

## Lecture 9: Acetals

### Objectives:

By the end of this lecture you will be able to:

- draw an arrow-pushing mechanism for acetal formation;
- draw an arrow-pushing mechanism for acetal hydrolysis;
- use acetals as protecting groups for aldehydes and ketones;
- use dithioacetals as protecting groups for aldehydes and ketones.

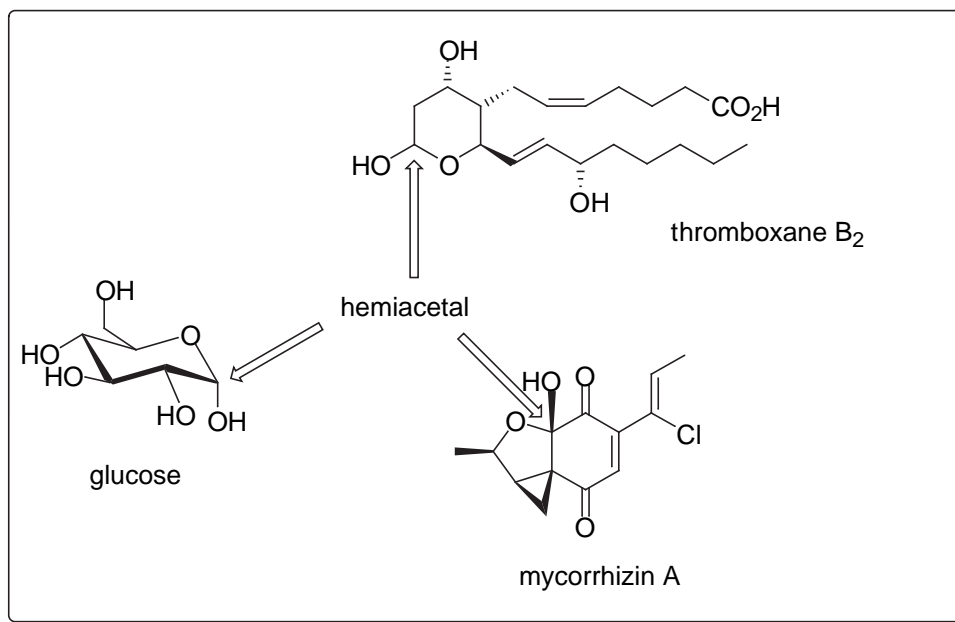
Acetals are functional groups characterised by an  $sp^3$ -C that is bonded to *two* oxygen atoms, which are themselves attached to a carbon atom. We have already seen related structures such as hydrates in earlier lectures.



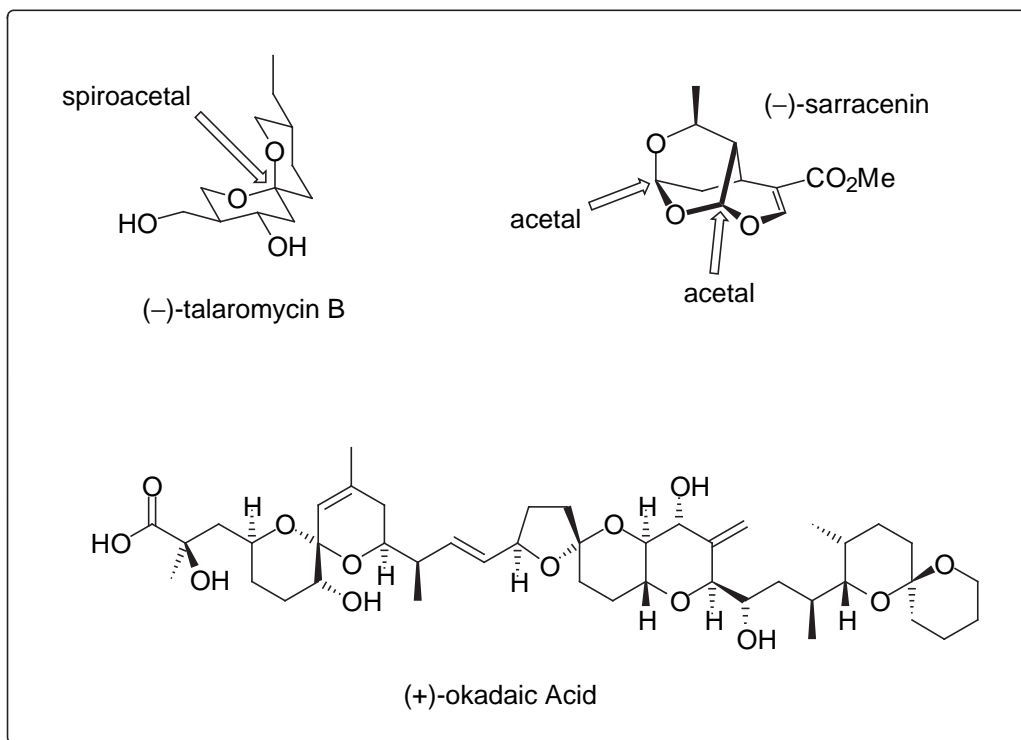
### Occurrence in Nature

Acetals and hemiacetals are common functional groups in natural products.

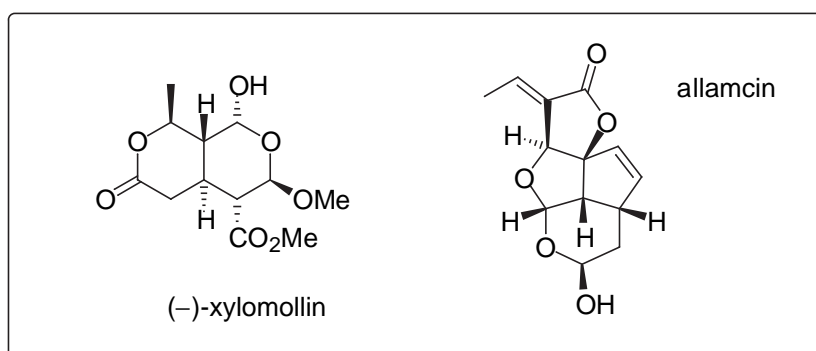
Some naturally occurring hemiacetals:



Some naturally occurring acetals.



Some natural products contain both acetal and hemiacetal functional groups:

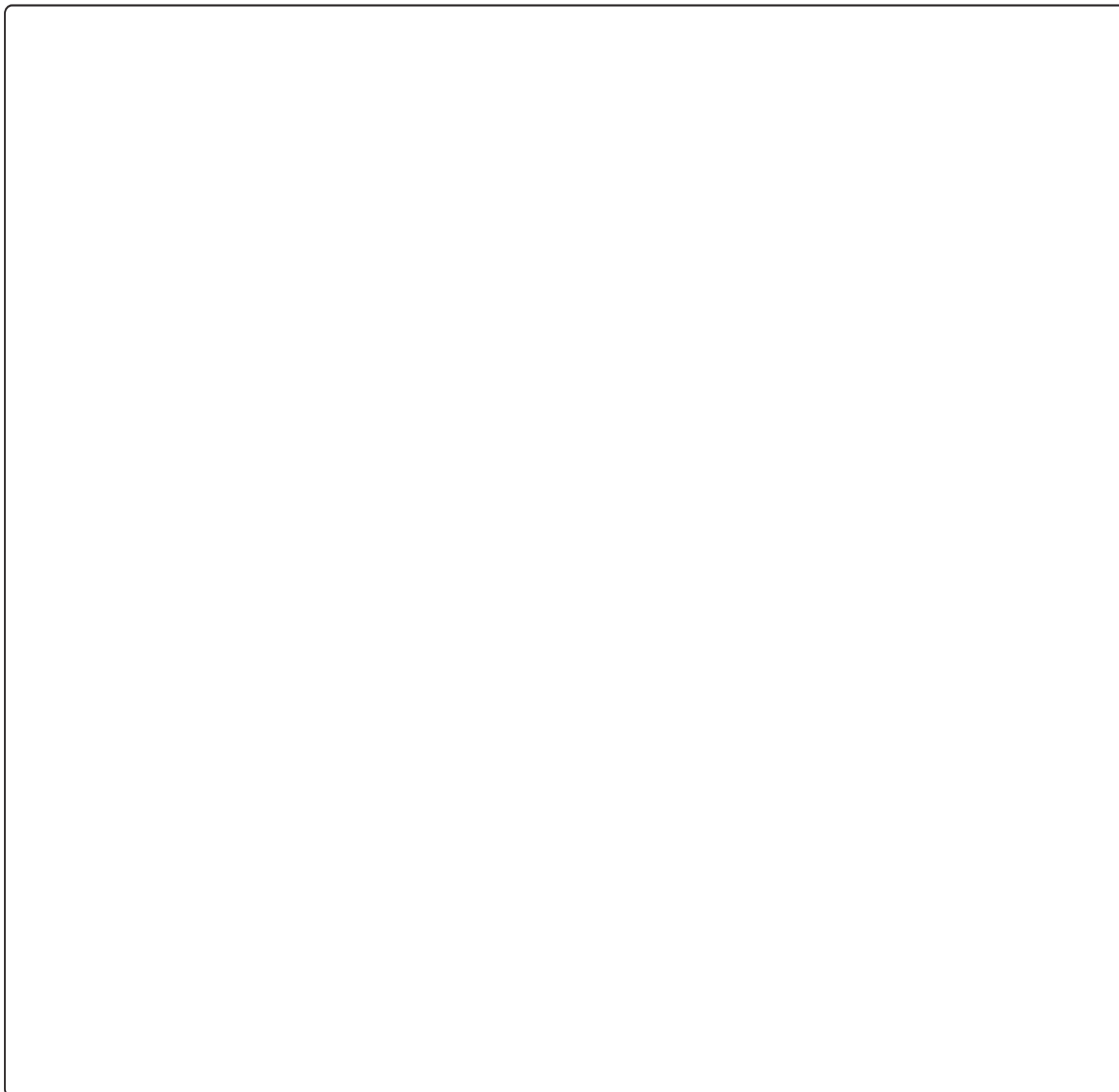


### Mechanism of Formation

Acetals, sometimes also known as ketals, are readily formed from *one molecule of an aldehyde or ketone and two molecules of an alcohol*. The reaction requires *acid catalysis* to proceed to completion since a late step in the mechanism involves the elimination of hydroxide (as water under acidic conditions) from a tetrahedral intermediate.

Under acidic reaction conditions, a small amount of the carbonyl group will be protonated. This protonated intermediate is highly electrophilic and will react with the nucleophilic alcohol in a standard fashion to provide, after proton transfer, the *hemiacetal* intermediate. Protonation of the

alcohol group in the hemiacetal generates a good leaving group, which can then be expelled with the aid of the adjacent alkoxy group (**neighbouring group participation**). The product from this dehydration step is a highly electrophilic oxocarbenium cation that will be trapped with another alcohol to provide, after loss of a proton, the acetal product.



- The rate-determining step is the expulsion of a water molecule *i.e.* the dehydration step.
- Acetal formation is an equilibrium process, therefore to drive the reaction over to product it is necessary to use an excess of alcohol or to provide a method for removing the water that is formed (*e.g.* use a dehydrating agent or remove the water by azeotropic distillation).
- In the absence of acid, acetals are *not* susceptible to hydrolysis *i.e.* the reverse reaction. They are therefore quite stable to neutral and basic reaction conditions.

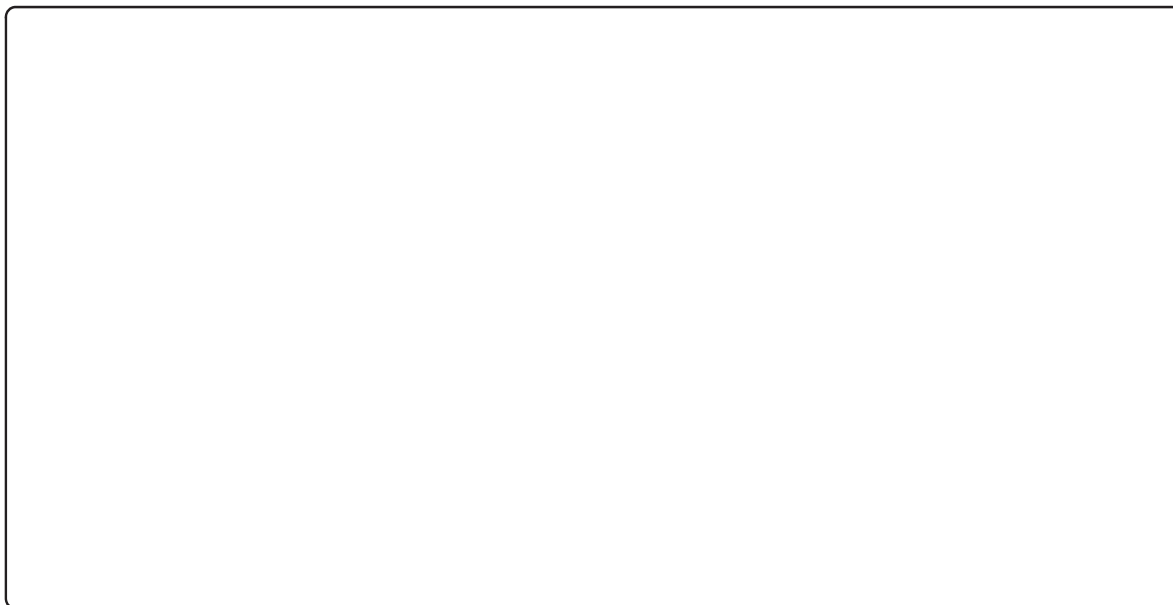
**The mechanism of acetal hydrolysis is the reverse of the mechanism of acetal formation.**

- Acetals are not stable to aqueous acid and are very readily hydrolysed back to the parent alcohol and carbonyl compound under these reaction conditions.

**How to identify the starting materials to prepare an acetal:**

1. Identify the acetal carbon - *i.e.* the  $sp^3$ -carbon atom that is directly bonded to two oxygen atoms.
2. Cleave the two C–O bonds.
3. Convert the two oxygen atoms into alcohols and make the  $sp^3$ -acetal carbon into the carbon of a carbonyl group.

Example 1.



Example 2



## Acetals as Protecting Groups for Aldehydes and Ketones

Aldehydes and ketones are reactive electrophiles. Sometimes the presence of such a functional group in a molecule can be a problem for reactions that need to be carried out on other parts of the molecule. In this case the reactive carbonyl group is usually *masked* in some way using a *protecting group*, such that it can no longer behave as an electrophile. The protecting group can then be removed at a later stage. This problem is readily illustrated in the following example:



Suppose we wish to reduce the ester to an alcohol but leave the aldehyde intact. Here we have a problem of *chemoselectivity*. Since aldehydes are much more electrophilic than esters, treating the molecule with a hydride reducing agent would result in preferential reduction of the aldehyde. It is therefore not possible to carry out the transformation in a single step. We therefore need to perform a multi-step sequence to carry out this overall transformation:

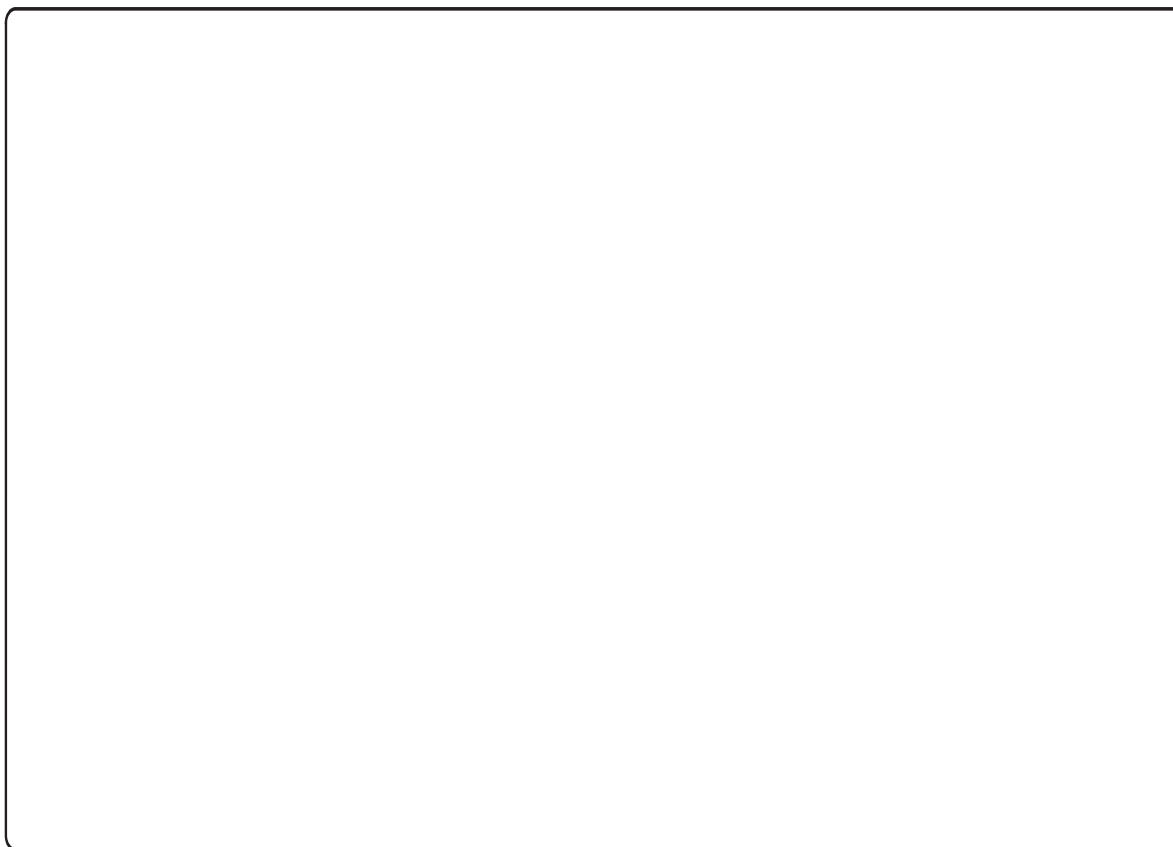
1. Protect the more electrophilic aldehyde.
2. Reduce the ester to the alcohol.
3. Re-install the aldehyde by removing the protecting group.

*What protecting group to use?*

Since esters are not strong electrophiles, we need quite a reactive reducing agent to reduce this functionality down to the alcohol. We have so far discussed two reducing agents,  $\text{NaBH}_4$  and  $\text{LiAlH}_4$ . The former is a mild reducing agent and, under standard conditions, does not reduce esters; the latter is very reactive and will have no problems reducing the ester to the desired alcohol. Thus we have a reagent for carrying out the desired transformation.

We now have to consider a protecting group that is not electrophilic *i.e.* one that will not react with the nucleophilic hydride reagent. Acetals are not electrophilic and would therefore satisfy this condition. They are also easy to prepare using reaction conditions that *will not affect the ester*; likewise deprotecting the acetal after the reduction can also be achieved *without affecting the alcohol functional group that has just been introduced*.

*A three-step strategy for reducing the ester is required:*



### **Dithioacetals**

Dithioacetals or *S,S*-acetals are the sulfur analogues of *O,O*-acetals. They are readily prepared from two equivalents of a thiol and one equivalent of a carbonyl group. In the absence of a catalyst, dithioacetal formation is slow; the rate of reaction can be increased by adding a Brønsted or more commonly, a Lewis acid such as  $\text{BF}_3 \cdot \text{OEt}_2$ . The mechanism of formation is the same as for the formation of *O,O*-acetals.



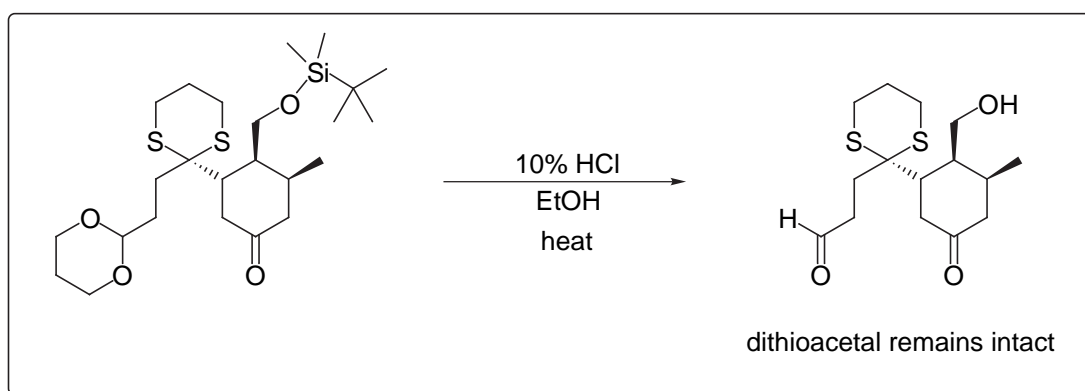
Dithioacetals are *far more stable* to acid than are *O,O*-acetals.

There are several reasons for this increased hydrolytic stability:

1. Sulfur is in period 3 which makes it a poorer Brønsted base than oxygen; *i.e.* it is more difficult to protonate on sulfur than it is on oxygen.
2. There is also a greater barrier to the formation of the thiocarbenium ion ( $\pi$  bond is formed from a 2p and a 3p AO) than there is to the formation of an oxocarbenium cation.



The increased hydrolytic stability of dithioacetals clearly makes it more difficult to unmask the carbonyl group.



A variety of methods have been used to hydrolyse dithioacetals to the parent carbonyl compound. One of the most common methods is to use mercury(II) salts which form strong bonds to sulfur.

Example:



Note: Dithianes have other important uses in organic synthesis. In future courses in Years 2 and 3 you will meet them again and see how they can be used as *acyl anion equivalents*.

### Summary

Acetals are formed when aldehydes and ketones react with alcohols in the presence of an acid catalyst. Two alcohol groups are required to react with one carbonyl group. They are easy to form and not surprisingly occur widely in Nature.

The reaction mechanism is similar to many we have seen before and is based on two nucleophilic addition steps to carbonyl groups, and a dehydration step. The acid catalyst plays two roles: the first is to activate the aldehyde or ketone to nucleophilic attack; the second is to generate a good leaving group for the dehydration step.

Acetal formation is a reversible process; hence the reverse reaction (acetal hydrolysis) is also acid-catalysed and proceeds through a mechanism that is the exact reverse of the forward reaction.

Aldehydes and ketones are reactive electrophiles whereas acetals (in the absence of Lewis and Brønsted acids) are not. The ease with which acetals can be prepared and later hydrolysed makes them ideal protecting groups for electrophilic carbonyl groups. Acetals are not stable to acid but are stable to neutral and basic reaction conditions. They can be used as protecting groups for carbonyl groups providing the intermediate reaction steps do not involve acidic (Brønsted or Lewis) reaction conditions.

Dithioacetals are the sulfur analogues of *O,O*-acetals. They are also easy to prepare and show increased stability towards acid than their oxygen analogues. Owing to their hydrolytic stability even in the presence of acid, they are also more difficult to deprotect and special reaction conditions (*e.g.* the use of heavy metal salts such as Hg(II)) are normally required to do this efficiently.