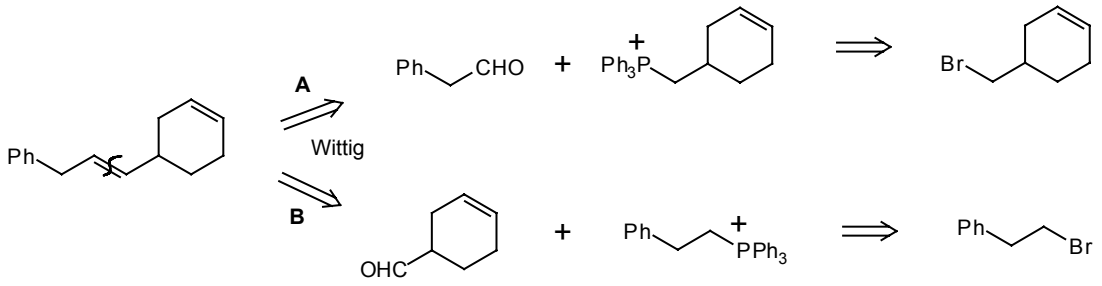
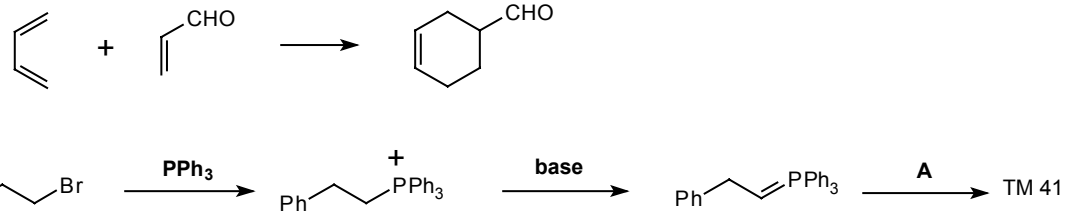
42. Choosing to disconnect the double bond outside the ring, as this will give us two fragments:



The starting materials for route **B** are recognisable as the halide we used in frame 41 and an aldehyde easily made by a Diels-Alder reaction. The other route could also be used but the starting materials are not so readily available. Write out the complete synthesis.

43.

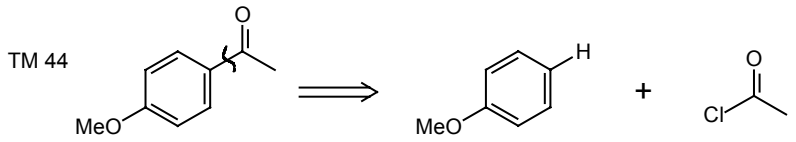


This is a good opportunity to mention our third criterion for a good disconnection - that it leads to recognisable starting materials. We have used this criterion already in frames 20 and 42.

---

5. DISCONNECTIONS OF ARYL KETONES

44. The Wittig reaction is important enough to be our second major one group disconnection. The first was the disconnection of alcohols to carbonyl compounds and Grignard reagents. Our third major one disconnects the bond joining an aromatic ring to an aliphatic side chain. So we would make TM 44 by the Friedel-Crafts reaction using acetyl chloride and aluminium chloride to attack the benzene ring:



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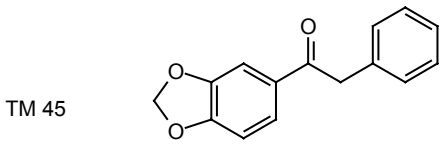
45. In principle we can disconnect any bond next to an aromatic ring in this way, though not always in practice. How would you make TM 45?



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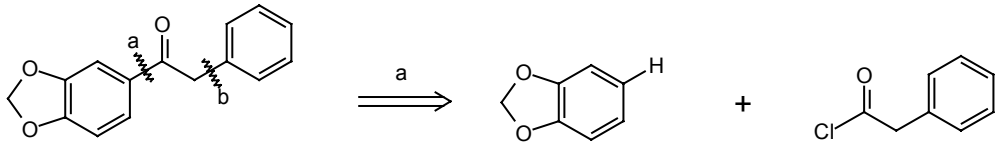
46. One of the two possible disconnections **a** is better as it gives us an acyl rather than an alkyl halide and an activated benzene ring.



If you're not sure about why this is so, or don't understand the mechanism of the Friedel-Crafts reaction, you will find help in Tedder, part 2, pages 212-215 or Norman, pages 363-370.

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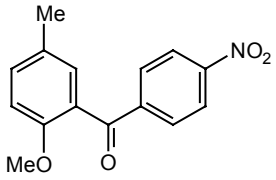
47. Sometimes a choice between two disconnections of this sort can be made by our first criterion (a good mechanism). How would you make TM 47?



TM 47

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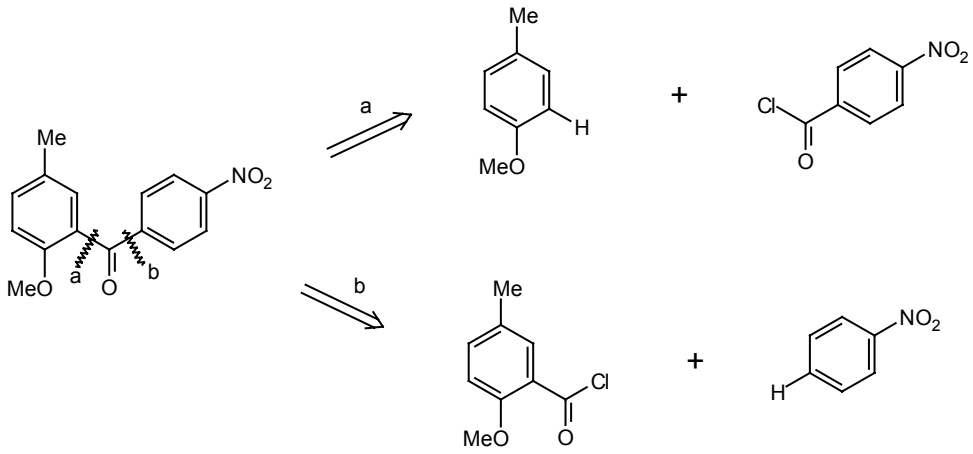
48. There are two possible disconnections:



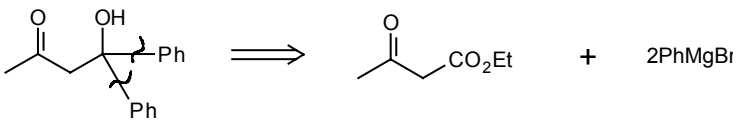
Disconnection **b** will not do as the nitro group is meta-directing and in any case nitro benzene will not react under Friedel-Crafts conditions. Disconnection **a** is fine as the **MeO** group is more powerfully ortho-directing than the **Me** group (Ber., 1907, 40, 3514).

---

6. CONTROL

49. Before we complete the disconnections of carbonyl compounds we shall look at some aspects of control in synthesis as a break from the systematic analysis.
Why might the obvious disconnection on TM 49 give trouble when the real reaction is tried?

TM 49



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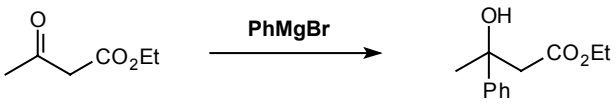
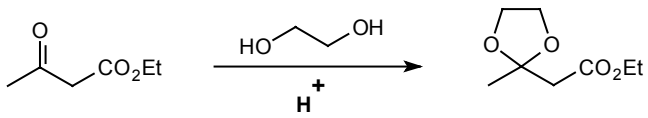
50. The Grignard reagent might first attack the ketone giving the wrong product.

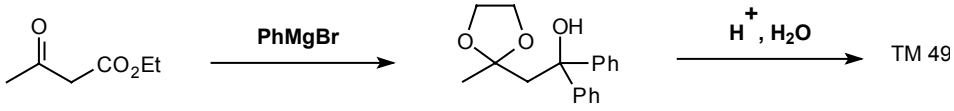


To stop this we protect the ketone by a reversible FGI. A common method is to make the cyclic ketal:



Now complete the synthesis.
If you're not sure of the mechanism of acetal formation or just want to know a bit more about acetals, read frames 1-21 and 62-64 of the Carbonyl Programme.

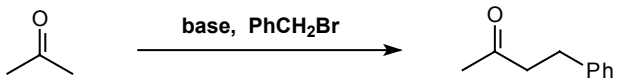
51.



Any functional group can act as a protecting group providing it can easily be added and removed and providing of course that it doesn't react with the reagent! We shall meet more examples as we work through the programme.

---

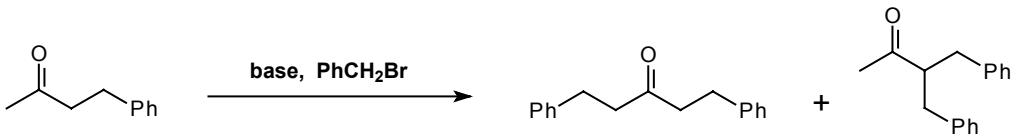
52. Sometimes, rather than <u>protect</u> one part of a molecule, it is better to <u>activate</u> another.



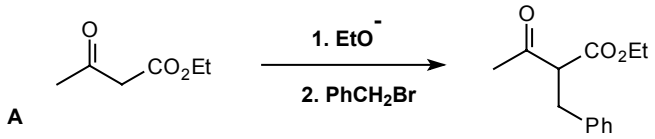
This reaction gives only a poor yield. Why? Enolisation is involved: if you're not sure about this, see frames 169 ff of the Carbonyl Programme.

---

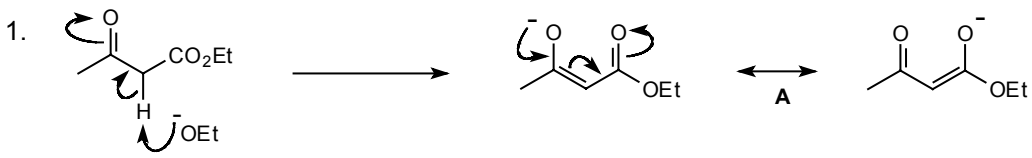
53. Because the product is at least as reactive as the starting material, and further reaction occurs:



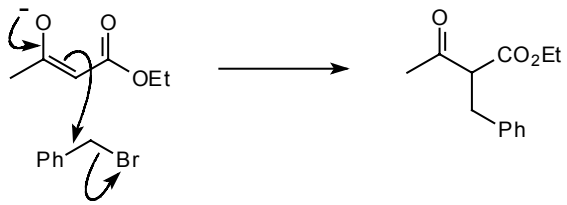
We can't protect the carbonyl group without stopping the reaction, so we <u>activate</u> one position by adding a **CO_2Et** group and using the ester **A** below, the synthetic equivalent of acetone, instead of acetone itself. Here is the reaction; draw a mechanism for it.



54.



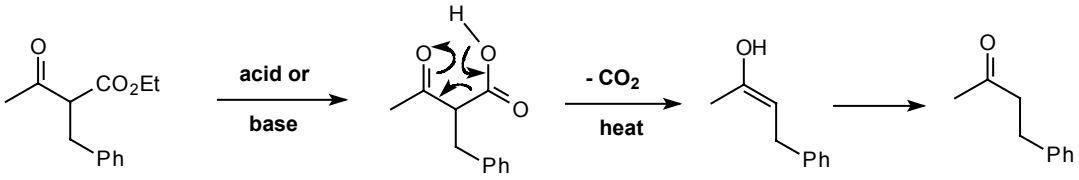
only this stable enolate **A** formed

2. 

Of course, we must now remove the activating group, **CO_2Et** in this case, just as we had to remove the protecting group before. How might we do this?

---

55. By hydrolysis and decarboxylation:



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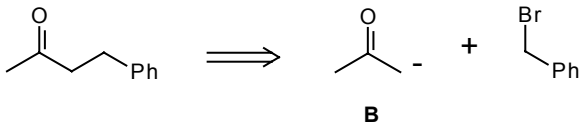
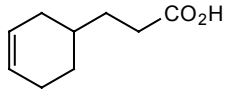
56. This is then a general synthesis for ketones and the corresponding disconnection is



The acetoacetate enolate ion (**A** in frame 54) is a reagent for the synthon B, the acetone anion. We shall discover how to add the **CO_2Et** activating group later.

---

57. Protection and activation give us a reagent for the synthon **$^-CH_2CO_2H$**. We protect the acid as an ester and add another ester group as activation, giving malonic ester: **$CH_2(CO_2Et)_2$**. How would you make TM 57?

TM 57 

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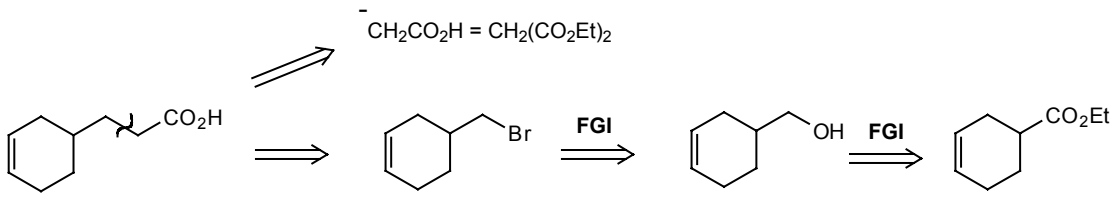
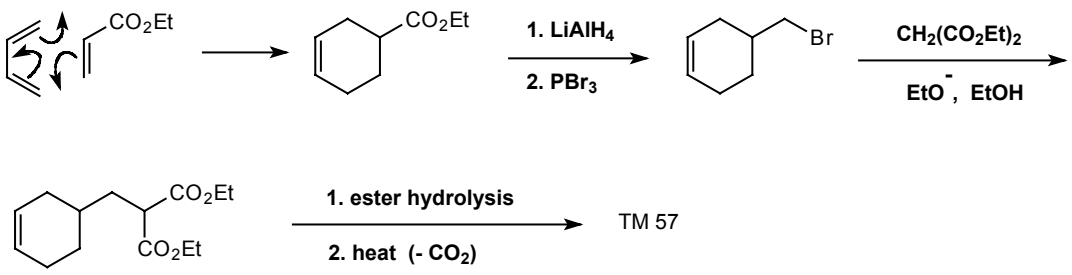
58. Analysis:



Choosing this disconnection because we recognise a starting material easily made by a Diels-Alder reaction (cf. frame 22).

Synthesis:



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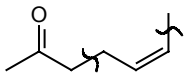
59. Here is quite a difficult problem: to solve it you will need to use both protection and activation. Two hints: the disconnections are shown and you might like to start by thinking how you would make a cis olefin. How can you make TM 59?

TM 59 

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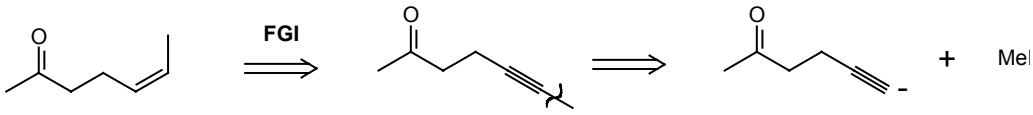
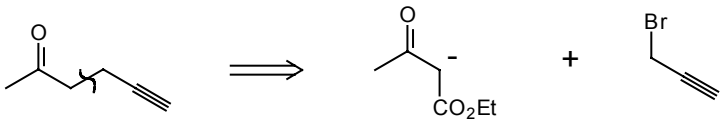
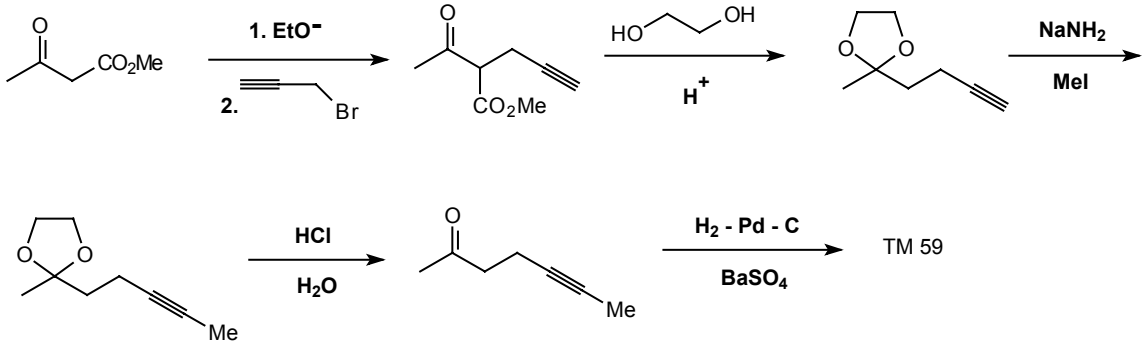
60. Analysis: This cis olefin will presumably come from an acetylene: we can then use an acetylide anion:



Now we can disconnect the ketone using our synthetic equivalent for the acetone anion:



Synthesis: (Crombie, J. Chem. Soc. (C), 1969, 1016). The acetylenic bromide corresponding to allyl bromide is called propargyl bromide and is reactive and readily available. We shall need to protect the ketone before we make the acetylene anion. It turns out that protection and decarboxylation can be done in one step.



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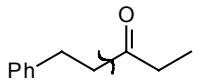
7. DISCONNECTIONS OF SIMPLE KETONES AND ACIDS

61. The section on control showed how we could make ketones by one disconnection. You already know another. How could you make this ketone (TM 61) by the disconnection shown?

TM 61 

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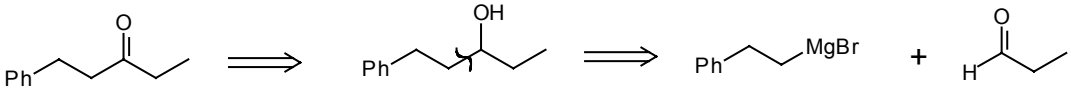
62. By first returning to the parent alcohol:



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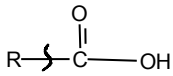
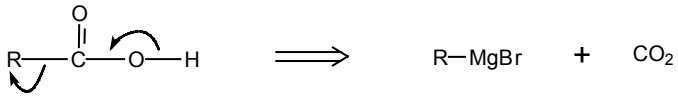
63. You also know how to make acids by FGI from a primary alcohol; but an acid is itself a hydroxyl compound and can be disconnected in the same way as alcohols. What do you get if you do this:

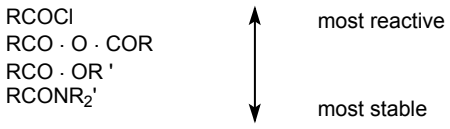


64.

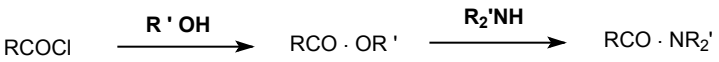


Acid derivatives are made directly from acids or by conversion from other acid derivatives depending on their stability. The most important are esters (**RCO_2Et**), amides (**RCO_2NR_2**), anhydrides (**RCO·O·COR**) and acid chlorides (**RCOCl**). Arrange these in an order of stability, the most reactive at the top of the list, the most stable at the bottom.

65.



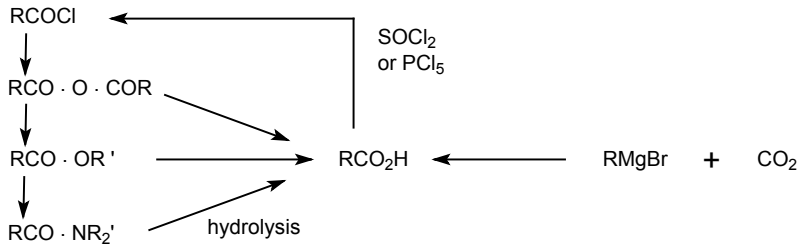
Conversions down the list are easy - simply use the appropriate nucleophile. Thus:



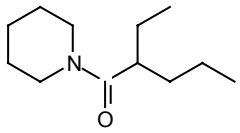
All can be hydrolysed to the acid, and the list can be entered at the top from the acid by using **$SOCl_2$** or **PCl_5** to make the acid chioride.

---

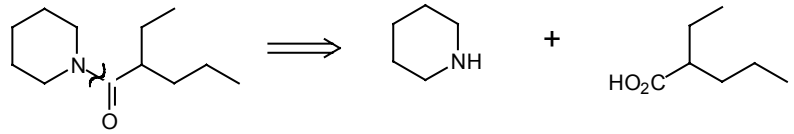
66. This gives us a complete chart for acid derivatives.



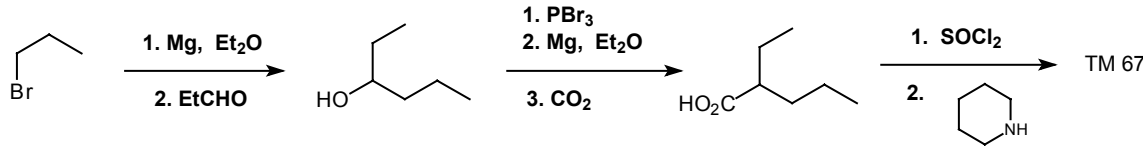
67. So how could you make this acid derivative?

TM 67 

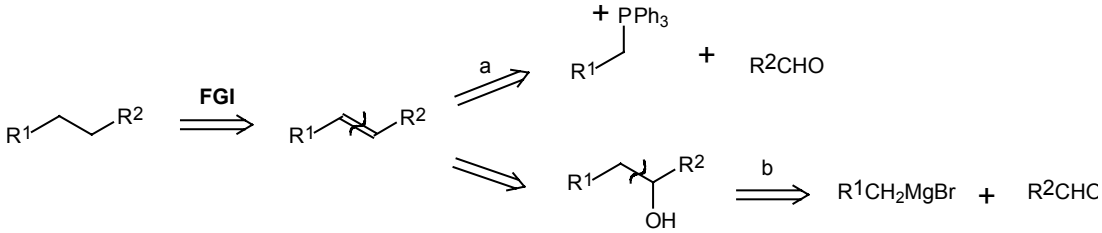
68. Analysis: Amide ∴ FGI back to carbo-xylic acid:
acid is branched at α-carbon ∴ use disconnection of **α** bond



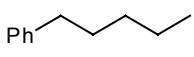
Synthesis:



69. Finally in our treatment of one group disconnections we ought to consider how to synthesise fully saturated hydrocarbons - compounds with no FG at all! These are often made by hydrogenation of a double bond, and so the disconnection can be made anywhere we like:



Using our principles for good disconnections, we shall obviously look for two roughly equal recognisable fragments. So how would you make TM 69?

TM 69 

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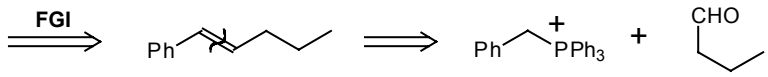
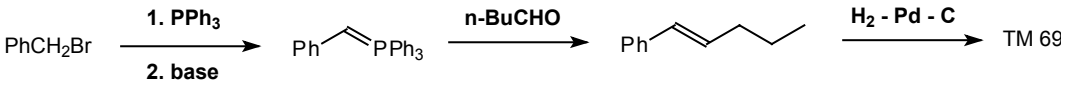
70. Analysis: There are many answers. One is to put the double bond as close to the benzene ring as possible:



Synthesis:



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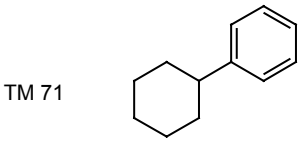
71. A guide we can sometimes use, particularly if we use disconnection **b** in frame 69, is to put the **OH** group at a branch point in the molecule, knowing that disconnection will be easy there. Try this:



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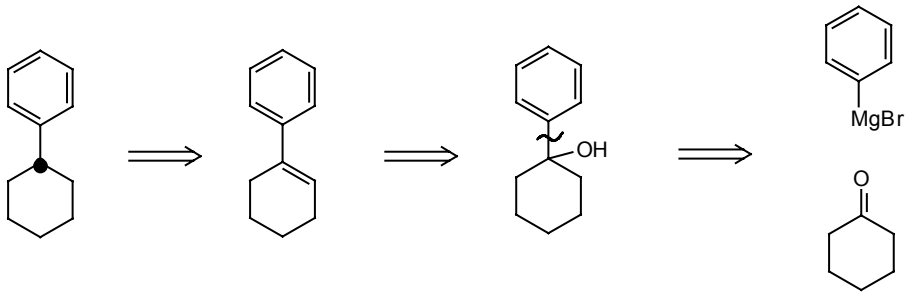
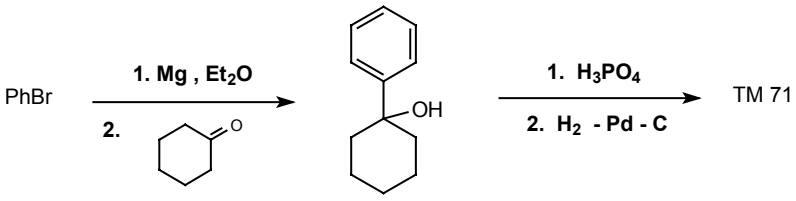
72. Analysis: Use branch point • as a guide.



Synthesis:



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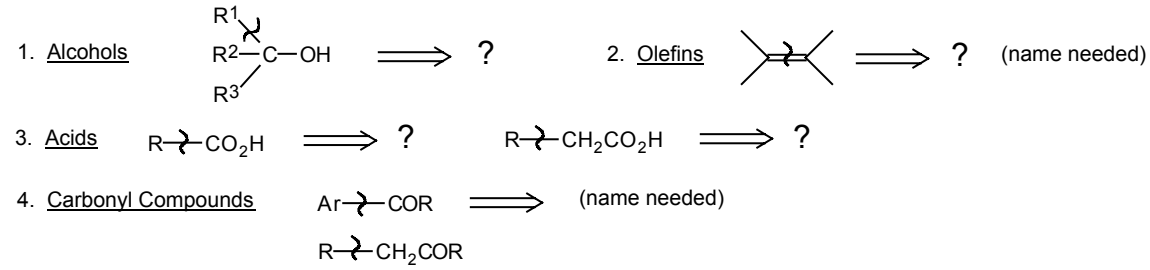
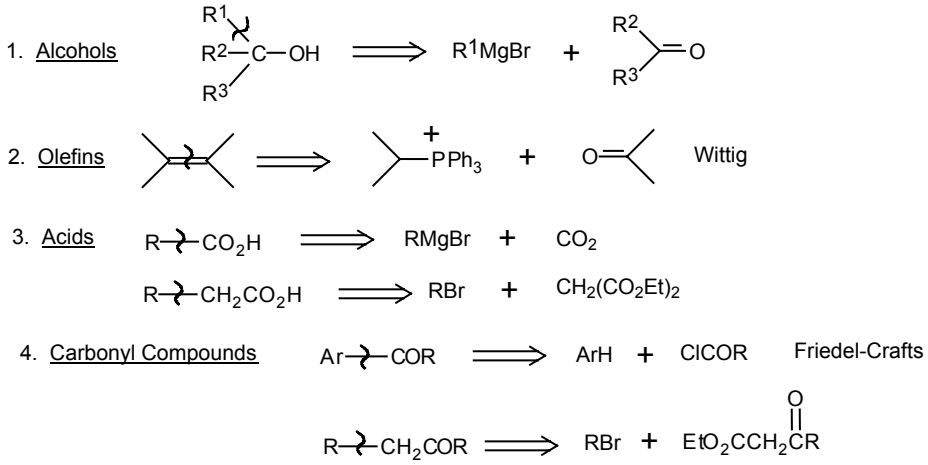
8. SUMMARY AND REVISION

73. Although you have analysed the synthesis of many compounds and considered mechanisms of many reactions, we have collected only a handful of important one group disconnections. Can you fill in the details of these:



74.



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75. We have three or four ways to recognise a good disconnection. Make a list of these.

76.

1. Good mechanism.
2. Greatest possible simplification.
3. Gives recognisable starting materials. (You might also have mentioned the use of the branch point as a guide).

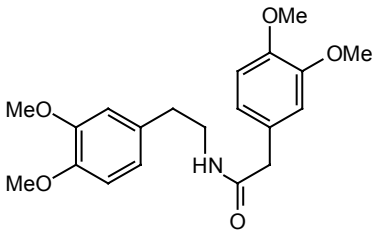
---

77. A useful thing to do at this stage would be for you to start making a chart, of your own design and for your own use, showing all the useful synthetic links between the various classes of compound. You can then add to this later but a colourful, well designed chart of the relationships between single functional groups is a good reference.

---

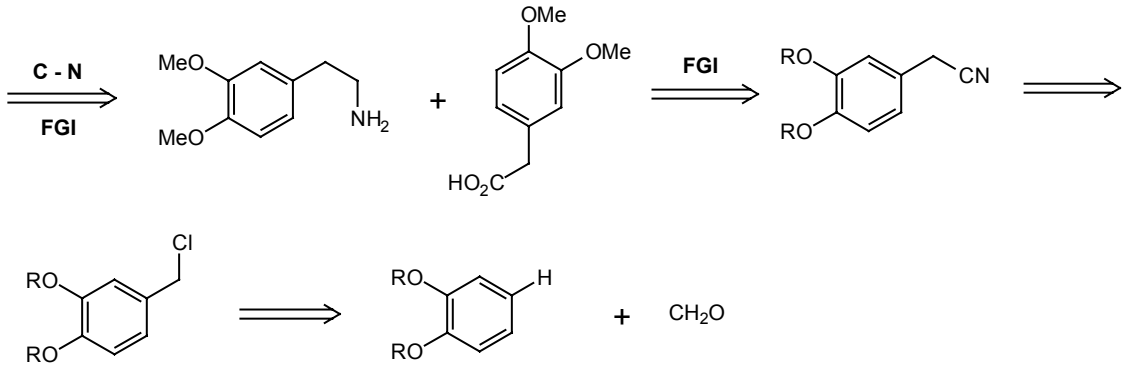
9. REVIEW PROBLEMS

78. Review Problem 4 This compound (TM 78) is an important intermediate in the synthesis of alkaloids: Treatment with **$POCl_3$** gives the poppy alkaloid papaverine. How would you make TM 78 from simple starting materials?

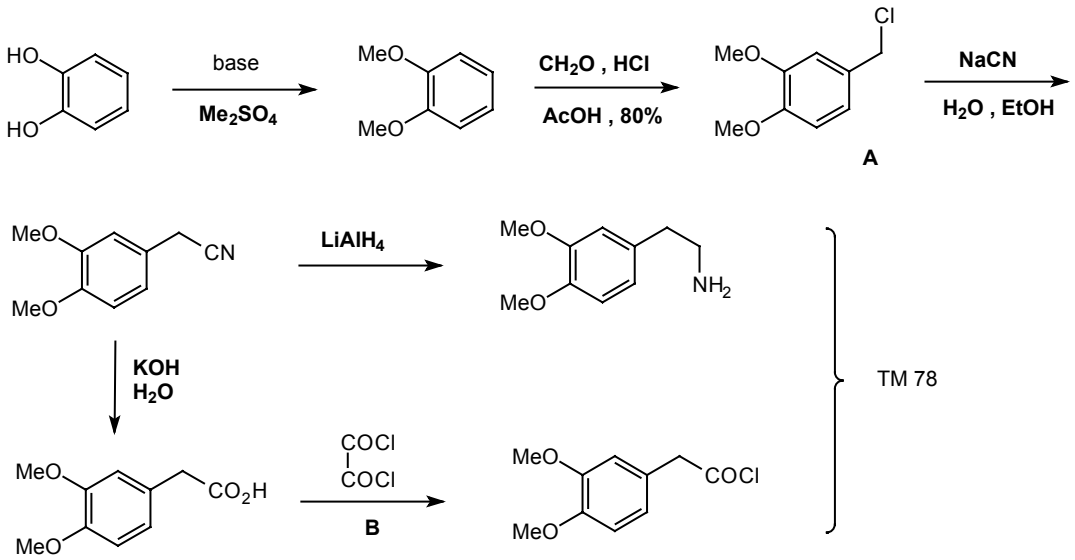


TM 78

79. Analysis: There are four ether groups, but they are peripheral and easily made. The key FG is the amide which we must disconnect first at the **C-N** bond. Both acid and amine could be made from the same nitrile.



Synthesis: from readily available catechol:



The reaction giving **A** is 'chloromethylation', a reliable method of adding a **CH_2OH** equivalent to an aromatic ring. You may have been surprised at the use of reagent **B** to make an acid chloride. **B** is oxalyl chloride and is often used when pure acid chlorides are wanted - the other products are gases (which?).

The nitrile is described in a patent (Chem. Abs., 1955, 15963); the last stages were carried out by A. R. Battersby's research group at Cambridge. Chloromethylation is described in Tedder, Vol 2, p.213 and Norman P.372-3.

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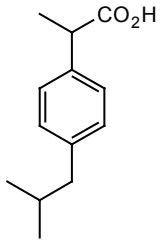
80. Review Problem 5: 'Brufen' (TM 80), Boots anti-rheumatic compound, is one of Britain's top ten drugs. How could it be made?

TM 80



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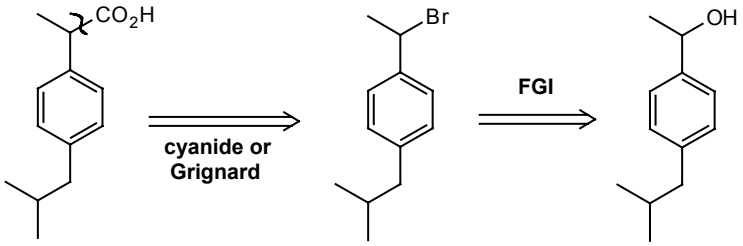
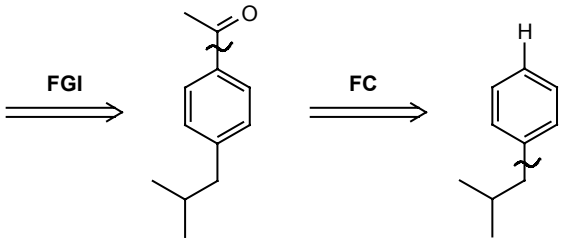
81. Analysis: The carboxylic acid is the only FG so we can start there:

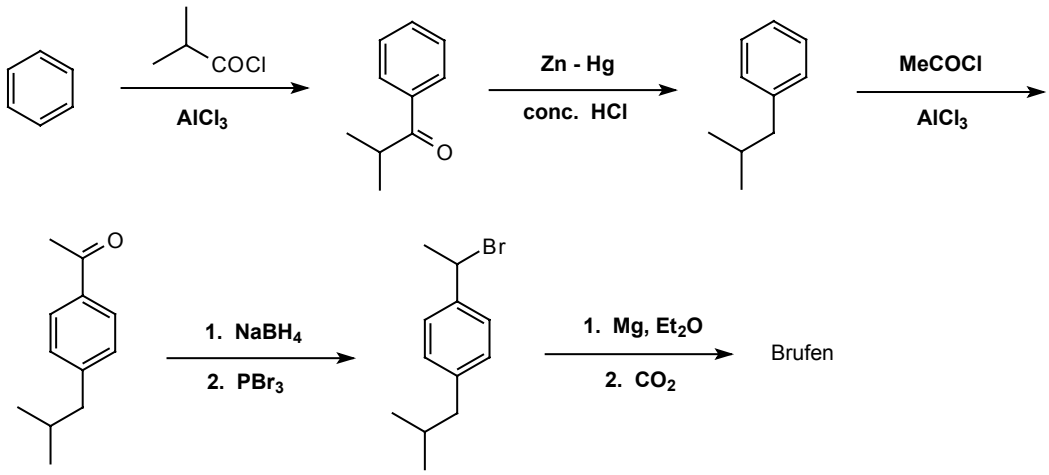


We now have a benzyl alcohol so we use Friedel-Crafts rather than Grignard:



Again we want to use Friedel-Crafts but we must use acylation rather than alkylation or we shall get rearrangement.

Synthesis: This is one possible approach - we don't actually know how it is done.



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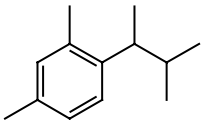
82. Review Problem 6: Some chemists who were investigating the possibility of reversible Friedel-Crafts reactions, wanted an activated aromatic ring connected to a branched alkyl chain and chose to make TM 82 . How would you do it?

TM 82 

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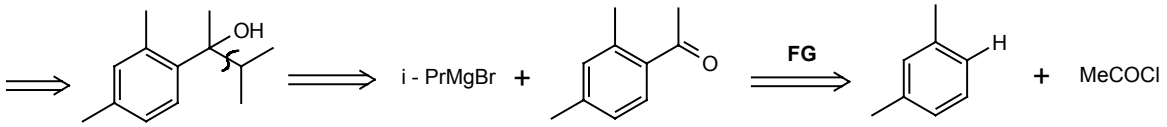
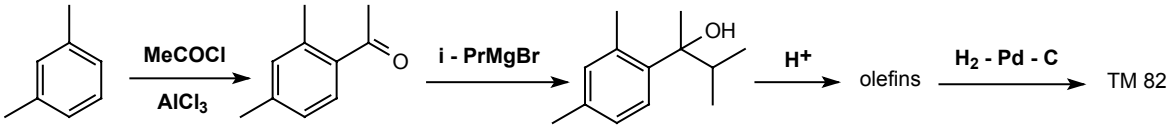
83. Analysis: Using the branch-point, in the largest side chain as a guide, we can put in a hydroxyl group (as in frame 72).



Synthesis: hote that there is only one activated site for the Friedel-Crafts reaction – o and p to the two methyl groups but not between them for steric reasons:



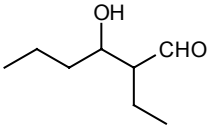
This was essentially the method used by the chemists who went on to investigate the chemistry of TM 82 (J. Org. Chem. 1942, 7, 6).

C. TWO-GROUP DISCONNECTIONS

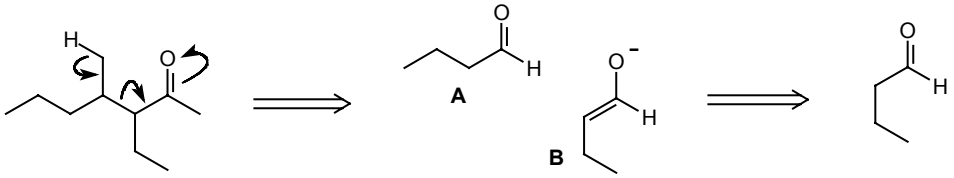
1. 1,3-DIOXYGENATED SCELETONS

(a) β-HYDROXY CARBONYL COMPOUNDS

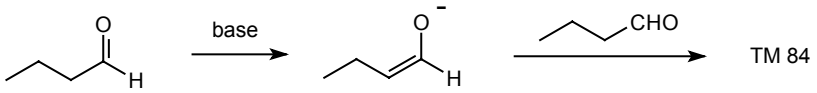
84. When a molecule contains two functional groups, the best disconnection uses the two together. So if you consider TM 84 as an alcohol, and use the carbonyl group to guide your disconnection, what do you get?

TM 84 

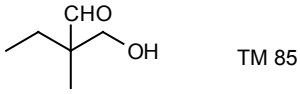
85.



The anion **B** is just the enolate anion of a carbonyl compound, actually the same as **A**. So there is no need to use a Grignard reagent or any other synthetic equivalent in this reaction: anion **B** itself can be the intermediate and we simply treat the aldehyde with mild base:



So how would you make TM 85?



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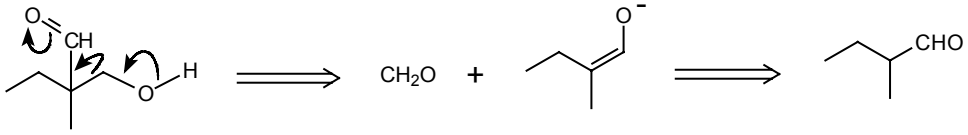
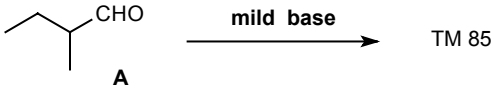
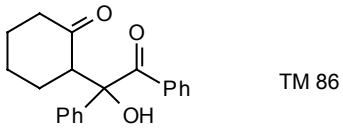
86. Analysis:



Synthesis:



You may wonder why aldehyde **A** doesn't react. with itself but reacts instead with formaldehyde. This is just one aspect of control in carbonyl condensations, treated thoroughly in frames 217-315 of the Carbonyl Programme. In this case, only aldehyde **A** can enolise but formaldehyde is more electrophilic. Now try this problem: How would you synthesise TM 86?



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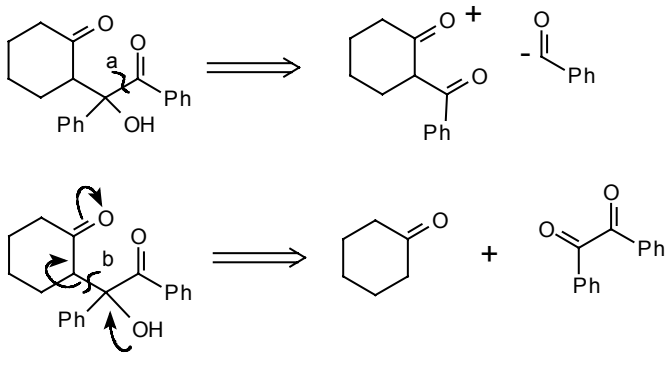
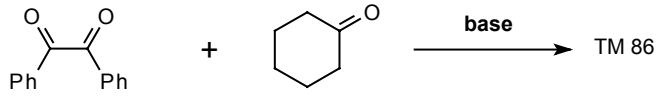
87. Analysis: It may be tempting to disconnect bond **a** but this would give the unknown and presumably very unstable **PhC=O**$^-$ synthon. The better disconnection is bond **b** giving two carbonyl compounds.

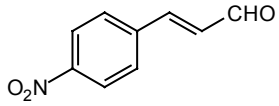


Synthesis: Only cyclohexanone can enolise, but the α-diketone is more electrophilic - no control needed:



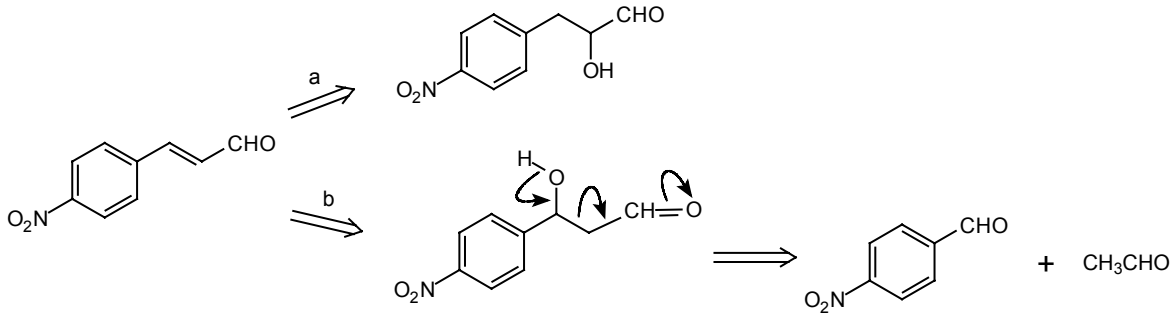
(b) α,β-UNSATURATED CARBONYL COMPOUNDS

88. Using one of our methods of analysing the synthesis of olefins, that is FGI to an alcohol, write down both the alcohols from which you might make TM 88 and see which you prefer.

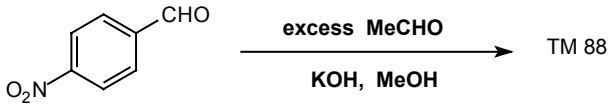
TM 88 

---

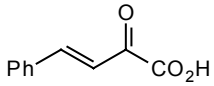
89. FGI (b) gives an alcohol we can disconnect easily:



Synthesis: The synthesis uses rather more vigorous conditions than those which gave the β-hydroxy carbonyl compounds. In fact (Bull. Chem. Japan, 1952, 25, 54, Chem. Abs.,1954, 48, 5143) you can either treat the β-hydroxy compound with **HCl** in acetic acid or do the condensation in base:



Only the acetaldehyde can enolise but the two aldehydes are about equally electrophilic: we use an excess of acetaldehyde to compensate for its self-condensation. What about TM 89?

TM 89 

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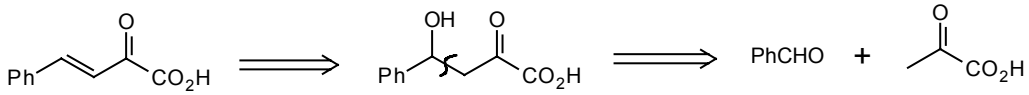
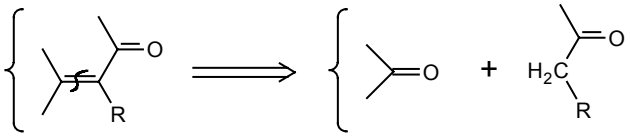
90. Analysis: by the same method:



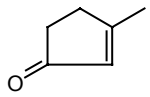
Synthesis: No control is need because only the ketoacid can enolise and the aldehyde is more electrophilic. TM 89 is formed in 80% yield when the two starting materials are mixed in **MeOH** with **KOH** at room temperature (Hely. Chim. Acta, 1931, 14, 783).

---

91. So we can disconnect any α,β-unsaturated carbonyl compound along the double bond, writing **CH_2** at one end and **C=O** at tbe other.



How about this one:



TM 91

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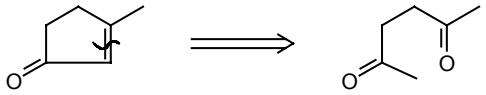
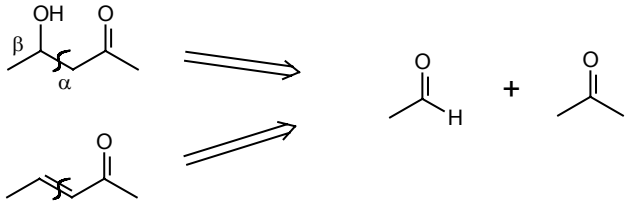
92. I hope you weren't put off by the ring:



We shall discover how to synthesise this starting material later.

---

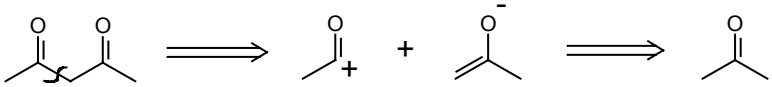
93. So to summarise these two-group disconnections: we can always disconnect the α, β bond in either of these structures:



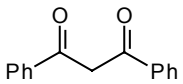
Mild conditions (usually base) give the alcohol, more vigorous conditions (acid or base) give the enone.

(c) 1,3-DICARBONYL COMPOUNDS

94. Disconnection of the same bond gives a good synthesis of 1,3-dicarbonyl compounds:



The reagent for the synthon **RCO**$^+$ will be **RCOX** where **X** is a leaving group, such as **OEt**. So how would you make TM 94?

TM 94 

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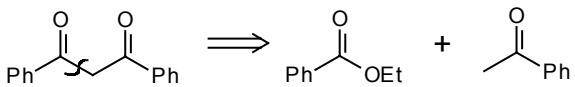
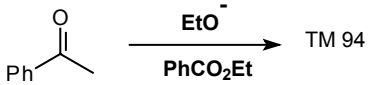
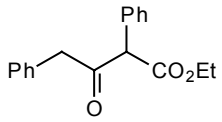
95. Analysis:



Synthesis:



Now what about TM 95?

TM 95 

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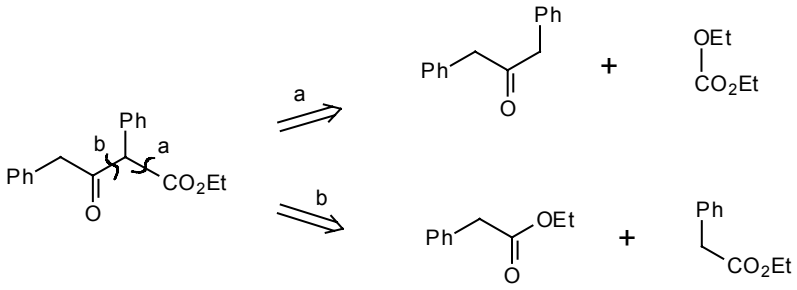
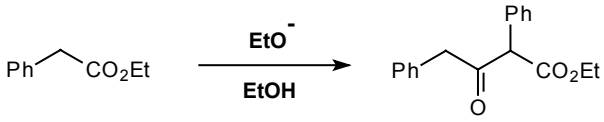
96. You had a choice between bonds **a** or **b**:



b has the advantage of greater simplification. It also has an advantage we used previously (in frame 85) that of symmetry: both starting materials are actually the same molecule. The synthesis is therefore the Claisen ester condensation.



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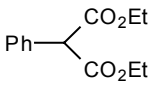
97. The other disconnection (**a** in frame 96) is very important if we want to add control in the form of a **CO_2Et** group. How would you make TM 97?

 TM 97

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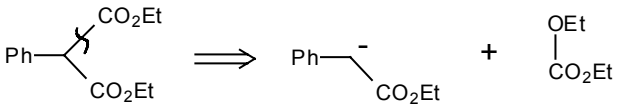
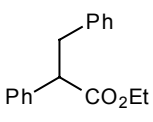
98. Simple:



The compound **$CO(OEt)_2$** is diethyl carbonate and is readily available. I hope you weren't seduced by the alternative:

as nucleophilic substitutions on aryl halides need special conditions (see Tedder, vol 2, p.157 ff., or Norman, p.401 ff.). You may remember from frames 57-58 that TM 97 is a reagent for **$PhCHCO_2H$**. How could we make TM 98 using it?

TM 98 

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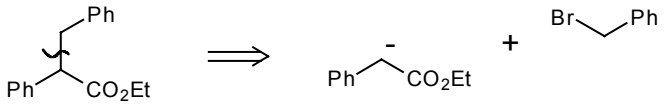
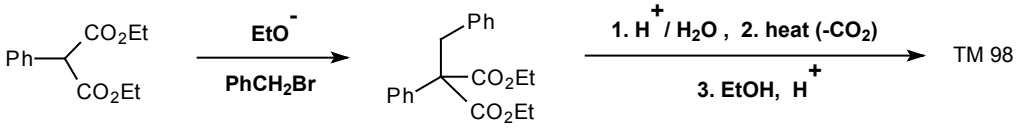
99. Analysis:



Synthesis:



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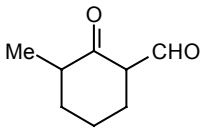
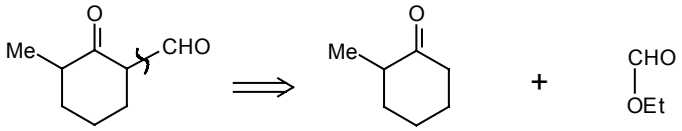
100. How would you make TM 100?

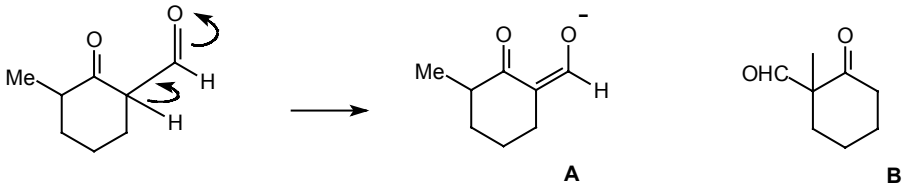


TM 100

101.

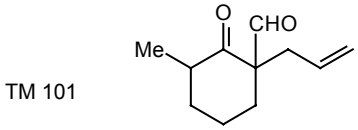


The one-carbon fragment is ethyl formate. This reaction is important as a method of control since it occurs only on one side of the carbonyl group: that is it is regioselective. The reason is that this product can itself enolise in

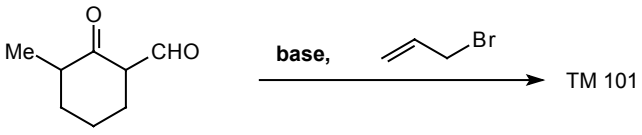


the basic reaction medium to form the stable delocalised enolate **A**. This drives the equilibrium over and would not be possible with the alternative product **B** since there is no hydrogen atom at the vital point.

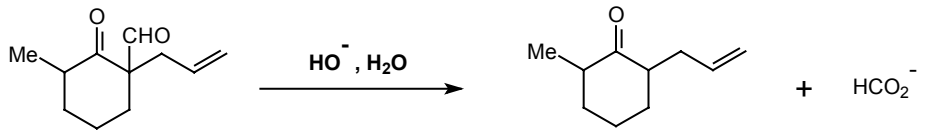
How could we develop this into a synthesis of TM 101?



102.



Only the more stable enolate (101A) is formed and this reacts well with allyl bromide. This activating group (**CHO**) can be removed by basecatalysed hydrolysis. Mechanism?



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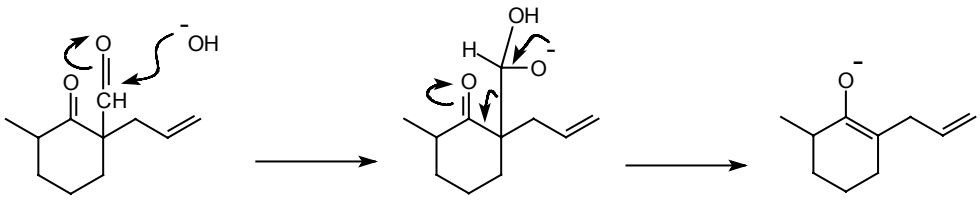
103. HO^- attacks the more reactive carbonyl group:



More details on this are given in Section V of the Carbonyl Programme, with a summary in frame 324.

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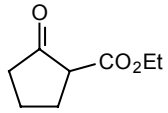
104. The one-carbon addition we used in frames 98 and 101 is all right if we just want to add an activating group to a readily available ketone, but is not otherwise good synthetic practice!

What alternative disconnection is alternative here?

TM 104



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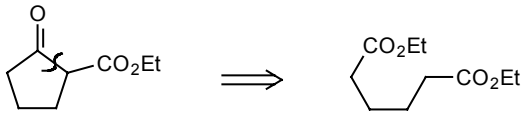
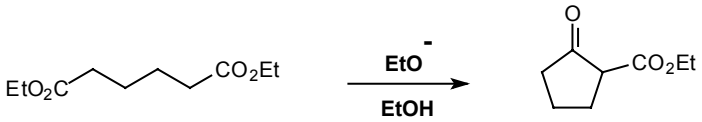
105. Analysis:



This starting material is symmetrical and happens to be readily available. (See frame 194 ff).

Synthesis: This cyclisation version of the Claisen ester condensation is sometimes called the Dieckmann Reaction.



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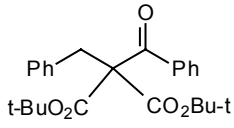
106. Sometimes we can be guided in our disconnection by the relative stabilities of the possible anionic fragments. How would you make TM 106?

TM 106



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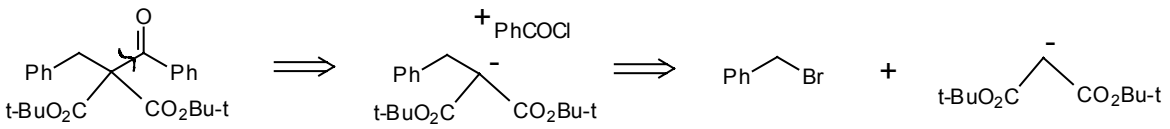
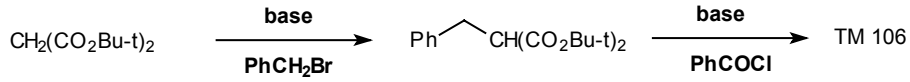
107. One disconnection gives a symmetrical stable anion derived from an easily made malonate ester.

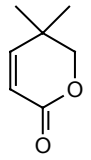


Synthesis:



(d) REVIEW PROBLEMS

108. Review Problem 7: α-β-Unsaturated lactones are useful intermediates in synthesis as they take part in Diels-Alder reactions to build larger molecules with more complex functionality. How would you make this one?

TM 108 

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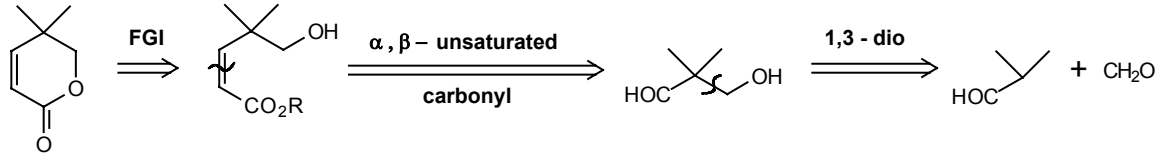
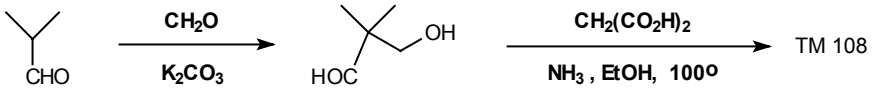
109. Analysis: We must first open the lactone ring:



Synthesis: No control is needed in the first step: there is only one enolisable **H** atom on either aldehyde. If we use malonic acid for the second step, cyclisation and decarboxylation will be spontaneous (Monatshefte, 1904, 25, 13).



If you're not sure of the details of this last step, try working it out as a mechanistic problem.

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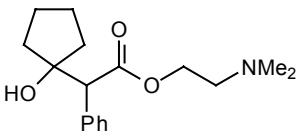
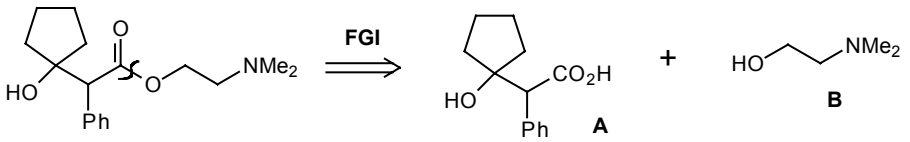
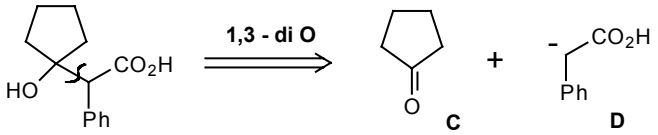
110. Review Problem 8: Suggest a synthesis of the mydriatic (dilates the pupils of the eyes) cyclopentolate, TM 110.

TM 110 

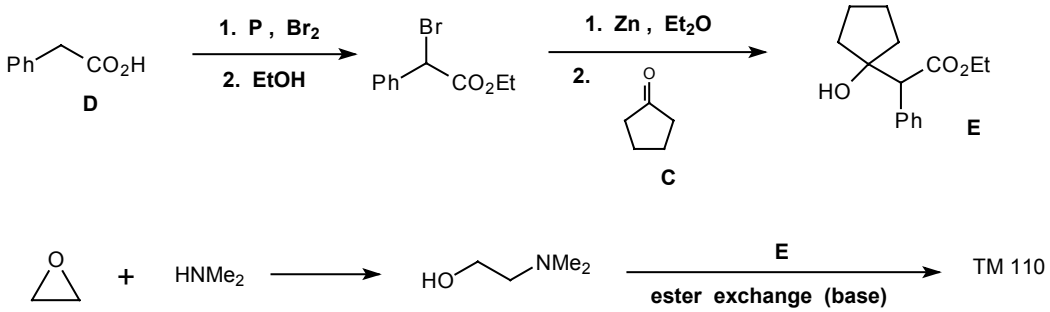
111. Analysis: We must first separate the ester into its, component parts:



The alcohol **B** is a typical amine-epoxide adduct, and the acid **A** is a 1,3-dioxygenated compound:



Synthesis: Control will be needed in the condensation as the ketone **C** is more reactive than the acid **D** both in enolisation and electrophilic power. The Reformatsky looks a good method. Again we don't know how this commercial product is actually made:

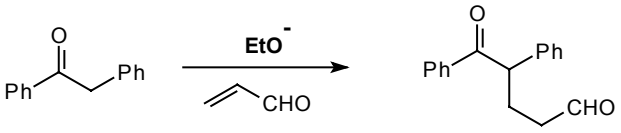


There is no danger that the tertiary alcohol group will form an ester under these conditions. Ester exchange is described in Norman p.134-5.

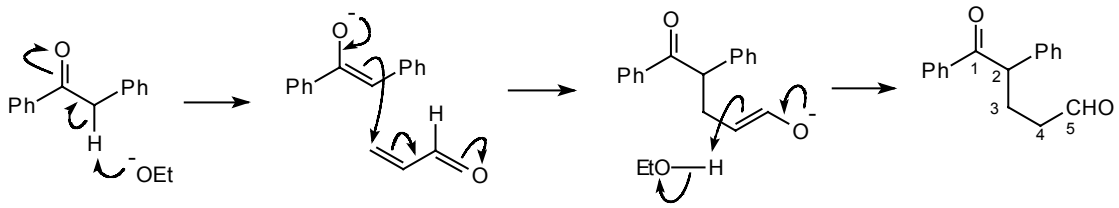
---

2. 1,5-DICARBONYL COMPOUNDS

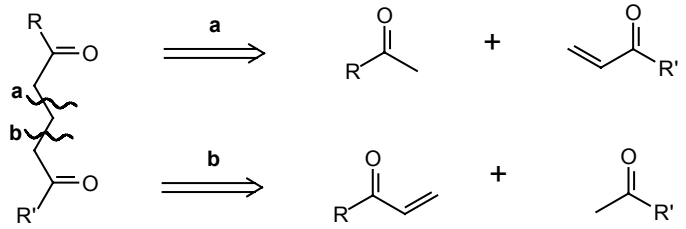
112. So far in this section we have combined enolate anions with other carbonyl compounds by direct attack at the carbonyl group. We can expand the scope of this reaction by using α,β-unsaturated carbonyl compounds as the electrophiles. This is the Michael reaction. Remind yourself of this by writing out the mechanism of a Michael reaction such as:



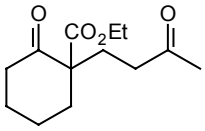
113.



You see that this reaction makes a 1,5-dicarbonyl compound: we can therefore disconnect any such compound at either of the two middle bonds.



Somtimes the choice is easy. How would you make TM 113?

TM 113 

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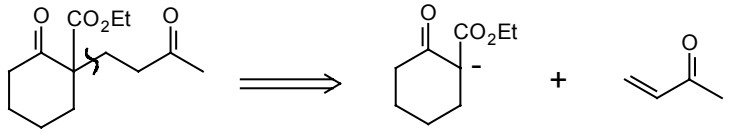
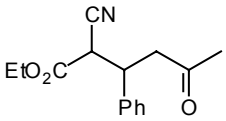
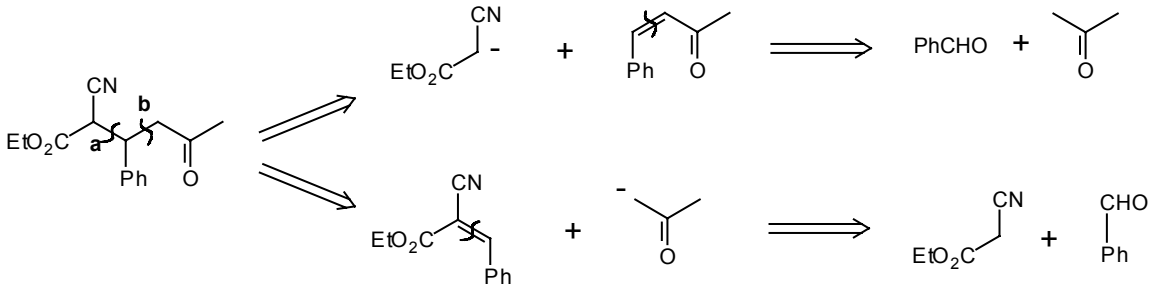
114. Only one of the two disconnections is possible:



This disconnection is also good because:
(a) it gives a stable anion
(b) both starting materials can easily be made by methods outlined in frames 97-99 and 104-106.
Sometimes we must make a choice between two mechanistically reasonable disconnections. How about TM 114?

TM 114 

115.

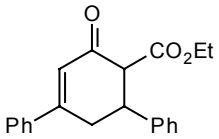


Both routes are acceptable and both get back to the same three starting materials. Route **a** uses a Michael reaction with a stable anion so this is preferable.

---

116. The Michael reaction plays a part in some more extended synthetic sequences of great importance. Analyse TM 116 as an α,β-unsaturated carbonyl compound and continue your analysis by the Michael reaction.

TM 116



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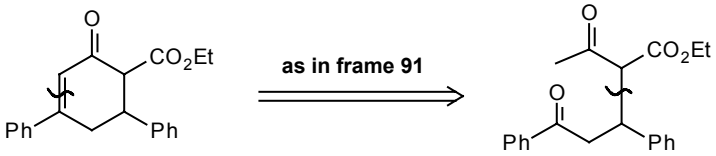
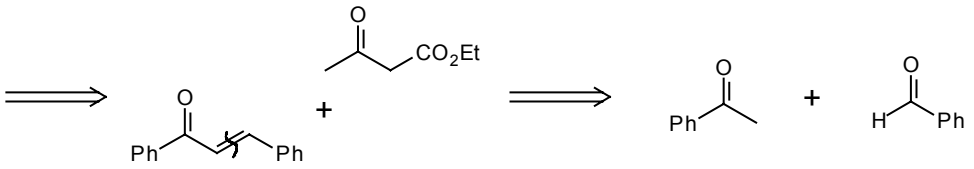
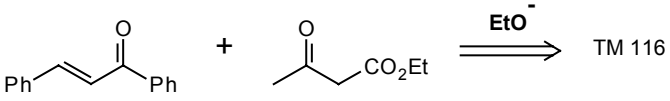
117. Analysis:



We now have a 1,5-dicarbonyl compound with one good disconnection:

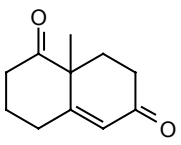


This sequence of Michael reaction and cyclisation is known as tile Robinson annelation since it makes a ring.



Analyse TM 117 in the same way.

TM 117



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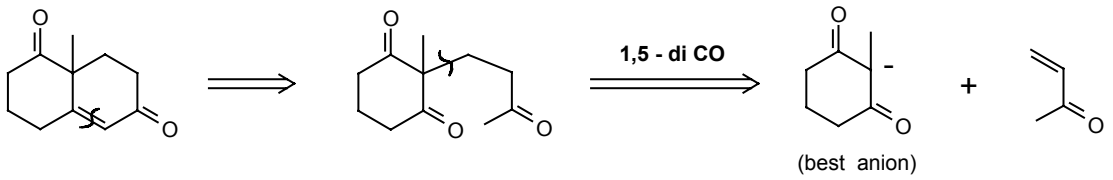
118. Starting as before with the α,β-unsaturated ketone:

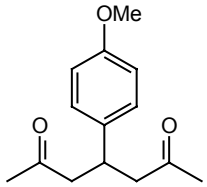


This sequence can be carried out in one or two steps and makes an important molecule for steroid syntheses. Further details are given in Fleming pages 59, 75 and 171 if you are interested.

---

119. If we want to make a simple 1,5-diketone we may have to use an activating group like **CO_2Et** to control the reaction. How would you make TM 119?

TM 119



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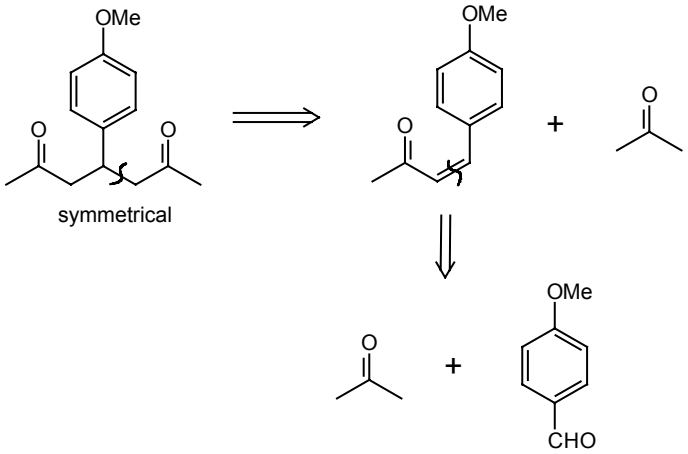
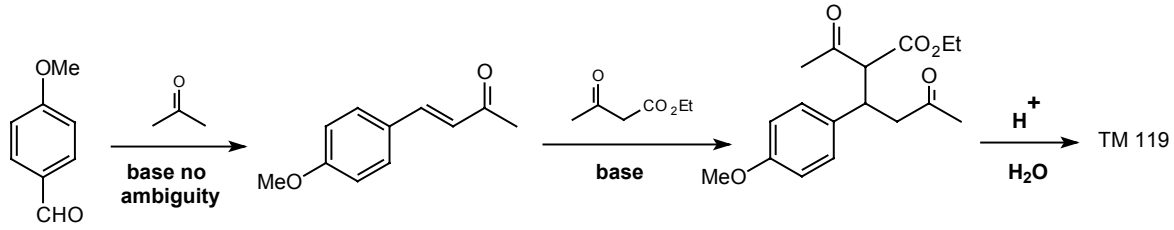
120. Analysis:

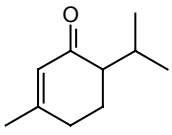


Synthesis: To ensure good yields, the reaction is best done on an activated compound, so the synthesis becomes:



Now what about TM 120?

TM 120



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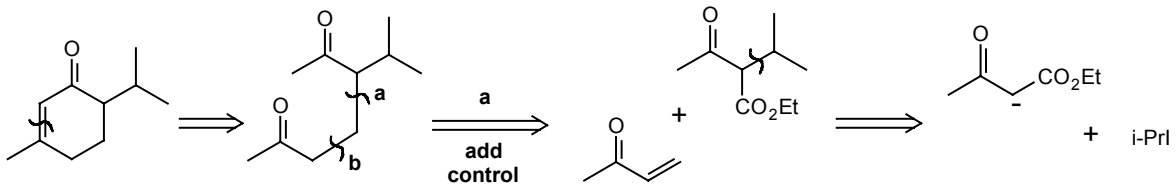
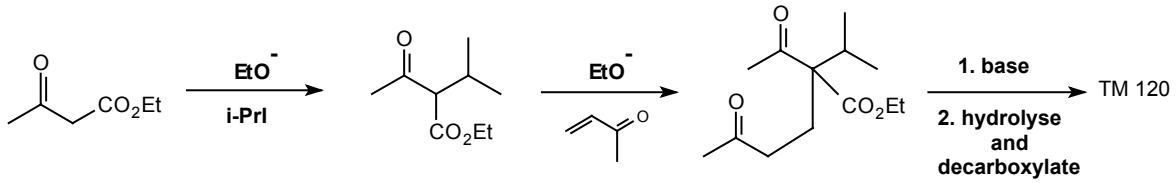
121. Analysis:



Choosing the Michael disconnection at a rather than b since we can then use the **CO_2Et** control group both for the alkylation and for the Michael reaction.

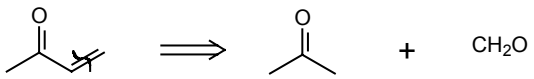
Synthesis:



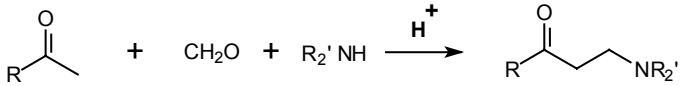
The final condensation could have gone the other way too, but it doesn't, presumably because attack on, the other carbonyl group is hindered. TM 120 is in fact piperitone, one of the flavouring principles of mint, and has been synthesised essentially by this route (J.C.S.,. 1935, 1583; Rec. Trav. Chim., 1964, 83, 464; Zhur. Obshchei Khim., 1964, 34, 3092, Chem. Abs., 1964, 61, 16098).

(a) USE OF THE MANNICH REACTION

122. There is one special case worth discussing in some detail. When vinyl ketones (e.g. TM 122) are needed for Michael reactions they may obviously be made by the usual disconnection;

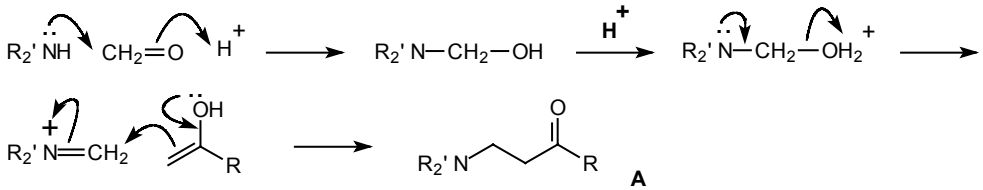


Which gives formaldehyde as one of the starting materials. Base-catalysed reactions with this very reactive aldehyde often give poor yields because of polymerisation and other side reactions. The Mannich reaction is used instead:

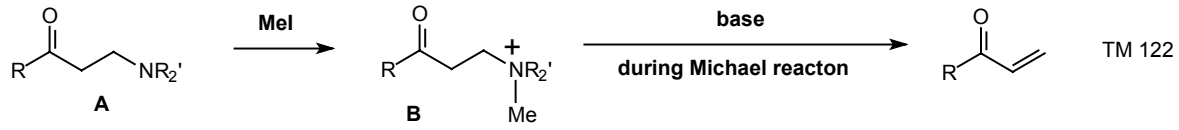


Write a mechanism for this reaction.

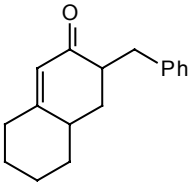
123.



Alkylation of the product (a 'Mannich Base' **A**) gives a compound (B) which gives the required vinyl ketone on elimination in base. This last step is usually carried out in the basic medium of tile Michael reaction itself so that the reactive vinyl ketone (TM 122) need never be isolated.



So how would you make TM 123?



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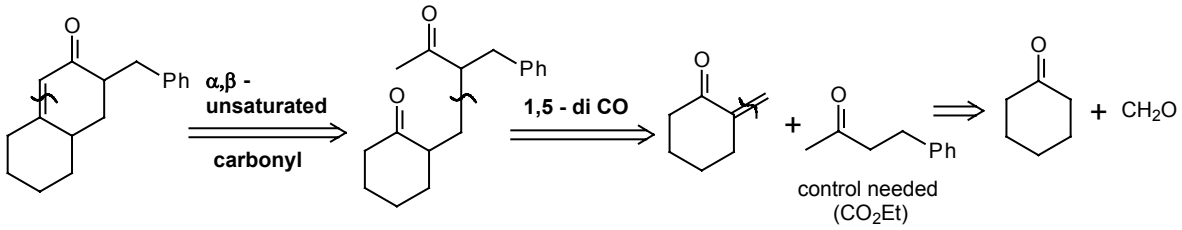
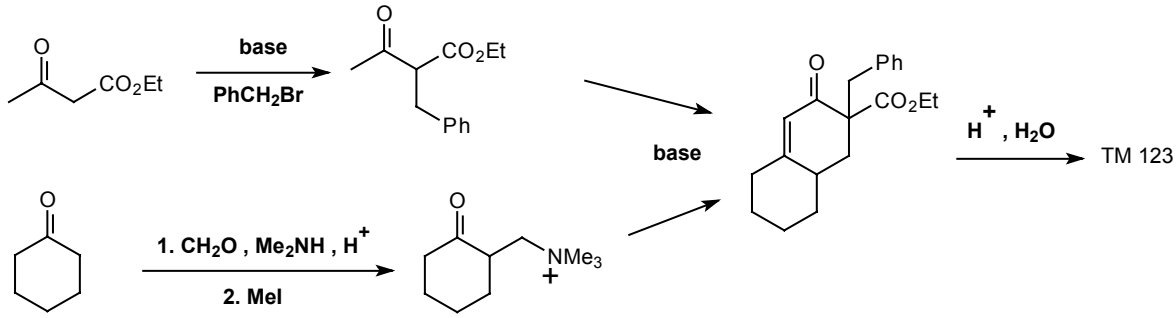
124. Analysis:



Synthesis: J. Amer.Chem. Soc., 1954, 76, 4127.



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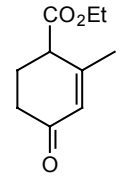
3. REVIEW PROBLEMS

125. Review Problem 9 – Suggest a synthesis of TM 125, a commonly used synthetic intermediate called Hagemann's ester.

TM 125 

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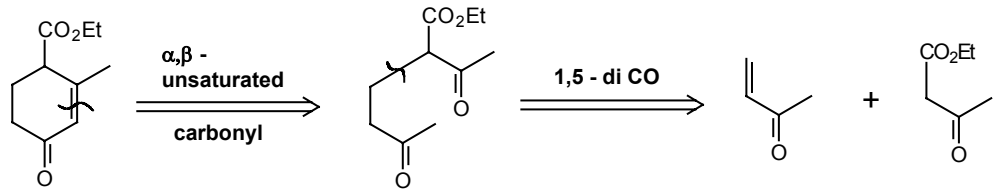
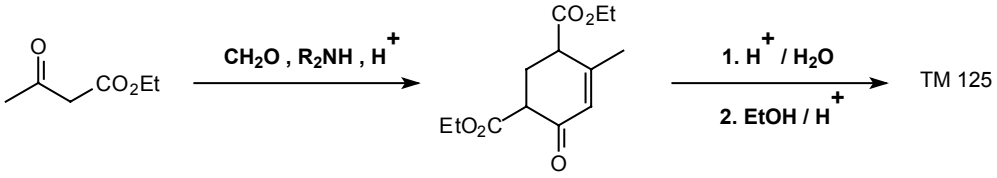
126. Analysis:



Synthesis: Though we could follow the stepwise pattern of the disconnections, it is easier to add an activating group to the acetone molecule so that our starting materials are two molecules of acetoacetate and formaldehyde. It turns out that Hagemann's ester can be made in two steps without having to alkylate the Mannich base:



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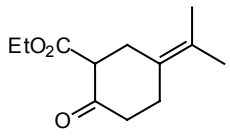
127. Review Problem 10 – Suggest a synthesis for

TM 127 

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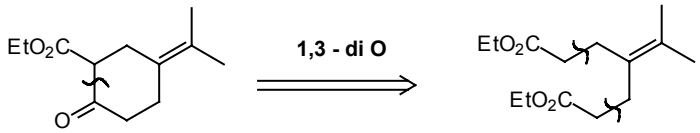
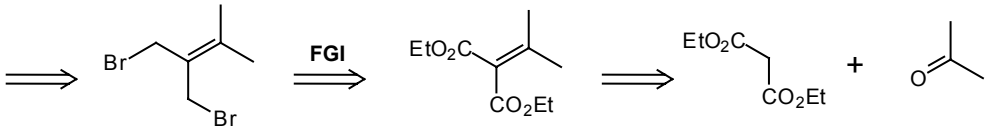
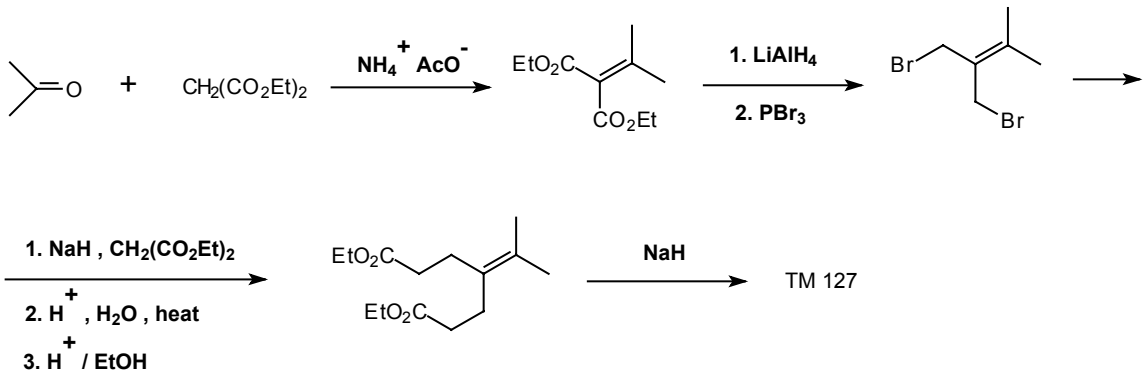
128. Analysls: Disregarding the remote and unhelpful double bond, we can disconnect as a 1,3-dioxygenated compound (frames 94-107).



Now note symmetry. Doubly allylic disconnection keeps symmetry, requires activation (frames 57-8 and 101-2).



Synthesis: actually done like this (Chem. Comm., 1967, 753; 1969, 26):



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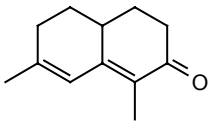
129. Review Problem 11 - suggest a synthesis for TM 129

TM 129 

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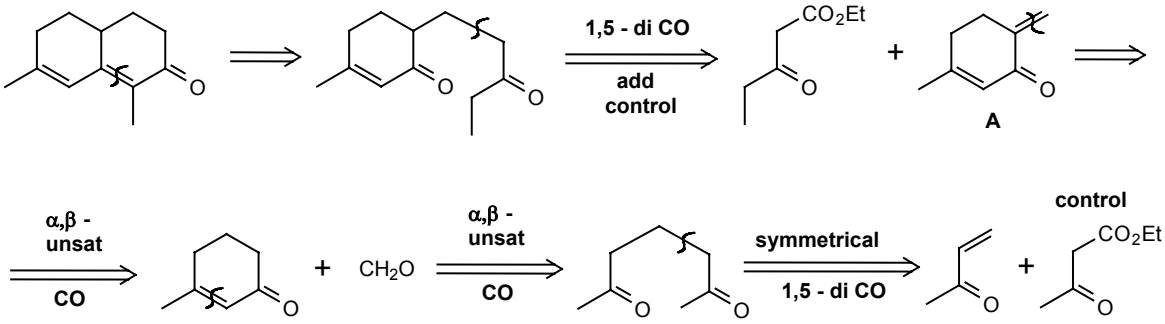
130. Analysis: Treat first as an α,β-unsaturated ketone:



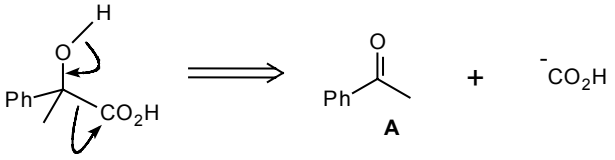
Synthesis: All by standard steps. Though the Michael addition on **A** could in the cry occur at either double bond, the unsubstituted position out of the ring is much more reactive than the disubstituted position in the ring and only the wanted reaction occurs. Bull. Soc. Chim. France, 1955, 8.

D. ILLOGICAL TWO-GROUP DISCONNECTIONS

1. THE 1,2-DIOXYGENATION PATTERN

(a) α-HYDROXY-CARBONYL COMPOUNDS

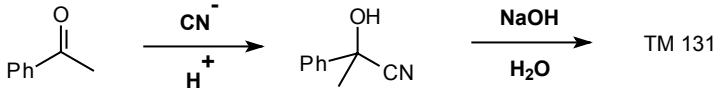
131. So far all our two group disconnections have sensible synthons with anions or cations all stabilised by functional groups in the right positions. This won't always be the case. Supposing we wanted to make the hydroxy-acid TM 131; we could treat it as an alcohol:

TM 131 

but we get the apparently absurd synthon $^{-}\mathbf{CO_2H}$. In fact there is a common reagent for this synthon - a simple one-carbon anion which adds to ketones and whose adduct with **A** could easily be converted into TM 131. What is it?

---

132. Cyanide ion! So the synthesis becomes:



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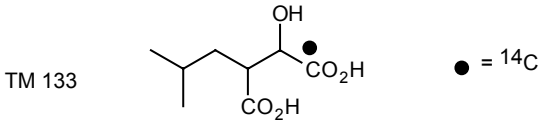
133. The aldehyde or ketone needed for this reaction is not always readily available. TM 133, labelled with radioactive $^{14}\mathbf{C}$ in one carboxyl group, was needed for a biochemical labelling experiment. How would you make it?



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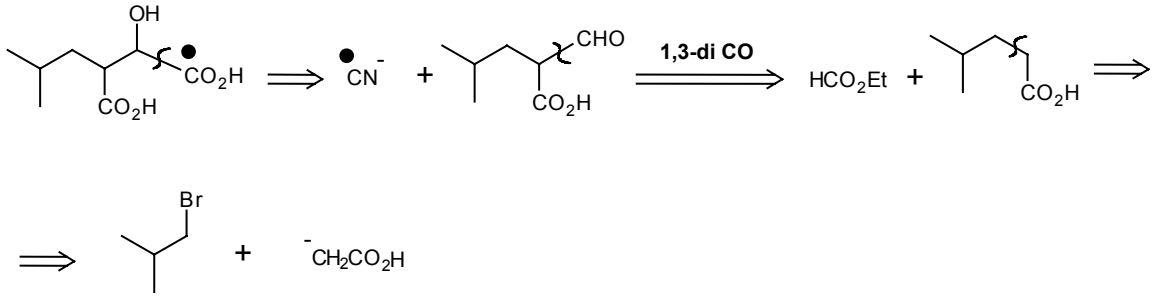
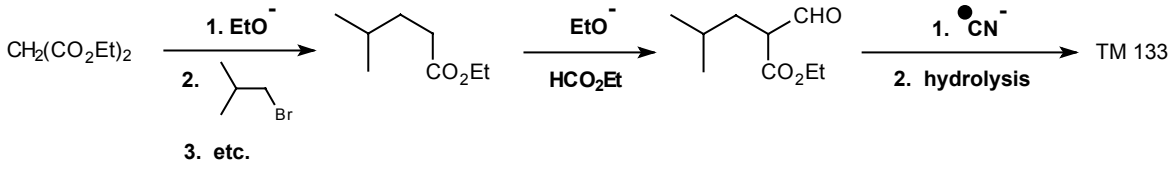
134. Analysis: The α-hydroxy acid can best be made from an aldehyde and $^{14}\mathbf{CN}^{-}$, then we can carry on as usual with a 1,3-dicarbonyl disconnection:



Synthesis: (J. Amer. Chem. Soc., 1976, 98 , 6380; Tetrahedron, 1972, 28, 1995).



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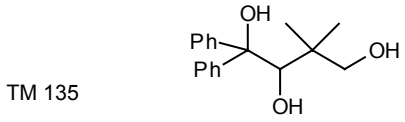
135. Here is a more difficult example based also on α-hydroxy acids. Use the two phenyl groups as a clue for your first disconnetion in designing a synthesis for TM 135:



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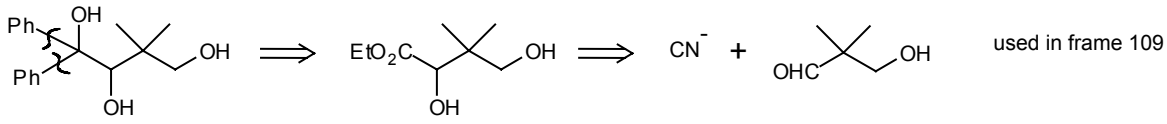
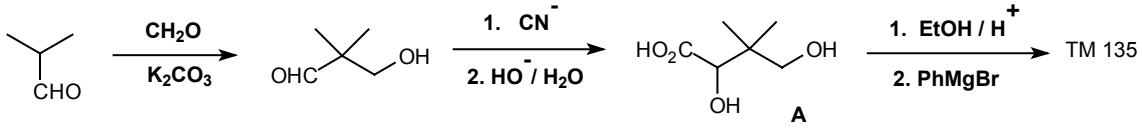
136. Analysis: Using the clue, we remove both phenyl groups to give an ester:



Synthesis:



We can either protect the two hydroxyl groups in **A** as a cyclic acetal or use four mols of **PhMgBr** and waste two of them.

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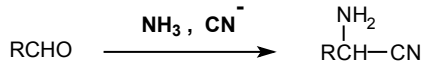
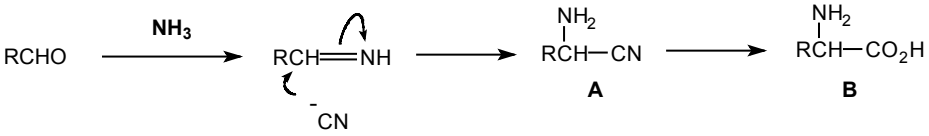
137. A more elaborate variation gives a generell amino acid synthesis. If the reaction between an aldehyde and cyanide is done in the presence of ammonia, the product is an α-amino-nitrile:



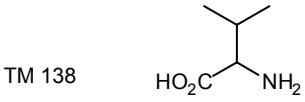
Can you see what intermediate is being trapped by the cyanide ion?

---

138. It must be the imine:



Under the right conditions, hydrolysis of the cyanide **A** occurs during the reaction to give the amino acid **B**. How could you make the amino acid Valine (TM 138)?



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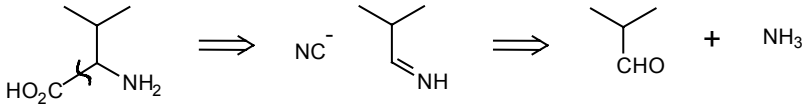
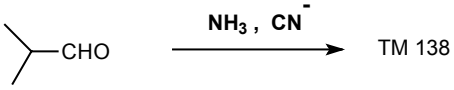
139. Analysis:



Synthesis:



This is the Strecker amino acid synthesis.

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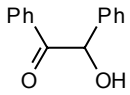
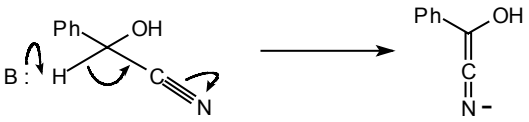
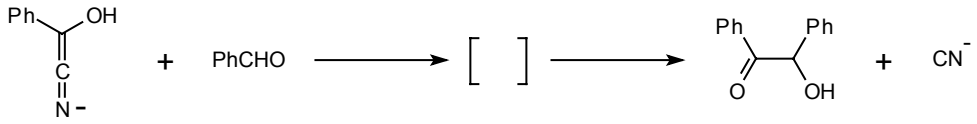
140. Strangely enough, cyanide ion is also involved in one special reaction giving an α-hydroxy-ketone. Can you show how the adduct **A** of' benzaldehyde and cyanide ion can give a stable 'carbanion'?

A 

141.

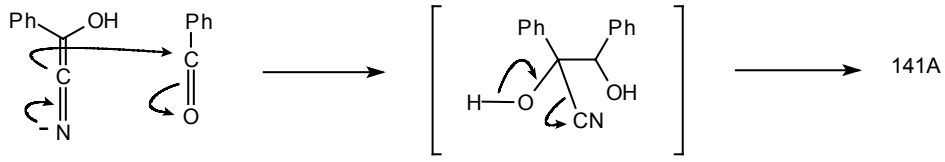


This anion now reacts with another molecule of benzaldehyde to give eventually the α-hydroxy-ketone 141A. Draw mechanisms for these steps:

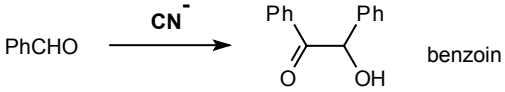


141A

142.



The product is called benzoin and the reaction is known therefore as the benzoin condensation. No base is needed other than cyanide ion.



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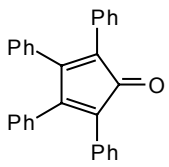
143. How could benzoin be elaborated into the more complex molecule TM 143?

TM 143 

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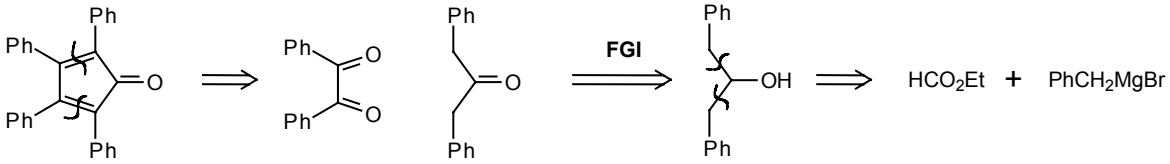
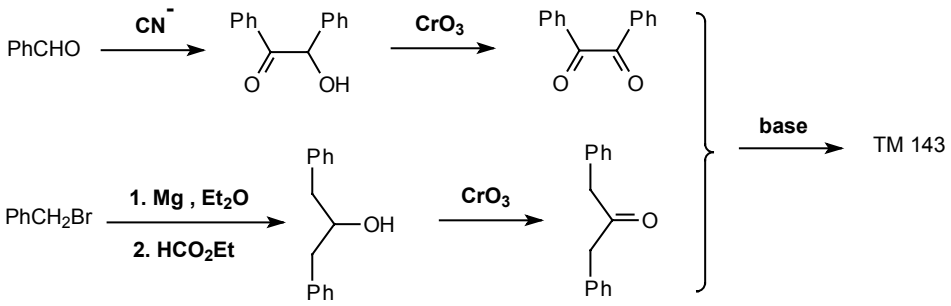
144. Analysis: We can disconnect both the symmetrical α,β-unsaturated carbonyl linkages:

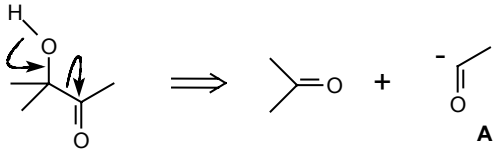


Synthesis:

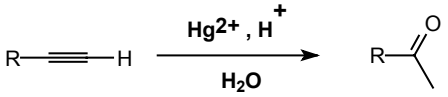


---

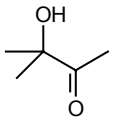
145. The same problem of illogicality arises with other α-hydroxyketones:



Again we need a reagent for an acyl anion synthon (A). We find this in the acetylide ion since substituted acetylenes can be hydrated to ketones:



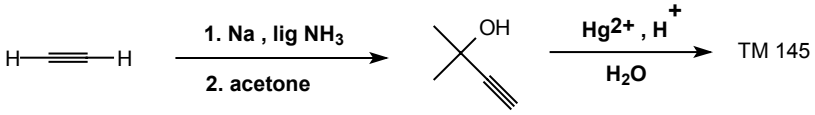
If you want to know more about this reaction, see Norman p.116 or Tedder, vol 1, p.108.

TM 145 

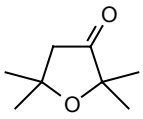
How then could one make TM 145?

---

146. Synthesis:

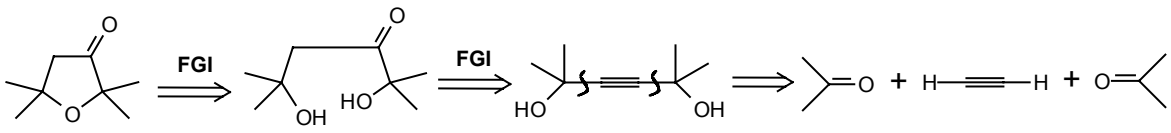


The reaction can be used for disubstituted acetylenes, but it is unambiguous only when they are symmetrical. Suggest a synthesis for TM 146.

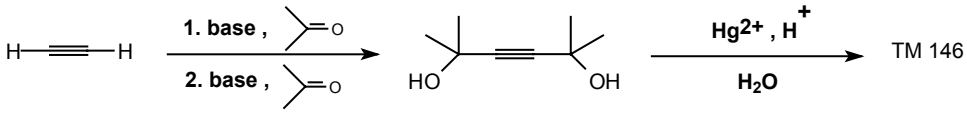
TM 146 

---

147. Analysis: The cyclic ether is obviously made from a diol, and that gives us a 1,2-dioxygenated skeleton of the right kind:



Synthesis: We need the symmetrical double adduct from acetone and acetylene.



The ether forms spontaneously from the tertiary alcohols in acid.

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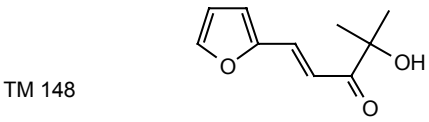
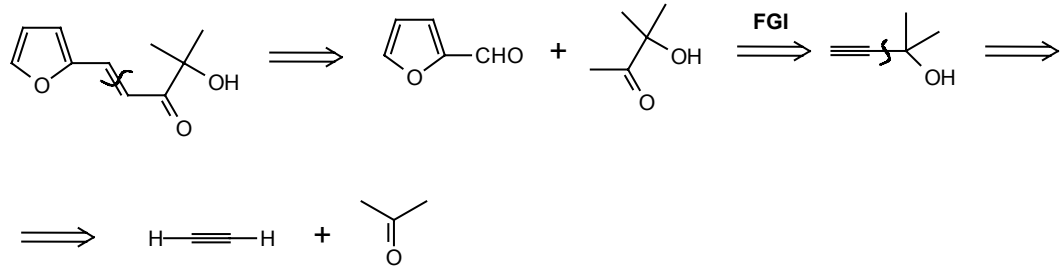
148. α-Hydroxy ketones take part in condensation reactions too. How would you make TM 148?

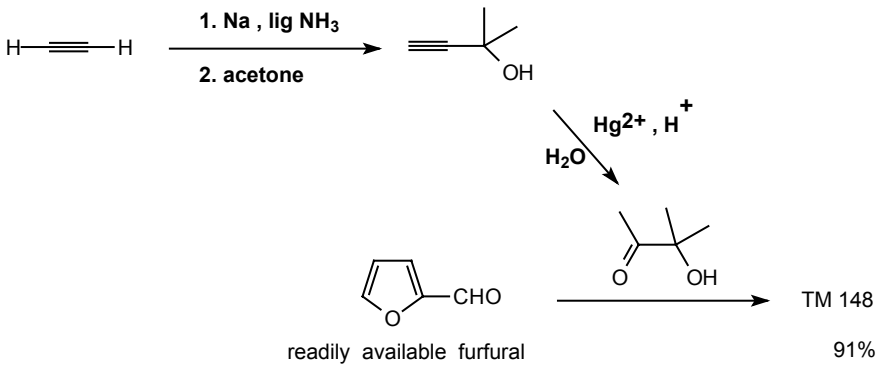


---

149. Analysis: Start with the α,β-unsaturated relationship as the alternative (the **1,2-di O**) is no good at the start. After the first disconnection we have a methyl ketone which can come from an acetylene:

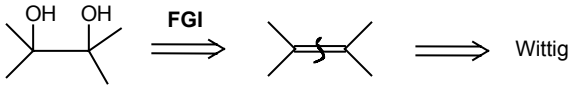


Synthesis: (Ber. , 1922, 55, 2903 for the later stages).

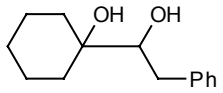


(b) 1,2 -DIOLS

150. A good approach to 1,2-diols is hydroxylation of an olefin with reagents such as **OsO_4** or **$KMnO_4$**. The olefin can be made by the Wittig reaction so the disconnections arc:



How could you make this diol (TM150)?

TM 150 

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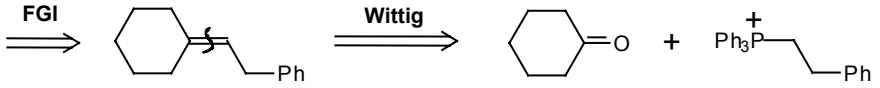
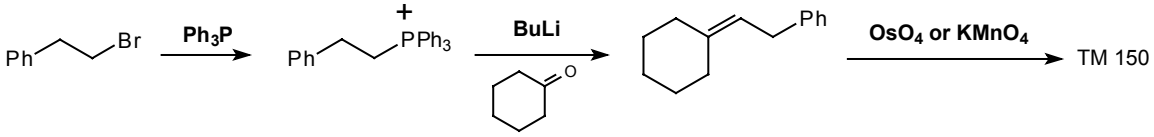
151. Analysis: Back to the olefin - either Wittig is possible but one pair of starting materials is more readily available:



Synthesis



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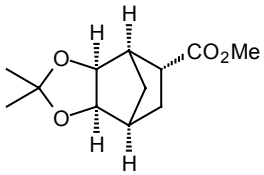
152. This hydroxylation gives cis addition to the double bond (see Norman p.502-3 or Tedder vol. 1, p.61-2 if you're not sure about this). How then could you make TM 152?

TM 152 

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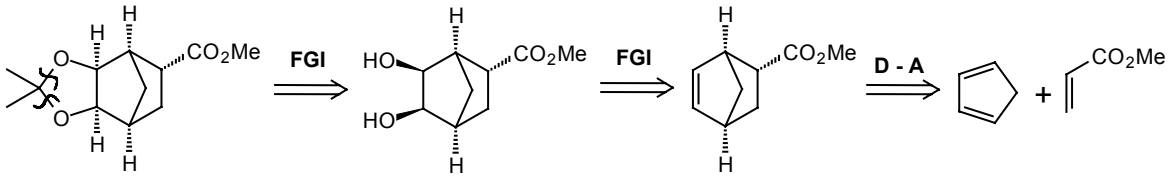
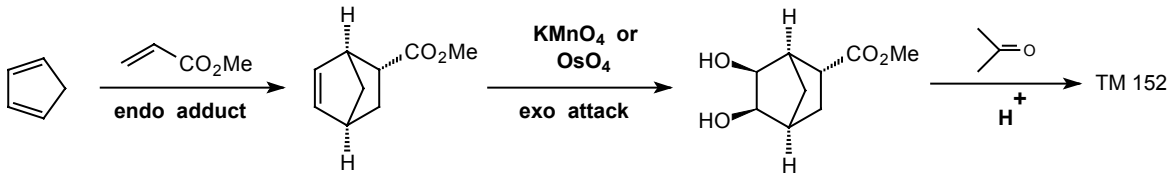
153. Analysis: The acetal FG had better be removed first:



Synthesis: Assuming the usual stereoselectivity for the Diels-Alder reaction and for the hydroxylation:



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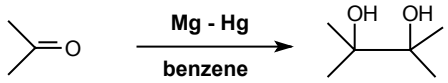
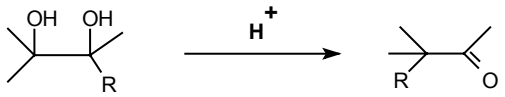
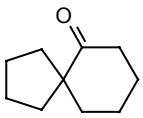
154. Symmetrical diols can be made by a radical reaction. Radical reactions are rarely much use in carbon-carbon bond formation as they often give poor yields and many products They are of course useful in some FGI reactions in things like allylic bromination and in functionalising remote carbon atoms. If you want to read more about this see Tedder, Part 2, Chapter 11 or Carruthers, Chapter 4. One useful radical reaction is the pinacol reduction:



The disconnection is obvious, and gives us one way of making symmetrical 1,2-diols. What makes it more than trivial is that the products undergo the pinacol rearrangement:



(see Tedder, Part 2, pp. 112-118, Norman, p.438-440 if you aren't familiar with this reaction). How could you use this route to make TM 154?

TM 154 

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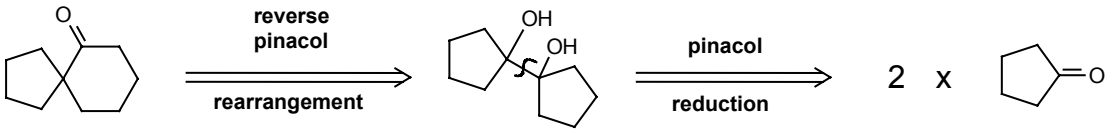
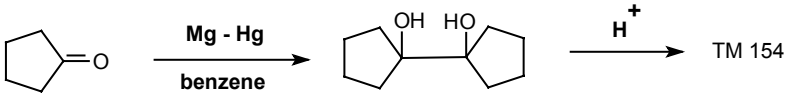
155. Analysis: This is a t-alkyl ketone so a pinacol rearrangement route will be possible:



Synthesis: Since the pinacol is symmetrical, there is no ambiguity.



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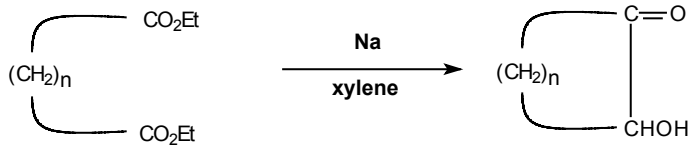
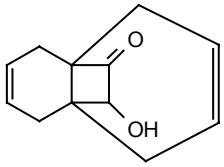
156. A closely allied reductive linking of carbonyl groups is an intramolecular version with esters, called the acyloin reaction, which again gives a 1,2-dioxygenated skeleton:



(details of the mechanism appear in Tedder, Part 3, p.193-4, or Norman, p.486-7). How could you make TM 156?

TM 156



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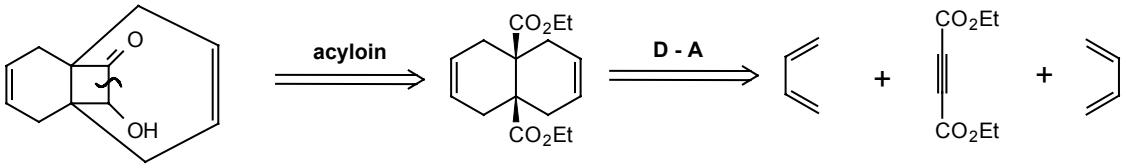
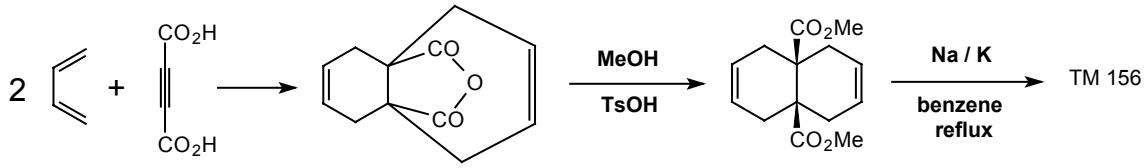
157. Analysis: First disconnect the acyloin product and the result is clearly made by **D-As**.

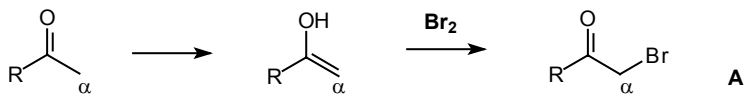


Synthesis: The conditions actually used were (J. Org. Chem., 1966, 31, 2017):



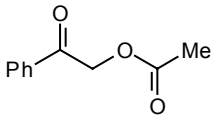
(c) 'ILLOGICAL' ELECTROPHILES

158. So far we have used 'illogical' nucleophiles and special methods to got round the difficulty of making 1,2-dioxygenated compounds. Another approach is obviously to use an 'illogicial' electrophile and among the most important of these are α-halo-carbonyl compounds. We can make these easily from carbonyl compounds by halogenation of the enol (sea frames 198-207 of the Carbonyl Programme).



A

The enol is nucleophilic at the α carbon atom but the α-bromoketone **A** is electrophilie at the a carbon atom: by halogenation we have inverted the natural polarity of the molecule. How could you make TM 158?

TM 158 

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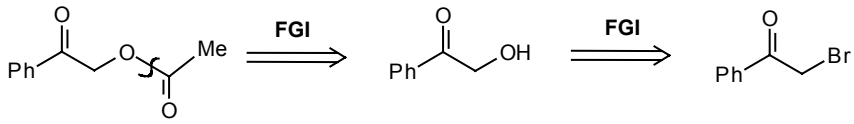
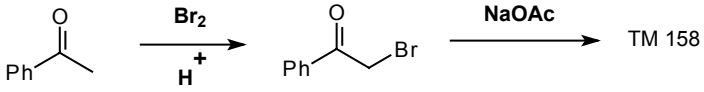
159. Analysis: As usual remove the ester first:



Synthesis: Since α-halo-carbonyl compounds are very reactive electrophiles, we can use a short cut:



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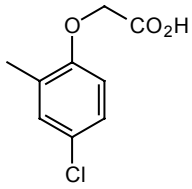
160. The hormone weed-killer MGPA (TM 160) is needed in large quantities. Suggest an economical synthesis for it.

TM 160 

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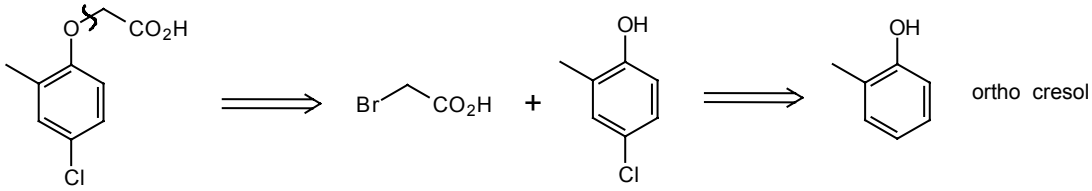
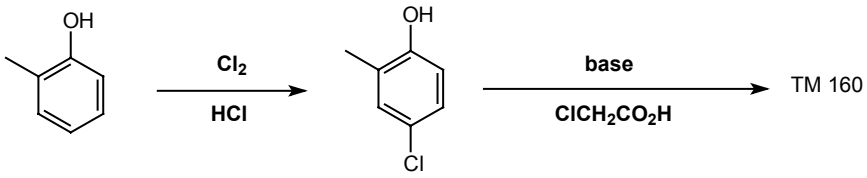
161. Analysis: The ether linkage can be disconnected directly on the alkyl side:



Synthesis: Chlorine is the cheapest of the halogens, so it will be better to use chloroacetic acid:



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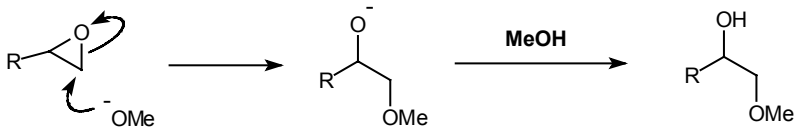
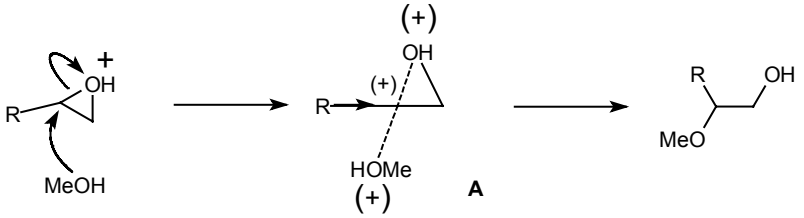
162. The other main illogical electrophiles are epoxides, easily made from an olefin and a per-acid, the usual one being m-chloroperbenzoic acid (**MCPBA**) a commercial product. A more detailed explanation comes later, in frames 276-7.

What product would you get from this and sodium methoxide in methanol?

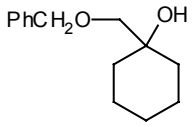
163.



In acid solution, the other regio isomer would be formed because the transition state (163A) has a partial positive change on carbon stabilised by **R**:

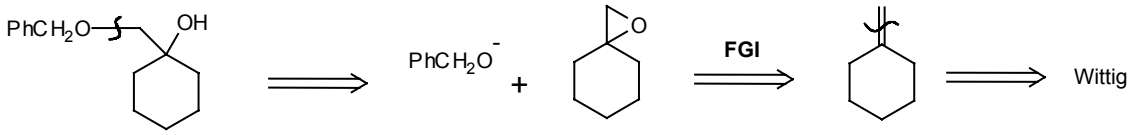


How would you make TM 163 from simple starting materials?

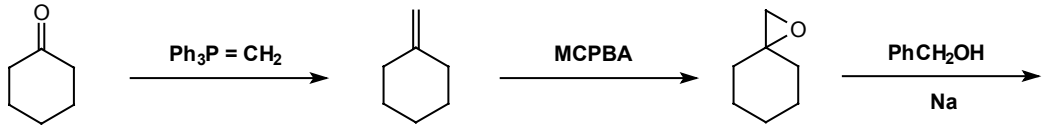


TM 163

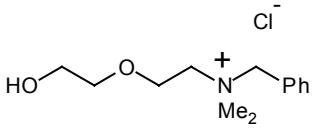
164. Analysis: This is the substitution pattern for a base-catalysed epoxide opening:



Synthesis:

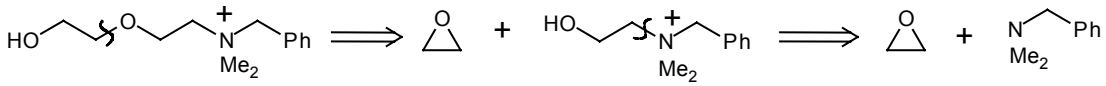


165. Amines also react with epoxides at the less substituted carbon atom. As a slightly more testing problem, suggest a synthesis of the alcohol (TM 165) whose derivatives are used in disinfectants ("phemeride" etc.).

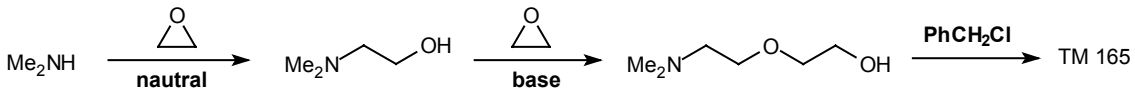


TM 165

166. Analysis: There is a series of 1,2 relationships here: it's easiest to start with the free hydroxyl group:



Synthesis: It might be better to add the benzyl group at the end so that we can use dimethylamine.

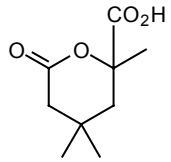


In base the **OH** becomes $\mathbf{O^-}$ and is more nuclecphilic than **N**. In neutral solution **N** is more nucleophilic than **OH**.

(d) REVIEW PROBLEMS

167. Review Problem 12: Suggest a synthesis of the lactone acid TM 167.

TM 167



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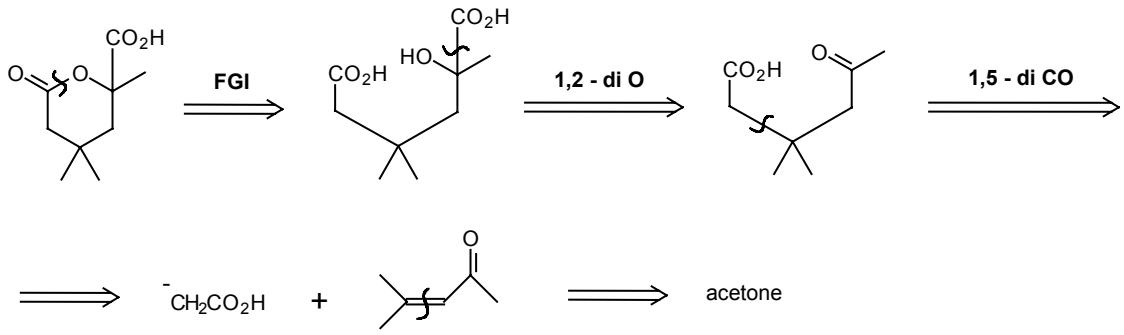
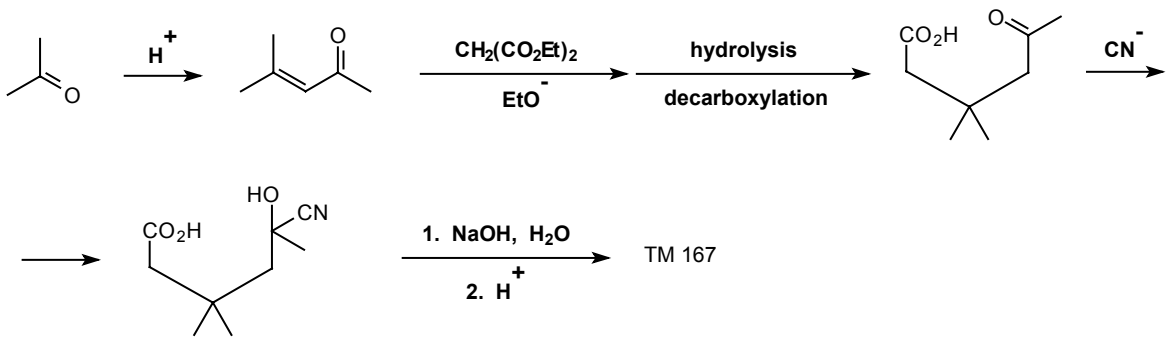
168. Analysis: Opening the lactone reveals 1,2-, a 1,5-, and a 1,6- di-oxygenation relationships. We must tackle the 1,2 first:



Synthesis: The first stages are well known and the two methyl groups assist the final cyclisation:



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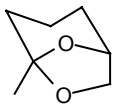
169. Review Problem 13: This odd looking molecule (TM 169) is closely related to multistriatin, a phenomone of the elm bark beetle, the insect which spreads Dutch elm disease. How would you synthesise a sample for testing on the beetle?

TM 169 

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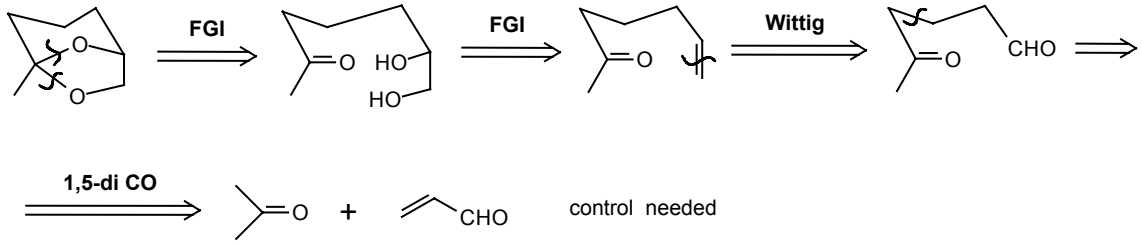
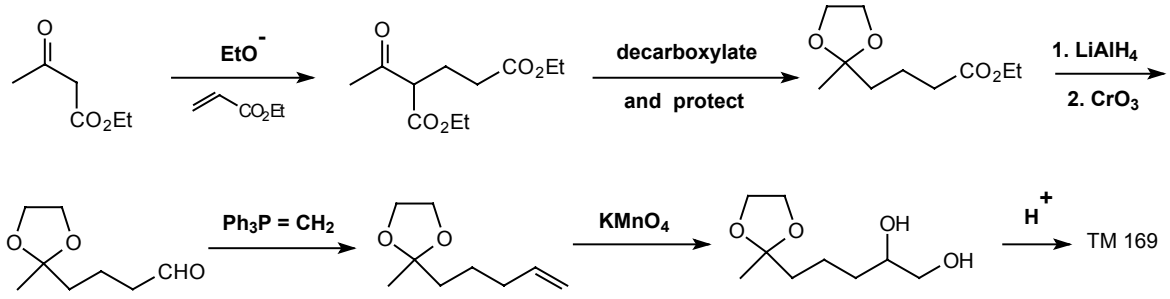
170. Analysis: The functional group is an acetal – once we've removed this, we can follow straightforward tactics.



Synthesis: We must be able to do a Wittig reaction on the aldehyde but not on the ketone, so we must protect the ketone: therefore add the aldehyde as an ester (there are many other solutions).



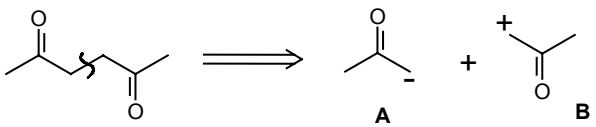
Cyclisation occurs by trans-acetalisation.

---

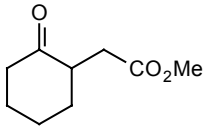
2. THE 1,4-DIOXYGENATION PATTERN

(a) 1,4-DICARBONYL COMPOUNDS

171. The obvious disconnection on a 1,4-dicarbonyl compound gives us a logical nucleophilic synthon (an enolate anion) **A** but an 'illogical' electrophilic synthon **B**:



We need for B a derivative of a ketone in which the normal polarity is inverted, and you will realise from frames 158-161 that the α-halo carbonyl compound is ideal. So how would you make TM 171?

TM 171 

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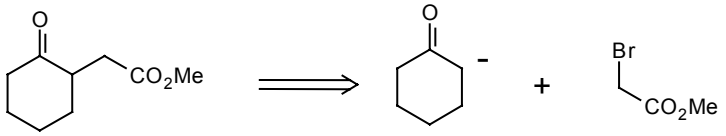
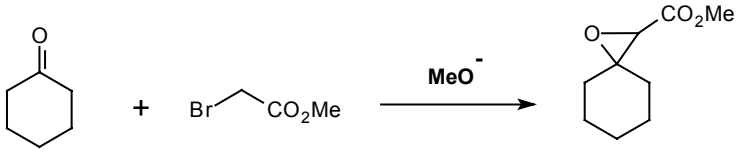
172. Analysis: Either way round will do, so let's arbitrarily chose ketone and α-halo ester:



Synthesis: Our problems are not yet over because if we combine ketone and α-halo ester in base, quite a different reaction occurs. Can you draw a mechanism for it?



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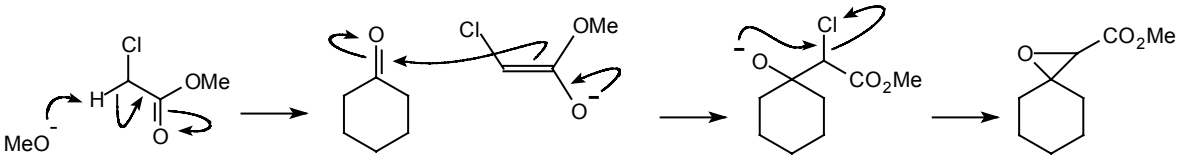
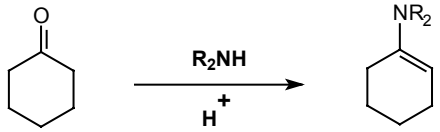
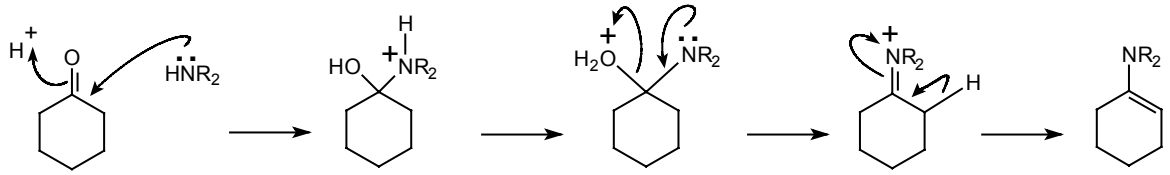
173. The most acidic proton is that next to the ester and the halide:



This, the Darzens reaction, is useful in other circumstances (frames 280-1) but a nuisance here. We must use some means to make the ketone act as the nucleophile in the initial condensation. One effective way is to convert it into an enamine. Draw a mechanism for this reaction.



174.



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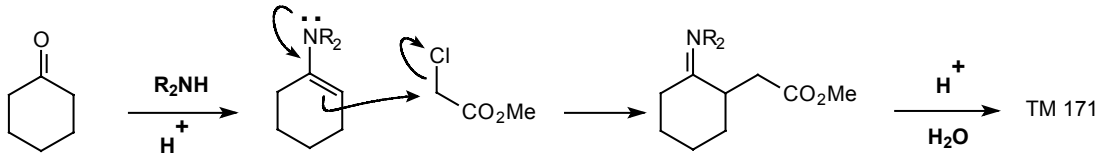
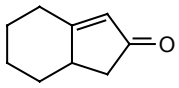
175. The complete synthesis of TM 171 now becomes:



The enamine attacks the reactive α-carbonyl halide rather than the carbonyl group itself. How could you make TM 175?

TM 175 

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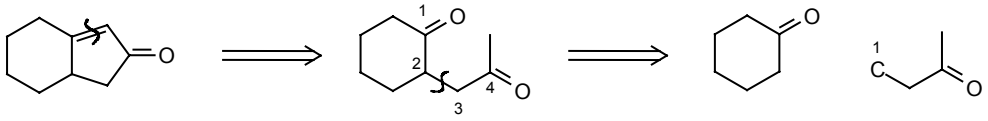
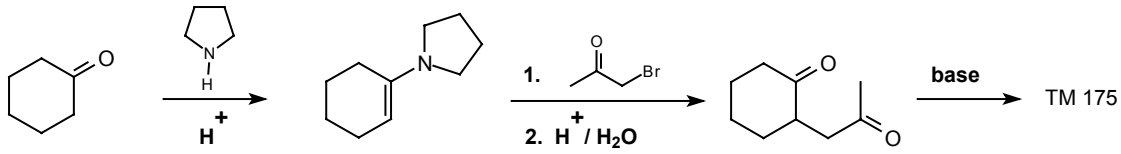
176. Analysis: Starting with the α,β-unsaturated ketone, we then have a 1,4-di ketone so we shall have to use our new method.



Synthesis: Actually done this way (J. Amer. Chem. Soc., 1958, 80, 6609):



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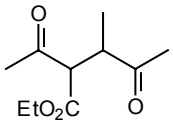
177. Enamines are not always necessary - sometimes the enolate anion is stable enough by itself. How would you make TM 177?

TM 177 

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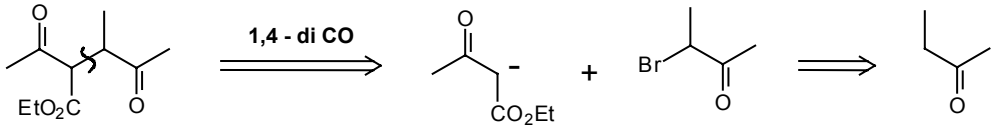
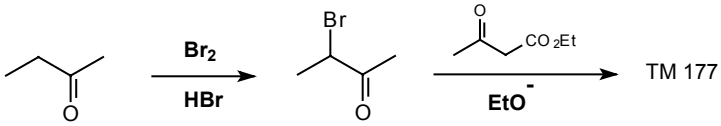
178. Analysis: The activating group gives us a guide:

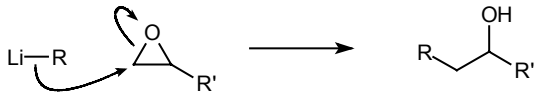


Synthesis: Bromination of butanone in acid gives predominantly the isomer we want, (see frames 198-201 of the Carbonyl Programme) and again the reactive α-carbonyl halide is a good electrophile:

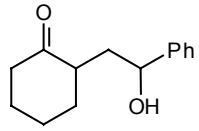


(b) γ-HYDROXY CARBONYL COMPOUNDS

179. The α-halo carbonyl compounds are reagents for the synthon $^{+}$**C-C=O**. At a lower oxidation level, epoxides are reagents for the synthons $^{+}$**C-C=O** as in their reaction with Grignard or organolithium reagents (see also frames 162-6).



How might you synthesise TM 179?



TM 179

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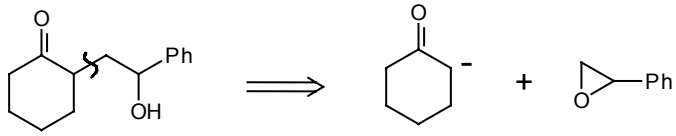
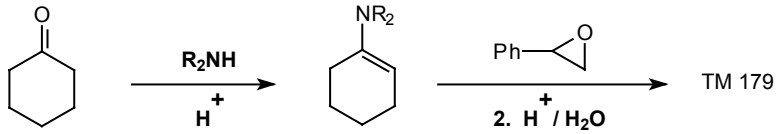
180. Analysis:



Synthesis: Again the enamine can be used to provide the enolate synthon:



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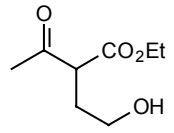
181. One particular sequence under this general heading is rather important. How would you make TM 181?



TM 181

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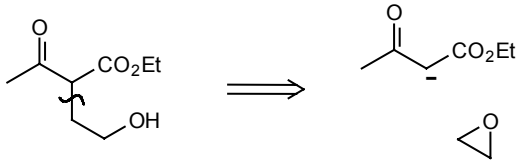
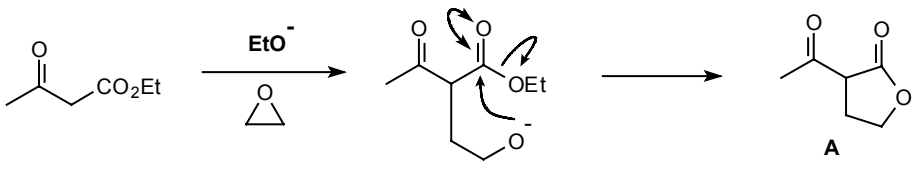
182. Analysis: The usual disconnection gives a stable anion:



Synthesis: In fact this combination of reagents doesn't give TM 181: instead the lactone 182A is formed. This lactone is useful in all the reactions for which we might plan to use TM 181.



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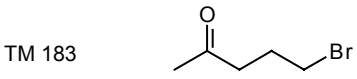
183. How then would you make the γ-halo ketone TM 183?



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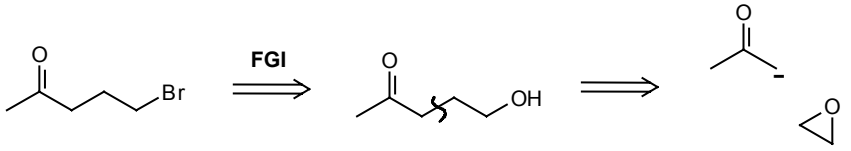
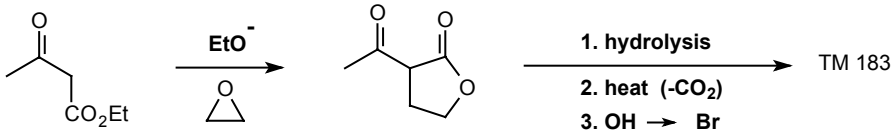
184. Analysis: The normal FGI gives the alcohol, and disconnetion of this in the usual way gives:



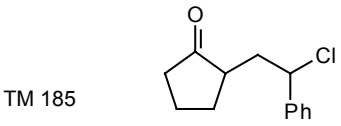
Synthesis: Using **CO_2Et** as the activating group:



It turns out that the last three steps can be accomplished simply by boiling with conc. **HBr**.

---

185. How would you make this γ-halo ketone?



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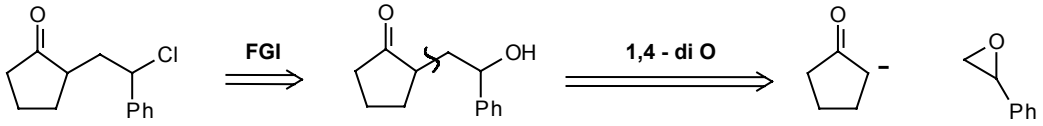
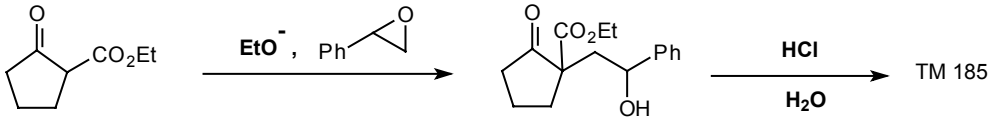
186 . Analysis:

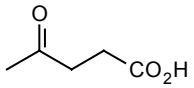


Synthesis: We shall need an activating group, and our starting material is actually TM 104!



(c) OTHER 'ILLOGICAL' SYNTHONS

187. Clearly other combinations of logical and illogical synthons could be used to make 1,4-dioxygenated compounds. How could you use cyanide ion (as the $^{-}\mathbf{CO_2H}$ synthon) to make a γ-keto acid such as

TM 187 

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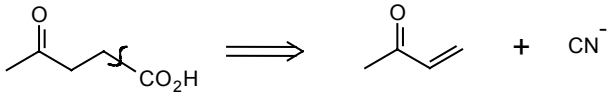
188. All we have to find is the electrophile:



How could you, make the same acid using prepargyl bromide $\mathbf{BrCH_2C{\equiv}CH}$ as your illogicaI fragment?

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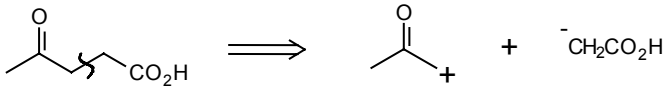
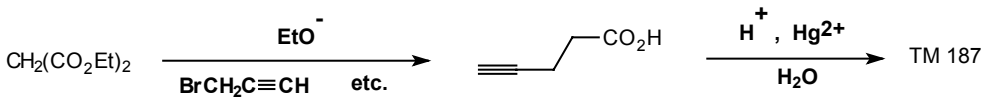
189. Acetylenes can be hydrated to give ketones (frame l45) so propargyl bromide must provide a $\mathbf{MeCOCH_2^+}$ synthon:



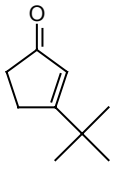
Synthesis: Activation will be needed:



You will meet other combinations of logical and illogical synthons in review problems later.

(d) REVIEW PROBLEMS

190. Review Problem 14: Cyclopentenones (e.g. TM 190) occur in nature and are important in prostaglandin synthesis. How would you make this one?

TM 190 

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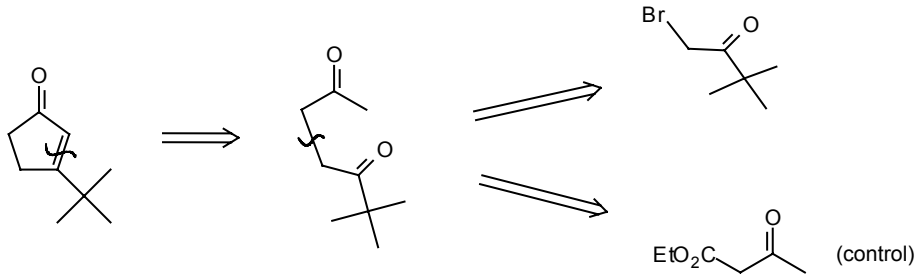
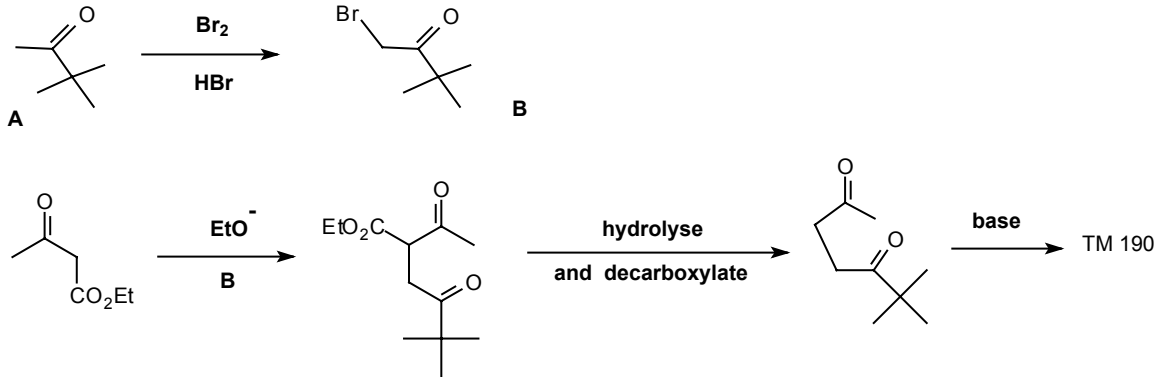
191. Analysis: Start with the α,β-unsaturated carbonyl:



Synthesis: Ketone **A** is just pinacolone, the product of the pinacol rearrangement (frames 154-5).



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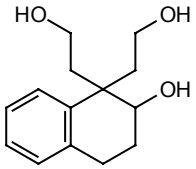
192. Review Problem 15: This triol (TM l92) can be taken as a 1,4- or a 1,5-dioxygenated compound. In fact only one of these will work. Suggest a synthesis.

TM 192



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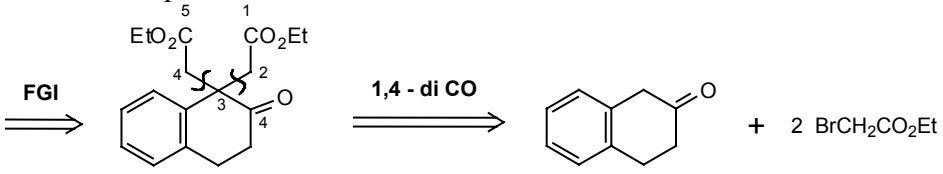
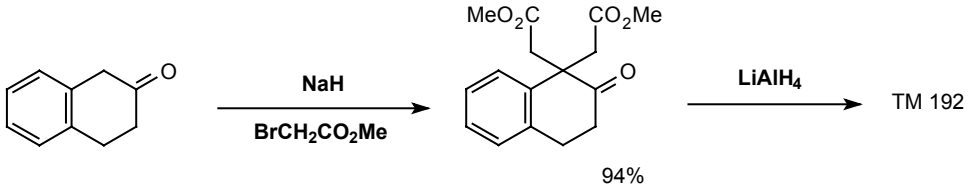
193. Analysis: We must go back to the corresponding tricarbonyl compound, writing **CHO** or **CO_2Et** for **CH_2OH**. Then we see that the 1,5-dicarbonyl relationship is no use as there isn't room for a double bond (e.g. 3-4) in the precursor we would have to write. We have to use the 1,4 relationships:



Synthesis: The ketone will enolise on the side we want because of conjugation with the benzene ring. It turns out that both alkylations happen at once:

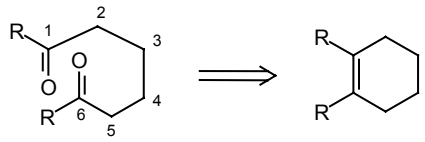


The first reaction was involved in a synthesis of morphine, the starting ketone being made by reduction of a substituted naphthalene (J. Amer. Chem. Soc., 1950, 72, 3704). No doubt an epoxide could have been used as the electrophile.

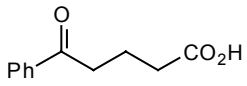
---

3. 1,6-DICARBONYL COMPOUNDS

194. Clearly, these too will be 'illogical disconnections' but we can get round the problem in a different way by using a 'disconnection' which actually links up the two carbonyl groups:



Try this for TM 194, analysing its synthesis back to simple starting materials.

TM 194 

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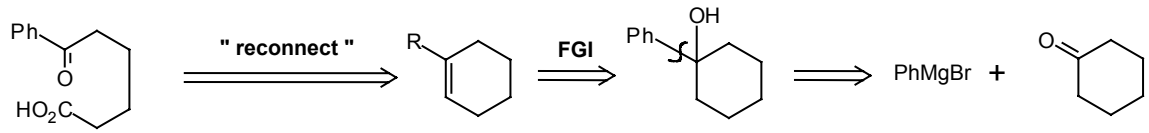
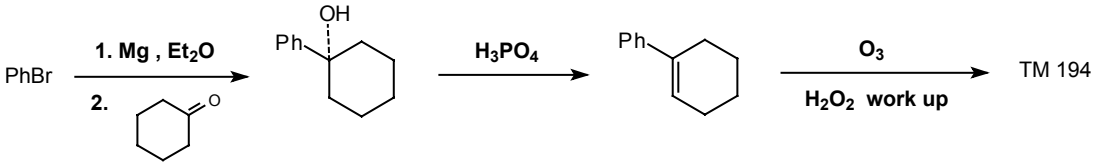
195. Analysis:



Synthesis:



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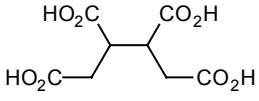
196. Since cyclohexenes can also be made by the Diels-Alder reaction (frames 5-8) we have access to a wide range of 1,6-dicarbonyl compounds. How about TM 196?

TM 196 

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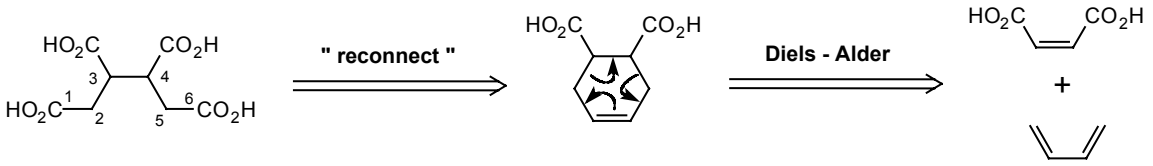
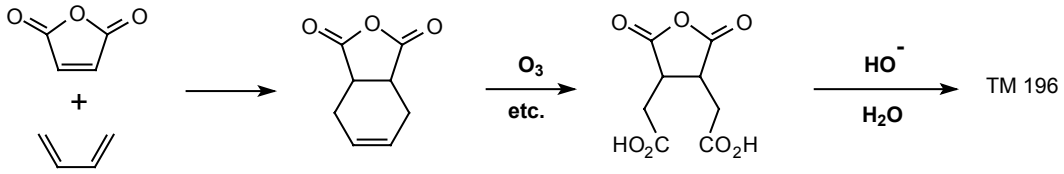
197. Analysis: Choosing the 1,6-dicarbonyl relationship first:



Synthesis: Maleic auhydride is the best reagent.



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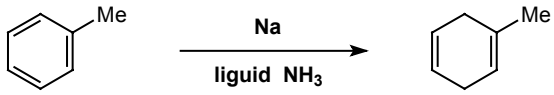
198. Another way to make cyclohexenes is by the partial reduction of benzene rings ('Birch reduction', described in Norman, p.553-557) such as:



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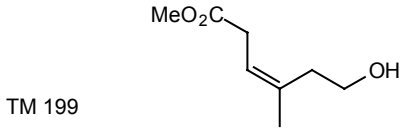
199. With that clue, how would you make:



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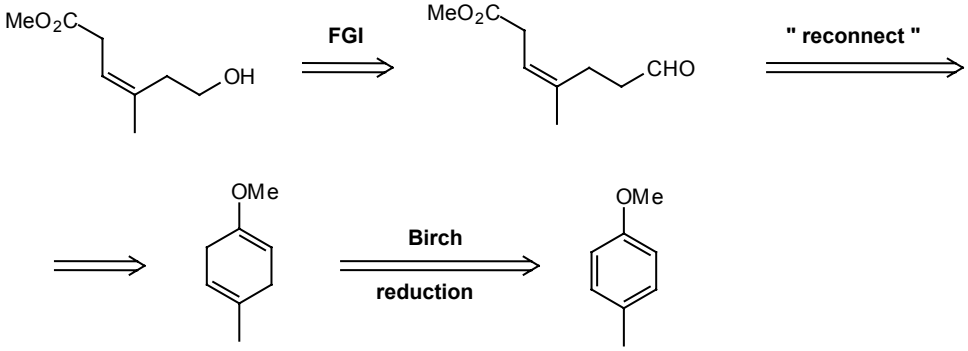
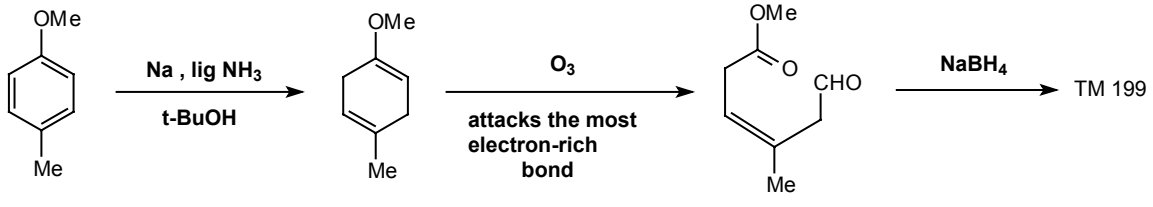
200. Analysis: First convert the 1,6-dioxygenated compound to a 1,6-dicarbonyl compound, keeping the two carbonyl groups different:



Synthesis: (E.J.Corey et al., J. Amer. Chem. Soc., 1968, 80, 5618).



Note that the sterochemistry of the remaining double bond must be right as it has come from a ring.

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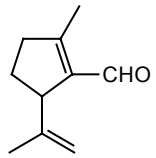
201. Disconnection of other combinations of functional groups can lead us back to a 1,6-dicarbonyl compound. Try this on TM 201.

TM 201 

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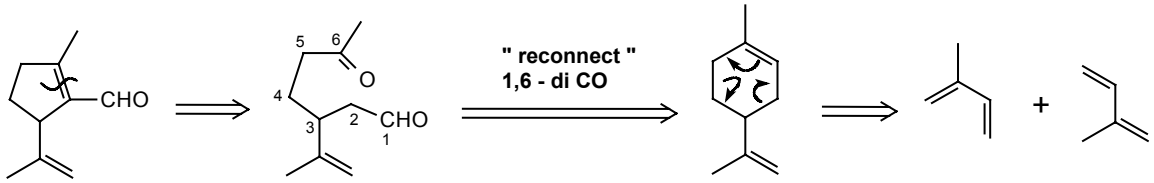
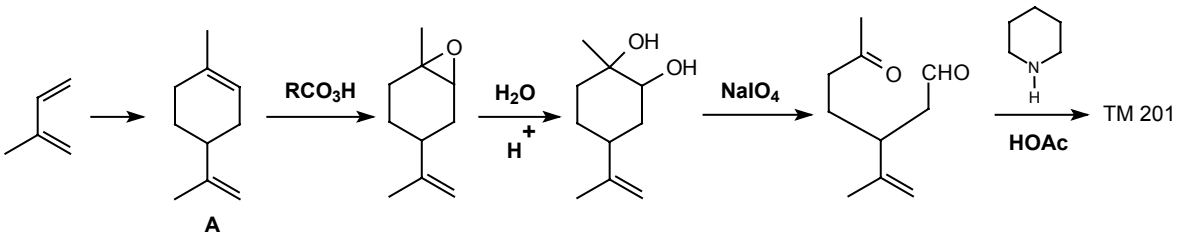
202. Analysis: Taking the α,β-unsaturated aldehyde first:



Synthesis: The Diels-Alder reaction is simply the dimerisation of isoprene to give the naturally occurring terpene **A**. Now we have to cleave one double bond and leave the other alone. It turns out that epoxidation is selective in this case.



The condensation conditions must be as mild as possible, because we want to get only the most stable of the three possible enols (from the aldehyde). Though you could not have predicted the exact conditions either for the double bond .cleavage or for the condensation, you should have seen that control was possible as in each case the two functional groups are different enough. (J. Amer. Chem. Soc., l960, 82, 636; J. Org. Chem., 1964, 29, 3740; Tetrahedron Letters, 1965, 4097).

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4. REVIEW SECTION. SYNTHESIS OF LACTONES

(This section may be worked now, or at any later stage for revision).

203. We have now considered all the simple two-group disconnections and you should be able to design reasonable syntheses for most small molecules. As a set of review problems, try to design good syntheses for these lactones. In each case only one or two answers are suggested, but others will be as good. Discuss your answers with someone else if they are substantially different from the suggestions.

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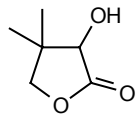
204. Review Problem 16: Design a synthesis for TM 204, an intermediate in Khorana's Coenzyme A Synthesis, J. Amer. Chem. Soc., 1961, 83, 663.

TM 204 

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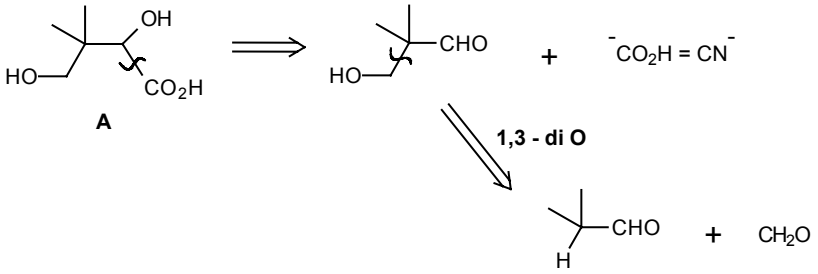
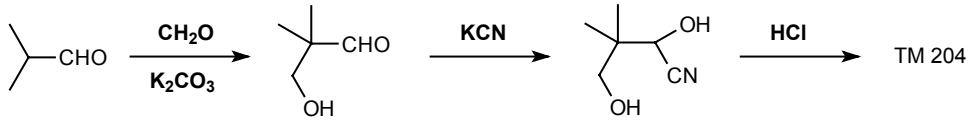
205. Analysis: First open the lactone to reveal the true target.



Synthesis: A mild base must be used to avoid the Cannizzaro reaction. The hydroxy acid **A** cannot be isolated and cyclises spontaneously. (Fleming p.92).



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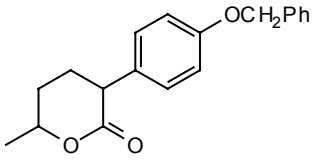
206. Review Problem 17: Design a synthesis for TM 206, an intermediate in Crandall and Lewton's biogenetically patterned synthesis of cedrene (J. Amer. Chem. Soc., 1969, 91, 2127).

TM 206 

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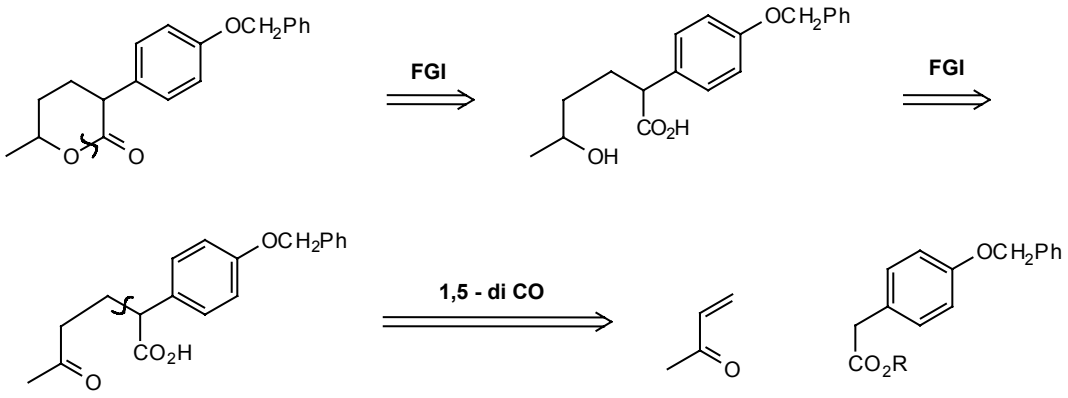
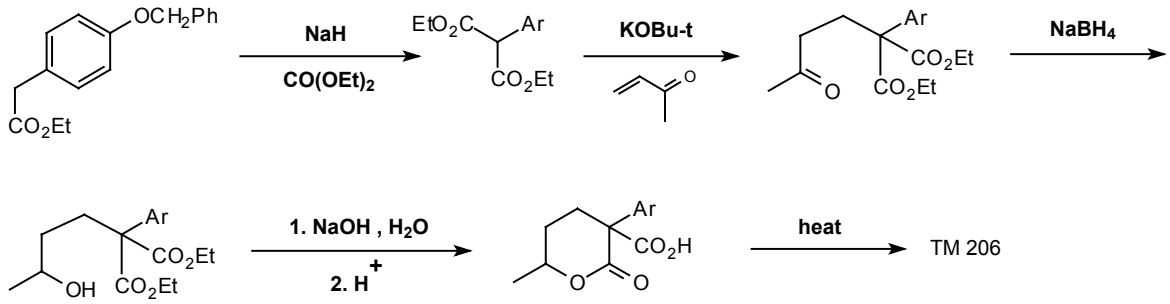
207. Analysis: This is a 1,5-dioxygenated skeleton, therefore further FGI is necessary to give a 1,5-dicarbonyl compound.



Synthesis: An activating group is necessary to control the Michael reaction:



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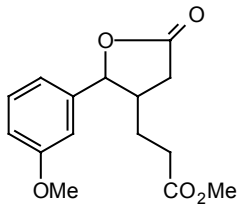
208. Review Problem 18: Design a synthesis for TM 208, an intermediate in Woodward's tetracycline synthesis (Pure and Applied Chemistry, 1963, 6, 651, J. Amer. Chem. Soc., 1968, 90, 439).

TM 208



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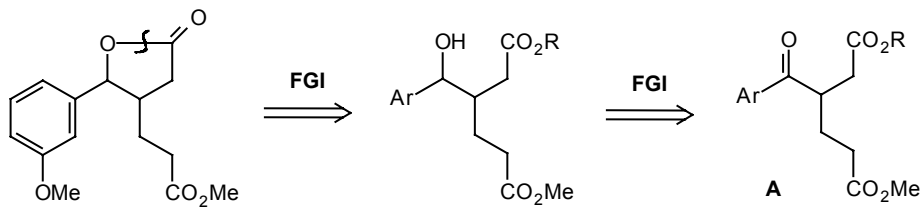
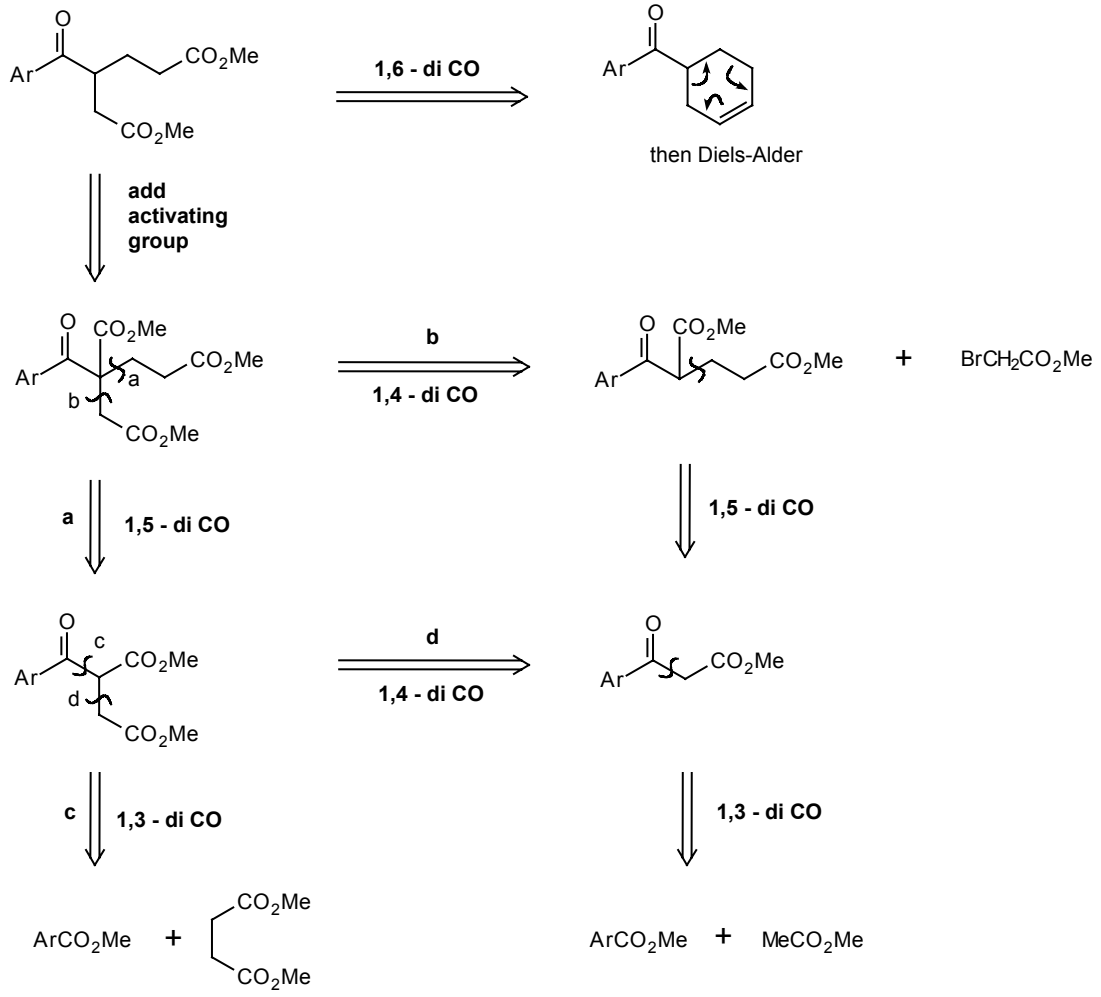
209. Analysis: The same FGI as in problem 5 gives us the key intermediate **A**.

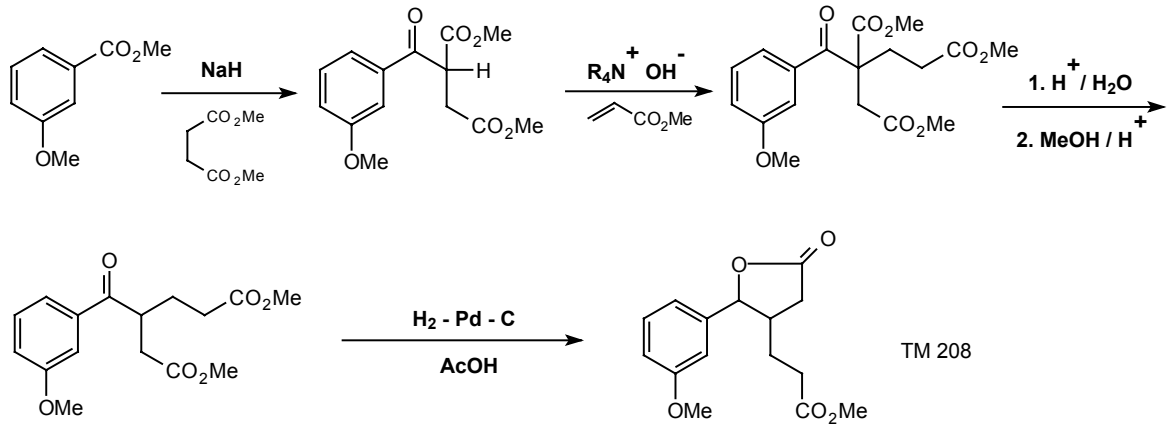


A contains 1,4-, 1,5-, and l,6-dicarbonyl relationships, so many disconnections are possible, summarised in the following chart.



Woodward tried all these different routes except the one based on the 1,6-dicarbonyl relationship. All were successful, but he eventually chose the route corresponding to **a** and **c**. He discusses this synthesis at length in the 1963 reference.

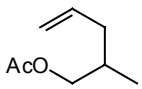
Synthesis: (Just this one route!) The hydroxy acid in the final atep could not be isolated.



E. GENERAL REVIEW PROBLEMS

210. Now that you have finished the second systematic section and are familiar with both one-group and two-group disconnections, it is important that you work through some general problems without being told which particular disconnection to do. The problems are meant to be graded in difficulty. I suggest you do as many as you need to convince yourself that you can cope. Later you can come back and do the rest.

Review Problem 19: Design a synthesis for TM 210.

TM 210 

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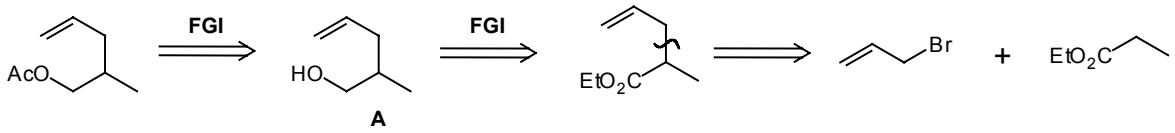
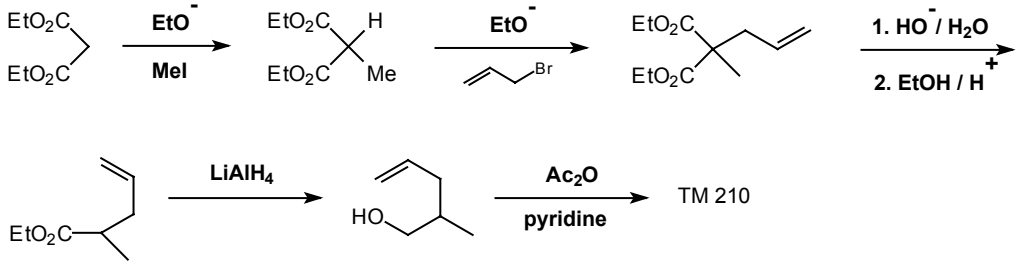
211. Analysis: The ester group is obviously just FGI, but immediate disconnection of the alcohol **A** doesn't get us very far so we do a bit more FGI. The double bond is the guide as it can be added as an allyl group:



Synthesis: An activating group will be needed:



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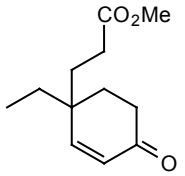
212. Review Problem 20: Suggest a synthesis for TM 212, an intermediate in Stork's synthesis of the complex alkaloid aspidospermine. J. Amer. Chem. Soc., 1963, 85, 2872).

TM 212 

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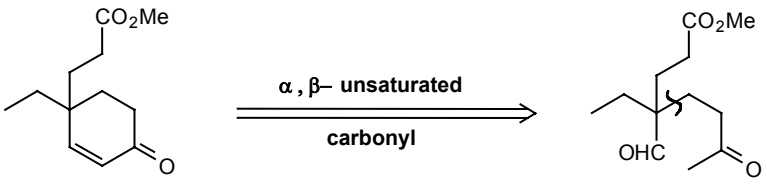
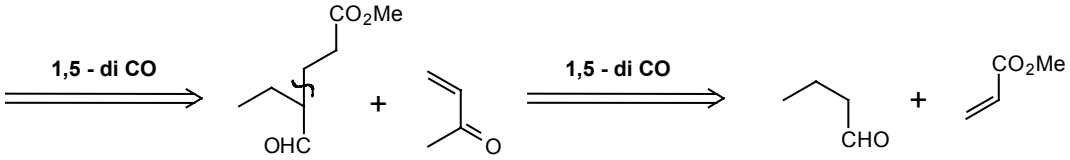
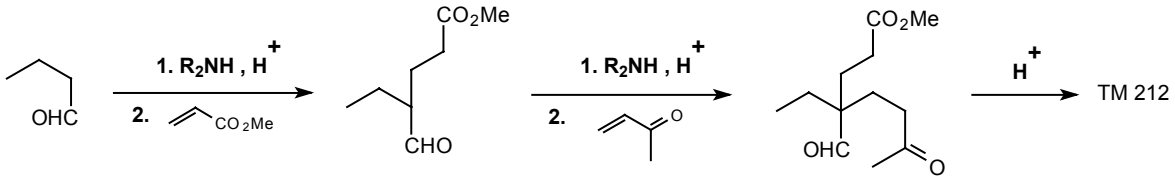
213. Analysis: Start with the only recognisably helpful relationship, the α,β-unsaturated ketone:



We now have two 1,5-diCO relationships: disconnect the more reactive one first.



Synthesis: We shall need the usual activating group for both Michael reactions: it can't be a **CO_2R** group as there isn't room, so it will have to be an enamine. The synthesis is therefore:



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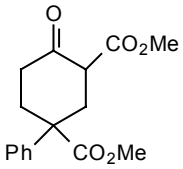
214. Review Problem 21: Design a synthesis for TM 214.

TM 214



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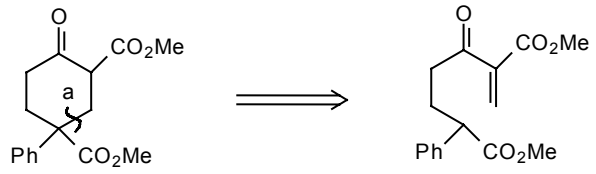
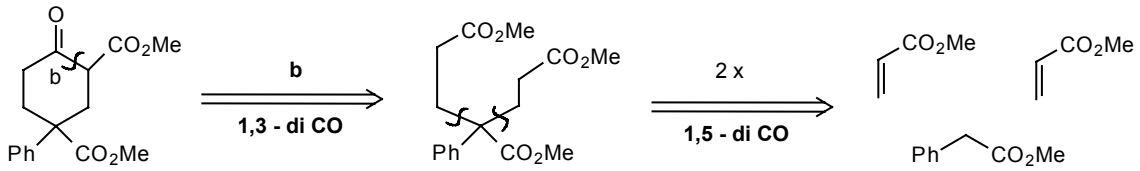
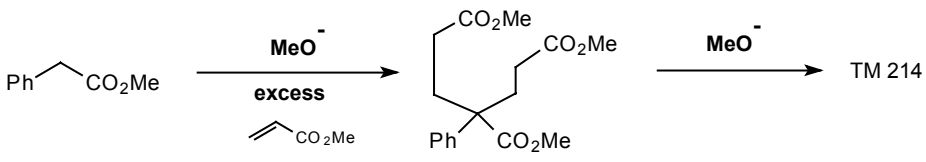
215. Analysis: You have two 1,5- and one 1,3-dicarbony1 relationships to consider. Disconnections like **a** hardly simplify the problem at all, whereas disconnecting the 1,3-dicarbonyl relationship **b** gives a symmetrical intermediate:





Synthesis:



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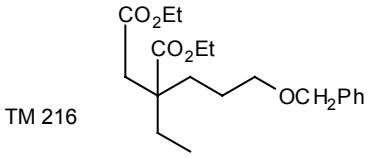
216. Review Problem 22: Design a synthesis for TM 216.



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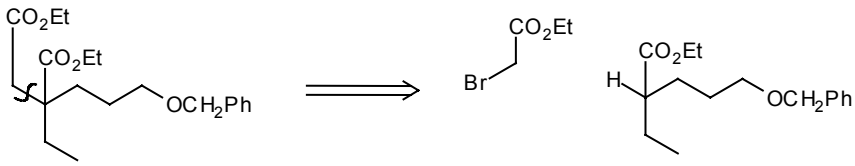
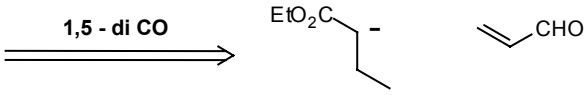
217. Analysis: This is part of a Kutney alkaloid synthesis (J. Amer. Chem. Soc., 1966, 88, 3667). There is a 1,4- and a 1,5-dioxygenation relationship; choosing the l,4- first as it is at the right oxidation level we get:



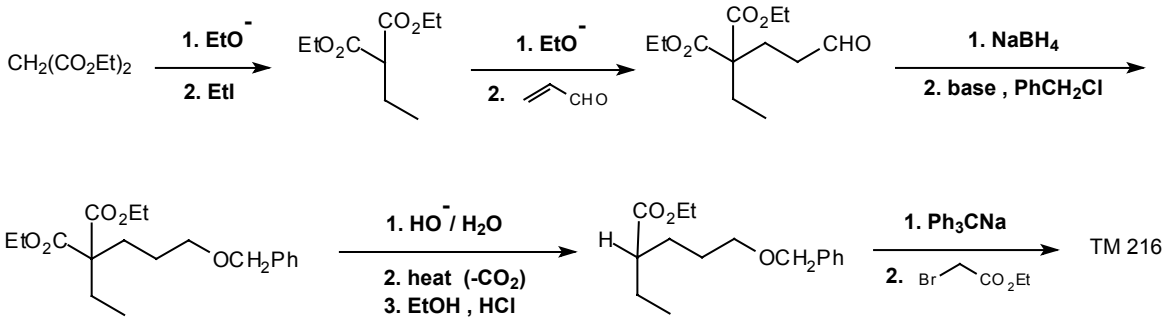
We shell need a strong base as there's no room for an activating group.

This is at the right oxidation level for a **1,5-diCO** disconnection.



An activating group will be needed.

Synthesis: This wae how Kutney did it - there are other orders of events.



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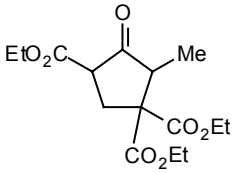
218. Review Problem 23: Design a synthesis for TM 218:



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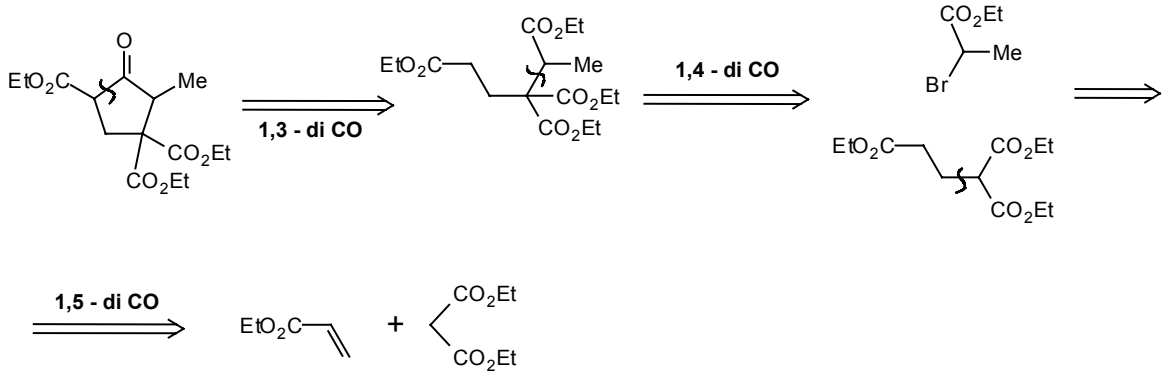
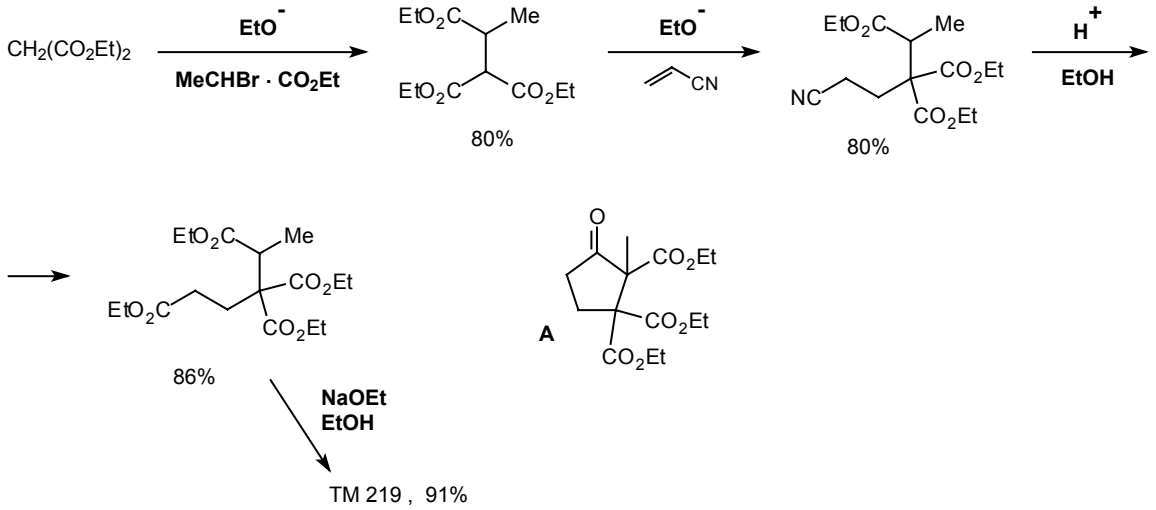
219. Analysis: This molecule has about every relationship in the book! One reasonable answer is this:



Synthesis: Russian workers actually carried out the synthesis in a different order the logic is the same:



The alternative condensation to give **A** does not happen because **A** cannot form a stable enolate ion, whereas TM 219 can. Zhur. Obshchei Khim., 1957, 27, 742; Chem. Abs., 1957, 51, 16313.

F. PERICYCLIC REACTIONS

220. The most important pericyclic reaction in synthesis, indeed one of the most important of all synthetic methods, is the Diels-Alder reaction. We have seen this many times before. What arc the clues for a Diels-Alder disconnection?

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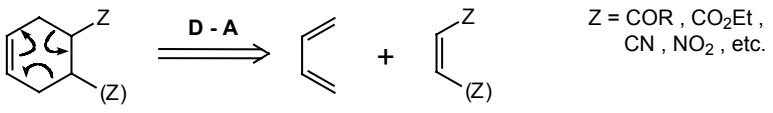
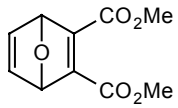
221. A cyclohexene with an electron-withdrawing group on the other side of the ring to the double bond:



So how would you make TM 221?

TM 221



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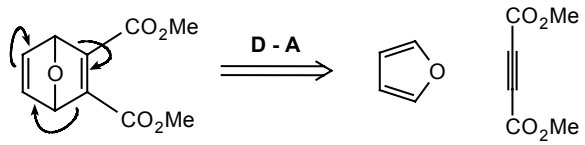
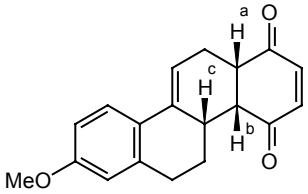
222. Simply reverse the Diels-Alder reaction:



Both starting materials are readily available. What about TM 222?

TM 222



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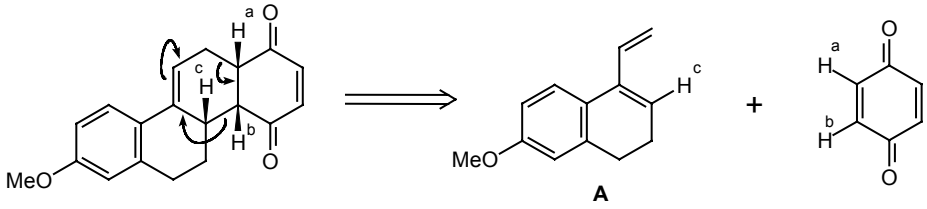
223. Again, simply reverse the Diels-Alder. It may have taken you a little time to find the right cyclohexene!



Note that the stereochemistry comes out right. H's **a** and **b** are cis because they were cis in the starting quinone and the Diels-Alder reaction is stereospecific in this respect. $\mathbf{H^c}$ is also cis to $\mathbf{H^a}$ and $\mathbf{H^b}$ because the Diels-Alder reaction is stereoselectively endo . These points are described in more detail in Norman p.284-6 and explained in Ian Fleming 'Frontier Orbitals and Organic Chemical Reactions', Wiley 1976, p.106-109. How would you make diene **A**?

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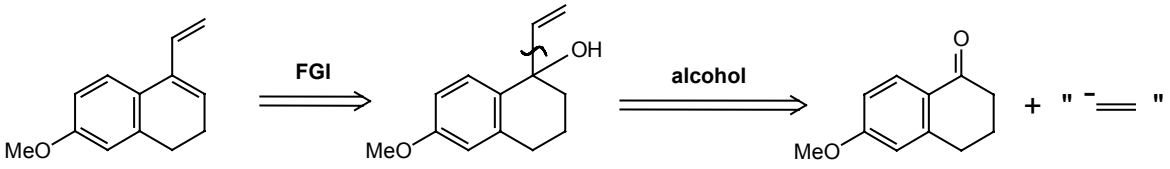
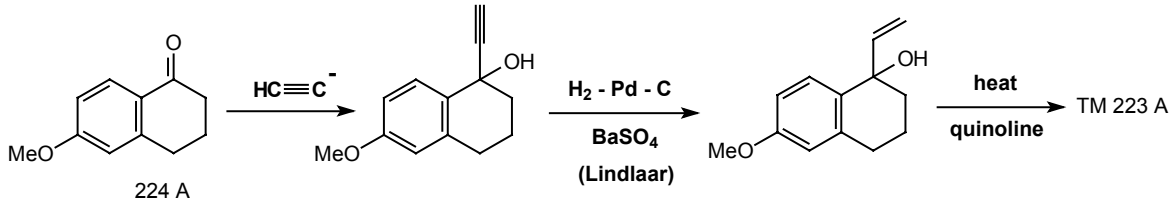
224. Analysis: We must put in a hydroxyl group instead of a double bond and the best place to do this is, as usual, at the branch point:



Synthesis: The vinyl anion synthon can either be the vinyl Grignard reagent or the acetylide anion, in which case the synthesis becomes:

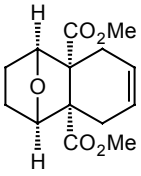


There are many syntheses of 224A which was a famous intermediate in early steroid syntheses (e.g. J. Amer. Chem. Soc., 1947, 69, 576, 2936).

---

225. Since the Diels-Alder reaction is so good it's worth going to some trouble to get back to a recognisable Diels-Alder product. Take TM 225 for example. The first **D-A** disconnection is obvious, but can you find your way back to a second?

TM 225



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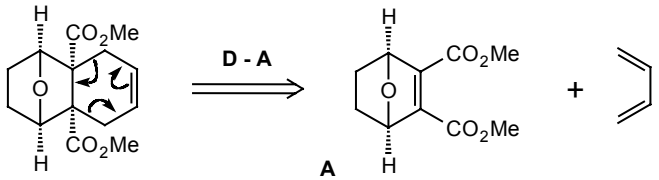
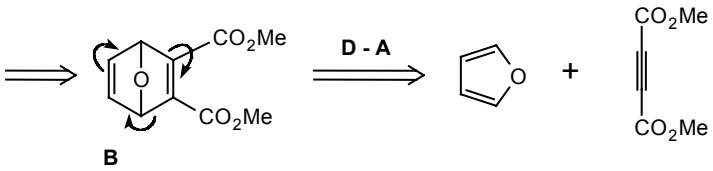
226. Analysis: The obvious **D-A** first!

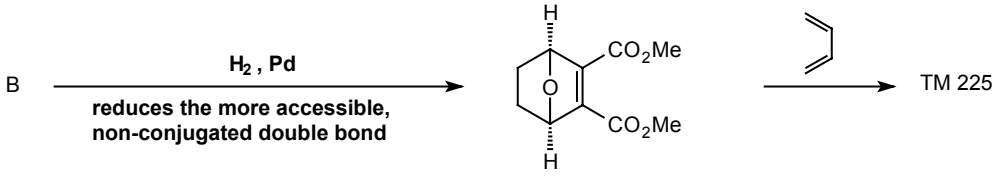


All we have to do for a second **D-A** disconnection is put another double bond into **A** in the right position.



B is actually TM 221.

Synthesis:



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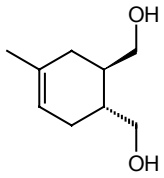
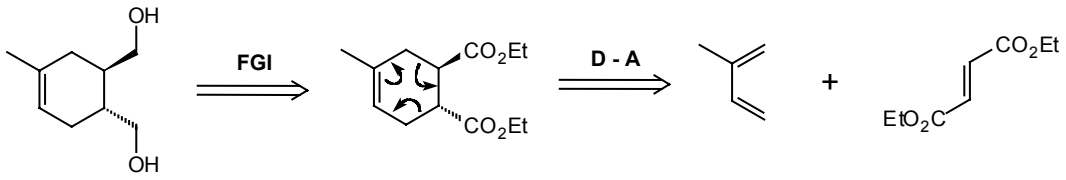
227. FGI of a different kind should give you another **D-A** disconnection on TM 227. Don't forget the stereochemistry!

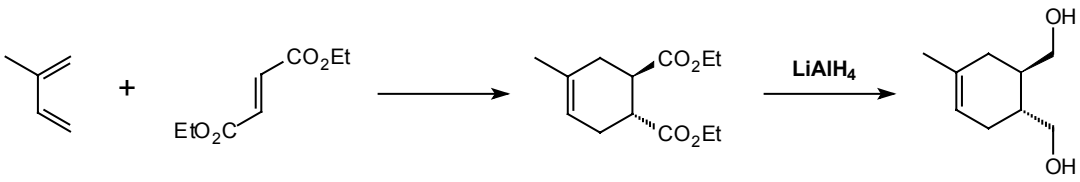
TM 227 

---

228. Analysis: We must first find some carbonyl groups somewhere:

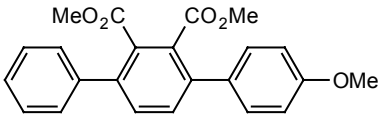


Synthesis: The ester must be a fumarate so that the stereochemistry of the final adduct is correct:



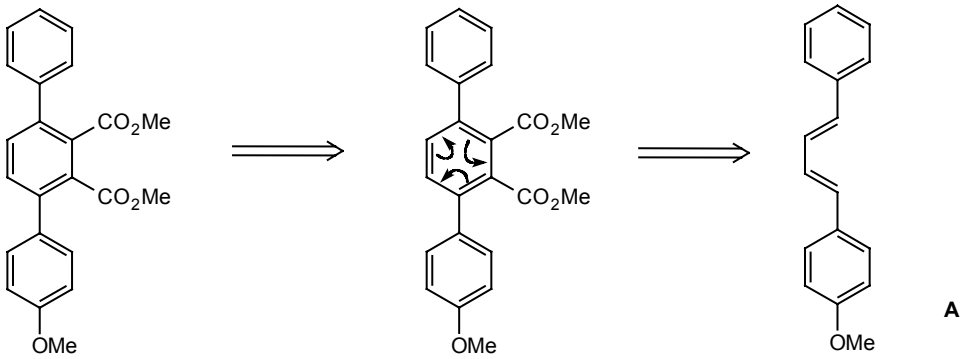
---

229. This next example is perhaps slightly less obvious - the problem of how to make an asymmetrically substituted terphenyl (e.g. TM 229) but inspection should show you which ring is made by the **D-A** reaction.

TM 229 

---

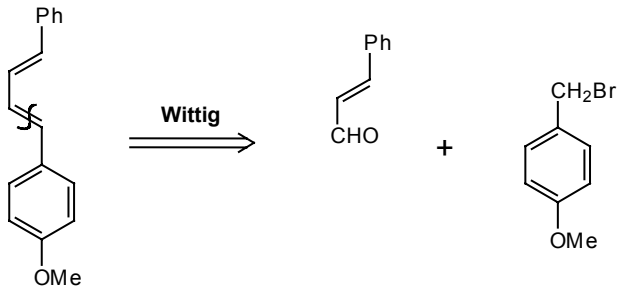
230. Analysis: The central ring has the electron-withdrawing substituents so all we have to do is to adjust the oxidation level:



Now, how would you make the diene **A**?

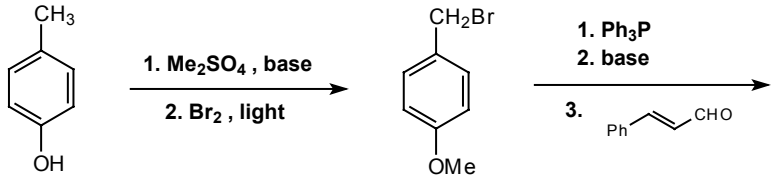
---

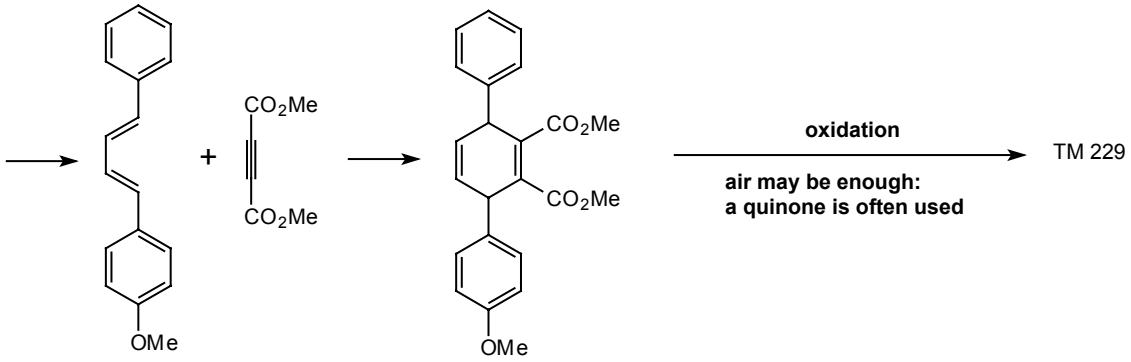
231. Analysis: A Wittig disconnection would give two readily accessible fragments:



The aldehyde is the readily available cinnamaldehyde; the bromide can be made from **p**- cresol.

Synthesis:





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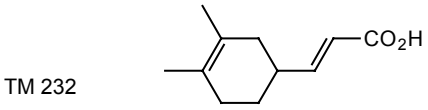
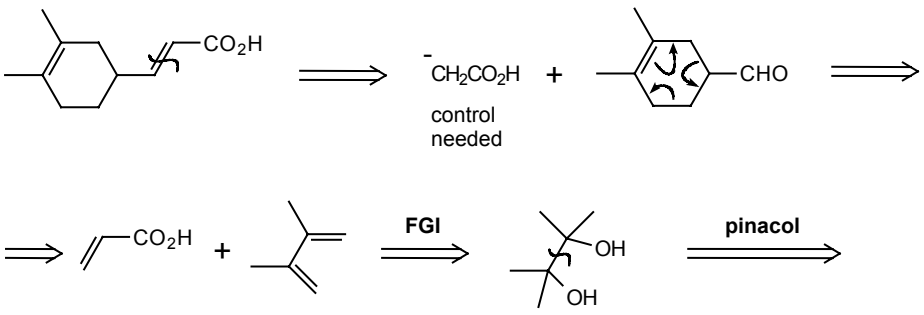
232. Review Problem 24: Design a synthesis for TM 232.

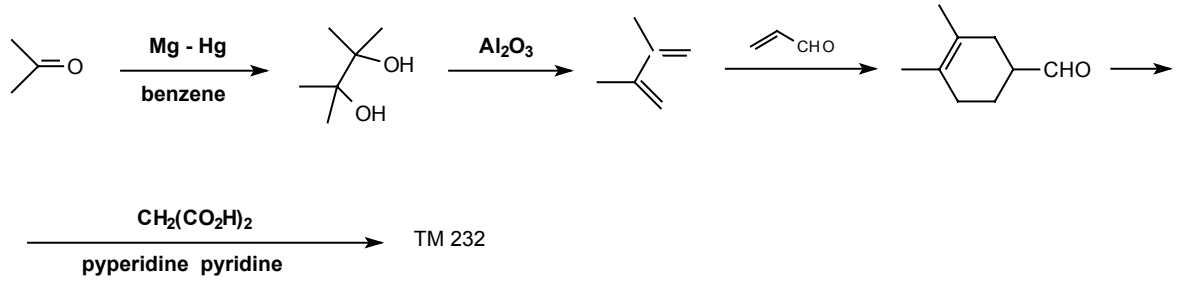


---

233. Analysis: Disconnect the α,β-unsaturated acid first and then an obvious **D-A** is revealed:



Synthesis: The conditions actually used were:



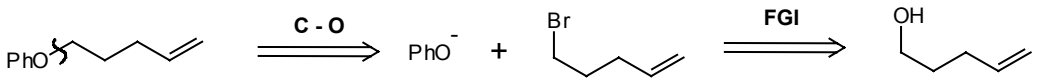
G. HETEROATOMS AND HETEROCYCLIC COMPOUNDS

1. HETEROATOMS, ETHERS, AND AMINES

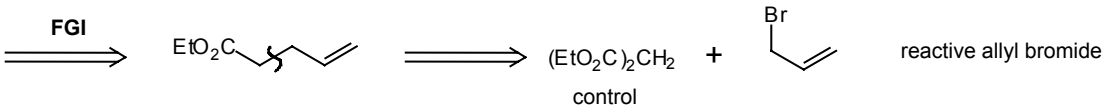
234. Any heteroatom (usually **O**, **N**, or **S**) in a carbon chain is a good point for a disconnection and I shall write **CO**, **CN**, or **CS** above the arrow when I use these disconnections. TM 234 can be made this way. How would you actually do it?

---

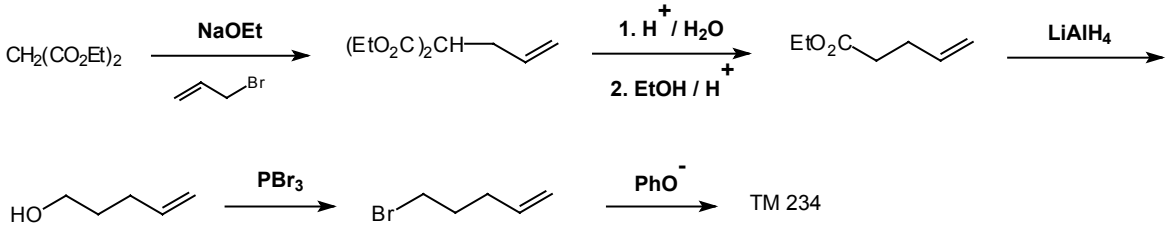
235. Analysis: We must choose the bond away from the aromatic ring as displacements on **PhBr** are almost impossible.



The double bond is so far away from the hydroxyl group that we shall have to alter the oxidation level before we can continue:



Synthesis:



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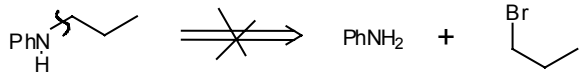
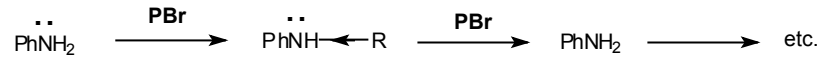
236. Amines are slightly more of a problem because the same disconnection is no good:



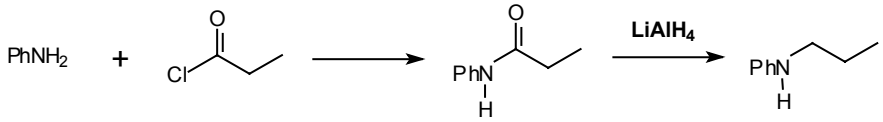
Why is it no good?

---

237. Because it will be impossible to prevent polyalkylation since the product is more nucleophilic than the starting material:



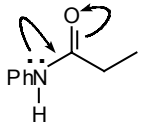
The trick used is to acylate the amine instead, since we can reduce the resulting amide with **LiAlH**, to give the product we want:



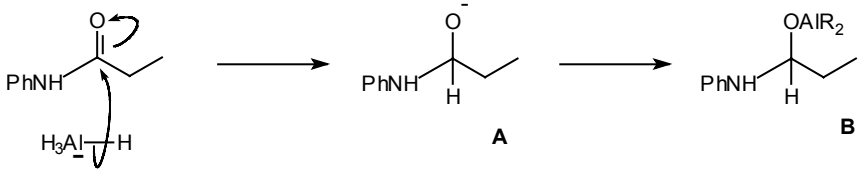
Why doesn't acylation go twice in the same way as alkylation?

---

238. Because the acylated product has a delocalised lone pair and is less reactive than **$PhNH_2$**. You may have been surprised that **$LiAlH_4$** reduction completely removes the carbonyl oxygen atom. To help explain this, please draw the likely intermediate.

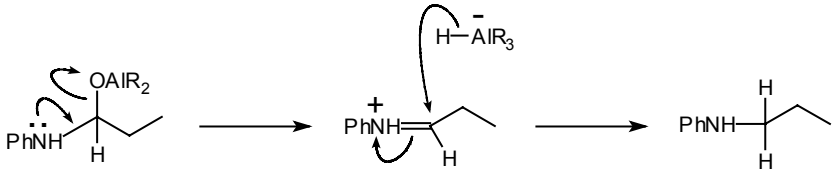


239.

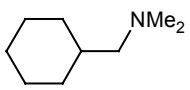


The obvious intermediate, 239A, will now react with some aluminium species to give an intermediate like 239B, which can react further if the lone pair on nitrogen halps to expel the oxygen atom. Try now to complete the mechanism.

240.



How then would you make TM 240?

TM 240 

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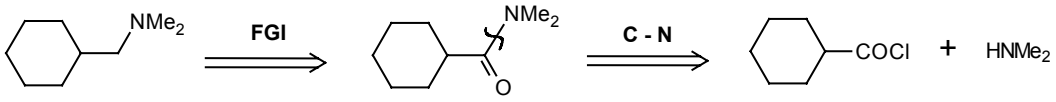
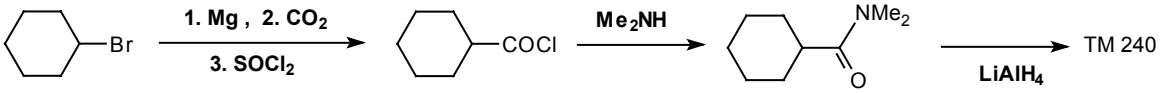
241. Analysis: The first step is to put in a carbonyl group next to nitrogen and then reverse the acylation:



Synthesis:



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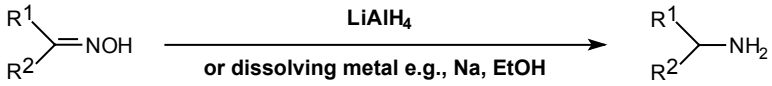
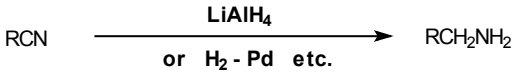
242. Reduction seems to be the keyword in amine synthesis since we can also raduce these functional groups to amines:

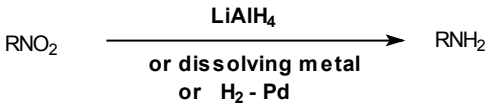
Oximes



Nitriles

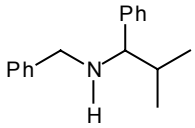


Nitro Compounds



How then would you make TM 242?

TM 242



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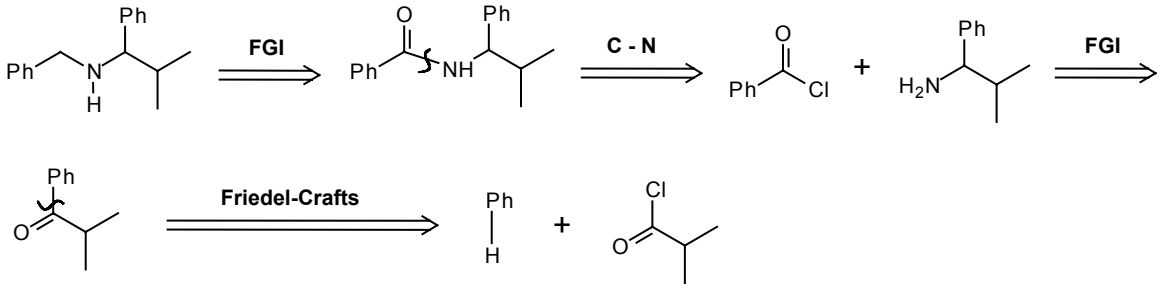
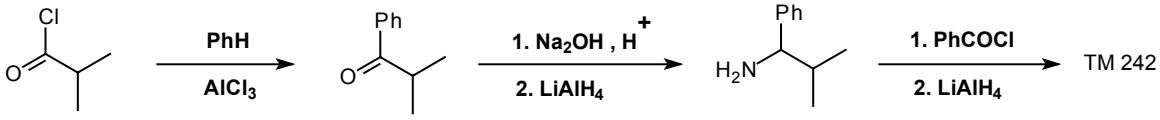
243. Analysis: The branchad chain can only be made by reduction of an oxime so we must disconnect the other (benzyl) side first.



Synthesis:



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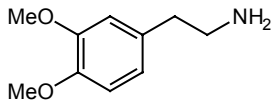
244. 2-Arylethylamines (e.g. TM 244) are important intermediates in the synthesis of alkaloids as you will see later. Suggest an approach to TM 244.

TM 244 

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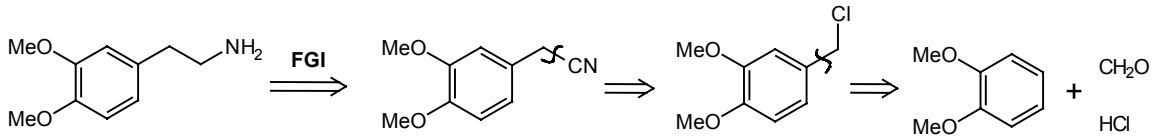
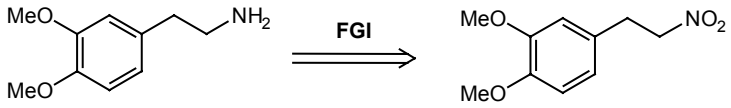
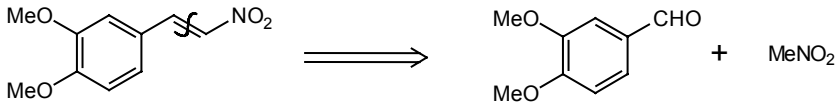
245. Analysis: There are two general ones based on reduction of nitrile or nitro compound:
(a) nitrile route



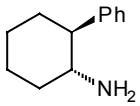
(b) nitro compound route



This compound could be easily made if it had a double bond. Since we are going to reduce it anyway, this doesn't matter.



Using the same idea of reducing a nitra compound and a double bond at the same time, how might we make TM 245?

TM 245 

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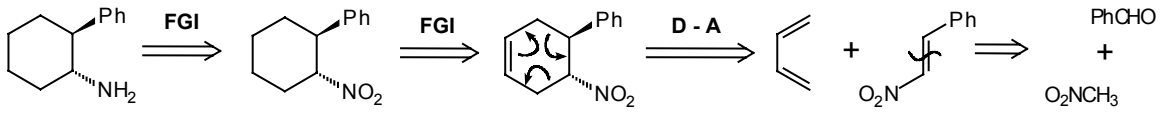
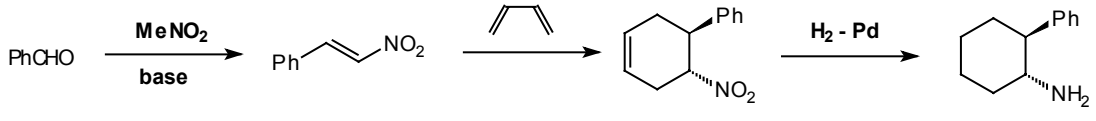
246. Analysis: The nitro compound looks like a Diels-Alder adduct, so we know where to put the double bond:

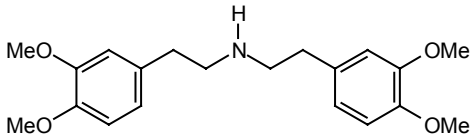


Synthesis: The trans nitro compound is the one we get by condensation as it is more stable than the cis compound.



Now back to TM 244. How could you develop it into TM 246?

TM 246



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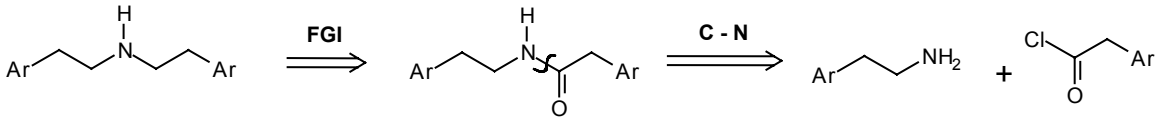
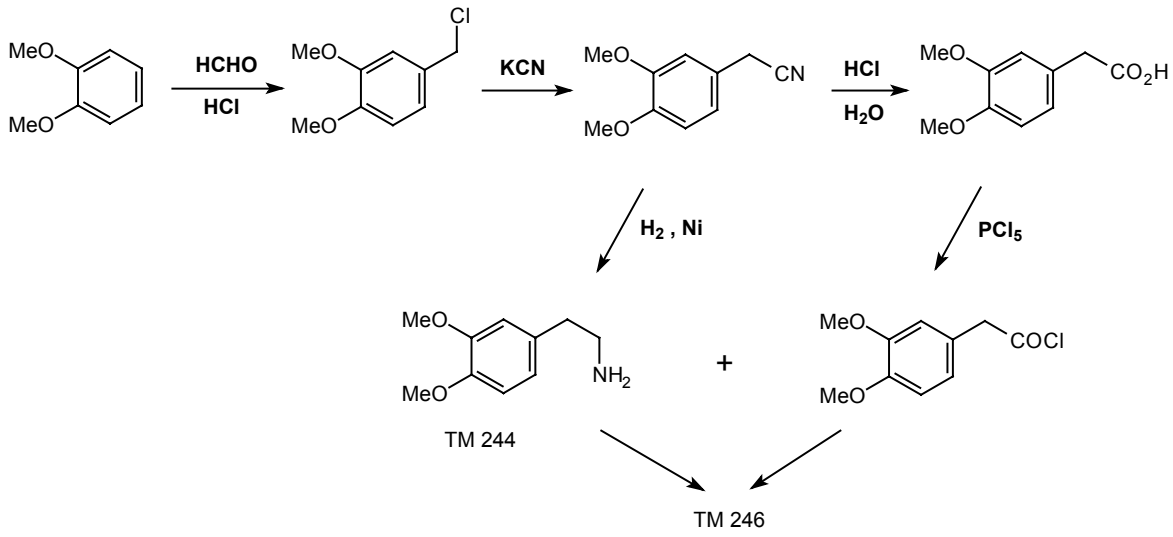
247. Analysis: We must put in a carbonyl group again:



Synthesis: The most economical route will therefore be to make both the acid chloride and TM 244 from the nitrile: (see Norman, p.614-5):



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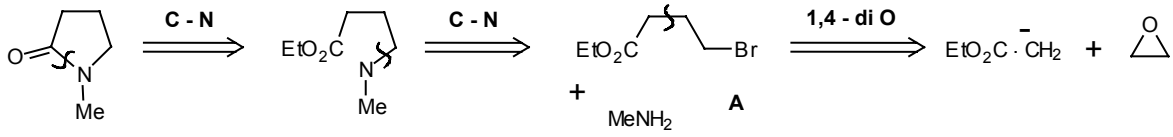
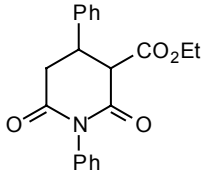
2 . HETEROCYCLIC COMPOUNDS

248. Intramolecular reactions are faster and cleaner than intermolecular reactions. When we want to make a **C-N** bond in a ring, therefore, we no longer have to take any special precautions and we can use a nitrogen nucleophile and any carbon electrophile. Two useful disconnections are:



Simply mixing **$MeNH_2$** and the γ-bromoester A will give the heterocycle in one step. How might you make TM 248?

TM 248



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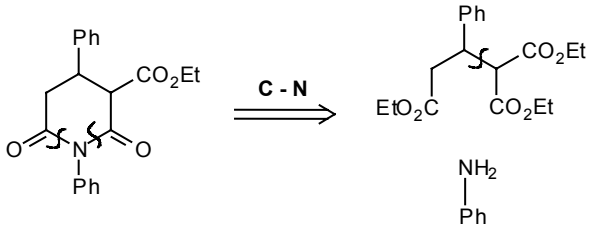
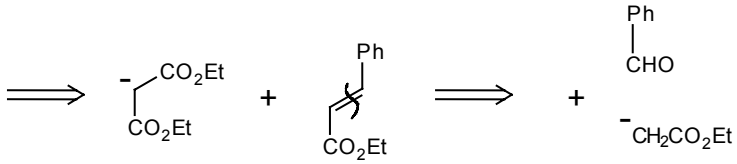
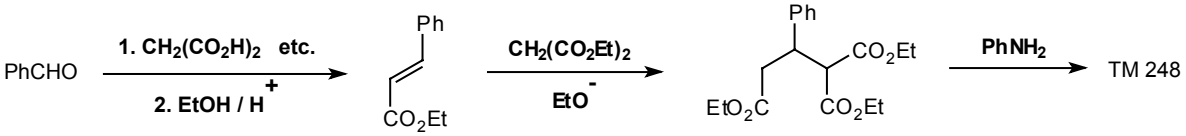
249. Analysis: It is quicker to disconnect both **C-N** bonds at once:



This is now a familiar 1,5-dicarbonyl problem: the extra **CO_2Et** group tells us where to disconnect.

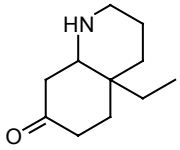


Synthesis:



The next example uses another carbon electrophile: how can you use the relationship of the two functional groups in TM 249 to design a synthesis of the molecule?

TM 249



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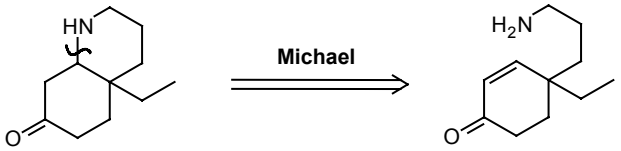
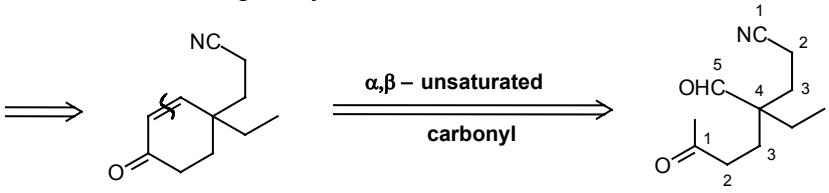
250. Analysis: The electrophile is an enone since a reverse Michael reaction cleaves the **C-N** bond:

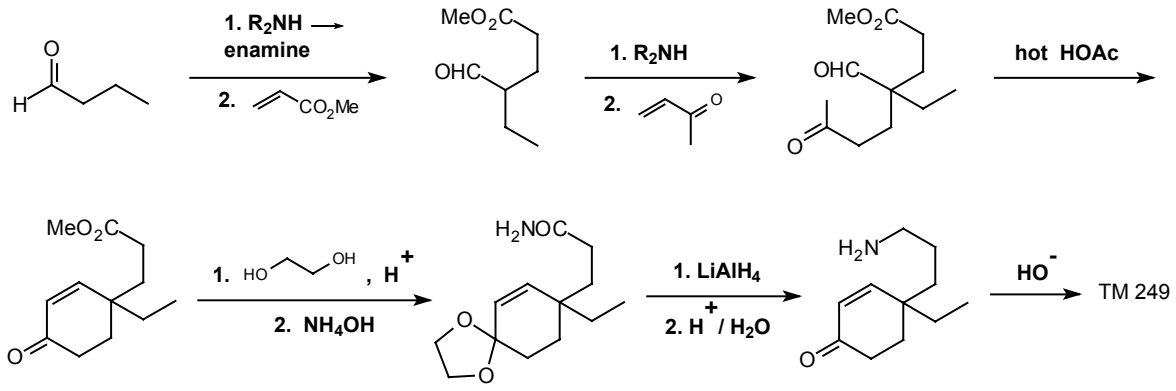


The long-chain amine can most quickly be reduced to size via the nitrile.



We now have two **1,5-diCO** relationships which we can disconnect in any order.

Synthesis: The final stages are very similar to Review Problem 20 (frames 212-3). TM 249 is an intermediate in Stork's synthesis of Aspidosperma alkaloids. Stork's method was actually a variation on the one we have proposed (J. Amer. Chem. Soc., 1963, 85, 2872):



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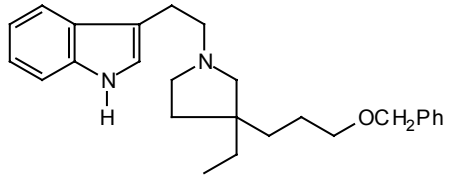
251. A more complicated structure doesn't always mean a more complicated disconnection when rings are being formed. Design a synthesis for TM 251.

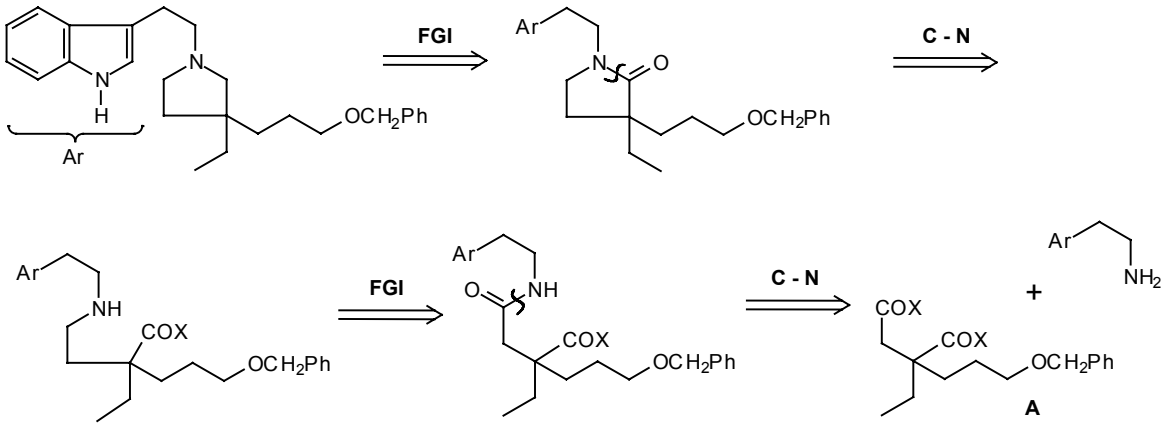


TM 251

Concentrate on the saturated five-membered ring part first.

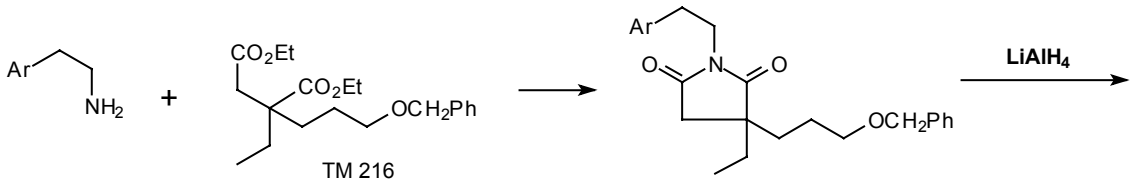
---

252. Analysis: We are clearly going to put carbonyl groups on each side of the five membered ring and disconnect the bond: e.g.



The analysis of intermediate **A** is given in frame 217.

Synthesis: This is part of Kutney's quebrachamine synthesis (J. Amer. Chem. Soc., 1966, 88, 3656). He found that if **X = OEt**, both **C-N** bond-forming operations could be carried out in one step. The synthesis is actually much easier to carry out than expected:



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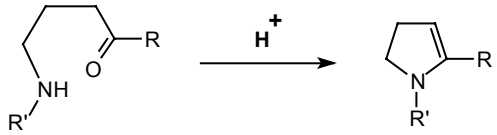
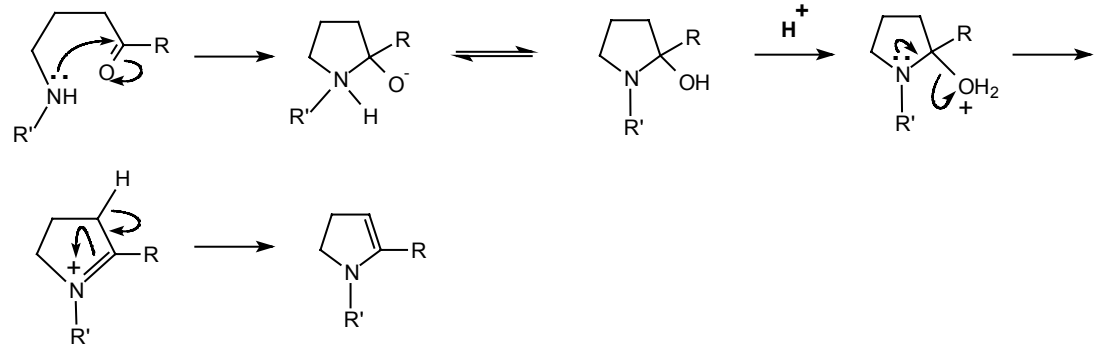
253. One extra disconnection is all we need to cope with unsaturated heterocycles. If a nitrogen atom is joined to a double bond in a ring, we have a cyclic enamine. This is made from an amine and a carbonyl compound in the same way as ordinary enamines:

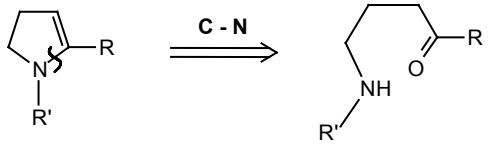


Draw a mechanism for this reaction.

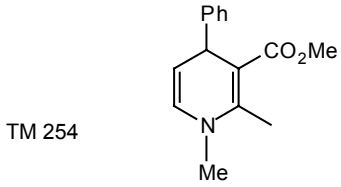
254.



The disconnection corresponding to this reaction is again of the **C-N** bond, writing an amine and a carbonyl group in the right places:



How then would you make TM 254?



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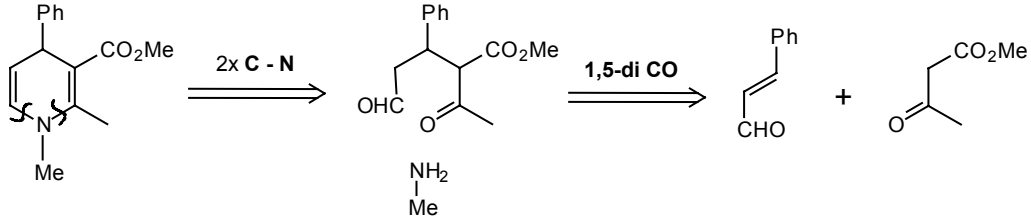
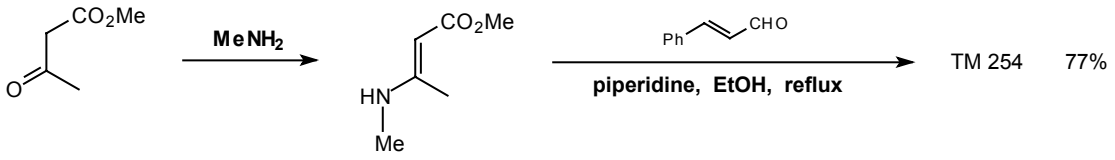
255. Analysis: Using the disconnection we' ve just learned:



Synthesis: (As carried out in J. Amer. Chem. Soc.. 1976, 98, 6650).



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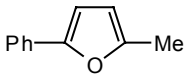
256. Many unsaturated heterocycles are made directly from dicarbonyl compounds. How would you make TM 256?

TM 256 

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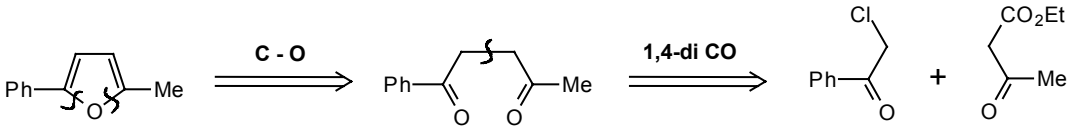
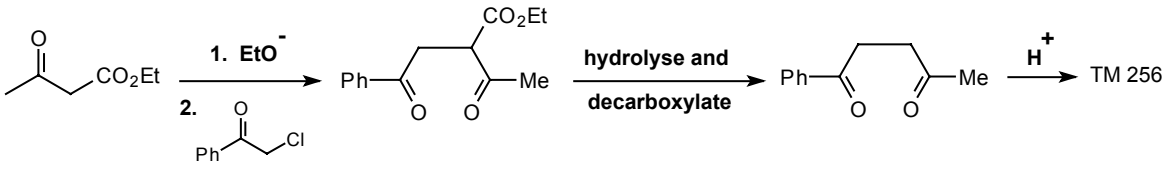
257. Analysis:



Synthesis:



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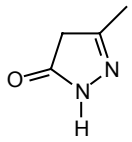
258. Heterocycles with two heteroatoms present no special problems and there are often several ways to do the first disconnection. One guide is to look for a small recognisable fragment containing the two heteroatoms. Try this one:

TM 258 

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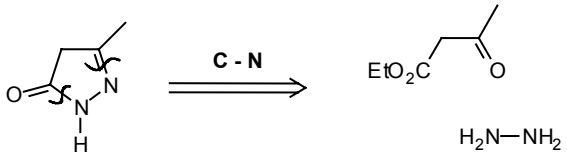
259. Analysis: The usual disconnections give us $\mathbf{NH_2NH_2}$ (hydrazine) immediately:



The synthesis is just to mix these two.

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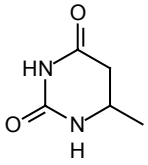
260. Here is one where the heteroatoms are apart:

TM 260 

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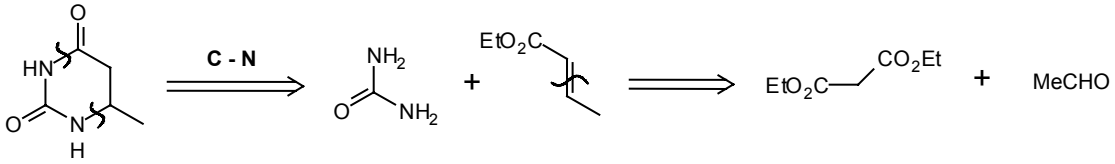
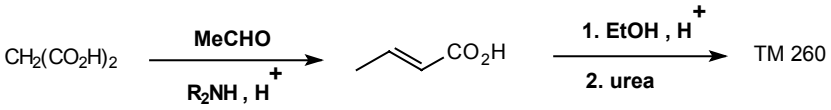
261. Analysis: Again the usual disconnection, making sure we choose a simple electrophilic fragmant:



Synthesis: The heteroatom fragment is urea.



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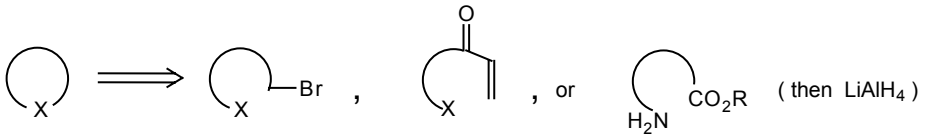
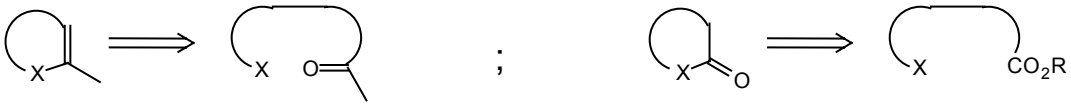
262. So, to summarise this last section, disconnections of heterocycles are usually good providing one checks the oxidation level:

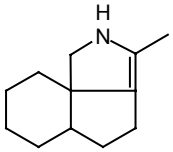




The heteroatom is the nucleophile in all these reactions: you just have to choose the right electrophile.

---

263. There are many special methods to making heterocycles: if you want to read about them, see Tedder, part 3, pp.115-131 and 205-220, or Norman, Chapter 18, p.588. We are more interested in applying these general methods to molecules in which a heterocyclic ring is only part of the problem. How would you make TM 263 from simple starting materials?

TM 263 

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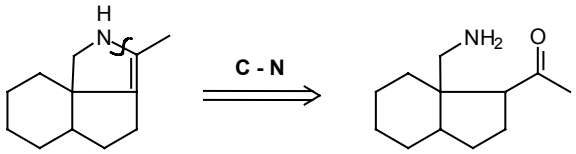
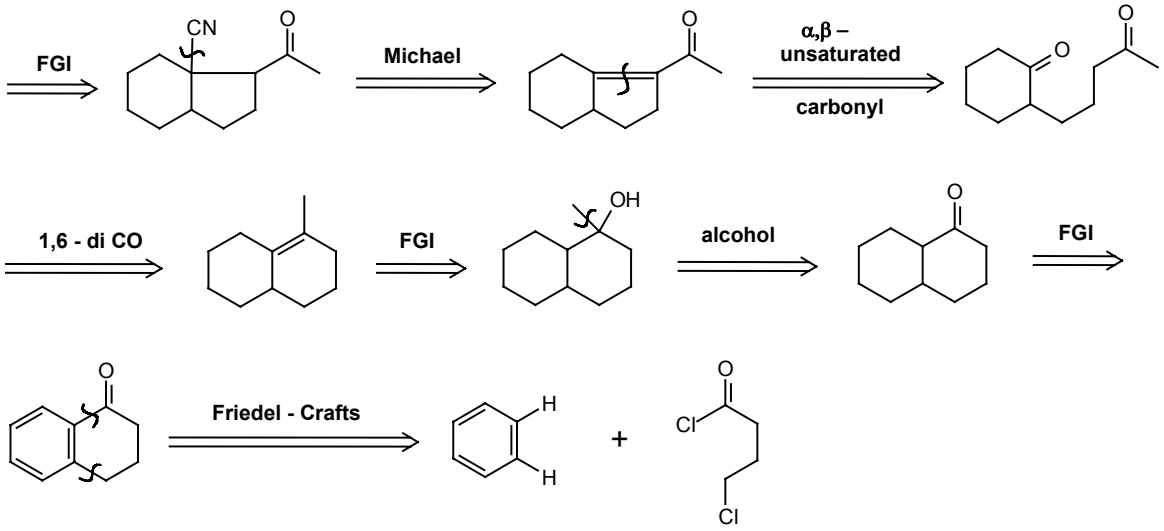
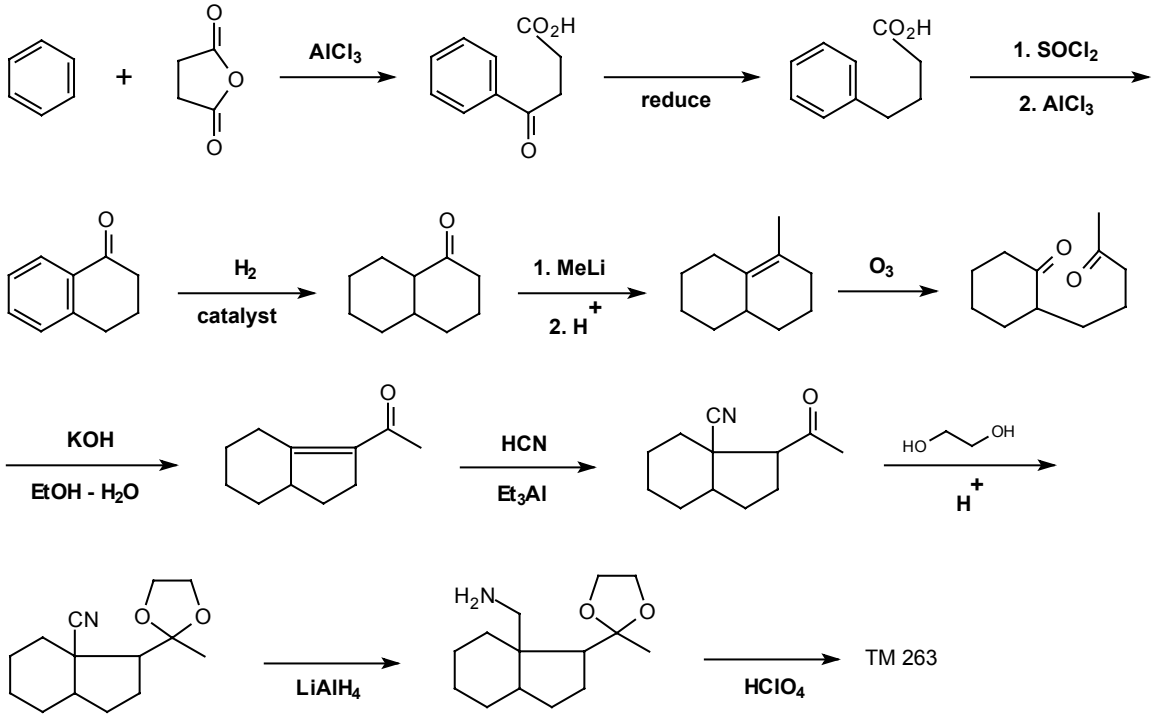
264. Analysis: The first disconnection is easy:



now if we make the primary amine from the nitrile, we shall have another good disconnection.



Synthesis: The early stages of this route are a well established method to make benzocyclohexanones; the later stages are adapted from Johnson's Conessine synthesis (J. Amer. Chem. Soc., 1962, 84, 1485):



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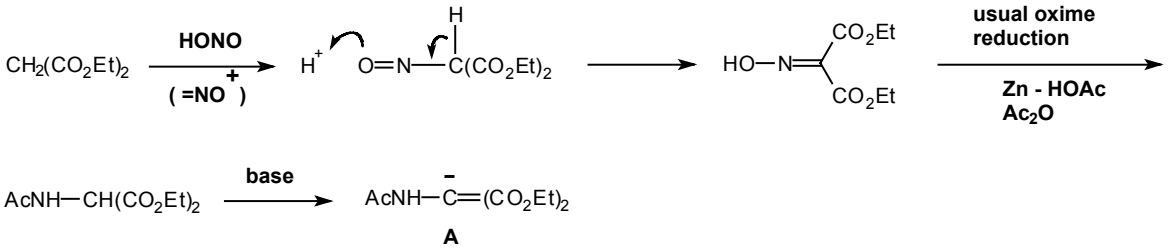
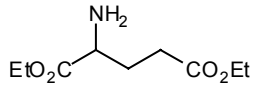
3 . AMINO ACIDS

265. You will have noticed that, throughout this chapter, the heteroatom has always been the nucleophile. There is one way to use nitrogen as an electrophile however and this provides a good synthon for amino acid synthesis:

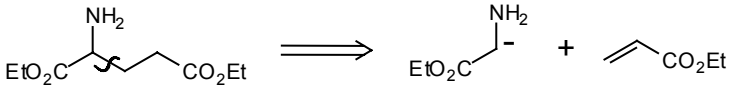


The anion **A** is a reagent for the synthon **H_2N-CH-CO_2H** and amino acids are derived this way. How could you make TM 265?

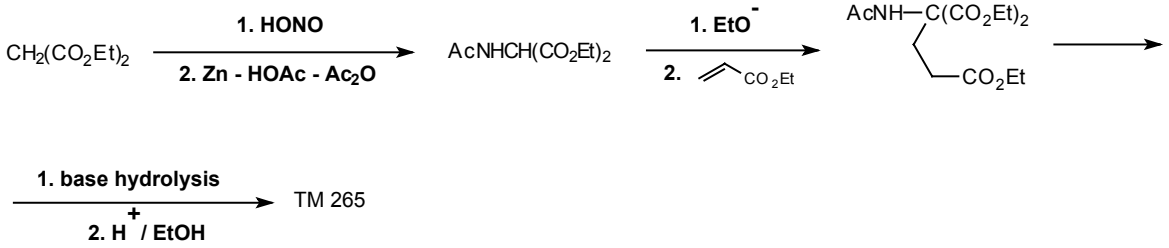
TM 265 

---

266. Analysis: Using the reagent we've just made, it's easy to see what the electrophile must be:



Synthesis:



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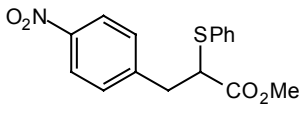
4. REVIEW PROBLEMS

267. Before we leave heterocycles and heteroatoms, here are three review problems to reinforce the ideas from this chapter. The first two involve sulphur: don't be put off by that, simply treat it as a special kind of oxygen.

Review Problem 25: Design a synthesis for TM 267.

TM 267 

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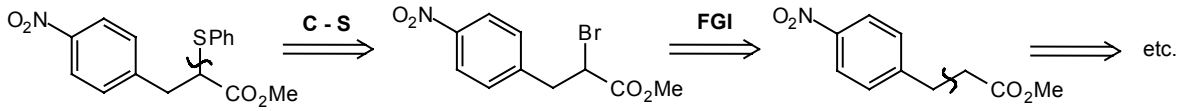
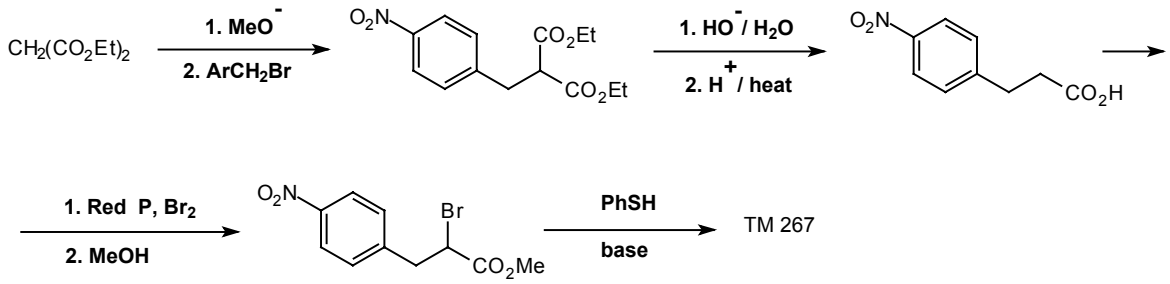
268. Analysis: As usual (see frame 235) we shall disconnect the alkyl-heteroatom bond:



Synthesis: PhSH is readily available.



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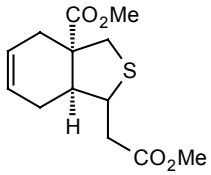
269. Review Problem 26: Design a synthesis for TM 269.

TM 269



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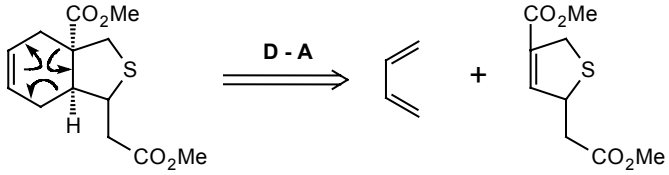
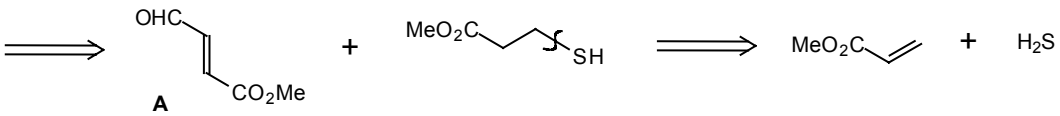
270. Analysis: We have an obvious Diels-Alder disconnection, some **C-S** bonds, and a 1,6-dicarbonyl relationship. The only one that gives any rapid simplification is the **D-A**, so we'll start with that:

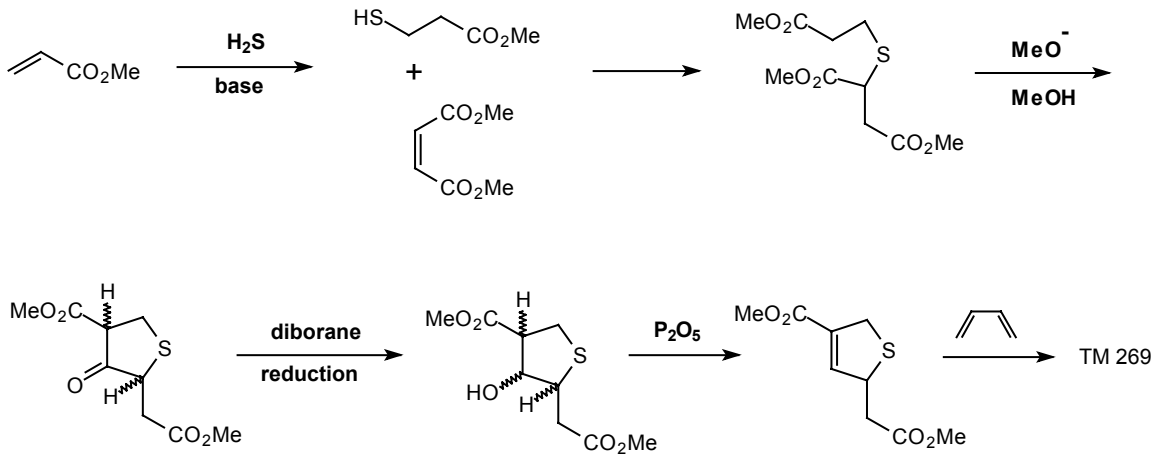


There's still no helpful **C-S** disconnection, so let's do the α,β-unsaturated ester next.

Both **C-S** bonds are now **β** to carbonyl groups and so can be disconnected in turn by reverse Michael reactions.



Synthesis: Fragment A is going to be very difficult: it would be much simpler to make it a diester and adjust the oxidation level later. This is the synthesis actually used by Stork (J. Amer. Chem. Soc., 1969, 91, 7780):



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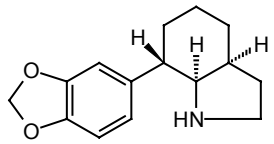
271. Review Problem 27: Design a synthesis for TM 271:

TM 271



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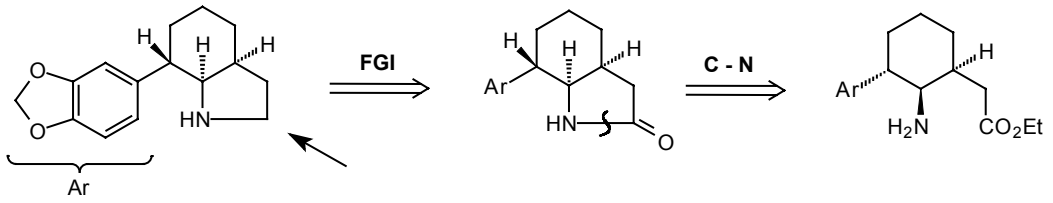
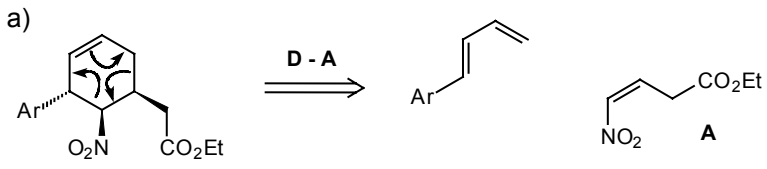
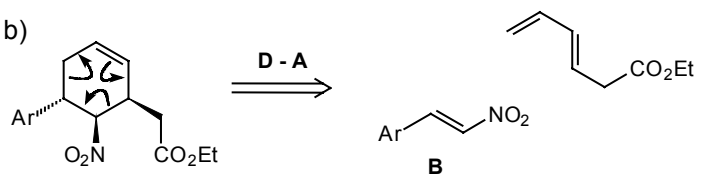
272 . This is perhaps the most difficult problem so far; there must be many possible solutions and I can give only one.

Analysis: Since there is one **CH_2** group next to the nitrogen atom, this might be a carbonyl group in our usual method of amine synthesis (frame 237).

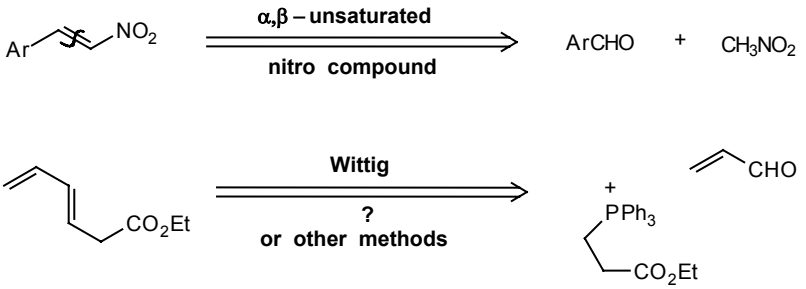


We must next disconnect the six-membered ring and the only way we know to set up these chiral centres specifically is by the Diels-Alder reaction. Two alternative sites for the double bond are possible if we convert our **NH_2** to give the necessary activating group: (**NO_2**)

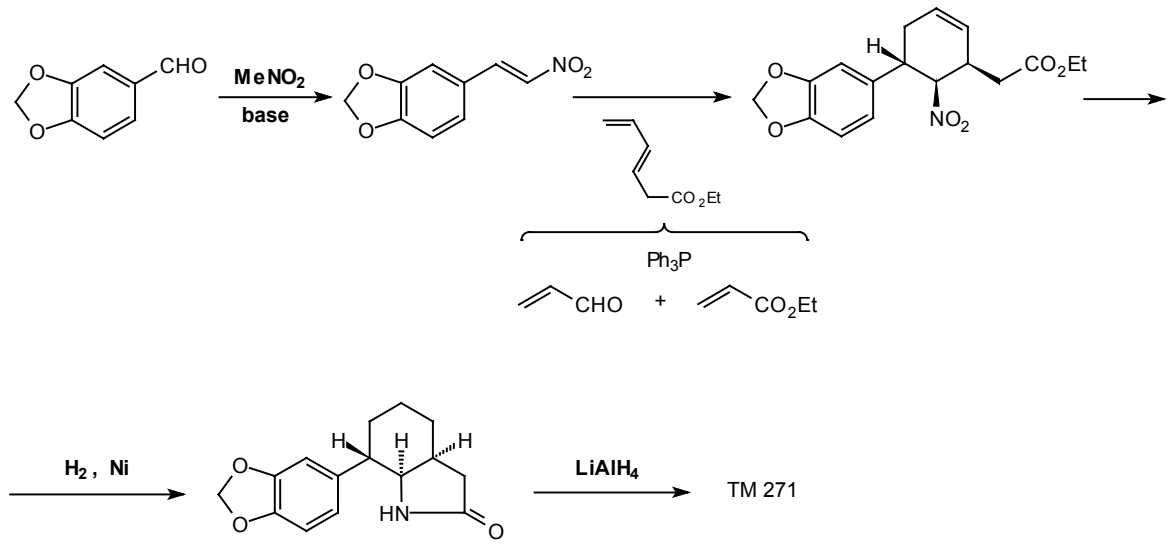




While we can make the trans nitro-alkene **B** easily enough, the cis-nitro alkene **A** would present problems, so let's try route **b**:



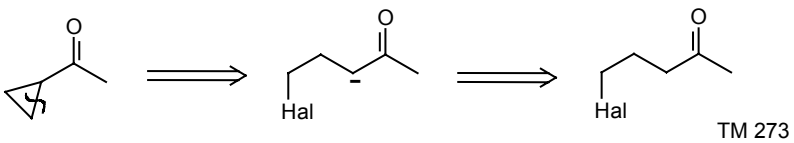
Synthesis: This is the method used in the synthesis of TM 271 as an intermediate for α-lycorane (J. Amer. Chem. Soc., 1962, 84, 4951).



H. SPECIAL METHODS FOR SMALL RINGS: 3- AND 4-MEMBERED RINGS

1. THREE-MEMBERED RINGS

273. Three membered rings are kinetically easy to form but are rather unstable. Some conventional methods work but are rather capricious. This obvious disconnection on cyclopropyl ketones turns out to be all right:



How would you make the γ-haloketone TM 273?

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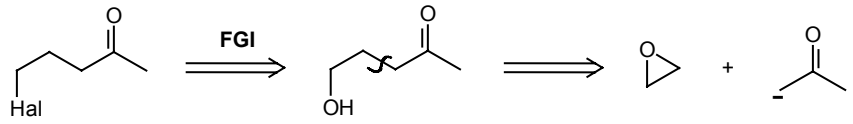
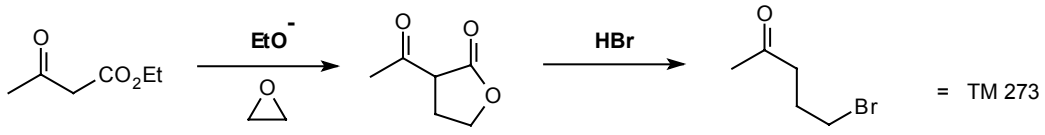
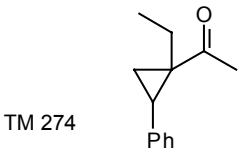
274. The obvious disconnection gives an epoxide and an enolate anion:



We have already explored this route (frame 184) and found that the reaction sequence actually is:



How then would you make TM 274?



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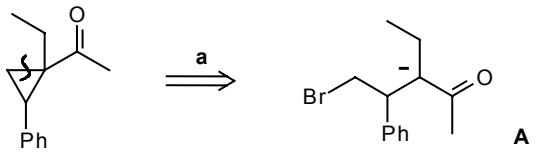
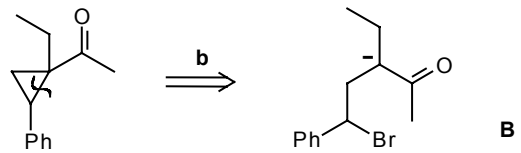
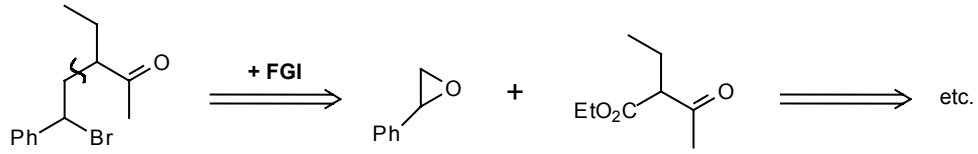
275. Analysis: We must consider two alternative disconnections of the three-membered ring:

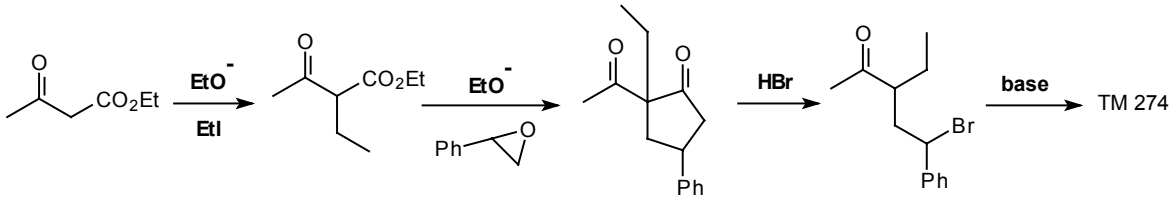




Since epoxides are attacked by anions at the less substituted carbon atom, we shall be able to make B but not **A**, so we continue.



Synthesis:



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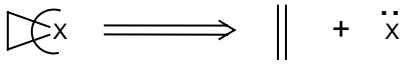
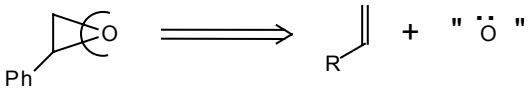
276. A more general route to three-membered rings is based on a new type of disconnection: the removal of an atom

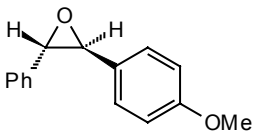


The synthon $\ddot{X}$ will be, in a lower valency state - if **X** is **C** then it will be a carbene or the synthetic equivalent of a carbene. Let's see how this disconnection works out for epoxides. Taking **X = O** first we have



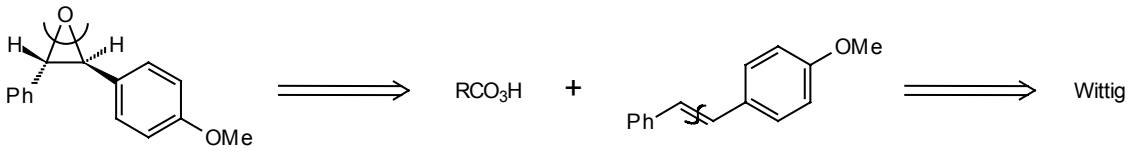
A reagent for the synthon is $\ddot{O}$ a peracid **RCO_3H**.
How then could you make TM 276?

TM 276



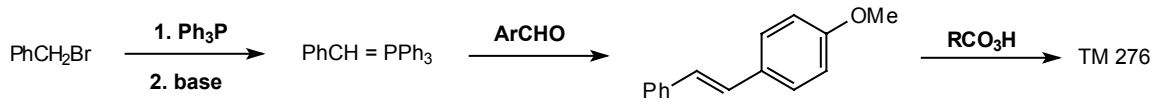
---

277. Analysis: Using our new disconnection:



Note that is must be the trans olefin as it is the trans epoxide we want. This is all right as the Wittig reaction can easily be controlled to give mostly the more stable trans olefin.

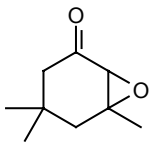
Synthesis:



---

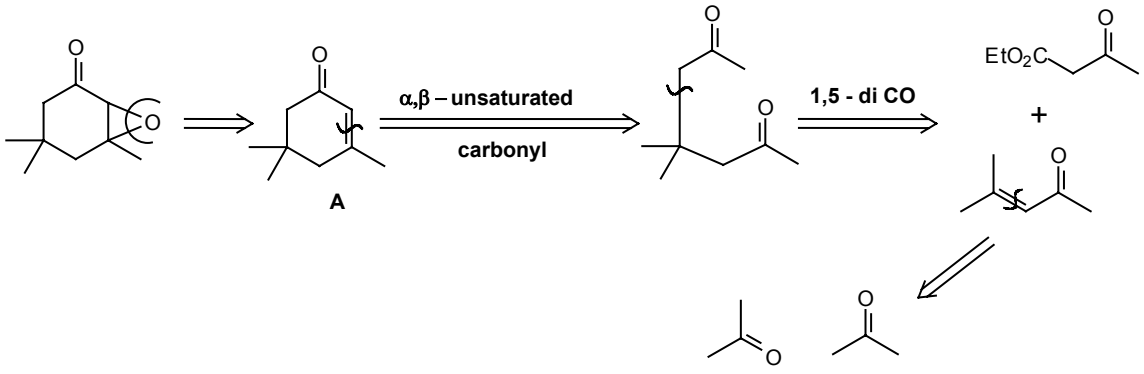
278. The reagent for the synthon O changes when the olefin is electrophilic as in an α,β-unsaturated carbonyl compound: then alkaline hydrogen peroxide (**HOO^-**) is usea. How could you make TM 278?

TM 278

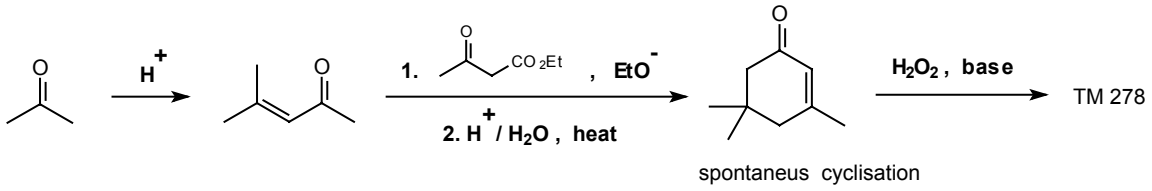


---

279. Analysis:

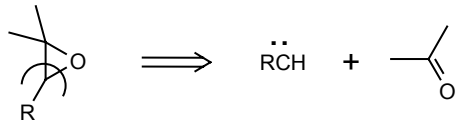


Synthesis: Intermediate **A** is manufactured but can be made by the route devised here:

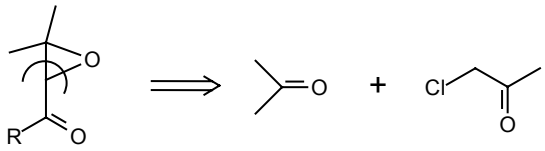


---

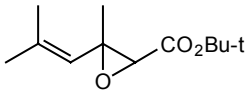
280. The alternative disconnection for an epoxide:



is also useful for epoxides of α,β-unsaturated carbonyl compounds when it becomes:

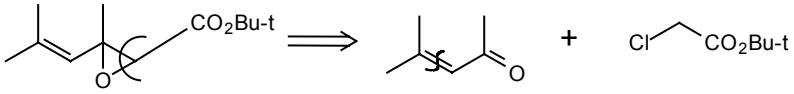


This is the Darzens reaction (frames 172-3) (see Norman, p.231 if you want more details). How would you make

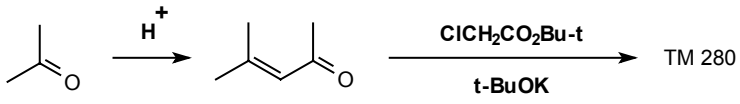
TM 280 

---

281. Analysis: Using the carbonyl group as a guide:

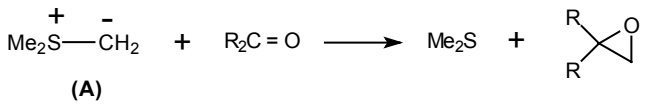


Synthesis:

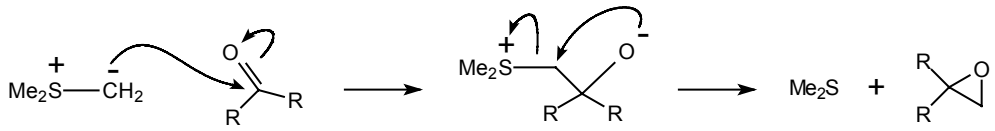


---

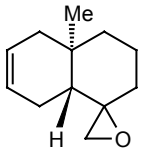
282. The same disconnection can be used with simple epoxides when the sulphur ylid (A) is used a reagent for the synthon $\mathbf{CH_2}$. Draw a mechanism for the reaction:



283.

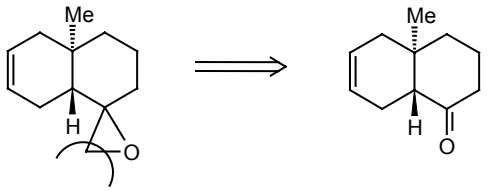


Notice that sulphur ylids behave quite differently from phosphorus ylids, which would of course do the Wittig reaction (frames 41-43).
How could you make TM 283?

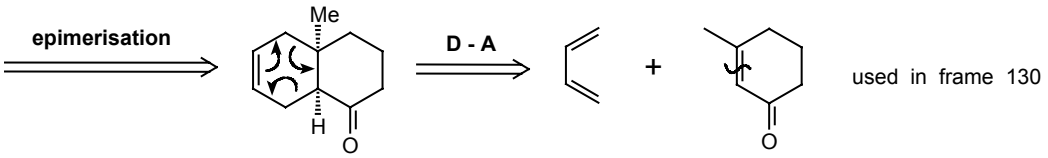
TM 283 

---

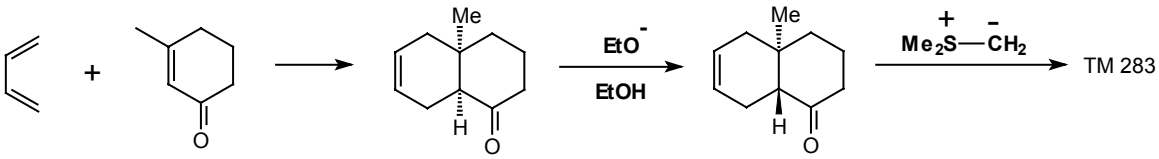
284. Analysis: Using our sulphur ylid disconnection:



This looks a Diels-Alder product, but the stereochemistry is wrong. However, the centre next to the **C=O** can be epimerised in base so:



Synthesis:



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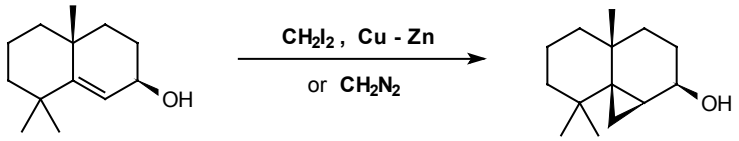
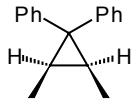
285. The same disconnection is also effective for cyclopropanes but the reagent for the carbene synthon is a diazocompound **$RCHN_2$** or a dihalo compound treated with a metal e.g.



How then might you make TM 285?

TM 285 

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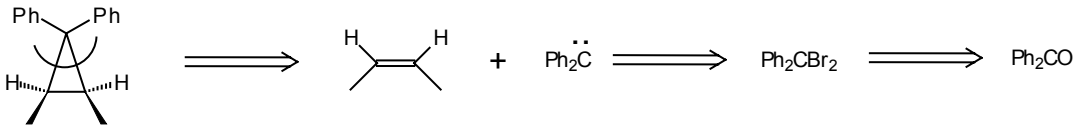
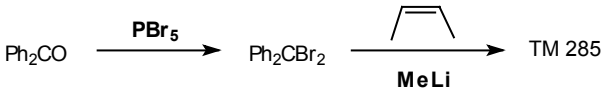
286. Analysis: Two disconnections are possible but the stereochemistry gives us the clue:



Synthesis:



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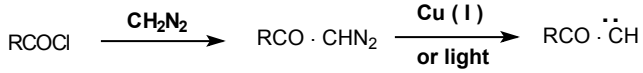
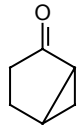
287. Diazo compounds are particularly easy to make with the diazo group next to a carbonyl group by this reaction:

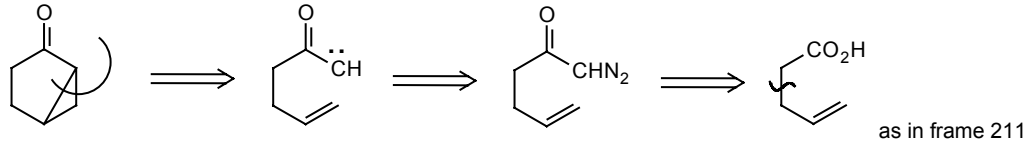


So how would you make TM 287?

TM 287 

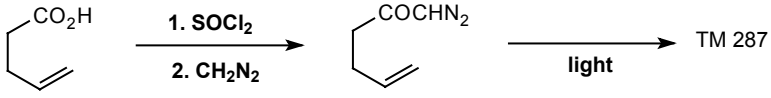
---

288. Analysis: Using the carbonyl group as a guide:



as in frame 211

Synthesis:



Similar to Tetrahedron, 1964, 20, 1870.

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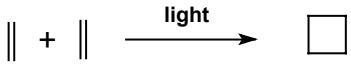
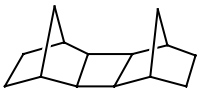
2. FOUR-MEMBERED RINGS

289. The most important disconnection for four-membered rings corresponds to the photochemical 2 + 2 cycloaddition of olefins:



This is the allowed process by the Woodward-Hoffmann rules (see Tedder, Part 3, pp. 383-387 or Norman p. 292 ff if you want to know more). There are obviously two disconnections for any given cyclobutane but it is often easy to see the better at once. How would you make:

TM 289 

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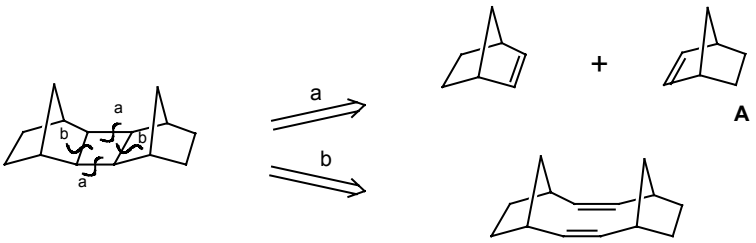
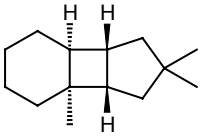
290. Analysis: The two possibilities are:



Far more is achieved by **a**, and TM 289 is simply synthesised by irradiating norbornene (A). The stereochemistry turns out all right. How about TM 290?

TM 290 

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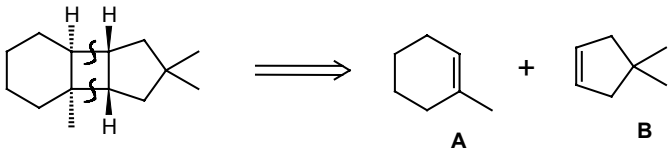
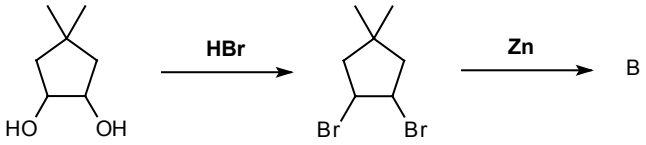
291. Analysis: TM 290 was used by Corey (J. Amer.Chem. Soc., 1964, 86, 1652) in his synthesis of α-caryophyllene alcohol. Again, only one disconnection is very productive:



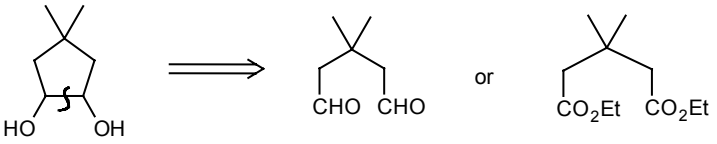
A is simply made, but the synthesis of **B** is not straightforward and it turns out that it is best done not from a mono-alcohol, but from a diol:



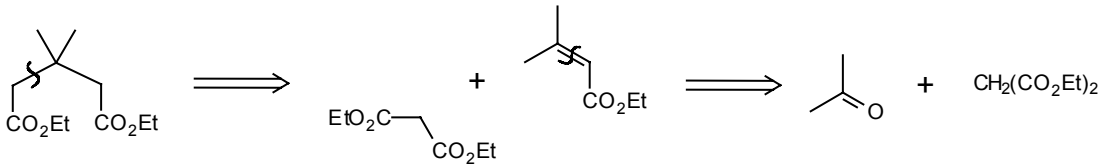
How might we make the diol (C)?

---

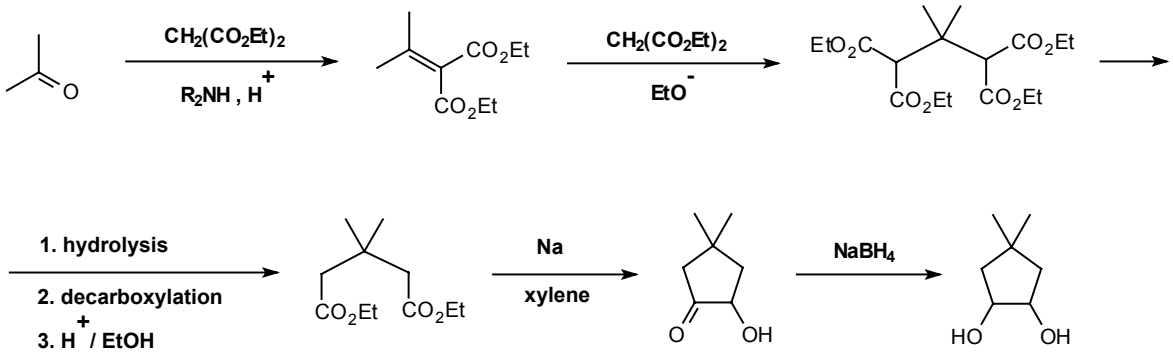
292. Analysis: Our methods for making 1,2-dioxygenated compounds (frames 154-157) involve reductive linking of a dicarbonyl compound:



These are 1,5-dicarbonyls so we shall make them by Michael reactions e.g.



the corresponding sequence with the aldehyde is not so easy to do. So one synthesis for **C** would be:



(Another version appears in J. Org. Chem., 1959, 24, 2060).

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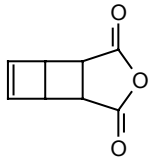
293. Just to show you that you can't automatically separate two rings to get the right disconnection (hint!). How could you make TM 293?

TM 293



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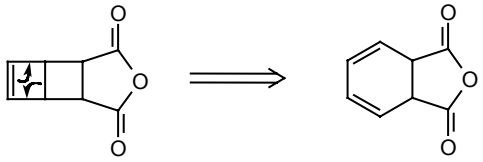
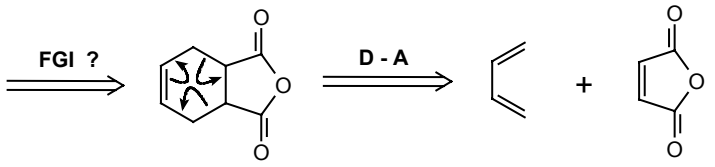
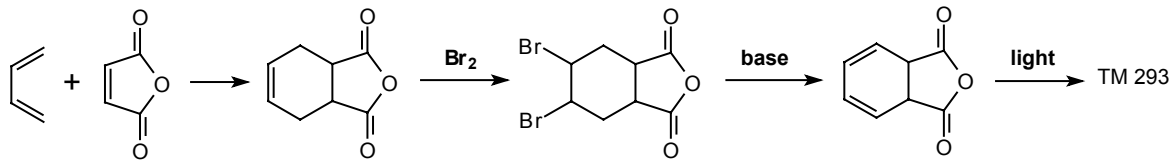
294. Analysis: Opening the cyclobutene gives this:



Now we need a Diels-Alder reaction so we must shed a double bond:



Synthesis: The FGI is easily done and the product was used by Van Tamelen (J. Amer. Chem. Soc., 1963, 85, 3297) in one of the early syntheses of a Dewar benzene:



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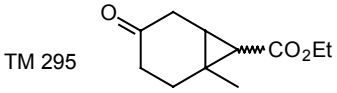
3. REVIEW PROBLEMS

295. Review problem 28: Design a synthesis for TM 295; an intermediate needed for a trichodermin synthesis.



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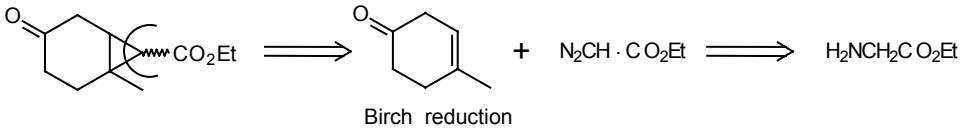
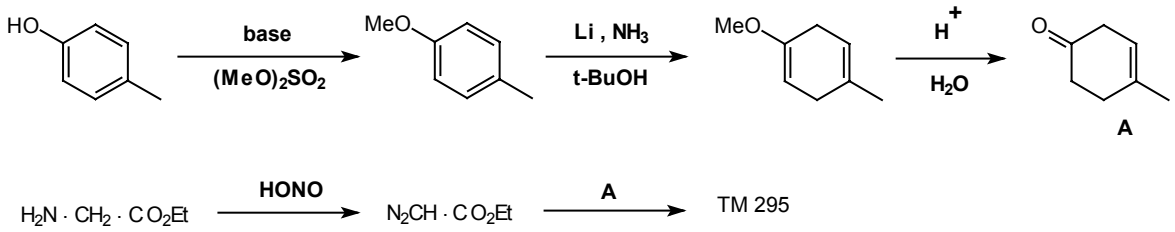
296. Analysis: Disconnecting the threemembered ring first:



Synthesis: The route used in Chem. Comm., 1971, 858:



(glycine ethyl ester)

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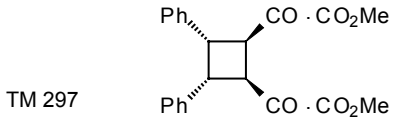
297. Review problem 29: Suggest a synthesis of TM 297.



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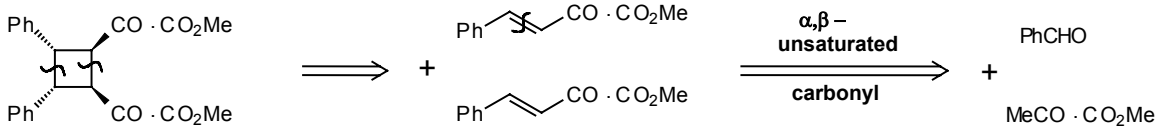
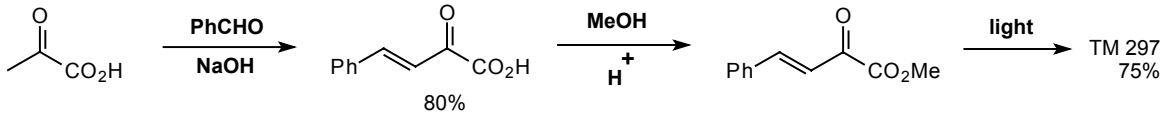
298. Analysis: Symmetry suggests that one of the two possible cyclobutane disconnections is better than other:



The keto-acid is the readily available pyruvic acid; there are many possible syntheses of this.

Synthesis: The reactions were actually carried out like this: (Stereo- and regio-selectivity turn out all right, J. Amer. Chem. Soc., 1924, 46, 783).



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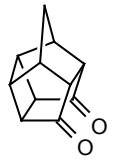
299. Review problem 30: This may look rather difficult, but concentrate on the small ring and use the disconnection you know. Suggest a synthesis for TM 299.

TM 299 

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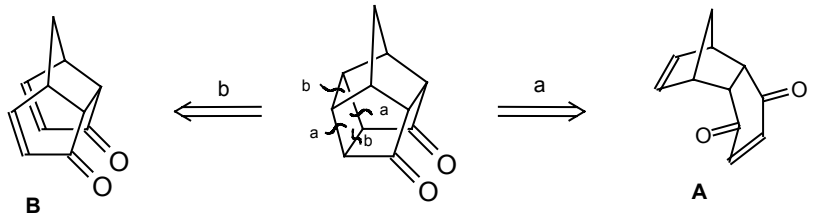
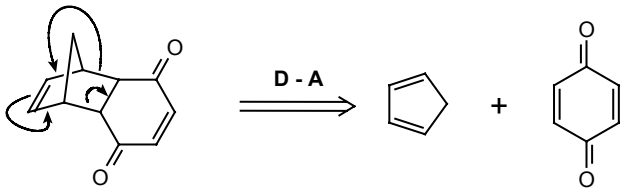
300. Analysis: This cage-like structure contains 6, 5 and 4-membered rings: we are most interested in the 4, and can disconnect this in two ways:

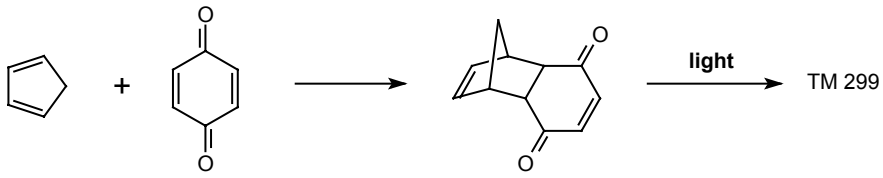


No doubt we could continue with **B** by disconnecting the α,β-unsaturated carbonyl groups, but intermediate **A** should be recognisable as a Diels-Alder product, and this is the shorter route:



both these starting materials are readily available.

Synthesis: Amazingly, this complicated molecule is made in just two steps!



I. GENERAL REVIEW PROBLEMS

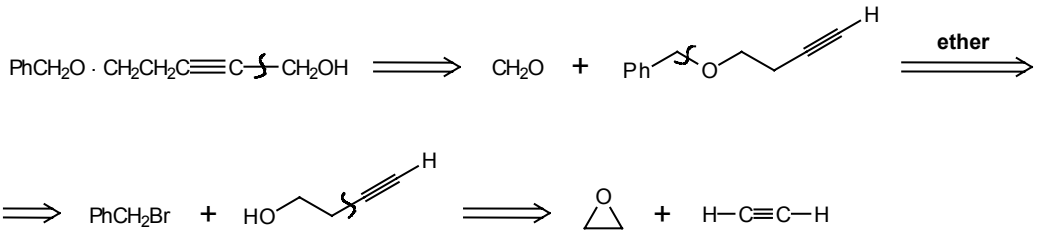
301. These problems may involve any disconnections from any section and by useful to you for revision material.

Review problem 31: Design a synthesis for TM 301.

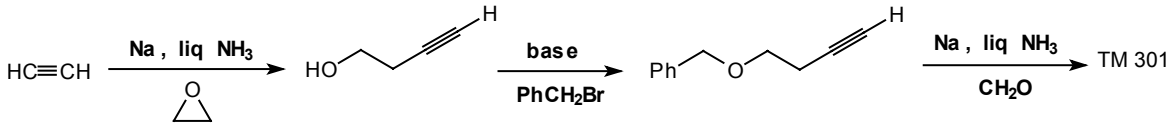
TM 301 $PhCH_2O \cdot CH_2CH_2C{\equiv}C \cdot CH_2OH$

---

302. Analysis: A simple problem to get you started – disconnect the unprotected side of the acetylene first.



Synthesis: (As described in J. Amer. Chem. Soc., 1966, 88, 3859).



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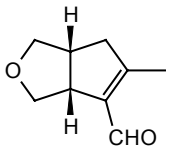
303. Review problem 32: Design a synthesis for TM 303, an intermediate used in the synthesis of substances found in ants.

TM 303



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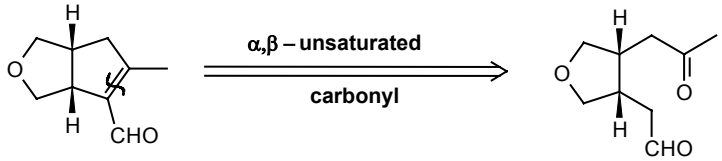
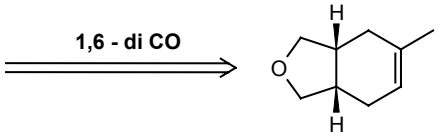
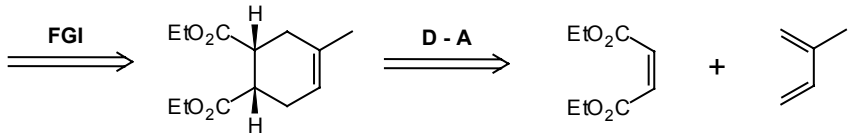
304. Analysis: We must first decide whether to disconnect the ether ring or the α,β-unsaturated aldehyde. No doubt reasonable routes could be produced for both, but I shall give one only:



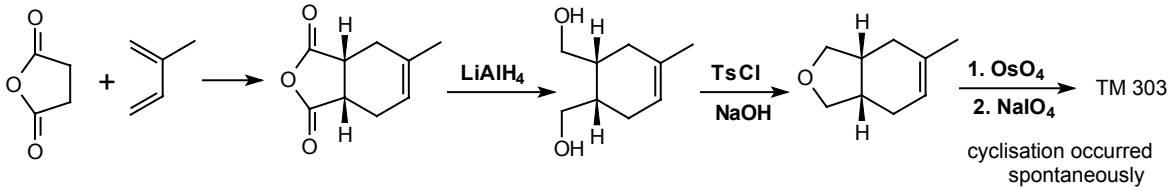
This is a 1,6-dicarbonyl compound so we must 're-connect' into a cyclohexene.



This has the oxygenation pattern of a Diels-Alder adduct if we convert it to a carbonyl compound.



Synthesis: A successful synthesis (J. Amer. Chem. Soc., 1958, 90, 3937) by this route actually uses maleic anhydride:



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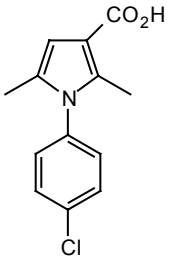
305. Review problem 33: Design a synthesis for TM 305, introduced in 1974 as the anti-inflammatory drug 'clopinac'.

TM 305



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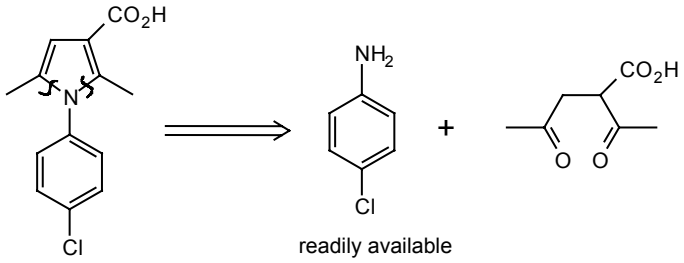
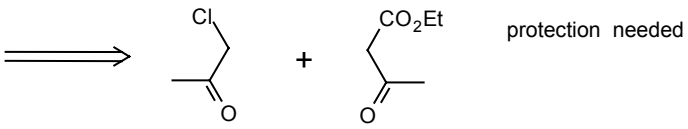
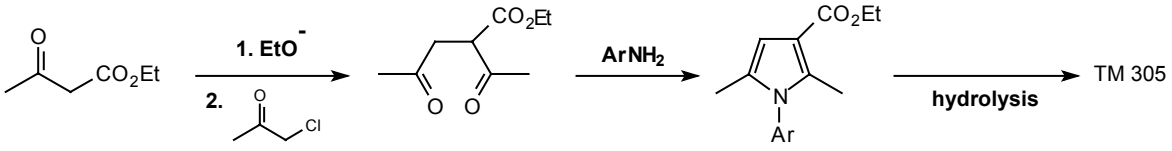
306. Analysis: The most sensible place to start is with the **N-C=C** bonds as that will give us some carbonyl groups (as in frames 253-7)



1,4-dicarbonyl, guided by the presence of the extra **CO_2H** group.



Synthesis: It's difficult to find out how drug companies make their products (understandably!) so we can only speculate:



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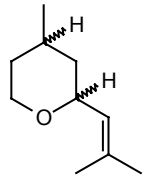
307. Review problem 34: Design a synthesis for rose oxide, TM 307, a perfume occuring in rose and geranium oils which is made at present by the oxidation of another natural product, citronellol.



TM 307

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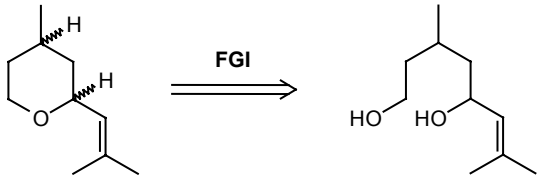
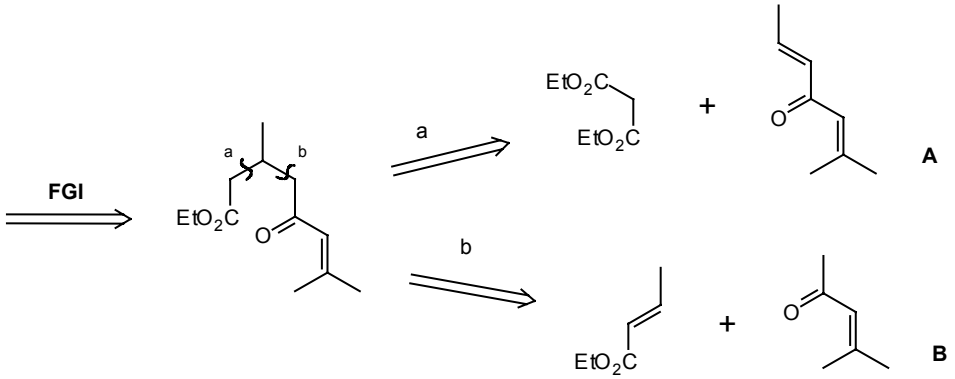
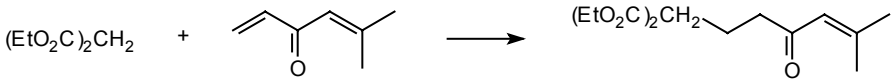
308. Analysis: The cyclic ether can clearly be made from the open-chain diol:



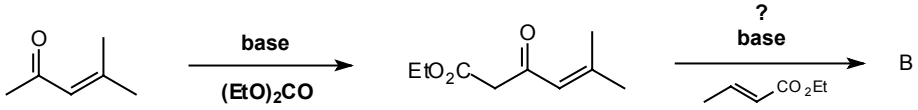
We now have a **1,5-di O** relationship which could be made by a Michael reaction if we have two carbonyl groups.



Synthesis: You will see that there are problems in both the routes found by the analysis. For route a it is known that malonate attacks exclusively the less hindered side of some Michael acceptors:



but whether it would be so selective for **A** with an extra methyl group is doubtful. For route **b**, the problem is to activate the methyl group of **B** and one method which might work is:



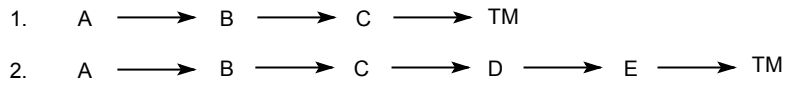
The last stages are simple enough.

The modern organic chemist has a variety both of reagents and reactions far beyond those we have looked at here. If you study organic chemistry to a more advanced level you should meet many of them but you will find that the principles of their design and use are the same as those you have learnt in this programme. We have now finished the basic types of disconnection and must look at the strategy of synthesis.

J. STRATEGY

1. CONVERGENT SYNTHESES

309. We have so far dealt mainly with the tactics of synthesis: "what is a good disconnection?" and only occasionally with strategy: "by what series of disconnection, even those which do not initially look very good, can I get back to good starting materials?" Now we must consider strategy – the overall plan of the synthesis. Our first criterion of a good synthesis is that it must be short. Work out for yourself the yield in each of these two syntheses: the yield in every step being 90%.



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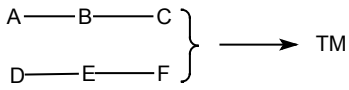
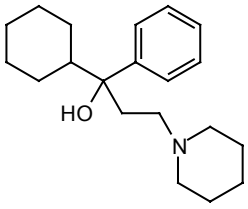
310. Yield for the 3-step synthesis (1.) is 73%
Yield for the 5-step synthesis (2.) is 59%
By the time you get to a ten step synthesis, the "arithmetic demon" ensures that the yield is down to a miserly 35%. And this with 90% yield in each step! So clearly a short synthesis is a good one. But we can cheat the arithmetic demon by making our five steps convergent rather than linear. The convergent version is this:



If the yield of each step is again 90%, what is the overall yield of this five step convergent synthesis?

---

311. Clearly it is the same as the three step synthesis, 73%. So it is better to assemble two more or less equal parts of a molecule separately and join them together at the end. Let's look at this in practice. What three alternative disconnections are immediately obvious on TM 311?



TM 311

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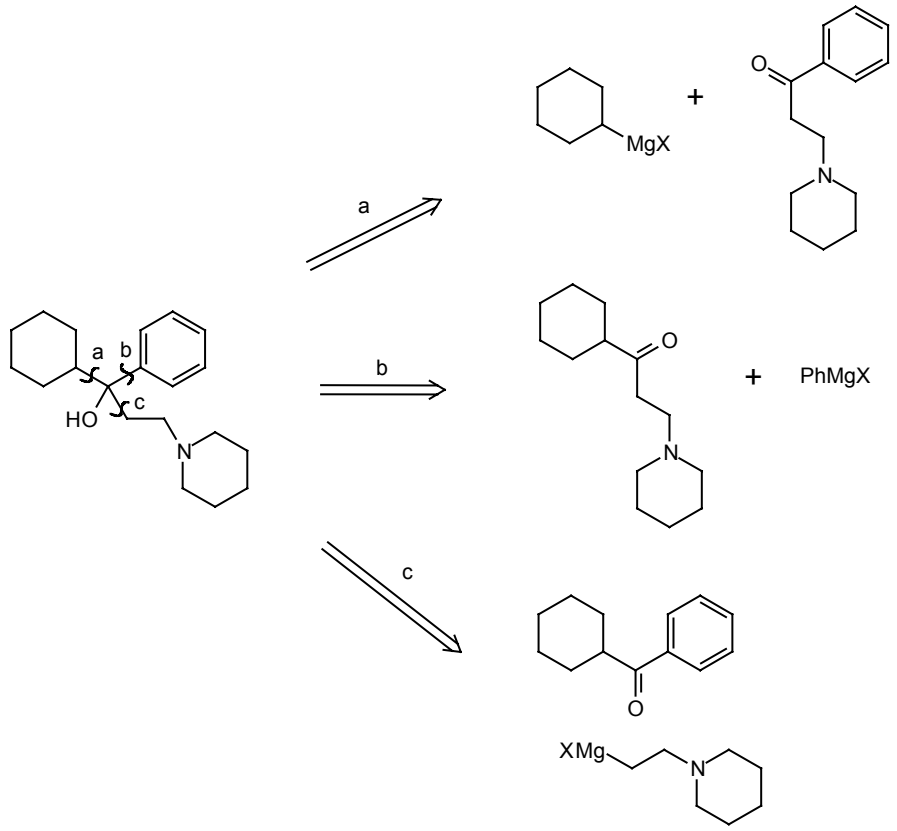
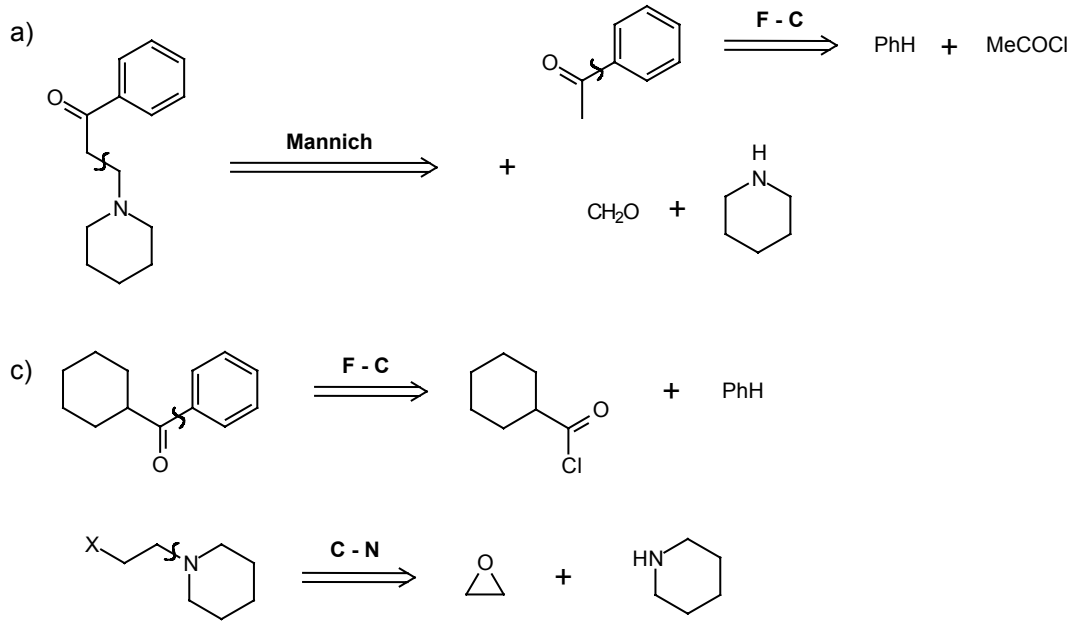
312. Analysis: Clearly we can remove any of the three groups from the tertiary alcohol.



Seeing the aromatic ketones in **a** and **c** we might have a Friedel-Crafts reaction in mind. Continue these two a stage further.

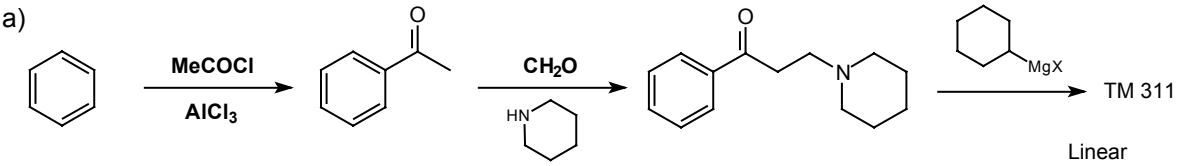
313.



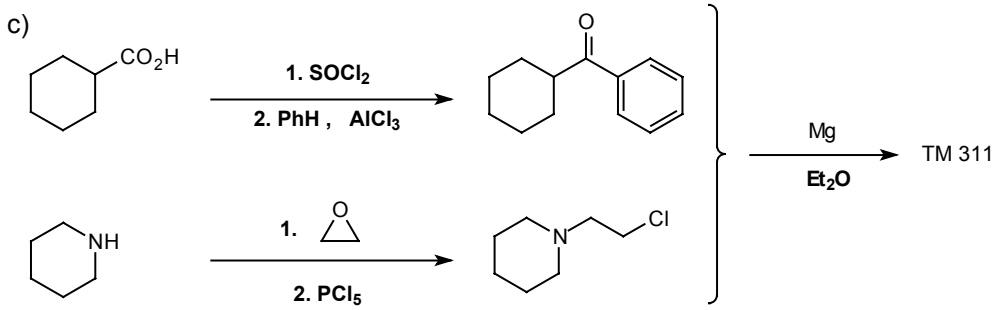
Perhaps you can see that one of these routes is linear and the other convergent. Write both out in full as syntheses to make this clear.

314.

a)



c)



TM 311 is in fact the anti-Parkinson's disease compound trihexylphenidyl and is made industrially by route **c** (Tedder, volume 5, p.418).

---

315. You may like to reflect on our criteria for good disconnections (see for example frame 76). Two of them could be called simply guides to help us find convergent syntheses. Which ones?

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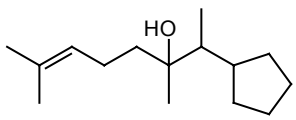
316. 1. the greatest possible simplification.
2. the use of a branch point.

With this in mind, suggest a convergent synthesis for TM 316.

TM 316



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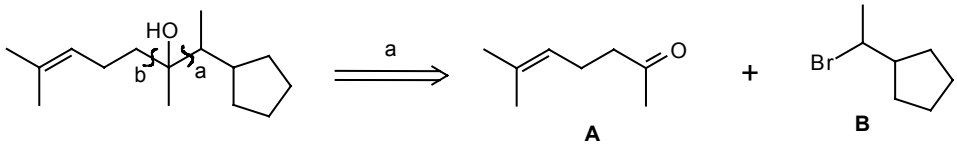
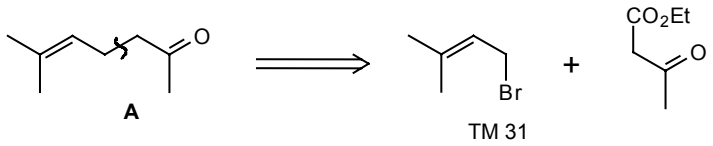
317. Analysis: Obviously we have to disconnect one of the groups next to the tertiary alcohol: two (**a** or **b**) give us plenty of simplification but only one (**a**) leads us back to a branch point:



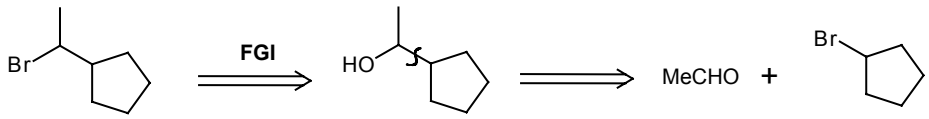
If you haven't yet considered it: how would you make **A** and **B**?

---

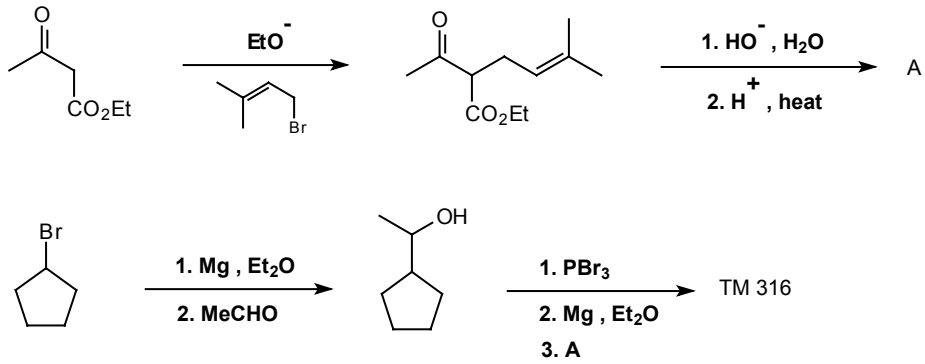
318. One of our stsndard disconnections on a ketone (frame 56) gives us a synthesis of **A** from TM 31.



B can be made by the usual methods:



Synthesis:



There are undoubtedly many other good approaches; as far as I am aware, this molecule has not been made by this route.

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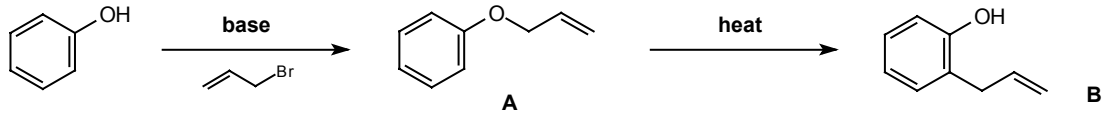
2. STRATEGIC DEVICES

(a) C - HETEROATOM BONDS

319. You have already seen that a carbon-heteroatom bond is easy to make, since we used such bonds as natural places for disconnections (frames 234 ff). It is good strategy therefore to make a carbon-heteroatom bond and then to transform it into a carbon-carbon bond. The Claisen rearrangement is one way to do this: an ortho allyl phenol (B) made from an allyl ether (A):



Draw a mechanism for the second step (A to B).

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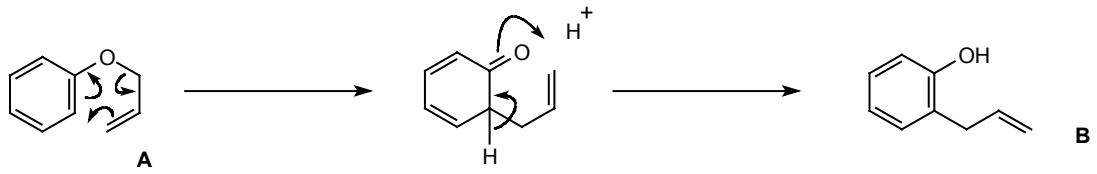
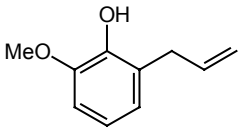
320. The reaction begins with a pericyclic step:



How then would you make eugenol (TM 320), a constituent of oil of cloves?



TM 320

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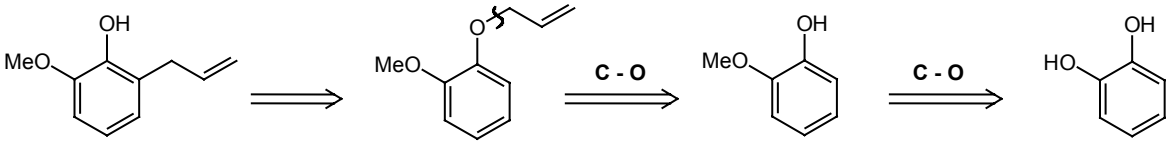
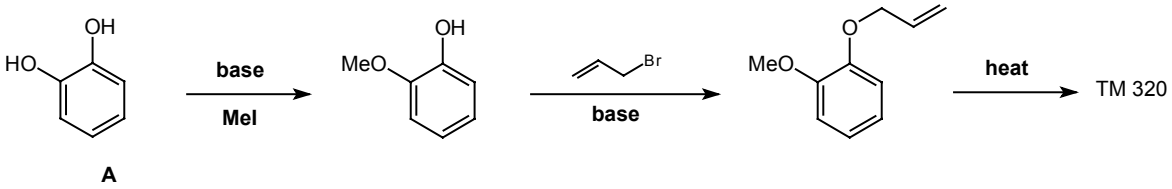
321. Analysis: The ortho arrangement of **OH** and allyl is the clue:



Synthesis: From readily available catechol (A):



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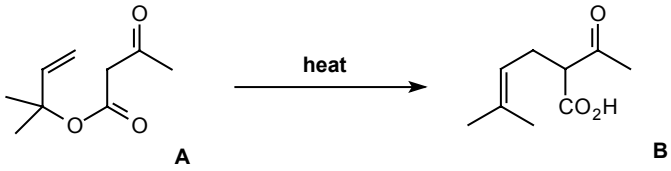
322. In an important industrial process, the "Carroll reaction", an aliphatic version of the Claisen rearrangement occurs. See if you can find the right mechanism:



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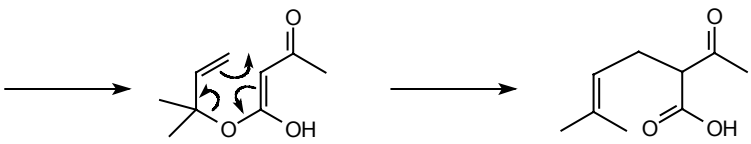
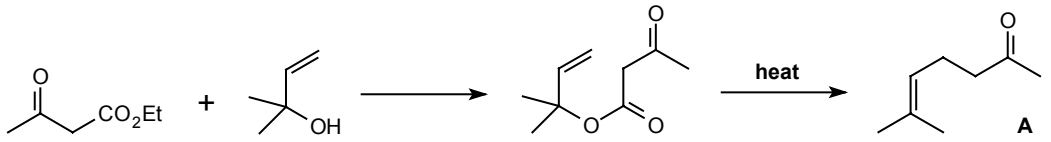
323. The trick is to make the enol – the stable enol of the β-keto ester:

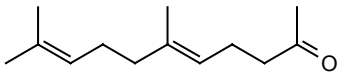


The ester 322A is made by ester exchange with ethyl acetoacetate and a suitable alcohol. The product 322B decarboxylates spontaneously on heating. Draw out the whole sequence starting from ethyl acetoacetate.

324.



We made this important intermediate (A) in a slightly different way (frame 318), but this is how it's made industrially for use in perfumes and flavours (Pure. Appl. Chem., 1975, 43, 527). How would you extend this synthesis to make TM 324?

TM 324 

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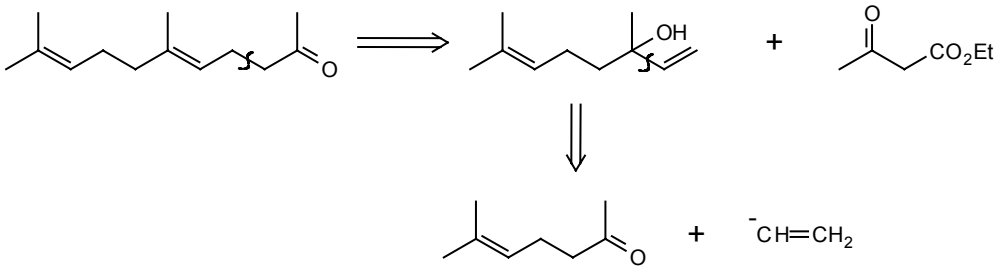
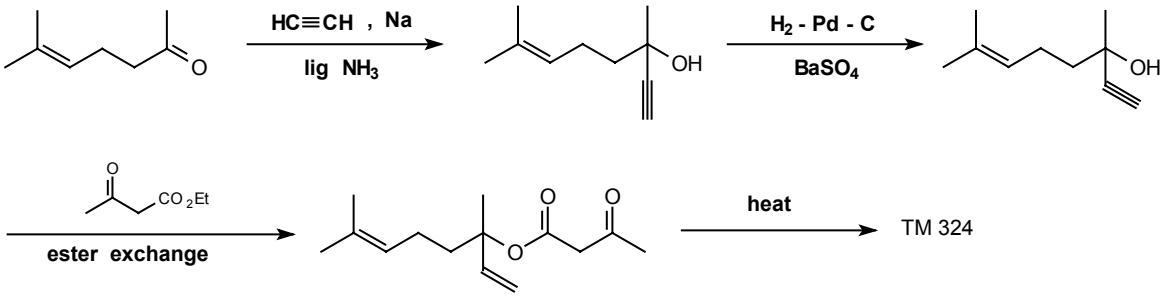
325. Analysis: Reversing the Carroll reaction:



The vinyl anion synthon is best represented by an acetylide ion (frame 33).

Synthesis:



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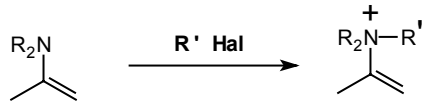
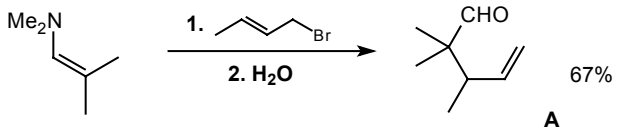
326. Another similar example concerns the alkylation of enamines. This reaction works well with reactive α-halocarbonyl compounds (frames 175ff) but simple alkyl halides often react on nitrogen:



Allyl halides do however give us good yields of alkylation at carbon:



Suggest how this might happen.

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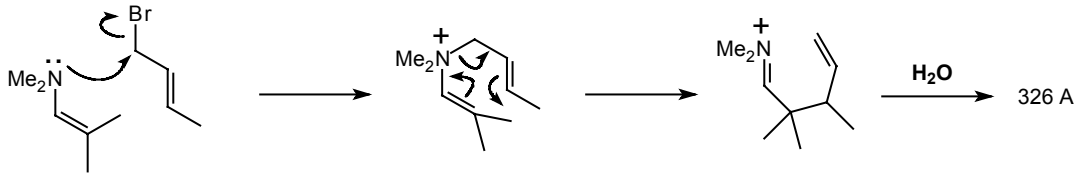
327. Since the allyl group has rearranged, it may have added to nitrogen first:



(J. Org. Chem., 1961, 26, 3576).

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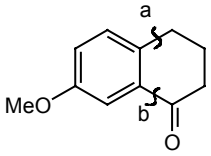
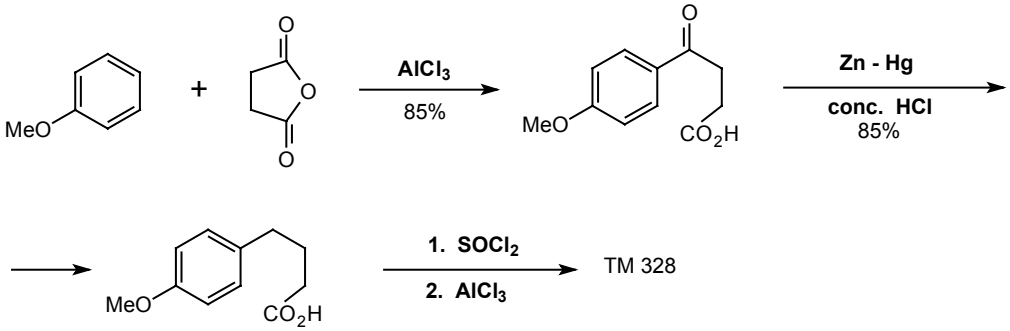
328. The strategy of using intramolecular reactions to set up the correct relationship between two groups is of more general importance. We obviously want to disconnect bonds **a** and **b** in TM 328 so that we add a four carbon fragment to **PhOMe** in the synthesis.

TM 328



It will be easy to put in bond **a** because it is para to the **MeO** group, but bond **b** might be difficult. The strategy is to put in bond **a** first and use an intramolecular reaction to force bond **b** to go in the right place. Succinic anhydride is a convenient four carbon electrophile:

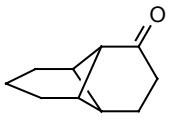


This approach is described in Org. Synth. Coll., 2, 81, 499, 571, and these particular compounds and reactions in J. Chem. Soc., 1934, 1950; J. Amer. Chem. Soc., 1936, 58, 1438, 2314; 1942, 64, 928. The final cyclisation can be done directly on the acid with anhydrous **HF** in 93% yield.

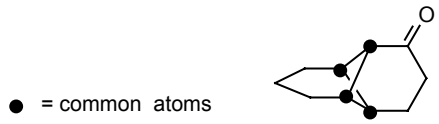
(b) POLYCYCLIC COMPOUNDS – THE COMMON ATOM APPROACH

329. Another strategic device applies specifically to polycyclic compounds. In the interests of simplification we want to remove some of the rings and give an intermediate with a familiar ring structure. We can do this by the "common atom' approach. In TM 329, mark all the carbon atoms which belong to more than one ring – the "common atoms".

TM 329



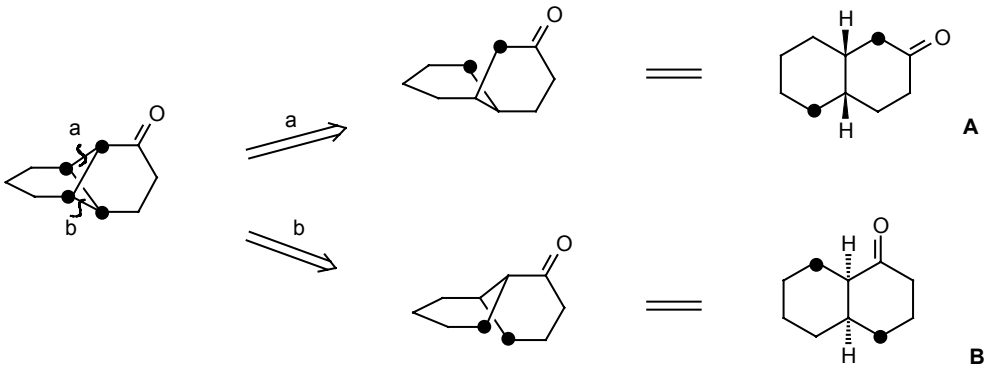
330.



Now disconnect any bond joining two common atoms and see if there is a good starting material.

---

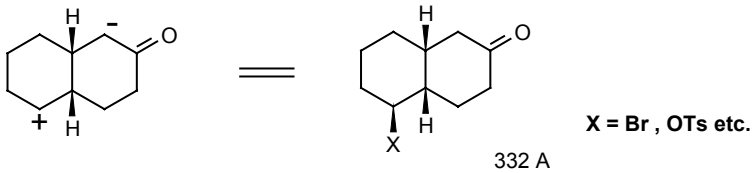
331. Because of the symmetry of TM 329 there are only two different disconnections of bonds between two common atoms.



One of the marked atoms in each intermediate will have to be + and one -. Can you see a good starting material here?

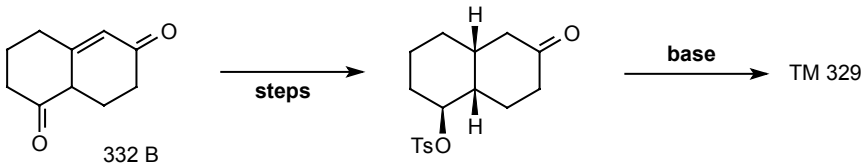
---

332. For A we can put the – next to the carbonyl group and provide a leaving group for the + :



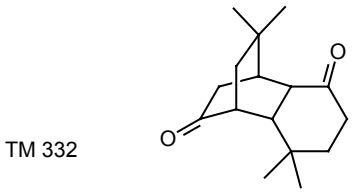
332 A

If you don't see why the stereochemistry should be as I have drawn it, I suggest you make a model of 332A and discover for yourself. There is a simple synthesis of 332A (**X = OTs**) from the Robinson annelation (frame 117) product 332B.



332 B

Using the common atom approach, design a synthesis of TM 332.



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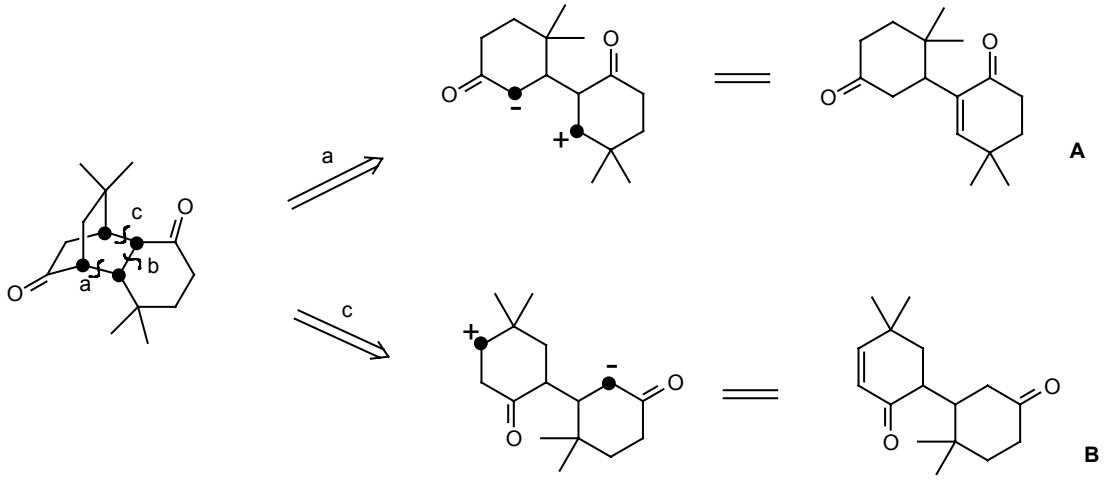
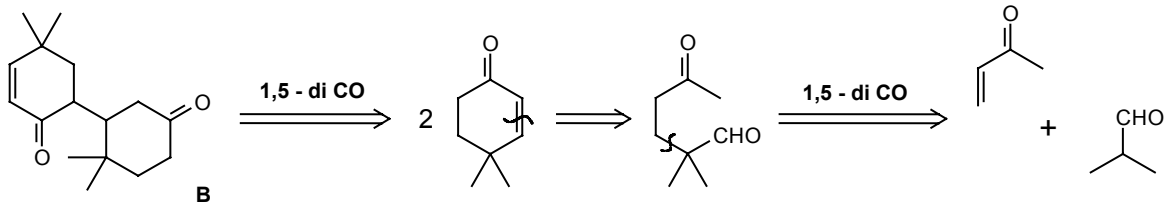
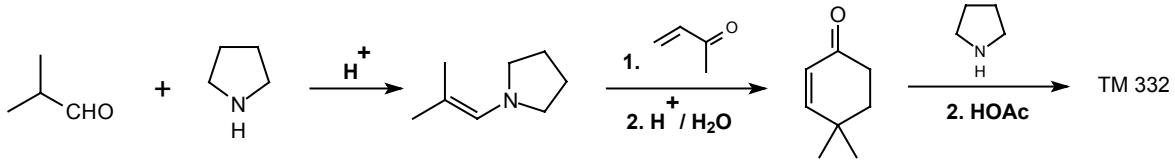
333. Analysis: Marking the common atoms we find there are three possible disconnections of bonds between them, but only **a** or **c** give us simpler precursors. Both also are 'logical' in that we can immediately write reagents for the synthons.



Both **A** and **B** are 1,5-dicarbonyl compounds, but only **B** can be disconnected in the usual way. The result is two molecules of an α,β-unsaturated ketone and we can continue the analysis:



Synthesis: Carried out by Lewis (J. Chem. Soc. (C), 1971, 753) using enamines for each step:



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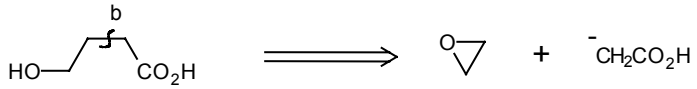
3. CONSIDERING ALL POSSIBLE DISCONNECTIONS

334. Apart from aiming for a convergent synthesis or using the two strategic devices we've just seen, special tricks in strategic planning are unimportant. The main thing is to find the shortest route with the best individual steps. To do this we ought to consider all possible disconnections even those which don't look very promising initially.

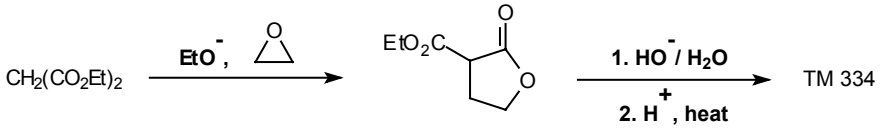
As an example, let's analyse the synthesis of γ-lactones (e.g. TM 334) and see how we may choose one of a number of strategies depending on the structure of the target molecule. We'll consider in turn each of the three **C-C** bond disconnections. The one with the most appeal is probably b: complete the analysis for this approach.

---

335. Analysis: This is the approach to 1,4-dioxygenated skeletons we used in frames 171-186. We need an 'illogical' electrophile – in this case an epoxide:



Synthesis: Protection and activation as usual:



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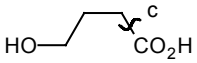
336. What possible synthons might we need for disconnection **c**:



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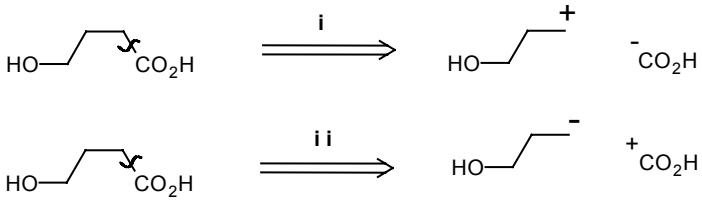
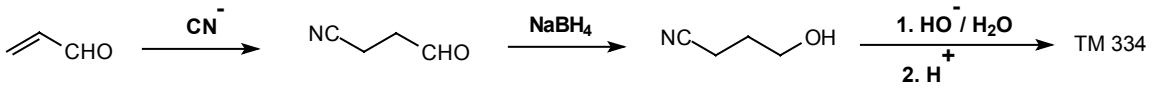
337. We can choose either polarity:



Both are possible but we are more used to (**i**) since we can use a Michael acceptor and cyanide ion for the two synthons. How would you actually do a synthesis this way?

338.



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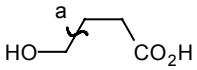
339. Now analyse the last disconnection, **a**, in the same way, writing the synthons and considering possible reagents for them.



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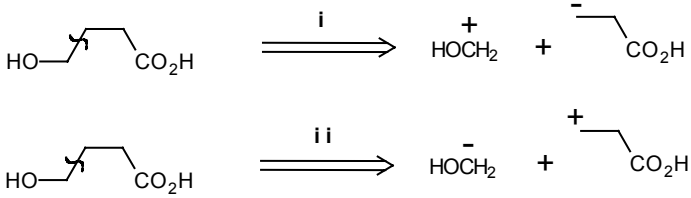
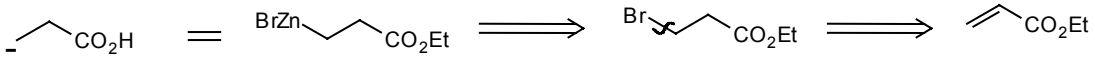
340. Again, either polarity is possible:



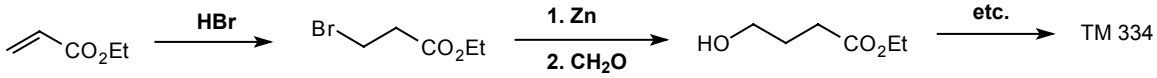
Route (**ii**) could use a Michael acceptor together with a suitable one carbon nucleophile such as **$MeOCH_2MgCl$**. Route (**i**) could have formaldehyde as the electrophile and a suitably protected and activated derivative for the nucleophile such as ...

---

341. By analogy with the Reformatsky reaction, the zinc derivative of a β-bromoester would do:



So the synthesis becomes:



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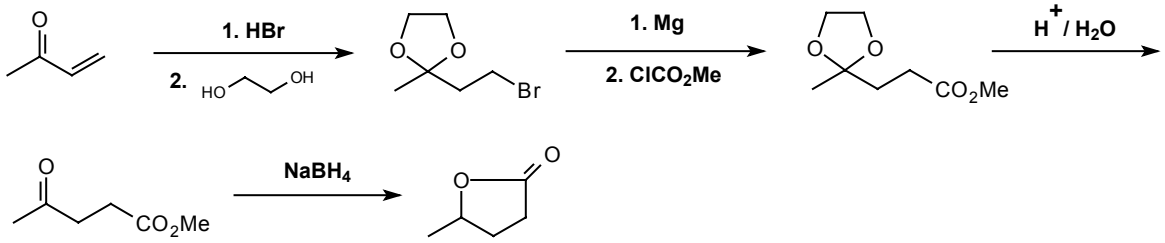
342. Each of these approaches may be the best for any given lactone: the one in the last frame for example would allow you to use any Michael acceptor and any aldehyde.

Which strategy is being followed here?



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343. One we hadn't explored in detail: it's strategy **c** (**ii**) outlined in frame 337 with **$ClCO_2Me$** for **$^+CO_2H$** and the protected β-bromoketone for **$MeCH(OH)CH_2CH_2^-$**.

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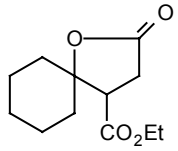
344. Now try this one for yourself: Suggest which strategy is most suitable for TM 344.

TM 344



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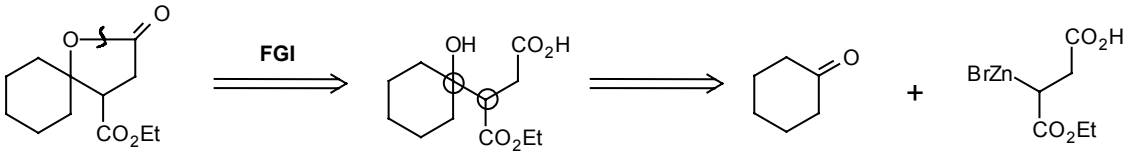
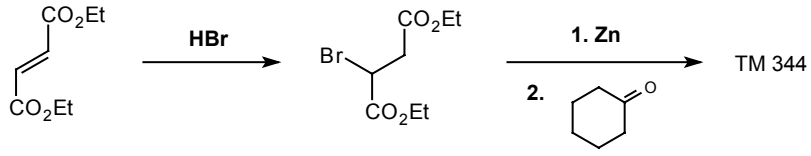
345. Analysis: Opening up the ring to see the true problem & using our branch point guide we really want to disconnect the bond between the two ringed atoms so that strategy **a** (**i**), frame 340 is best.



Synthesis: Putting **R = Et**, this is easy:



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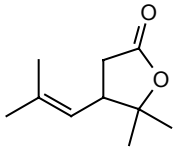
346. now try your hand at this more challenging example.

TM 346 

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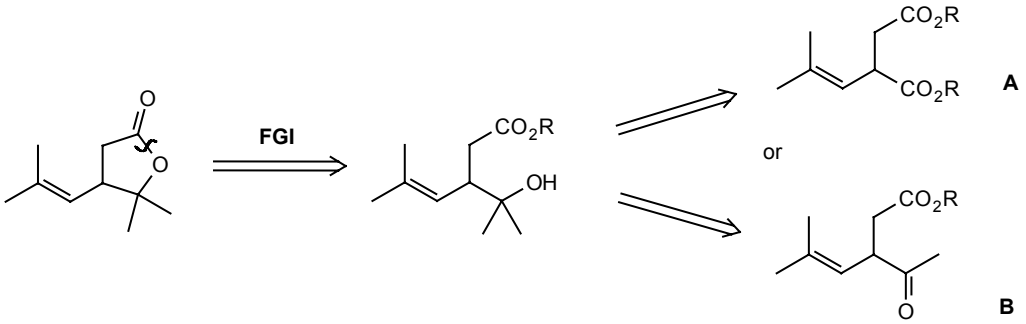
347. Here is one possible solution:

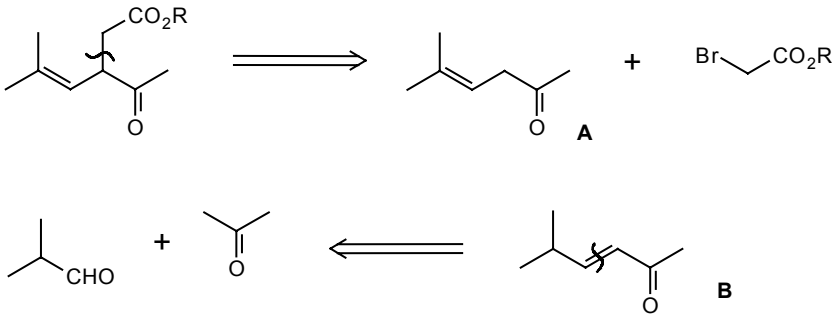
Analysis: As usual, we open the ring first: the tertiary alcohol can be made by adding one or two mols of **MeMgI**.



A is no good because **MeMgI** would have to attack the more crowded ester first. So, how do we make **B**?

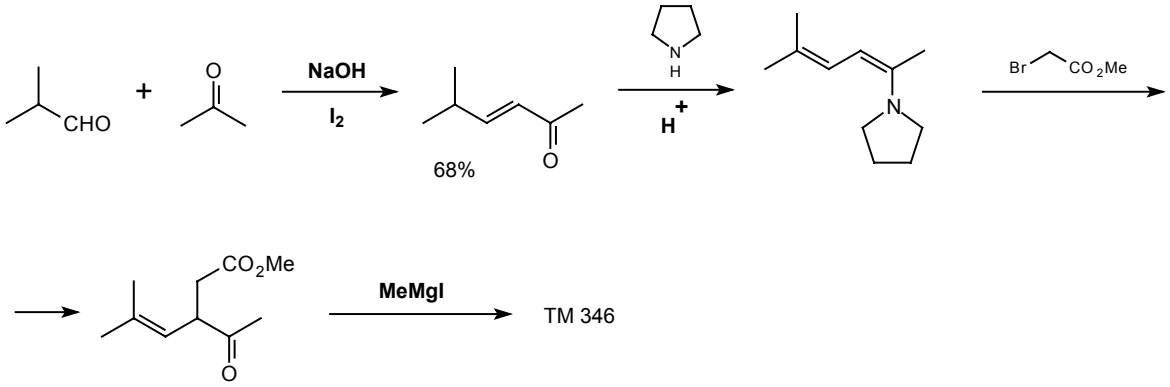
---

348. Analysis: The most suitable disconnection follows the strategy we originally used (**b**, in frames 335, and 171-175). But can we make the right enamine from the unsaturated ketone, and does it alkylate in the right place? It turns out that it can and does.



Either 348A or **B** gives the right enamine, but **B** is an α,β-unsaturated ketone and so easier to disconnect.

Synthesis: (Bull. Soc.Chim. France, 1955, 1311; 1962, 2243).



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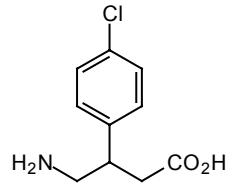
4. ALTERNATIVE FGIs BEFORE DISCONNECTION
The Cost of a Synthesis

349. The γ-lactone problem is made easier because the FGs are all based on oxygen. The molecule can therefore be disconnected without FGI except for oxidation or reduction. Let's now look at the synthesis of a molecule with a 'difficult' FG: the muscle relaxant 'baclofen' TM 349. What is the difficult FG?



TM 349

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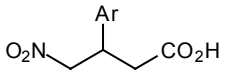
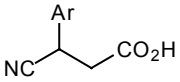
350. The amino group.
What FGI's on TM 349 give us molecules we can disconnect? There are in fact three, but you may not see one of them.

---

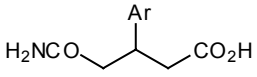
351. We have meet **NO_2** and **CN** before, but a primary amine can also be made from an amide by the Hofmann degradation (see Norman p.446-7 or Tedder, vol.2, p.281-2).



351 A



351 B



351 C

To make 351C we need to convert a dicarboxylic acid into its half amide. How might we do this?

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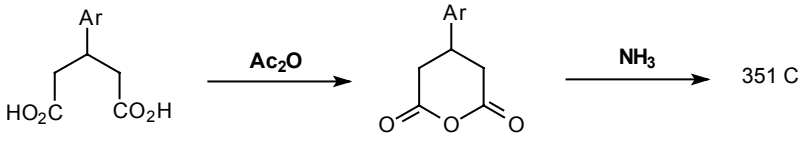
352. Since the molecule is symmetrical, attack of ammonia on the cyclic anhydride will do it:

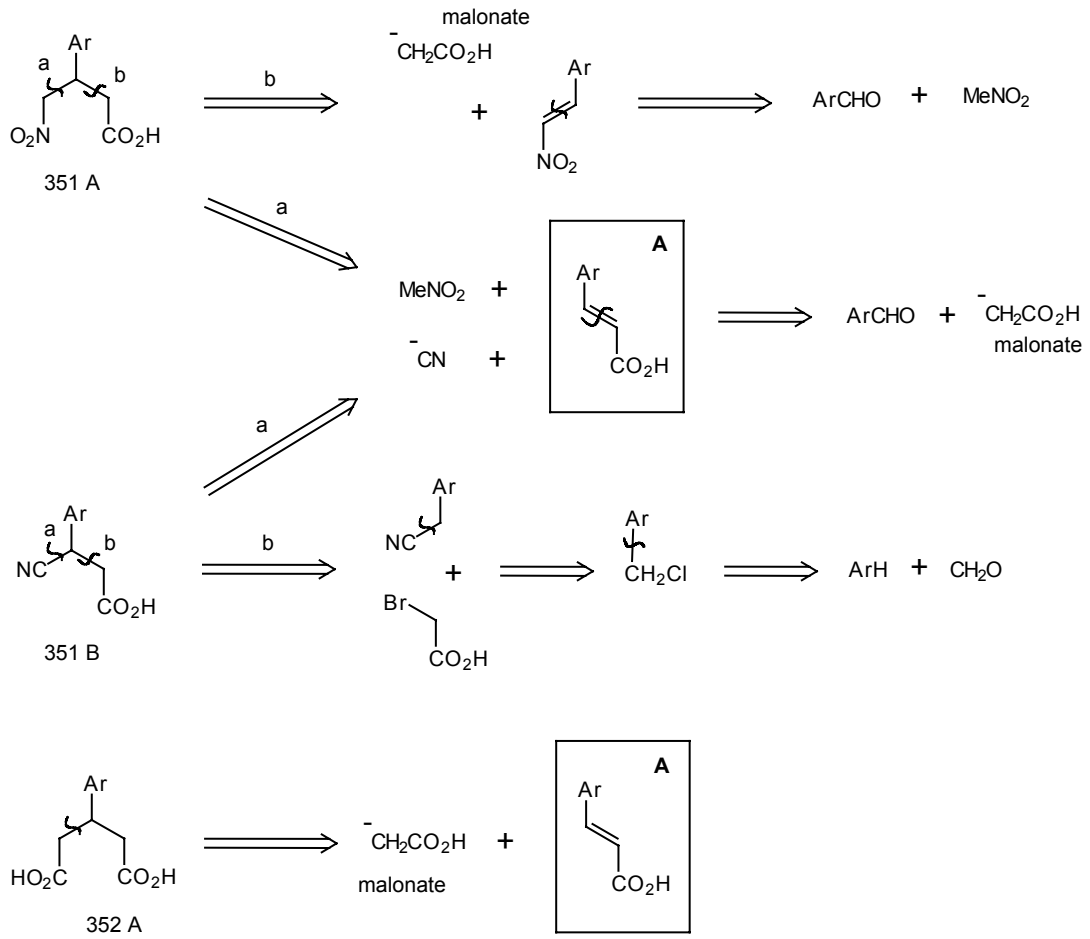


352 A

So we really need to disconnect 351A and B and 352A. Analyse possible disconnections of these three on the same chart since they will have several starting materials in common.

---

353. Analysis: All by familiar disconnections.



All these routes use known reactions and are about the same length. Do you notice that no less than three have the unsaturated acid 353A as an intermediate. If we need to try out new reactions it is best to choose a route with a common intermediate (353A here) so that if one route fails we can use the same intermediate for another. We can then choose between the three routes on cost. The 1977 prices of the starting materials are:

p-chlorobenzaldehyde &9.80/500g
diethyl malonate &2.80/500g
sodium cyanide &2.07/500g
nitromethane &6.80/kg

Assume solvents etc., cost the same for each route. Which route will you try first?

---

354. Cost per mole is the relevant figure:

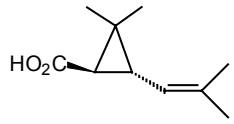
p-chlorobenzaldehyde, MW 140.5, costs &2.75 per mole.
Diethylmalonate, MW 160, costs &0,89 per mole.
Sodium cyanide, MW 49, costs &0.20 per mole.
Nitromethane, MW 61, costs &0.41 per mole.

353A is common to all the routes we are considering but it is obviously cheaper to use a mole of cyanide or nitromethane rather than another mole of malonate. In fact, though, these contribute relatively little to the cost, the main part being p-chlorobenzaldehyde. So, use whichever route you like!

5. FEATURES WHICH DOMINATE STRATEGY

355. Chrysanthemic acid (TM 355) is an important constituent of pyrethrins – naturally occurring insecticides which are virtually harmless to mammals. What feature of this molecule will dominate our strategic thinking?

TM 355



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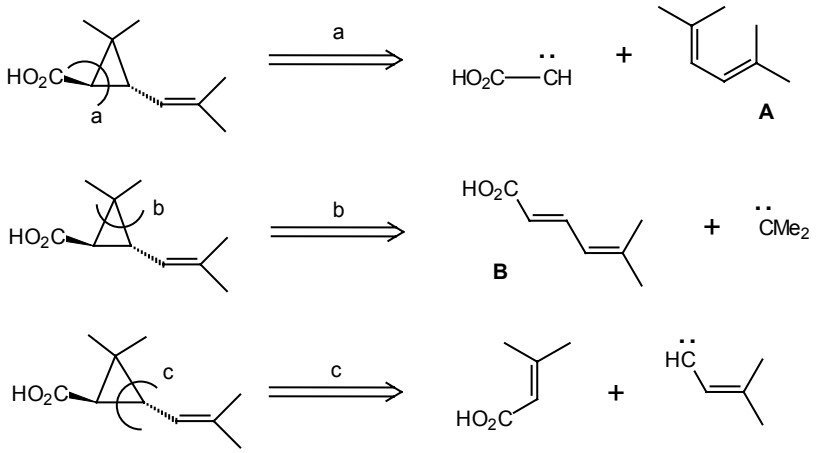
356. You might reasonably have said stereochemistry, but the best answer is the three membered ring. Which three 'carbene' disconnections might we consider? (See frames 276-288 if you've forgotten all this!).

---

357. We disconnect two bonds at once to give us a 'carbene' and an olefin:

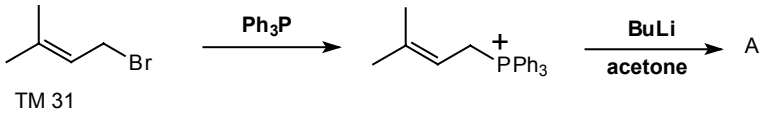


How would you actually carry out **a** and what do you think of the prospects?

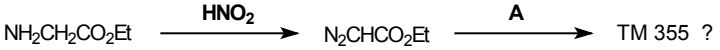
---

358. Analysis: The carbene synthon is easy: it can be ethyl diazoacetate **N_2CHCO_2Et**. The diene can be made by the Wittig reaction from a familiar allylic bromide (TM 31).

Synthesis:



TM 31



Comments: The diene **A** is symmetrical so it doesn't matter which double bond is attacked by the carbene. On the other hand, it may be difficult to stop carbene addition to the second double bond. The only control over the stereochemistry will be that the trans compound we want is more stable. Japanese chemists have recently synthesised optically active trans chrysanthemic acid by this route (Tetrahedron Letters, 1977, 2599).

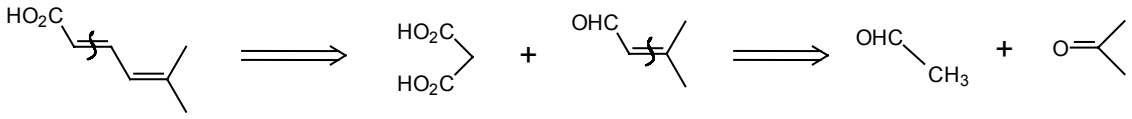
It turns out thatthe less stable cis can be converted into the trans by treating the ethyl ester with **EtO^-** in **EtOH**. (ibid., 1976, 2441).

---

359. Now consider strategy **b**. How would you make the diene acid **B**, what reagent would you use for the carbene synthon, and how do you rate the chances of this route?

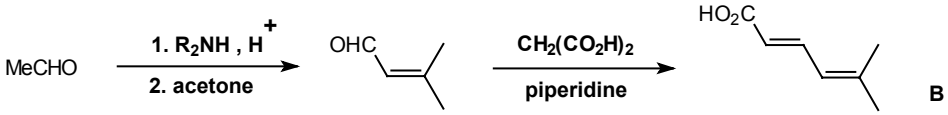
---

360. Analysis: The normal approach to the diene looks all right:

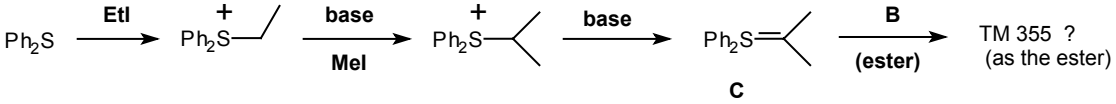


The carbene synthon might be difficult, but since the olefin is conjugated with a carbonyl group we could try a sulphur ylid as a nucleophilic carbene equivalent (as in frame 283).

Synthesis: The diene could be made by this route:



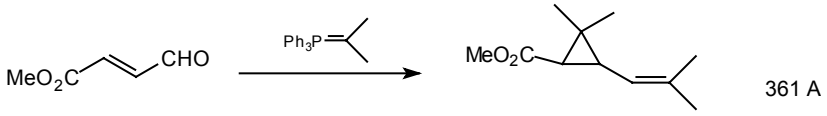
One example of a suitable suitable sulphur ylid is the one below (C) (Corey, Tetrahedron Letters, 1967, 2325) and ylids of this sort have been added to α,β-unsaturated ketones (Tetrahedron Letters, 1966, 3181):



Comments: We have to explore new chemistry here and the main problem does seem to be getting the right combination of diene and carbene reagent. Perhaps not such a good route.

---

361. However, things don't always conspire against us in synthesis! In 1976 Krief (Tetrahedron Letters, 1976, 3511) carried out an innocent-looking Wittig reaction which might reasonably have given the ester of diene 360B. Instead it gave the ester of TM 355 in good yield! Can you explain what has happened?



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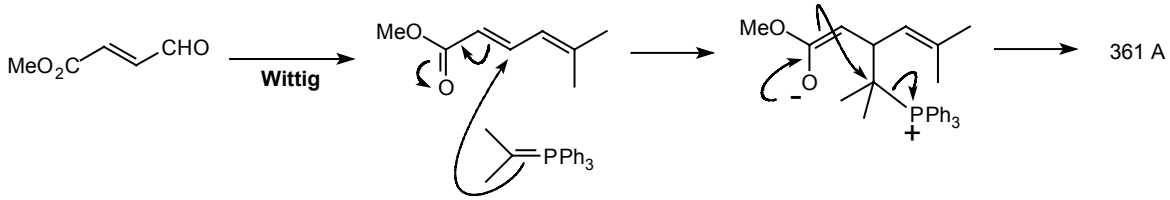
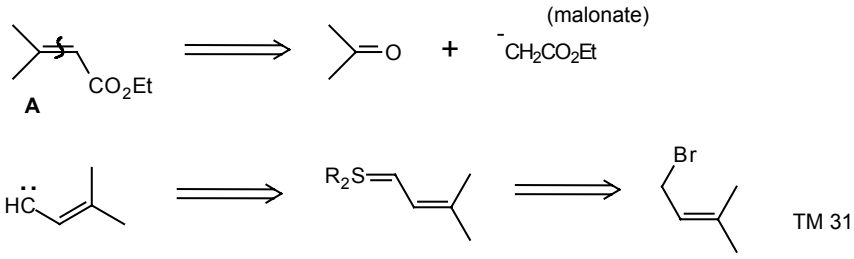
362. First the normal Wittig reaction, and then a second mol of Wittig reagent must be behaving as a carbene equivalent, just as we hoped the sulphur ylid would.



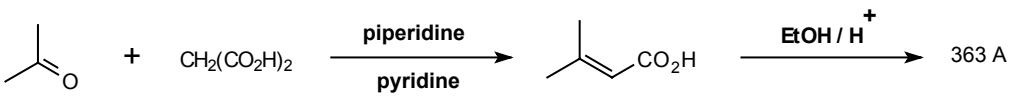
So this strategy turns out to be all right too. Now how might you realise strategy **c** in frame 357?

---

363. Analysis: The unsaturated acid (or better ester) is easy enough while the carbene reagent might be a sulphur or phosphorus ylid based on our old friend TM 31:



Synthesis: Though the ester 363A has been made this way (J. Indian Chem. Soc., 1924, 1, 298) in 60% yield, the rest of the synthesis has not yet been tried as far as I know.



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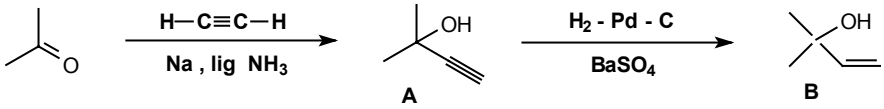
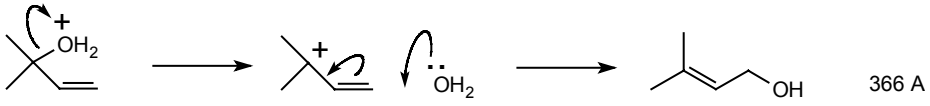
364. Perhaps the most sensational synthesis of chrysanthemic acid uses this strategy. You may remember that TM 31 is usually made from the adduct of acetylene and acetone. Draw out the stages of this reaction sequence.

365.

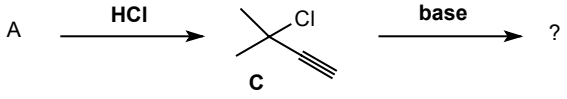


Raphael has devised a commercial synthesis using intermediates 365A and **B** to provide the two halves of the molecule. **B** is converted in aqueous acid to an isomeric alcohol. Draw this.

366.



Now **A** is converted into its chloride, (C) and this is treated with base. Which proton will be removed?



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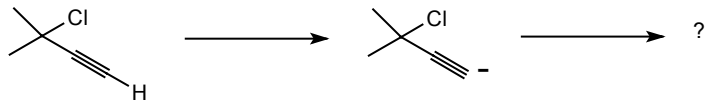
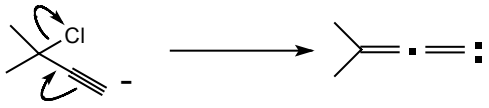
367. The acetylenic proton! The carbanion now eliminates $\mathbf{Cl^-}$ to give a most odd-looking carbene. Can you see what it is?

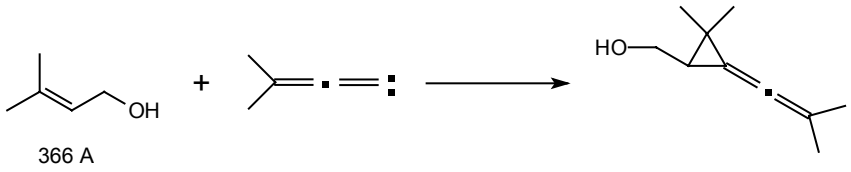


368.



This allenic carbene is now added to the alcohol 366A. What will be the product?

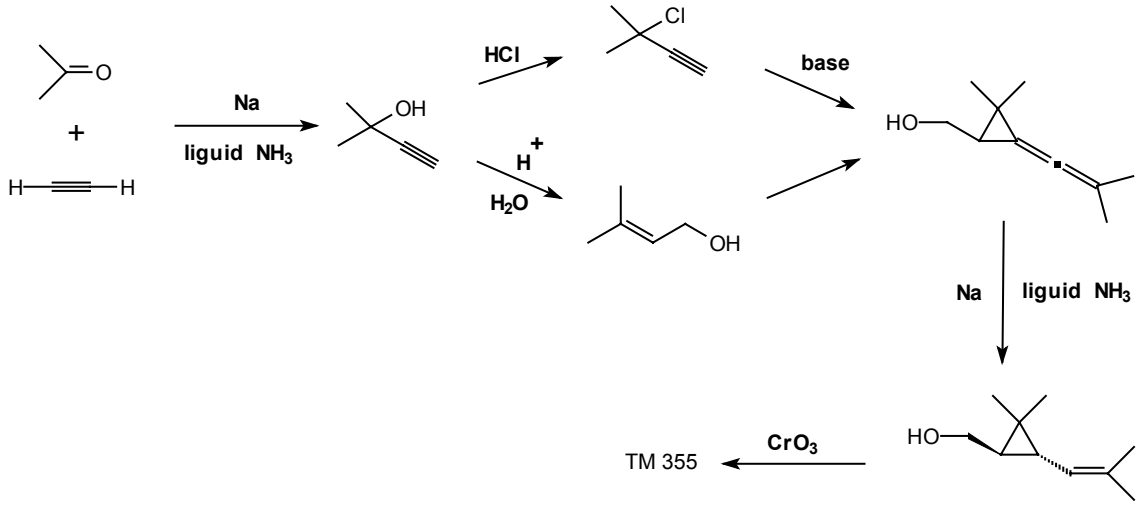
369.



Note that no stereochemistry has been introduced so far. Reduction (sodium and liquid ammonia) selectively gives trans chrysanthemic alcohol which can be oxidised to the acid with **CrO_3**. Draw out the whole synthesis as a chart.

---

370. This is Raphael's complete synthesis of chrysanthemic acid (Chem. Comm., 1971, 555; J. C. S. Perkin I, 1973, 133):



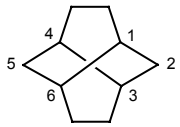
In all, only six steps are involved, making this a most economical synthesis. Chrysanthemic acid is important enough to have been made in many other ways too (e.g. Tetrahedron Letters, 1976, 2441; Bull. Soc. Chim. France, 1966, 3499).

---

6. FUNCTIONAL GROUP ADDITION

(a) STRATEGY OF SATURATED HYDROCARBON SYNTHESIS.

371. Perhaps you can see from these examples that it is possible to mould quite poorlooking initial disconnections into good overall strategies. We need to be particularly flexible in designing the synthesis of hydrocarbons since we have no functional groups to guide us. Take 'twistane' (TM 371) for example. This molecule has a six-membered ring (numbered) fixed in the twist boat conformation and the molecule was needed to study this unusual feature. In designing a synthesis of twistane, which bonds might we want to disconnect?



TM 371

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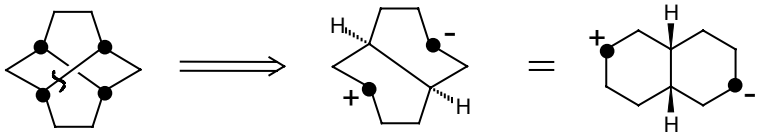
372. Using our strategic device of marking atoms common to more than one ring (see frames 329-333), we find there is only one disconnection of a bond joining two common atoms as the molecule is symmetrical:



Now we must introduce some functional groups to turn this synthon into a reagent. What do you suggest?

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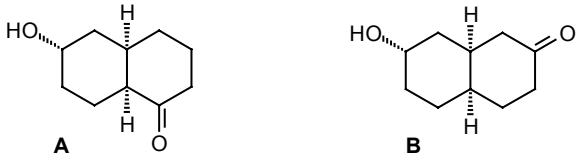
373. The obvious ones are a carbonyl group next to the anion and an **OH** group (which can easily be converted into a leaving group) for the cation giving two possibilities:



One of these has a familiar oxygenation pattern Which?

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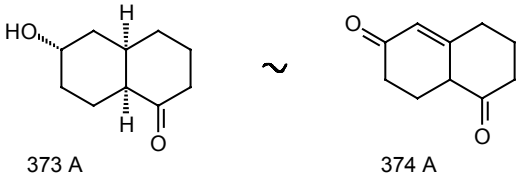
374. A has the same oxygenation pattern as the Robinson annelation product 374A (frames 117-8).



How might the conversion be done?

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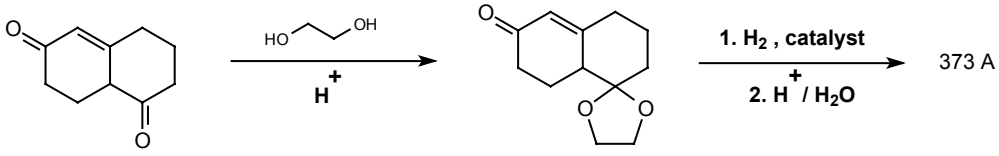
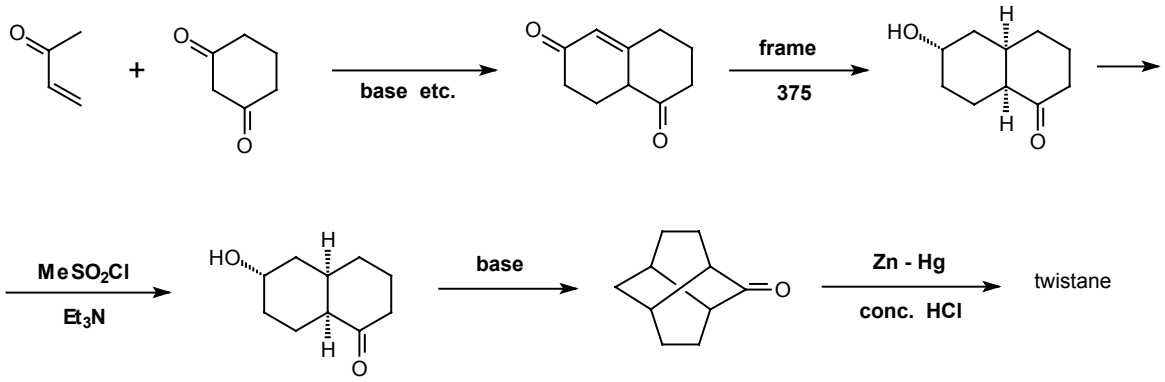
375. The saturated ketone is more reactive than the conjugated ketone so we shall need to protect the one before reducing the other.

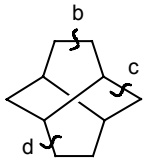


Now draw out the rest of the synthesis, before and after 373A.

376.



Twistane has been synthesised using this approach, though with different details, and also by roites using three other reasonable disconnections (**b**, **c**, and **d**). These are described in the kind of language used in this programme by Hanson and Young (Austral. J. Chem., 1976, 29, 145).



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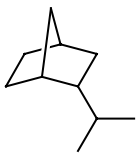
377. The most important point in analysing the synthesis of a hydrocarbon is where to put the carbonyl group, and this can depend on features other than common atoms. What strategies might you use in the synthesis of TM 377?

TM 377 

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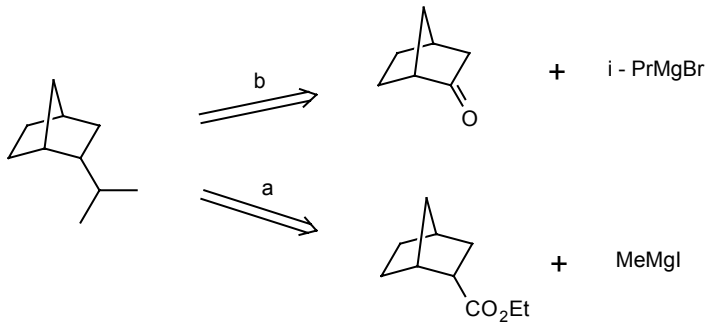
378. The isopropyl group could be derived from a carbonyl group and a Grignard reagent in two ways:



followed in each case by elimination of water and reduction of the olefin. Further thoughts?

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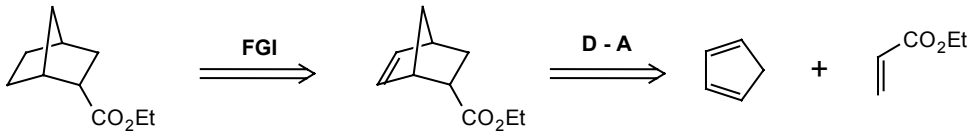
379. Strategy **a** can lead back to a Diels-Alder reaction if we put in another double bond – a trivial step since we are going to reduce out all double bonds at the end:



Write out the synthesis.

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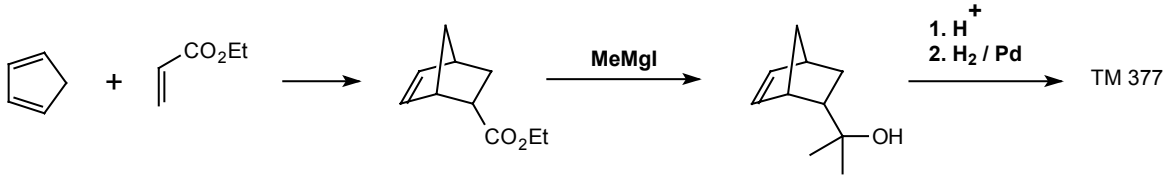
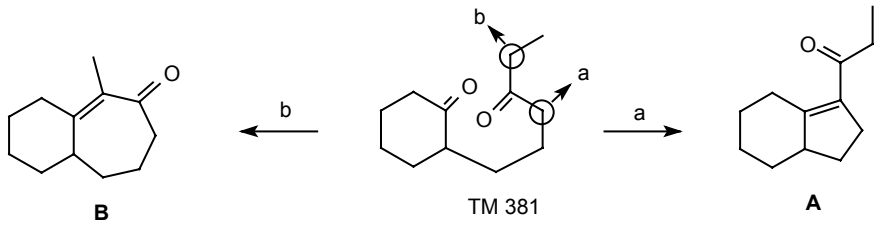
380. Synthesis:



(b) FUNCTIONAL GROUP ADDITION TO INTERMEDIATES

381. Consider this problem: We have always assumed that intramolecular carbonyl condensations giving 5 or 6 membered rings are preferred over those giving 4 membered rings. But what about 7 membered rings? Some chemists recently wanted to investigate this point and chose to cyclise TM 381 to see if **A** or **B** were formed. First, TM 381 has to be made. How do you suggest they do it?



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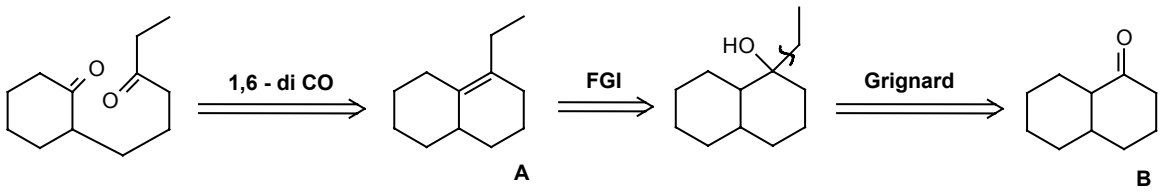
382. Analysis: This is a 1,6-dicarbonyl compound so a reconnection is called for. The next obvious series (frames 36-8) of disconnections ends up at 382B – not an easy compound to make. Where could we put a carbonyl group in 382A to allow some more helpful disconnections?



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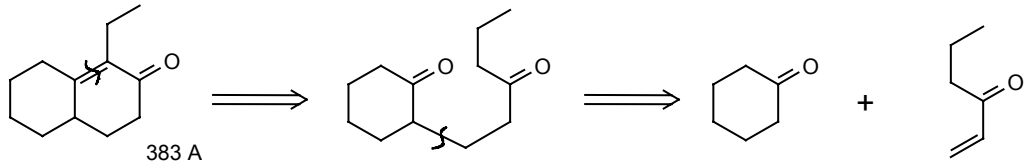
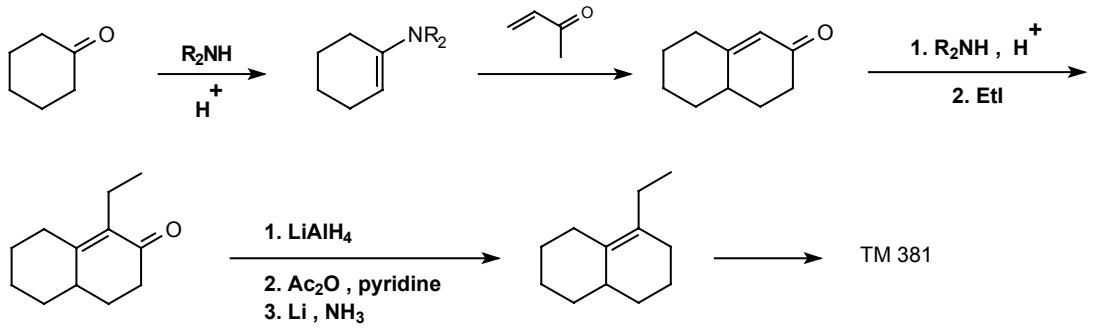
383. Analysis continued: I suggest to give 383A since one can then disconnect the α,β-unsaturated ketone and get a starting material with only one ring:



Synthesis: This was in fact done by a minor variation on our strategy, the ethyl group being added later:



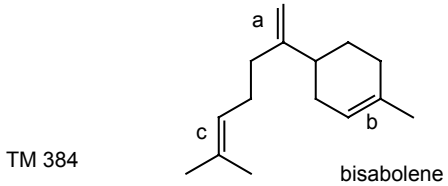
When they treated TM 381 with base (**MeO^-** in **MeOH**) it was in fact 381A which was formed, so five membered rings are better than seven membered rings (J. Org. Chem., 1976, 41, 2955).

Though you can in principle add a carbonyl group anywhere in a target molecule, remember it means extra steps in the synthesis so use it only as a last resort.

---

7. MOLECULES WITH UNRELATED FUNCTIONAL GROUPS

384. Saturated hydrocarbons were a problem because they have no functionality. It can be just as bad when a molecule has several functional groups all apparently unrelated. Bisabolene (TM 384) has three double bonds, all rather widely separated. Comment on possible strategies in terms of the likely origin of each double bond and the probable order of events.

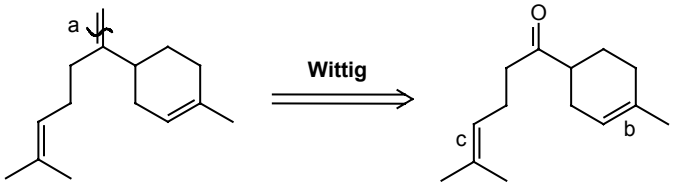


TM 384 bisabolene

385.

(a) This double bond almost certainly comes from a Wittig reaction with **$Ph_3P{=}CH_2$** on the corresponding ketone. A good place to start.
(b) This could come from **MeMgI** addition to a ketone, from a Diels-Alder reaction, Birch reduction, or Robinson annelation. Not a good place to start.
(c) This could come from a Wittig reaction (either way round) or by addition of **$Me_2C{=}CH{\cdot}CH_2Br$** (TM 31) to some other compound. Quite a good place to start.
On balance it looks best to start with **a**. Do the first disconnection and suggest what might come next.

386.



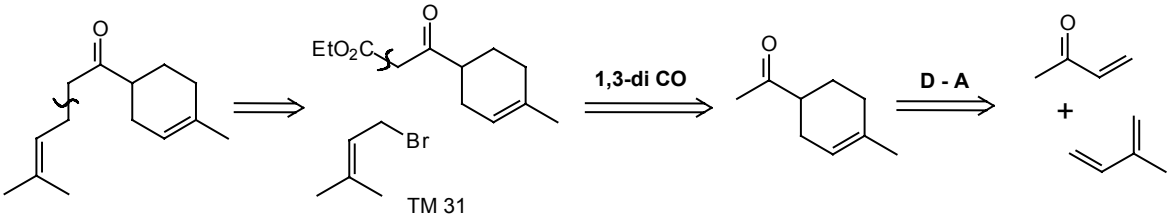
Now we can choose between the alternatives in frame 385 for **b** and **c**. Consider these if you've not already done so.

---

387. For **b** the Diels-Alder now looks best. For **c** alkylation with the allyl halide looks good. There are of course other solutions, but continue the analysis along these lines.

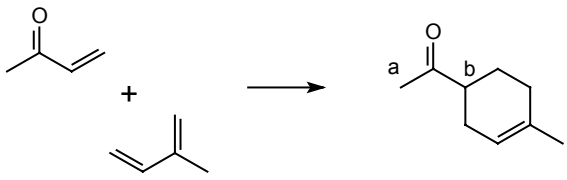
---

388. If you work through both orders of events it turns out better to do **c** first and **b** next:

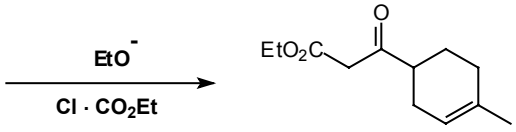


Now draw out the synthesis and comment on the selectivity we need and whether we are likely to find it.

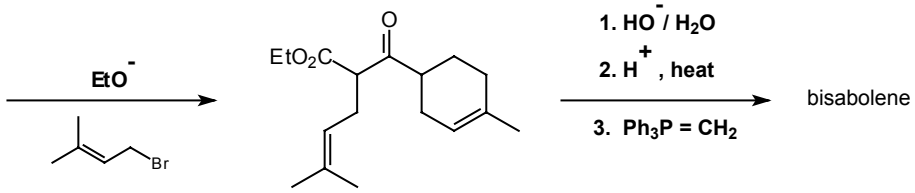
389.



Could have given the other regio-isomer, but actually gives mostly the compound we want.



Atoms **a** or **b** could enolise but only this product can from a stable anion (frame 101) so this is all right too.



This is the synthesis carried out by Vig and his group. (J. Indian Chem. Soc., 1966, 43, 27). Bisabolene has been made in several other ways.

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390. You have now reached the end of the systematic instruction provided by the programme. If you have worked your way through to this stage and have understood most of what you have done then you are certainly ready to move on to more difficult problems. The problems I have given you so far have all been chosen because they could be solved reasonably easily. Many molecules present a greater challenge and while you will of course use the logic of the programme in designing syntheses for them, you will have to extend it. In the next frame you will find some suggestions for further study on these lines.

K. FURTHER STUDY

391. Choose some, or all of these for your next step.

1. Review Problems: Scattered throughout the programme were review problems so that you could check on your progress. These are also useful now so that you can check that you can still remember material you met earlier on:

Review problems .....1-3 frames 29-35
Review problems .....4-6 frames 78-83
Review problems .....7-8 frames 108-111
Review problems .....9-11 frames 125-130
Review problems .....12-13 frames 167-170
Review problems .....14-15 frames 190-193
Review Section:
Synthesis of Lactones:
Review problems .....16-18 frames 203-209
General review problems .....19-23 frames 210-219
Review problems .....24 frames 232-233
Review problems .....25-27 frames 267-272
Review problems .....28-30 frames 295-300
General review problems .....31-34 frames 301-308

2. Revision Problems: For those of you who have already done all the review problems, there are some not too difficult revision problems in the next section. All have answers.

3. Problems in Strategy: Our discussion on strategy was limited to the more straightforward aspects. This section has some challenging problems without worked answers. These are more difficult than the revision problems.

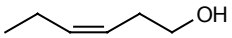
4. Problems with several published solutions: This section gives you some 'real' problems which have alresdy been solved by several different routes. You can check your answer against these published routes.

5. Further reading: Now that you know what the problems are, you will probably get a lot of value out of studying published syntheses of large molecules. Some excellent examples appear in Fleming (see book list at the front)

E.J.Corey was the originator of this analytical approach to synthesis and you might like to read some of the articles in which he first explains it. Here is a selection: J. Amer. Chem. Soc., 1964, 84, 478; 1972, 94, 440; 1974, 96, 6516; 1975, 97, 6116; 1976, 98, 189; Pure Appl. Chem., 1967, 14, 19, and Quart. Rev: 1971, 25, 455.

L. REVISION PROBLEMS

392. Revision Problem 1: Leaf alcohol (TM 392) is widespread in plants and has the characteristic smell of green leaves and grass. The cis isomer alone has this smell and is used in perfumery. How would you make it?

TM 392 

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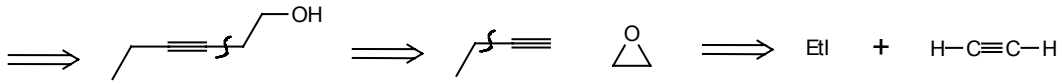
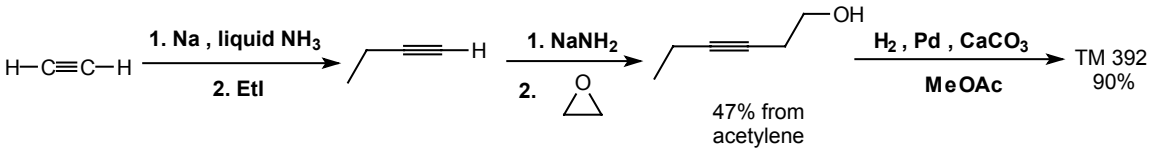
393. Analysis: The cis olefin can come from an acetylene and so we are guided into our disconnections:



Synthesis: Sondheimer (J. Chem. Soc., 1950, 877) made leaf alcohol this way.



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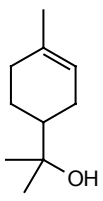
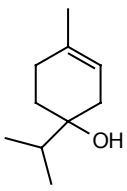
394. Revision Problem 2: α-Terpineol also occurs widely in plants and was one of the first natural products to be isolated pure. There was originally some doubt as to whether its structure was TM 394A or TM 394B. Suggest syntheses of both these compounds so that they can be compared with the natural product.

TM 394 A 



TM 394 B

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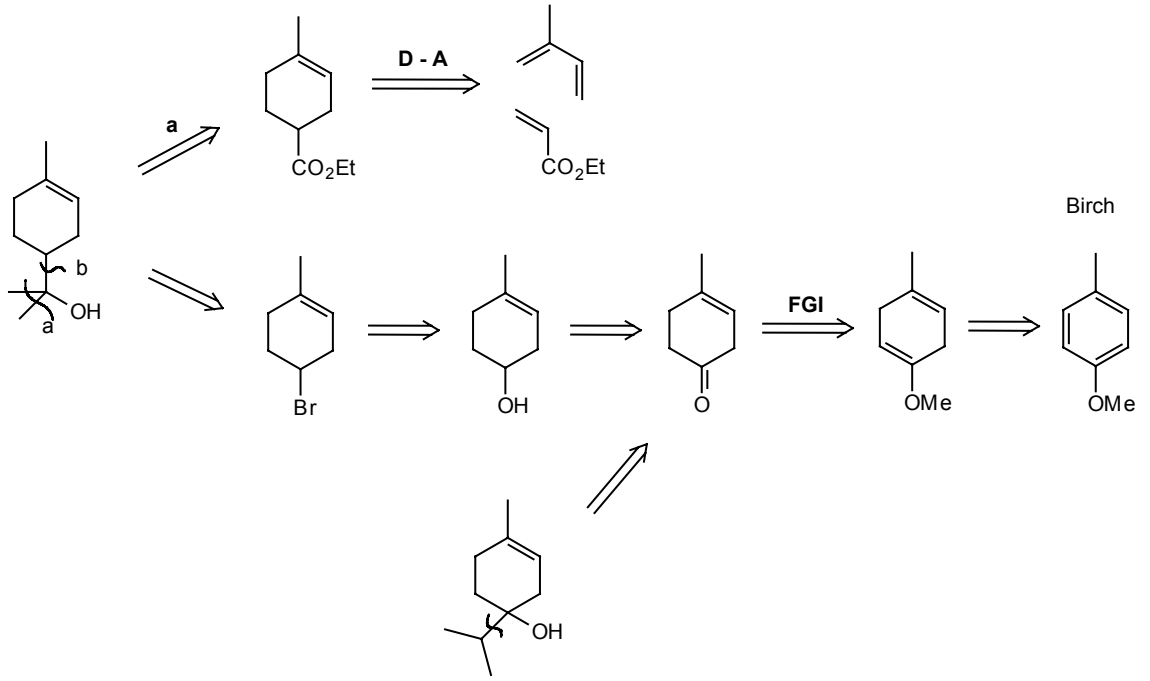
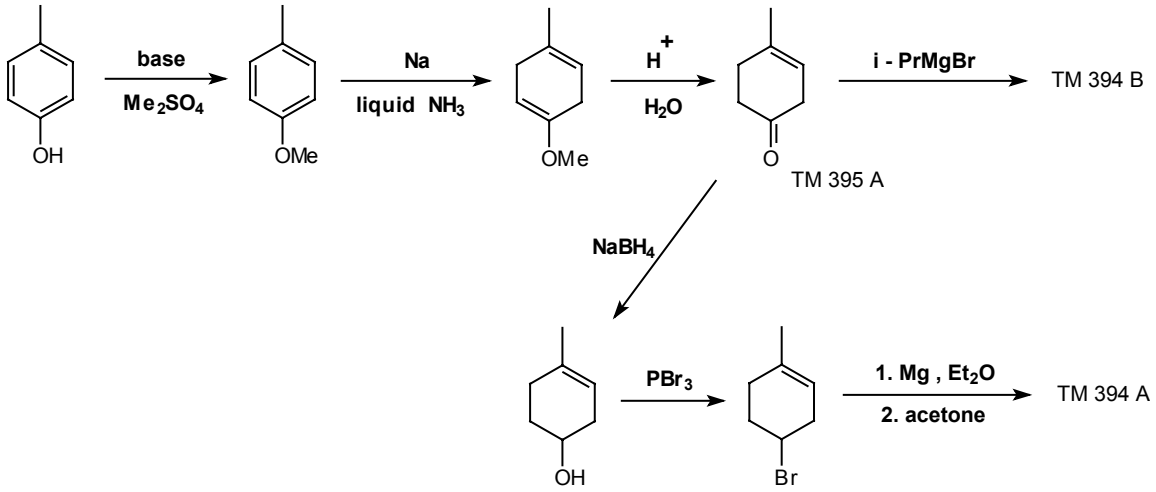
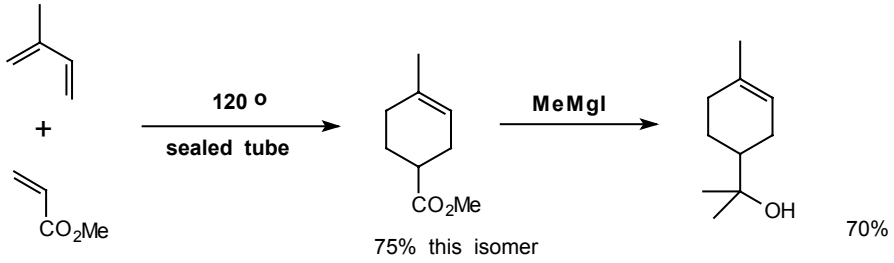
395. Analysis: The strategy for any modern syntheses of these compounds would be based on the Diels-Alder reaction or the Birch reduction:



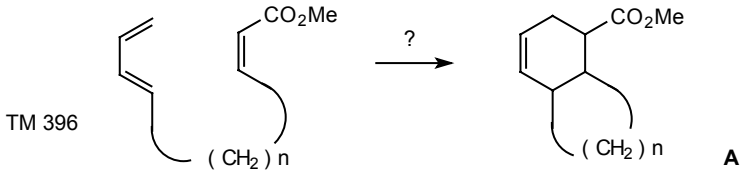
Synthesis: Since we can make both compounds from the same intermediate 395A, we'll use the Birch reduction route:



In the event, TM 394A proved to be α-terpineol and the shortest synthesis is by Alder and Vogt (Annalen, 1940, 564, 109) using the Diels-Alder reaction:



396. Revision Problem 3: House (J. Org. Chem., 1965, 30, 1061) wanted to study intramolecular Diels-Alder reactions and wanted molecules like TM 396 in which n is 3 or 4, so that the product will have a 5 or 6 membered ring if the reaction works. It would obviously be a good thing if the synthesis can easily be modified to make other size rings as well. What do you suggest?



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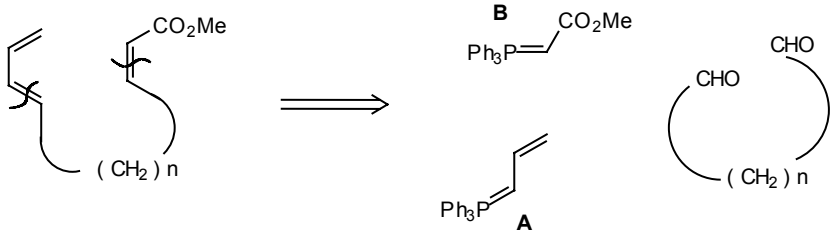
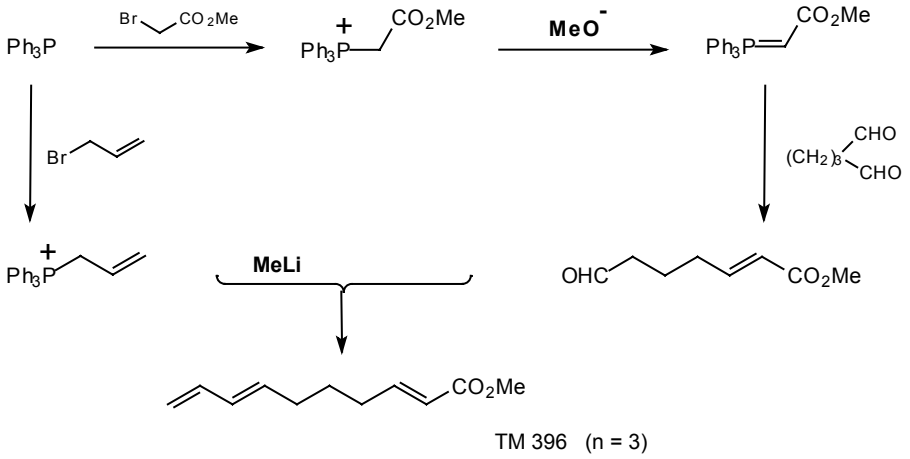
397. Analysis: If we take out the central portion of the molecule we can use any size of n we want. The most obvious method is two successive Wittigs:



If we use the rather unreactive B first we should be able to react one aldehyde at a time. The various dialdehydes are available or can be made by the usual 1,n-dicarbonyl routes.

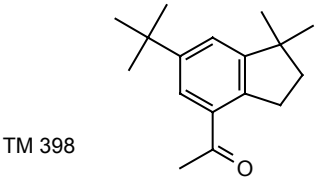
Synthesis: This is what House did:



To complete the story, when this molecule was heated an intramolecular Diels-Alder reaction did indeed take place to give a new fivemembered ring, (396A, n=3).

---

398. Revision Problem 4: Musks are compounds which have some pleasant smell themselves, but function chiefly by retaining and enhancing the perfume of other compounds. How might 'celestolide', a modern musk, (TM 398) be made?



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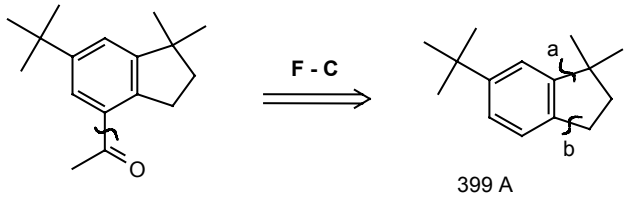
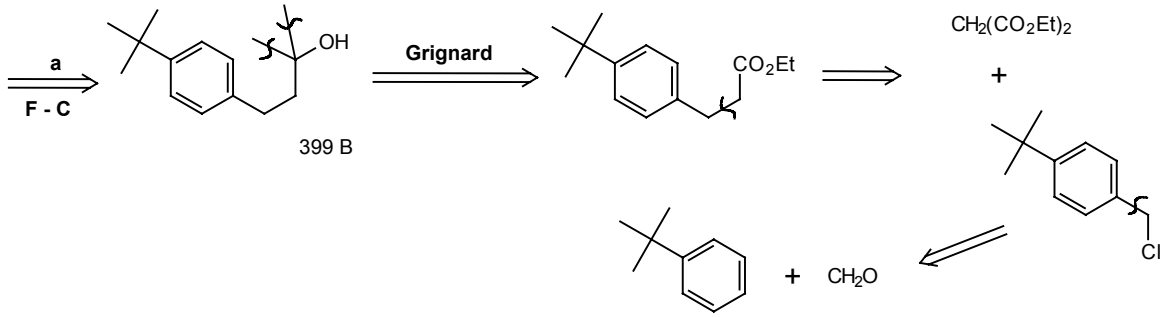
399. Analysis: The one functional group is something of a red herring since we shall put in the acetyl side chain by a Friedel-Crafts reaction on the real target molecule, 399A:



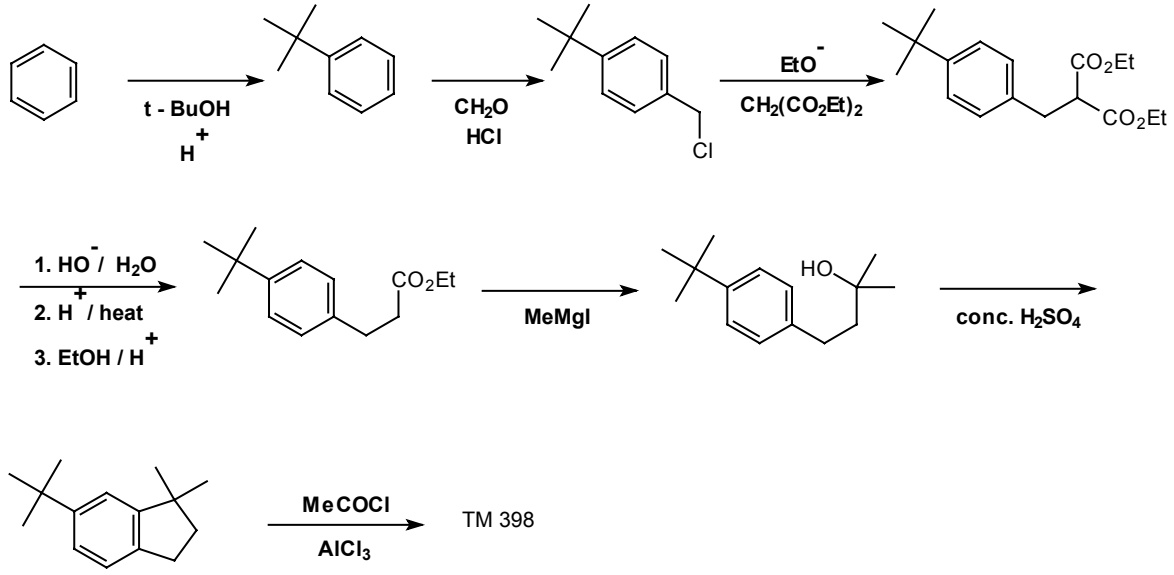
399 A

This will clearly be made somehow by disconnections **a** and **b** but the order of events is important. We must disconnect first, that is synthesise last, the bond with the 'wrong' orientation – i.e. **a**, meta to the t-butyl group. The reaction will then be intramolecular and orientation doesn't matter. This gives us 399B, and I show one possible route from that.



399 B

Synthesis: This route has been carried out successfully (Rec. Trav. Chem., 1958, 77, 854). Note that no **$AlCl_3$** is needed for Friedel-Crafts alkylation with easily formed t-alkyl compounds.



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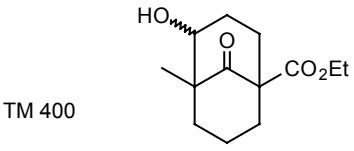
400. Revision Problem 5: This molecule (TM 400) was used by Raphael in his synthesis of the natural product clovene. How could you make it.



TM 400

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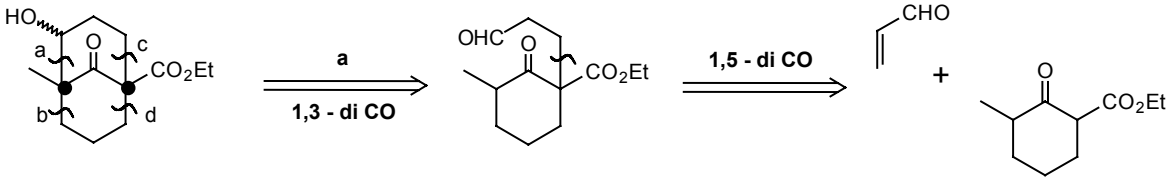
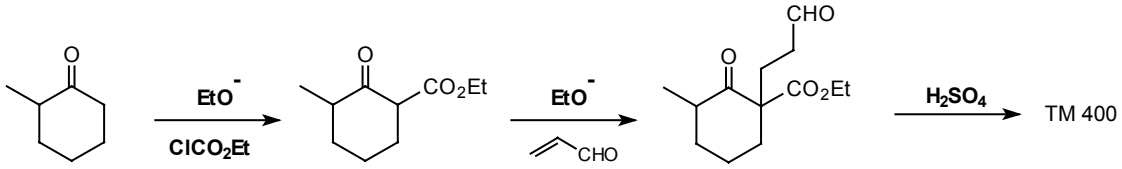
401. Analysis: We want to disconnect any of the bonds to the common atoms • to give us a simple six-membered ring. We can best disconnect bond a as it is part of a 1,3-di oxygenated system:



Synthesis: The starting material is similar to TM 100, so we shall use the same method:



Only isomer **A** will be formed as the alternative cannot give a stable enolate anion (see frame 101). This is nearly the synthesis used by Raphael (Tetrahedron, 1962, 18, 55; Proc. Chem. Soc., 1963, 239).

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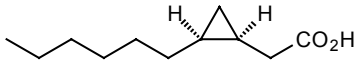
402. Revision Problem 6: Cascarillic acid occurs naturally in Euphorbiaceae plants (spurges). How could you synthesise it?

Cascarillic acid



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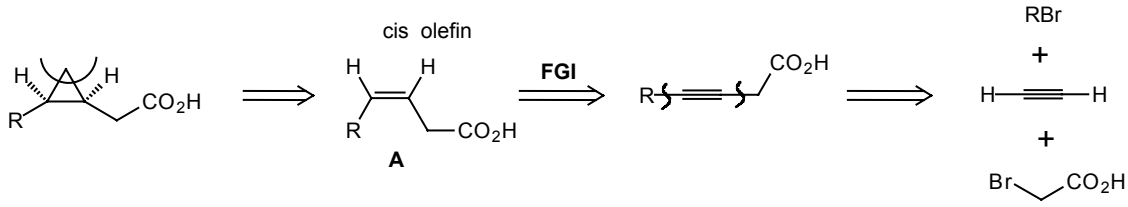
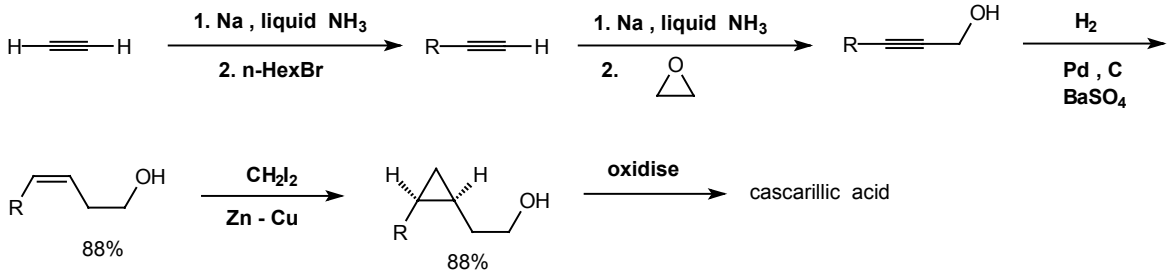
403. Analysis: the small ring will dominate the strategy, and only one disconnection will make the stereochemistry secure. Writing **R = n-hexyl**:



Synthesis: The **CO_2H** group spells trouble. We would certainly have to use an ester, but the α-bromoester is too reactive to use with an acetylene. Also there is a danger that the double bond in **A** will move into conjugation. We can get round all these problems with an epoxide and then oxidise at the end:



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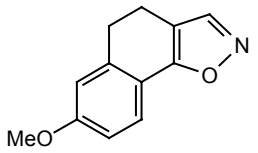
404. Revision Problem 7: TM 404 was needed as an intermediate in a steroid synthesis. How might it be made?

TM 404 

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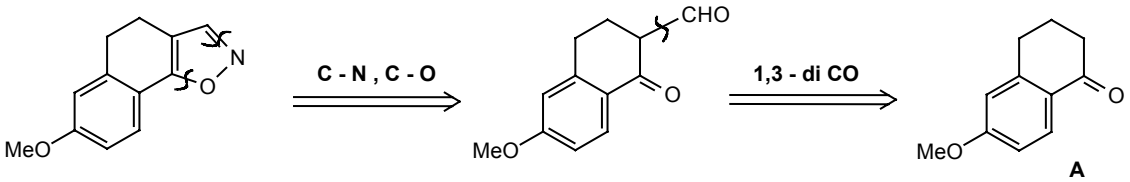
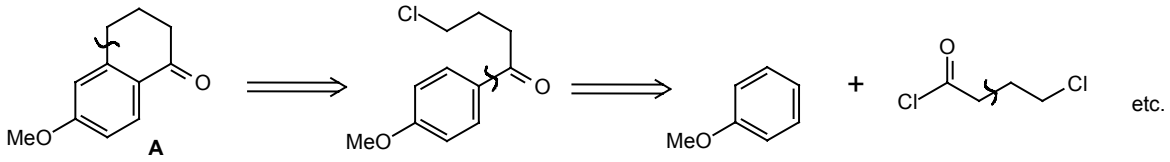
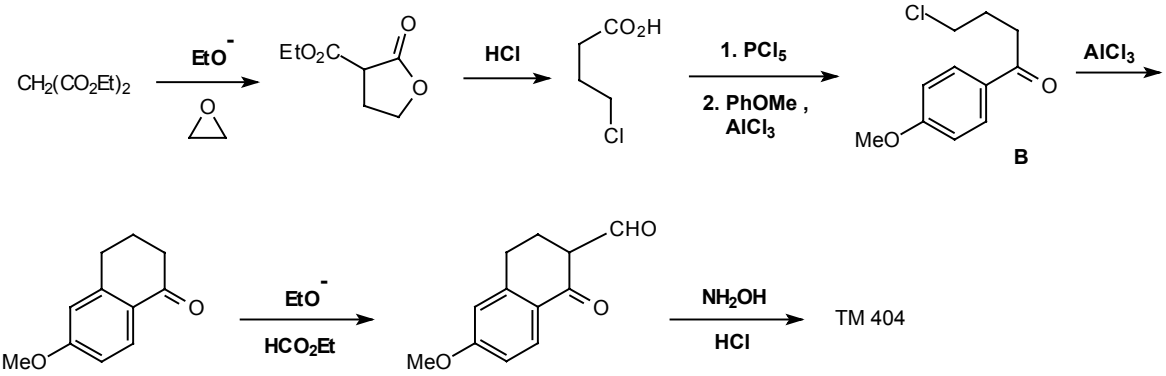
405. Analysis: Taking the heterocyclic part first, we can remove the two heteroatoms as hydroxylamine (the approach of frames 258-261) to give us a 1,3-dicarbonyl compound.



This starting material **A** (also 224A) is an isomer of the ketone we made in frame 328, and is easy to make using the intramolecular strategy of that frame:



Synthesis:



This synthesis was first carried out by Velluz, Angew. Chem., 1960, 72, 725. The lactone can be used instead of the γ-chloro acid, see Org. Synth. Coll., 4, 898. Other approaches to A are outlined in J. Amer. Chem. Soc., 1947, 69, 576, 2936 and it is probable that the reaction actually given here – the cyclisation of **B** – would give a five membered ring instead (J. Chem. Soc., 1956, 4647). The usual, if illogical way to make **A** is by reduction of β-naphthol methyl ether and oxidation of the product with $\mathbf{CrO_3}$.

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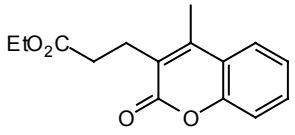
406. Revision Problem 8: TM 406 is a synthetic intermediate related to the cannabinoids, naturally occurring hallucinogenic compounds. How could it be synthesised?

TM 406 

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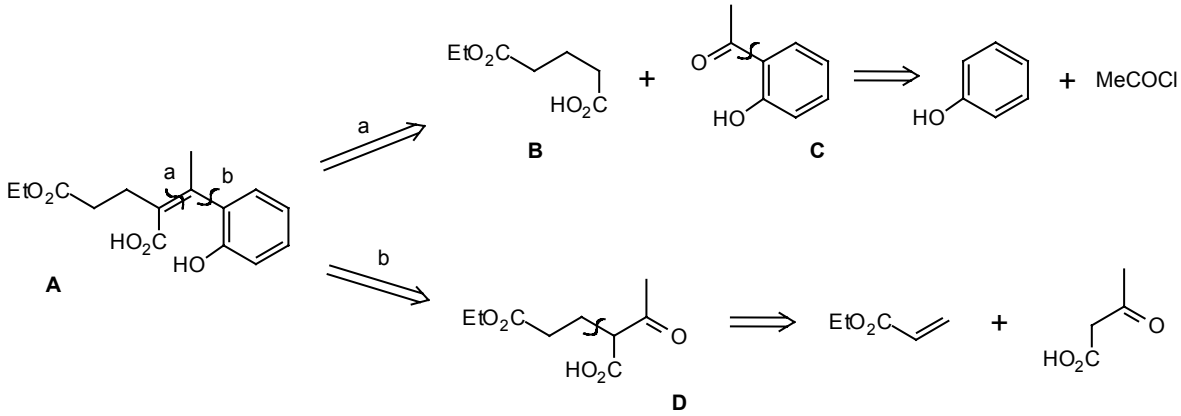
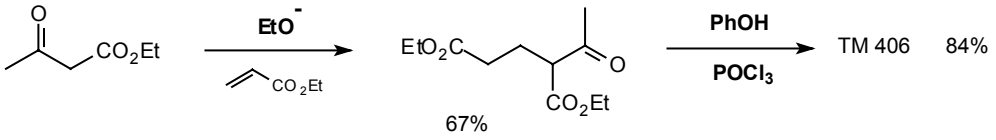
407. Analysis: Another lactone! FGI reveals the true TM (A). Our normal disconnection **a** of an α,β-unsaturated carbonyl compound gives us the 1,5-dicarbonyl compound (B) and the ketone (C) clearly derived from phenol. Alternatively we could disconnect bond **b** to the keto-ester (D) with the further disconnection shown:



Whichever route we choose, we need ortho substitution. For (C) we can do this via the Fries rearrangement (**PhOH + MeCOCl → PhO·COMe** which rearranges to **C** with **$AlCl_3$**) see Norman p.457-8 or Tedder vol.2 p.214. Howevwr, we still need the right geometrical isomer of **A**! The other route solves this problem because reaction of **D** with phenol gives TM 406 directly: ester exchange makes the **C-O** bond first and the condensation follows. This is the strategy we discussed in frames 319 ff.

Synthesis: Chem.Ber., 1948, 81, 197; J. Amer. Chem. Soc., 1967, 89, 5934: All in two steps!



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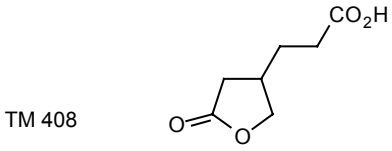
408. Revision Problem 9: Suggest a synthesis for TM 408.



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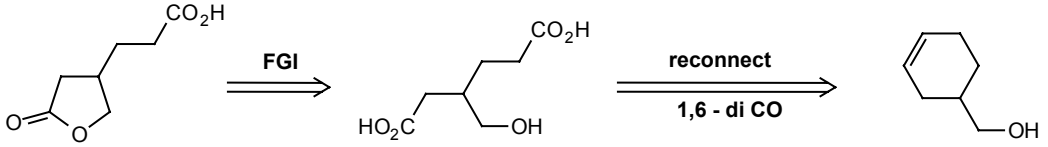
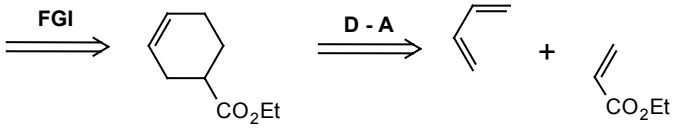
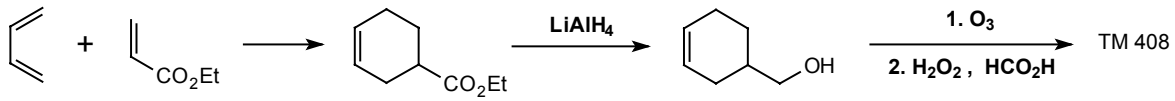
409. Analysis: This is a γ-lactone and we spent time considering possible strategies for these compounds in frames 334-348. First open the lactone ring. This gives us a compound with 1,4- 1,5- and 1,6-dioxygenation relationships. I'll follow the 1,6 through.



Now we are nearly at a Diels-Alder disconnection so a change in the oxidation state to aldehyde or ester is needed:



Synthesis: As described in Acta Chem. Scand. B, 1977, 31 189.



Cyclisation to give the five-mambered ring is spontaneous.

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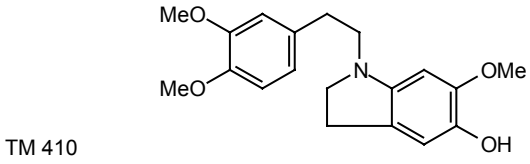
410. Revision Problem 10: This compound is an intermediate in the synthesis of an alkaloid. Don't worry about the half ether aspect – there is a solution to this which will emerge as you go along.



TM 410

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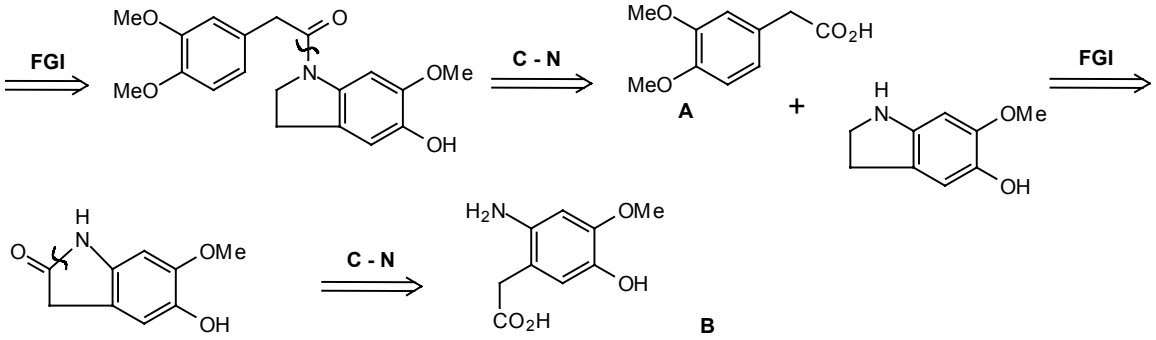
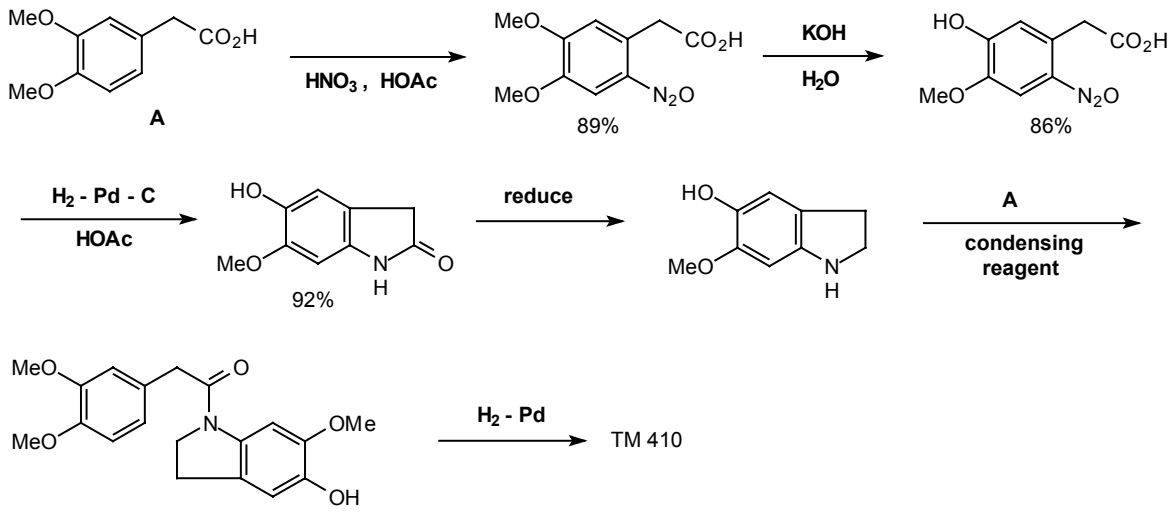
411. Analysis: The nitrogen atom is clearly the key to the problem and we can put a carbonyl group on either adjacent **CH_2** group. Strategically we make more progress by using the exocyclic **CH_2** group first:



It looks as though we can get **B** from **A** (which is used in frame 247) and so the nitro group is the obvious source of the amino group. It will also allow us to hydrolyse one ether specifically by nucleophilic aromatic substitution.

Synthesis: Starting material as in frame 247, then (E. McDonald and R.Wylie, unpublished work at Cambridge 1976-7):

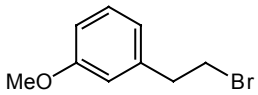


M. PROBLEMS IN STRATEGY

412. These are problems without solutions intended to lead you onto more challenging things.

Strategy Problem 1: "The wrong substitution pattern". Making aromatic compounds m-substituted with two o,p-directing groups is always a problem. What strategies can you suggest? An example (TM 412) is the alkyl halide used in the synthesis of some steroids.

TM 412



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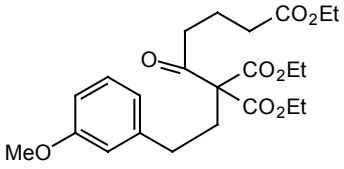
413. Hint – how do you make any m-disubstituted compound? Which of the two side chains is easier to add? How?

Further development: How would you make TM 413 using the alkyl bromide you have just made? This molecule is obviously on the way to a steroid and you can read more about it in Helv. Chim. Acta., 1947, 30, 1422 and J. Amer. Chem. Soc., 1942, 64, 974.

TM 413



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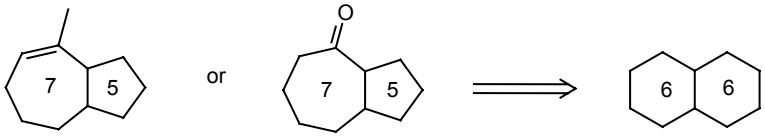
414. Strategy Problem 2: "The wrong ring sizes". We have said nothing so far about seven membered rings. The common arrangement in natural products is a fused seven-five ring system as in the molecules below. They are often synthesised from six-six fused systems because we understand them so much better. What particular six-six fused molecules might you use to make these molecules:



You can find some answers in J. Amer. Chem. Soc., 1966, 88, 4113; 1969, 91, 6473; 1971, 93, 1746; Org. Synth. Coll., 5, 277.

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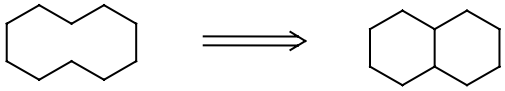
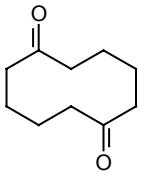
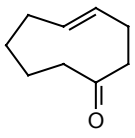
415. Strategy Problem 3: "Too large a ring". Medium rings are also tricky problems and one way to make them is to cleave a bond in a bicyclic compound, e.g.



What kind of reactions could be used to implement this strategy? How in particular might you make these compounds:



TM 415 A



TM 415 B

note trans olefin

You will find some solutions in: J. Amer. Chem. Soc., 1963, 85, 362; 1964, 86, 485, Ber., 1933, 66, 563. Tetrahedron Letters, 1976, 4409.

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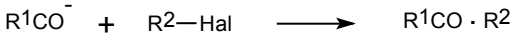
416. Strategy Problem 4: "The wrong polarity". You have seen how important it is to have reagents corresponding to as many synthons as possible. One we haven't mentioned is the acyl anion **R-CO$^-$** for which we had one reagent if **R=Me** (frame 145 if you've forgotten!). Can you devise any more general reagents for this synthon? Ideally we should like to make ketones this way:



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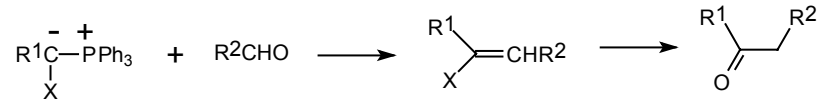
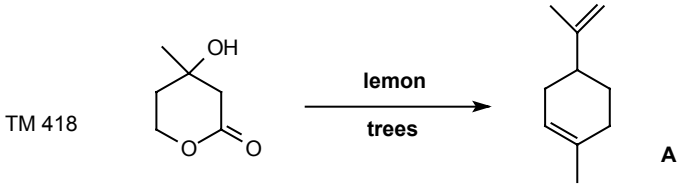
417. This is a very challenging problem indeed. You may find some solutions by setting up two substituents on the carbon atom. For example, how about a substituted Wittig reagent:



What could X be for this sequence to be feasible? You will find an account of some modern solutions in Tetrahedron, 1976, 32, 1943 and Synthesis, 1977, 357.

---

418. Strategy Problem 6: A labelled compound for biosynthetic studies. Mevalonic acid (TM 418) is an intermediate in the biosynthesis of terpenes and steroids (Tedder, volume 4, p.217 ff). To study exactly what happens to each carbon atom during its transformation into, say, limonene (418A), we need separate samples of mevalonic acid labelled with **^{14}C** in each carbon atom in the molecule. This turns our normal strategy on its head since we must now look for one carbon disconnections. You can use reagents like **$^{14}CH_3I$, $Na^{14}CN$**, and **$^{14}CH_3CO_2H$**. See if you can find approaches to some of the labelled compounds.



Some solutions can be found in Tetrahedron, 1959, 5, 311, Chem. Abs., 1966, 65, 614, J. Amer. Chem. Soc., 1975, 97, 4144 and see J.W. and R.H.Cornforth in "Natural Substances formed Biologically from Mevalonic Acid", ed., T.W.Goodwin, Academic Press, 1970, p.5 where all the different routes are explained.

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419. Strategy Problem 7: Synthesis of a single enantiomer. Many compounds such as pharmaceuticals, flavourings, and insect control chemicals must not only have the right relative stereochemistry but must be optically active too if they are to be of any use. Consider the strategy of synthesising one enantiomer:

(a) should you start with an optically active compound?
or (b) should you resolve at some point?
if so (c) which is the best point for a resolution?
and (d) what do you do with the unwanted enantiomer?
You can take some examples from this list for your consideration:
Target molecules in frames: 133, 135, 152, 216, 242, 249, 251, 377.

Review Problems	8 (frame 110)
	26 (frame 269)
	27 (frame 271)
	32 (frame 303)
Revision Problems	6 (frame 402)
	9 (frame 408)
γ-Lactones	(frames 342-348)
Baclofen	(frames 349-354)
Chrysanthemic acid	(frames 355-370)

---

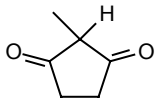
420. Briefly, the answers to the questions are:

(a) Yes, if one is available – it usually isn't.
(b) You probably have to.
(c) As early as possible.
(d) Recycle it or use it to resolve something else.

The question of stereochemical control has been a theme running throughout the programme and as you progress to more complicated molecules it becomes more important. This is very clear from many of the syntheses described in Fleming.

N. PROBLEMS WITH SEVERAL PUBLISHED SOLUTIONS

421. This cyclopentadione is needed to provide ring **D** in some steroid synthesis. Unlike the corresponding six-membered ring compound it is difficult to make. Can you suggest any solutions?



Published Solutions: Bull. Soc. Chim. France, 1955, 1036; 1965, 645; Org. Synth., 1967, 47, 83; J. Org. Chem., 1967, 32, 1236; Angew. Chem., 1967, 79, 97, 378; Chem. Ber., 1967, 100, 2973; 1969, 102, 3238.

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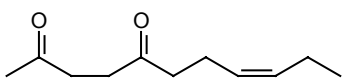
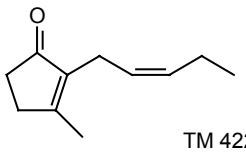
422. Cis-Jasmone (TM 422) is an important ingredient inmany perfumes. There are several obvious disconnections and it may help you to know that cyclisation of the diketone 422A does indeed selectively give cis-jasmone.



TM 422 A



TM 422

Published Solutions: J. Chem.Soc., 1969 (C), 1016, 1024; Chem. Comm., 1972, 529; Tetrahedron Letters, 1972, 1233; 1976, 4867; 1971, 1569, 2575; 1973, 3267, 3271, 3275; 1974, 3883, 1237, 4223. J. Amer. Chem. Soc., 1964, 86, 935, 936; 1970, 92, 7428; 1971, 93, 5309, 3091; 1972, 94, 8641; 1973, 95, 4446, 4763. Canad. J. Chem., 1972, 50, 2718. J. Org. Chem., 1972, 37, 341, 2363; 1966, 31, 977; 1971, 36, 2021. Chem. Lett., 1972, 793; 1973, 713.

Fourteen syntheses of cis-jasmone are given in chart from in 'Natural Products Chemistry' ed. K.Nakanishi et. al., Academic Press, New York, 1975, vol.2, p.21.

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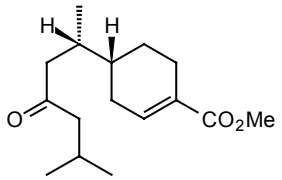
423. Juvabione is a substance produced by some conifers in imitation of a hormone in an insect pest. It may be a kind of natural control of the pest as it prevents it reaching maturity.



Juvabione

Published Solutions: Tetrahedron Letters, 1967, 2515, 4677; 1969, 351; Tetrahedron, 1968, 24, 3127; Chem. Comm., 1968, 1057; Canad. J. Chem., 1968, 46, 1467; J. Amer. Chem. Soc., 1970, 92, 366.

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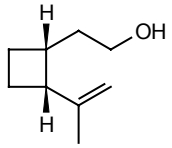
424. Grandisol, with a four-membered ring, is another insect hormone, the male sex hormone of the boll weevil to be precise. It may also be useful as a highly specific pest control. How might it be made?



Grandisol

Published Solutions: Science, 1969, 166, 1010; J. Amer. Chem. Soc., 1970, 92, 425; 1974, 96, 5268, 5270, 5272; 1976, 98, 4594; J. Org. Chem., 1972, 37, 54.
