Organic Chemistry-4

Semester-4, CBCS

Course: CEMA CC-4-8-TH

Course taught by: Kaushik Basu, Department of Chemistry, SPCMC, Kolkata

email: chiralkaushik@gmail.com

Recommended texts:

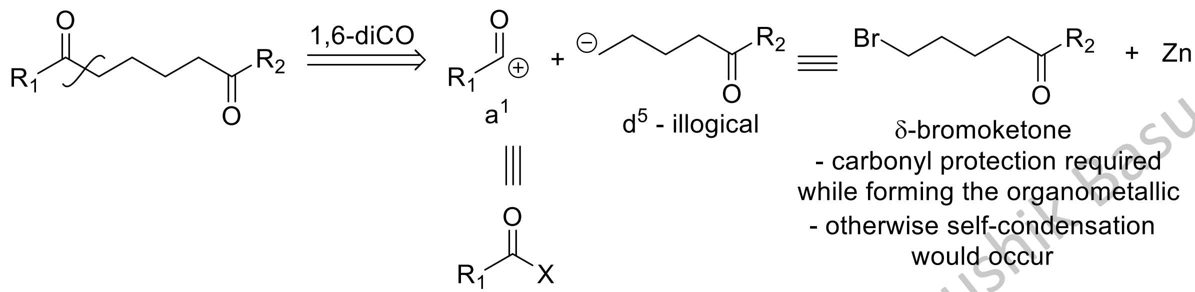
1. Study Guide to Organic Chemistry, Volume 2, by Saha, Chakraborty, Saha & Basu, Techno World, ISBN 9788192669588,
2. Organic Chemistry, Second Ed. by Clayden, Greeves & Warren, OUP, ISBN 9780198728719

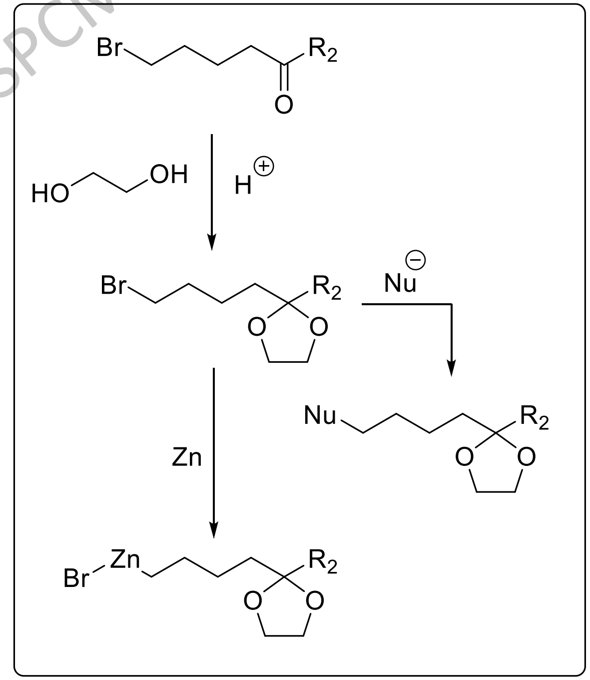
The Logic of Organic Synthesis: Analysis of bifunctional target molecules:

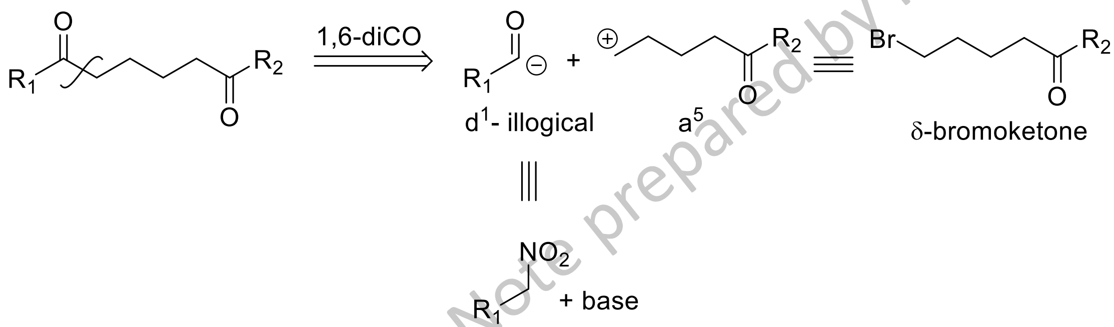
E] 1,6-bifunctional compounds:

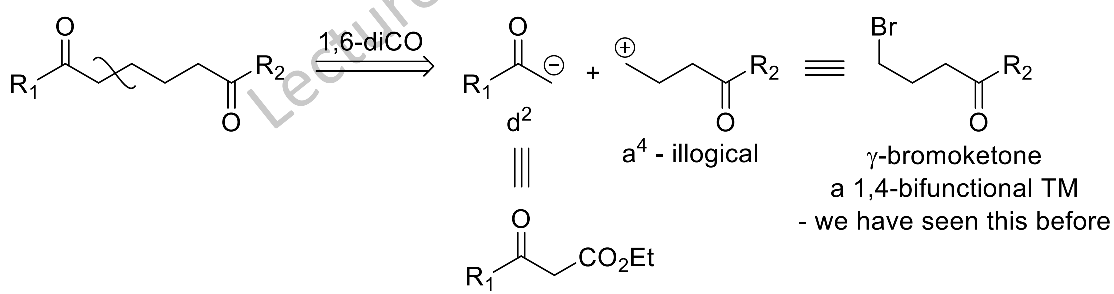
The following is a summary of the retrosynthetic strategies one can adopt when the target molecule contains two heteroatom-based functional groups placed at an 1,6-relation. These target molecules are dissonant systems, so umpolung strategy will be involved.

Let us consider a few generalised disconnection strategies:

1. 



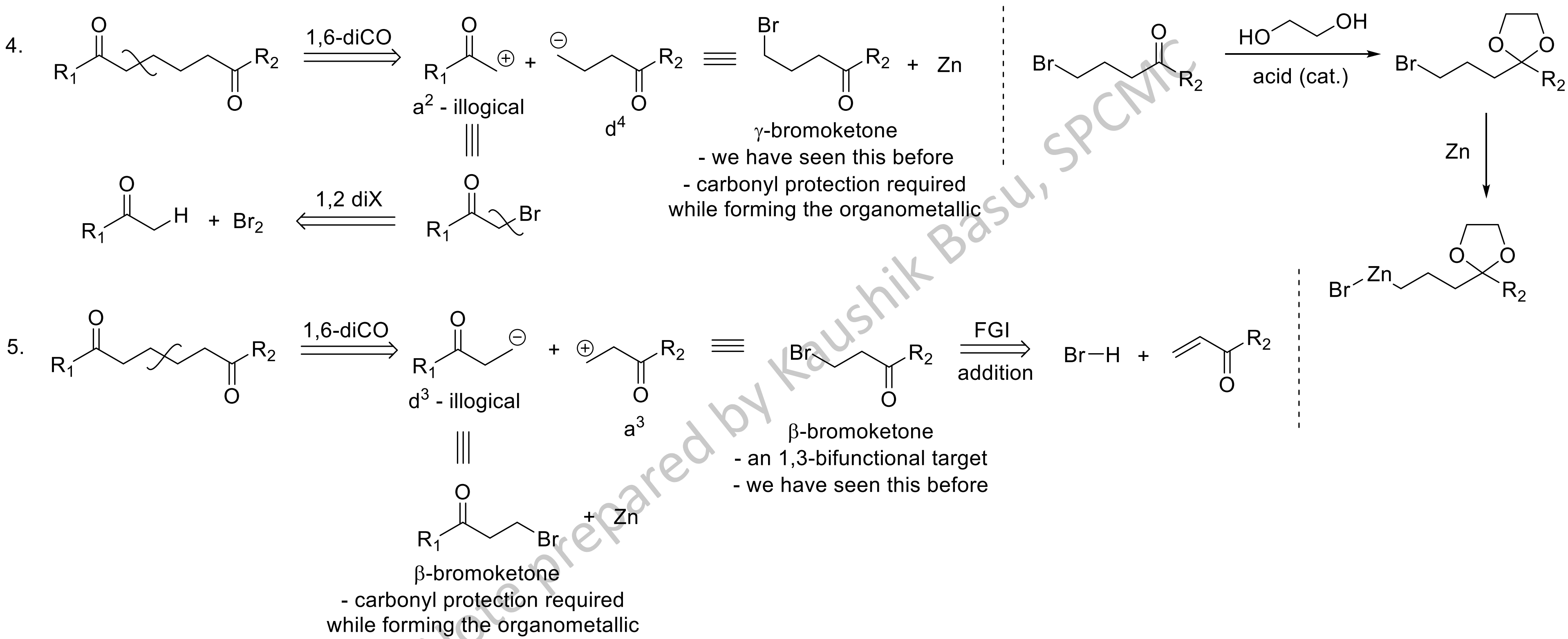
2. 

3. 

The Logic of Organic Synthesis: Analysis of bifunctional target molecules:

E] 1,6-bifunctional compounds (contd.):

Let us consider a few generalised disconnection strategies:



However, none of these look very promising.

The two oxygenated functional groups in these targets have the largest through bond distance that we have seen till now.

If we adopt the ***strategy of reconnection*** here, i.e. join up the two oxygenated carbons by removing the two =O groups and placing between those carbons a double bond, we are presented with a cyclohexene ring system as our revised target. This six-membered system is easily accessible and sometimes available from natural sources as well.

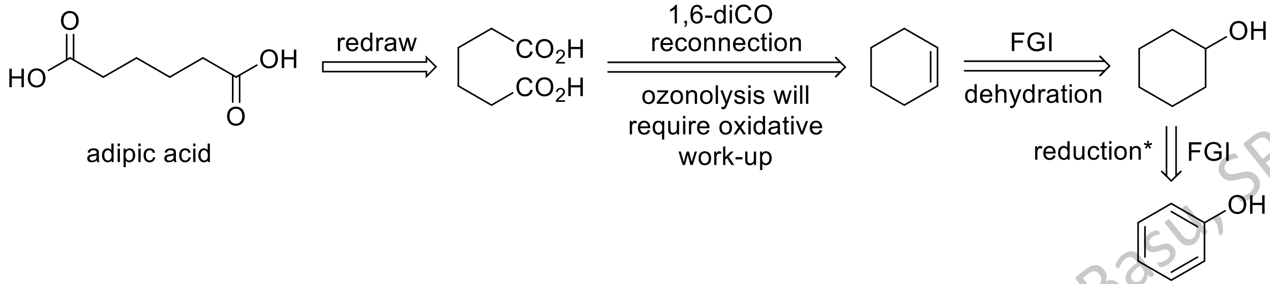
Of course, in the forward synthesis this C=C bond of the cyclohexene system needs to be oxidatively split into two carbonyl fragments. A good candidate for such a transformation is the ozonolysis with its variety of work-up procedure that allows for easily accessing different oxidation levels. The forward synthesis utilising this concept is generally much more efficient than any other strategy one might think of.

The Logic of Organic Synthesis: Analysis of bifunctional target molecules:

E] 1,6-bifunctional compounds (contd.):

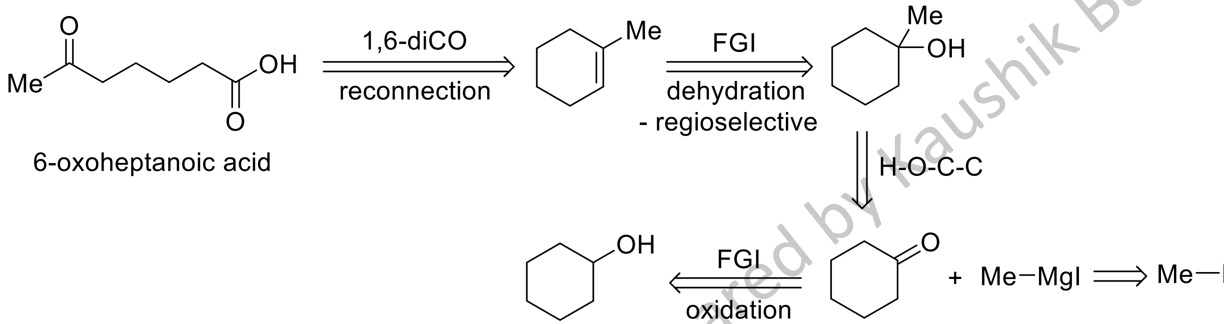
Let us now consider a few examples that use the *strategy of reconnection*:

1.

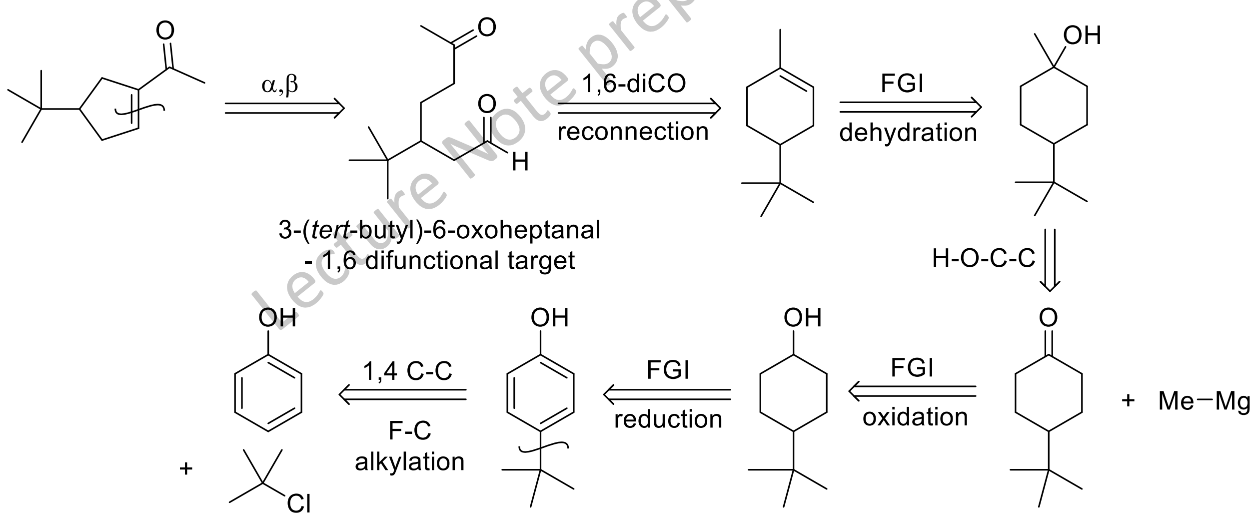


* reduction with H_2-Ni

2.



3.



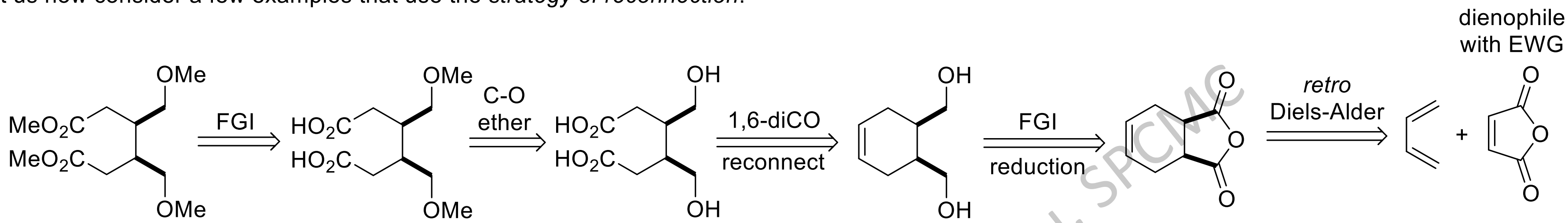
non-oxidative work-up (with Me_2S) required to get aldehyde through ozonolysis

The Logic of Organic Synthesis: Analysis of bifunctional target molecules:

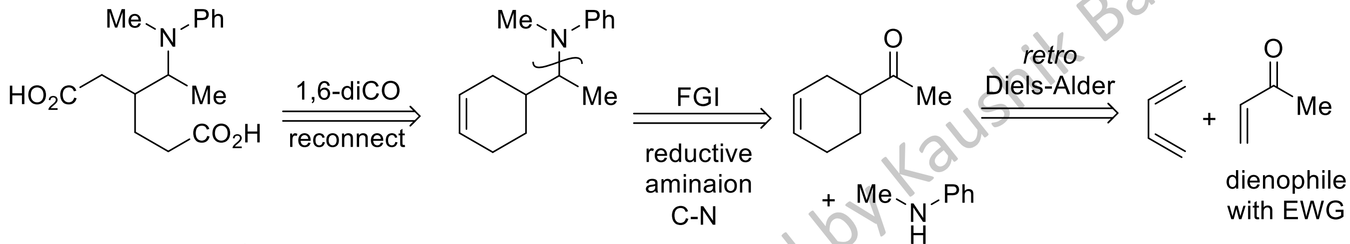
E] 1,6-bifunctional compounds (contd.):

Let us now consider a few examples that use the *strategy of reconnection*:

4.

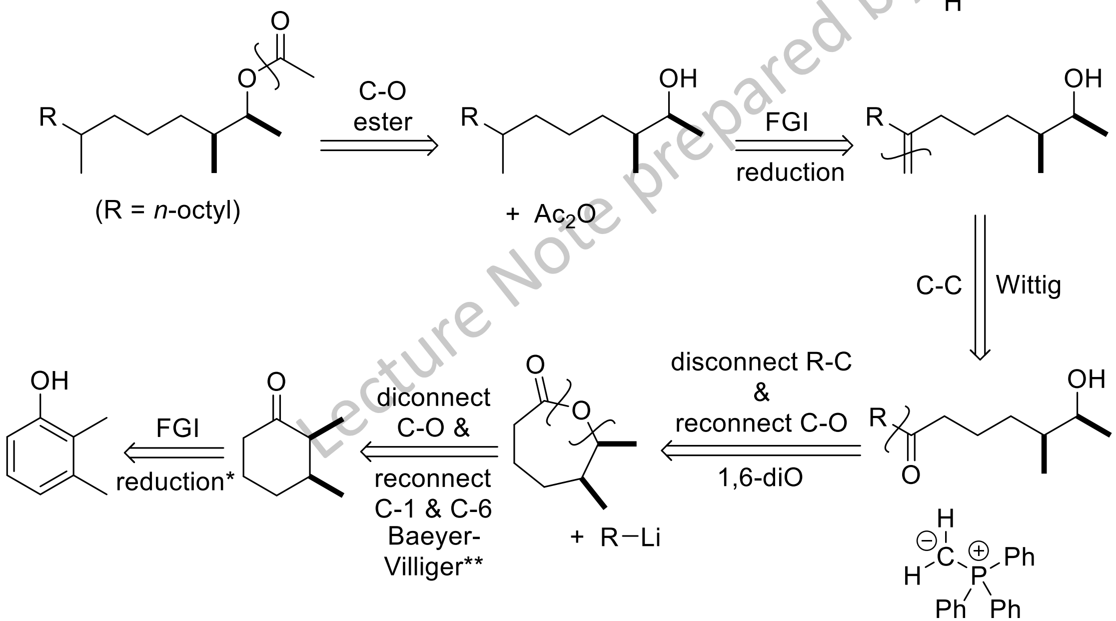


5.



Diels-Alder reaction is an excellent method to access properly substituted cyclohexenes that can serve as 1,6-dicarbonyl source

6.



* *cis*-product separated from other isomers by chromatography

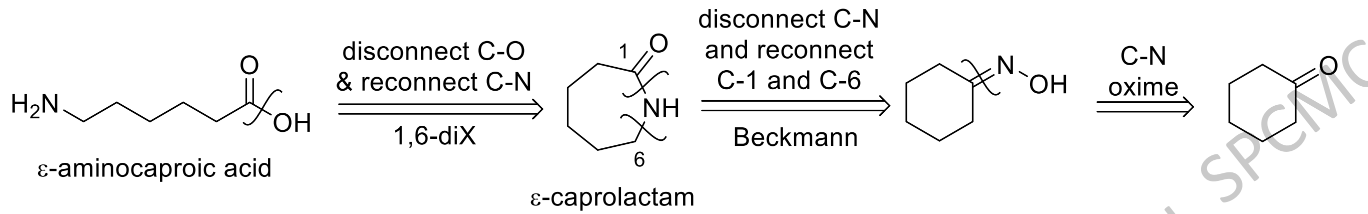
** B-V oxidation is regioselective, *O* inserted on the more substituted side, It is also stereospecific, proceeds with retention in configuration at the migrating group

The Logic of Organic Synthesis: Analysis of bifunctional target molecules:

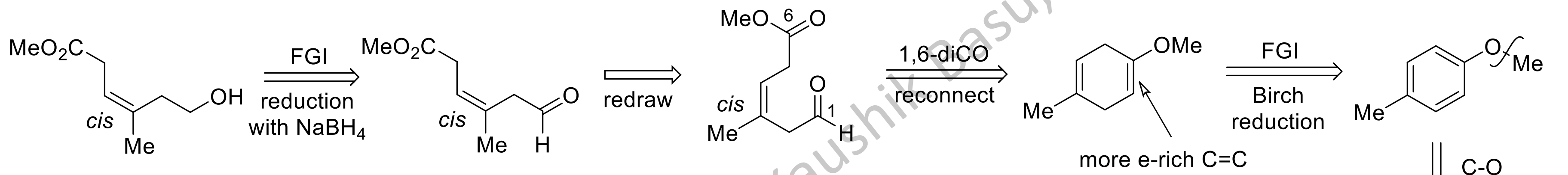
E] 1,6-bifunctional compounds (contd.):

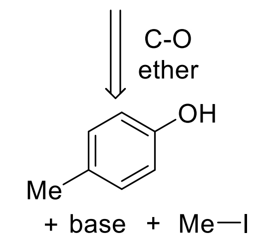
Let us now consider a few examples that use the *strategy of reconnection*:

7.



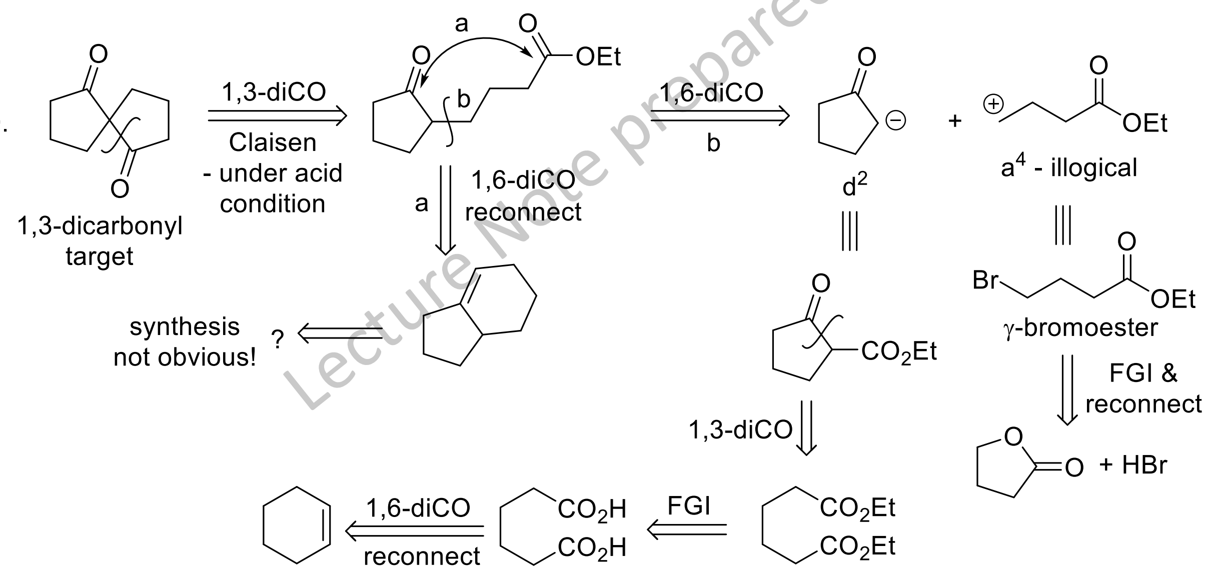
8.





Birch reduction of anisole affords a cyclohexene derivative that can be cleaved preferentially at the enol ether linkage; ozone targets the most electron-rich C=C selectively

9.



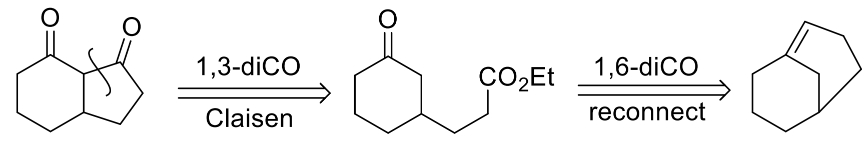
This last example demonstrates that reconnection is not the only way out, 1,6-dicarbonyls can also be made from conventional methods, provided that the illogical synthon can be accessed relatively easily.

The Logic of Organic Synthesis: Analysis of bifunctional target molecules:

Study Guide to Organic Chemistry
- Saha et al. Volume 5 (ISBN 9788193853085)

E] 1,6-bifunctional compounds (contd.):

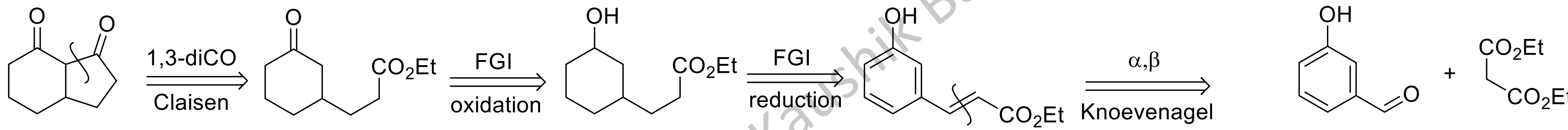
Finally, we provide one example where reconnection strategy does not work:

10. 

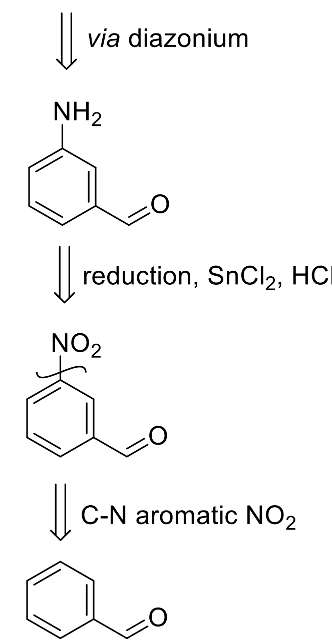
1,3-dicarbonyl target — 1,6-dicarbonyl target — impossibly strained - cannot exist

So, how to synthesise this β-diketo compound?
We have already done that, remember? No?
Alright, here's another alternative to what we already did:

Alternate strategy:

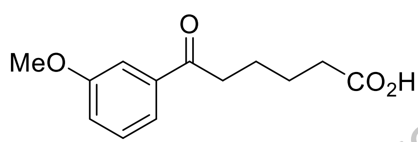


1,3-dicarbonyl target — 1,6-dicarbonyl target — *m*-hydroxybenzaldehyde

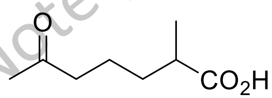


oxidation with CrO_3, AcOH; reduction with H_2, Raney Ni,
Knoevenagel with malonic acid, esterification needed after decarboxylation.

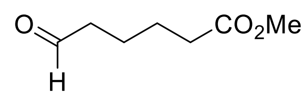
Try these yourself:



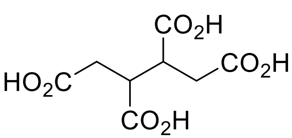
[E.1]



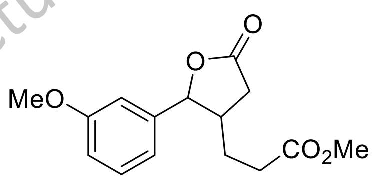
[E.2]



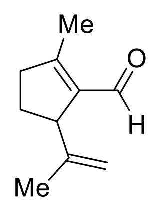
[E.3]



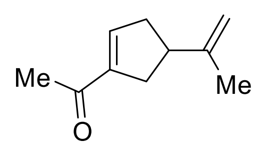
[E.4 and E.5]
(both *meso* as well as *active* varieties)



[E.6]
(exploiting any 1,6-diCO relation that you can reveal)



[E.7]



[E.8]