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**

\[
\begin{align*}
\text{SCHEME C} & \\
\text{Scheme C} & \\
\end{align*}
\]

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

**SCHEME D**

The initial disconnection maximises the **symmetry** of the approach – the two esters which combine in the Claisen condensation to make the intermediate \( \beta \)-ketoester are **identical**! (We might have been tempted to disconnect to give another \( \beta \)-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