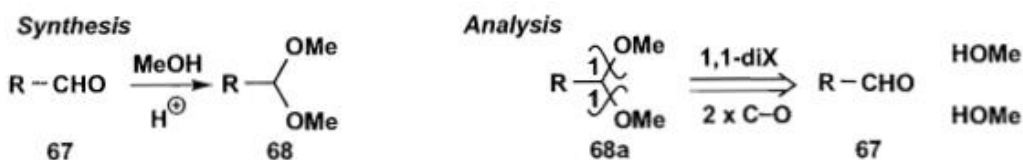


## Lecture # 7

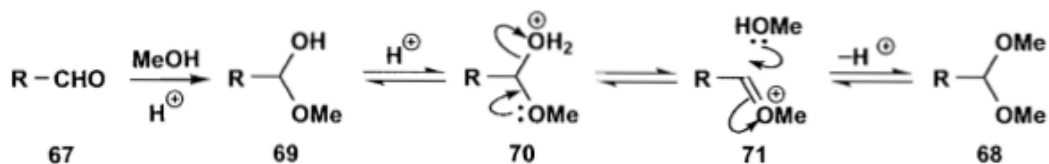
### The 1,1-diX Relationship

The label '1,1-diX' may look strange but all it means is that the two functional groups are joined to the same carbon atom. You already know how to make acetals **68**: you combine an aldehyde **67** with an alcohol, say methanol, in acidic solution. The disconnection **68a** is therefore of both C–O bonds. This reveals a valuable truth: two heteroatoms joined to the same carbon atom are at the carbonyl oxidation level (two C–O bonds to the same C atom in both **67** and **68**) and the TM is probably made from a carbonyl compound.

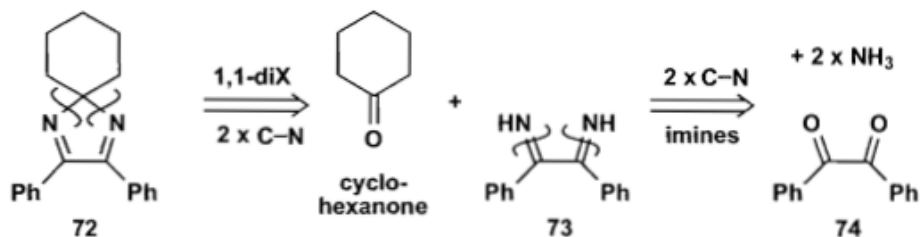


Again you may think that we are not using the two groups in cooperation. But we are. The key step in acetal formation and hydrolysis is the expulsion of one OR group by the other. In the synthesis, protonation of the hemiacetal **69** is followed by expulsion of a molecule of water **70** and the addition of the second molecule of methanol **71** is possible because of the first. In the

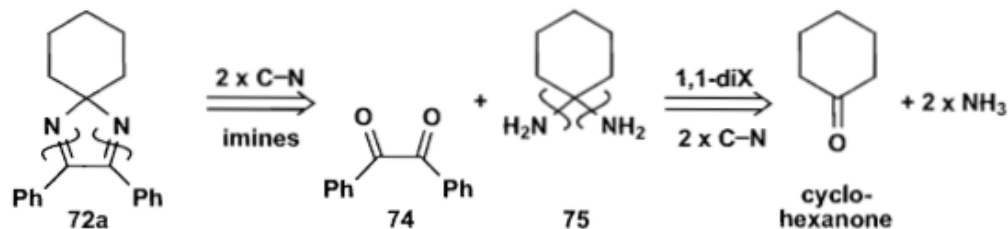
hydrolysis, these steps happen in reverse. Acetals are not 'just ethers'—they are more reactive compounds because of the two RO groups joined to the same carbon atom.



If the two heteroatoms are the same, it is usually best to disconnect both C–X bonds, choosing the ones to the same carbon atom, and write a carbonyl group at that atom. The heterocycle **72** has two C–N bonds to the same carbon atom. If we disconnect both, we get cyclohexanone and a very unstable looking imine **73**. We know how to make imines: combine a carbonyl group with an amine so disconnecting both imines we end up with the diketone **74** and two molecules of ammonia.

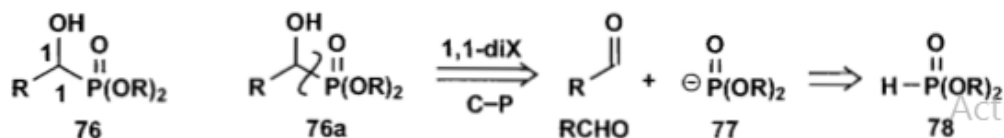


Supposing you had not noticed the 1,1-diX relationship but had spotted the imines. Disconnection **72a** takes us directly to the diketone **74** and a very unstable diamine **75**. Now you can't avoid the 1,1-diX disconnections **75** and we get the same starting materials whichever analysis we follow.

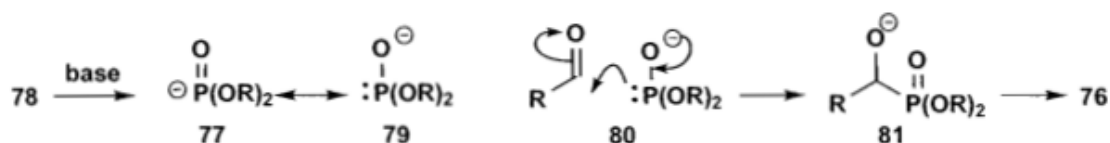


But what about the synthesis? When we are making stable 5- or 6-membered rings, syntheses are often very forgiving as you will discover in chapters 29 and 39. All you need to do is to mix together the two ketones with ammonium acetate, to provide both a source of ammonia and an acid catalyst, and **TM72** is formed in good yield.<sup>7</sup>

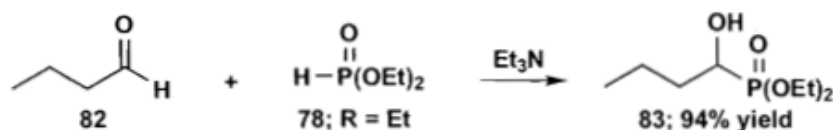
If the heteroatoms are different and one of them is oxygen, it makes more sense to disconnect the other so that the oxygen of the carbonyl group remains. The phosphonate **76** is an example. The nucleophilic synthon is **77** and this can be made by deprotonation of **78**.



As this chemistry may be unfamiliar, you may like to know that **78**; R=Et, known as diethyl phosphite, is available and forms the anion **77**, better drawn as **79**, with bases and adds **80** to aldehydes to give the anion **81** of the TM.

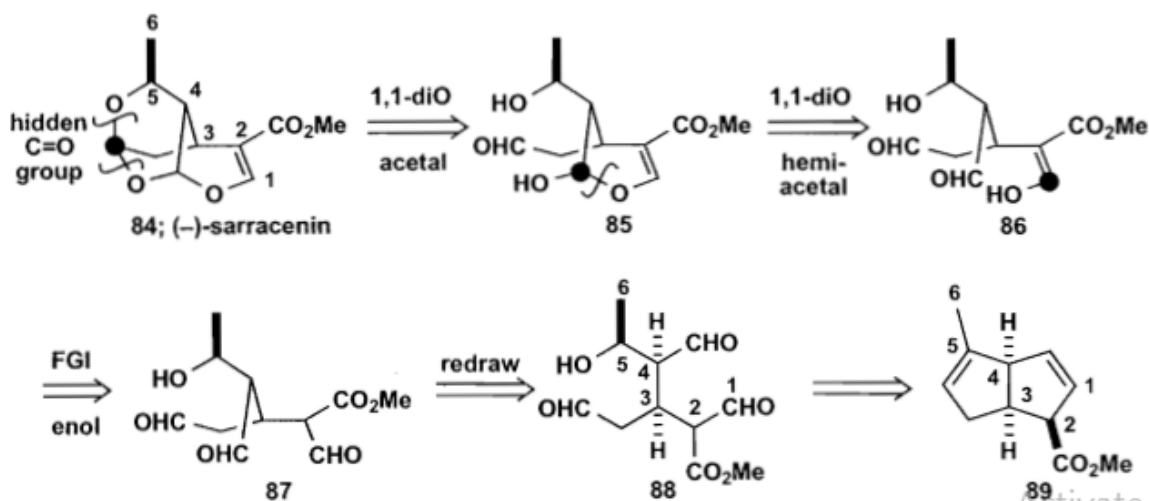


A real life example is made from **82** and **78**; R=Et with the weak base Et<sub>3</sub>N. This produces some of the anion **79**; R=Et and the ammonium salt protonates the anion of the TM to give **83** in excellent yield.



## Two-Group C-X Disconnections as a Preliminary to a Full Analysis

A brief inspection of the polycyclic cage structure of the natural product sarracenin **84** makes it appear a formidable target for synthesis. As we move forward into the book, it will become more and more important to identify any continuous pieces of carbon skeleton and an essential preliminary for that is to disconnect any structural C-X bonds, preferably using two-group disconnections. That strategy works spectacularly well here. Sarracenin **84** has several C-O bonds in its skeleton. One obvious 1,1-diO relationship is marked with a black blob in **84** showing where an acetal indicates a hidden carbonyl group. The black blob on **84** is the aldehyde in **85**. Disconnecting the acetal gives **85** with two fewer rings.



Further into the skeleton is another hidden carbonyl group **85** masked as a hemiacetal rather than an acetal. Disconnection there shows up an enol **86** and conversion of the enol into the aldehyde gives the simplest structure we have yet seen **87** without any rings at all. Indeed if we redraw that structure in a more conventional way **88**, we can see that it is one continuous piece

of carbon skeleton. One published synthesis<sup>8</sup> reconnects the two aldehydes on the right to give one alkene and the aldehyde and alcohol on the left to give another **89**. This compound looks a great deal simpler than sarracenin but in fact has exactly the same number of carbon atoms. We shall meet the reconnection strategy in chapter 27.