Organic Chemistry-4

Semester-4, CBCS

Course: CEMA CC-4-8-TH

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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:

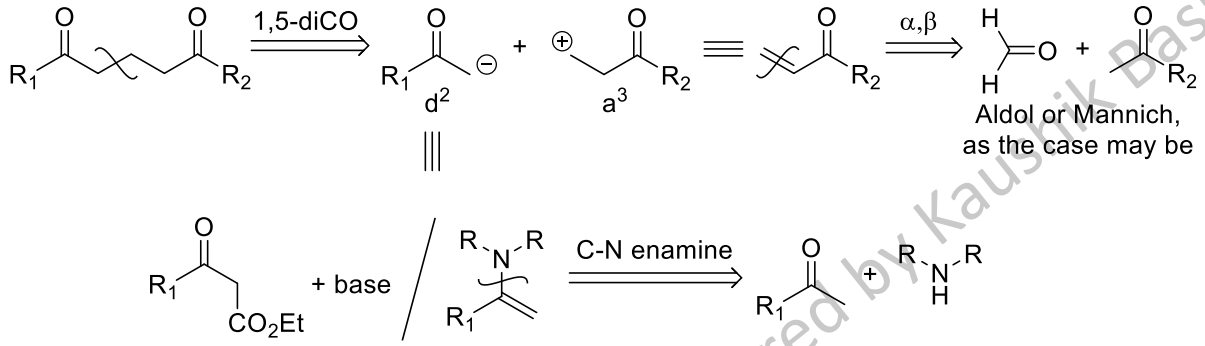
D] 1,5-bifunctional compounds:

The following is a summary of the retrosynthetic strategies one can commonly adopt when the target molecule contains two heteroatom-based functional groups placed at an 1,5-relation. These target molecules are consonant systems, so umpolung strategy will not be necessary in general.

The most important method for synthesising these targets is the **Michael reaction**, an 1,4-addition of a stabilised carbanion (enolate derived from a carbonyl compound known as the Michael donor, representing a d^2 synthon) to the β-carbon of an α,β-unsaturated carbonyl compound (a Michael acceptor, representing an a^3 synthon).

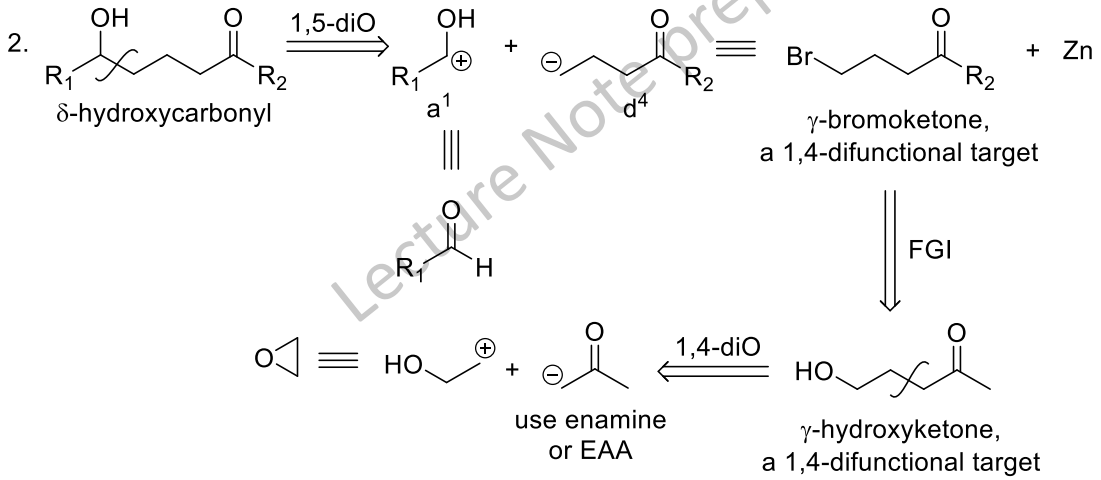
Let us consider a few generalised disconnection strategies:

1.

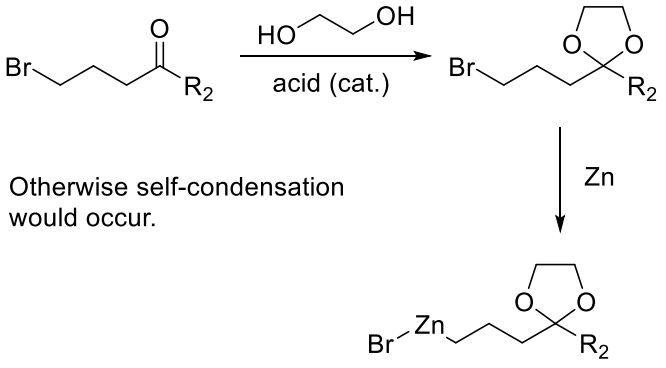


Michael donor must be a soft anion promoting reversibility of the addition, (in order to counter potential 1,2-addition); need to have EWGs on it to stabilise the negative charge and make it softer as well as a weak base. The basicity is important because we want the 1,4-addition product (which is itself an enolate) to preferentially get protonated once it forms. If that does not happen we will have undesired side reactions.

2.



Carbonyl protection required while forming organozinc:

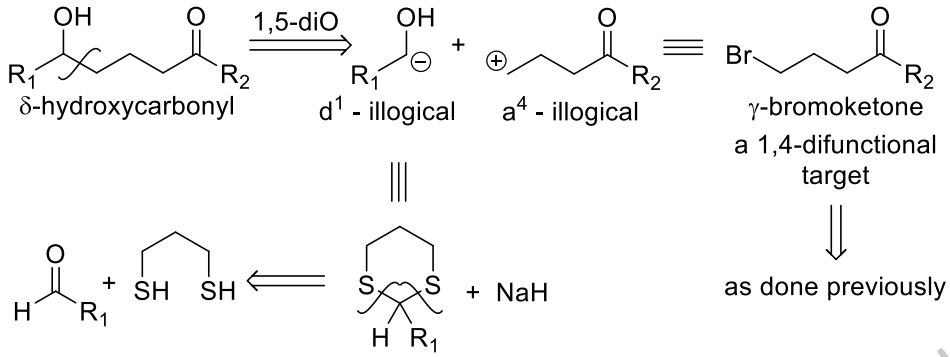


Otherwise self-condensation would occur.

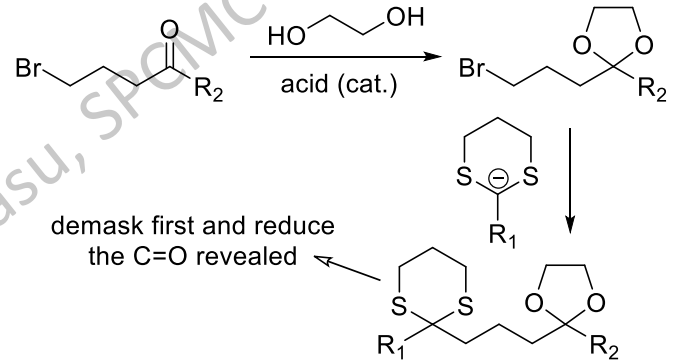
The Logic of Organic Synthesis: Analysis of bifunctional target molecules:

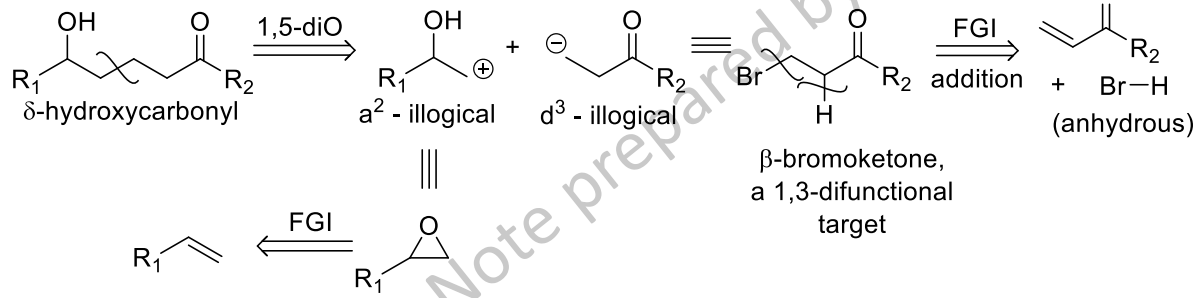
D] 1,5-bifunctional compounds (contd.):

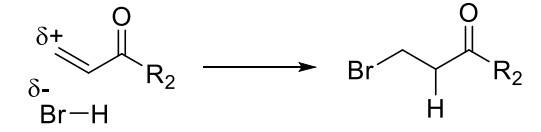
Let us consider a few generalised disconnection strategies:

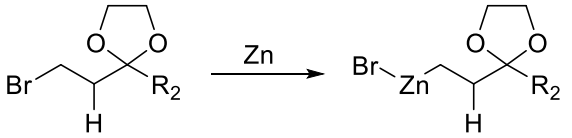
3. 

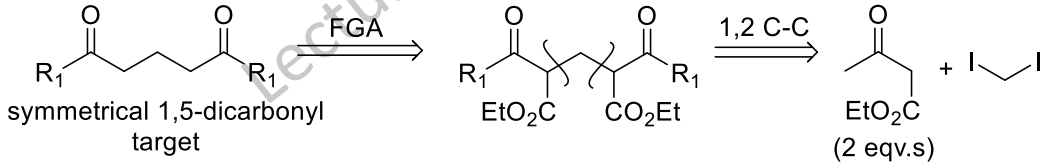
Carbonyl protection required when reacted with acyl anion eqv:



4. 





5. 

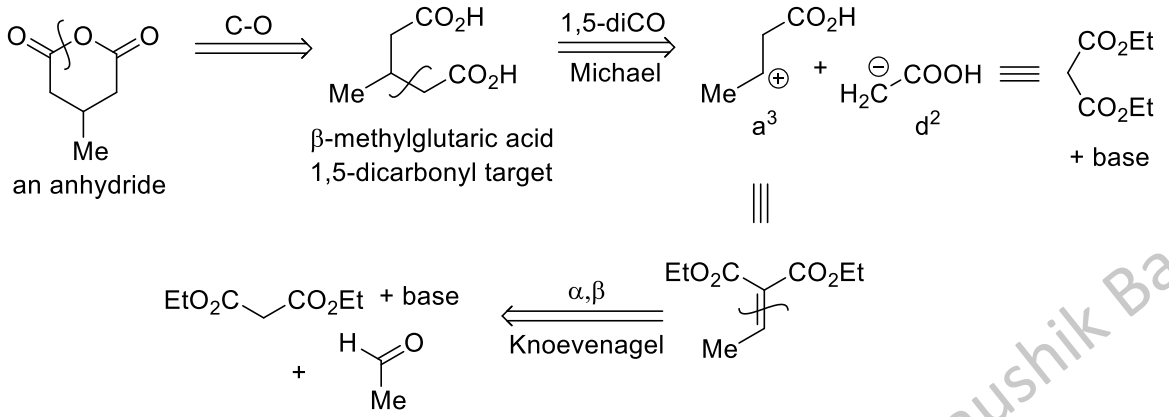
The strategies 2, 3, and 4 involve umpoled reagents which are difficult to access. Several protocols have been explored and developed in these lines. But the Michael reaction remains the most useful method to synthesise 1,5-dicrbonyl compounds. We will concentrate on that.

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

D] 1,5-bifunctional compounds (contd.):

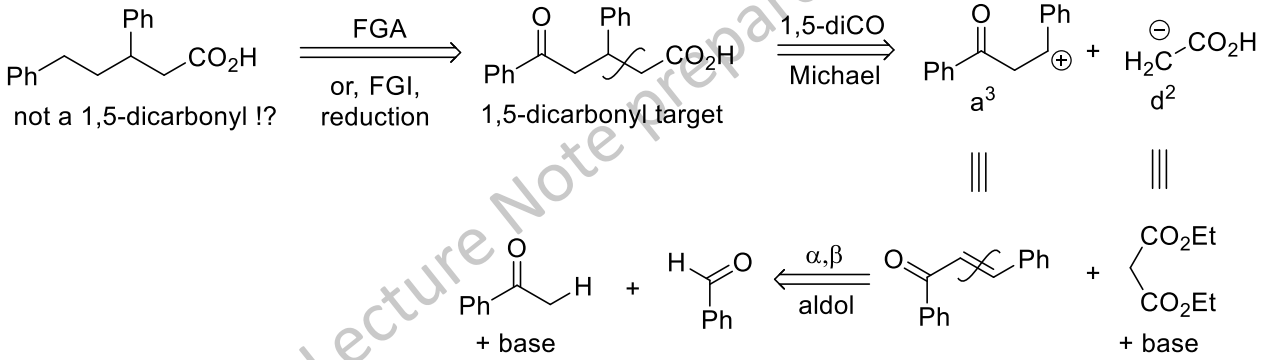
Let us now consider a few examples:

1.



In this one-pot reaction, Knoevenagel condensation and Michael addition happens one after the other in a cascade fashion.
2 eqv.s of DEM and 1 eqv. of acetaldehyde is mixed in presence of piperidine, AcOH and refluxed in benzene.
The product on hydrolysis and decarboxylation affords β-methylglutaric acid.

2.



The final deoxygenation is done with the Wolff-Kishner reduction; a chemoselective way to deoxygenate a carbonyl group in presence of COOH

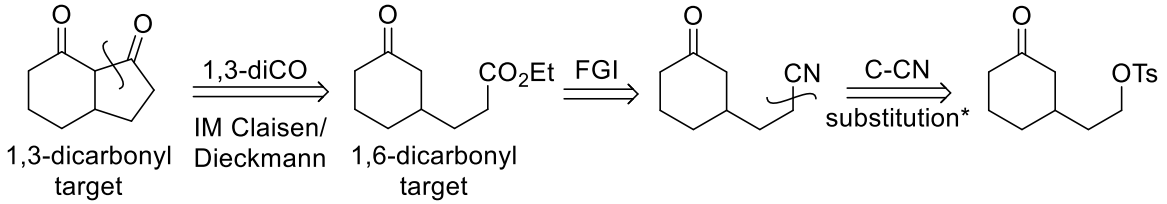
No control required for cross-aldol as the more electrophilic component benzaldehyde cannot enolize

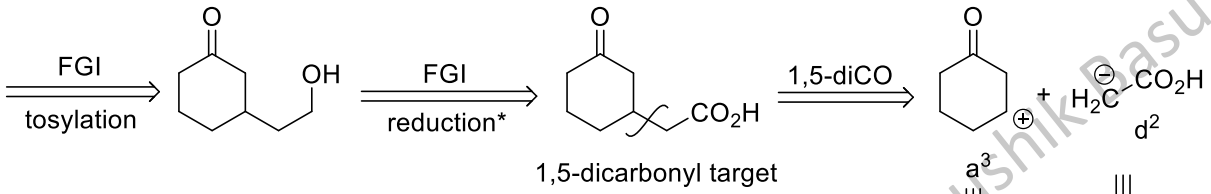
The Logic of Organic Synthesis: Analysis of bifunctional target molecules:

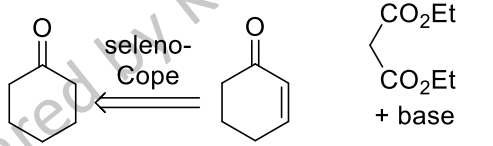
D] 1,5-bifunctional compounds (contd.):

Let us now consider a few examples:

3.

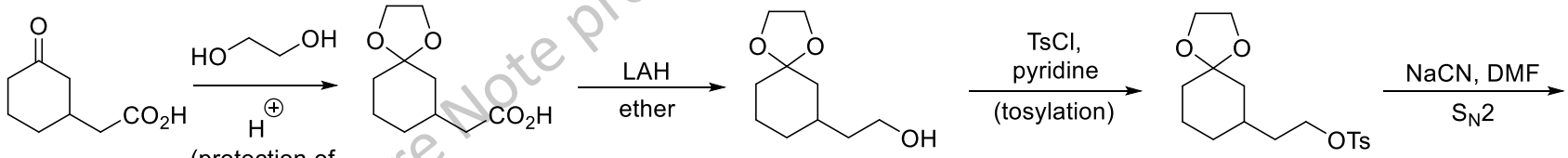


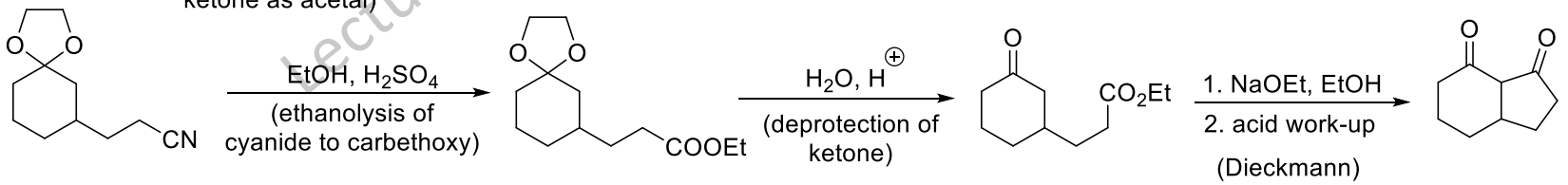




*the ketone needs to be protected in the form of an acetal while reducing the less reactive CO_2H; the protection is carried out to avoid the possibility of cyanohydrin formation in the substitution step; ketone is deprotected only after the CN is converted to CO_2Et to effect the final cyalisation.

Part forward synthesis:



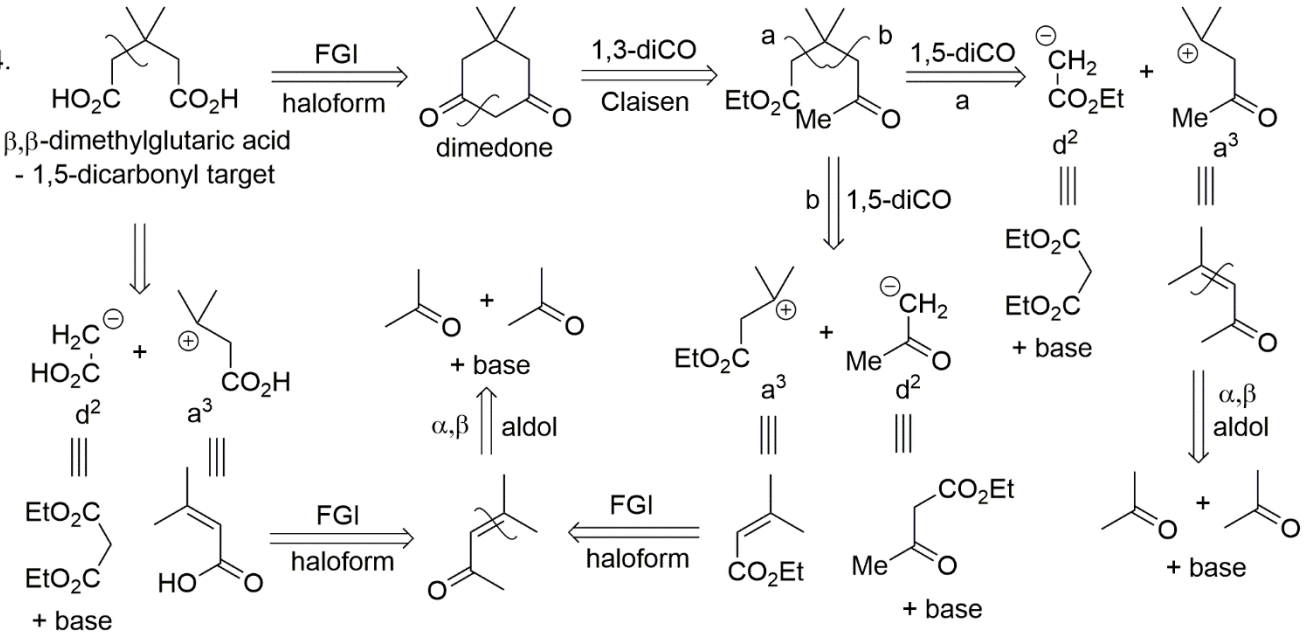


The Logic of Organic Synthesis: Analysis of bifunctional target molecules:

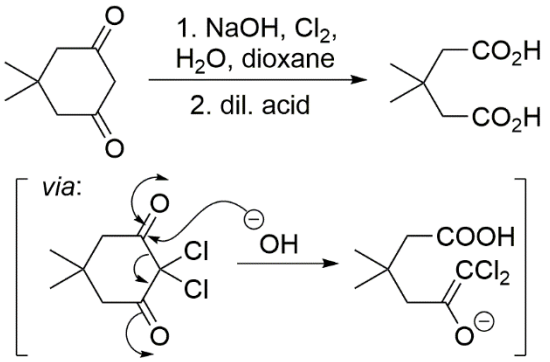
D] 1,5-bifunctional compounds (contd.):

Let us now consider a few examples:

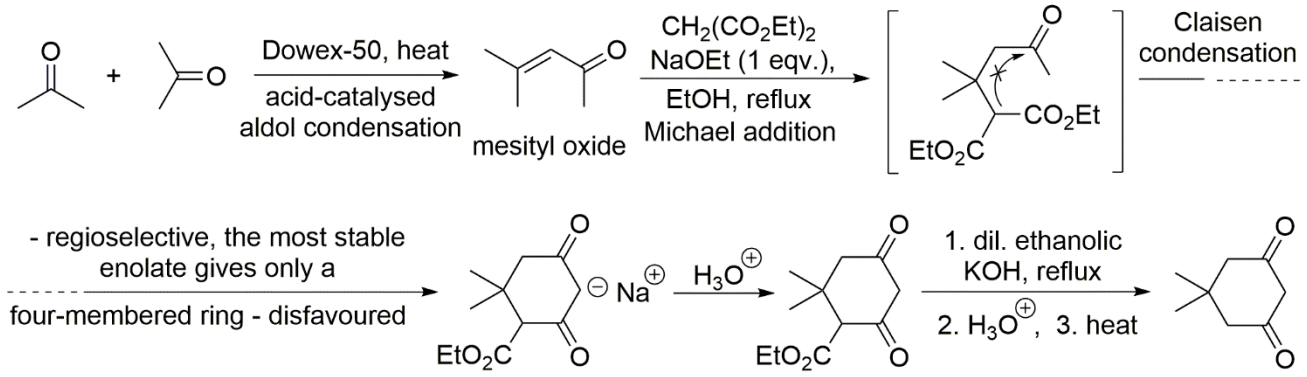
4. β,β-dimethylglutaric acid - 1,5-dicarbonyl target



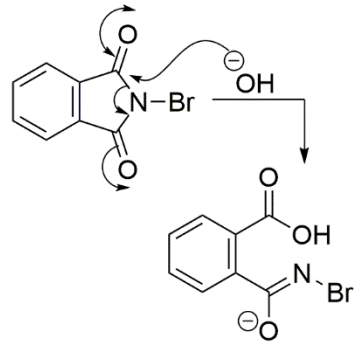
Note carefully that the haloform reaction of dimedone results in a C-C bond cleavage, which is kind of unusual considering you can replace only two α-hydrogens by the halogen here, as opposed to the usual three hydrogens for the ketomethyl group. But the cleavage is facilitated because the resulting anion enjoys resonance stabilisation from an adjacent C=O:



Also note that in the synthesis of dimedone, irrespective of the strategies you take, the Michael addition is followed by an intramolecular Claisen condensation that closes the six-membered ring.



Similar to Hofmann degradation of phthalimide, despite not having the required two Hs on N, it responds:

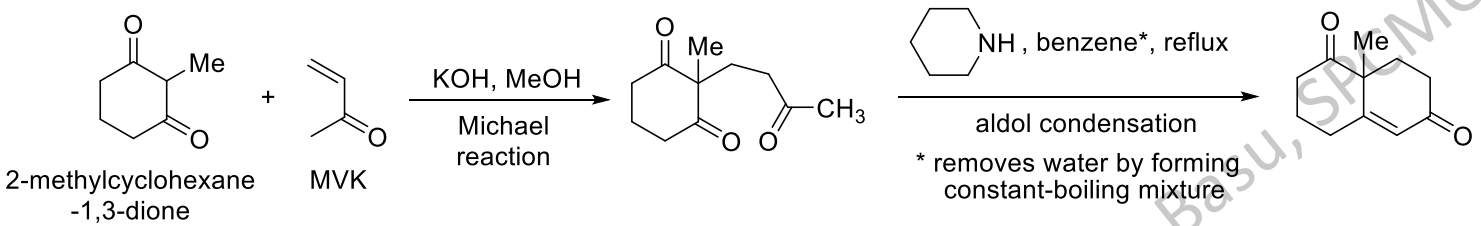


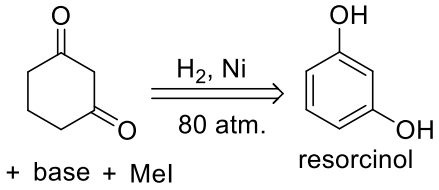
The Logic of Organic Synthesis: Analysis of bifunctional target molecules:

D] 1,5-bifunctional compounds (contd.):

Let us now consider a few examples:

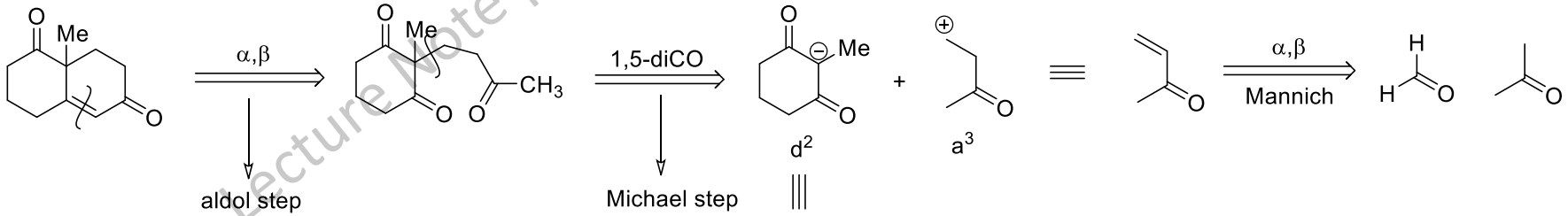
In one widely used variation/extension of the Michael reaction, the addition product of the reaction can be subjected to an intramolecular aldol condensation that closes a ring:





This sequence of tandem Michael reaction-aldol condensation leading to ring closure is an example of the **Robinson Annulation**. The bicyclic diketone product shown above is the Wieland-Miescher ketone.

The retrosynthetic analysis of the TM is like the following:



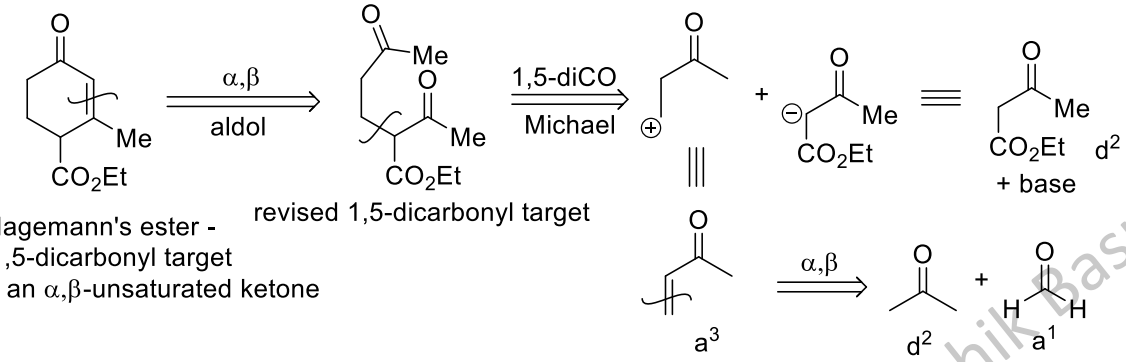
Note how in the retrosynthetic analysis aldol comes first and then Michael, and this order of event will be just the opposite to what you will do while writing the forward synthesis.

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

D] 1,5-bifunctional compounds (contd.):

Let us consider a few more target molecules' retrosynthetic analyses that uses this Robinson annulation strategy:

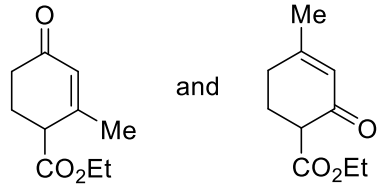
5.



Hagemann's ester - a 1,5-dicarbonyl target as well as an α,β-unsaturated ketone

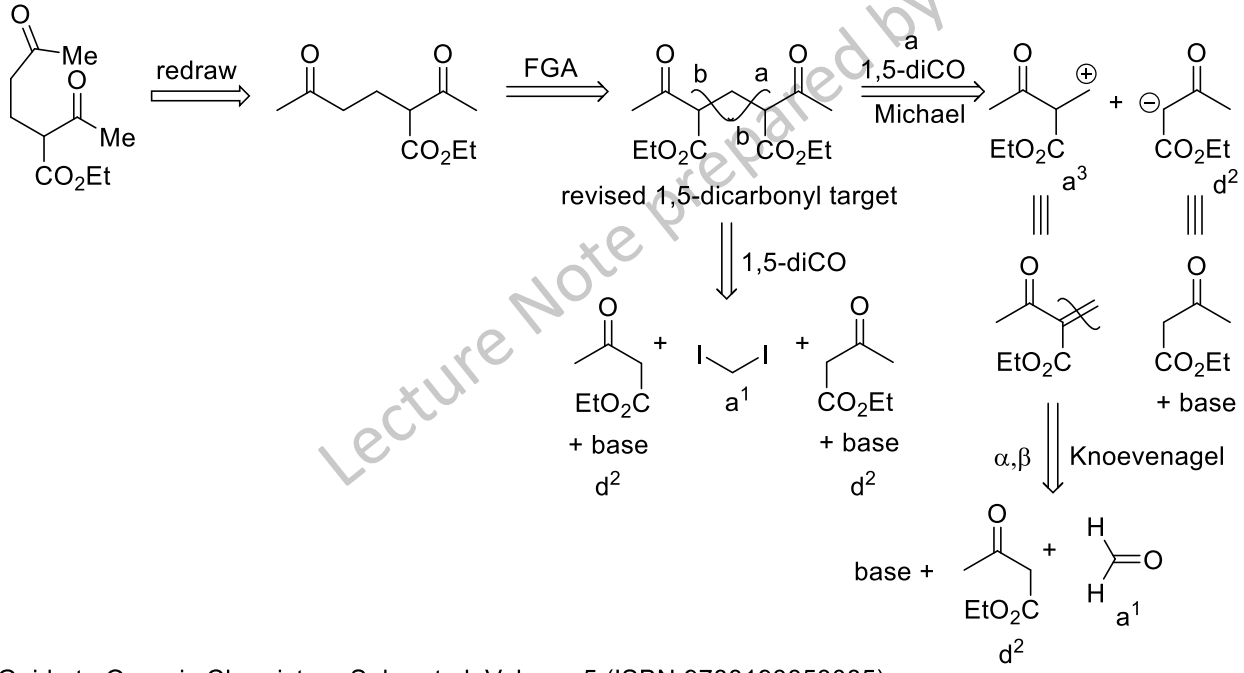
revised 1,5-dicarbonyl target

The strategy outlined above would work. But as the revised 1,5-dicarbonyl target lacks symmetry, the aldol cyclocondensation would suffer from a regioselectivity problem and a mixture of products would form, compromising the overall yield:

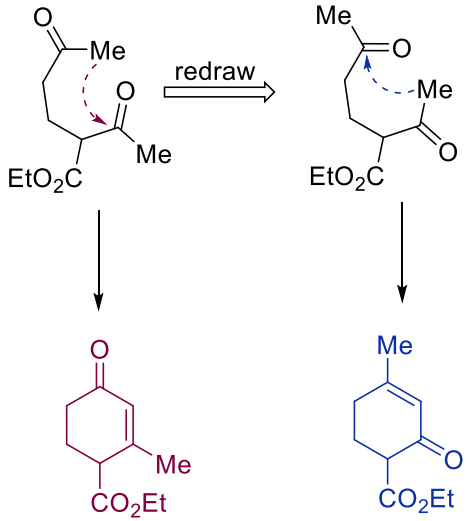


desired undesired

To avoid this formation of mixtures, a better strategy would be to symmetrise the unsymmetrical revised 1,5-dicarbonyl by an FGA and then continue the analysis:



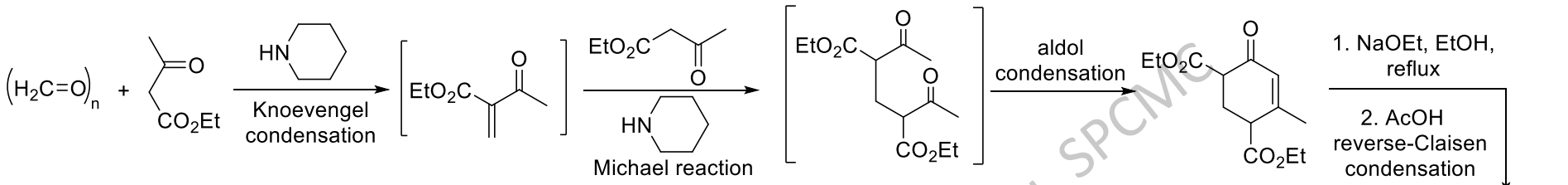
Think carefully how the second product is forming.



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

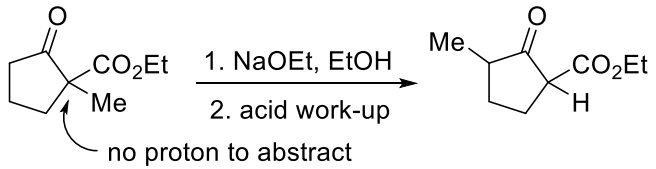
D] 1,5-bifunctional compounds (contd.):

The forward synthesis of Hagemann's ester that adopts the Robinson annulation protocol is outlined below:



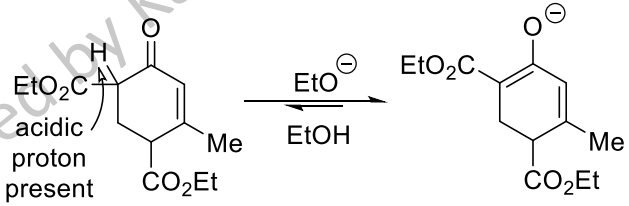
The very last step demonstrates a reverse-Claisen condensation that knocks of the α-carbethoxy group. This may at first seem unusual to you because your previous exposures to reverse-Claisen reaction involved β-ketoesters that do not have any protons on the carbon flanked by the two C=O groups. In this case *we do have a proton there*. So how come the reverse-Claisen is happening? Shouldn't there be just a proton abstraction and the end of story?

reverse-Claisen, as you have seen till now:

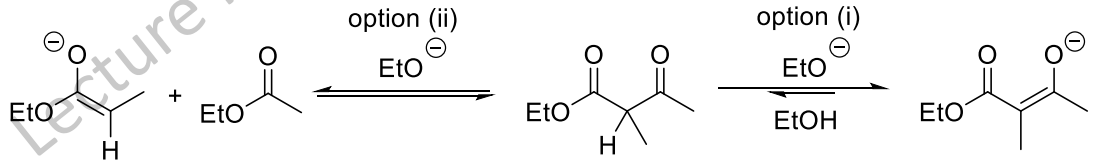


versus

what you expect when Hagemann's ester is treated with NaOEt:



Recall that the Claisen condensation is reversible. Once the Claisen product forms, two things can happen; ethoxide will - i) either abstract the proton (if available) from the position activated by the two carbonyls, i.e., it is acting as a base, or ii) induce a reverse-Claisen reaction so that the newly-formed C-C is cleaved again, i.e. attacks the keto carbonyl of β-ketoester as a nucleophile:



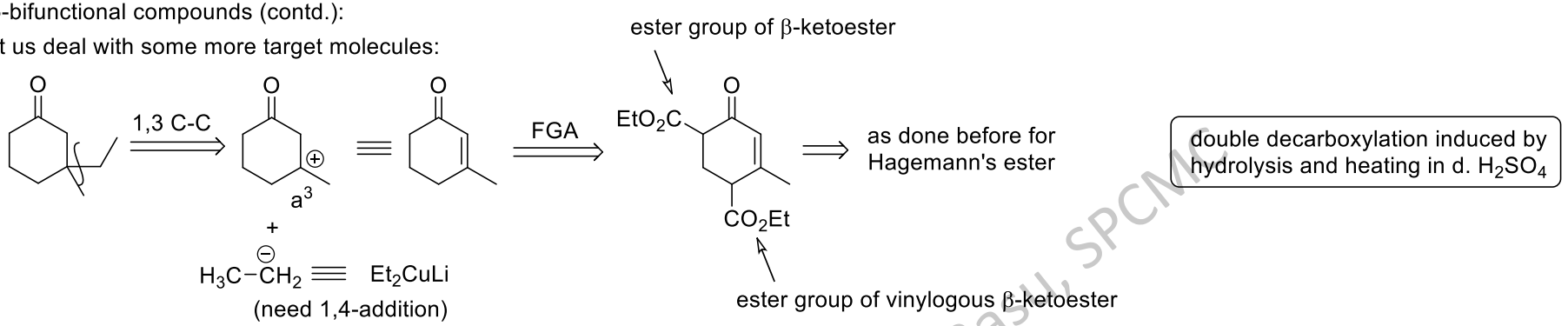
If that acidic proton is absent, only option ii) is exercised and the Claisen condensation remains unsuccessful with ethoxide. When that acidic proton is available, option i) is favoured, but that does not mean that option ii) won't ever be explored here. By enforcing the appropriate reaction condition, a reverse-Claisen condensation may yet be induced in these cases as well.

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

D] 1,5-bifunctional compounds (contd.):

Let us deal with some more target molecules:

6.



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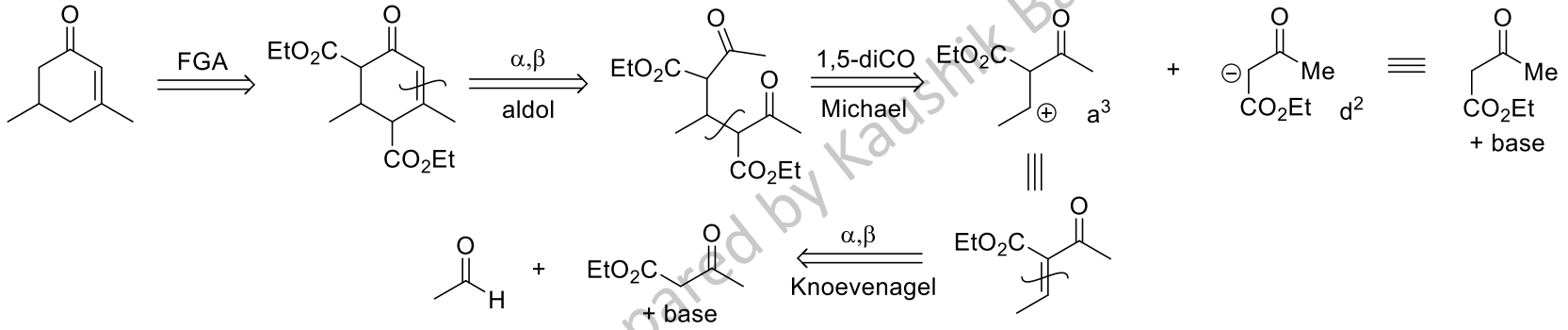

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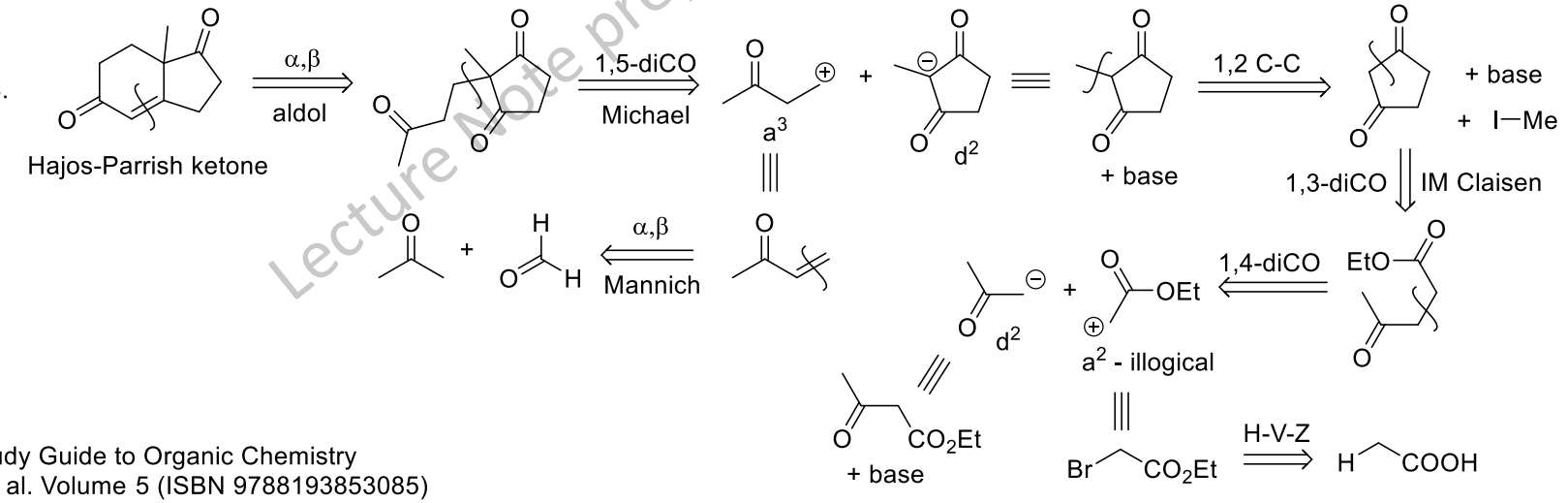

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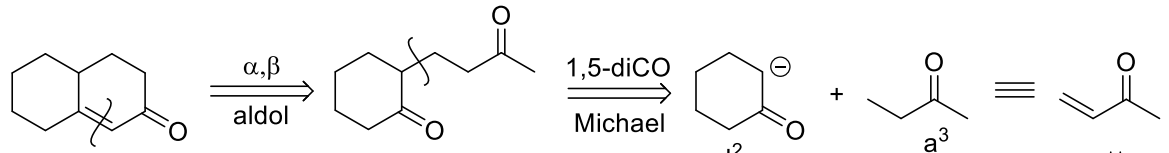
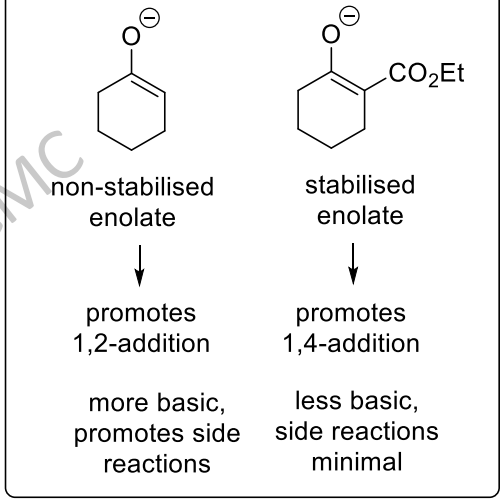
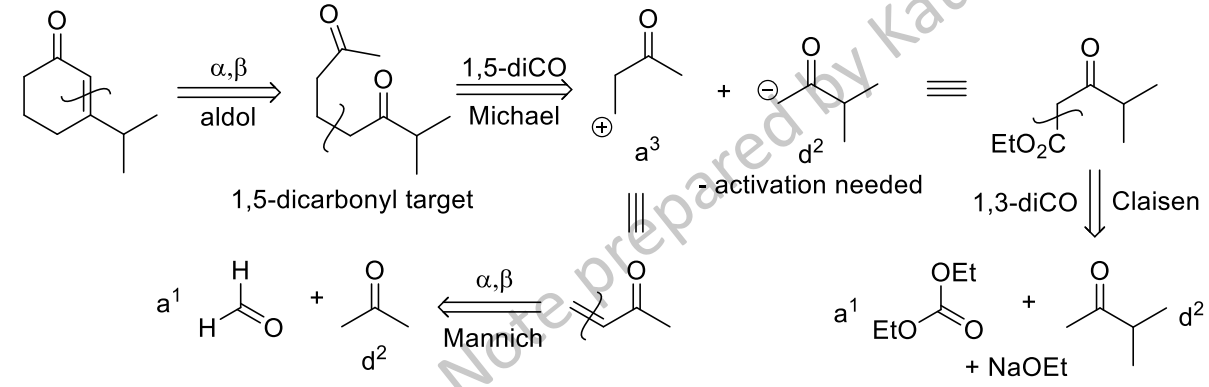
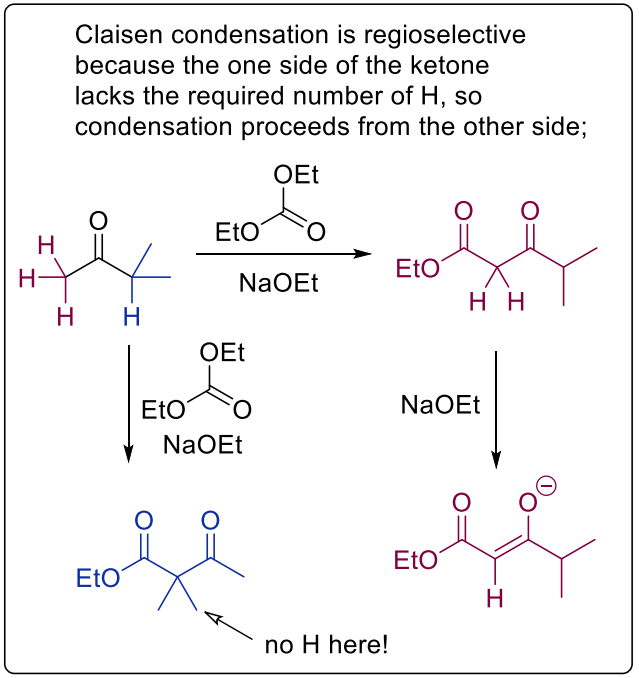
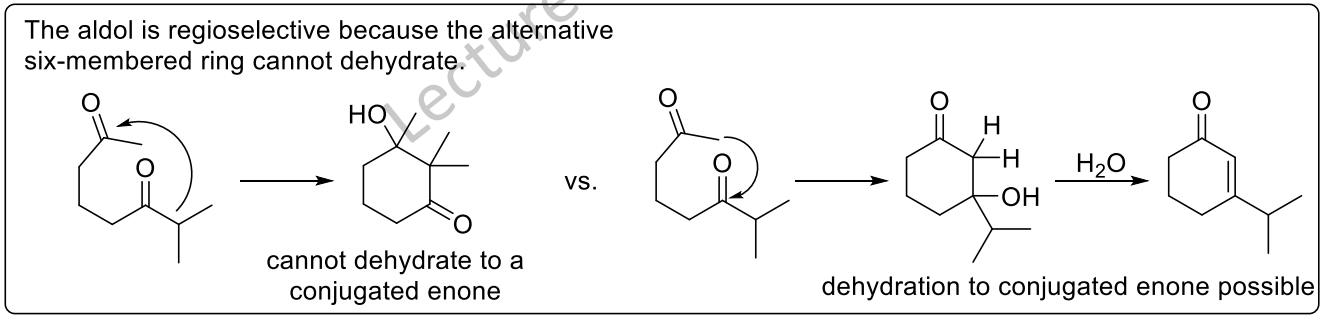
9. 



10. 



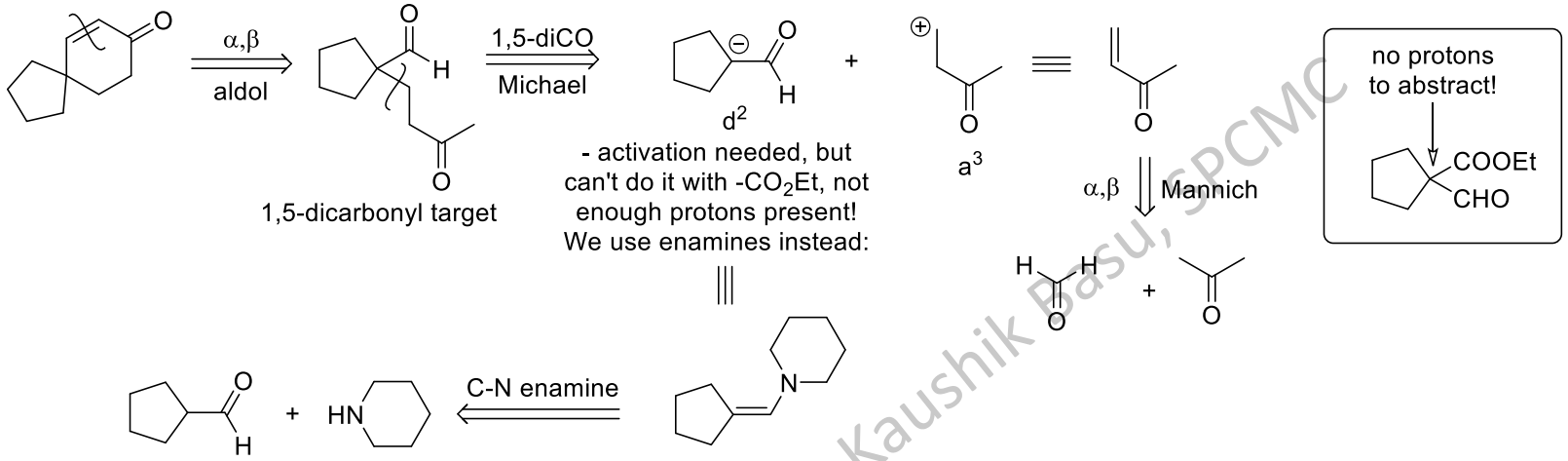


The Logic of Organic Synthesis: Analysis of bifunctional target molecules:

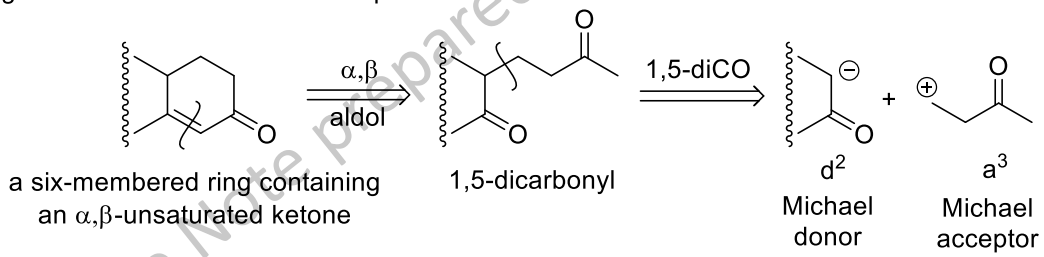
D] 1,5-bifunctional compounds (contd.):

Let us deal with some more target molecules:

11.



Retrosynthetic analyses of targets 5-11 makes use of Robinson anuulation strategy. By this time, the structural pattern in these targets should be evident to you - a six-membered ring containing an α,β-unsaturated ketone; first disconnect the C=C to reveal the 1,5-dicarbonyl, then go for the 1,5-diCO disconnection to get the Michael donor and acceptor:



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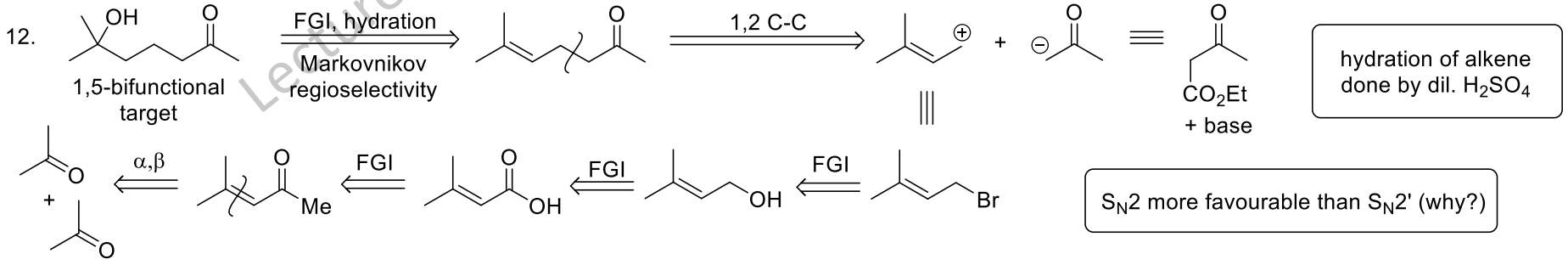

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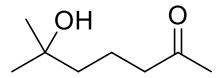
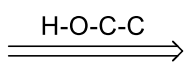
D] 1,5-bifunctional compounds (contd.):

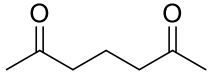
Let us deal with some more target molecules:

13. 

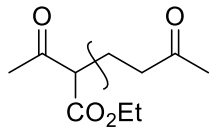
δ-hydroxycarbonyl target

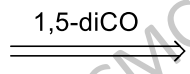
(alternative, using the Michael approach)

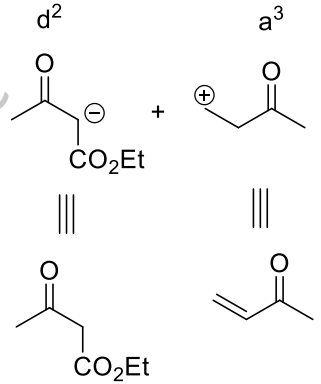




+ Me−MgI

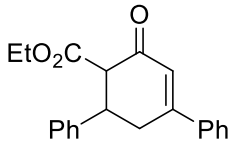




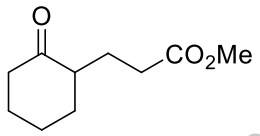


+ base

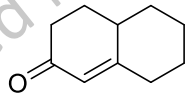
Try these yourself:



[D.1]

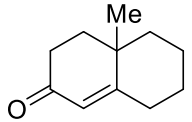


[D.2]

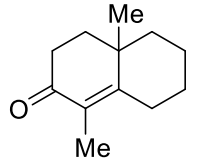


[D.3]

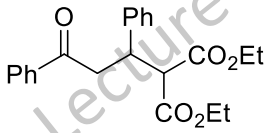
(other than the one shown)



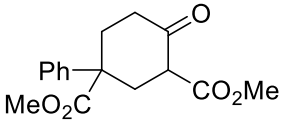
[D.4]



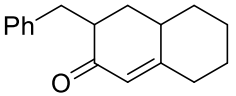
[D.5]



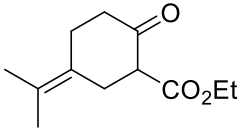
[D.6]



[D.7]



[D.8]



[D.9]