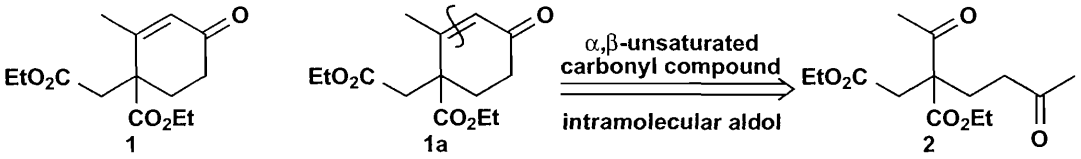
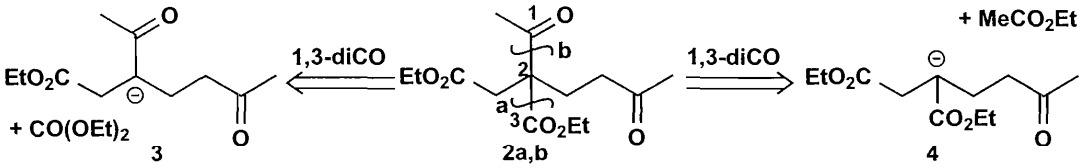
28 General Strategy B: Strategy of Carbonyl Disconnections

This chapter links the carbonyl disconnections of the last 10 chapters with the general principles established in chapter 11. We shall find some new principles but the main idea is to discover why, in designing the synthesis of a particular molecule, some disconnections prove more helpful than others.

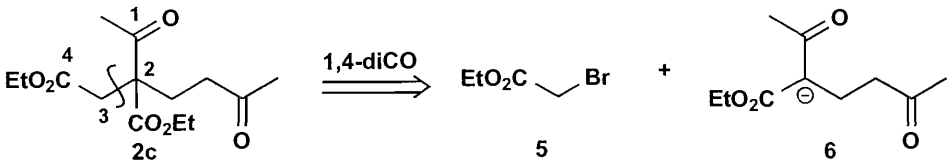
We could look at every possible C–C carbonyl disconnection and decide which we prefer. For any even moderately complex molecule, this can be an exhausting process and we shall do it for just one target molecule. Thereafter we shall choose disconnections as we go along and go back to the target only if that strategy proves poor. Pratt and Raphael[1] needed the keto-diester **1** for a synthesis of the anti-tumour compound vernolepin. Our first disconnection is easy as the α,β-unsaturated carbonyl unit suggests the classic aldol **1a** disconnection to **2**.



Compound **2** has 1,3-, 1,4-, 1,5- and 1,6-dicarbonyl relationships. Disconnecting the 1,3-diCO in the two possible directions **2a** and **2b** gives a one- or two-carbon fragment and enolates **3** and **4** that would be very difficult to control. There is in any case little simplification in either of these disconnections so we shall not pursue this strategy.



The 1,4-diCO disconnection **2c** looks promising as the required enolate **6** is of a stable 1,3-dicarbonyl compound and the electrophile is available bromoacetate **5**. Much will depend on how easy it is to make **6**.



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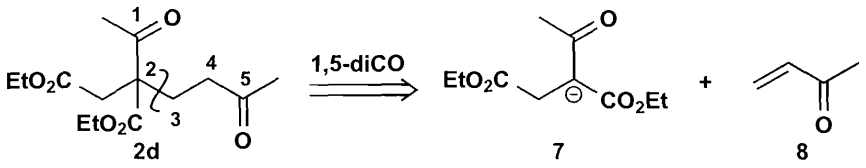
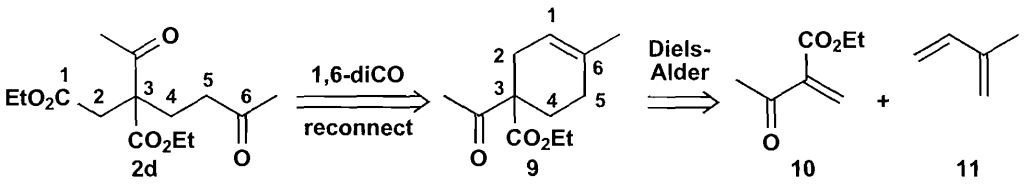
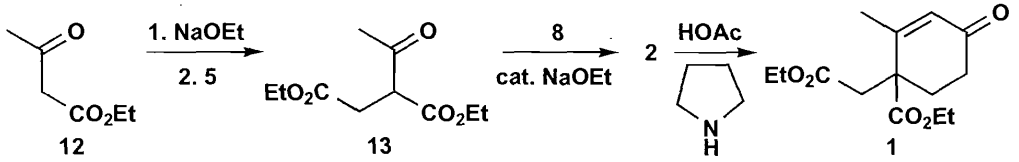
The 1,5-diCO disconnection **2d** also looks promising as the required enolate **6** is again stable and the electrophile is the available enone **8**. At the moment there is little to choose between these disconnections **2c** or **2d** but the ease of making of **6** or **7** may be decisive.



Finally we can investigate the 1,6-dicarbonyl approach by reconnection **2d** to give a cyclohexene that seems destined for synthesis by a Diels-Alder reaction from isoprene **11** and the enone **10** that can probably be made by a Mannich reaction on ethyl acetoacetate.

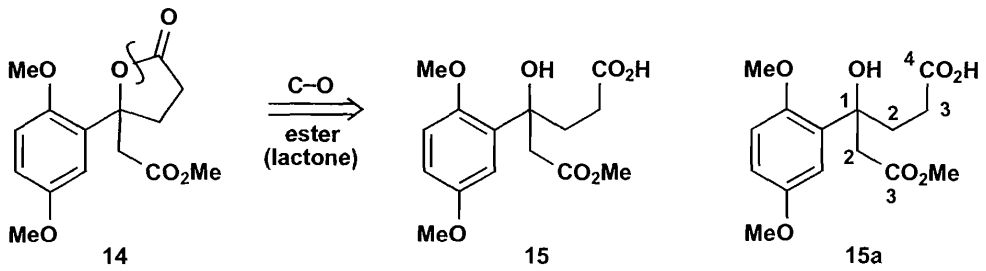


So we have three promising approaches. But the reactions in the first two are the same: they are just done in the reverse order. So the sensible thing is to try one of those so that the starting materials can be used for the other if necessary. Pratt and Raphael found that the 1,5-diCO strategy via enolate **7** was successful. The others may be successful too. Note that the final cyclisation of **2** required only weak acid and weak base.

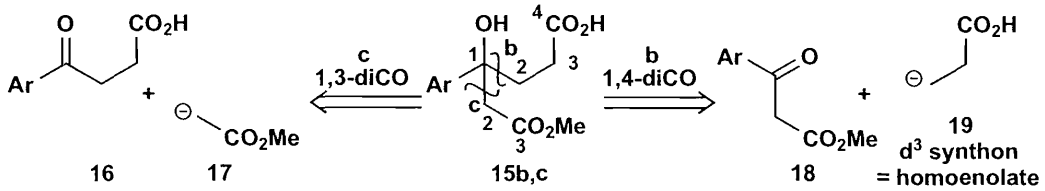


The Synthesis of a Lactone

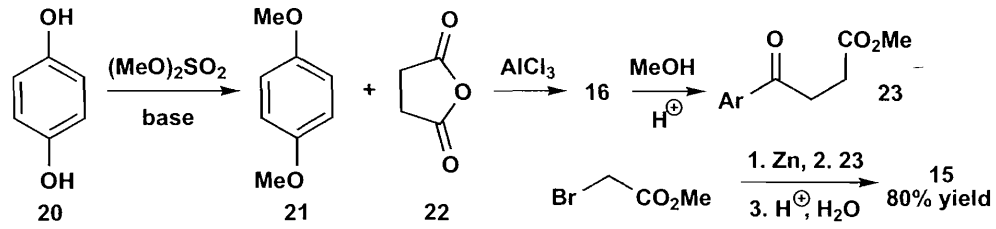
Where there are structural C–X bonds in the target molecule, it makes sense to disconnect them first as we can then see the carbon skeleton displayed and count the relationships between the functional groups. So the lactone **14** has the carbon skeleton of **15** and this compound has 1,3- and 1,4-diCO relationships **15a.**



We can continue both strategies by disconnections at the branchpoint, each needing simple aryl ketones **16** and **18**, but **15b** requires a homoenolate reagent for the d^3 synthon **19** and we should rather avoid that, while **15c** needs a simple enolate **17** and we prefer that.

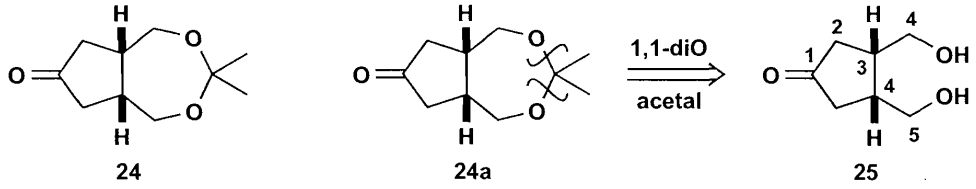


The keto-acid **16** is going to be made by a Friedel-Crafts reaction and the best reagent is succinic anhydride **22** so that the disconnection is outside the 1,4-diCO system as explained in chapter 25. The starting material **21** can be made by methylation of **20** with dimethyl sulfate and the enolate chosen for the last step was the organo-zinc derivative (Reformatsky reagent) of methyl bromoacetate. The methyl ester protecting group used in **23** disappears during lactonisation.[2]

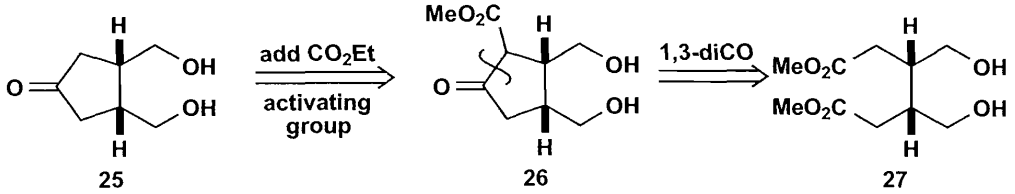


Synthesis of a Symmetrical Cyclic Acetal

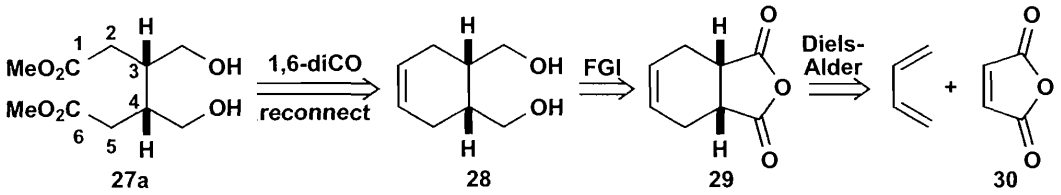
The keto-acetal **24** was needed for a prostaglandin synthesis.[3] Disconnection of the acetal **24a** reveals the symmetrical carbon skeleton **25** having 1,4- and 1,5-diCO relationships. There is another 1,4-diCO relationship between the two alcohols.



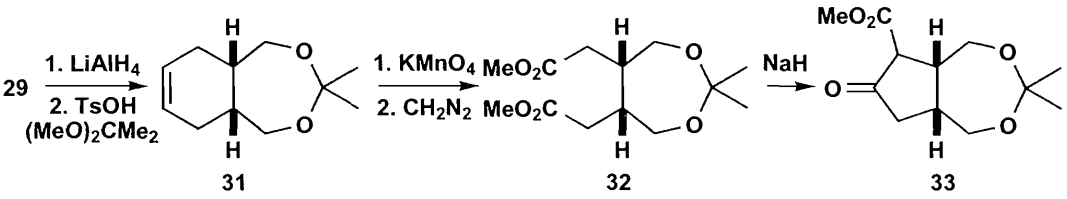
None of these relationships looks very promising, in part because any C–C disconnection would destroy the symmetry. We can get round this problem by using a trick that appeared first in chapter 19. We add an extra functional group (CO_2Me) to give us a 1,3-diCO relationship that can be disconnected **26** without destroying the symmetry.



This new intermediate **27** has all the 1,4- and 1,5-diCO relationships of **25** but it also has a 1,6-diCO relationship **27a** that can be reconnected to **28** again without destroying the symmetry. An adjustment of functionality gives an obvious Diels-Alder adduct **29** of butadiene and maleic anhydride **30**.

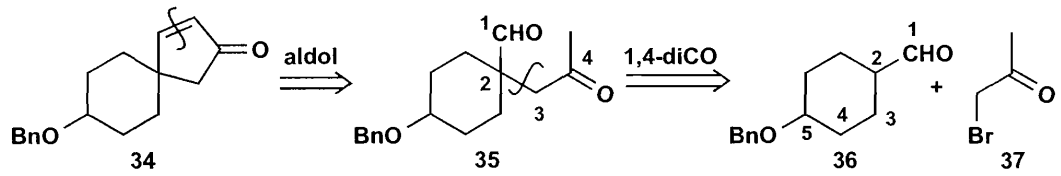


Since the two hydrogen atoms in maleic anhydride **30** are *cis*, they must also be *cis* in the adduct **29**. Reduction and protection are needed before the oxidative cleavage so that the difference between the left- and right-hand halves of the molecule is preserved. Hydrolysis of the ester in **33** and decarboxylation in acid gave **24**.

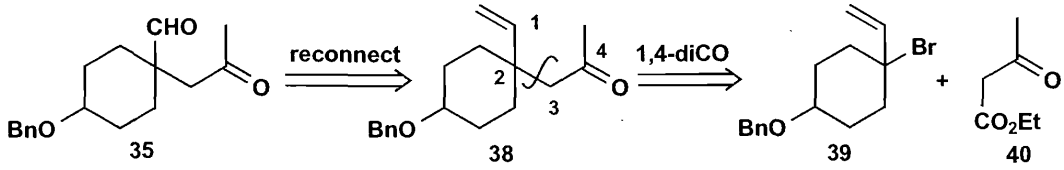


Synthesis of a Spiro Enone

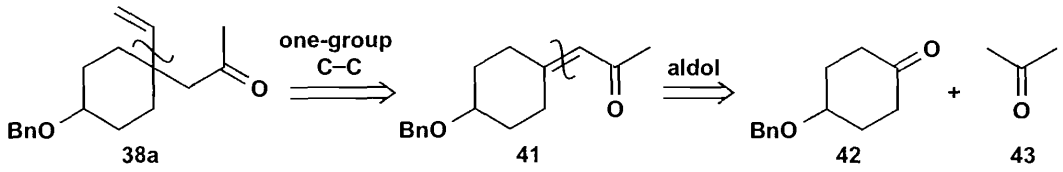
Corey needed the spiro-enone **34** for his synthesis of gibberellic acid.[4] The obvious enone disconnection reveals a keto-aldehyde **35** with a 1,4-relationship between the carbonyl groups and disconnection at the branchpoint suggests some enol(ate) equivalent of the aldehyde **36** and the bromoketone **37**.



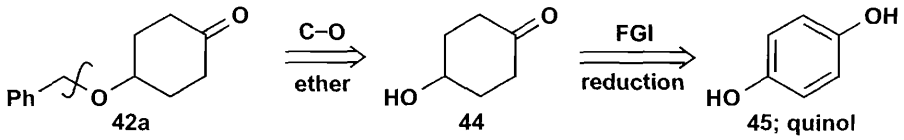
The planning for this synthesis involves the repeated disappointment of rejection of good-looking strategies. For example, the aldehyde **36** has a 1,5-diCO relationship but cannot easily be made by conjugate addition as that would require conjugate addition of an acyl anion equivalent. One alternative might be to use an allylic bromide **39** (reconnection strategy—chapter 26) and the enolate of ethyl acetoacetate **40**.



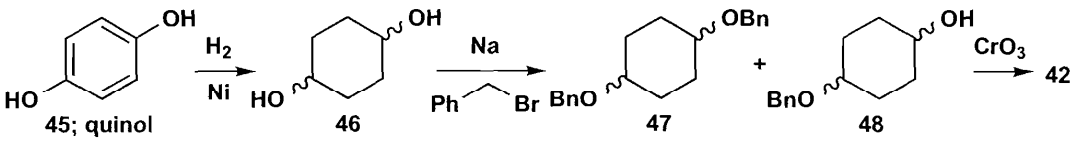
But this strategy is doomed too as the allylic bromide will almost certainly react at its less hindered end on the vinyl group. However, we might choose the alternative branchpoint disconnection **38a** and consider conjugate addition of some vinyl-metal (copper?) derivative to the enone **41** that could be made by some aldol process from the ketone **42** and an enol(ate) of acetone **43**.



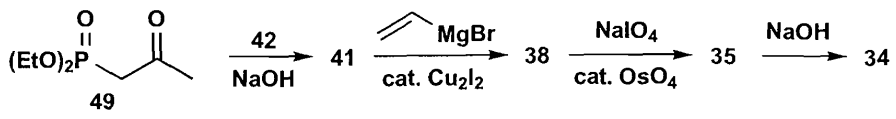
The ether **42** can obviously be made from the hydroxyketone **44** and, as we shall see in chapter 36, a good way to make 1,4-difunctionalised cyclohexanes is by reduction of a cheap aromatic compound such as quinol **45**.



This approach requires a basic kind of chemoselectivity (chapter 5) to distinguish the two phenolic hydroxyl groups in **45** so that one may be alkylated and one oxidised. Trial and error revealed that the best way was to reduce completely first and benzylate to give a mixture of unreacted diol **46**, mono-ether **48** and diether **47**. This is the statistical method (chapter 5) that is expected to give about 50% of **48** and 25% of **46** and **47**. Fortunately these can easily be separated and recycling **46** directly and **47** after debenzylation gives a good conversion. Oxidation of **48** then gives **42**. In any case, the benzylation is an early step in the synthesis and can be carried out on a large scale with such cheap materials.[5]

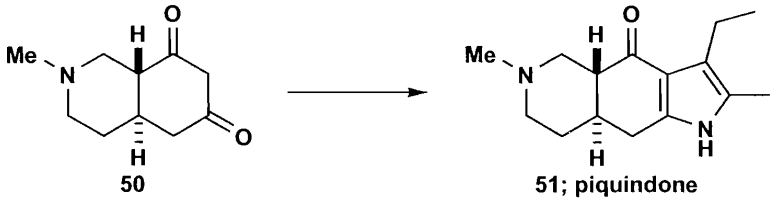


Corey chose a Wittig-style (HWE) reaction to control the 'aldol' process and copper-catalysed addition of vinyl Grignard for the conjugate addition. Oxidation with $NaIO_4$ and catalytic OsO_4 gave the keto-aldehyde **35** which cyclised cleanly under equilibrating conditions.

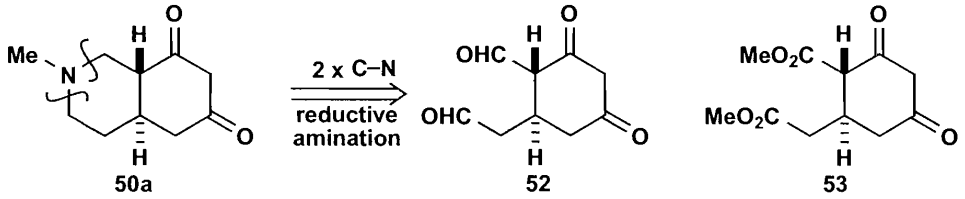


The Synthesis of Piquindone

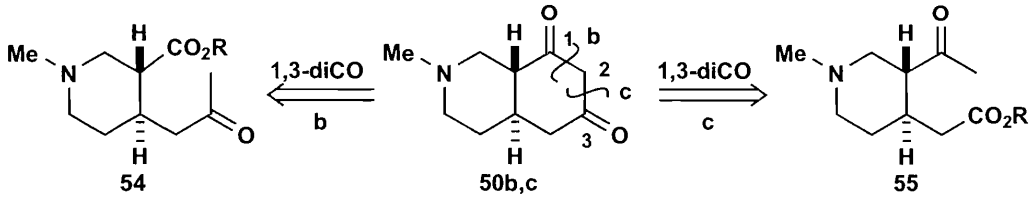
Our final example is the heterocyclic diketone **50**, an intermediate in the Hoffmann-La Roche synthesis of piquindone **51**, an anti-psychotic agent.[6]



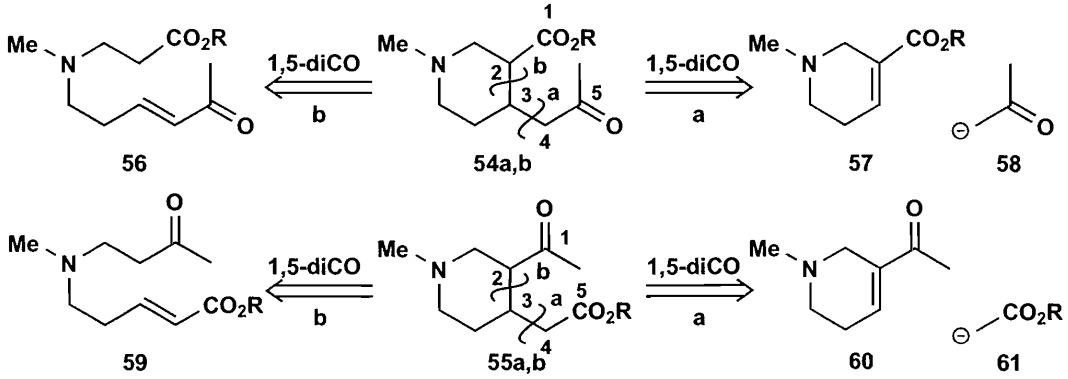
We might first think of removing the structural heteroatom—the ring nitrogen. With reductive amination in mind we might consider imines from **52** or amides from **53**. But these compounds have four different carbonyl groups and obviously problems of selectivity arise.



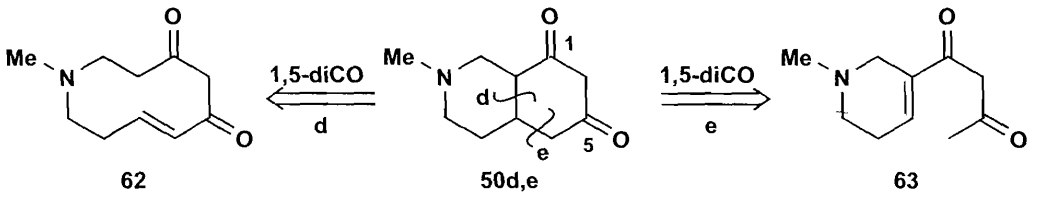
It might be better to start on the carbonyl disconnections immediately. The most obvious come from the 1,3-dicarbonyl relationship **50b, c** and suggest two keto-ester starting materials **54** and **55**.



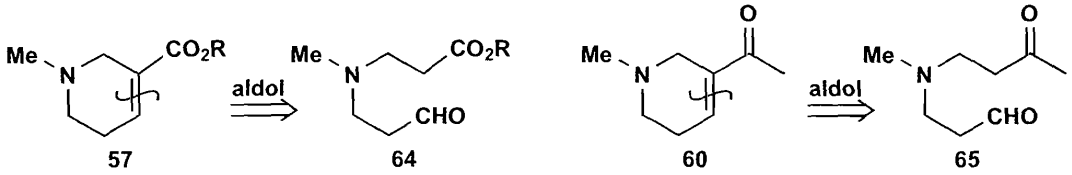
These two intermediates **54** and **55** each have a 1,5-diCO relationship that can be disconnected in two ways. Both **54b** and **55b** disconnect a ring bond and give unsimplified starting materials **56** and **59**. But the others **54a** and **55a** achieve some simplification and suggest simple cyclic enones **57** and **60** in combination with enol(ate)s of acetone **58** or an acetate ester **61**. These are much more promising and we shall come back to them.



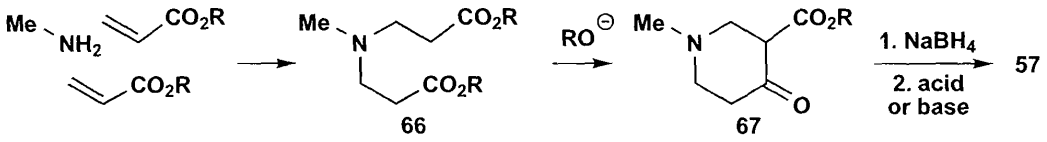
Incidentally, the 1,5-diCO relationship is present in the target molecule **50** too and attempts to disconnect it **50d,e** reveal a most unpromising 10-membered ring **62** or a more promising diketone **63**. Continuing the analysis of **63** would lead us back to **57** or **60**.



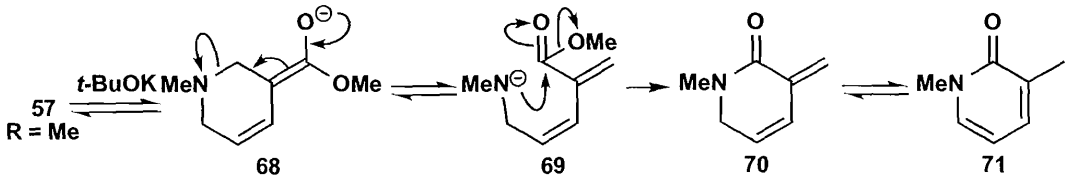
Returning to **57** and **60**, the α,β-unsaturated carbonyls suggest aldol-style disconnections to **64** and **65**. You may by now be reminded of something we saw in chapter 19: compounds like **64** and **65** with 1,3-diX relationships between nitrogen and a carbonyl group. There the carbonyl groups were both esters: here one must be an aldehyde and the other either an ester or a ketone.



We could presumably make **57** from **67** (compound **44** in chapter 19) by reduction and elimination. Addition of, say, acetoacetate anion should give **63**.

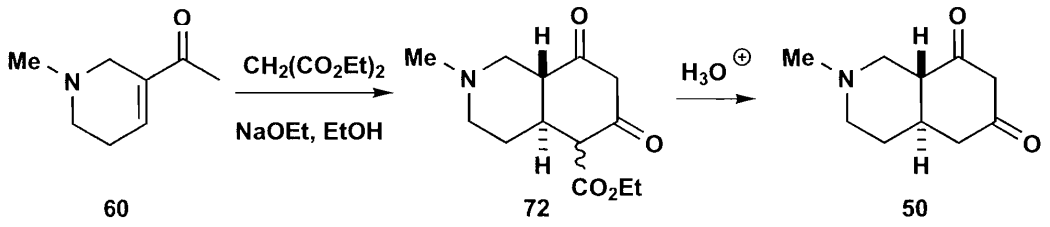


In fact, it isn't necessary to make **57** as, when R=Me, it is the natural alkaloid arecoline. However, when the synthesis was continued by attempted conjugate addition of the enolate of methyl acetoacetate to **57** only very low yields (12–18%) of products could be found. The problem turned out to be the base-catalysed rearrangement of **57** into the aromatic pyridone **71**.



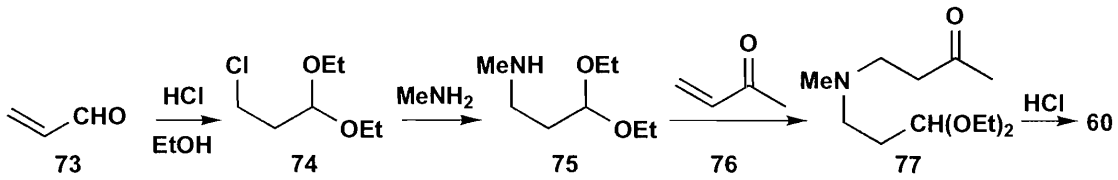
Using **60** and malonate solved this problem. The intermediate **72** and the diketone **50** could be isolated and characterised but it was better in the manufacturing process, to continue with

the formation of the drug **51** in the same process. The drug has potent and selective dopamine antagonist activity.



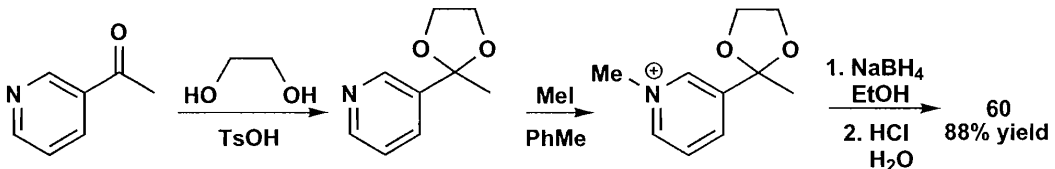
60 72 50

There remained the synthesis of **60**. An old synthesis[7] used essentially the strategy we have outlined via **65**: alkylation of $MeNH_2$ with the chloro-acetal **74**, conjugate addition of **75** to butenone **76** and cyclisation in acid solution. It was very low yielding. One reason is the poor amine synthesis by alkylation (chapter 8) and another is presumably that the acetal **77** hydrolyses to the aldehyde **65** but control in the cyclisation is poor.



73 74 75 76 77

The workers at Roche chose to make **60** by a completely different strategy inspired by the availability of a pyridine **78** with the same skeleton. Protection and methylation gave the pyridinium salt in very high yield and reduction and hydrolysis gave **60**. The paper[6] describing the search for a good synthesis of **51** is worth longer study.



78 79; 96.4% yield 80; 99.3% yield

Summary of General Approach to the Design of Syntheses

1. Convert all FGs to those based on oxygen (OH, CO etc.) by FGI or C–X disconnection so that the carbon skeleton is exposed.
2. Identify the relationships between the functional groups. This means *counting*!
3. Adjust oxidation level if necessary and disconnect using reactions from chapters 18–28.
4. Continue to examine all possible relationships (e.g. by counting both ways round a ring) until a good synthesis emerges.
5. If necessary, add extra FGs or activating groups to make reactions possible.
6. If a bad step must be included, try to make it the first step.

References

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3. H. Naki, Y. Arai, N. Hamanaka and M. Hayashi, *Tetrahedron Lett.*, 1979, 805.
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