Synthetic Strategy – Lecture 5 (DC, 11.2.04)

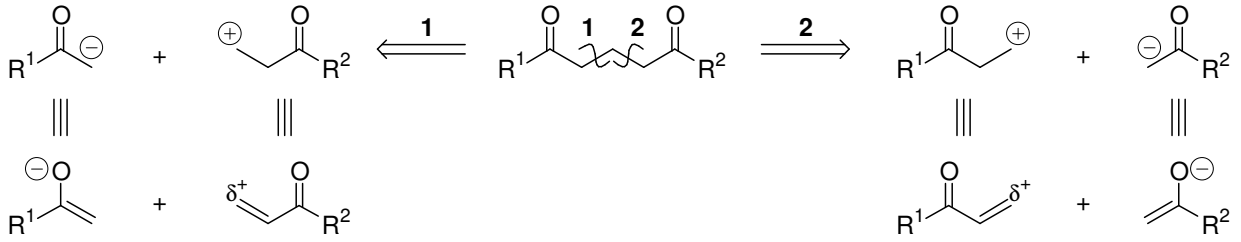
1,5-Dioxygen relationships (Warren textbook, ch. 20 p 170-)

During the last two lectures of this part of the course, Dr Armstrong has shown that a general method for identifying useful disconnections is to look at the relationship between oxygen-based functional groups in the target molecule (*i.e.* the "distance" between them). He focused firstly on the very powerful disconnection of 1,3-relationships between FGs (a "natural polarity" disconnection) and then went on to look at the disconnection of target molecules possessing 1,4-difunctionalisation, an "unnatural polarity" disconnection. This lecture will look at another type of natural polarity disconnection, namely those of compounds possessing **1,5-dioxygen relationships**, and analogous target molecules.

1,5-Dicarbonyl compounds: the fundamental disconnection

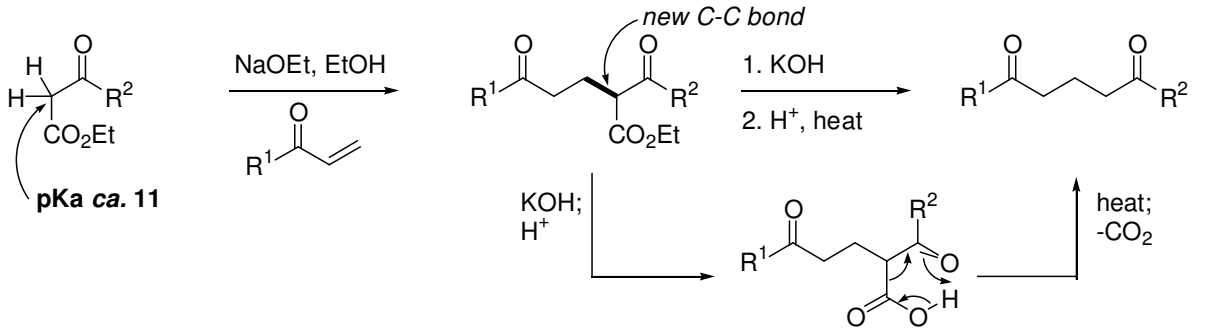
There is one bread-and-butter disconnection which underpins most of the analysis in today's lecture. Simple, acyclic 1,5-dicarbonyl compounds may be disconnected using one of two possible **reverse Michael** disconnections:

SCHEME A



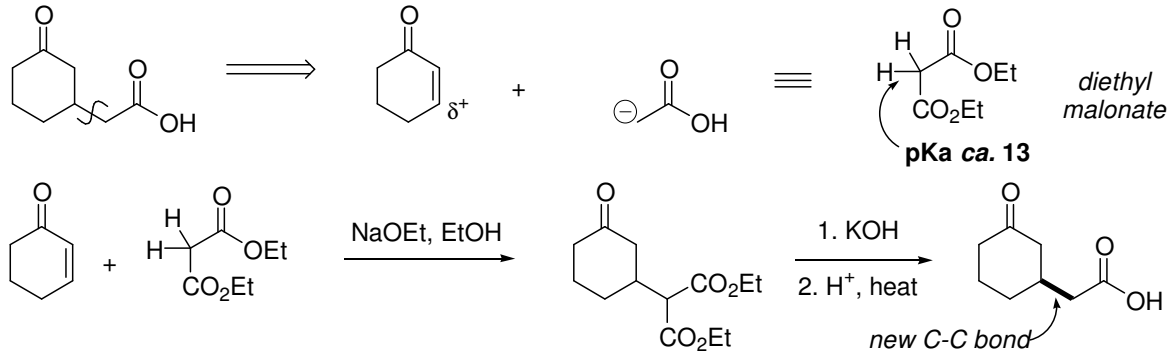
Clearly the disconnection leads us back to an enolate and a Michael acceptor (**not** a β-halocarbonyl compound!!!). But we know that the Michael acceptor is an **ambident** electrophile (it may be attacked both at the carbonyl carbon atom and the β-position), so to ensure that the correct sense of addition is obtained, we use an activating group on the enolate (this also means that there is no ambiguity about which carbonyl α-position acts as the nucleophile); ester is usually the activating group of choice, since it is easy to remove after C-C bond formation (AA lecture 3).

SCHEME B



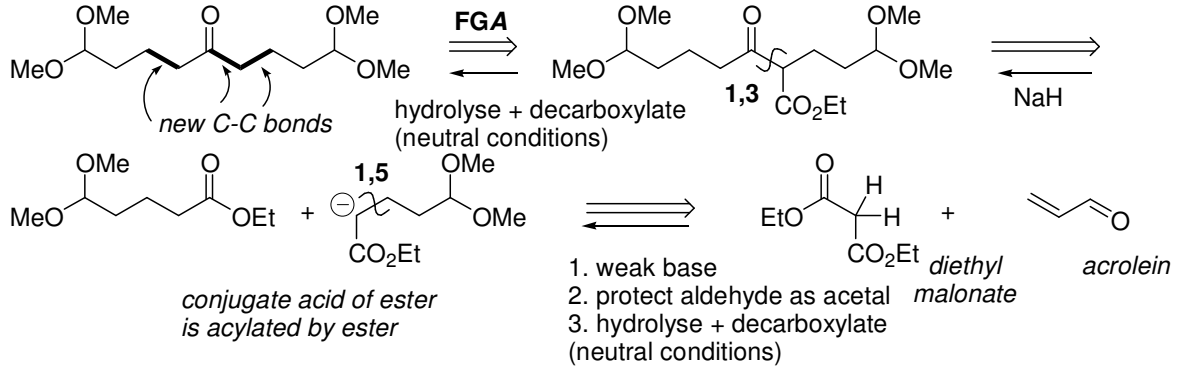
Of course these principles apply equally well to cyclic compounds also, whether the enolate or the Michael acceptor (or indeed both!) are part of a ring.

SCHEME C



The following example (Warren textbook, p. 171-2) nicely illustrates a combination of 1,3-dicarbonyl and 1,5-dicarbonyl disconnections.

SCHEME D

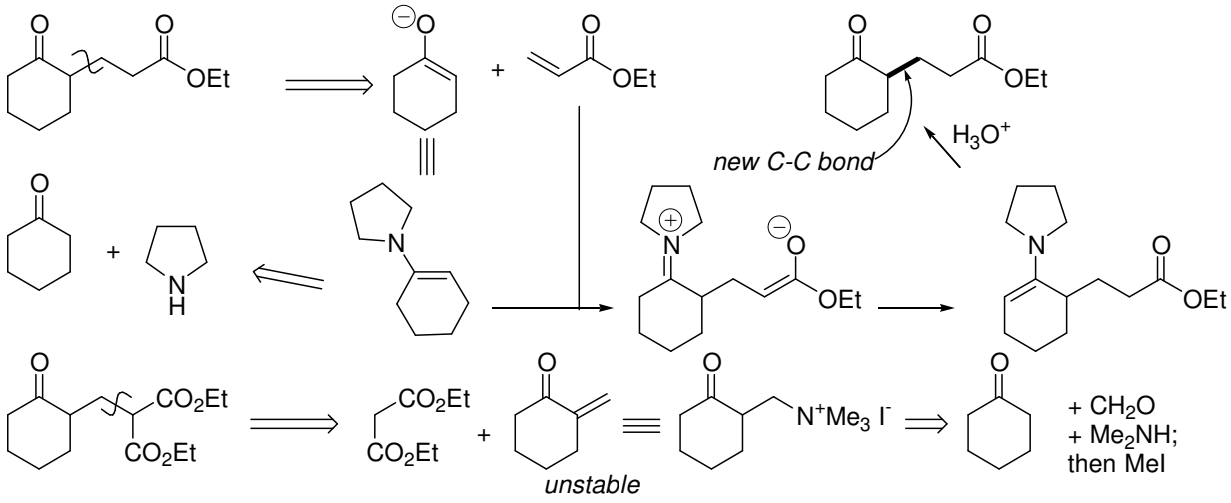


Note that the initial disconnection maximises the **symmetry** of the approach – the two esters which combine in the Claisen condensation to make the intermediate β-ketoester are *identical*! (We might have been tempted to disconnect to give another β-ketoester and a Michael acceptor, but this would have required more steps.)

1,5-Dicarbonyl compounds: variations on a theme

It's useful to know that we're not obliged to use activated ketones and stable, off-the-shelf Michael acceptors. Indeed, some Michael acceptors are so powerfully electrophilic that they're **unstable**, and we need to be able to generate them *in situ*; this is conveniently done using the **Mannich reaction** (AA lecture 3). The mild alternatives to the activated ketones are **enamines**.

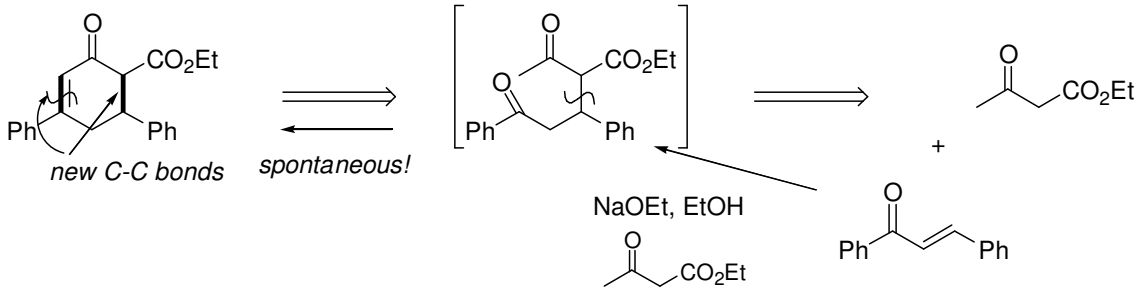
SCHEME E



1,5-Dicarbonyl compounds: substrates for the synthesis of 1,3-difunctionalised compounds

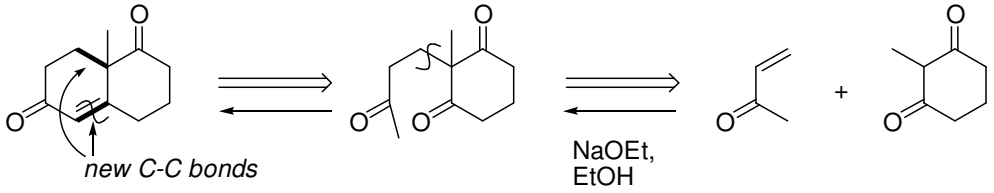
α,β-Unsaturated, six-membered cyclic ketones are 1,3-difunctionalised target molecules which are disconnected to reveal 1,5-dicarbonyl precursors. Therefore, a very straightforward synthesis involves Michael addition followed by intramolecular aldol condensation. The carbonyl group stabilising the negative charge in the Michael donor becomes the electrophile in the subsequent cyclisation…

SCHEME F



When the enolate is part of a ring, this chemistry provides a route for building an additional ring onto a pre-existing cyclic structure. Yes, you've recognised the **Robinson annelation**!

SCHEME G



Next time (Wed 18th Feb at 11am): advanced strategy