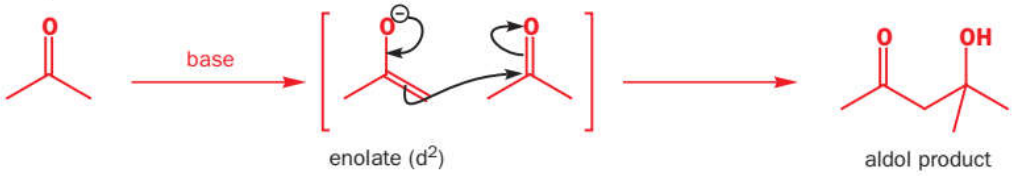
# Course 12

## 1)

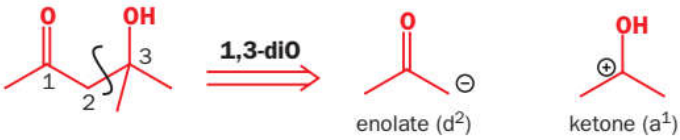
# Two-group C–C disconnections

### 1,3-Difunctionalized compounds

It's not only Grignard reagents that will react with aldehydes or ketones to make alcohols: enolates will too—we spent Chapters 27 and 28 discussing this reaction, the aldol reaction, its variants, and ways to control it.




The aldol reaction is extremely important in organic synthesis because it makes compounds with two functional groups in a 1,3-relationship. Whenever you spot this 1,3-relationship in a target molecule—think aldol! In disconnection terms we can represent it like this.

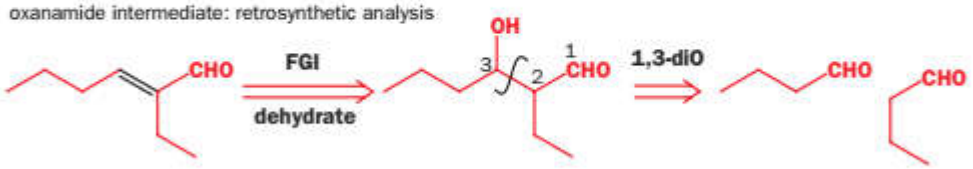



We call this disconnection a **two-group C–C disconnection**, because we are using the OH and the C=O groups together to guide our disconnection. The disconnection gives us a $d^2$ synthon for which

## 2)

The β-hydroxy carbonyl products of aldol reactions are often very easily dehydrated to give α,β-unsaturated carbonyl compounds and, if you spot an α,β-unsaturated carbonyl group in the molecule, you should aim to make it by an aldol reaction. You will first need to do an FGI to the β-hydroxy carbonyl compound, then disconnect as before.

oxanamide intermediate: retrosynthetic analysis

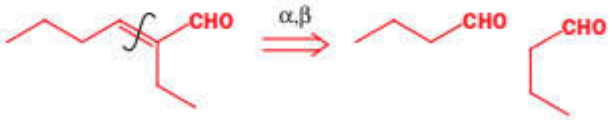



This aldehyde is an intermediate in the synthesis of the tranquillizer oxanamide. Because both components of the aldol reaction are the same, no special precautions need to be taken to prevent side-reactions occurring. In the synthesis, the dehydration happened spontaneously.

oxanamide intermediate: synthesis


Because this disconnection of unsaturated carbonyl compounds is so common, it's often written using a shorthand expression.

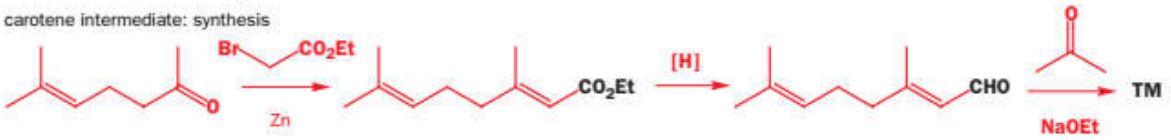
oxanamide intermediate: retrosynthetic analysis



The aldehyde generated by this first disconnection is also α,β-unsaturated, so we can do another α,β disconnection, back to a ketone whose synthesis we have already discussed (p. 000).

An aldol reaction using the enolate of acetaldehyde and requiring it to react with a ketone is doomed to failure: acetaldehyde itself is far too good an electrophile. In the forward synthesis, therefore, this first step was carried out at the ester oxidation level (using a Reformatsky reaction), and the ester was subsequently converted to the aldehyde by a reduction of the kind discussed in Chapter 24.

carotene intermediate: synthesis



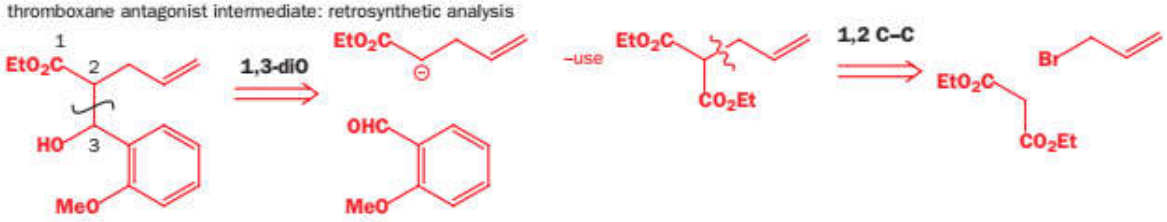

There was no problem with selectivity in the second aldol reaction because the aldehyde is not enolizable. The Reformatsky reaction in this sequence illustrates the fact that, of course, aldol-type

reactions happen at the ester oxidation level as well, and you should equally look to disconnect β-hydroxy or α,β-unsaturated esters, acids, or nitriles in this way. Just remember to look for 1,3-relationships, convert the functional groups to oxygen-based ones, and disconnect them to $d^2$ plus $a^1$ synthons.

## 3)

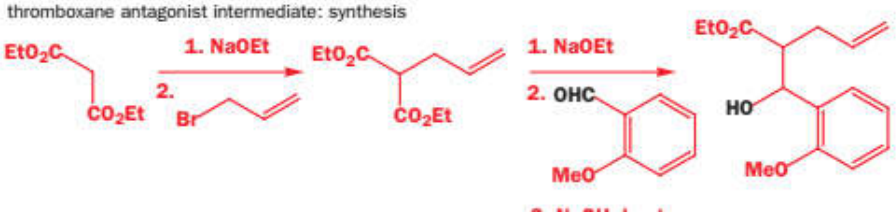
The next compound was needed by ICI when chemists there were developing a thromboxane antagonist to inhibit blood clot formation. You can immediately spot the 1,3-relationship between the ester and the hydroxyl group, so 1,3-diO disconnection is called for.

thromboxane antagonist intermediate: retrosynthetic analysis




A good equivalent for the 'ester enolate' $d^2$ synthon is a β-dicarbonyl compound, because it can easily be disconnected to diethyl malonate and an alkylating agent.

thromboxane antagonist intermediate: synthesis

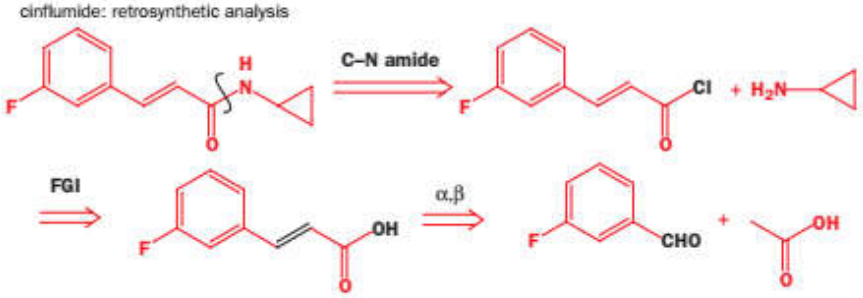


# Course 13

## 1)

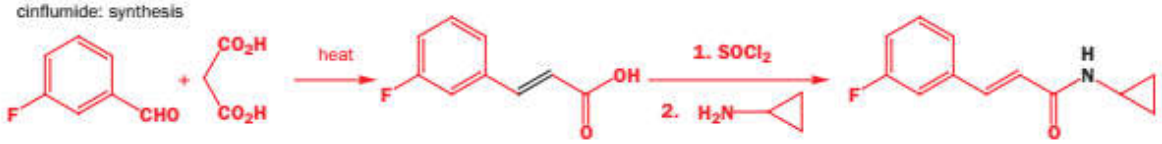
This unsaturated amide is known as cinflumide and is a muscle relaxant. Disconnection of the amide gives an acid chloride that we can make by FGI from the acid. You should then spot the α,β-unsaturated carbonyl disconnection, a masked 1,3-diO disconnection, back to *m*-fluoro-benzaldehyde.

cinflumide: retrosynthetic analysis




Again, the forward reaction was best done using malonate chemistry but the variant with malonic acid was used. The cyclopropyl amine unit (here as an amide) is present in many biologically active compounds and the free amine is available.

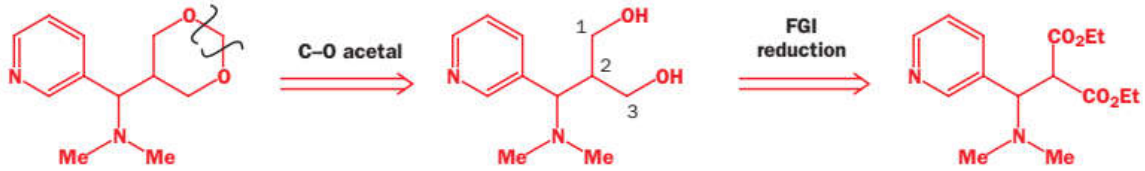
cinflumide: synthesis




## 2)

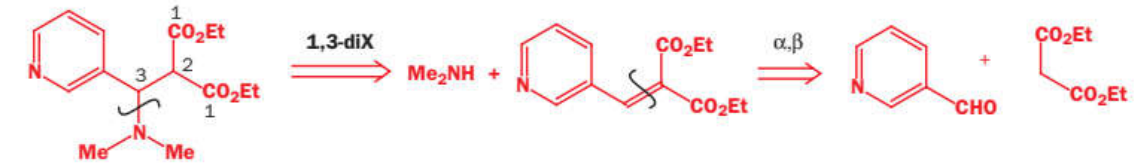
# Functional group relationships may be concealed by protection

doxpicomine: retrosynthetic analysis I

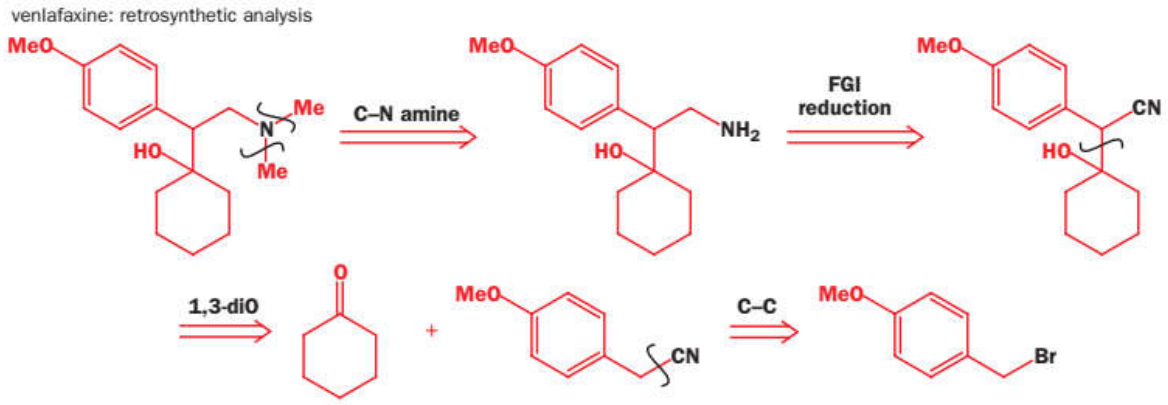



The diester has a 1,3-diCO relationship and could be disconnected but we have in mind using malonate so we would rather disconnect the alternative 3-amino carbonyl compound (the $Me_2N$ group has a 1,3-relationship with both ester groups) by a 1,3-diX disconnection giving an unsaturated ester. This α,β-unsaturated ester disconnects nicely to a heterocyclic aldehyde and diethyl malonate.

doxpicomine: retrosynthetic analysis II



**3)**


venlafaxine: retrosynthetic analysis
MeO
HO
N
Me
Me
C–N amine
NH2
FGI
reduction
CN
1,3-diO
O
+
C–C
Br

# Course 14

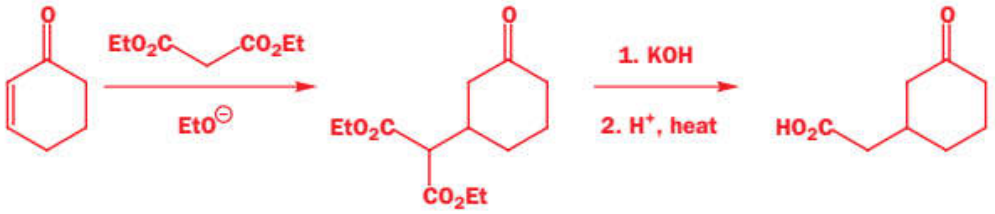
## 1)

## 1,5-Related functional groups

This compound has a 1,5 rather than a 1,3 relationship between two carbonyl groups. Disconnection to give an enolate as one reagent therefore requires an $a^3$ rather than an $a^1$ synthon: in other words a **Michael acceptor.**

1,5-dicarbonyl compounds: retrosynthetic analysis

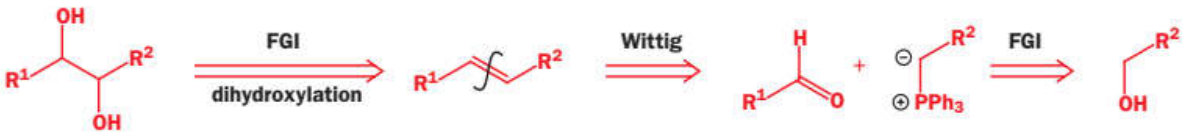

The synthesis will be successful only if (1) the right reagent enolizes and (2) the nucleophile undergoes conjugate (and not direct 1,2-) addition to the unsaturated carbonyl compound (Chapter 29). Malonate derivatives enolize easily *and* do Michael additions and are therefore a good choice for this type of reaction.




## 2)

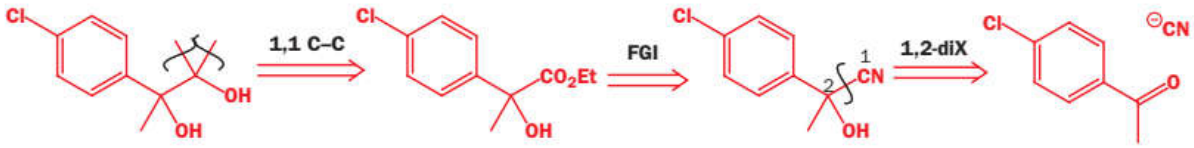
### 1,2-Difunctional compounds

You met ways of making 1,2-difunctionalized compounds when we first talked about two-group disconnections, and we used an epoxide as an $a^2$ synthon. Epoxides are, of course, also 1,2-functionalized, and in fact this is often the key to making 1,2-functionalized compounds: use something with the 1,2 relationship already in place. You saw lots of examples of this type of strategy earlier in this chapter. Perhaps the simplest approach is electrophilic addition to alkenes. If the alkene is made by a Wittig reaction, the disconnection is (eventually) between the two functionalized carbon atoms in the target molecule. This example shows dihydroxylation as the electrophilic addition but there is also epoxidation, bromination, and bromination in water to give Br and OH as the functional groups.



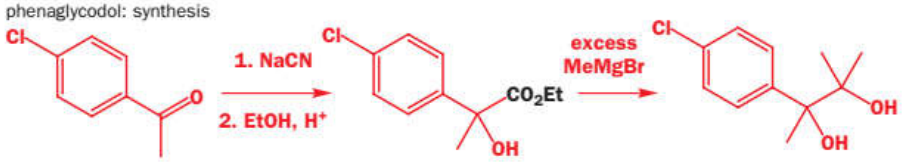
A normal C–C disconnection is also a possibility, but disconnection to the 'natural' $a^1$ synthon and the umpolung $d^1$ is necessary. One very useful umpolung reagent is cyanide, and you can see it in action in this synthesis of the tranquillizer phenaglycodol. The tertiary alcohol with two R groups the same should prompt you to think of doing a double Grignard addition to an ester. FGI then reveals the nitrile functional group necessary for a 1,2-diX disconnection to cyanide plus ketone.

phenaglycodol: retrosynthetic analysis




The starting material is obviously available by a Friedel–Crafts acylation of chlorobenzene and the rest of the synthesis follows. Note that the nitrile can be converted directly into the ester with acidic ethanol and that an excess of Grignard reagent is needed because the free OH group destroys some of it.

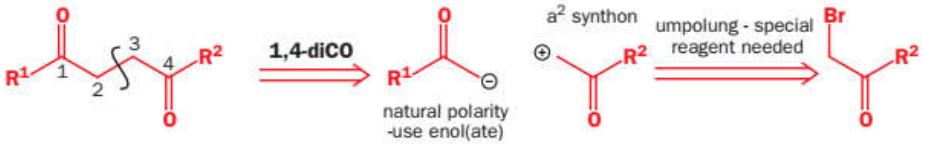
phenaglycodol: synthesis




**3)**

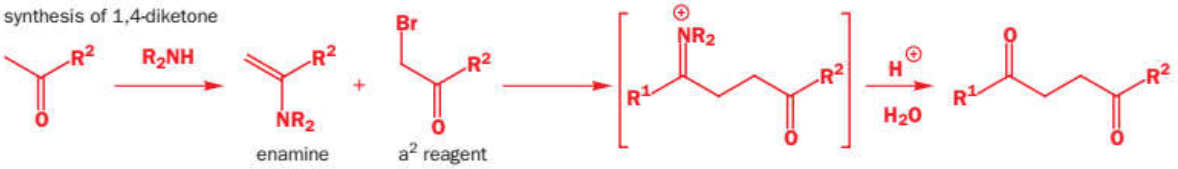
## 1,4-Difunctional compounds

There are more possibilities here and we shall finish this chapter with a brief analysis of them to show you how much of this subject lies beyond what we can do in this book. If we start with a 1,4-dicarbonyl compound we might consider first disconnection of the central bond.




We can use an enolate for one reagent but the other will have to have umpolung. This is not a very serious kind of umpolung as an α-bromo carbonyl compound will do the job nicely if we select our enol(ate) equivalent carefully. In Chapter 26 we suggested enamines for this job. The synthesis becomes:

synthesis of 1,4-diketone



If we attempt the disconnection of one of the other bonds, two possibilities are available because the two fragments are different. We can use either a $d^1 + a^3$ strategy or an $a^1 + d^3$ strategy. In each case we have one natural synthon and one with umpolung.