

①

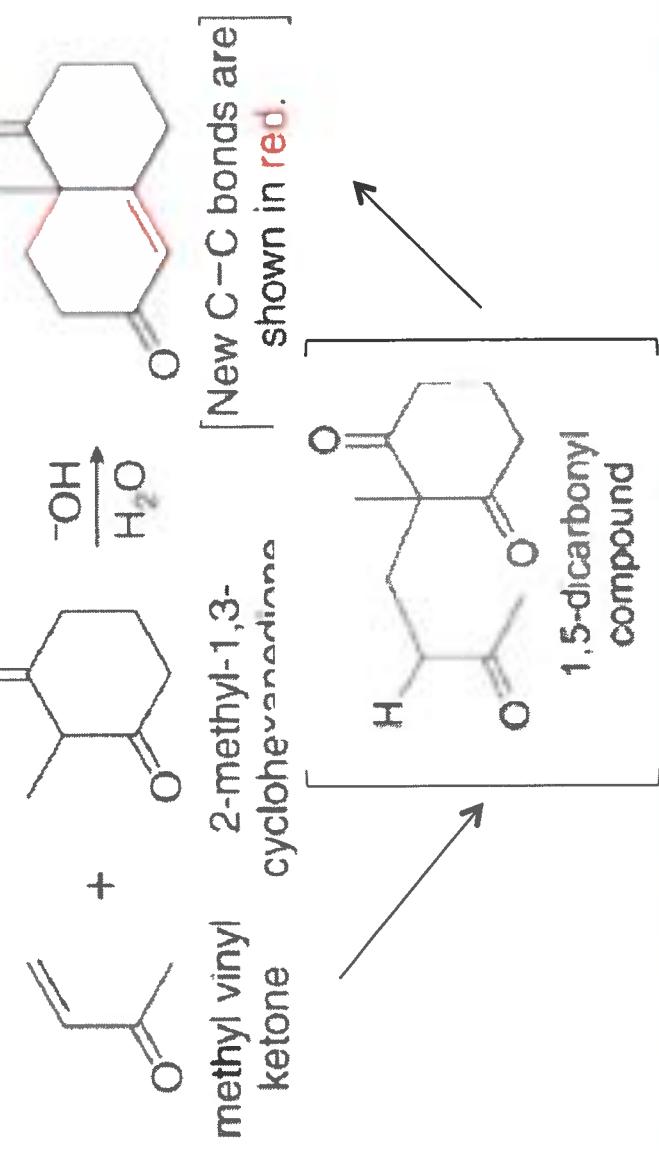
Upcoming office hours:  
This week:

ERJ Today 2-3, NS1 4114  
Alissa Fri 2-3, RH 523

# Today: Robinson Annulations Mannich Reactions, Start Ch 25

**Next week:**

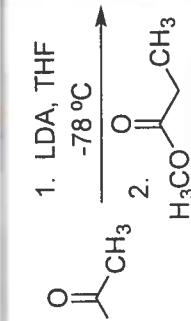
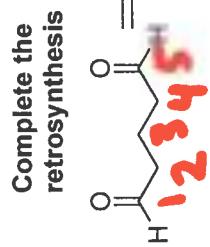
Kirsten: Tues 9-10, RH 523  
ERJ: Tues 10-11, NS1 4114  
Alissa: Tues 5pm, RH 523  
Tristan: Wed 11-12, RH 523  
ERJ: Wed 2-3, NS1 4114



Midterm 2 is next Friday!  
Will cover up to and including Ch 25  
(selected topics)

Old midterms on website  
Tutors will go through M2-S19  
Monday May 20, 5-7 pm @ BS3  
1200

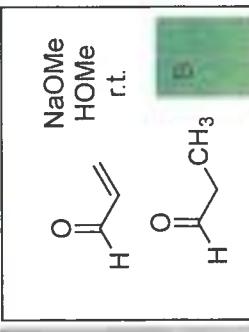
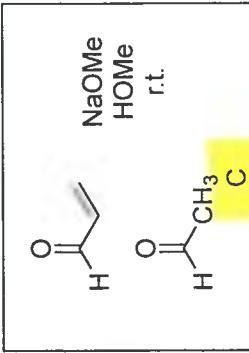
Capercard:



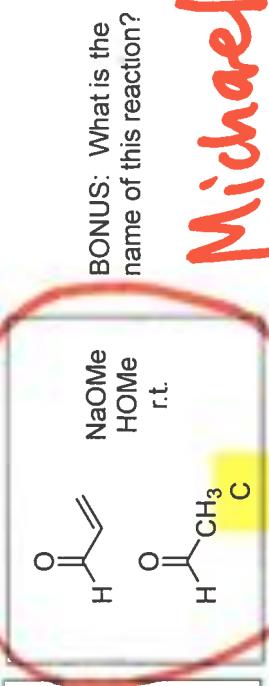
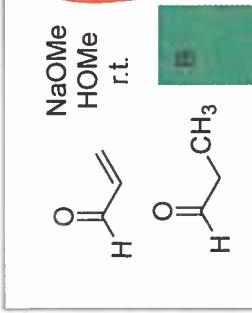
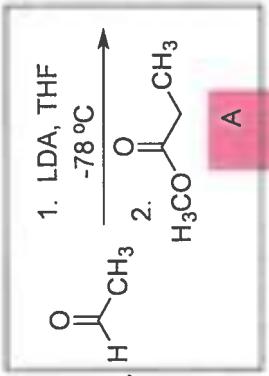
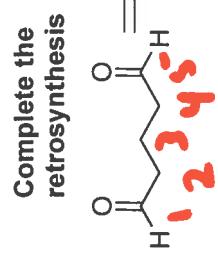
ABC (Jackson Five)      Easy as 1, 2, 3

A Robinson annulation is as easy as (1) Michael addition  
(2) Intramolecular aldol (3) E1cb

BONUS What is the name of this reaction?



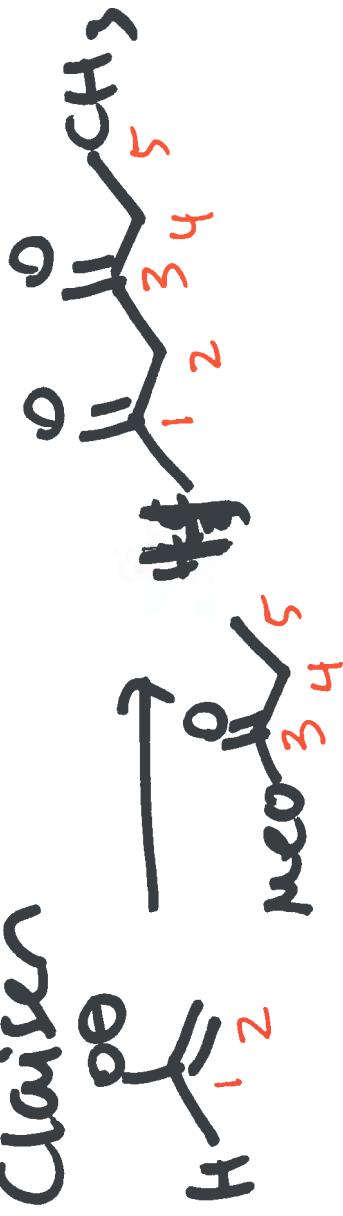
(2)



BONUS: What is the name of this reaction?

Michael

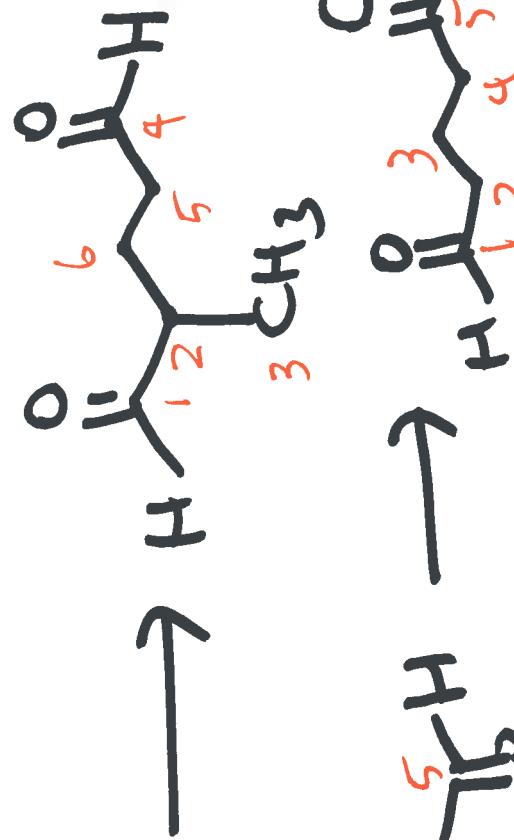
A: Claisen



B: Michael

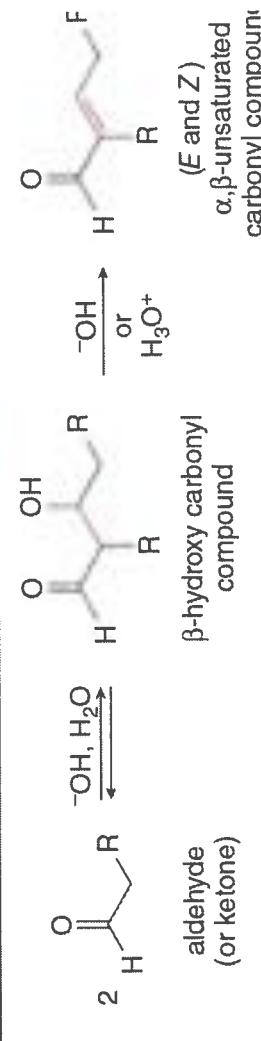
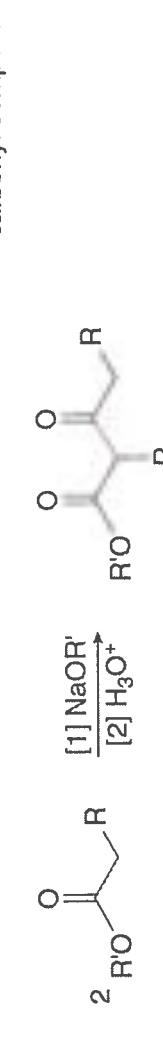
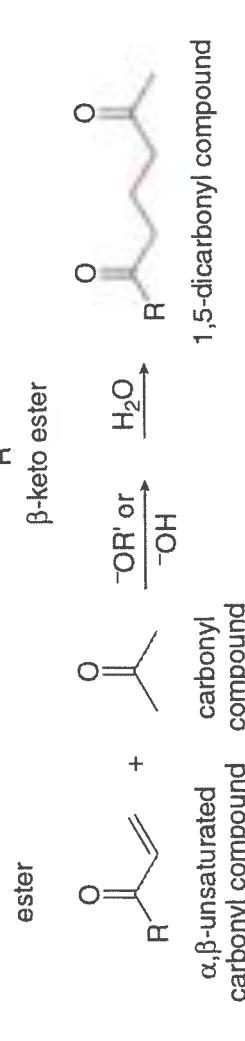
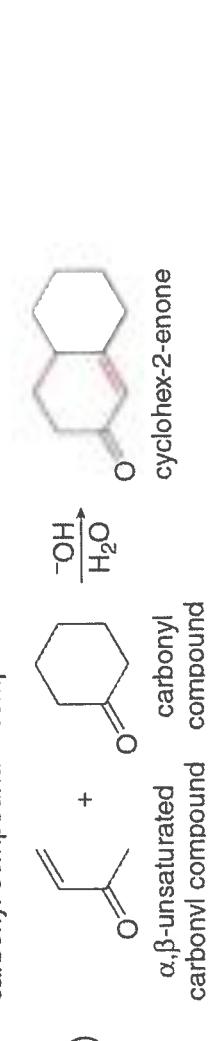


C: Michael



# Ch 24 Road map

Reaction type      Reaction [New C–C bonds are shown in red.]

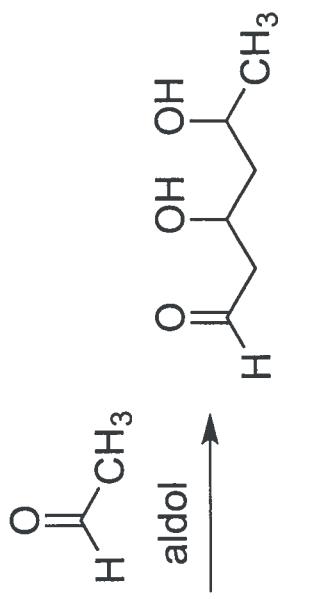
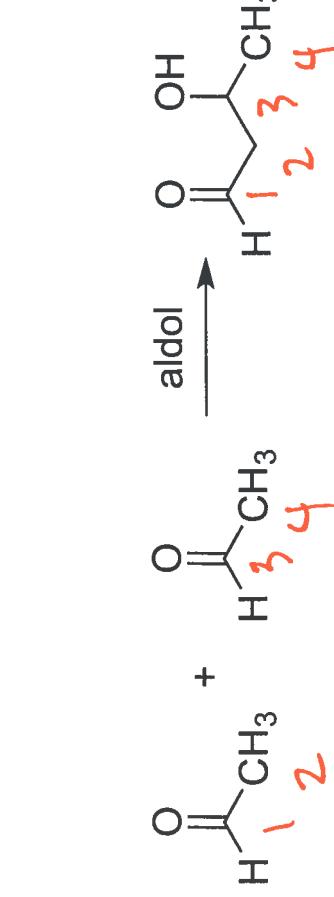
[1] Aldol reaction (24.1)		 $\xrightarrow{-\text{OH} \text{ or } \text{H}_3\text{O}^+}$ $\alpha,\beta\text{-unsaturated carbonyl compound}$
[2] Claisen reaction (24.5)		 $\xrightarrow{\text{[1] NaOR'} \text{ [2] H}_3\text{O}^+}$ $\beta\text{-keto ester}$
[3] Michaelis reaction (24.8)		 $\xrightarrow{-\text{OR}' \text{ or } \text{H}_2\text{O}}$ $1,5\text{-dicarbonyl compound}$
[4] Robinson annulation (24.9)		 $\xrightarrow{-\text{OH} \text{ or } \text{H}_2\text{O}}$ $\text{cyclohex-2-eneone}$

+ today

(4)

## Synthesis of Polyketide Natural Products

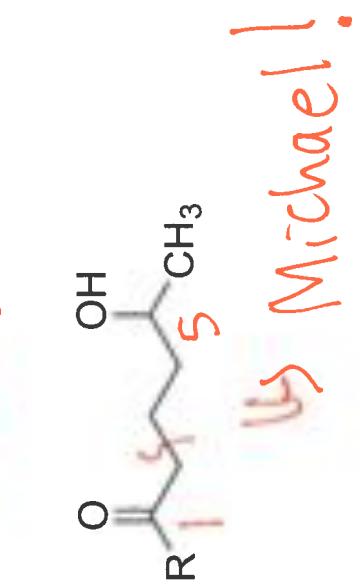
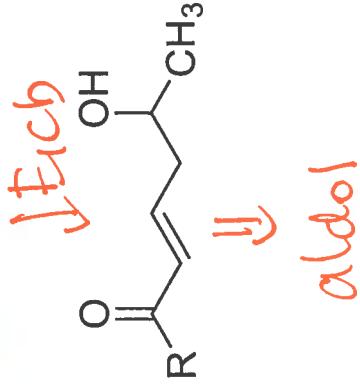
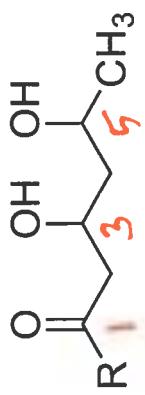
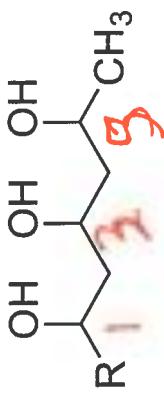
Conceptually:  
Use aldol reactions to assemble carbon-carbon framework



Adjust oxidation states accordingly

$\beta,\beta$ -oxygenation

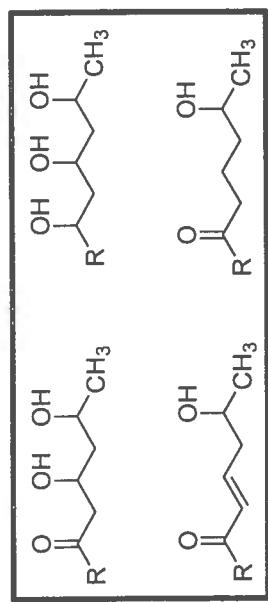
$\Rightarrow$  Aldol.



5

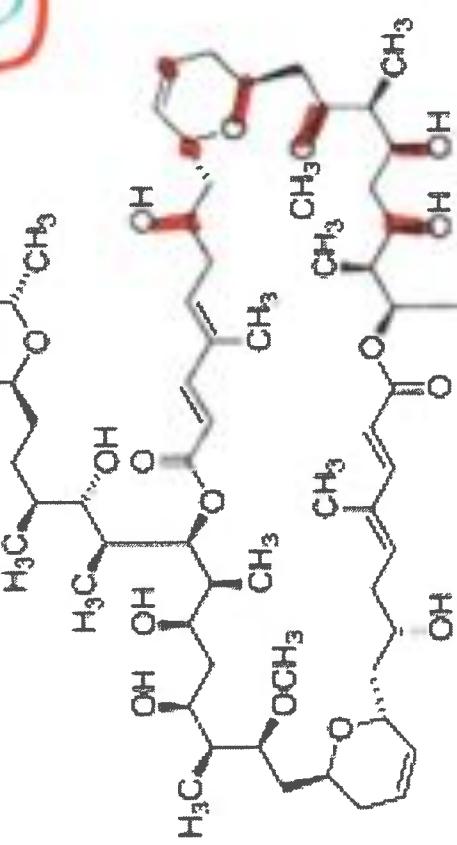
## Polyketide Natural Products

### Polyketides



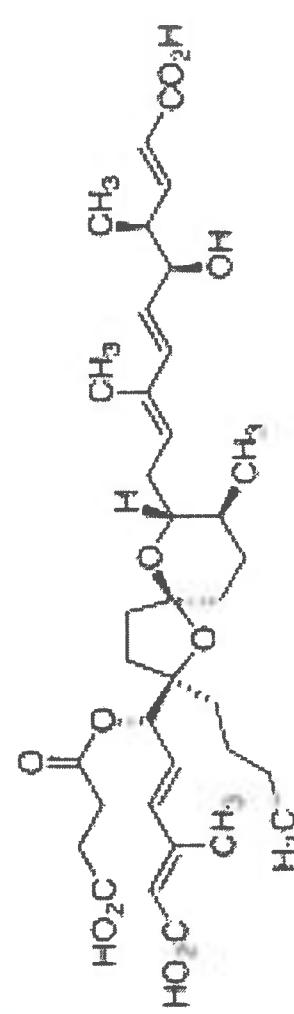
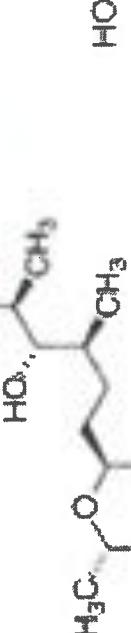
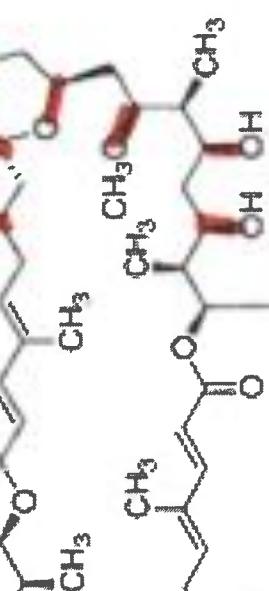
1: (+)-Discodermolide  
Binds tubulin  
(anti-cancer)

1: (+)-Discodermolide



Binds tubulin  
(anti-cancer)

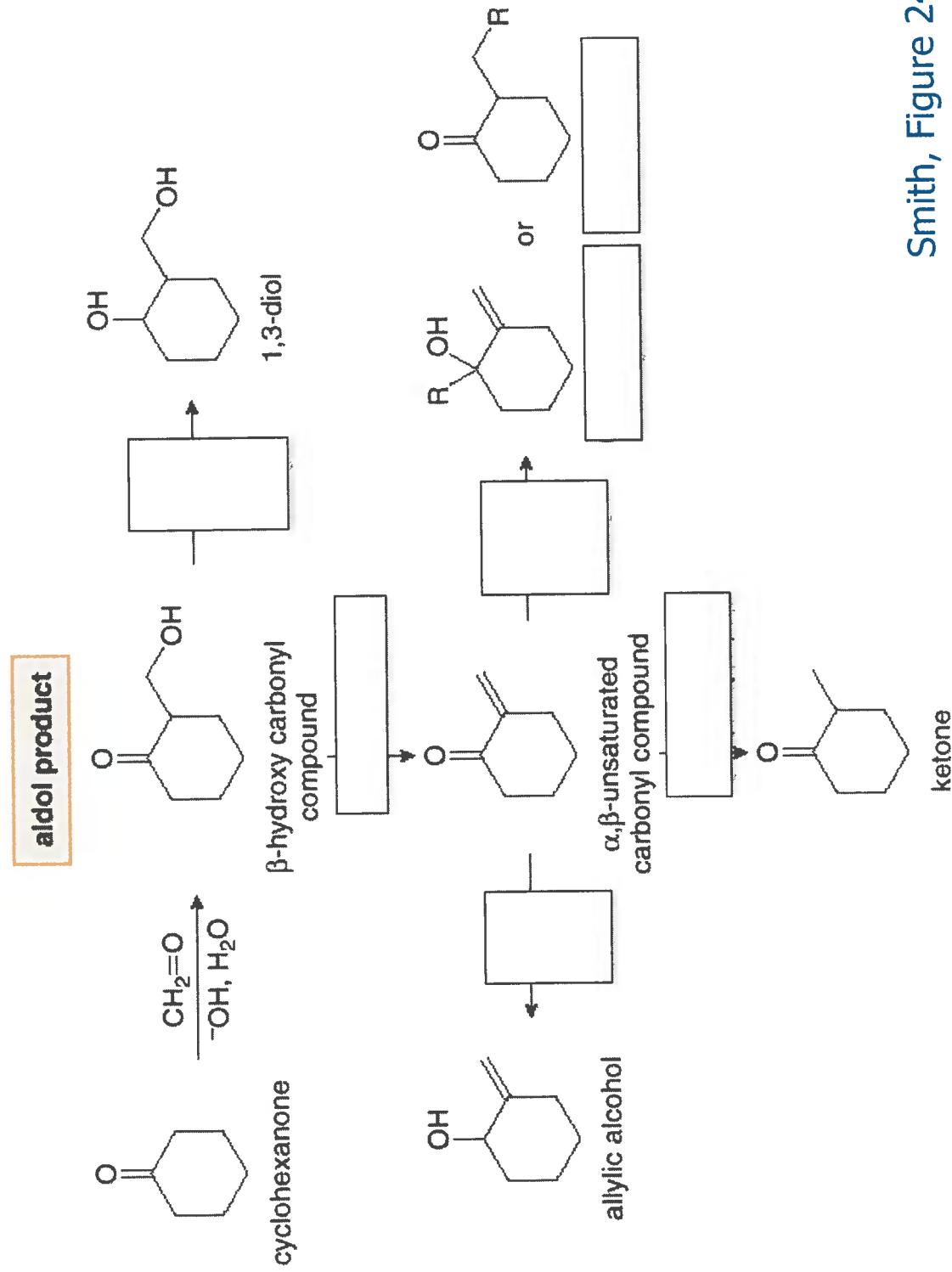
$R = H; n=1: \text{epothilone A (108)}$   
 $R = CH_3; n=1: \text{epothilone B (107)}$   
 $n = 1.5$



Revoromycin B (109)  
antibiotic

Swinholide A (33)  
Binds actin  
(anti-cancer)

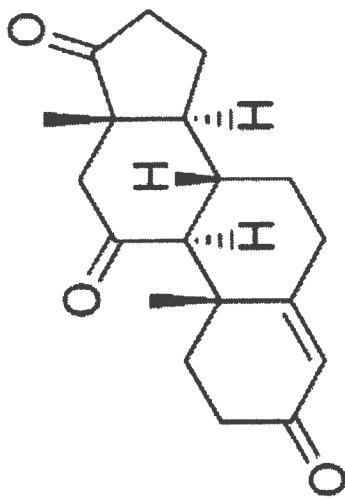
**Aldol products: Useful synthetic intermediates**



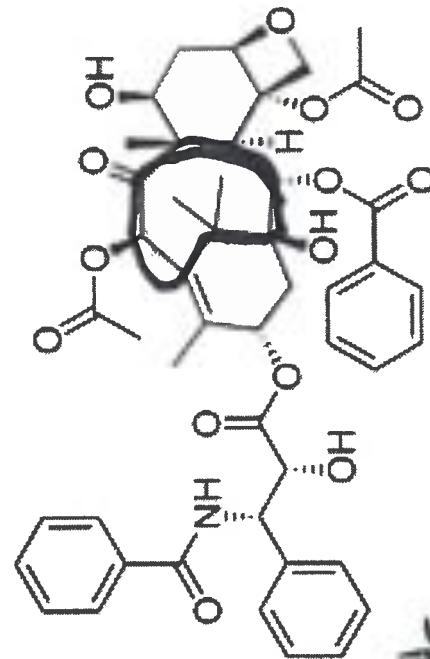
Smith, Figure 24.3

7

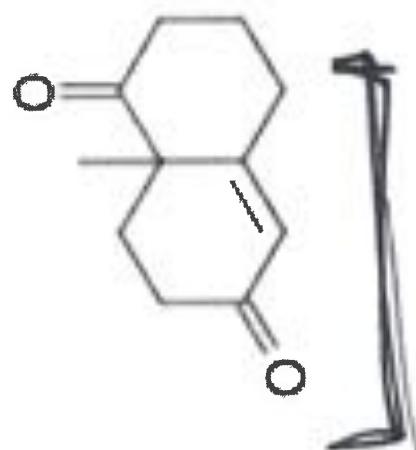
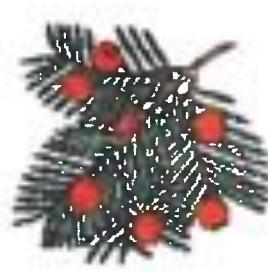
## Robinson Annulation: the Wieland-Miescher ketone



Adrenosterone  
(human hormone)

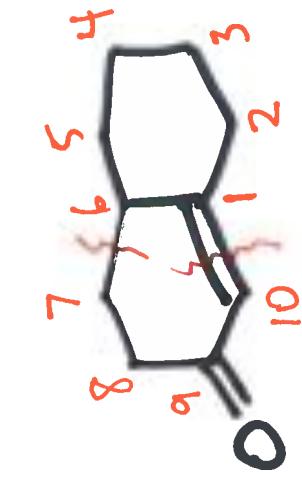
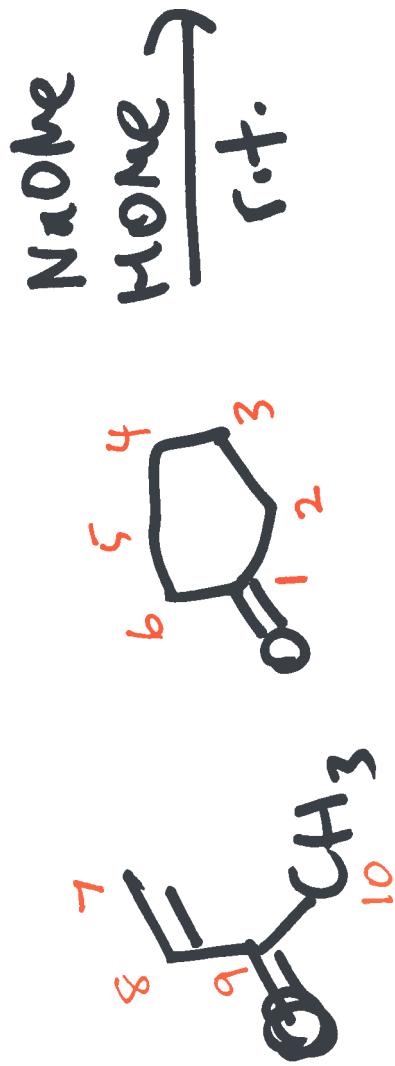


Taxol®  
From Yew tree



Prepared by  
Robinson  
Annulation

## Robinson Annulation:



ketone

$\alpha, \beta$ -unsaturated  
carbonyl

ketone  
(generate  
enolate)

$\alpha, \beta$ -unsaturated  
cyclohexenone

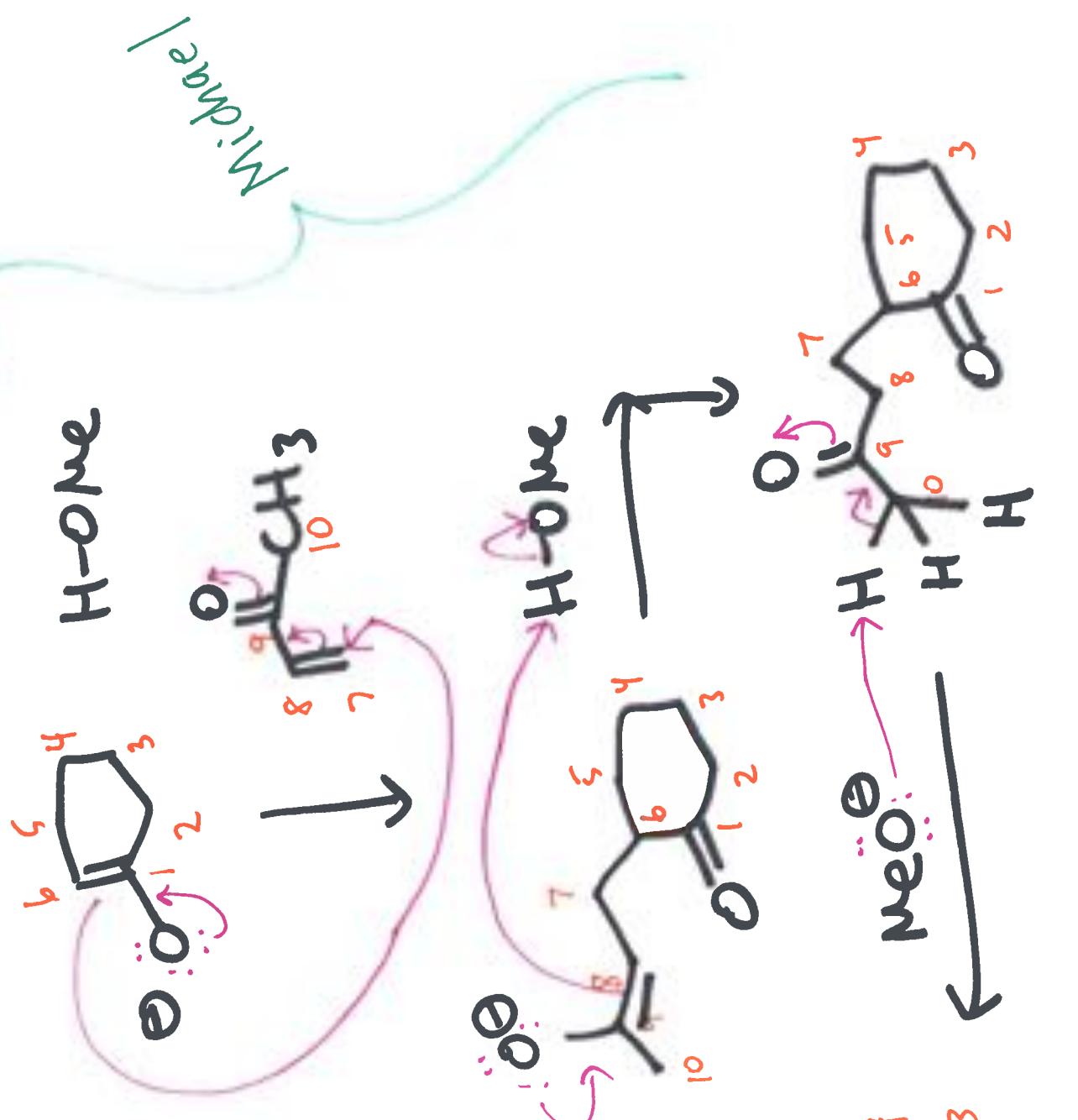
① Michael addition

② intramolecular aldol reaction

③ E1cb elimination

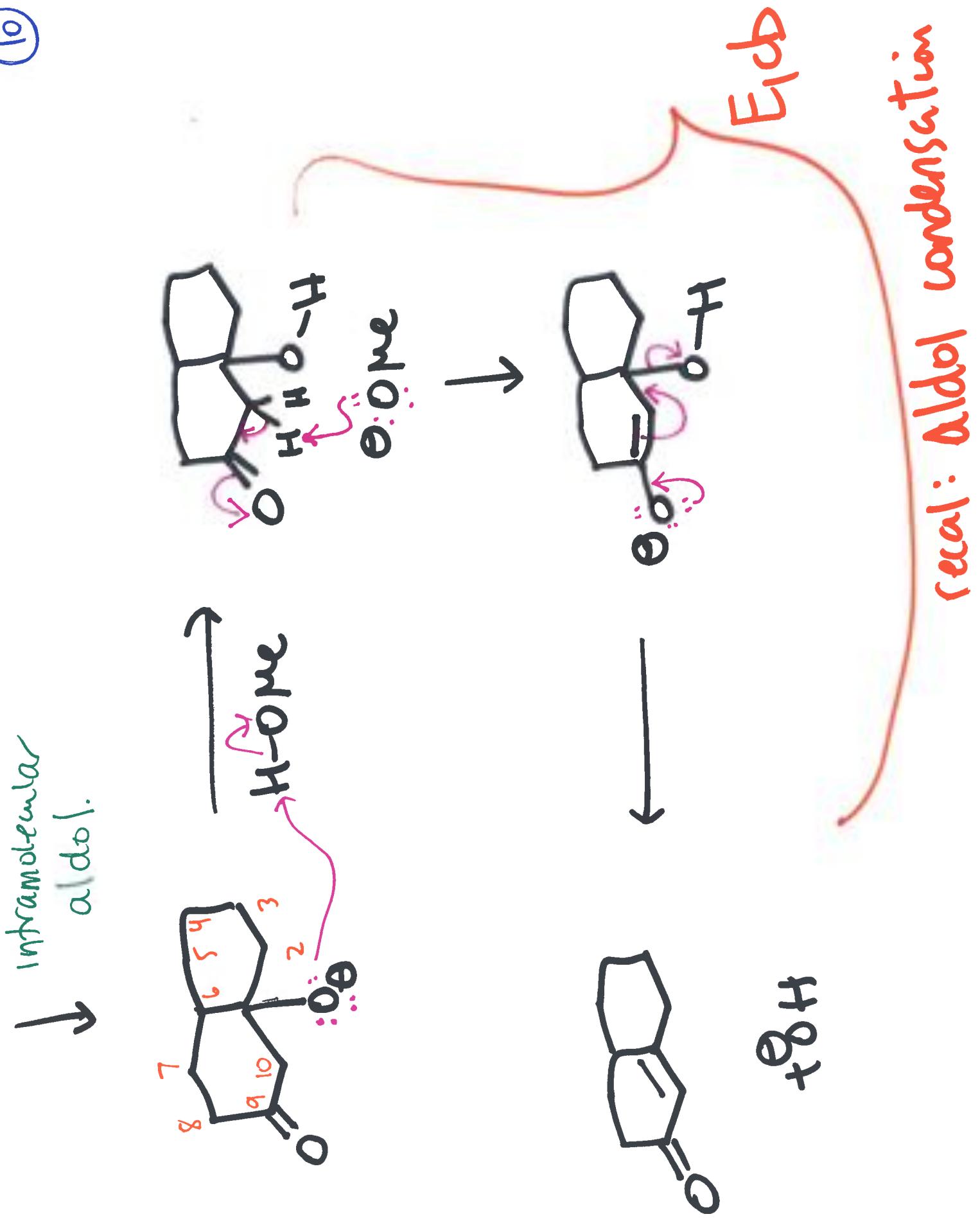
## Mechanism:

Start: Michael addition



(9)

(10)



How do I know

Robinson or Michael?

or Michael?

- Draw Michael product
- can I generate an enolate?
- can a 5- or 6-membered ring form?

Then: YES! Robinson.

No! just Michael

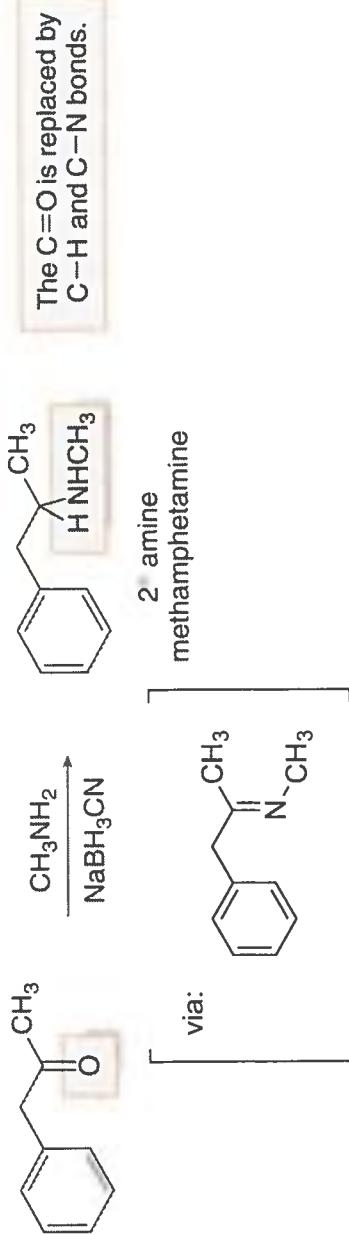
Cu 25: Amines

Synthesis of Amines.

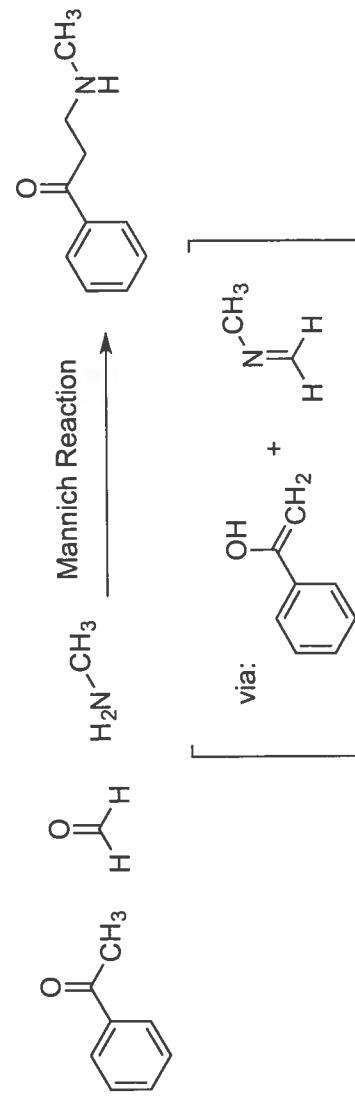
(13)

## Reductive amination

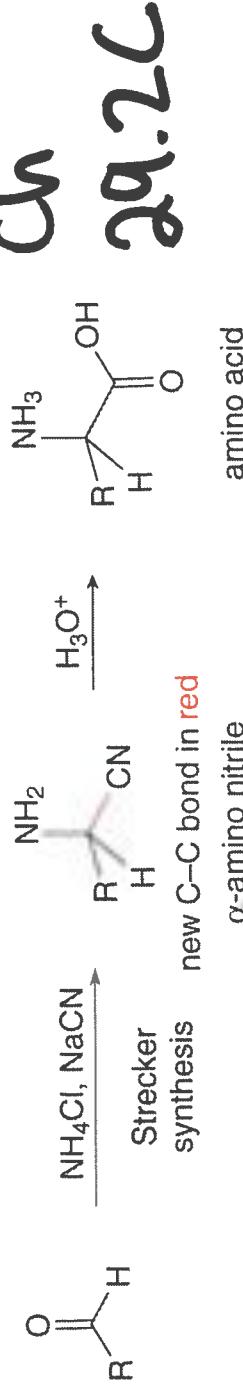
## Additions to imines ✓



## Mannich reaction



## Strecker reaction

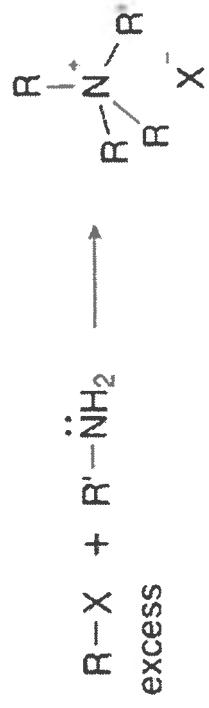


Ch  
29.2c

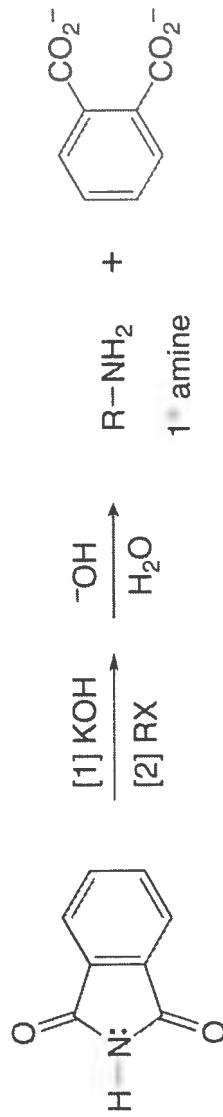
## Alkylation reactions

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### Simple alkylation with alkyl halides

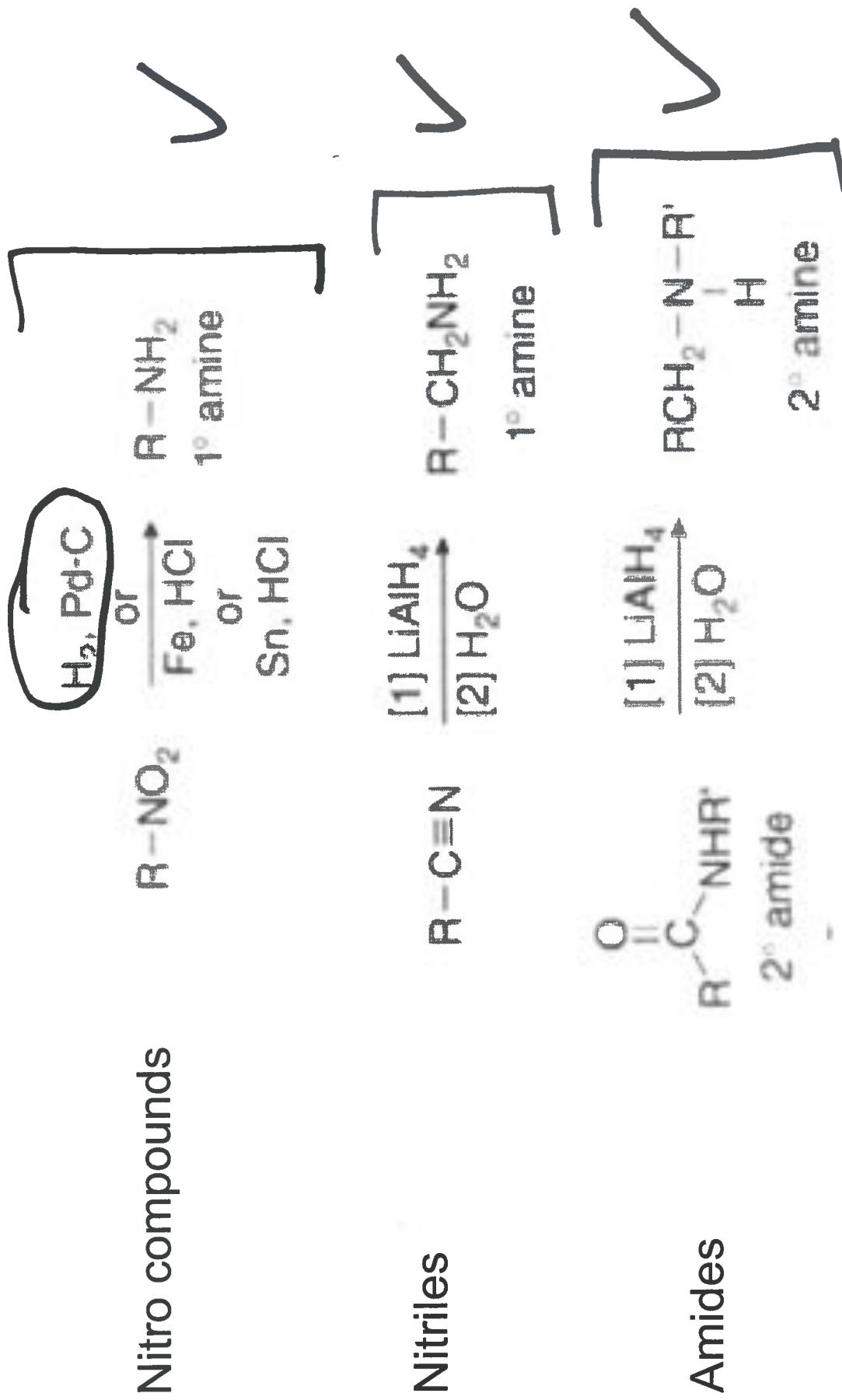


### Gabriel synthesis



(15)

## Preparation of amines: By reduction

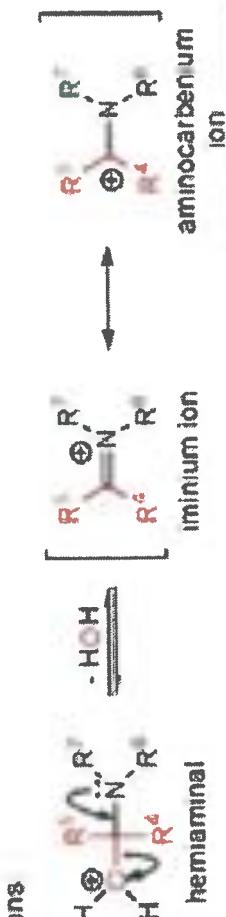


## Mannich reaction

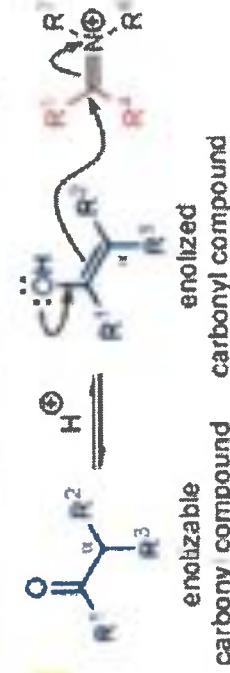
### Mechanism: 6,50,12-14

The mechanism of the *Mannich reaction* has been extensively investigated. The reaction can proceed under both acidic and basic conditions, but acidic conditions are more common. Under acidic conditions the first step is the reaction of the amine component with the protonated non-enolizable carbonyl compound to give a hemiaminal, which after proton transfer loses a molecule of water to give the electrophilic iminium ion.<sup>50</sup> This iminium ion then reacts with the enolized carbonyl compound (nucleophile) at its  $\alpha$ -carbon in an *aldol-type reaction* to give rise to the Mannich base.

Formation of the reactive iminium ion under acidic conditions



Alkylation of the enolized carbonyl compound:

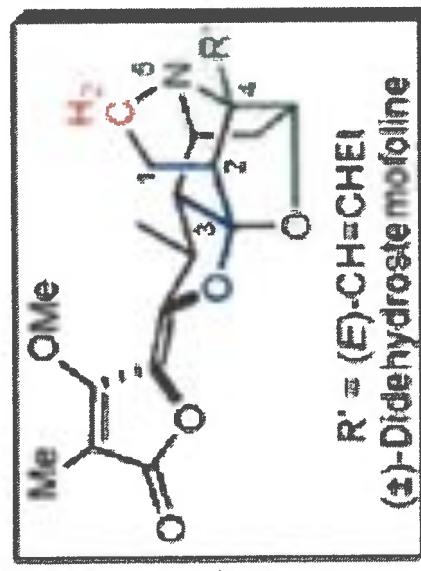
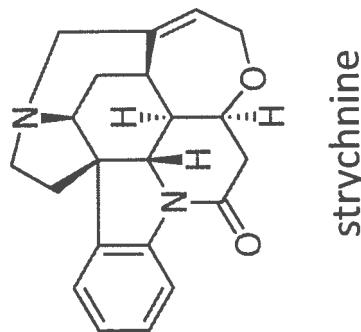
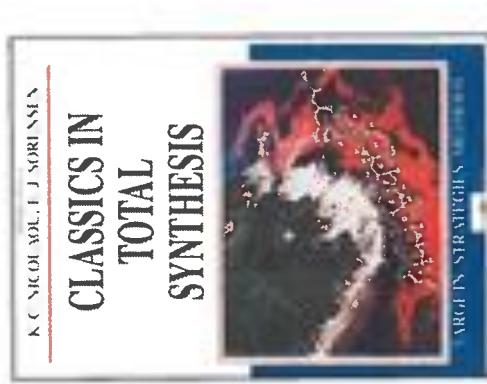


Taken from: Strategic applications of name reactions in organic synthesis (Kurti and Czako)  
<http://books.google.com/books?id=MdxkSyzhcdCC&printsec=frontcover#v=onepage&q=mannich&f=false>

## VCI

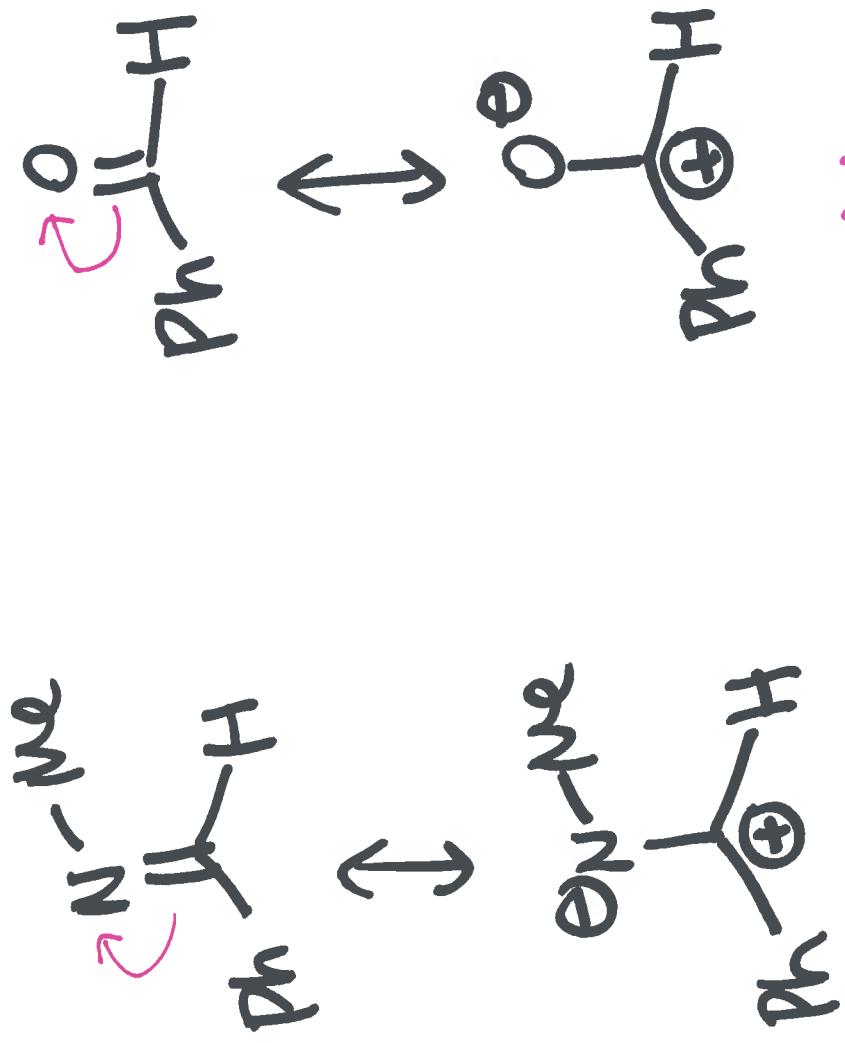
## Application of Mannich reaction: Pioneering chemistry at UCI

One of the most well-known applications of the **Mannich reaction** is its use in a **tandem fashion** with the ***aza-Cope rearrangement*** to form heterocycles. This reaction was the cornerstone of the strategy in the research group of L.E. Overman during the total synthesis of  $(\pm)$ -**didehydrostemooline** (asparagamine A). The bicyclic amine hydrogen iodide salt was exposed to excess paraformaldehyde, which led to the formation of the first iminium ion intermediate that underwent a facile [3,3]-**sigmatropic rearrangement**. The resulting isomeric iminium ion spontaneously reacted with the enol in an **intramolecular Mannich cyclization**.



Taken from: Strategic applications of name reactions in organic synthesis (Kurti and Czako)  
<http://books.google.com/books?id=MdxkSyzhcdC&printsec=frontcover&v=onepage&q=mannich&f=false>

CN 25: addition to imines.



- 18
- imines are also electrophiles
  - aldehydes are electrophilic
  - nucleophilic attack on carbonyl carbon.
  - nucleophilic attack on them.

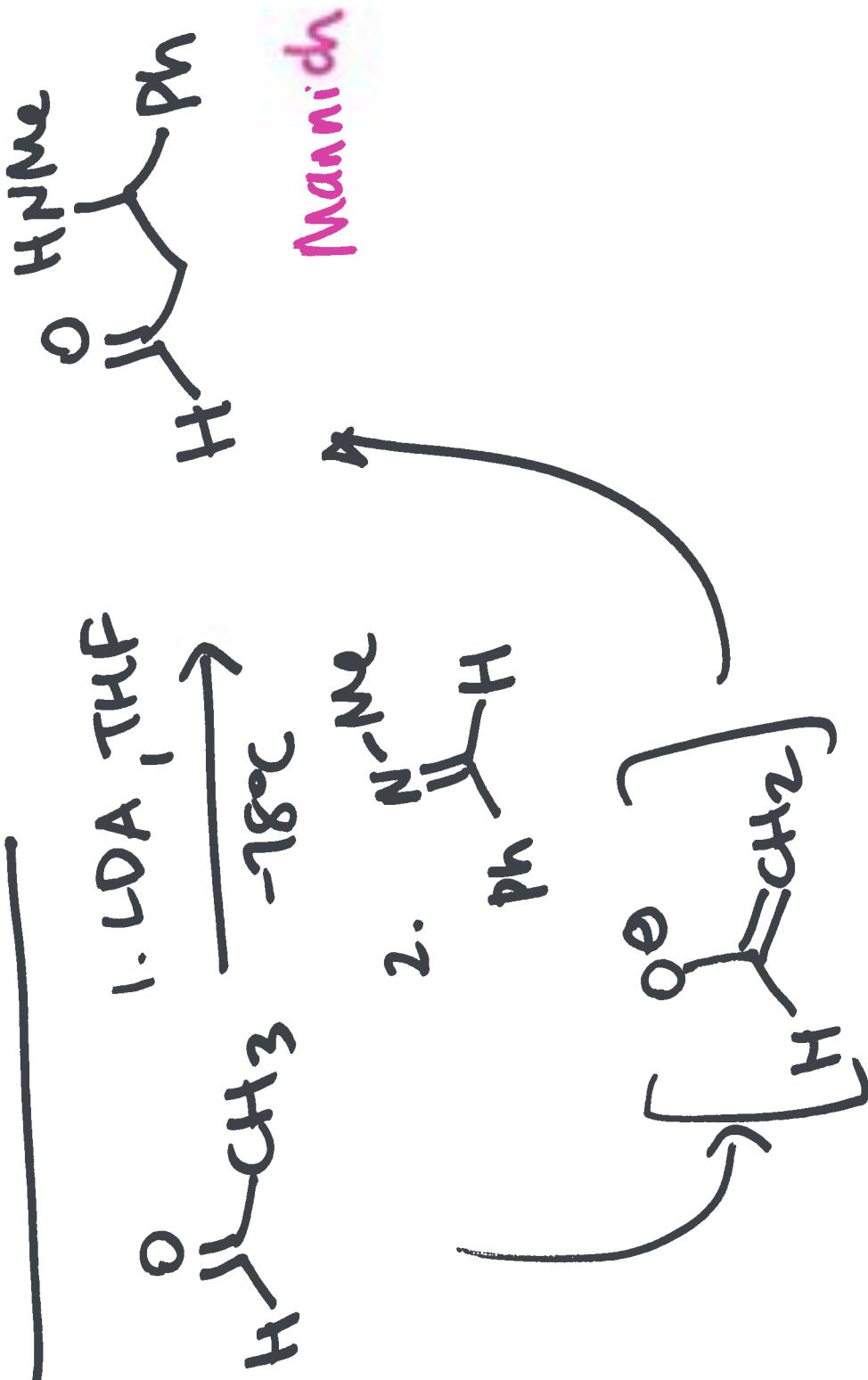
(1a)  
Reactions:

Name	
Mannich	$\text{Na}^+ \text{H}_2\text{B}-\text{H}$ (hydride)
	$\text{Na}^+ \text{O}^- \text{CN}$

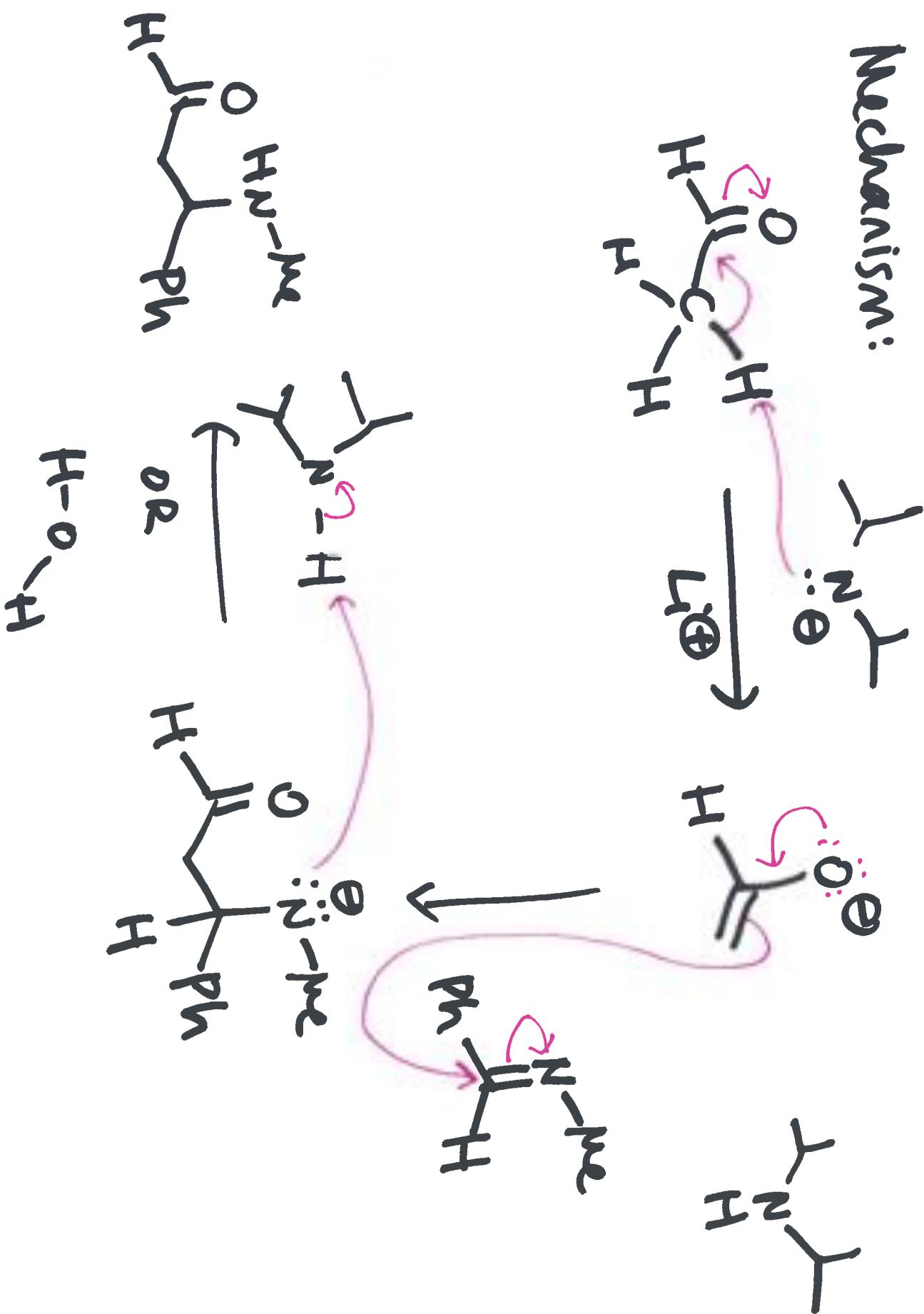
reductive  
amination

Similar mechanisms!

## Mannich reaction

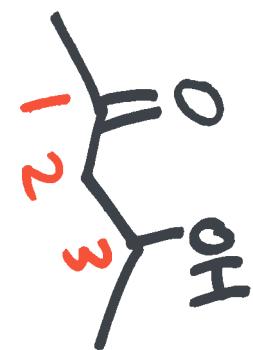


# Mechanism:

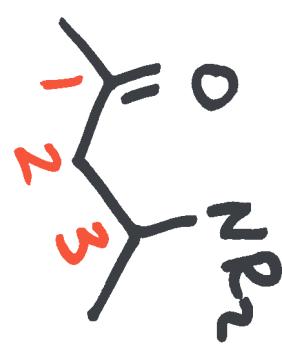


(21)

In synthesis



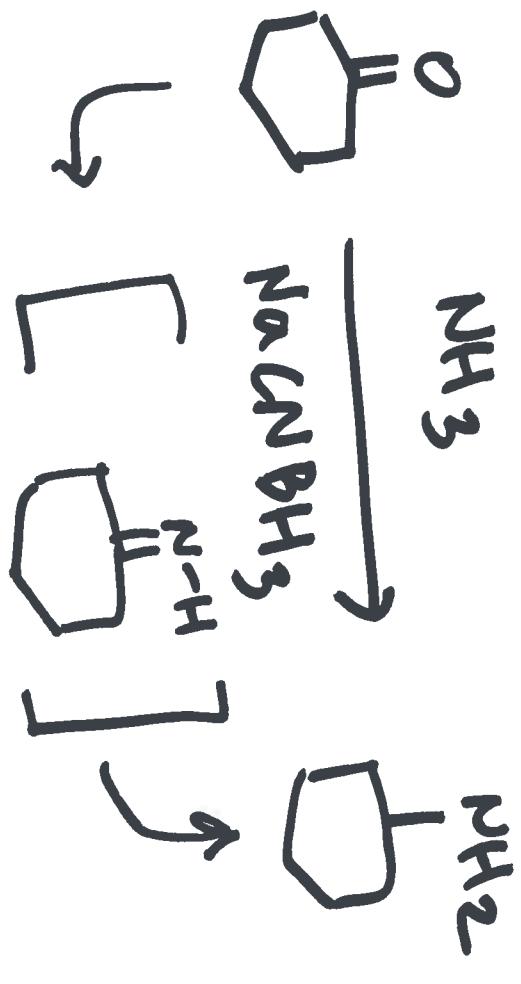
aldol



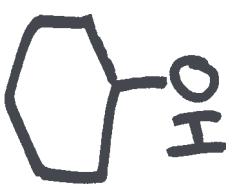
Mannich.

Next addition to Imine: Hydride reagents!

Reductive amination



imine generated  
by mixing carbonyl  
+ amine



$\text{NaBH}_4$



$\text{Na}^+$



$\text{NaBH}_4$   
 $\text{H} \cdots \text{Be}^{\text{+}} \text{H}$   
 $\text{H} \diagup \text{B} \diagdown \text{H}$

$\text{NaCNBH}_3$   
 $\text{N} \equiv \text{C} \cdots \text{B}^{\text{+}} \text{H}^{\text{-}}$   
 $\text{H} \diagup \text{B} \diagdown \text{H}$

$\text{Na}^+$

Reduce aldehydes  
+ ketones.  
Reduce imines.

Examples: can use  $\text{NH}_3$ ,  $\text{RNH}_2$ ,  $\text{R}_2\text{NH}$

(24)

