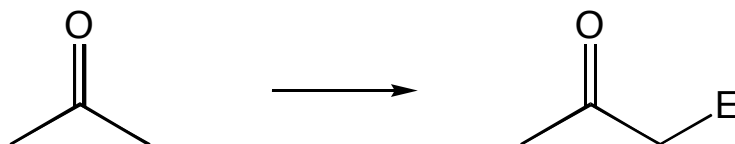
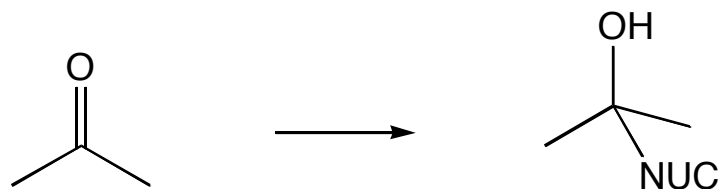


Enols and Enolates

A major type of reaction with carbonyl compounds is an α -substitution

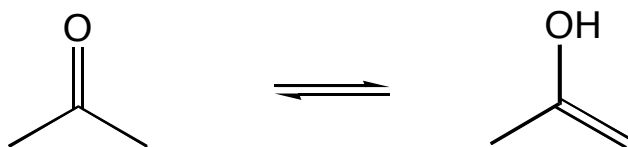


In the preceding chapters we were concerned with the carbonyl reacting as an electrophile



Enols

As observed previously an enol and a ketone are tautomers



Usually the ketone is far more stable than the enol and it predominates

Under either slightly basic or acidic conditions the concentration of enol can be increased

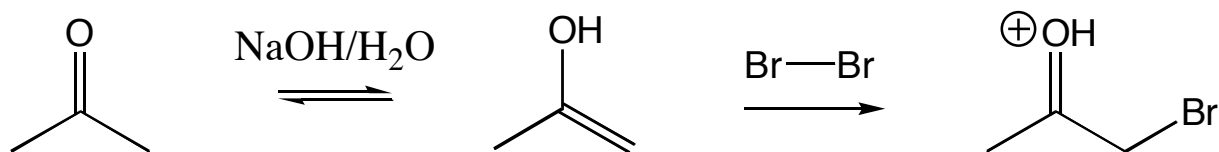
The keto form still predominates

With aldehydes there is relatively more enol form than with ketones

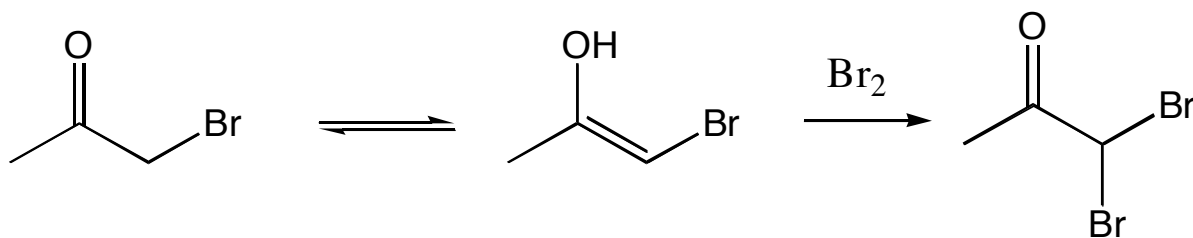
Reactions of Enols

The enol form can react with electrophiles

A common reaction is halogenation



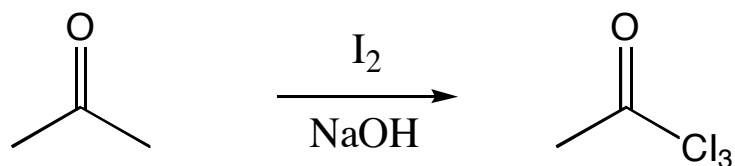
under basic conditions it is hard to stop at one addition because hydrogen abstraction of product is more favored than starting material



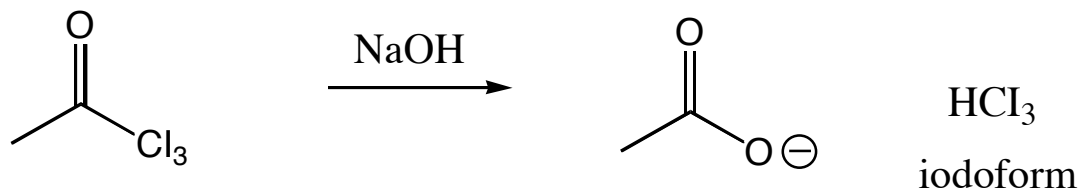
Haloform Reaction

This polyhalogenation is exploited with a haloform reaction

A methyl ketone will react until three halogens have been substituted on α -carbon



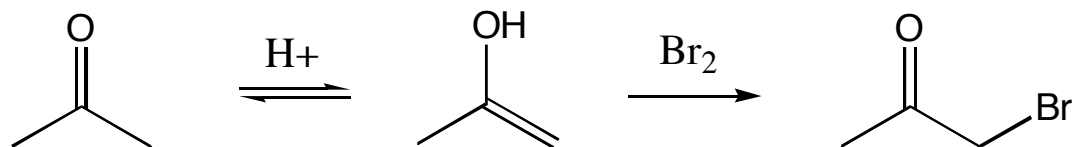
with three halogens attached to the carbon it becomes a good leaving group



the three halogens stabilize the negative charge of the leaving group

Acid Catalyzed Enol Formation

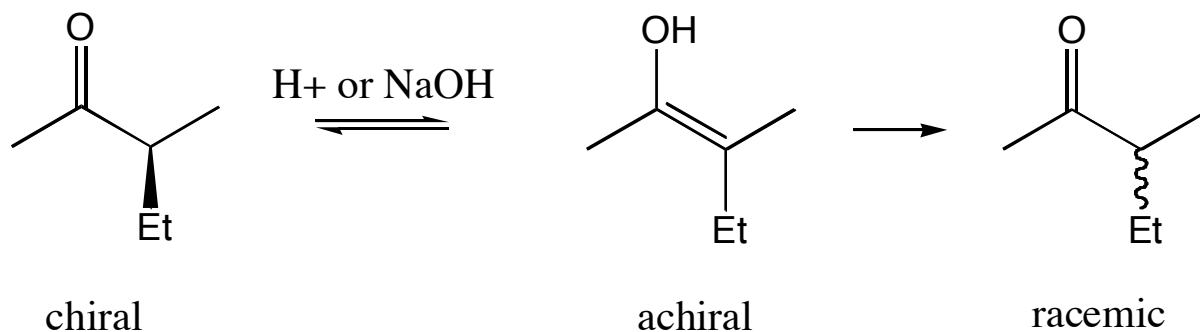
Under acidic conditions the enol can react with halogen and stop after one addition



with acidic conditions we do not form anion adjacent to halogen as in basic mechanism
therefore the reaction can be stopped after one addition

Enolizable Positions

A consequence of the ability to form enols is that chiral carbons can racemize

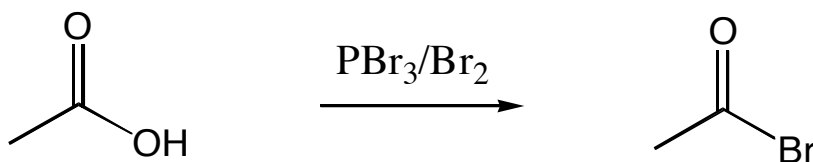


since the α -position can form an enol, and the enol is achiral, chiral atoms that are α to carbonyls will lose chirality whenever enol formation is favored

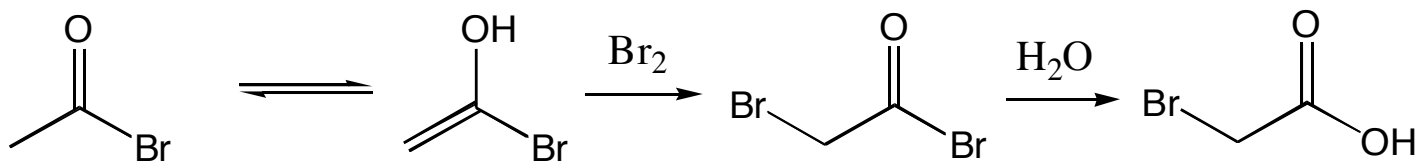
Bromination of Acids

Carboxylic acids can also be brominated

First need to convert carboxylic acid into acid halide (labile H would interfere)



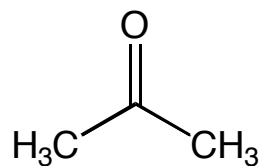
this acid bromide can form enol under these conditions, which will react with Br₂



Enolates

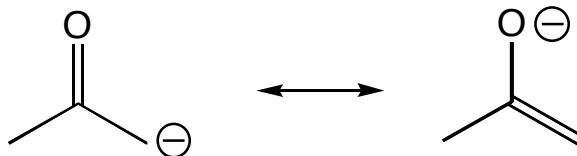
Enolates are similar to enols but they are far more nucleophilic

In order to generate an enolate need a base to abstract an α -hydrogen



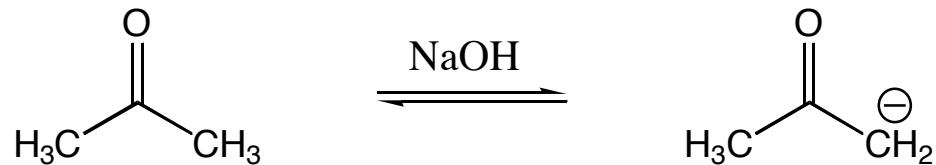
pKa of α -hydrogens \sim 20

the α -hydrogens are more acidic than normal alkane hydrogens due to electron withdrawing carbonyl group that can delocalize the resultant negative charge



Base Abstraction

Since the pK_a of an α-hydrogen of a ketone is ~20 the choice of base will determine extent of enolate formation



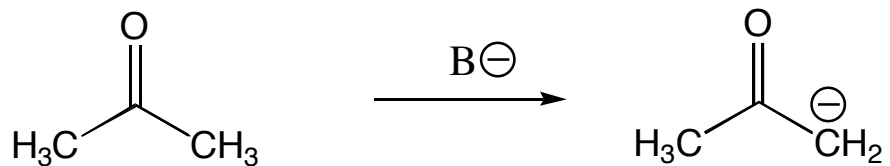
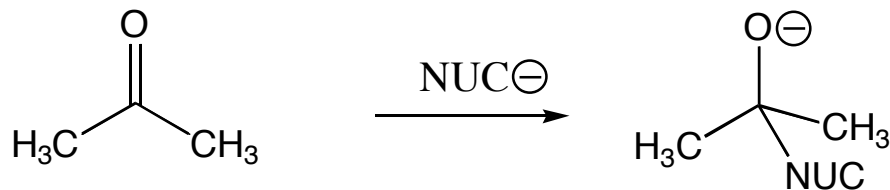
both water (pK_a of ~15.7) or alcohols (pK_a ~>16) are less acidic
therefore with these bases the majority of the compounds will be in the keto form

Basicity vs. Nucleophilicity

Most strong bases are also strong nucleophiles - remember S_N2 vs. E2

With carbonyls need to balance two different type of reactions:

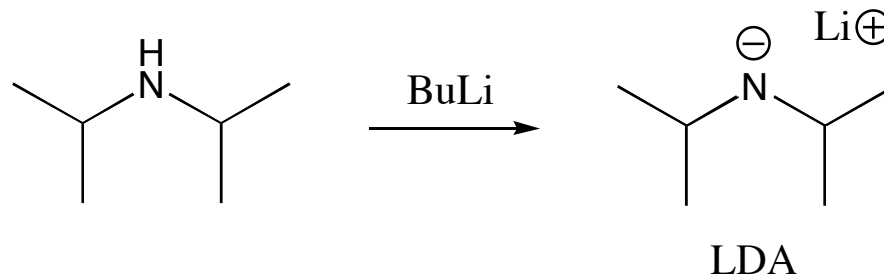
A strong nucleophile reacting with the carbonyl and a strong base abstracting α -hydrogen



Enolate

To generate enolate need to use a base that will not act as a nucleophile

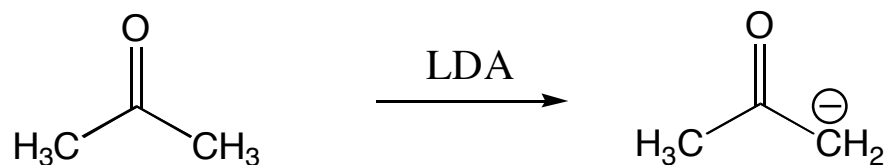
Common choice is to use lithium diisopropylamine (LDA)



LDA is a strong base (pK_a of conjugate is close to 40)

At the same time it is very bulky so it will not react as a nucleophile

LDA will quantitatively form enolate



using LDA the enolate will be formed quantitatively
with weaker bases will only form the enolate in a small fraction

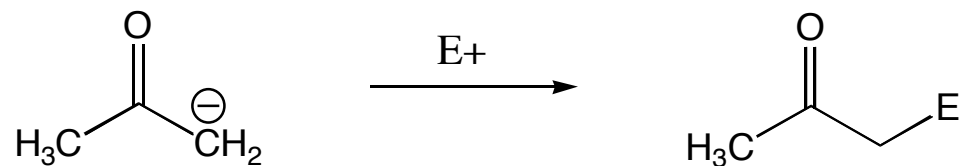
Enolate as a Nucleophile

We have already seen many reactions with a nucleophile reacting

-see any S_N2 reaction

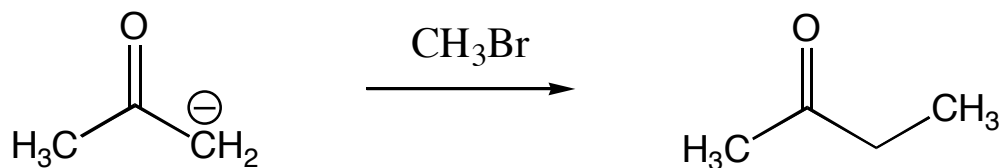
an enolate is simply another type of nucleophile

it can react in exactly the same manner we have observed other nucleophiles react



Alkylation of Enolates

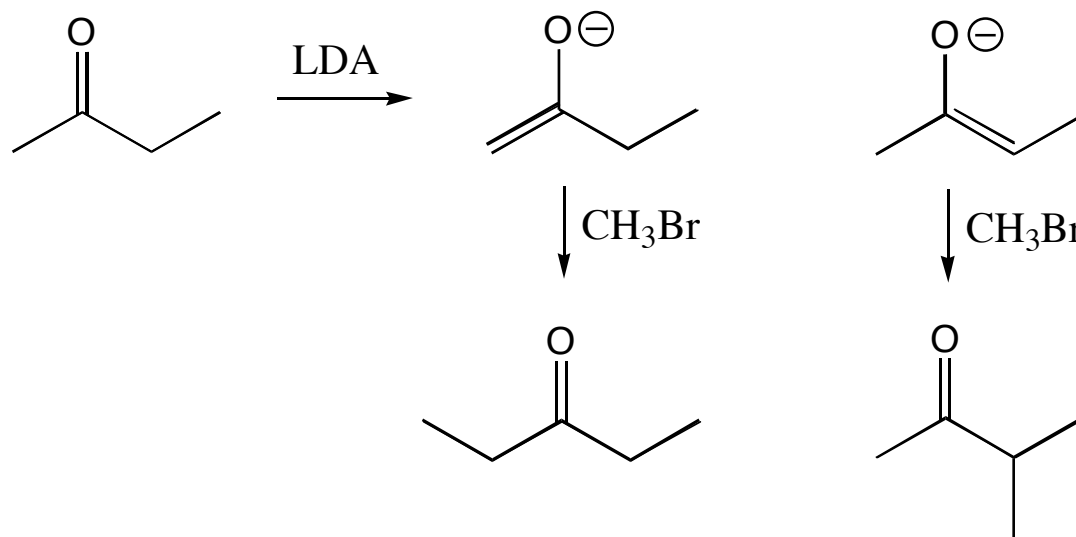
One common reaction is to alkylate the enolate



This reaction will place an alkyl substituent at the α -position of a carbonyl
Any electrophile that will react in an $\text{S}_{\text{N}}2$ reaction can be used in this reaction

Unsymmetrical Carbonyls

With an unsymmetrical carbonyl can obtain two different enolates

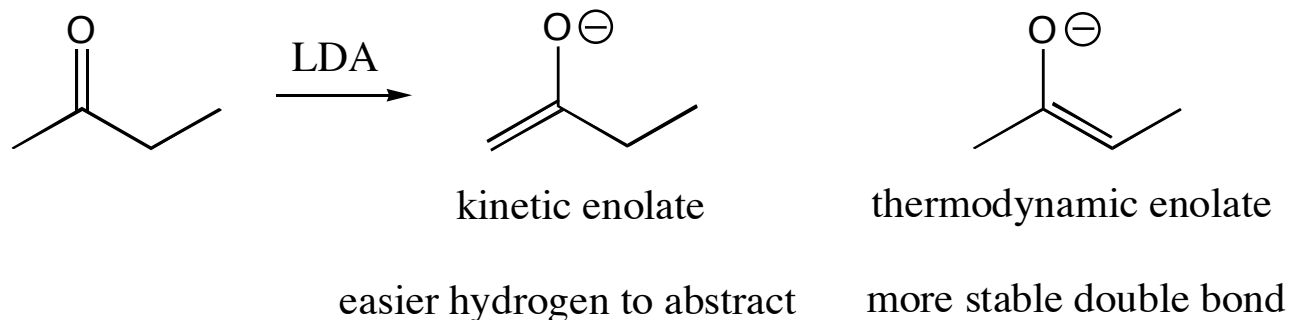


how to obtain one product preferentially?

Thermodynamic vs. Kinetic Control

The key is which enolate is generated

The enolate can be preferentially generated at either site depending upon conditions

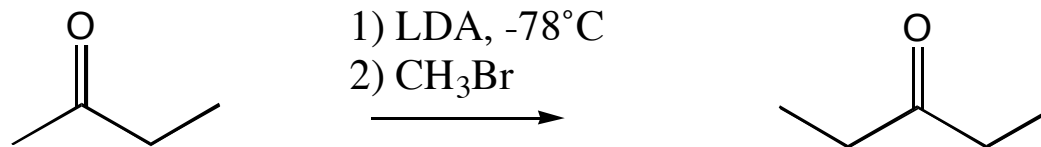


lower temperatures favor kinetic product

higher temperatures (in this case usually room temp. and above) favor thermodynamic

Product Formation

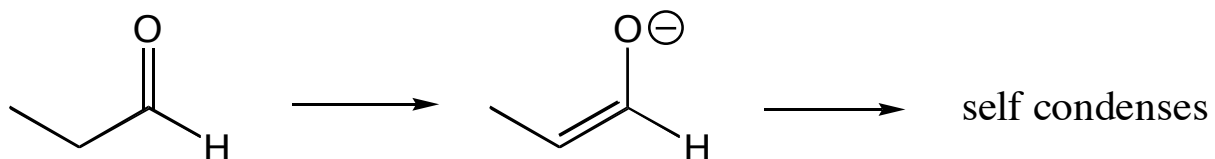
By controlling which enolate is generated,
where the α -substitution occurs can be controlled



Cannot follow this procedure with Aldehydes

Will not obtain α -substitution with aldehydes through enolate chemistry

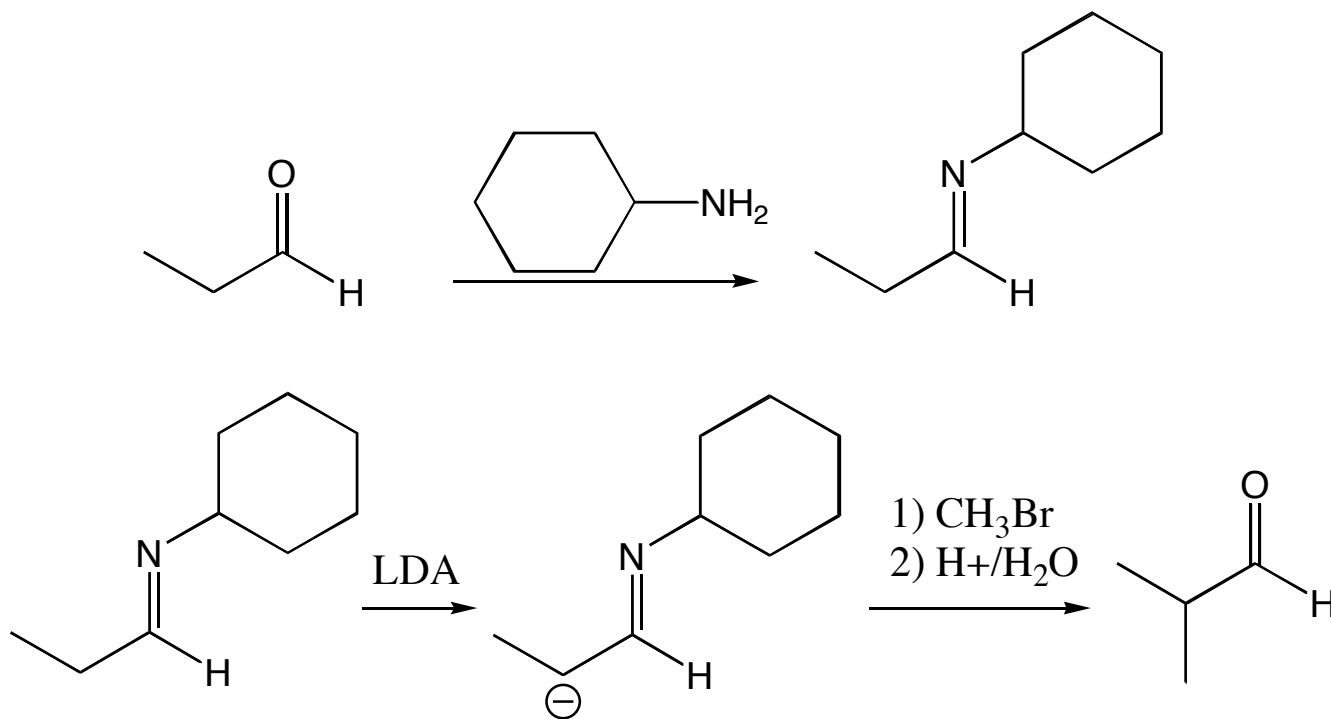
The aldehyde carbonyl is too reactive and it will interfere
with the formation of the enolate



α -Alkylation of Aldehydes

to alkylate an aldehyde we first need to convert the aldehyde to a less reactive system

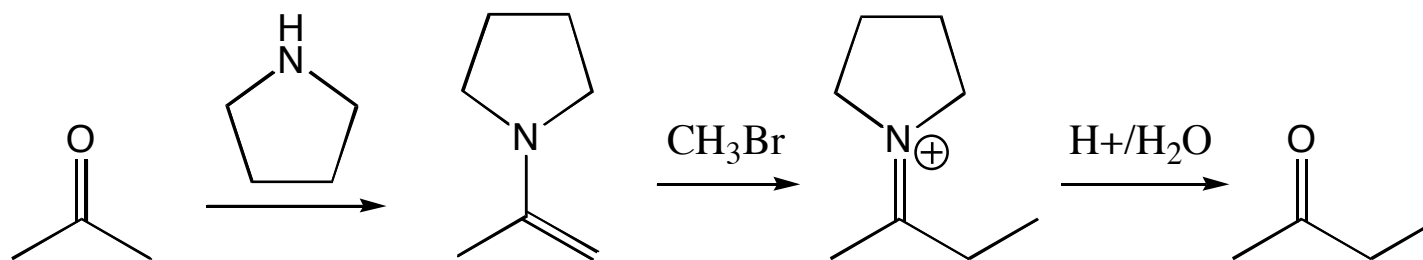
an imine or imine derivative is used most frequently



Enamines

Another option instead of enolate formation is to form an enamine

React carbonyl with 2° amine

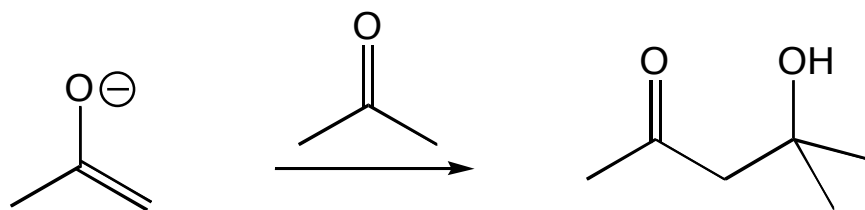


the enamine is not as reactive as an enolate but it is more reactive than an enol

Aldol Condensation

Instead of reacting the enolate with an alkyl halide
We can also react the enolate with a carbonyl compound

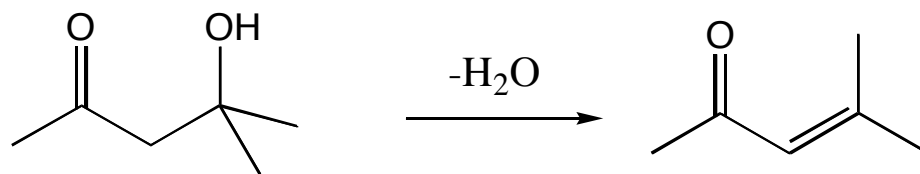
The carbonyl can react as an electrophile



upon work-up obtain a β -hydroxy ketone

Dehydration of Aldol Product

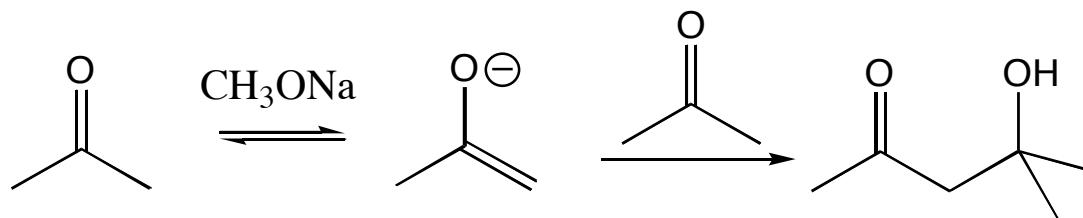
The β -hydroxy ketone that is formed can also lose water to form an α,β -unsaturated ketone



the loss of water can sometimes occur during work-up,
it can be driven to this product through heat and either acidic or basic conditions

Procedure for Aldol Reaction

When reacting in a self-condensation can use an alkoxide base

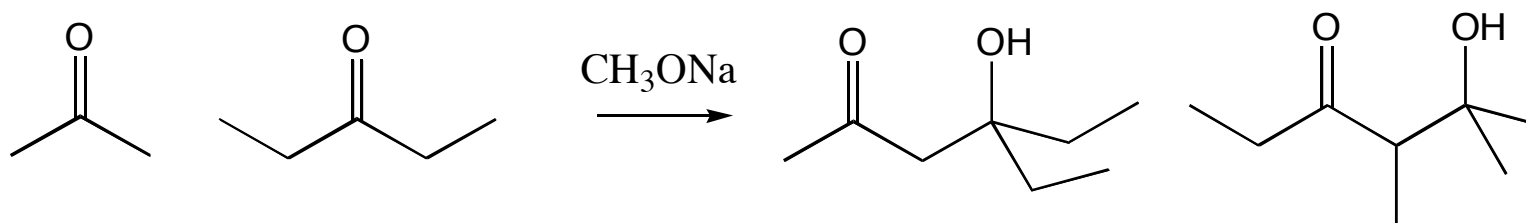


the alkoxide base will only deprotonate a small proportion of ketone,
but those enolates will react quickly with keto forms in an aldol reaction

can drive the reaction to completion

Using Different Carbonyl Compounds

If there are different carbonyl compounds (a mixed aldol or crossed aldol)
then conditions need to be considered

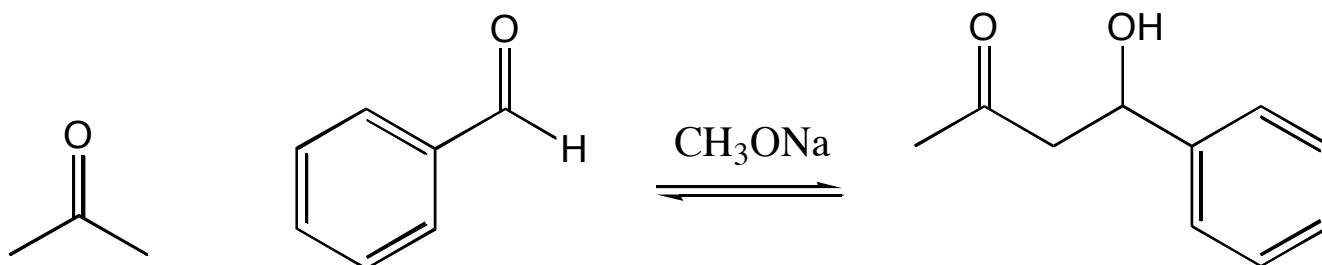


if using unsymmetrical ketones than will obtain four regioproducts for this reaction

A couple of options to reduce number of products

Use one carbonyl that does not have α -hydrogens

Therefore there are no hydrogens to abstract and can only react as electrophile

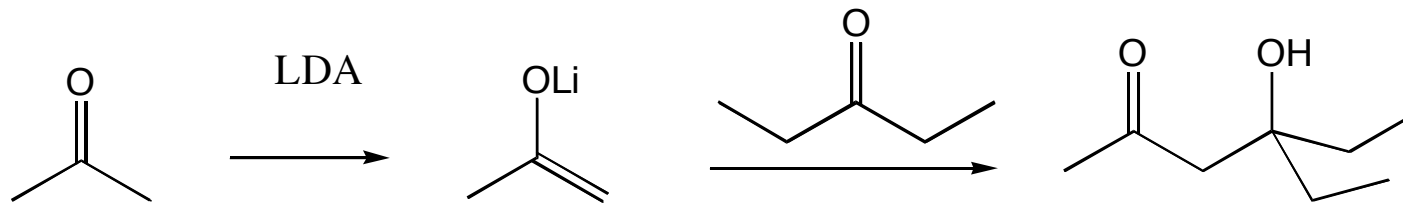


want to add compound with α -hydrogens (acetone in above example)

slowly to basic benzaldehyde solution

Another option: quantitatively form enolate first

If need to use two carbonyls that both contain α -hydrogens need to first generate the enolate quantitatively (strong base) and then add the second carbonyl compound



can generally obtain high yield of the desired aldol product with this method

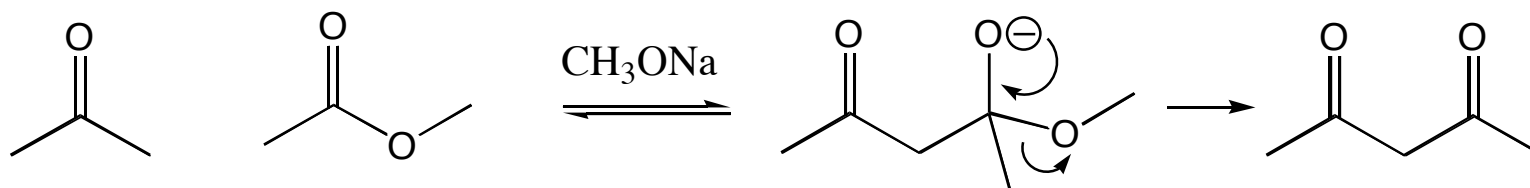
remember that with weak base will obtain a mixture of products with these reactants

Claisen Condensation

There are many "Name" reactions that are modifications of the aldol condensation

A Claisen condensation is an aldol where one carbonyl is an ester

By using an ester this changes the chemistry due to the presence of a leaving group



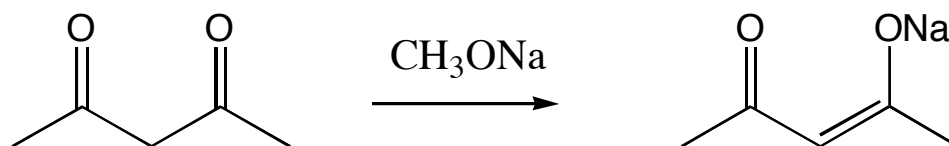
can run this reaction with both carbonyls present and a weak base

due to differences in pK_a (ketones are ~20 and esters are ~24)

Reactions are Driven to Completion

Unlike other aldol reactions, which are under equilibrium control, Claisen condensations give very high yield without adjusting equilibrium conditions

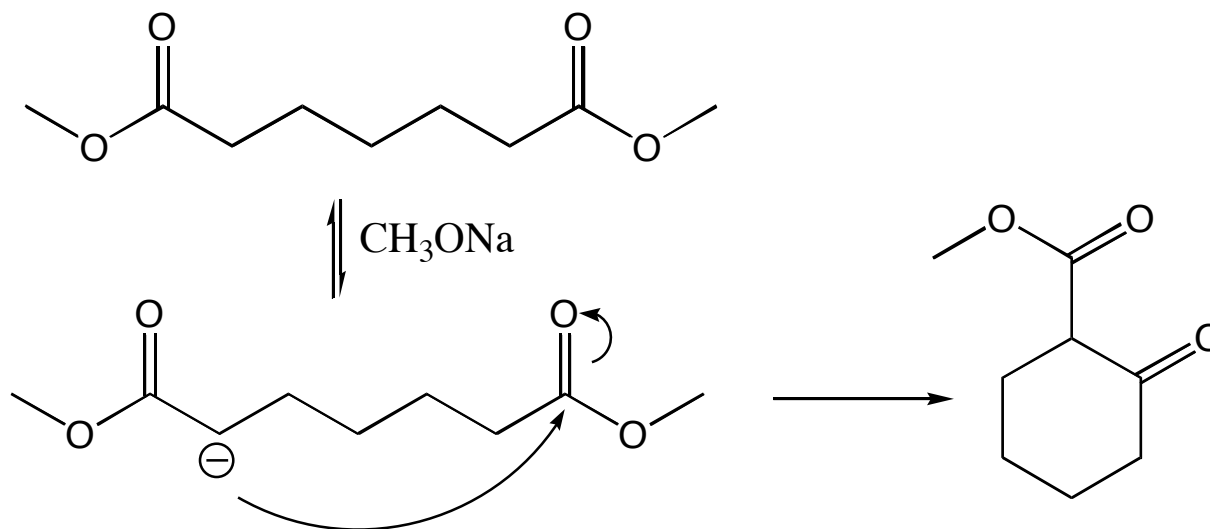
The last step generates an alkoxide with a β -diketone



diketones have a $pK_a \sim 10$, therefore methoxide will quantitatively abstract the hydrogen

Dieckmann

A Dieckmann condensation is an intramolecular Claisen condensation

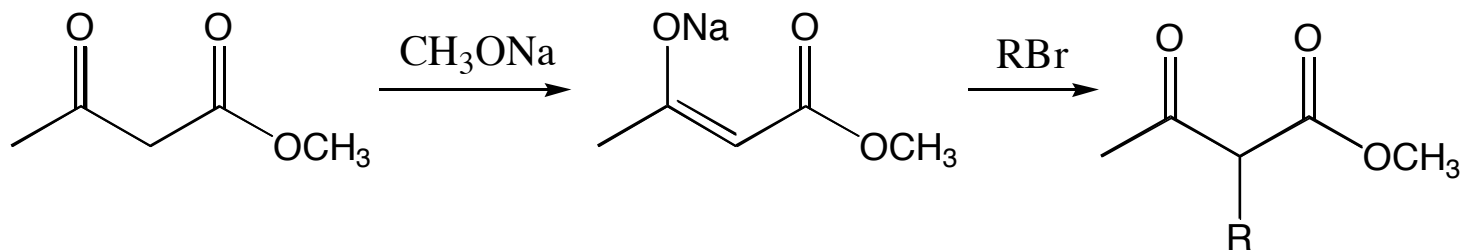


convenient method to form 5- or 6-membered rings

β -Dicarbonyls

both Claisen and Dieckmann condensations form β -dicarbonyl compounds

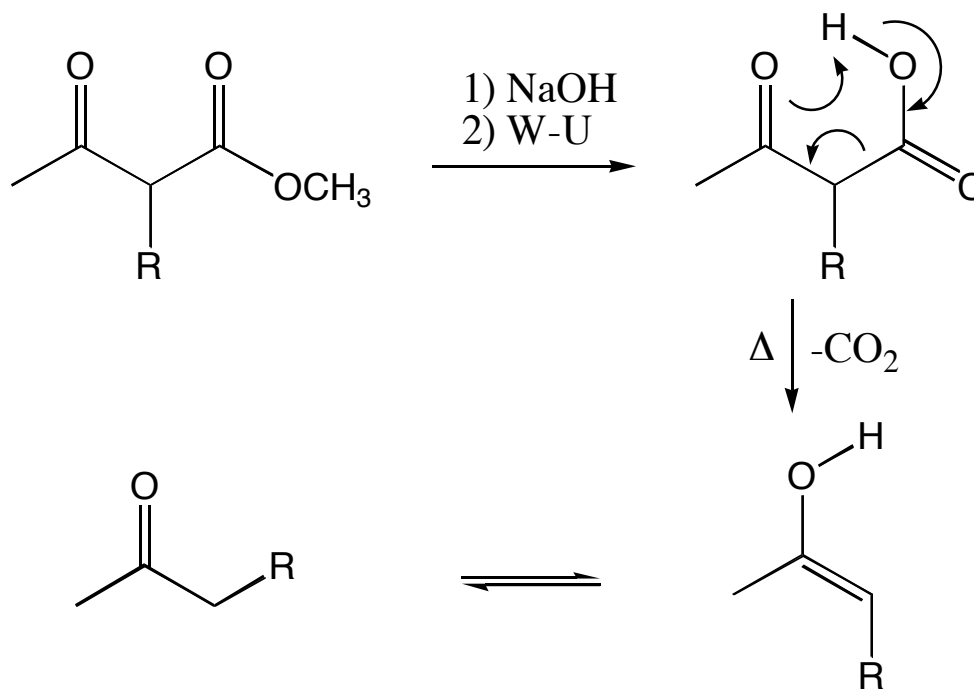
β -keto esters are another type of dicarbonyl systems that are very useful synthetically



due to the acidity of the methylene position alkylation reactions are easy to perform,
with only one carbonyl often need to use LDA to quantitatively form enolate

Decarboxylation

After alkylation, the ester group can be hydrolyzed and then decarboxylated

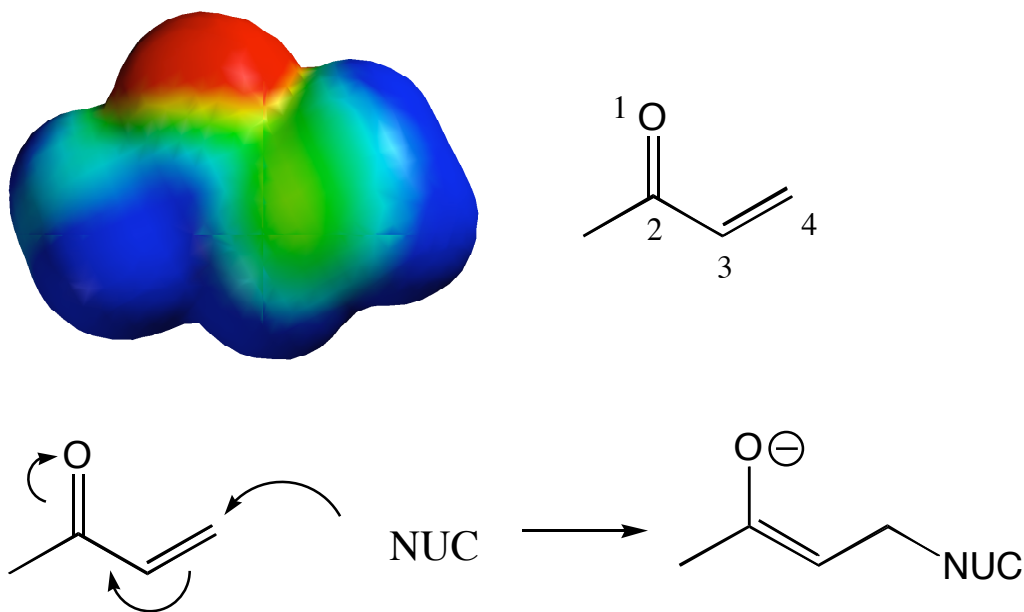


allows alkylation of ketone in much milder method than starting with ketone

Michael Addition

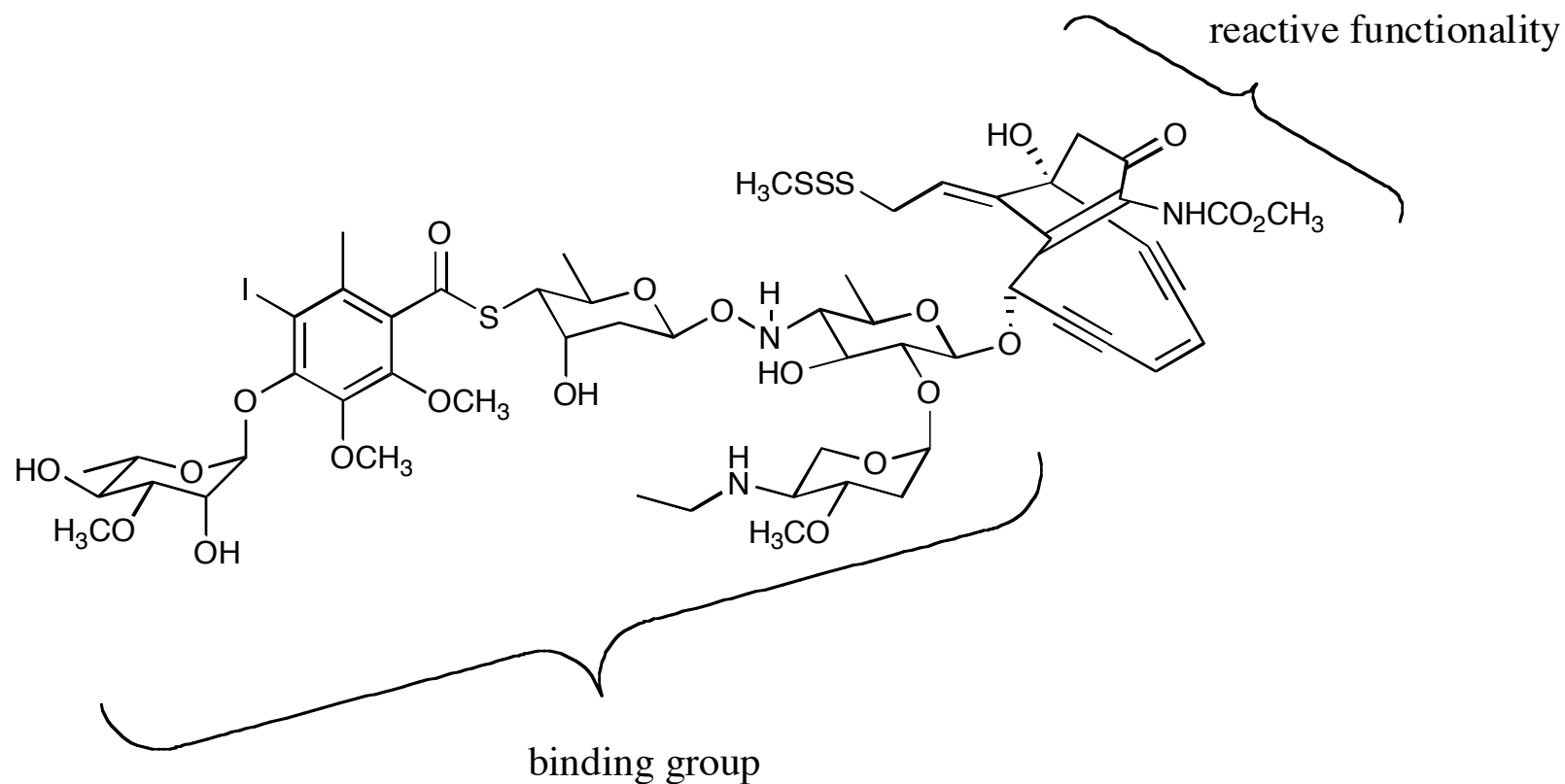
If we add enolate to α,β -unsaturated system the reaction often reacts with 1,4-addition

Called Michael addition

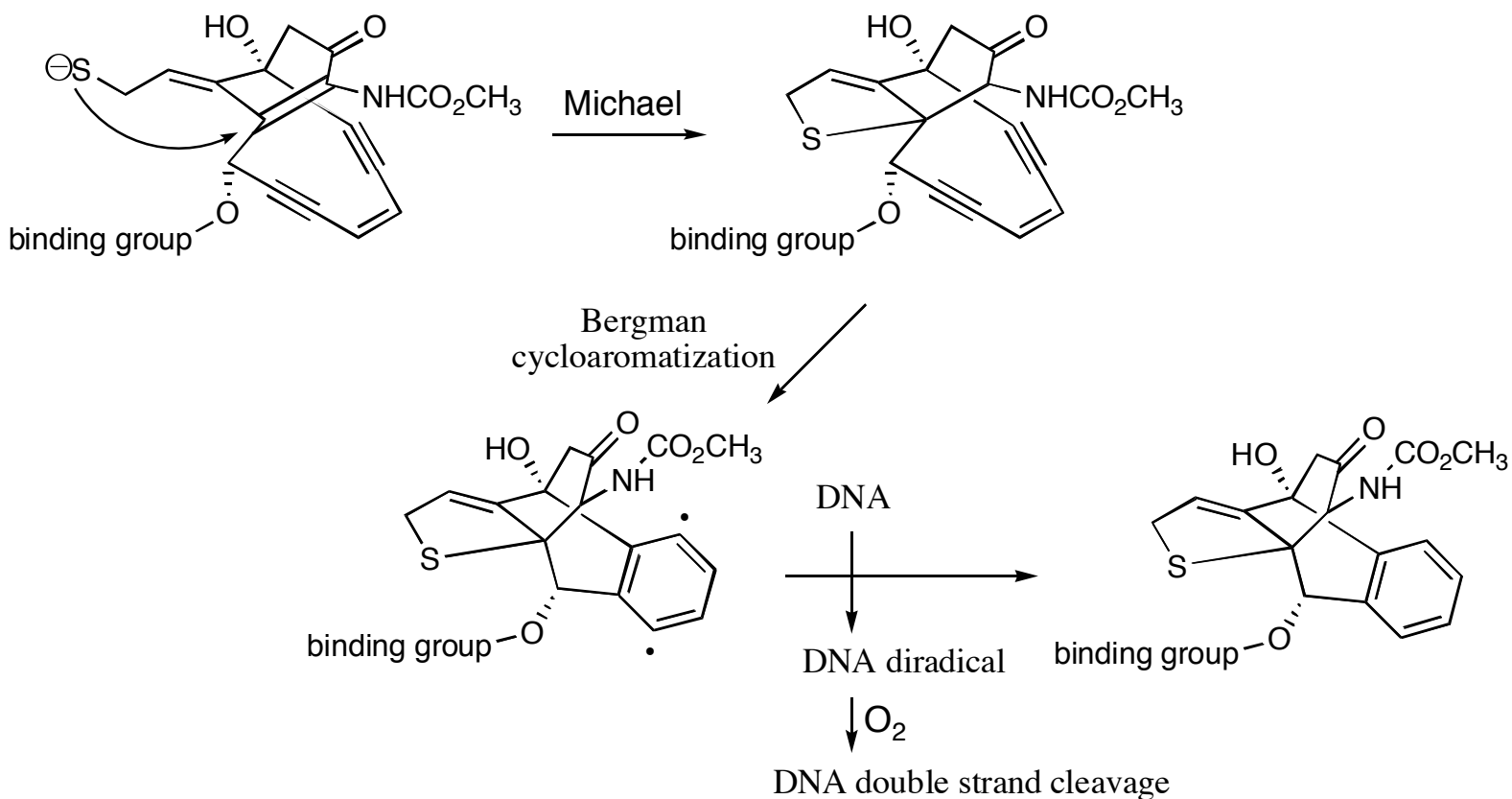


Calicheamicin γ_1^1 : An Example of Michael Addition in Drug Action

In chapter 4 we first saw a drug that uses a Michael addition



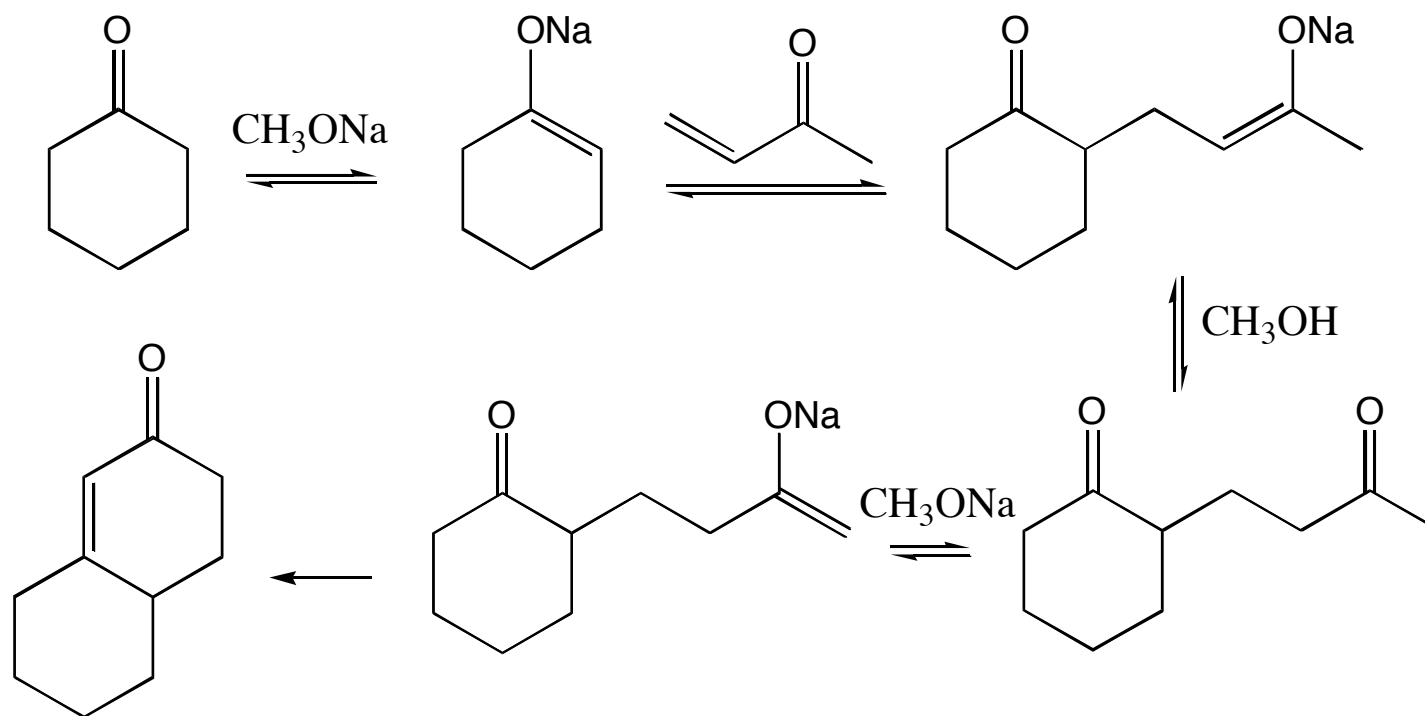
After the sugar binding group binds in the minor groove of DNA a sulfide is generated



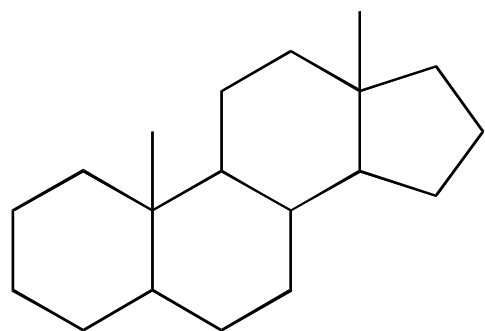
After the Michael addition occurs, the conformational change causes the Bergman cyclization to occur eventually leading to cell death after DNA cleavage

Robinson Annulation

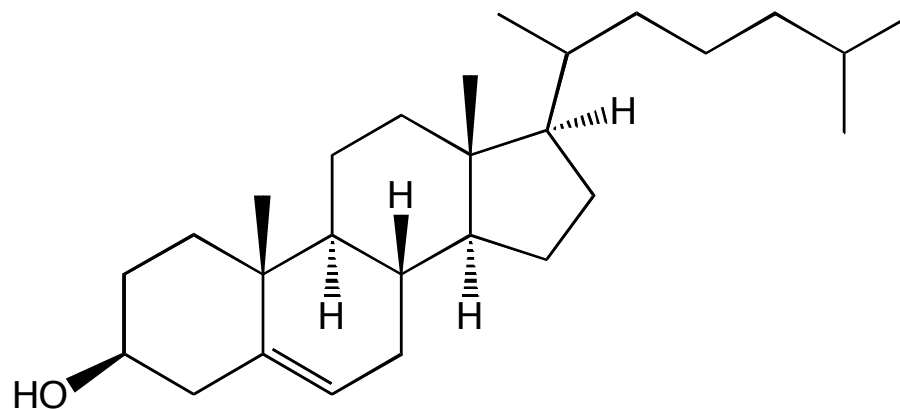
This is a very convenient method to form 6-membered rings
Perform a Michael addition followed by an aldol condensation



Convenient Method to Synthetically Produce Multi-Ring Systems



steroid ring system



cholesterol

nature has more efficient ways to synthesize steroids but you can see how Robinson Annulation can be used to prepare 6-6 and 6-5 ring junctions in a one pot reaction