



***DISCONNECTION APPROCH:
Retrosynthetic Principles and Synthetic
Applications***

**XV Summer School in Pharmaceutical and
Medicinal Chemistry**

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Disconnection Approach

Retrosynthetic Analysis: the logical process of analysing the structure of a target molecule to discern a possible synthesis step by step

Retrosynthetic arrow is: $A \Rightarrow B$ (B is a precursor of A)
 \Rightarrow (Means “can be made from”)

Functional group interconversion (FGI)

Functional group addition (FGA)

Functional group removal (FGR)

Disconnection: the formal reverse of a bond forming reaction (conceptual cleavage of a bond to break the molecule into possible starting materials)

d_n synthon: Functionalized nucleophile (d, donor) with the heteroatom of the functional group joined to the nth carbon atom

a_n synthon: Functionalized electrophile (a, acceptor) with the heteroatom of the functional group joined to the nth carbon atom

Reagent: A chemical compound used in practice for a synthon

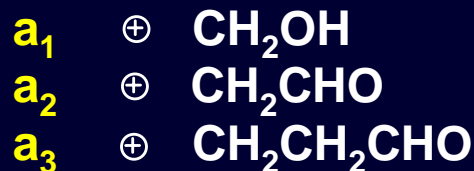
Disconnection Approach

Synthons and Reagents

dn synthon: Functionalized nucleophile (d, donor) with the heteroatom of the functional group joined to the n^{th} carbon atom.

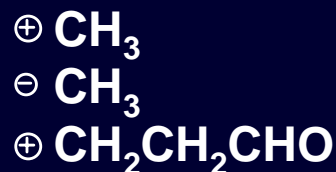


an synthon: Functionalized electrophile (a, acceptor) with the heteroatom of the functional group joined to the n^{th} carbon atom.

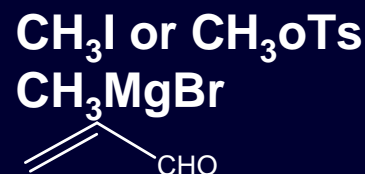


Reagent: A chemical compound used in practice for a synthon.

Synthon

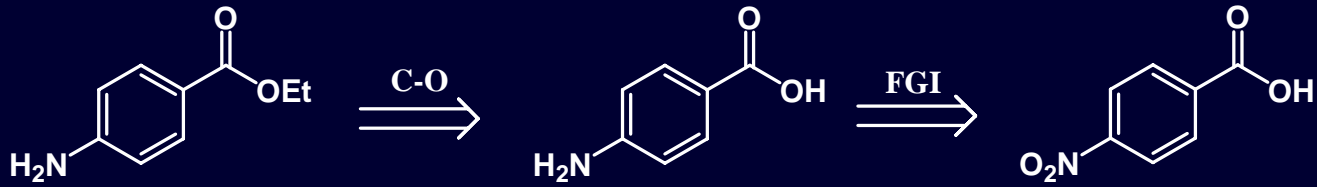


Reagent



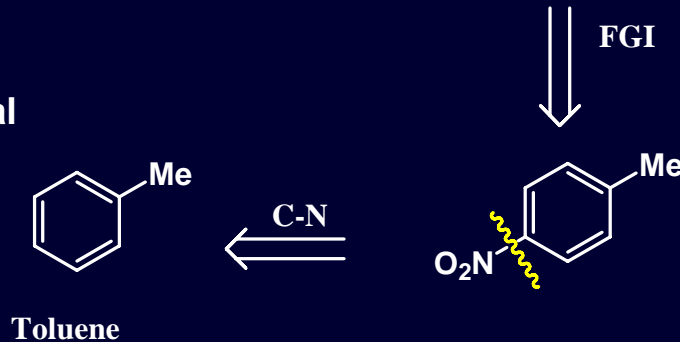
Retrosynthesis of Benzocaine

Retrosynthetic Pathway: Benzocain from toluene

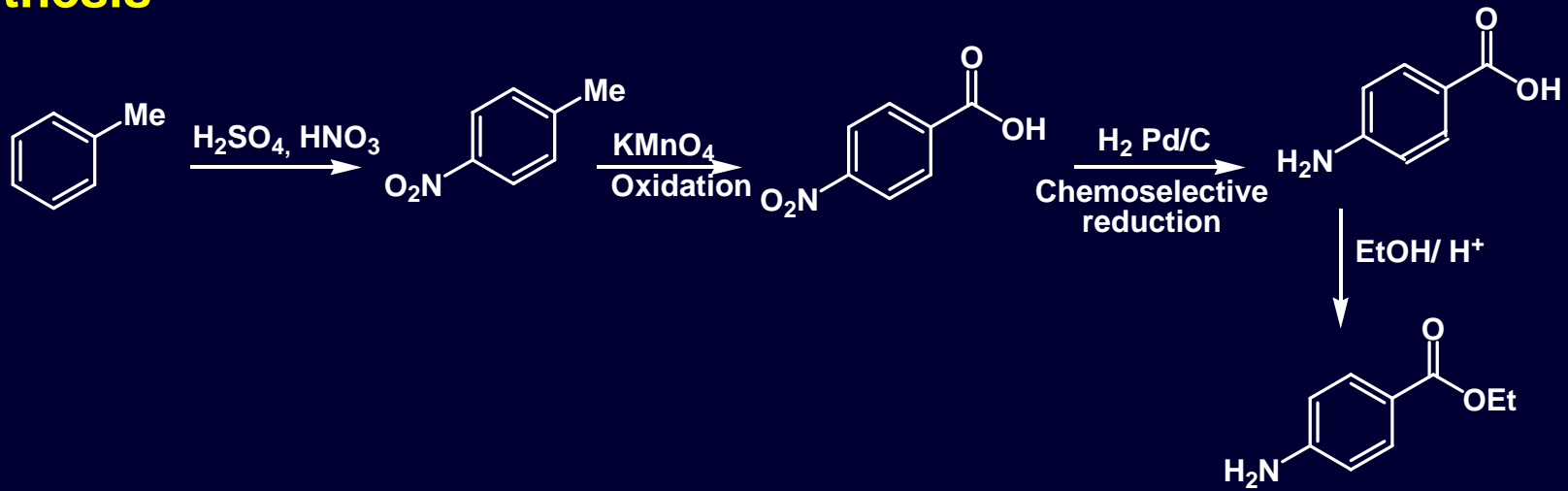


Benzocaine

- Toluene is a readily available starting material
- Me is activating and ortho/para-directing
- We know reagents for the synthon NO_2^+



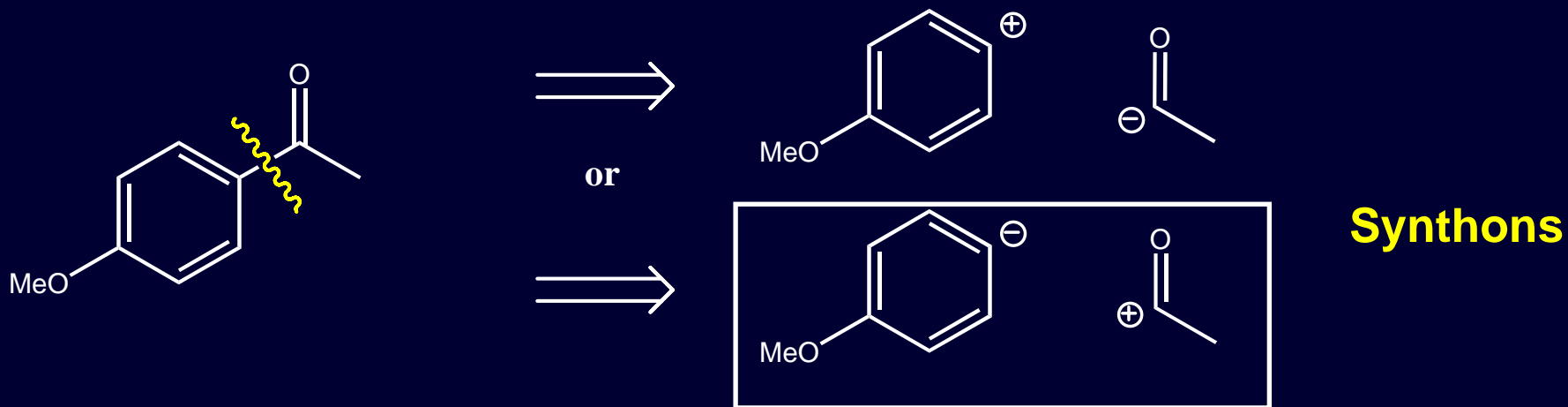
Synthesis



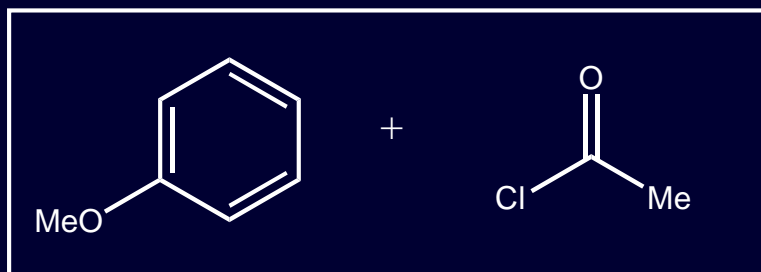
Eletrophilic Aromatic Substitution

How to identify the most suitable synthons and reagents?

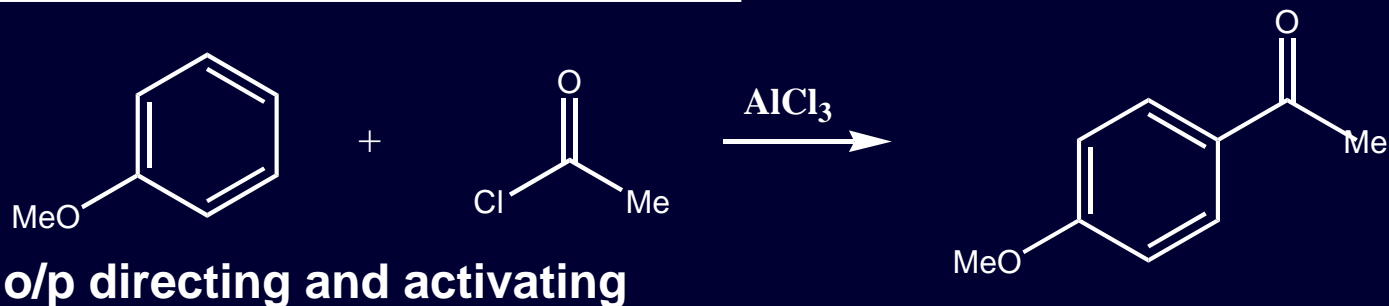
Which disconnection and which sense of polarity?



Reagents



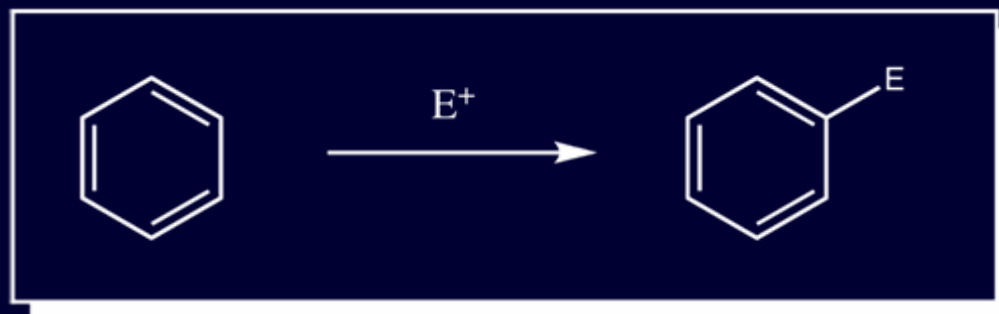
Synthesis



Eletrophilic Aromatic Substitution

How to identify the suitable synthons and reagents

Key reactions and Reagents for FGI in the context of Aromatic Chemistry



Synthon

Reagent

Reaction

R^+

RBr with Lewis acid

Friedel Craft alkylation

RCO^+

ROH/ H^+

Friedel Craft acylation

NO_2^+

$RCOCl$ with Lewis Acid

Nitration

Cl^+

HNO_3/H_2SO_4

Chlorination

Br^+

$Cl_2/FeCl_3$

Bromination

SO_3

Br_2 and Lewis Acid

Sulfonation

H_2SO_4

Electrophilic Aromatic Substitution

How to identify the most suitable synthons and reagents?

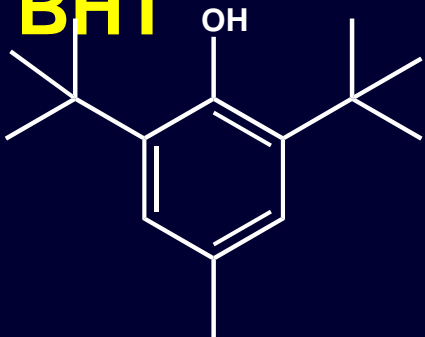
Key reactions and Reagents for FGI in the context of Aromatic Chemistry



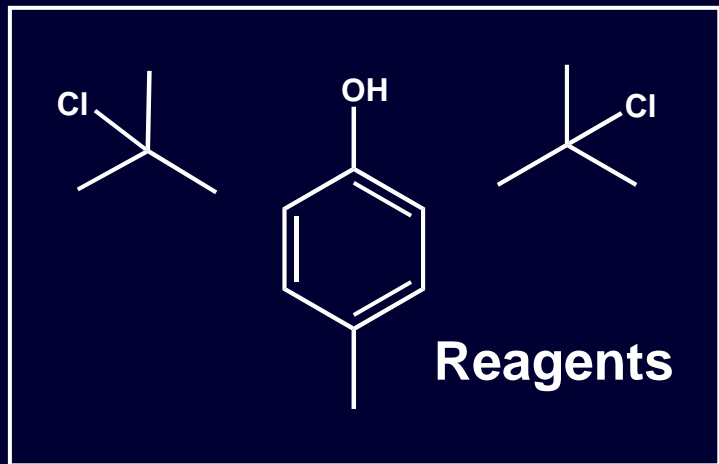
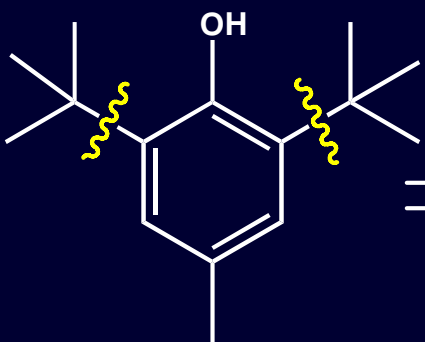
Y	X	Reagent
NO ₂	NH ₂	H ₂
COR	CH(OH)R	NaBH ₄
COR	CH ₂ R	Zn/Hg
CH ₃	COOH	KMnO ₄
COR	OCOR	RCO ₃ H
CN	COOH	Hydrolysis

Eletrophilic Aromatic Substitution

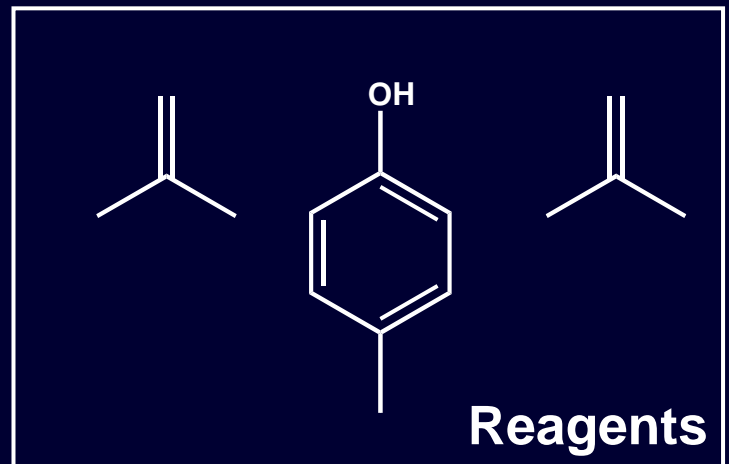
Retrosynthesis of BHT



Retrosynthesis of BHT = Butylated Hydroxy Toluene
BHT is an antioxidant and is used as a food preservative.

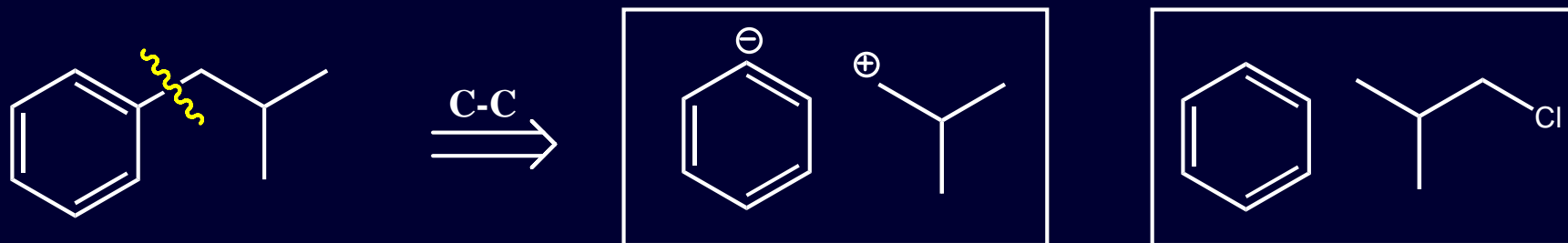


OR



Eletrophilic Aromatic Substitution

Friedel-Craft alkylation or acylation

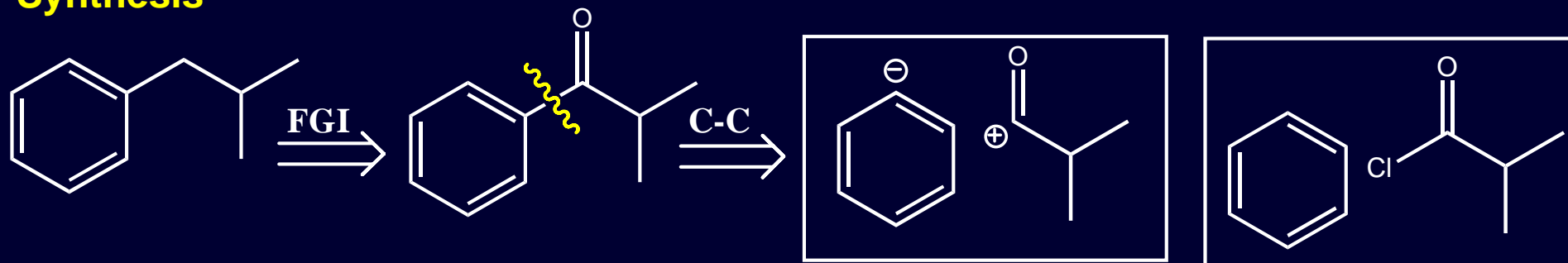


Problems:

1. Rearrangement of alkyl for more stable carbocation.
2. problem of polyalkylation



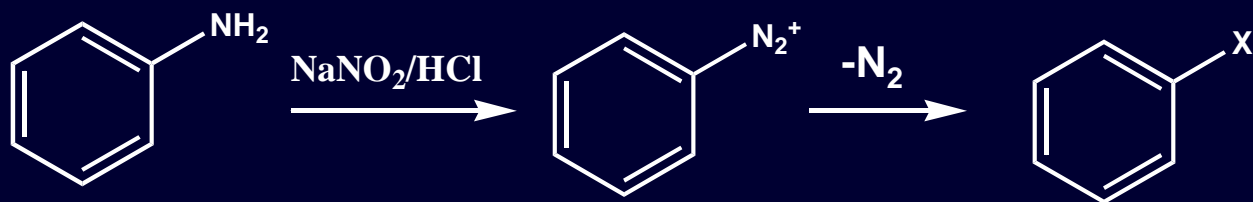
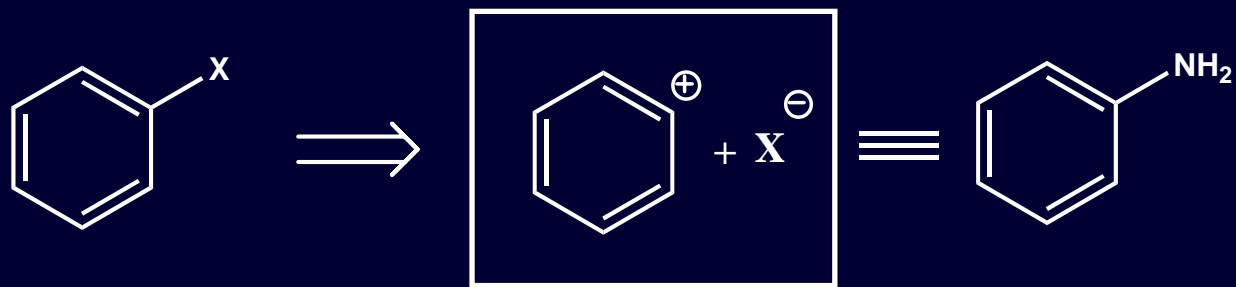
Synthesis



SUITABLE

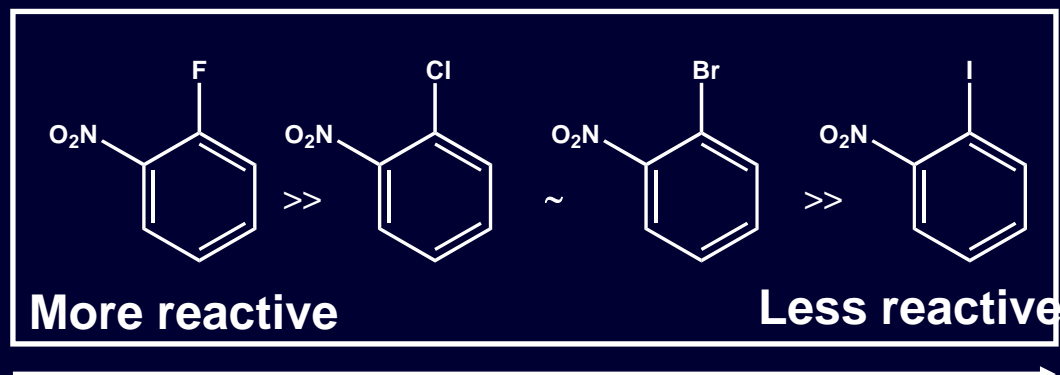
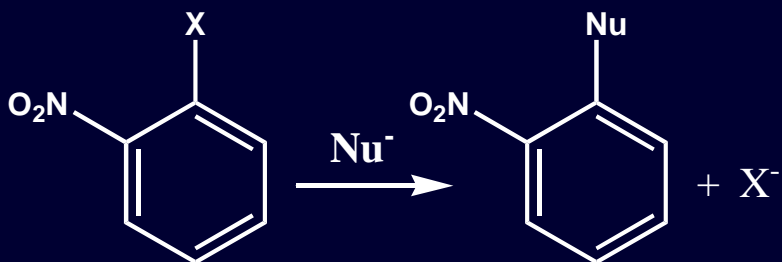
Nucleophilic Aromatic Substitution

SN₁ for nucleophilic aromatic substitution: Diazonium Chemistry



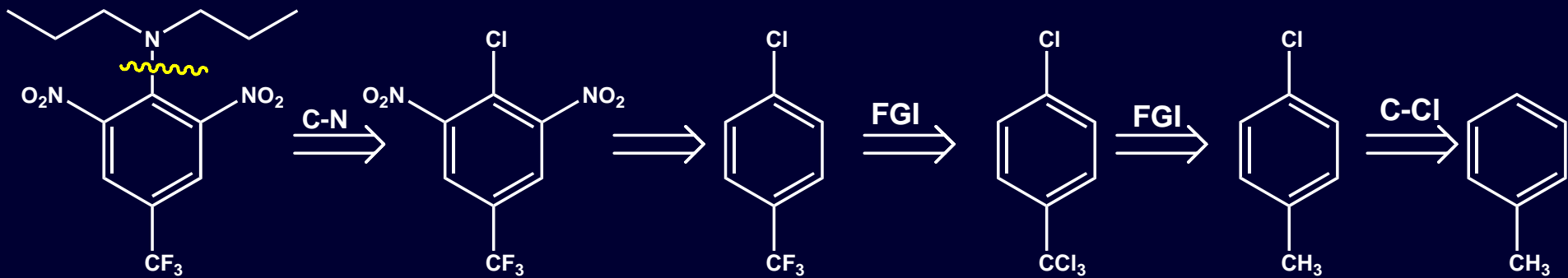
X	Reagent
OH	H ₂ O
OR	ROH
CN	CuCN
Cl	CuCl
Br	CuBr
I	KI
Ar	ArH
H	H ₃ PO ₂

Addition-Elimination

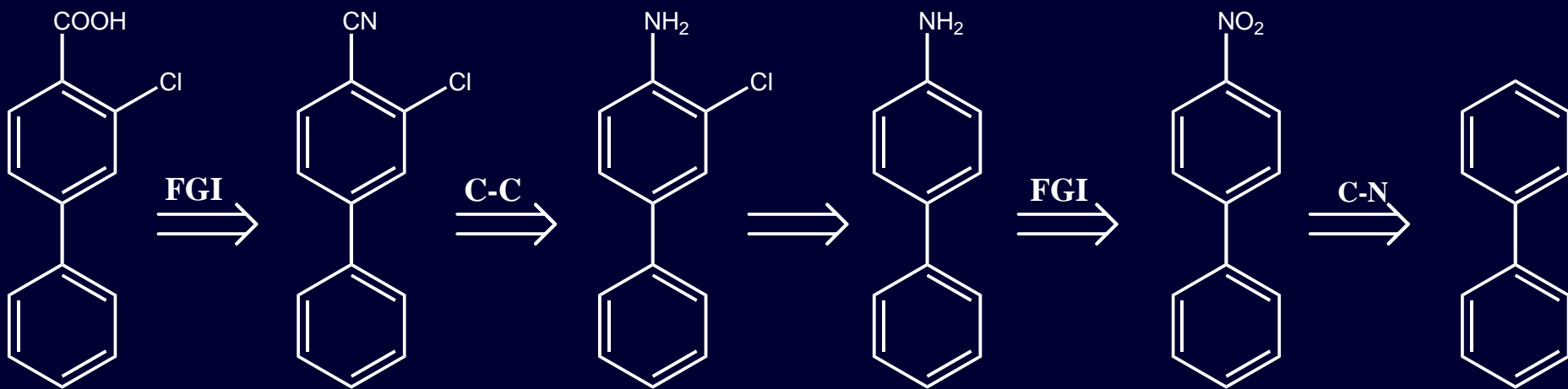


Aromatic Substitution

Retrosynthesis of Trifluoralin B Herbicide



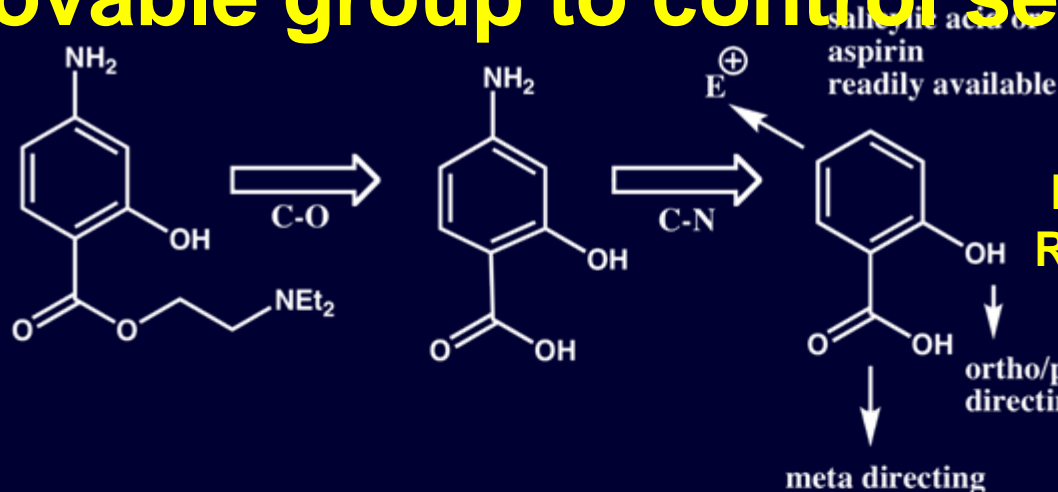
Retrosynthesis of biphenyl derivative



Aromatic Substitution

The use of removable group to control selectivity

Retrosynthesis
of Propoxycaine
Local anaesthetic

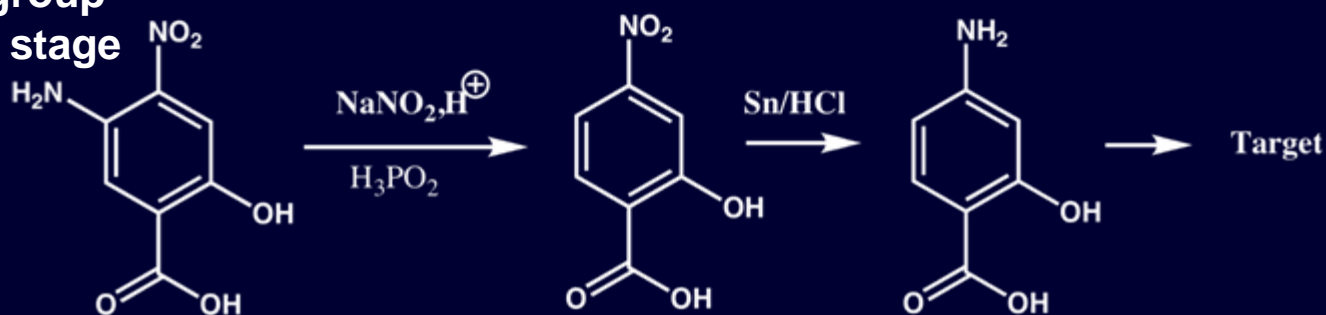
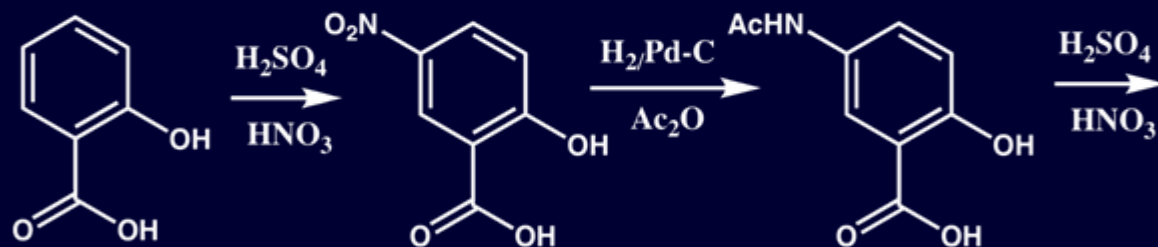


Problem of
Regiocontrol

Synthetic Route
to Propoxycaine

Solution:

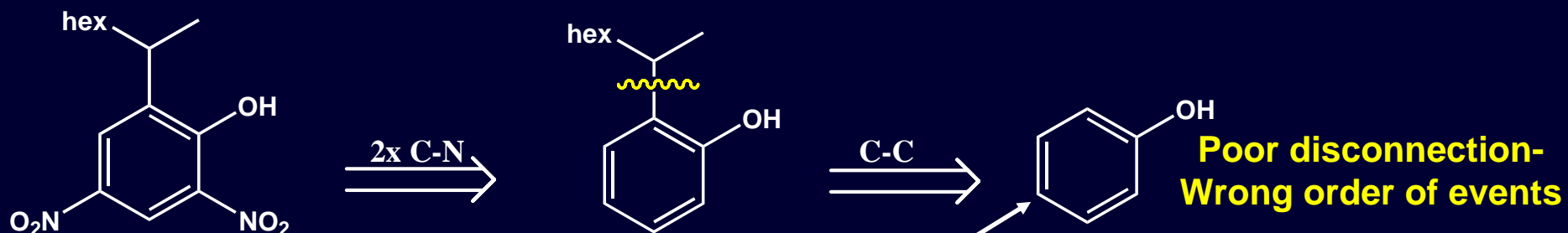
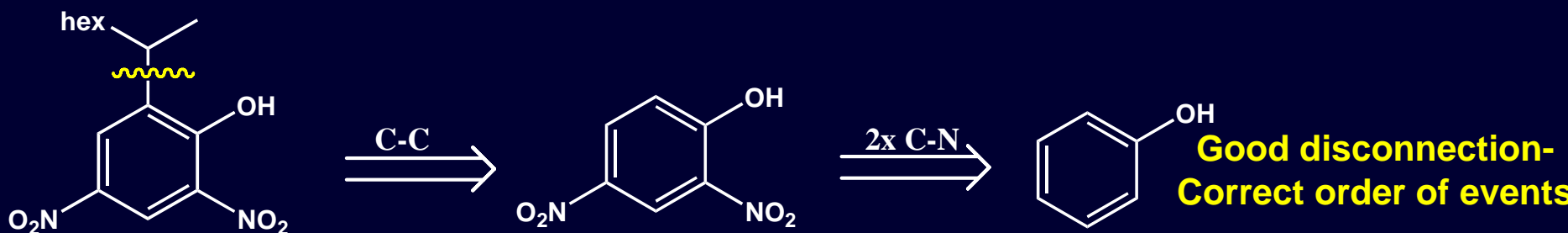
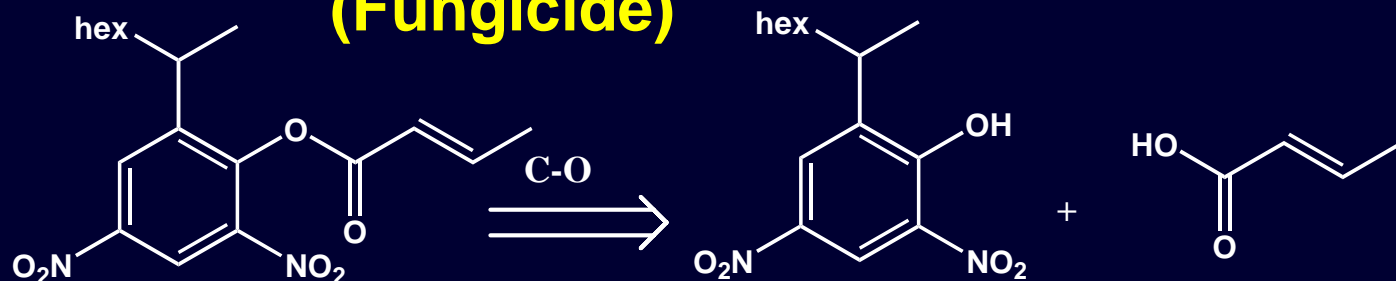
Introduction of a temporary group
that will be removed at a later stage
of the synthesis



Aromatic Substitution

The importance of order of events- disconnection

Retrosynthesis of Dinocap (Fungicide)



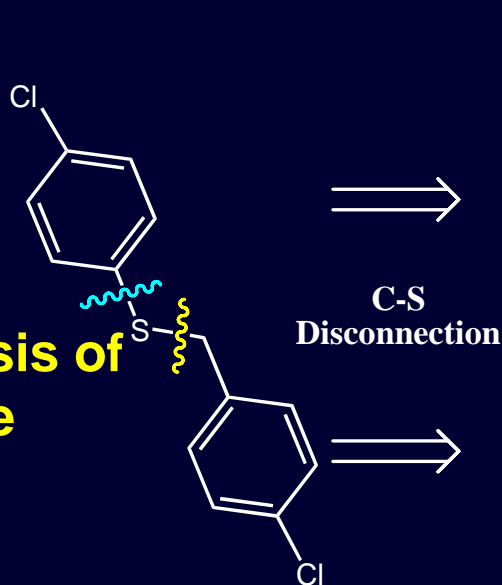
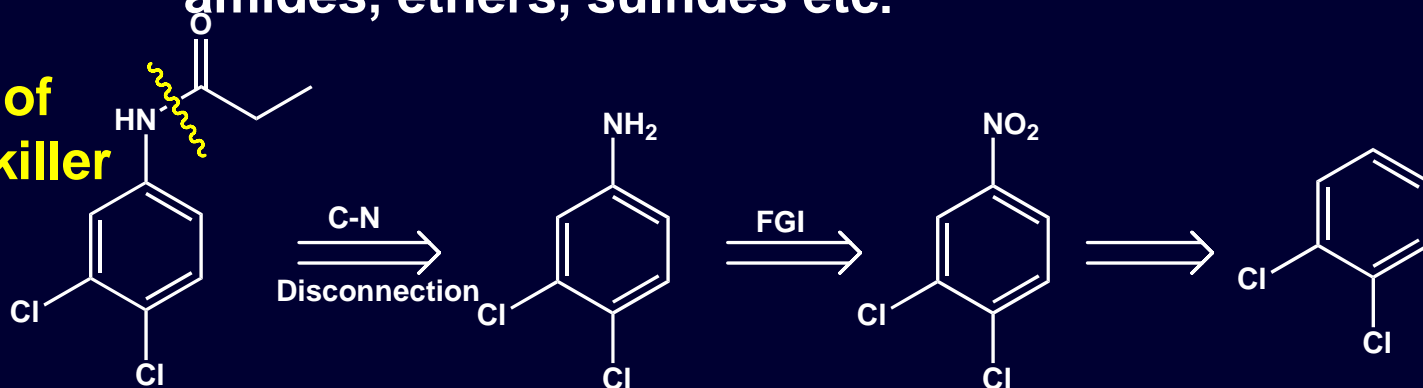
Para position not blocked to force alkylation ortho

One Group and Two Groups Disconnection

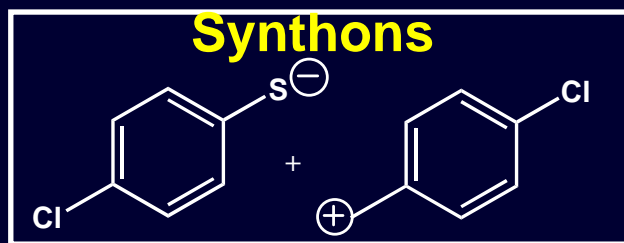
One Group C-X Disconnection

For compounds consisting of two parts joined by a heteroatom (X), disconnect next to the heteroatom. This guideline works for esters, amides, ethers, sulfides etc.

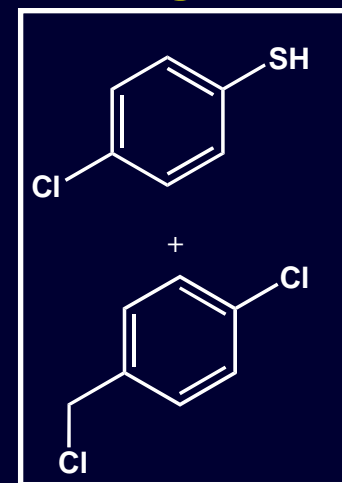
Retrosynthesis of Propanil Weed killer



Synthons



Reagents



One Group and Two Groups Disconnection

Chemoselectivity

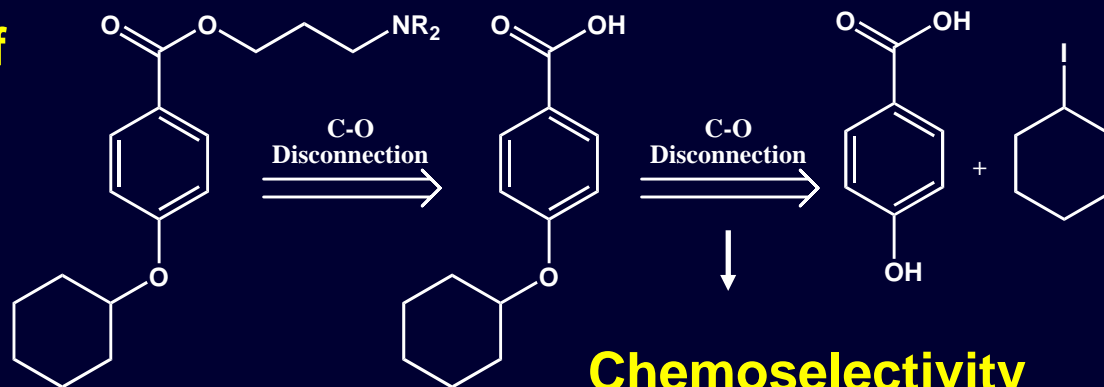
Chemoselectivity arising from two groups of different reactivity.

The preferential retrosynthetic route should avoid chemoselectivity problems.

In practice, this means that one should disconnect reactive groups first.

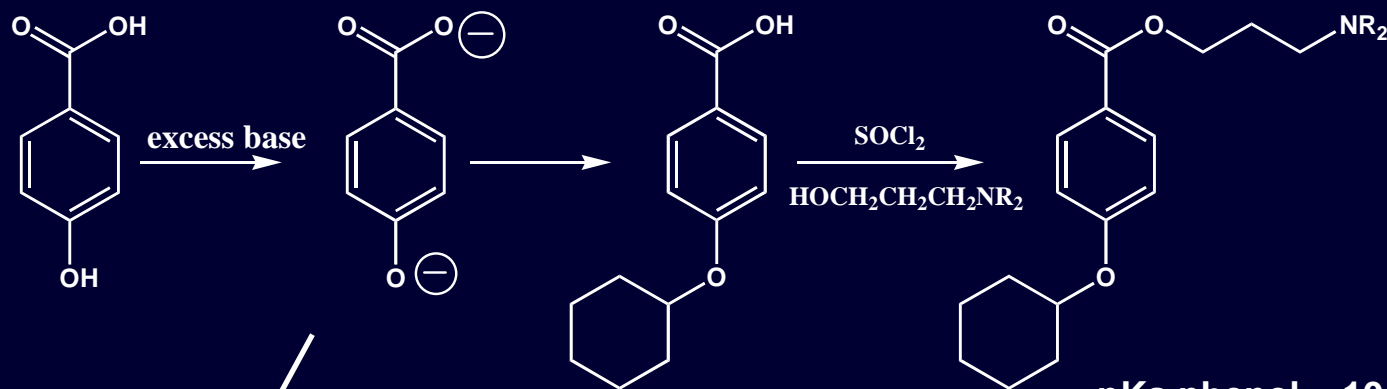
To solve chemoselectivity problems, it is very often critical to choose carefully reaction conditions for the forward synthetic step.

Retrosynthesis of Cyclomethycaine (anaesthetic)



Chemoselectivity

Synthesis of Cyclomethycaine



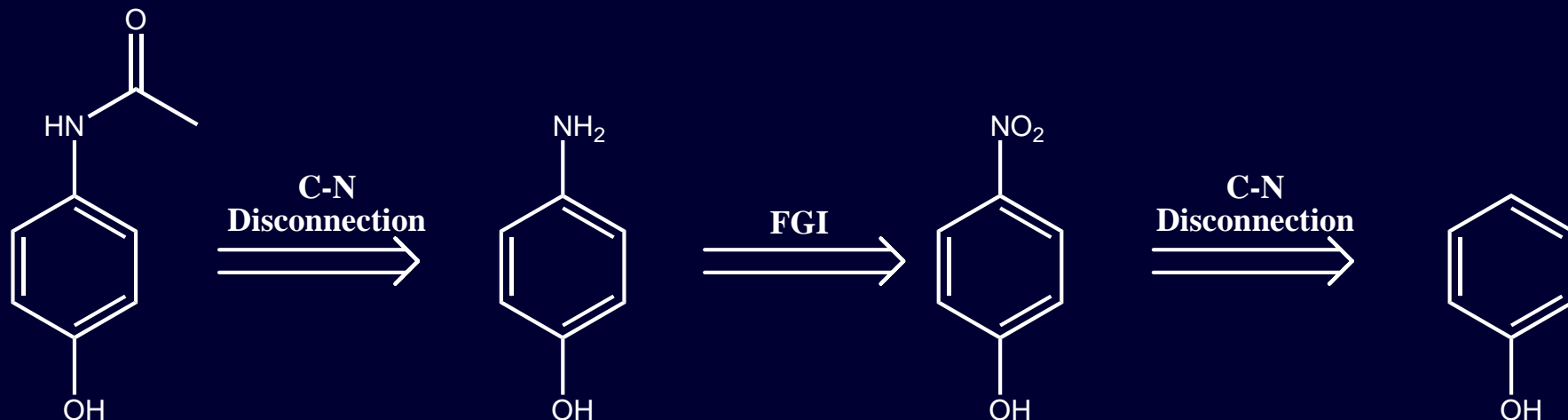
pKa phenol ~ 10
pKa benzoic acid ~ 4

Both groups ionised pH > 10

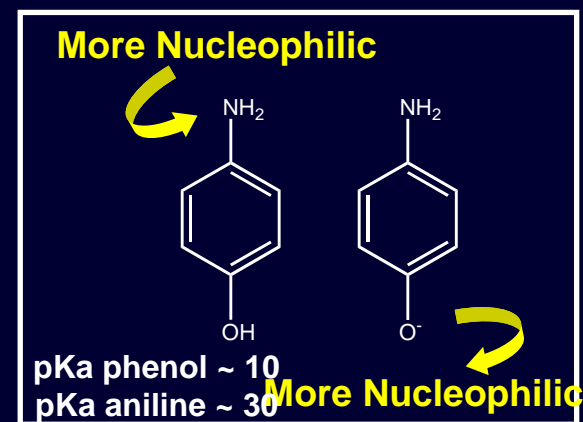
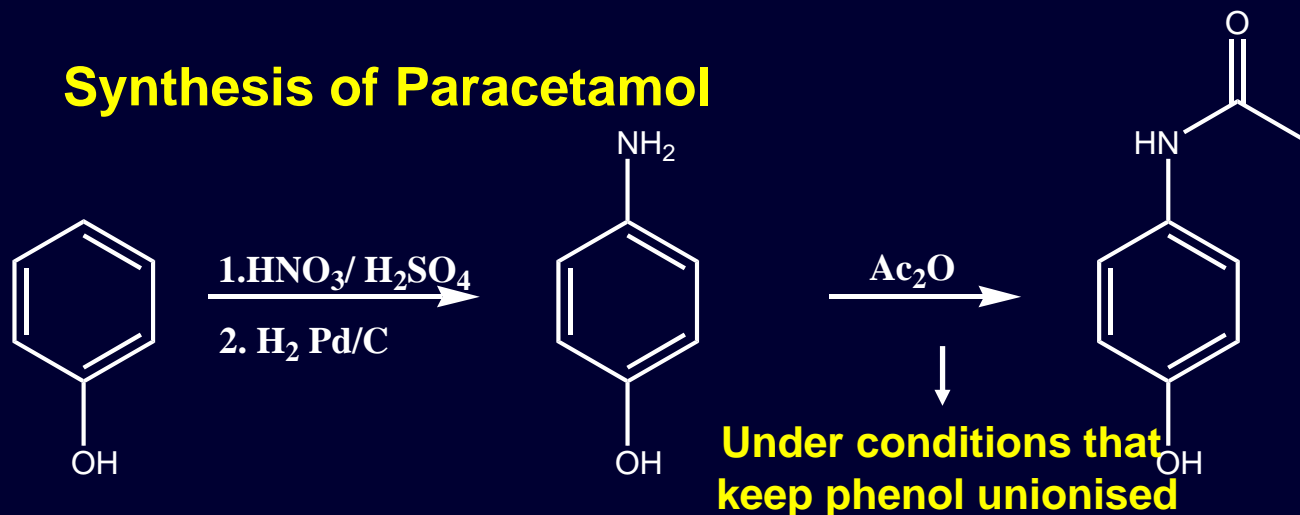
One Group and Two Groups Disconnection

Chemoselectivity

Retrosynthesis of Paracetamol (Analgesic)



Synthesis of Paracetamol



Two Groups C- X Disconnection

1,1-Difunctionalised compounds

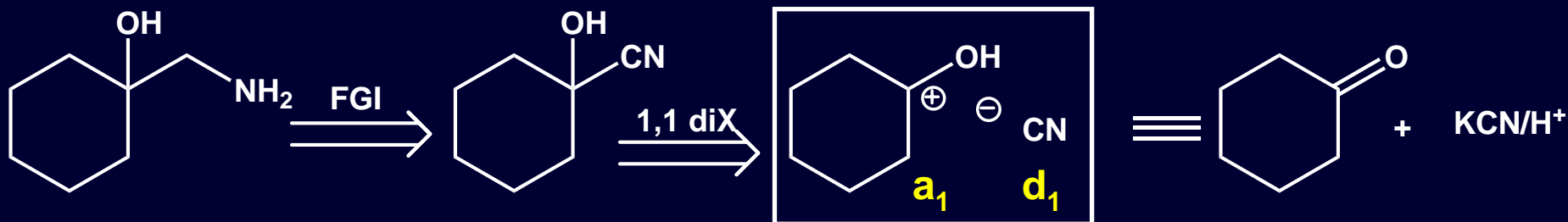
Example 1



Example 2



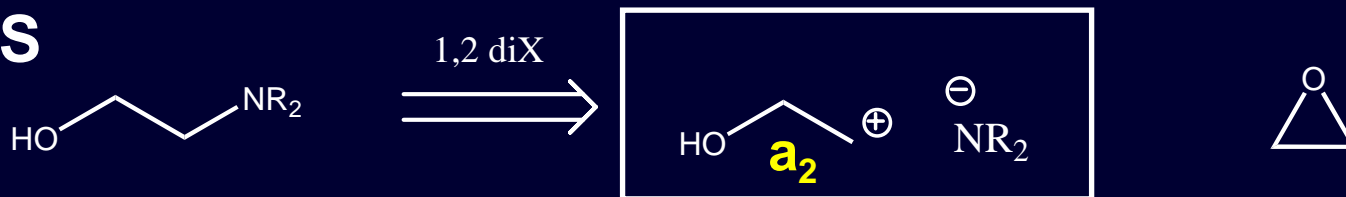
Example 3



Two Groups C- X Disconnection

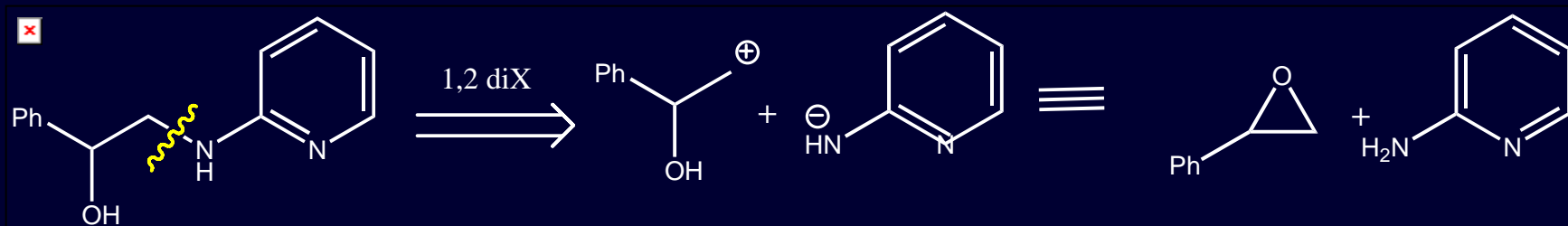
1,2-difunctionalised compounds

ALCOHOLS

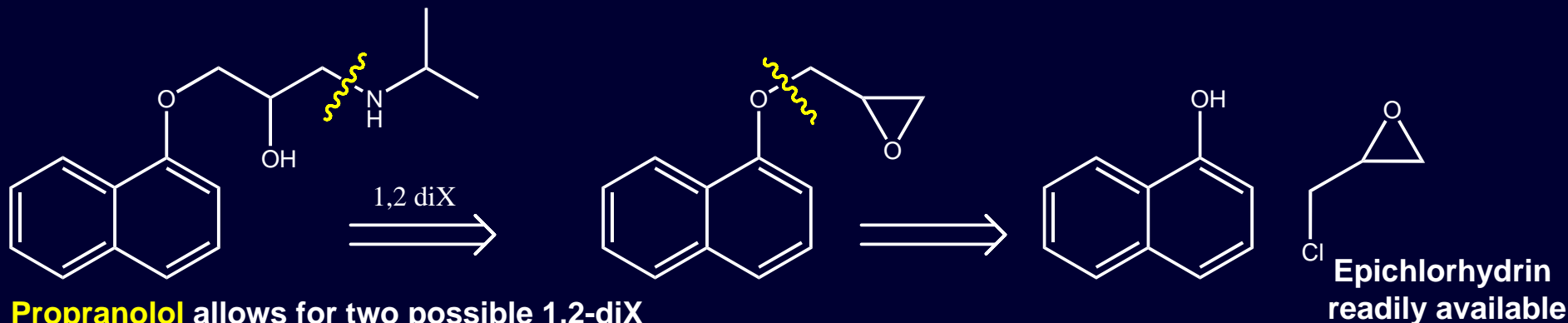


Important synthon Reagent is epoxide

Example 1: Phenyramidol (muscle relaxant)



Example 2: Propranolol (beta-blocker reduces blood pressure)

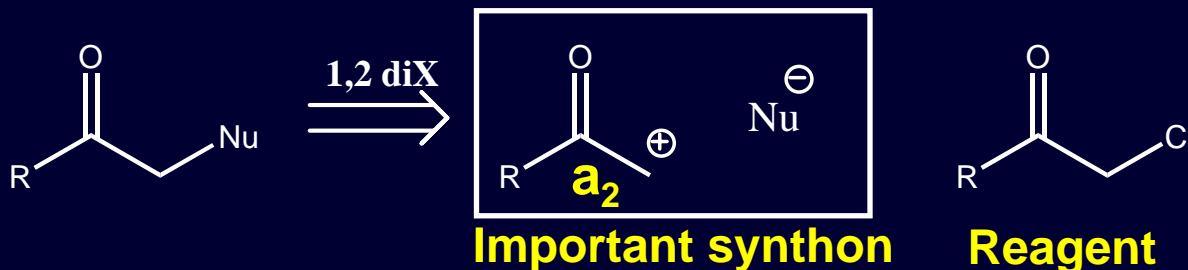


Propranolol allows for two possible 1,2-diX but it is best to disconnect the more reactive amine group first.

Two Groups C-X Disconnection

1,2-difunctionalised compounds

CARBONYLS



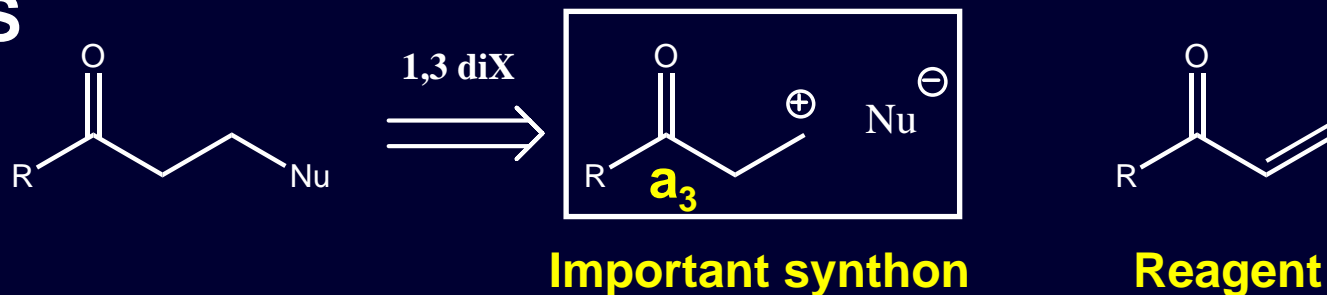
Note: α -chloro or bromo highly reactive electrophiles and Control of mono-*versus* polyhalogenation.

	k rel
Me-Cl	200
iPrCl	0.02
allylCl	80
MeOCH ₂ Cl	920
PhCOCH ₂ Cl	10000

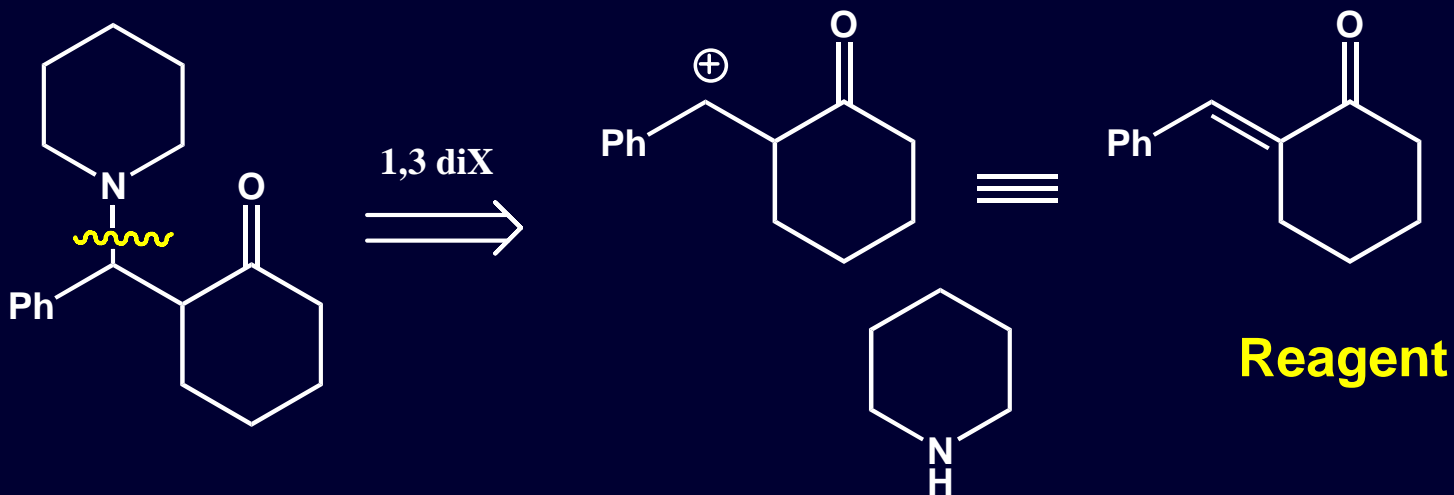
Two Groups C- X Disconnection

1,3-difunctionalised compounds

CARBONYLS



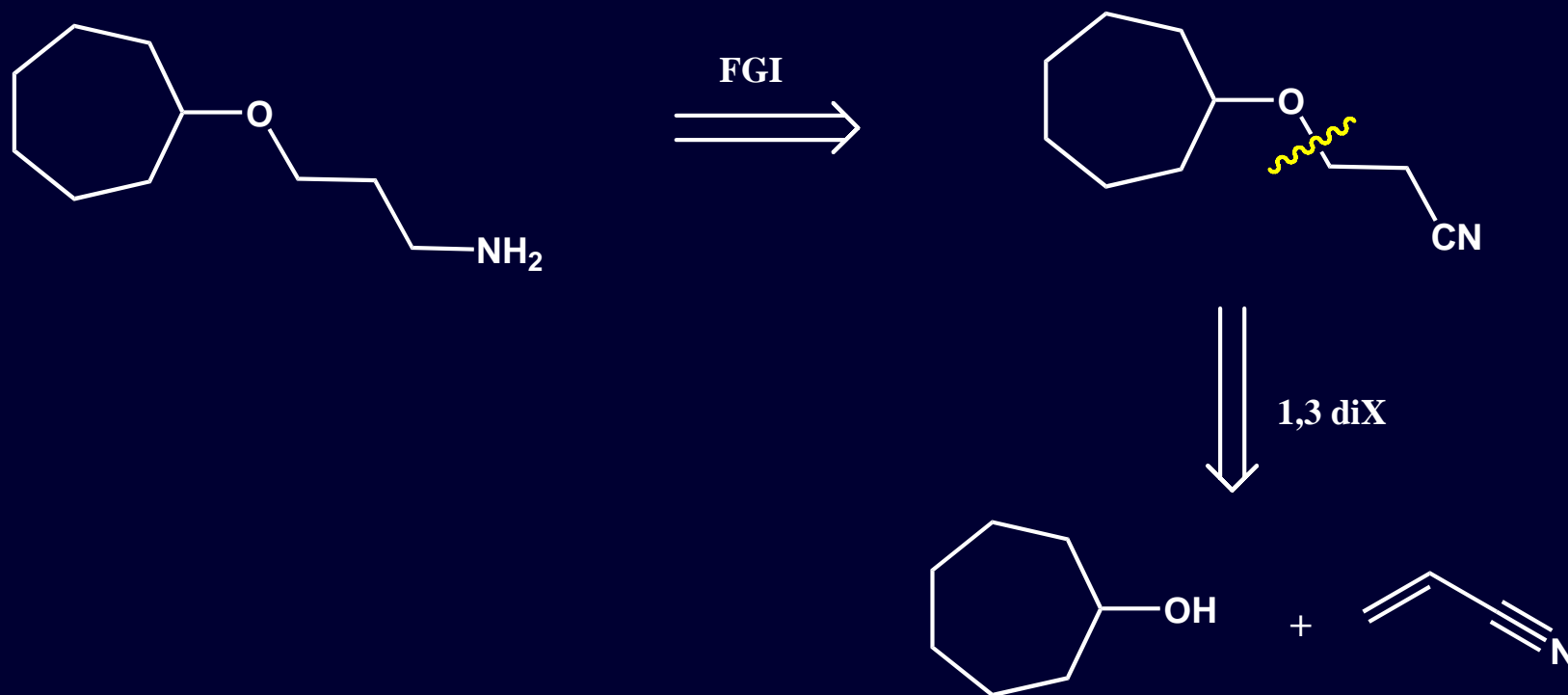
Example 1: Atropine (Muscle relaxant)



Two Groups C- X Disconnection

1,3-difunctionalised compounds

NITRILES



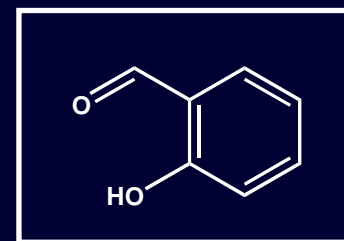
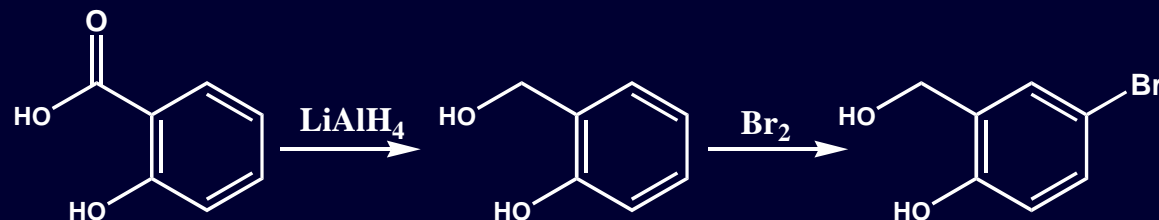
Protecting Group Chemistry

To avoid if you can... Each protection event adds two steps:
protection-deprotection

Synthesis requiring protecting group chemistry

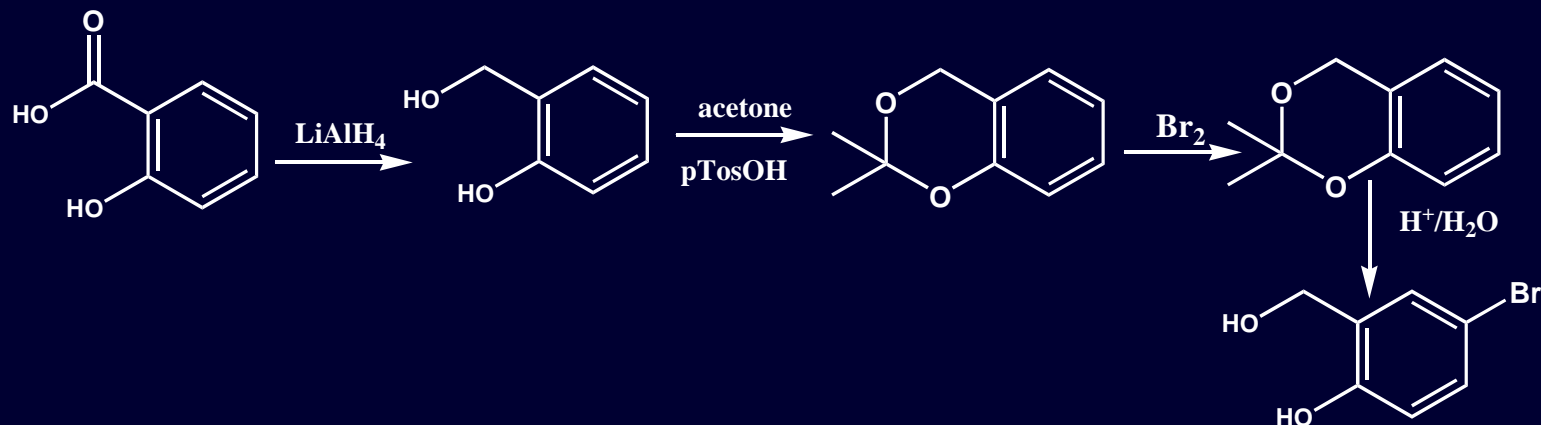


Synthesis:



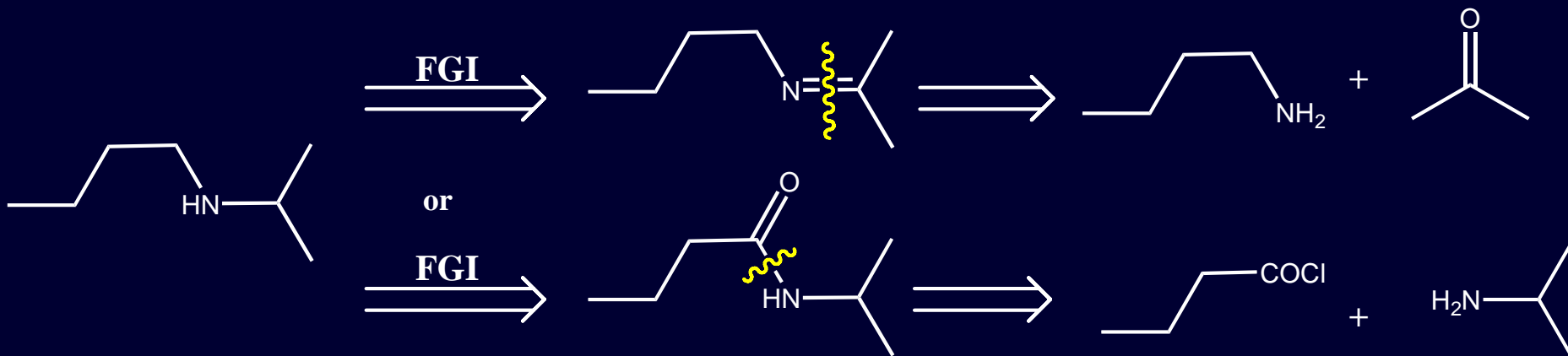
Side-product
 Br_2 is also an oxydant

Revised Synthesis:

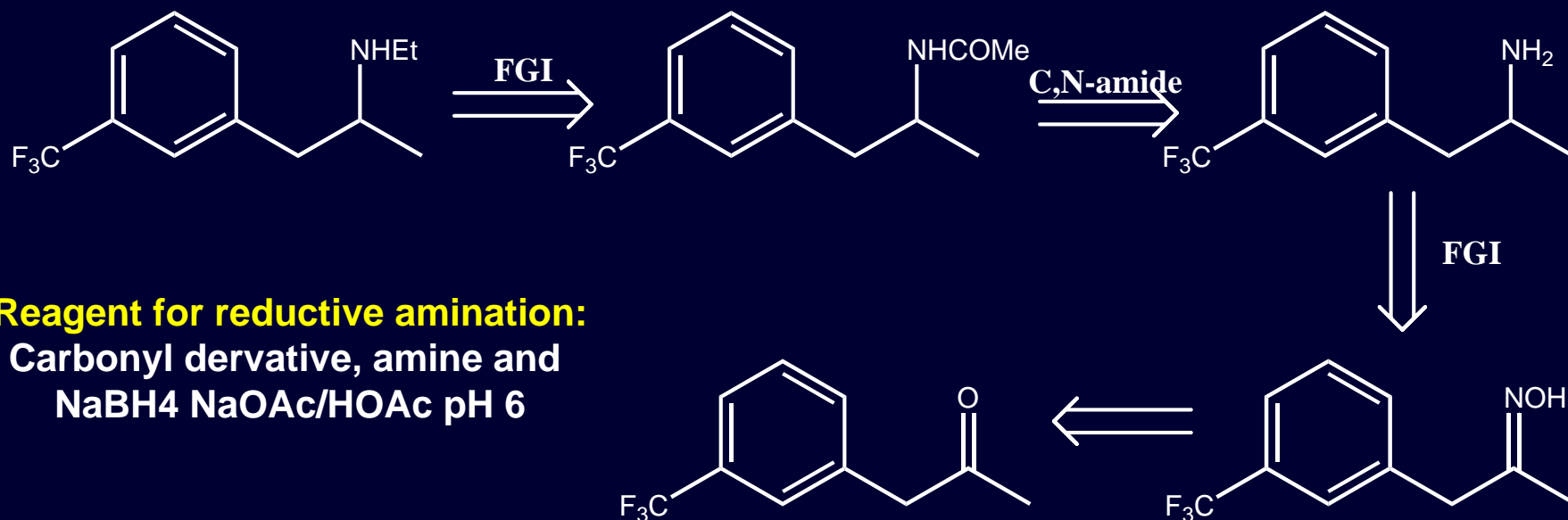


Amines and One Group C-C Disconnections

Synthesis of secondary amines



Retrosynthesis of Fenfluramine (Drug CNS)



Reagent for reductive amination:
Carbonyl derivative, amine and
NaBH₄ NaOAc/HOAc pH 6

Amines and One Group C-C Disconnections

Synthesis of primary amines

These targets are not conveniently prepared from unsubstituted imines [unstable] or primary amides.

Alternative and better solutions are available and include:

- the reduction of *cyano* group
- the reduction of *azido* group
- the reduction of *oximes*
- alkylation and reduction of *nitro* compounds
- the *Ritter* reaction followed by hydrolysis
- the *Gabriel* synthesis

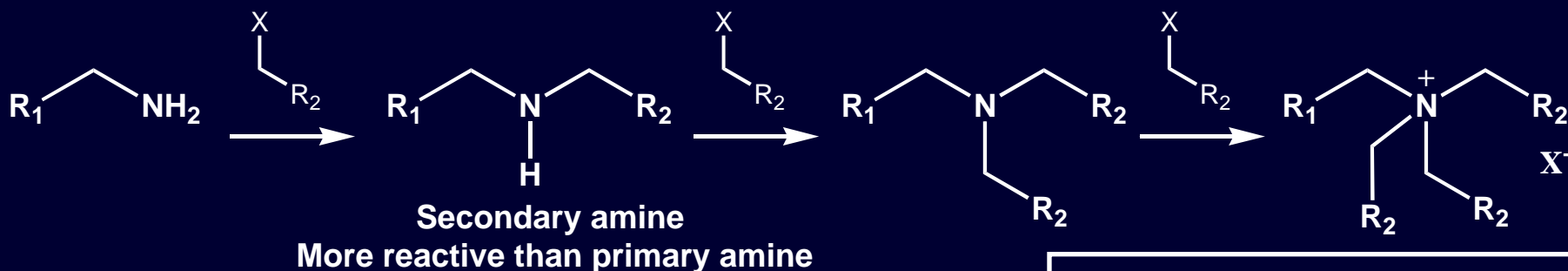
Amines and One Group C-C Disconnections

The synthesis of amines is slightly more complicated in comparison with the synthesis of e.g. ethers or sulfides because the product of an N-alkylation is at least as reactive as the starting material, therefore leading to complex reaction mixtures.

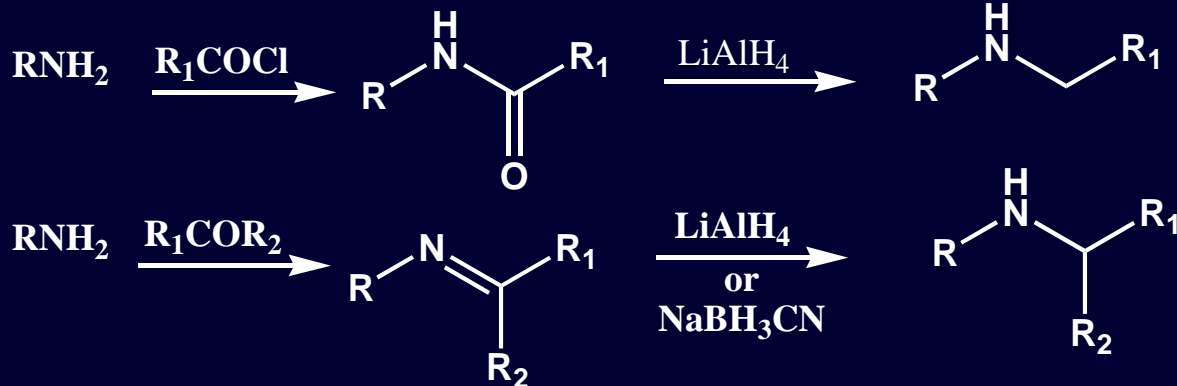


Bad disconnection

The problem of polyalkylation



The solution: FGI prior to disconnection

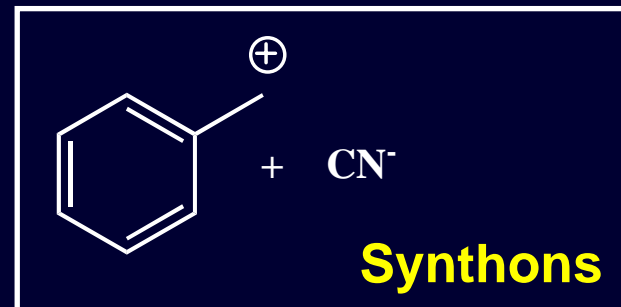
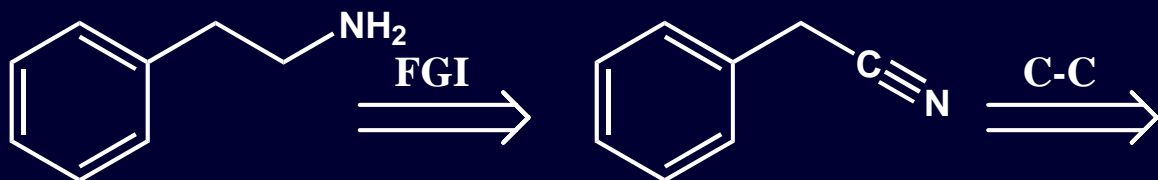


Suitable FGI involved amides, imines or oximas.

Amines and One Group C-C Disconnections

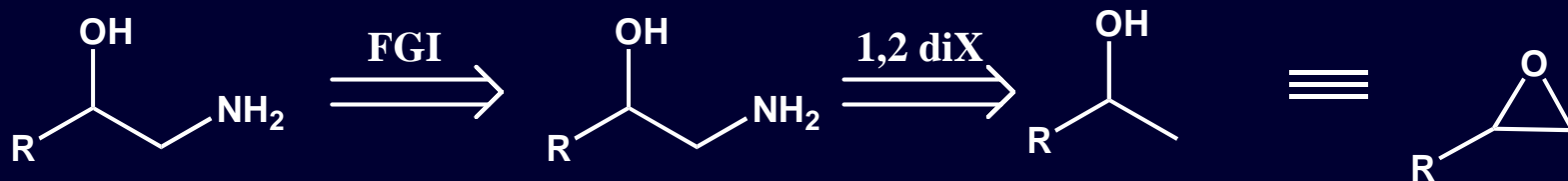
Example 1

AMINES



Reagent for reduction of cyano into amine is LiAlH_4

Example 2



Reagent for reduction of azide into amine: $\text{PPh}_3 + \text{NaN}_3$

Example 3



Amines and One Group C-C Disconnections

AMINES

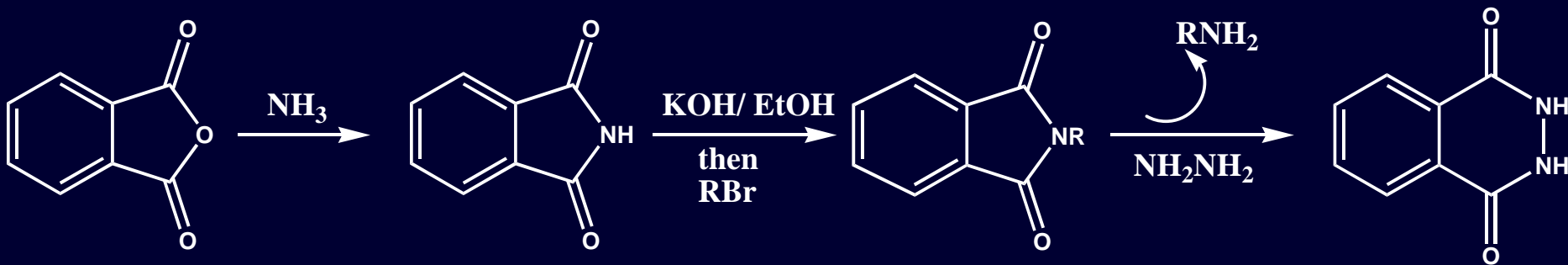
Example 4 Ritter Reaction



Ritter Reaction: VIA CARBOCATION

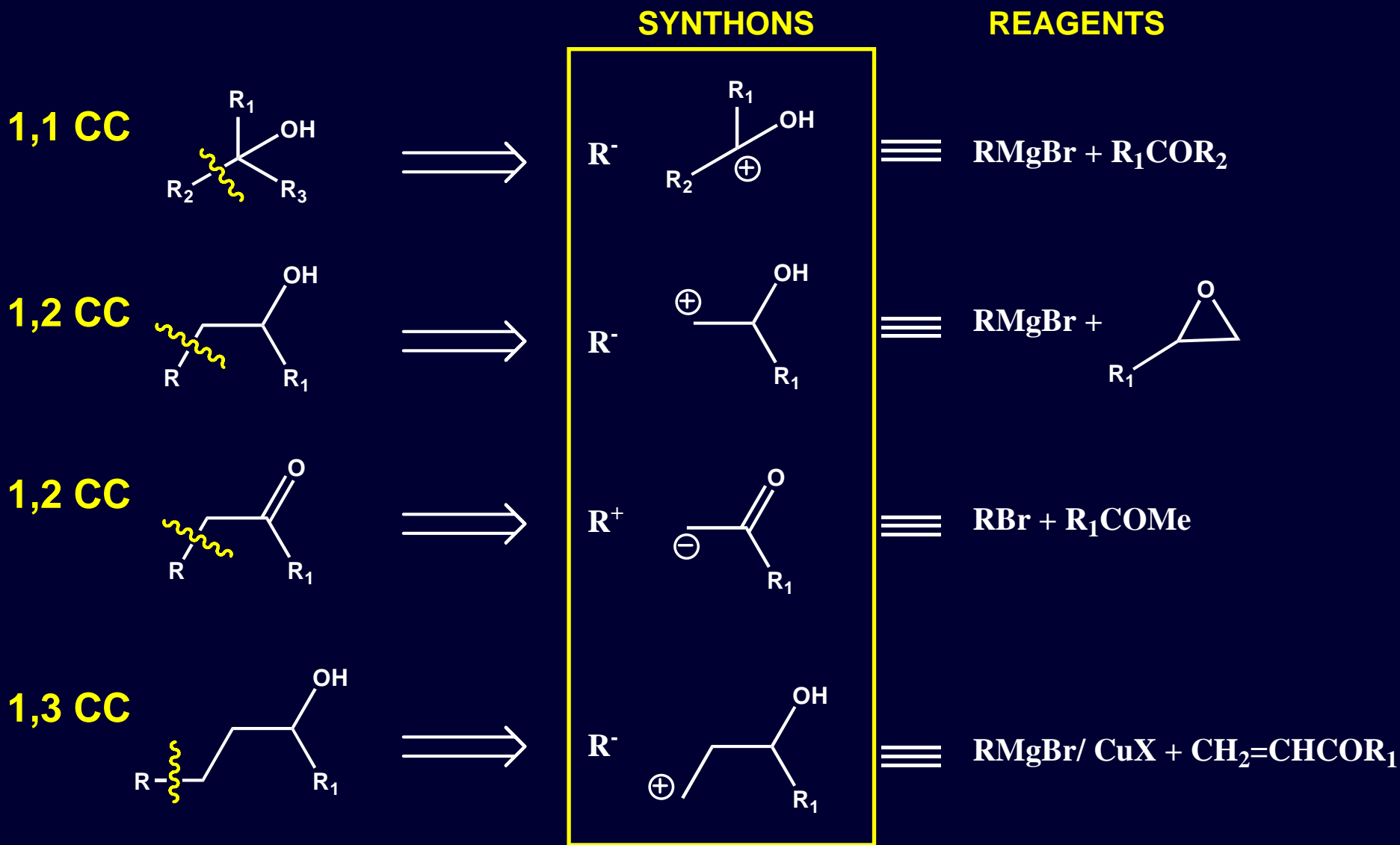


Example 5 Gabriel Reaction



Amines and One Group C-C Disconnections

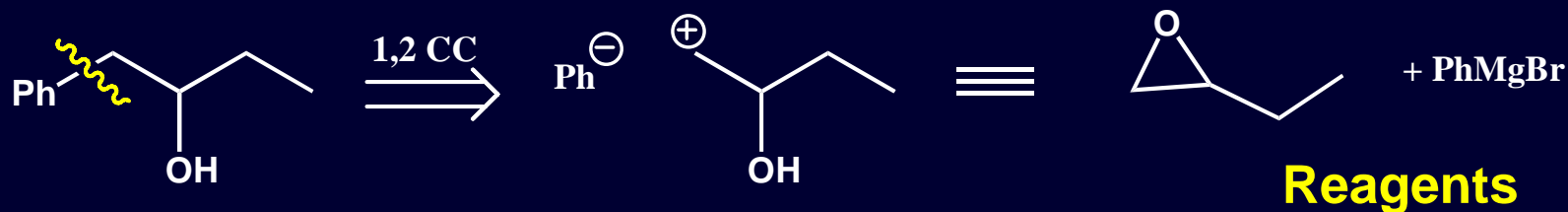
One Group C-C Disconnection



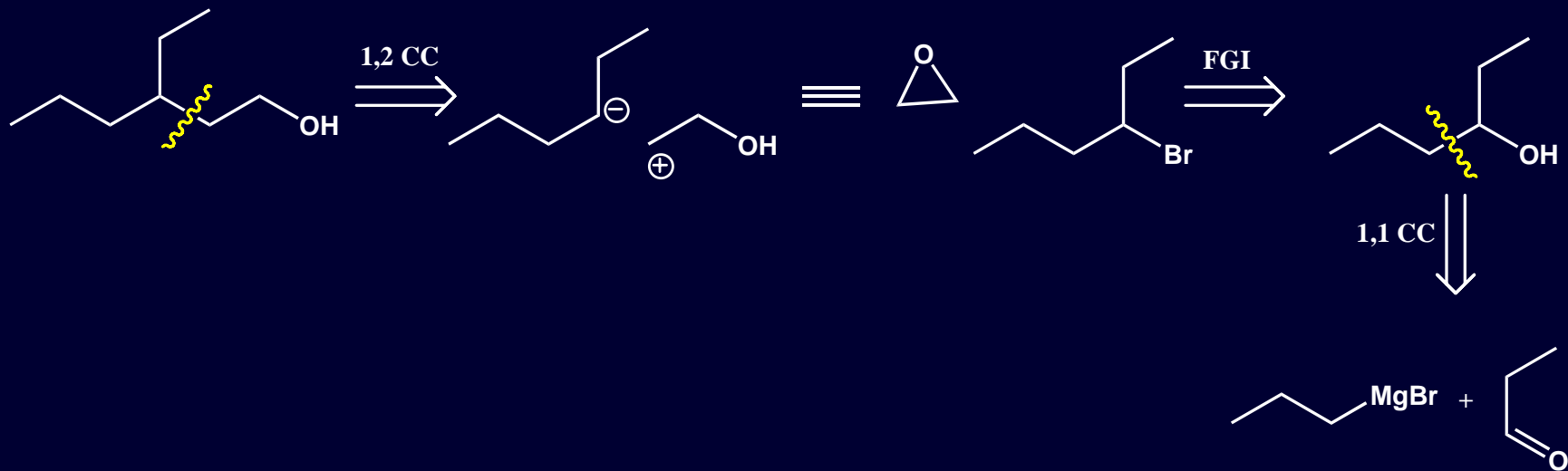
Amines and One Group C-C Disconnections

One Group C-C Disconnection- Alcohols

1,2CC Disconnections leading to alcohols



Example

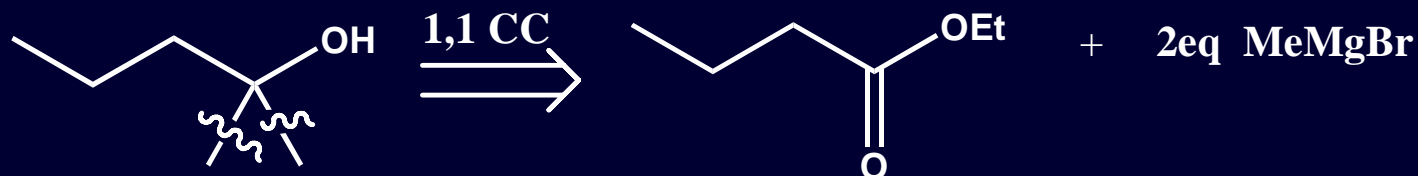


Reagents: PBr_3 or the Apple Reaction [$\text{PPh}_3 / \text{CBr}_4$]

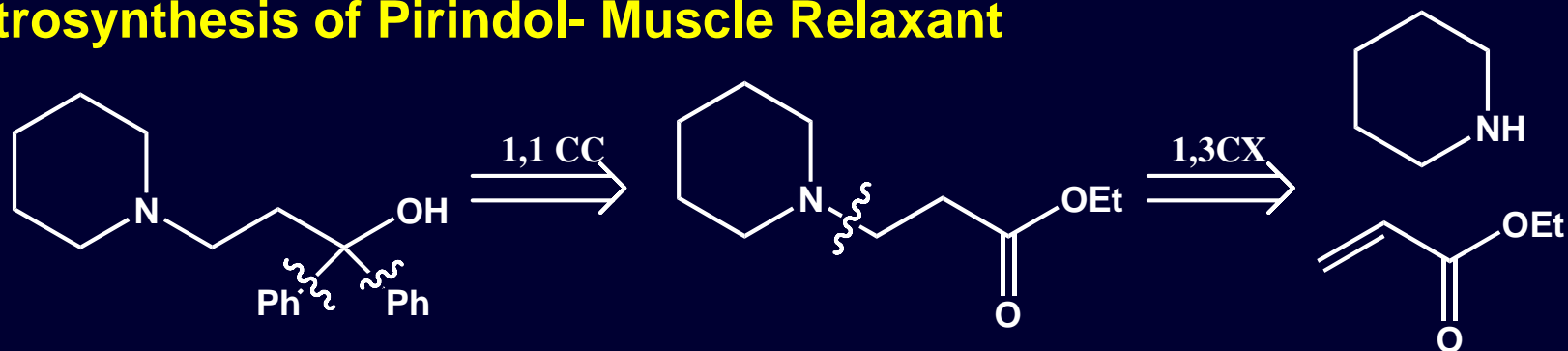
Amines and One Group C-C Disconnections

One Group C-C Disconnection- Alcohols

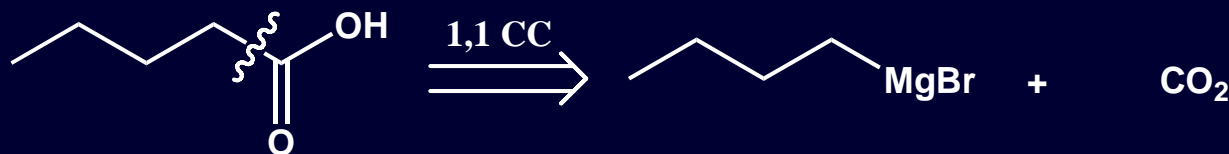
1,1CC Disconnection leading to alcohols



Retrosynthesis of Pirindol- Muscle Relaxant



1,1CC Disconnection leading to carboxylic acid



Synthons **Reagents**

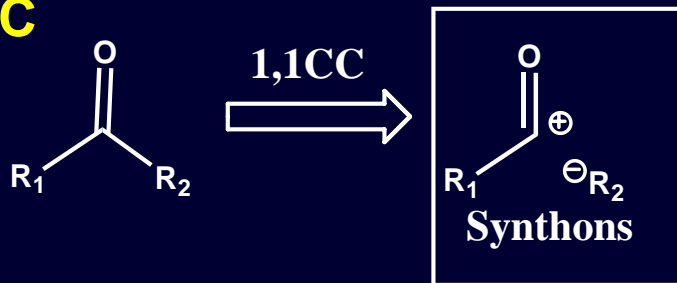
COOH
COOH

CO₂
NaCN

Amines and One Group C-C Disconnections

One Group C-C Disconnection- Carbonyl Compound as Target

1,1 CC

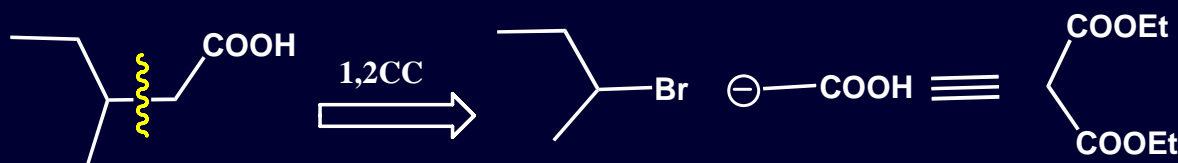


1) The use of ester and Grignard as double addition will generate the alcohol

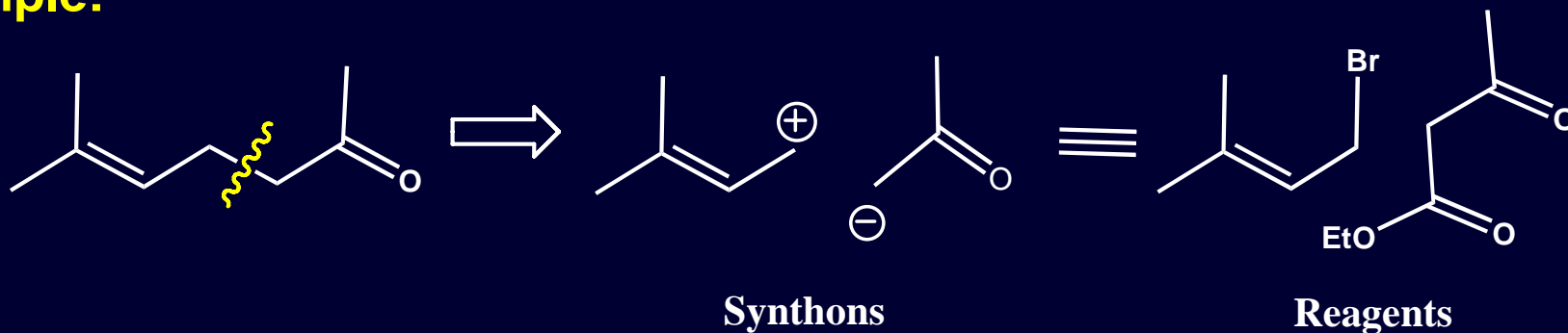
2) The use of less reactive organocadmium like R₁CdR₂

Alternative routes are: ketones from nitriles, from acids and from Weinreb amides

1,2CC

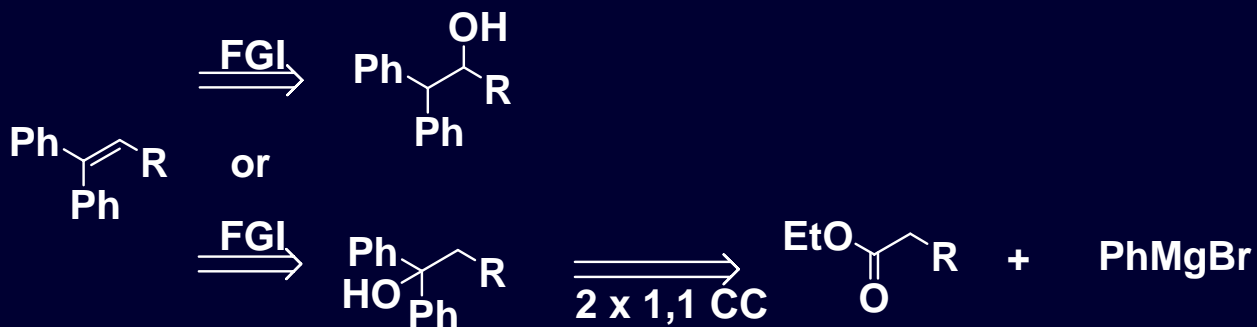


Example:

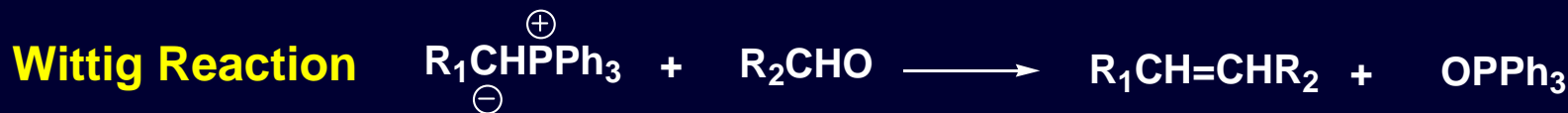
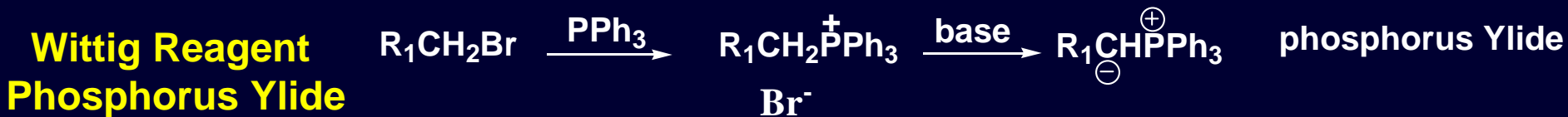


Synthesis and Use of alkenes and Alkynes

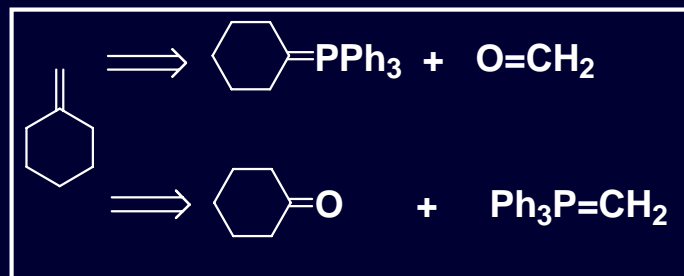
Synthesis of Alkenes via elimination



Synthesis of Alkenes via Wittig Olefination

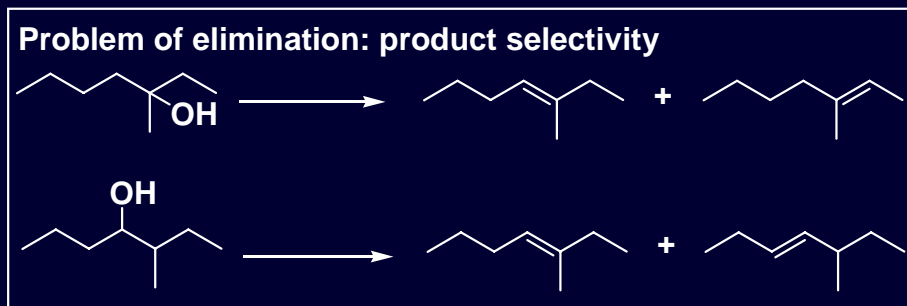
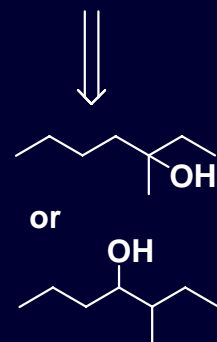
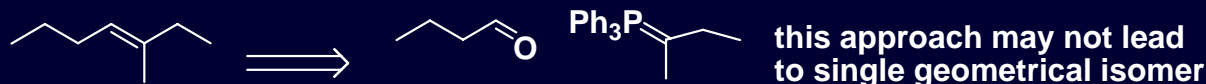


Decision making:



Synthesis and Use of alkenes and Alkynes

Elimination or Wittig Olefination?

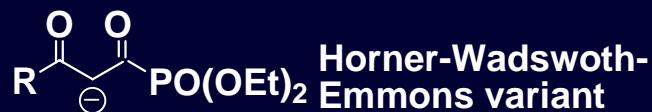


Stereochemistry of the Wittig Reaction

E/Z geometry is a function of the structural features of the phosphorus ylid

STABILISED YLIDE \longrightarrow E ALKENES

UNSTABILISED YLIDE \longrightarrow Z ALKENES

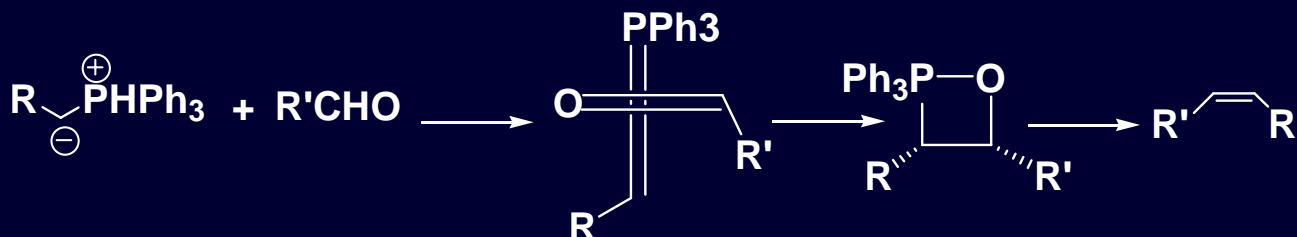


Synthesis and Use of alkenes and Alkynes

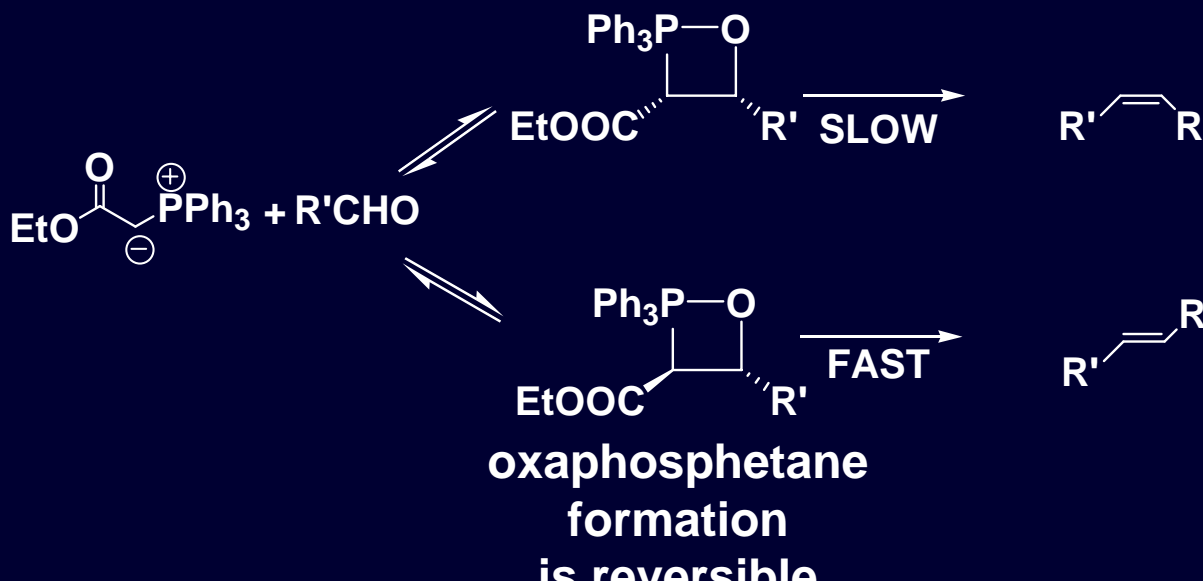
Stereochemistry of the Wittig Reaction

E/Z geometry is a function of the structural features of the phosphorus ylid

Z selective Wittig IRREVERSIBLE



E selective Wittig REVERSIBLE



Synthesis and Use of Alkenes and Alkynes

Synthesis of E,E or E,Z Diene

→ Solution needs to take into account E,Z or E,E geometry of the diene



Synthesis Alkenes upon reduction of Alkenes

For Z isomer Hydrogenation [Lindlar's catalyst]

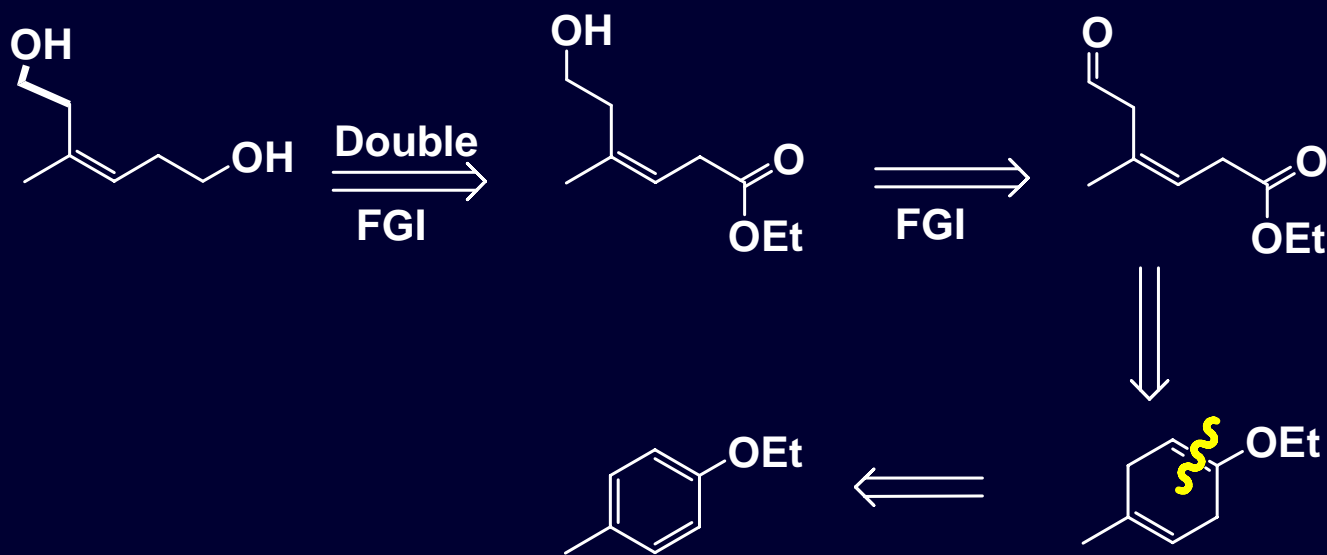
For E isomer Na/NH₃ reduction

Revision: Mechanism of Na-ammonia reduction SET - origin of E selectivity

Synthesis and Use of Alkenes and Alkynes

Problem for trisubstituted alkenes: Control over E/Z geometry

One solution to the problem: Synthesis involving a cyclic intermediate

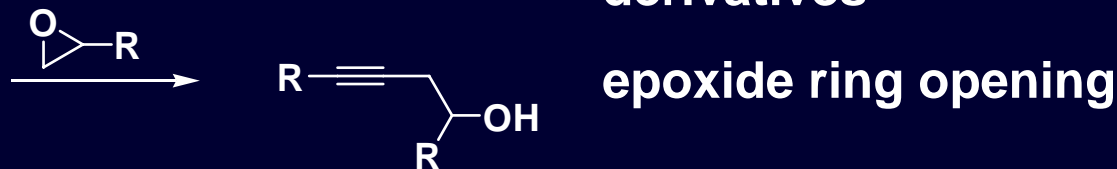
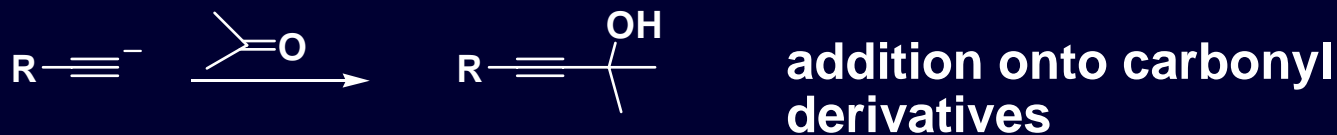
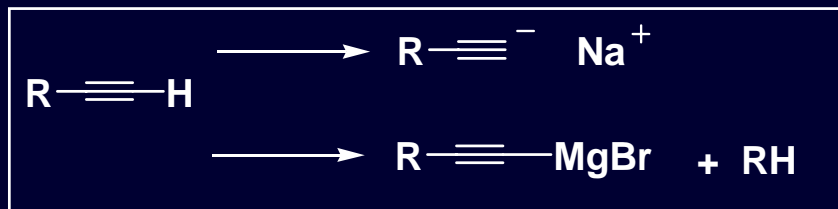


Revise Birch reduction:

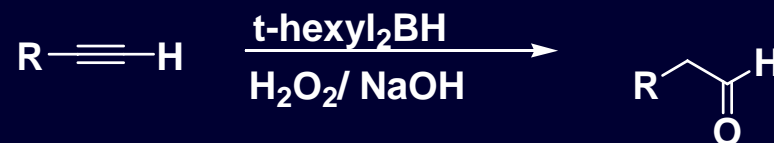
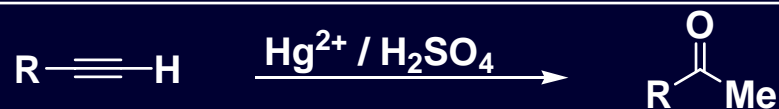
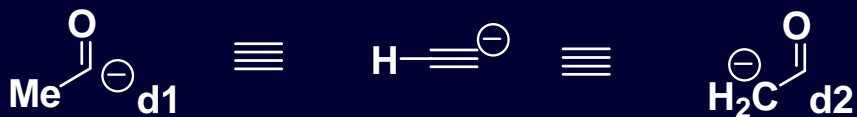
the Mechanism and the issue of Product Selectivity

Synthesis and Use of Alkenes and

Alkynes and key transformations

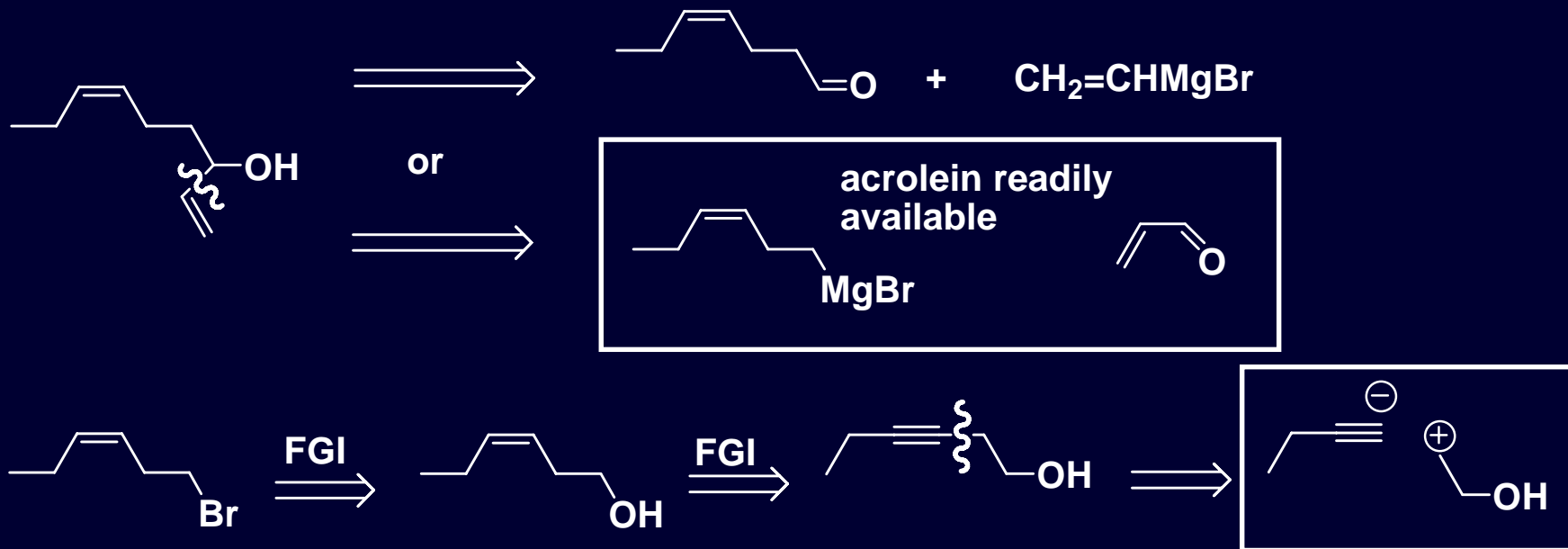


Conversion of terminal Alkynes into Carbonyl Derivatives

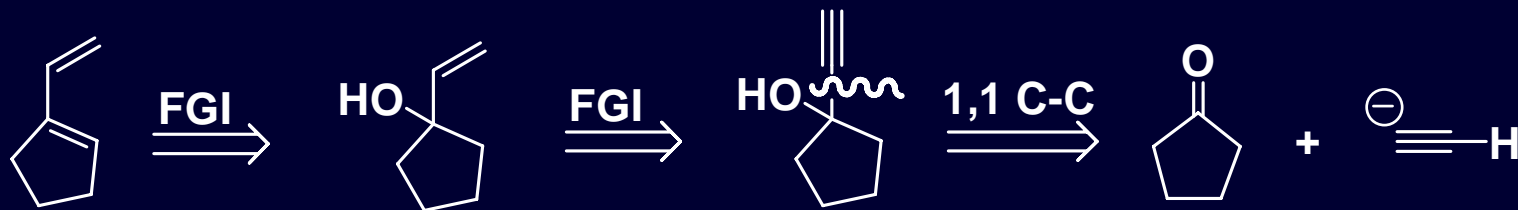


Synthesis and Use of Alkenes and Alkynes

Example 1

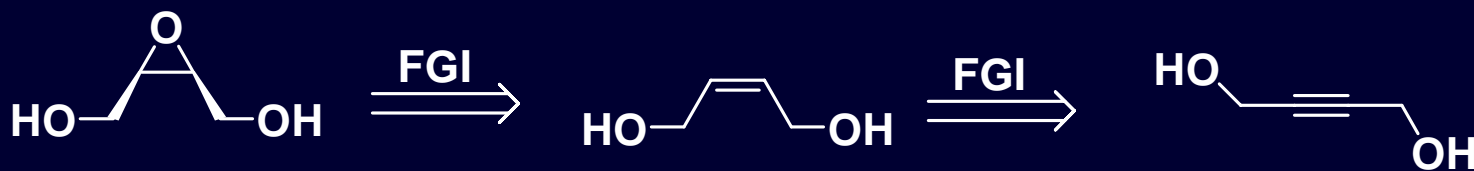
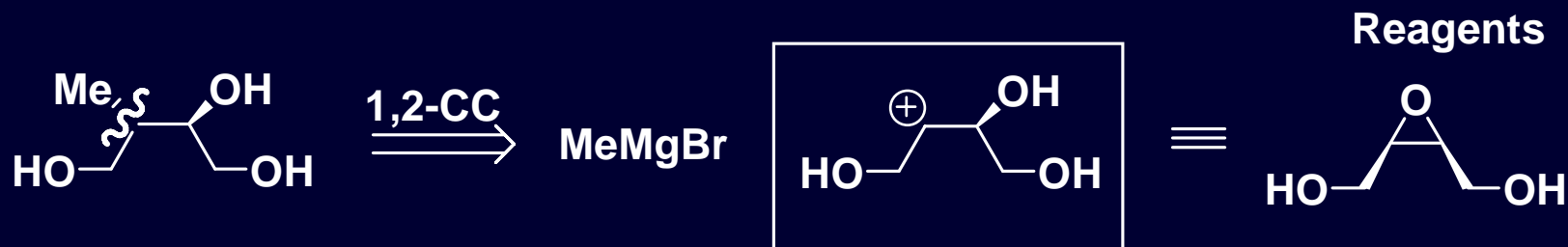
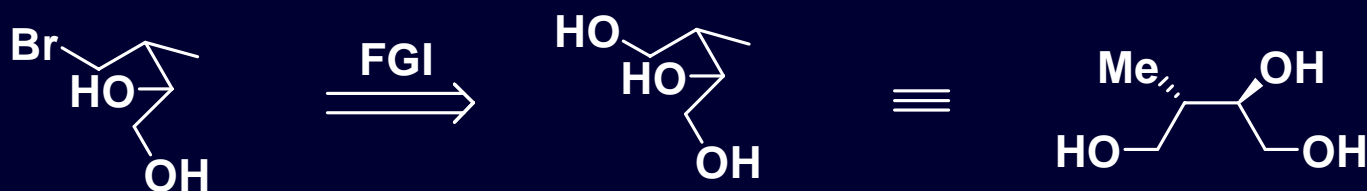
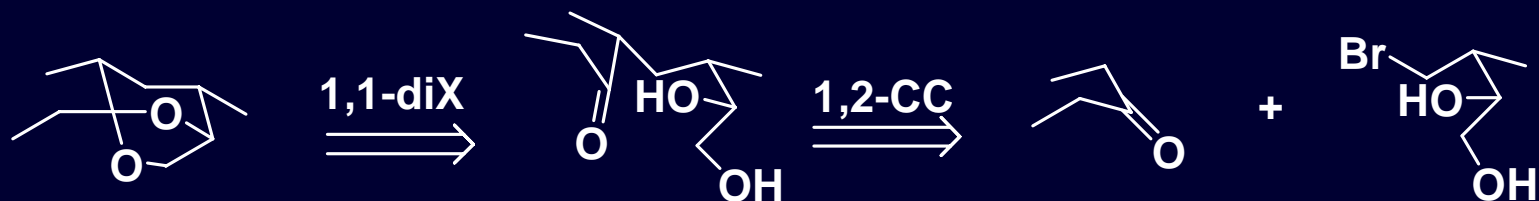


Example 2



Synthesis and Use of Alkenes and Alkynes

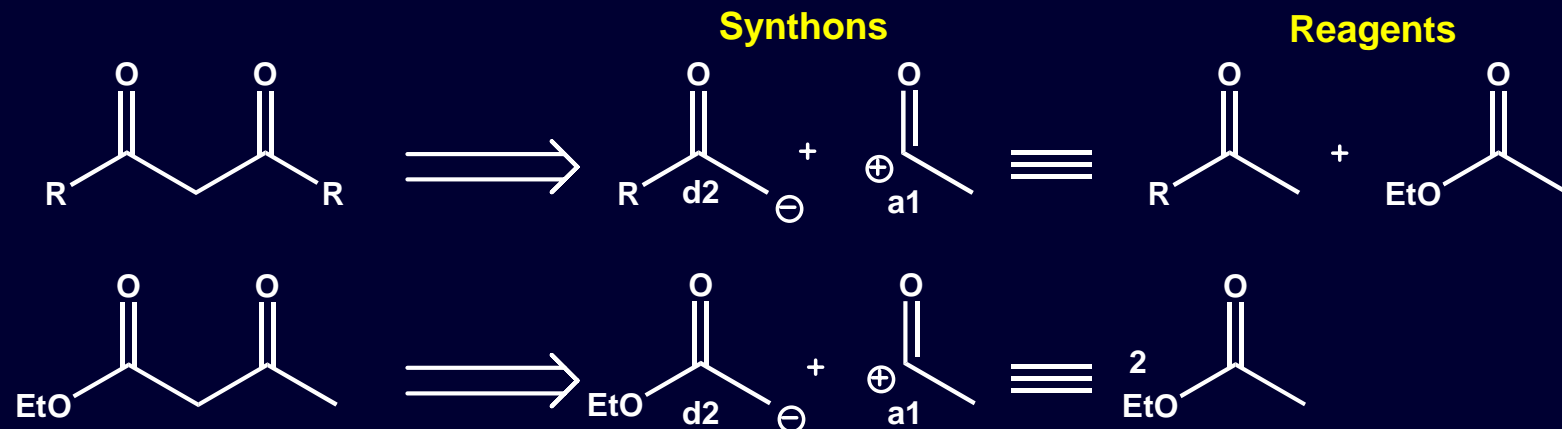
Multistriatin Retrosynthesis



Two Group Disconnections

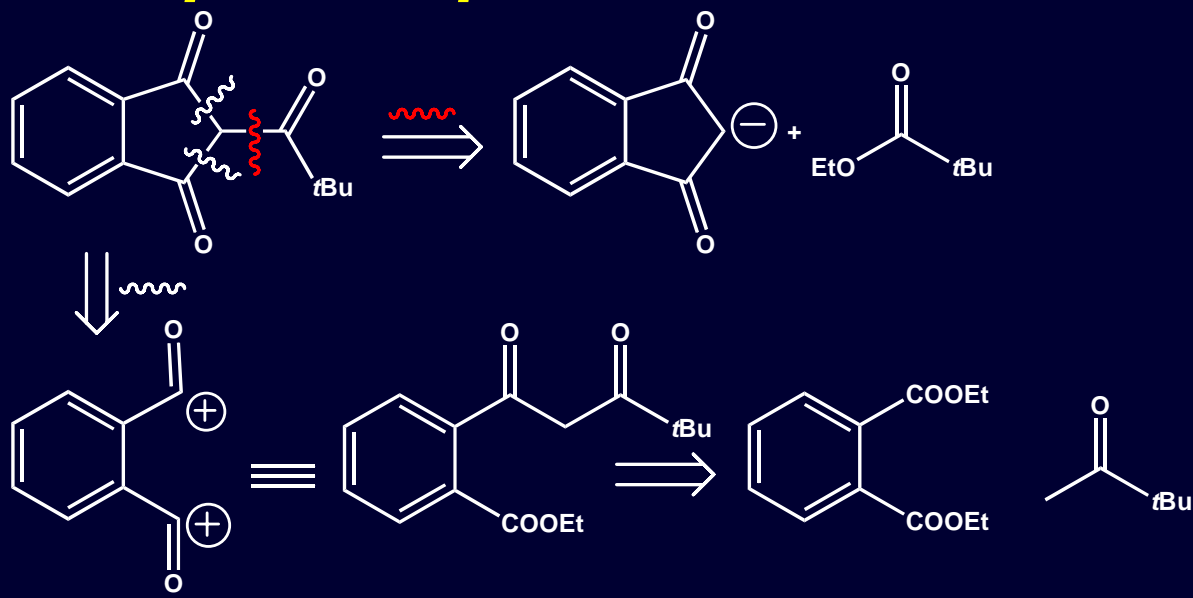
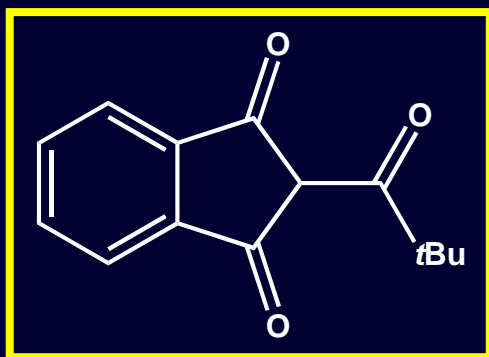
1,3-, 1,5- and 1,2- Difunctionalised Compounds

- 1,3-Dicarbonyl Compounds and their derivatives



Note: Mechanism of Claisen condensation

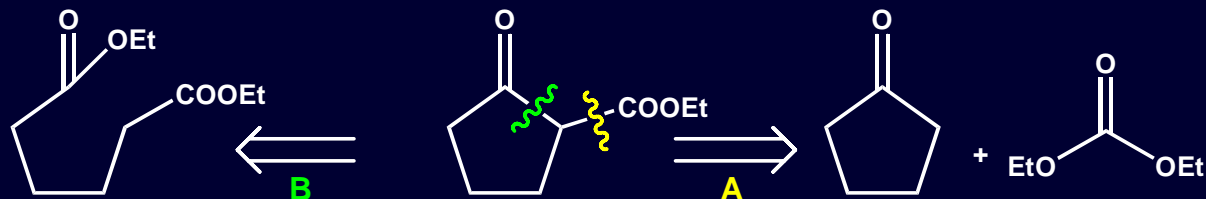
- Example 1: Synthesis of Pival [Rat Poison]**



Two Group Disconnections

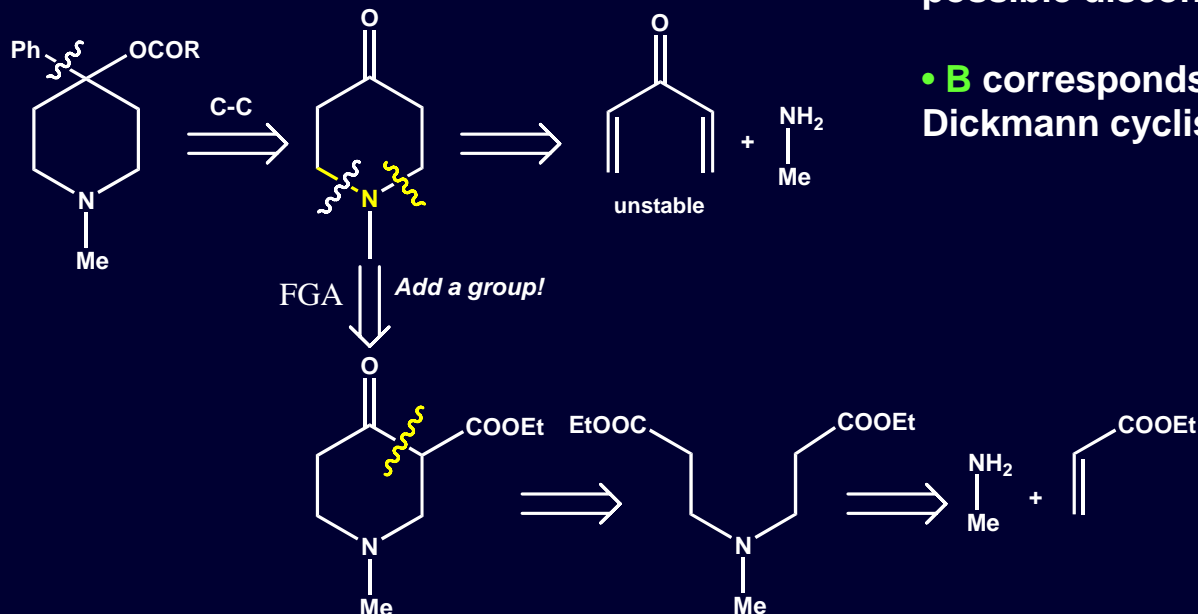
1,3-Difunctionalised Compounds

- *Example 2*



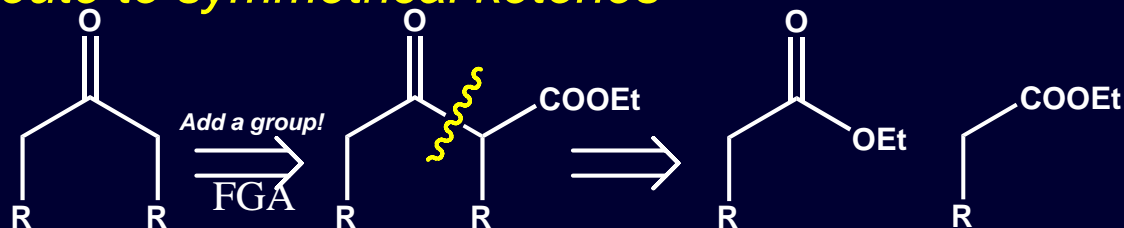
- **A** and **B** are the two possible disconnections

- *Example 3*



- **B** corresponds to the Dickmann cyclisation

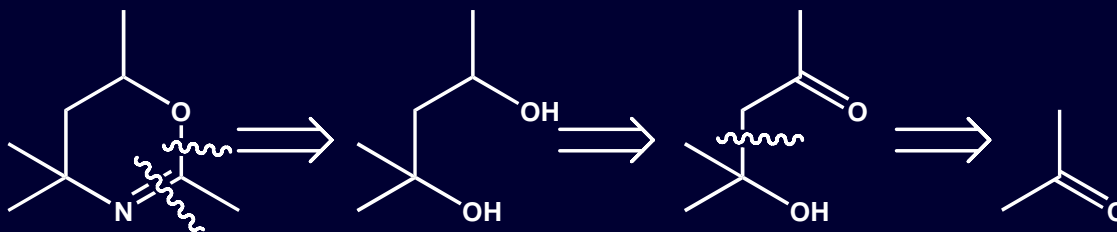
- *Example 4 Route to symmetrical ketones*



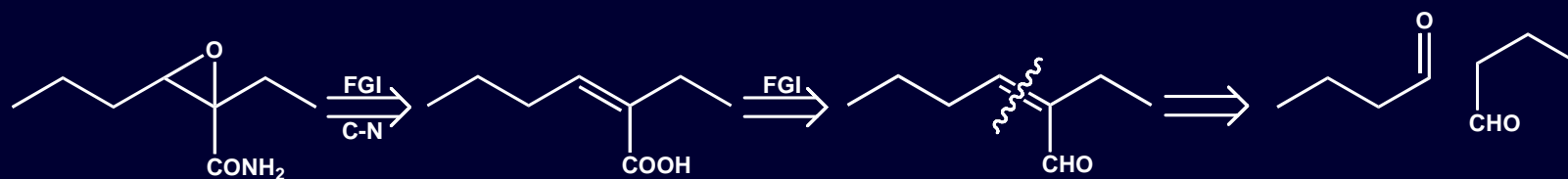
Two Group Disconnections

1,3-Difunctionalised: β -Hydroxycarbonyl and α,β -Unsaturated carbonyls

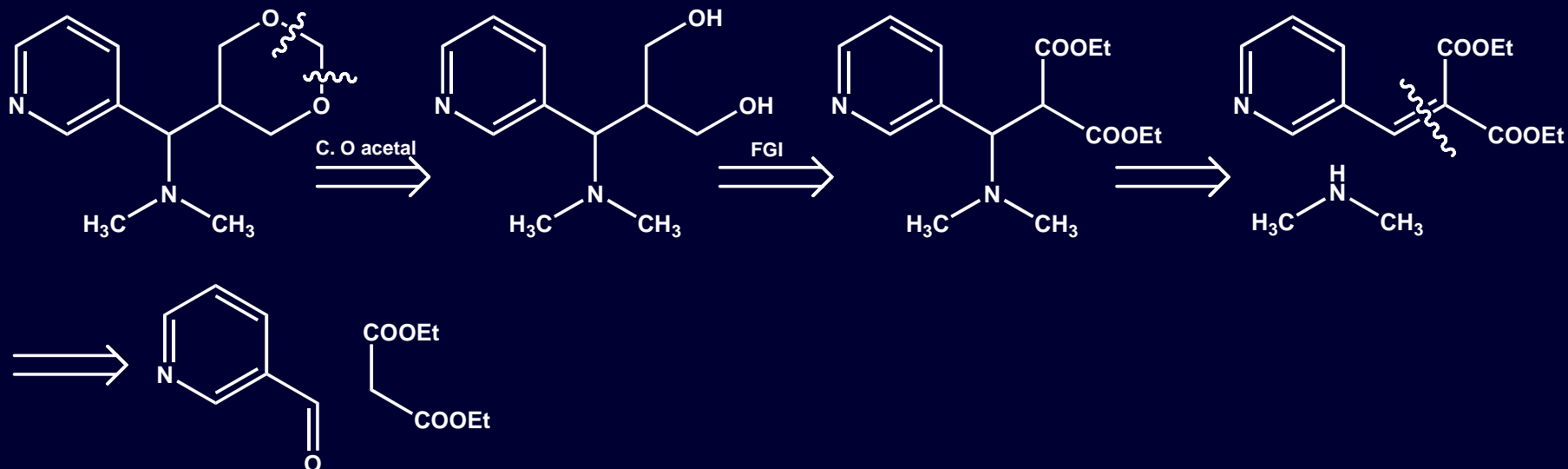
- **Example 1**



- **Example 2 Oxanamide (tranquilliser)**



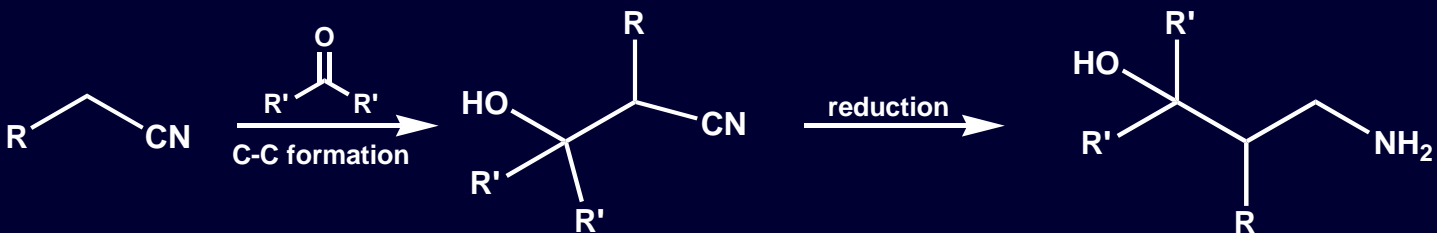
- **Example 3 Doxipicoline (analgesic)**



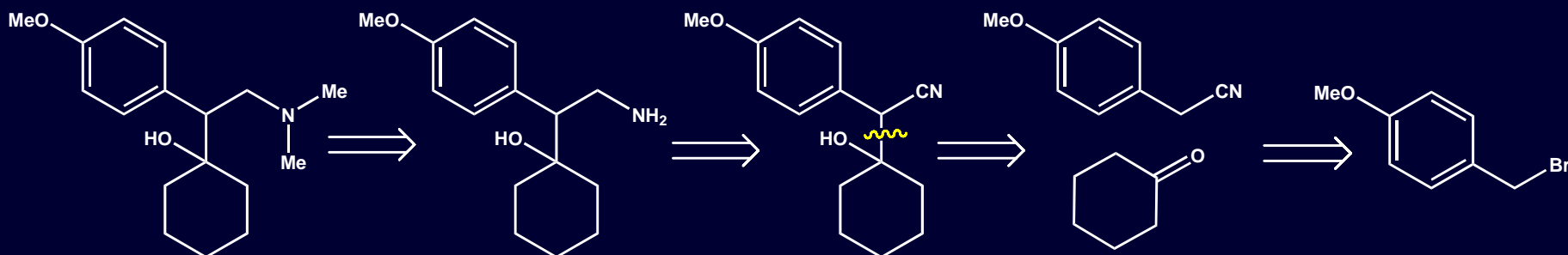
Two Group Disconnections

1,3-Difunctionalised Compounds – Amino alcohols

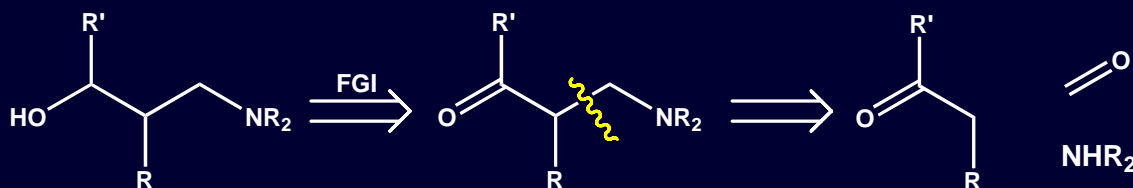
• Reduction of nitriles



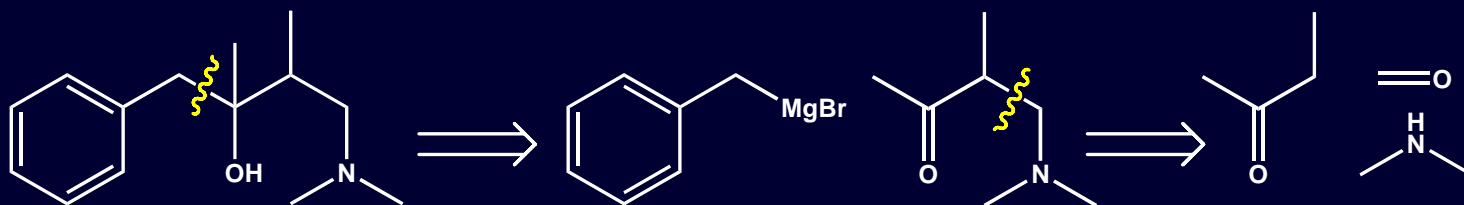
Example Venlafaxine (Antidepressant)



• Mannich Reaction

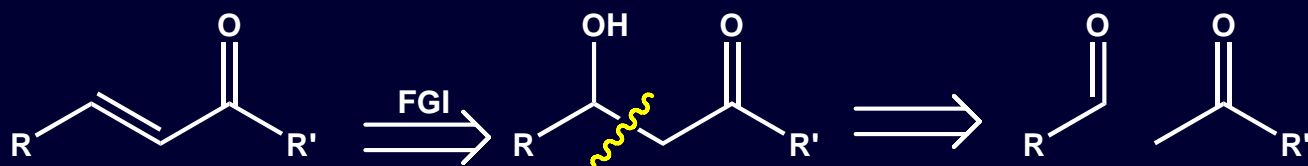


Example Clobutinol (Cough Medicine)

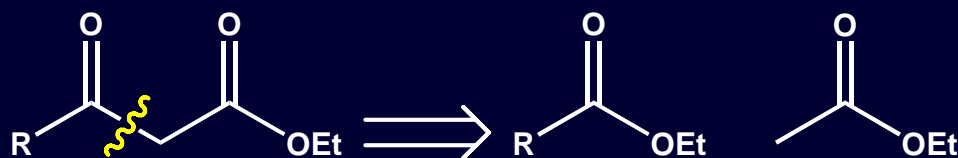


Two Group Disconnections

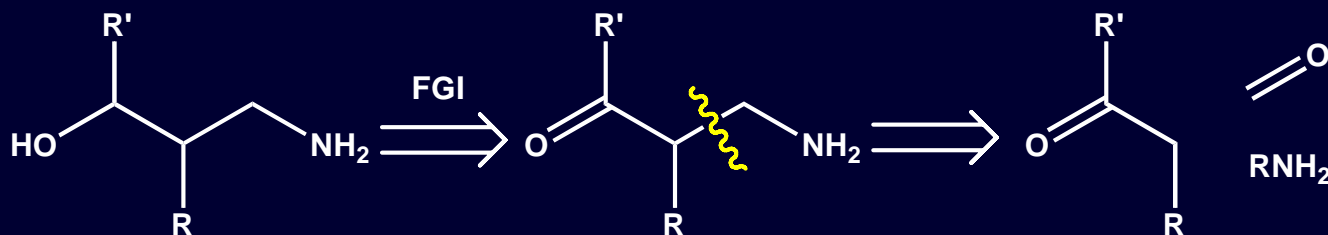
1,3-Difunctionalised Compounds – Summary



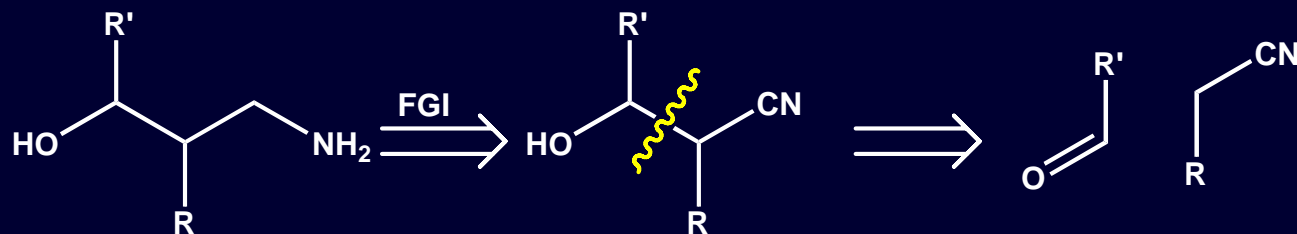
ALDOL and Variants



CLAISEN and Variants



MANNICH and Variants

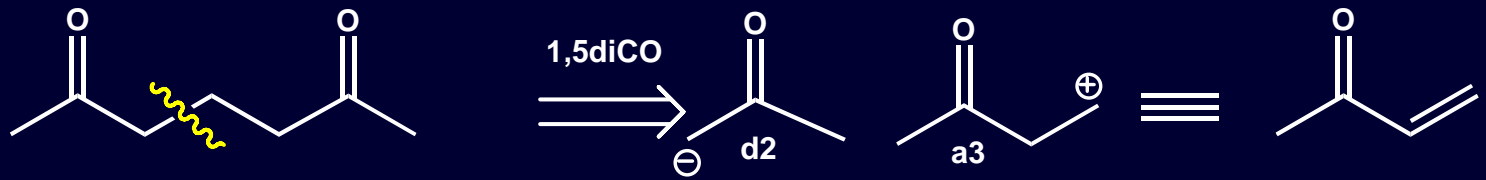


NITRILE and Variants

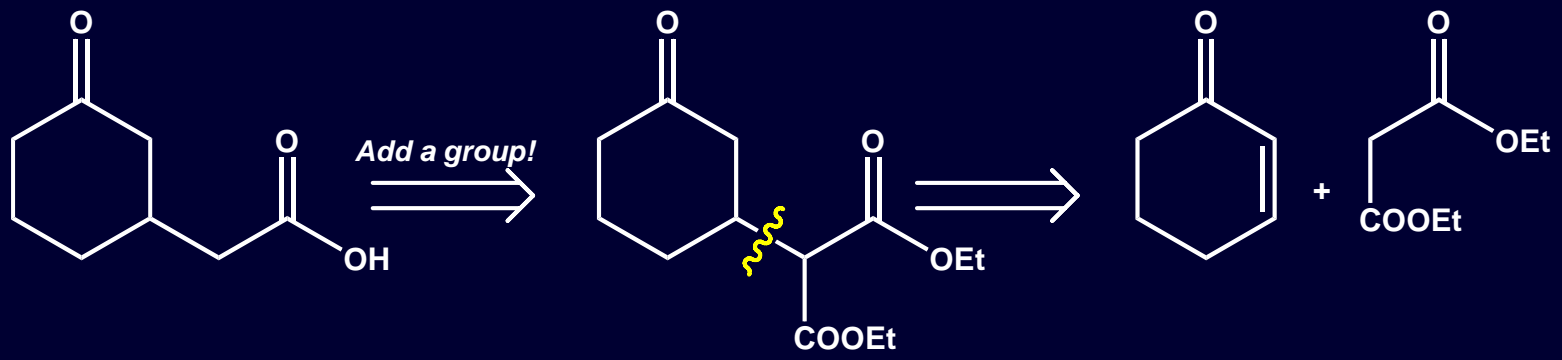
Two Group Disconnections

1,5-Difunctionalised Compounds

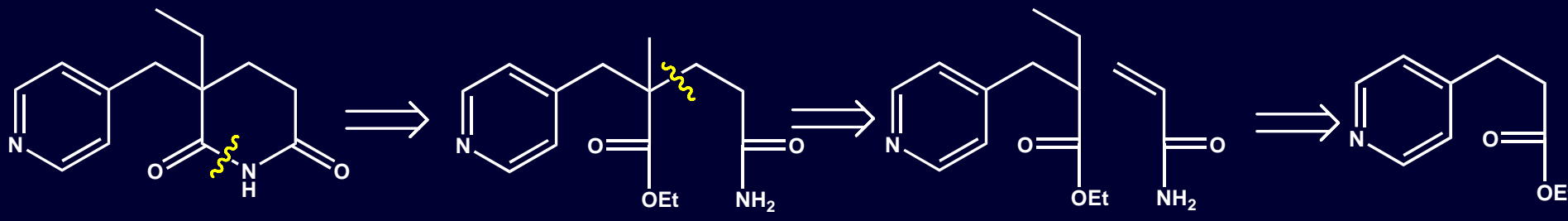
- 1,5-Dicarbonyl Derivatives



Example



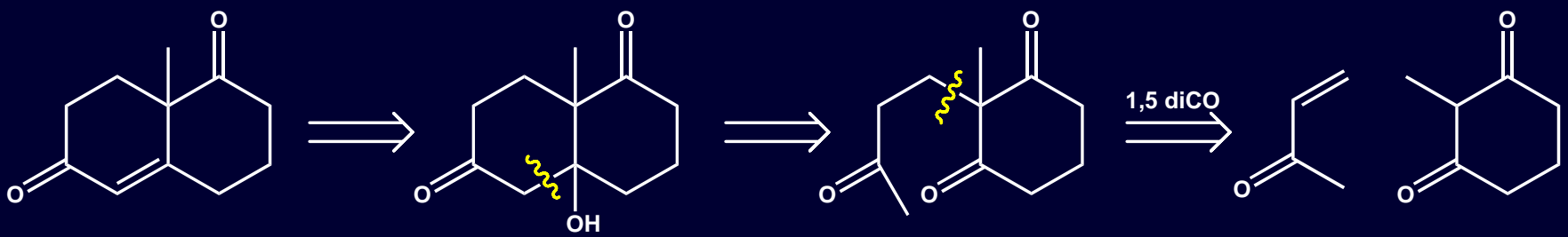
Example Rogletimide (Sedative)



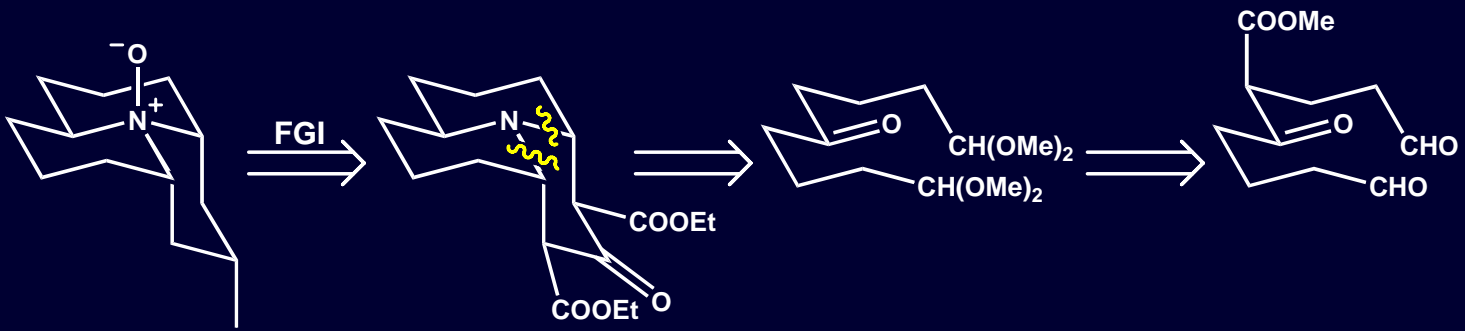
Two Group Disconnections

1,5-Difunctionalised Compounds

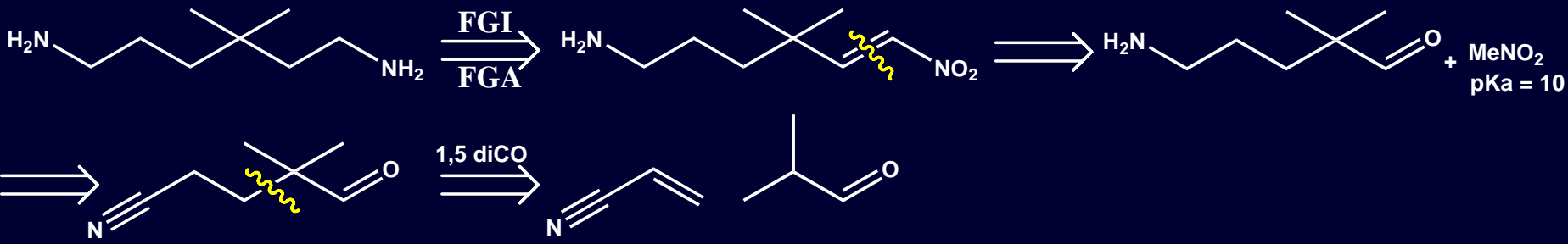
- *Robinson Annulation*



- *Synthesis of Coccinelline*



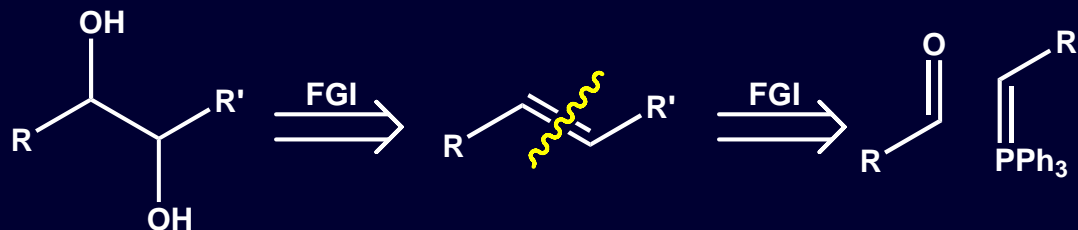
- *Synthesis involving an intermediate featuring a 1,5-Difunctionality*



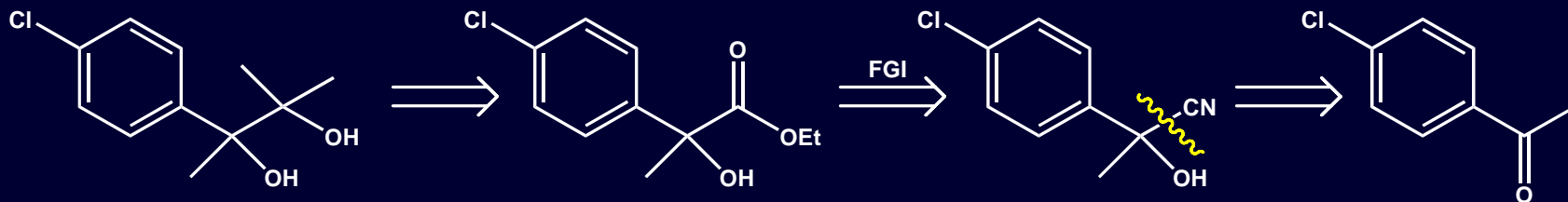
Two Group Disconnections

1,2-Difunctionalised Compounds

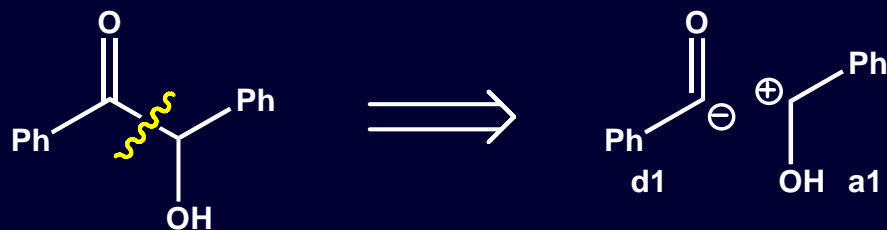
- 1,2-Diols via alkenes



- 1,2-Diols via cyanhydrins

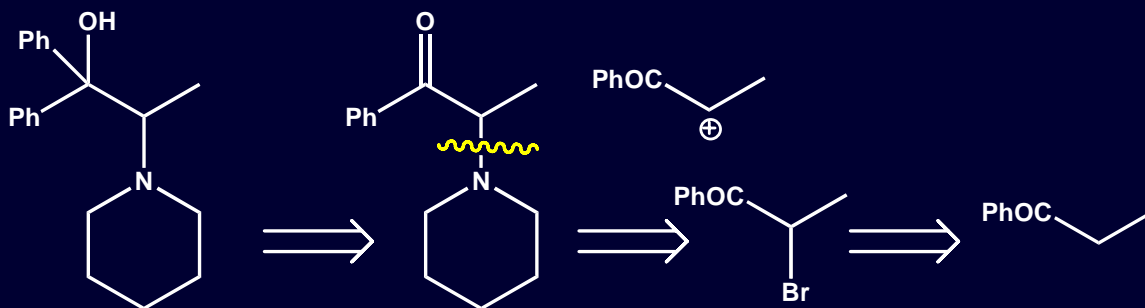


- α -Hydroxyketones via benzoin condensation



Also Revise: acyloin condensation

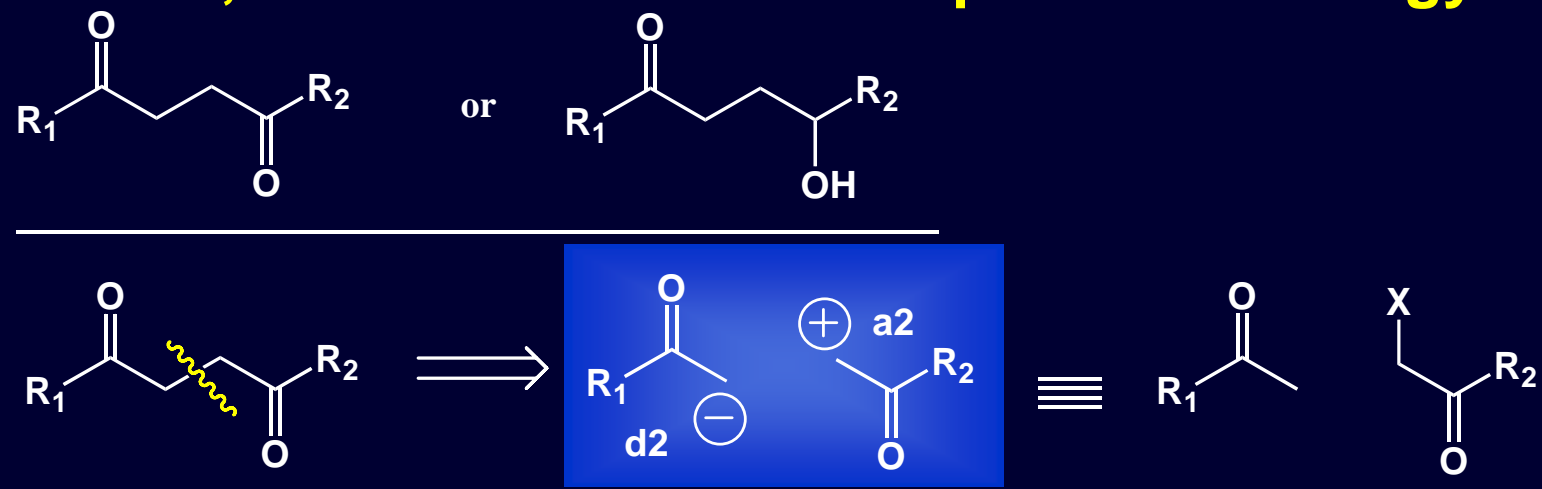
- α -Functionalisation of carbonyl compounds



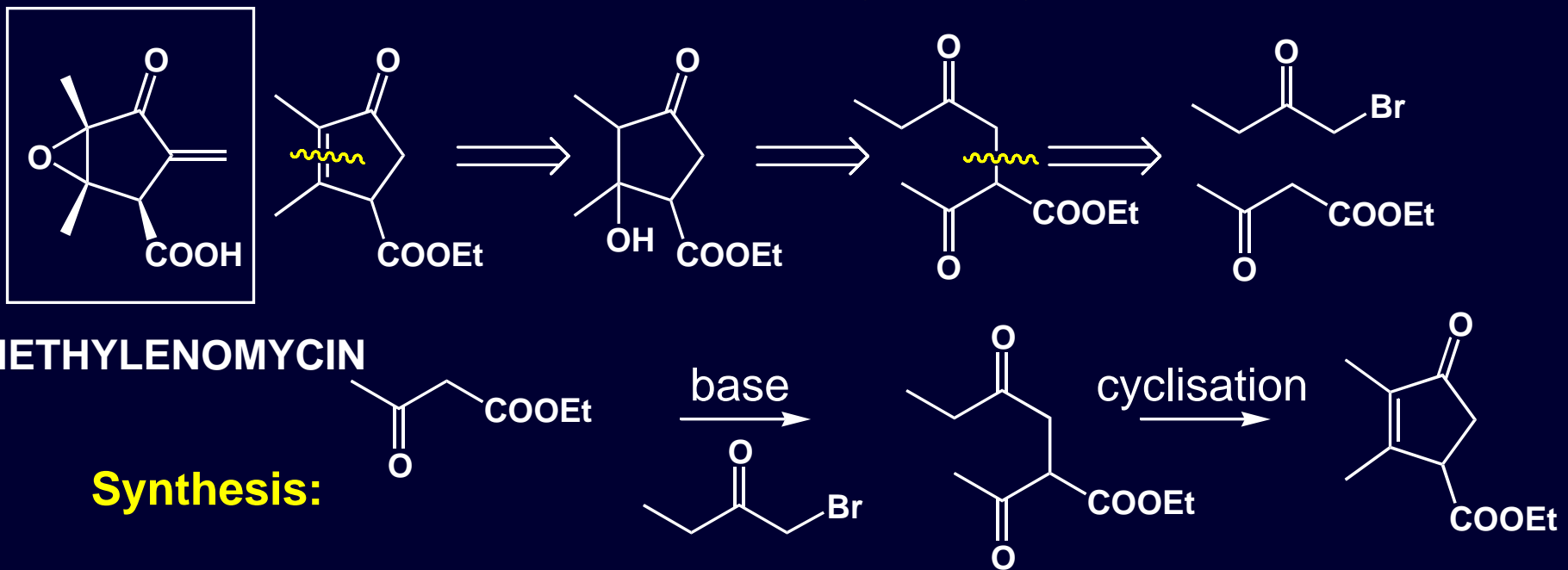
Diphepanol
spasmolytic

Two Group Disconnection

1,4-Difunctionalised Compounds: Strategy 1

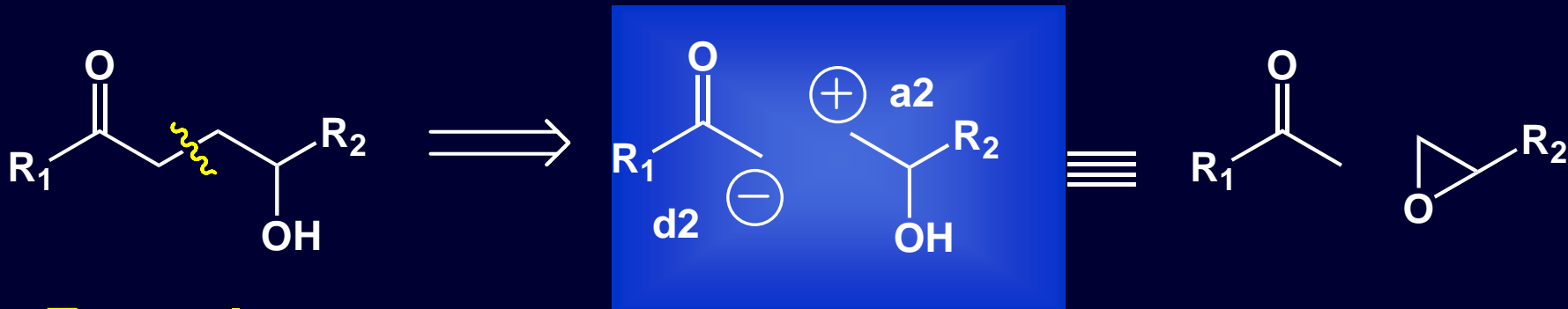


Example: Precursor of antibiotic methylenomycin

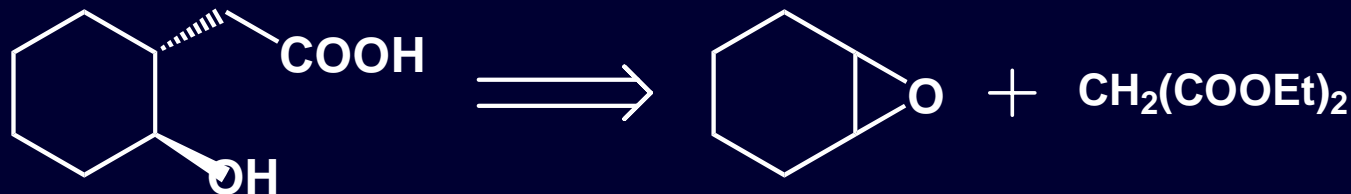


Two Group Disconnection

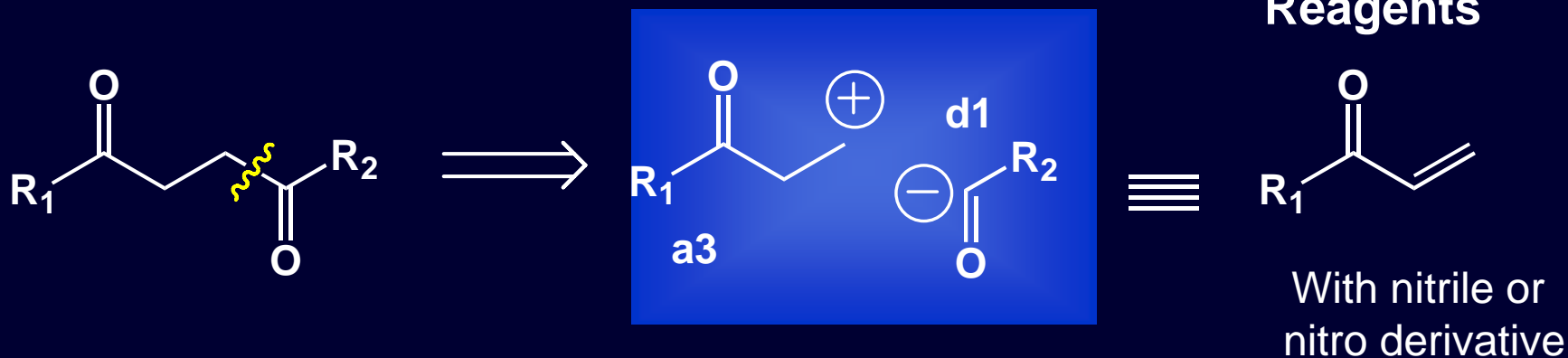
1,4-Difunctionalised Compounds: Strategy 2



Example:

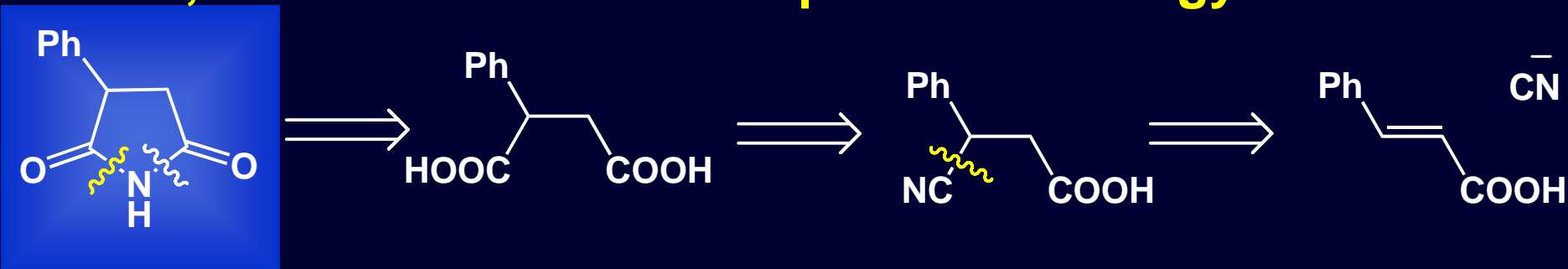


1,4-Difunctionalised Compounds: Strategy 3

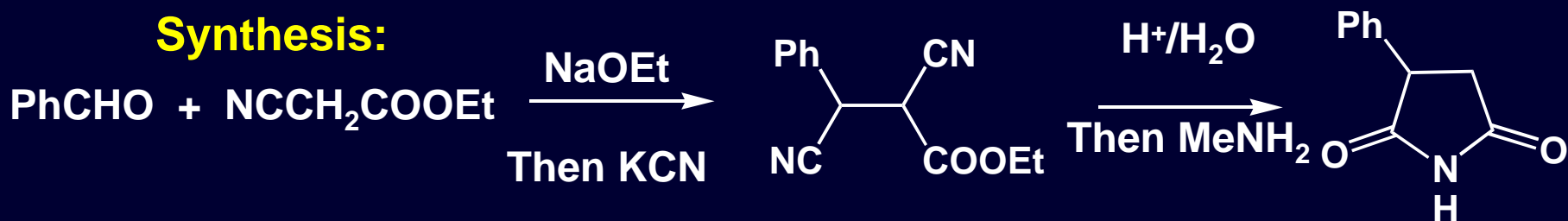


Two Group Disconnection

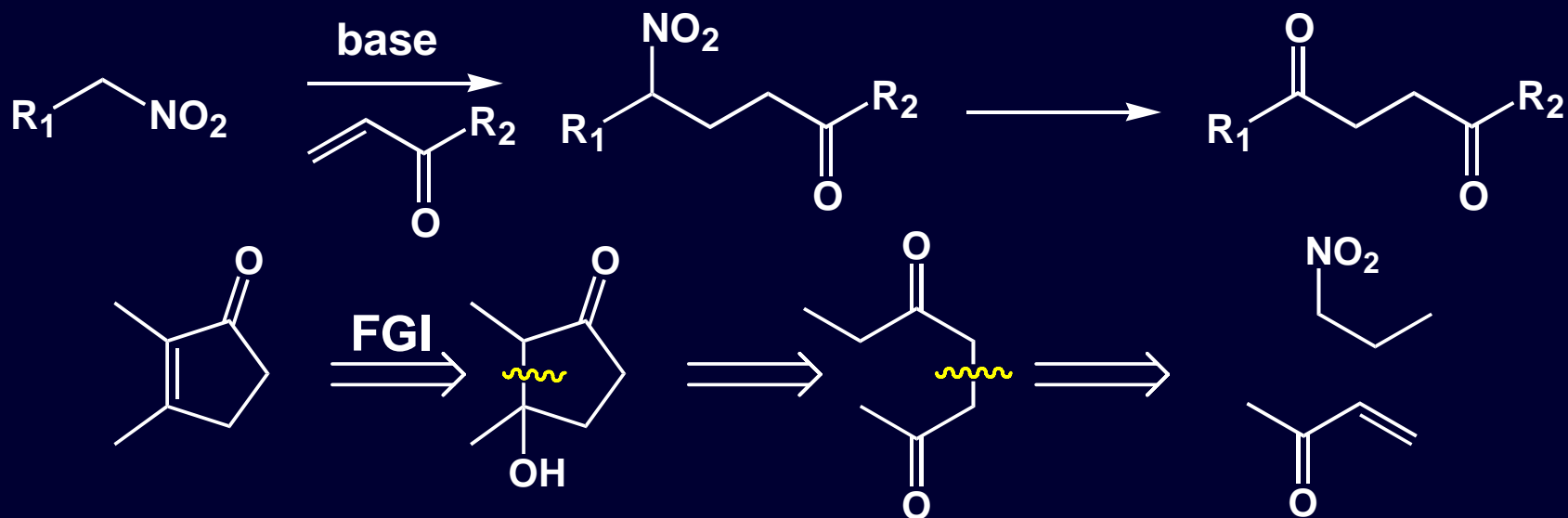
1,4-Difunctionalised Compounds: Strategy 3 Nitrile



Synthesis:

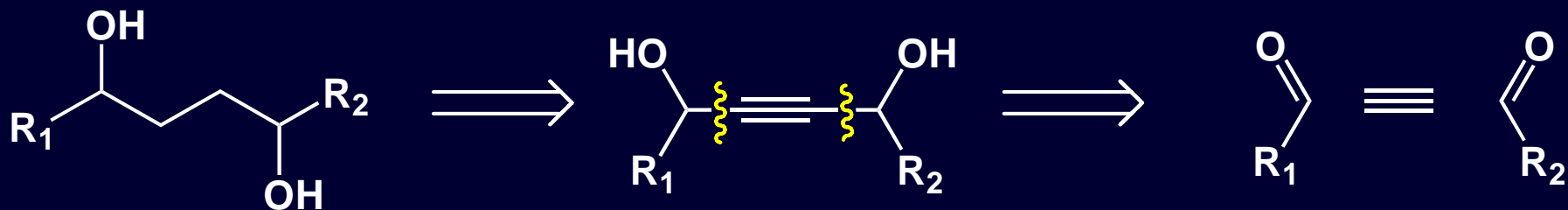


1,4-Difunctionalised Compounds: Strategy 3 Nitro

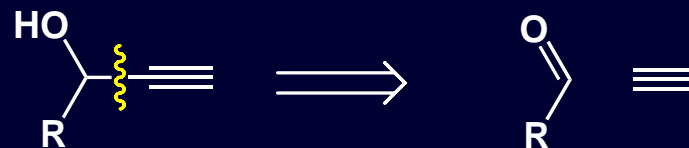
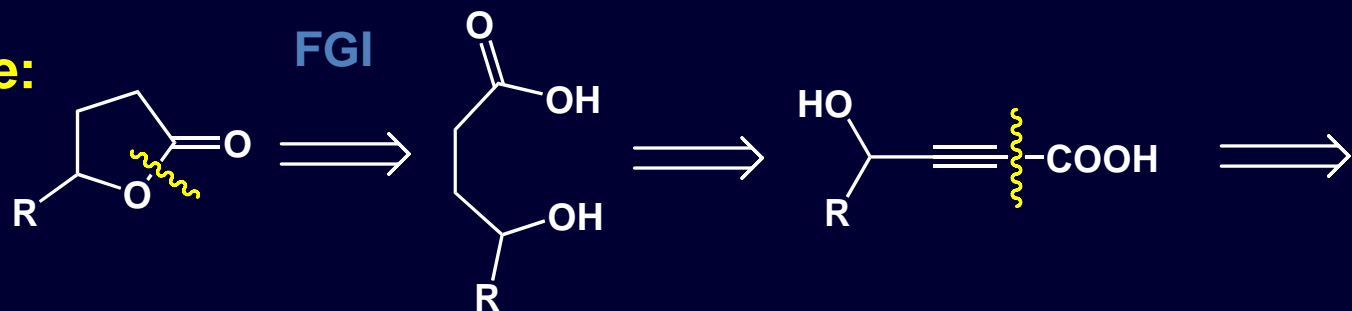


Two Group Disconnection

1,4-Diols and derivatives: Strategy 4 Alkynes



Example:



1,4-Difunctionalised Compounds: Strategy 5 Allylation

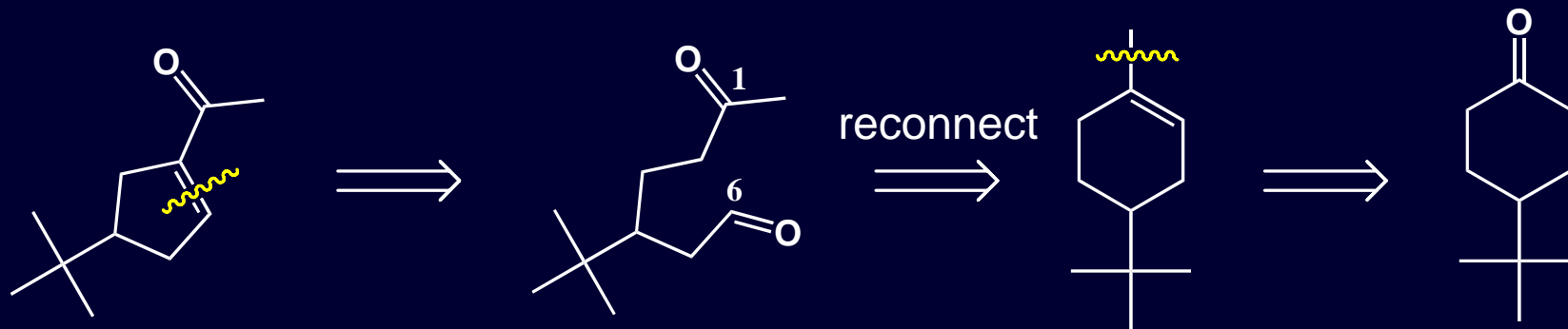
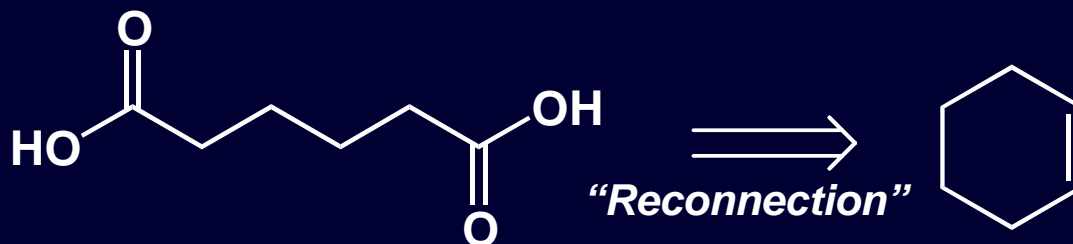


Two Group Disconnection

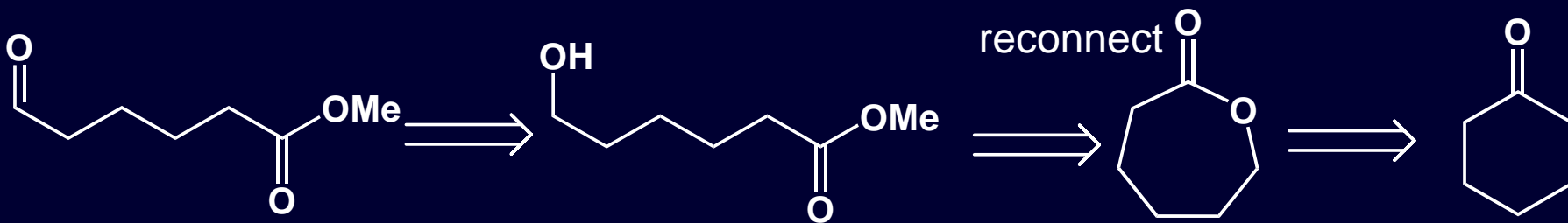
1,6-Difunctionalised Compounds: Ozonolysis

“Reconnection” is a reliable strategy for synthesising 1,6-difunctionalised compounds since the cyclohexenes required for the oxidative cleavage are easily accessible

Example:



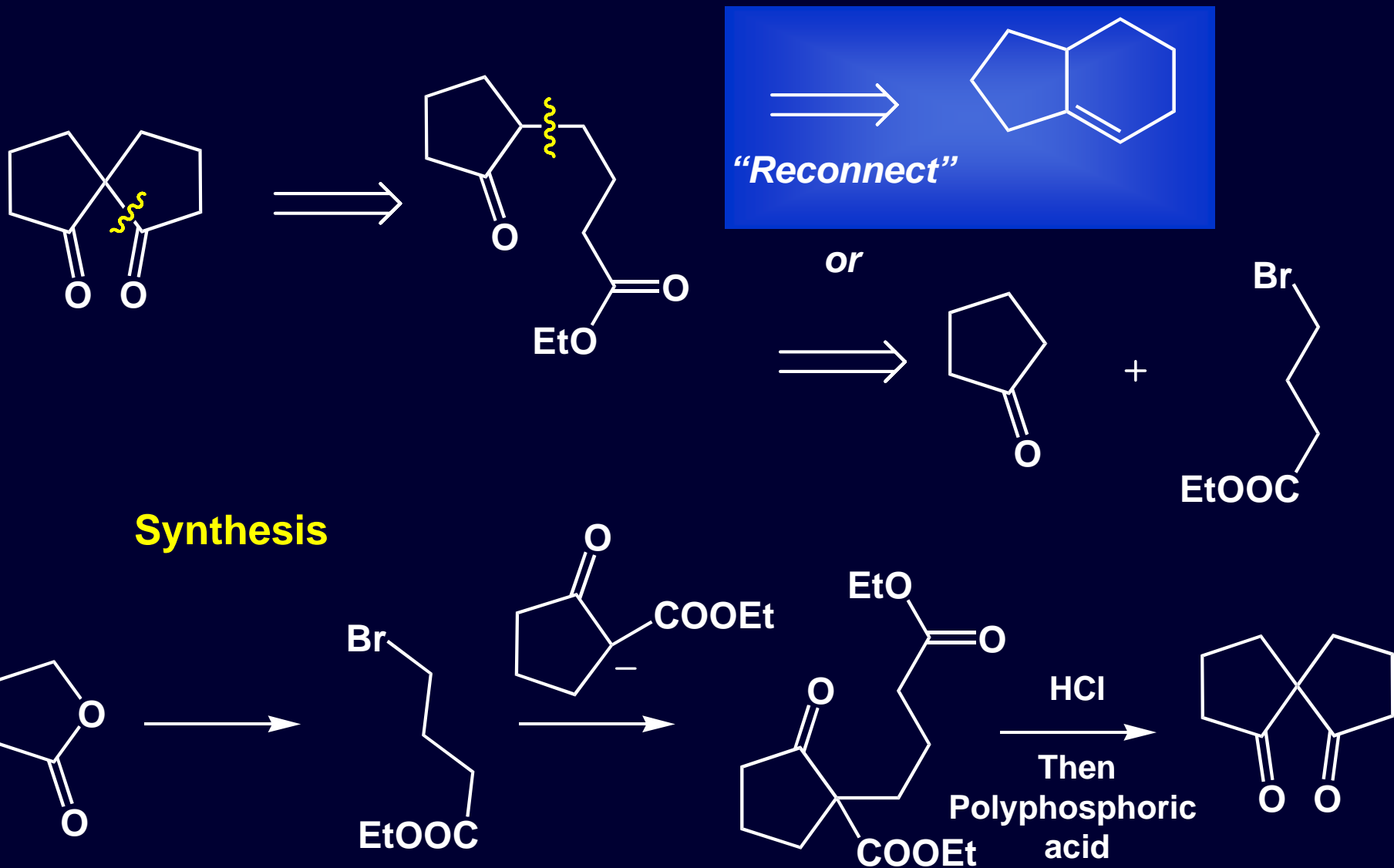
1,6-Difunctionalised Compounds: Baeyer-Villiger



“Revision”: mechanism of Baeyer-Villiger reaction and migratory aptitude

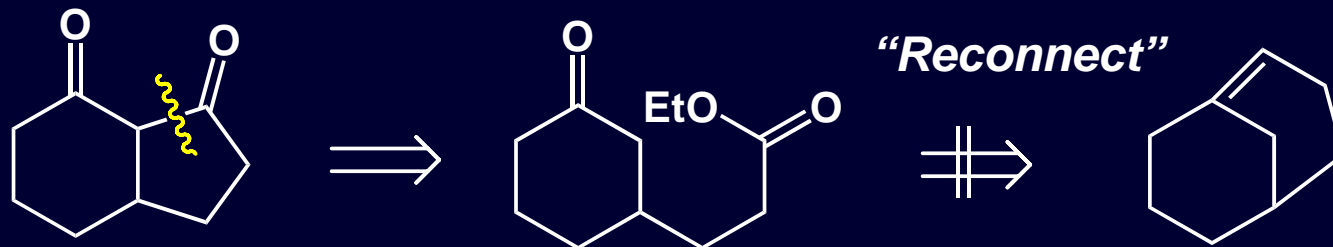
Two Group Disconnection

1,6-Difunctionalised Compounds

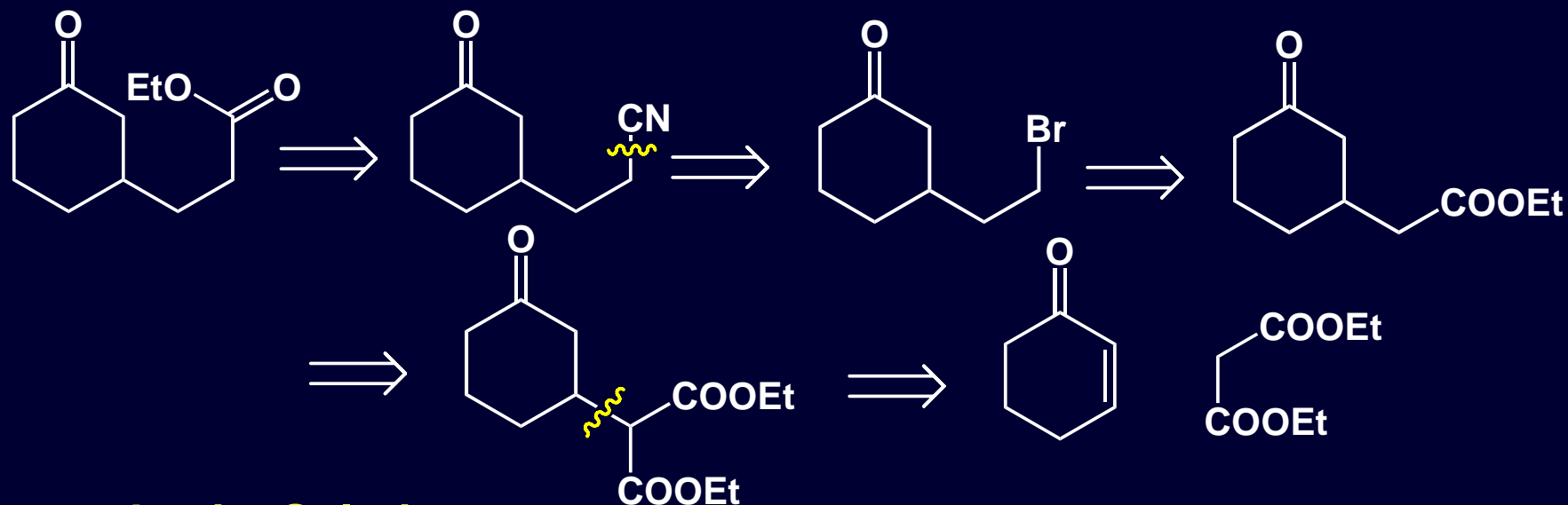


Two Group Disconnection

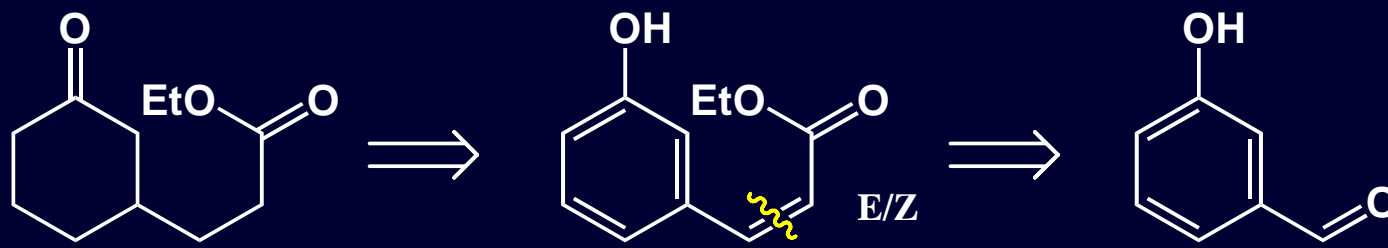
1,6-Difunctionalised Compounds



Retrosynthesis- Solution 1



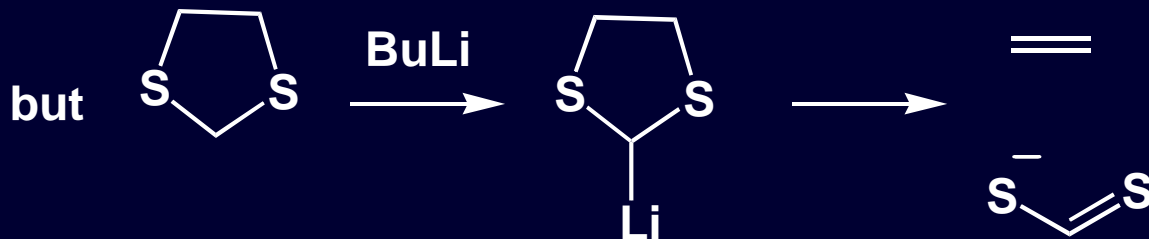
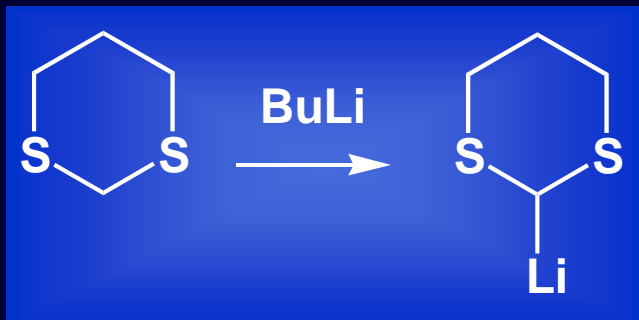
Retrosynthesis- Solution 2



Dithianes are d1 Reagents

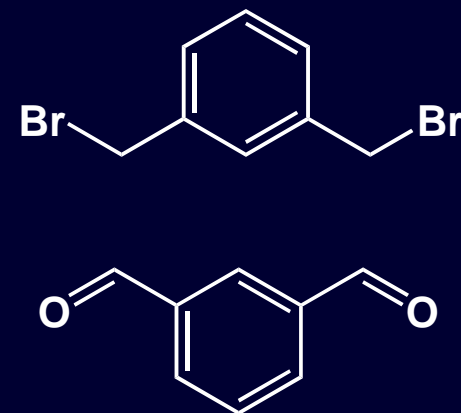
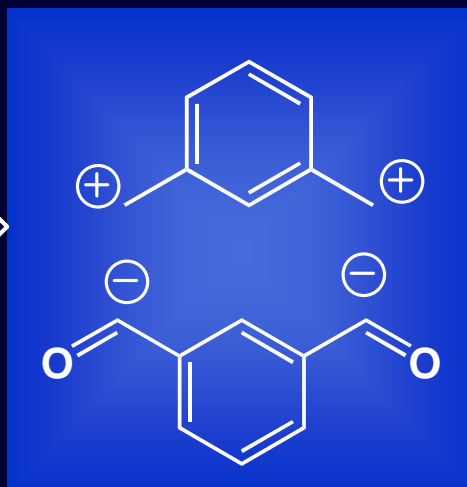
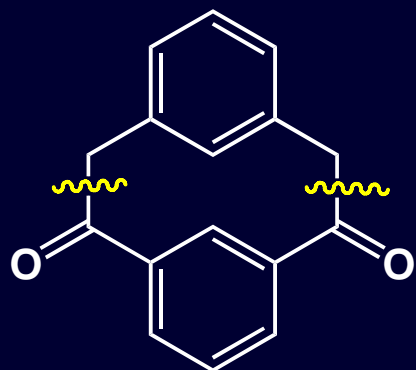
Acyl anion equivalents

Which dithiane?



Not stable

Example

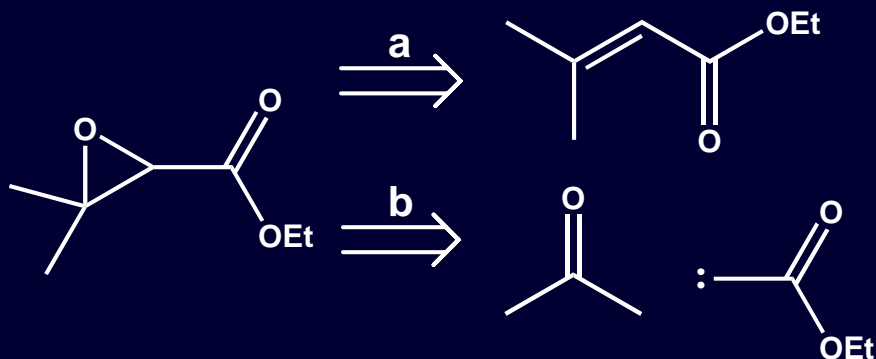


Revision: pKa and mechanism/reagents to transform dithianes into aldehydes or ketones HgCl_2 , oxidation or alkylation

Ring Synthesis

Three-membered rings

- *Three-membered rings*

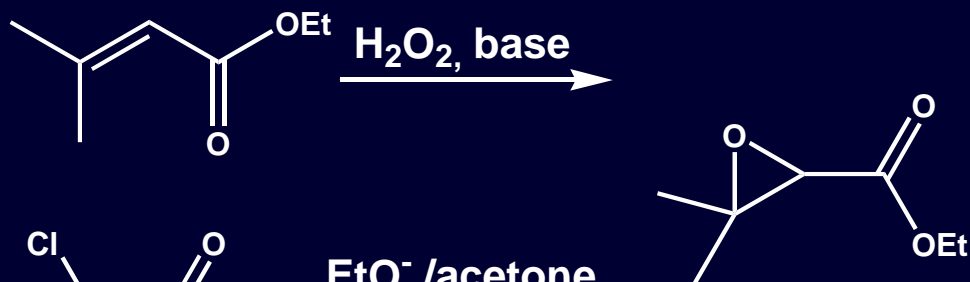


Mechanisms

Epoxidation

Ring closure

Synthesis a:



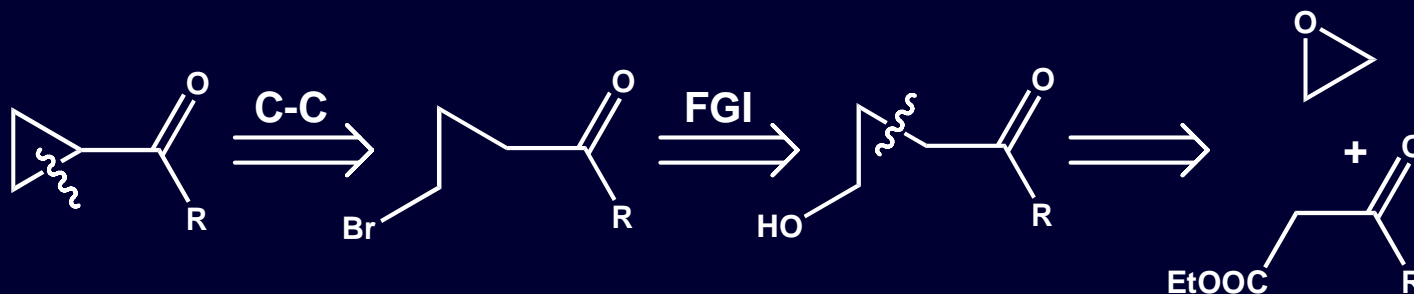
Synthesis b:



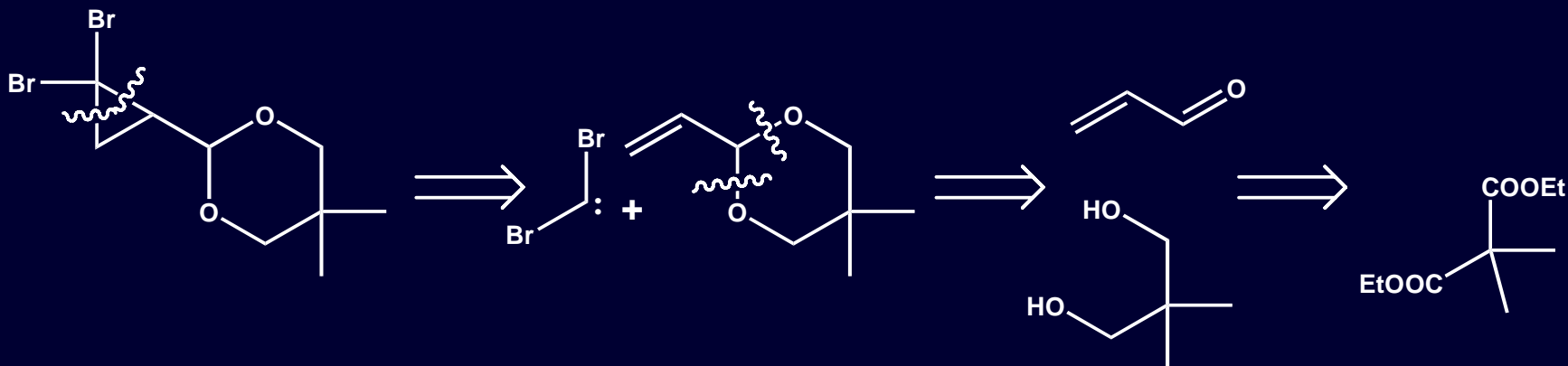
Ring Synthesis

Three-membered rings

- Three-membered rings

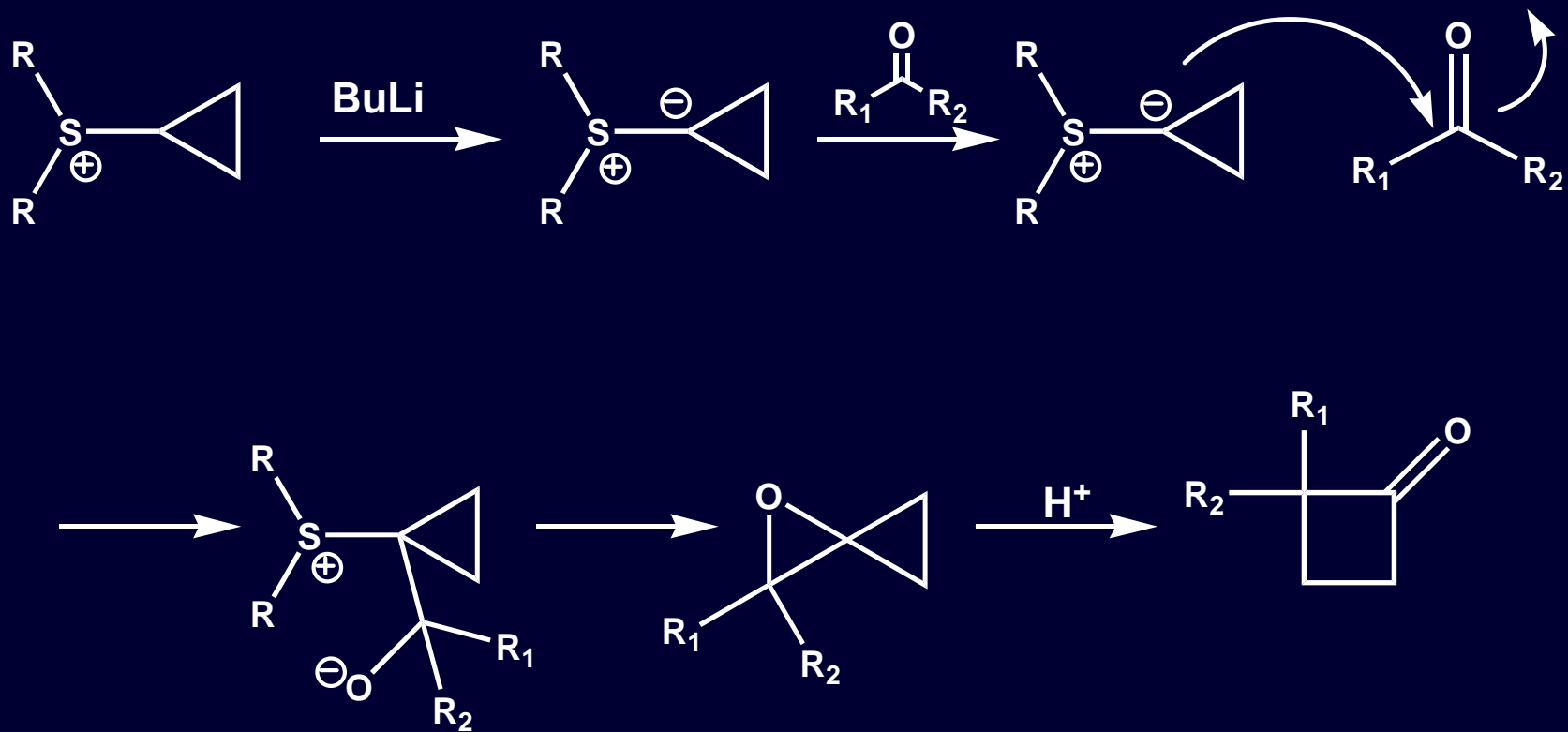


- Three-membered rings



Ring Synthesis

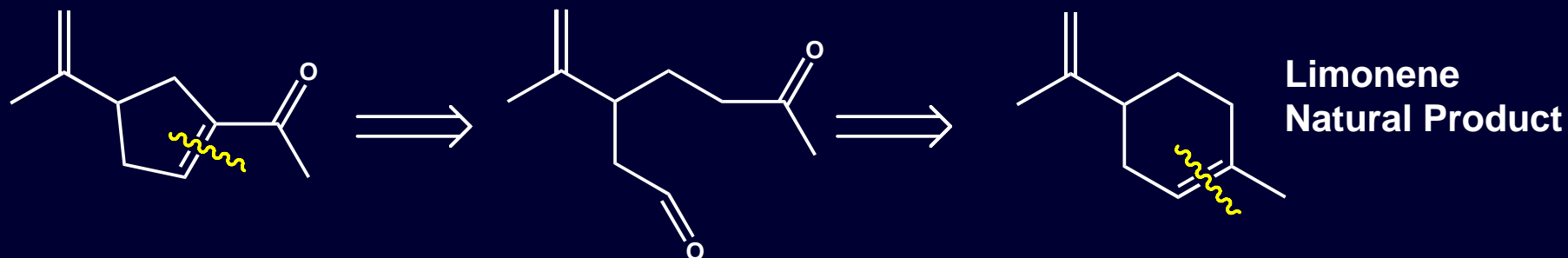
Four-membered rings



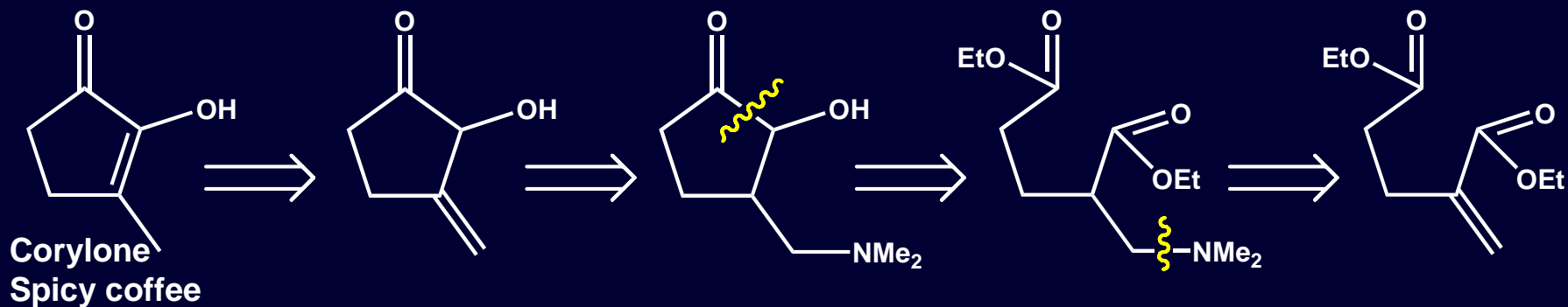
Ring Synthesis

Five-membered rings

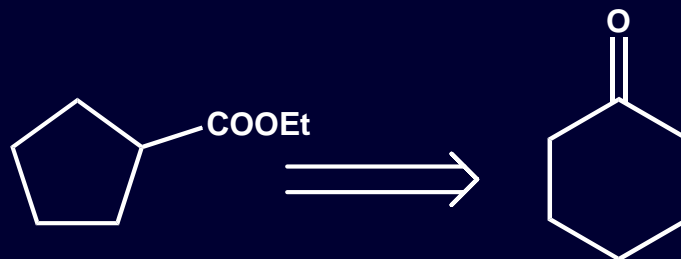
- *Five-membered rings: chemoselectivity ozonolysis, control over recyclisation step*



- *Acyloin condensation as a key step for the synthesis of 5-membered rings*



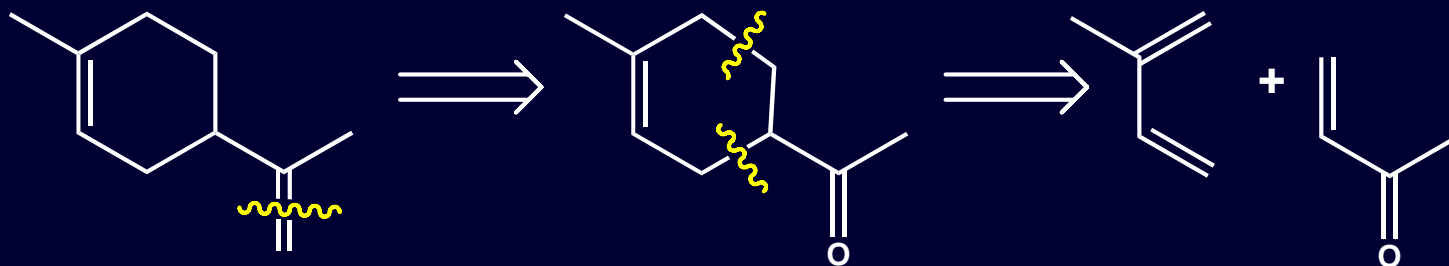
- *Favorskii Ring Contraction*



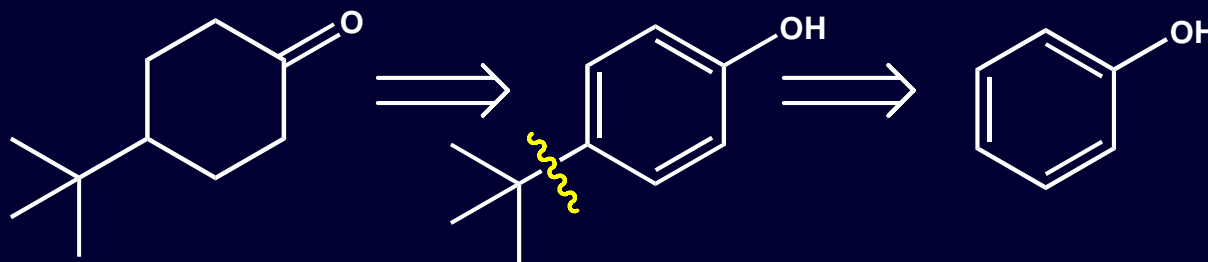
Ring Synthesis

Six-membered rings

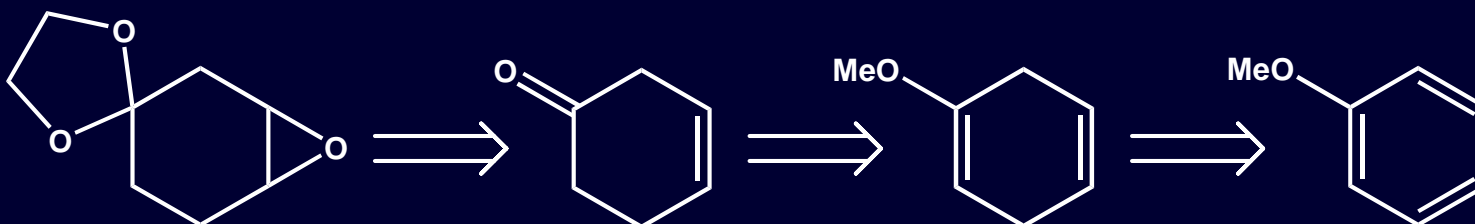
- Six-membered rings via Diels-Alder Cycloaddition



- Six-membered rings via complete Reduction

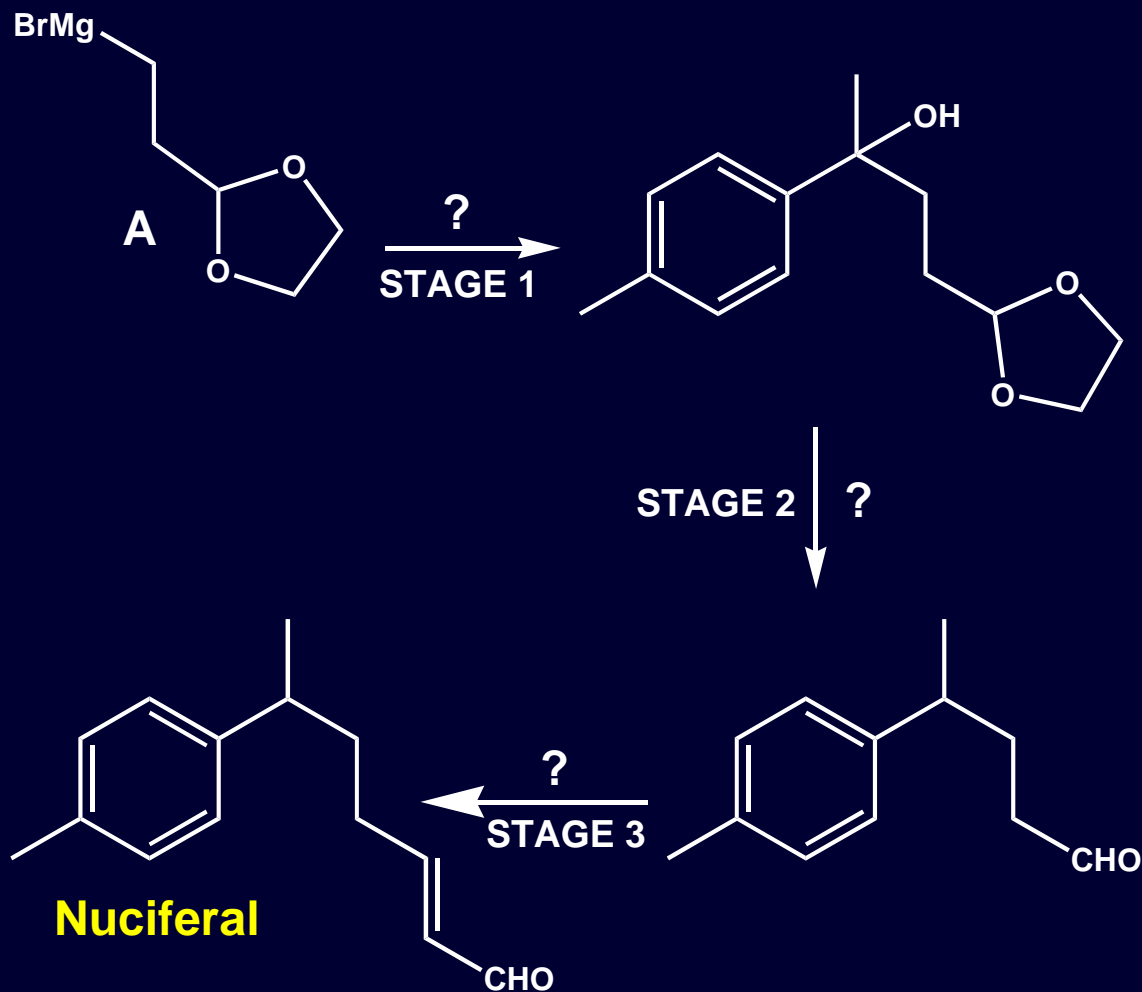
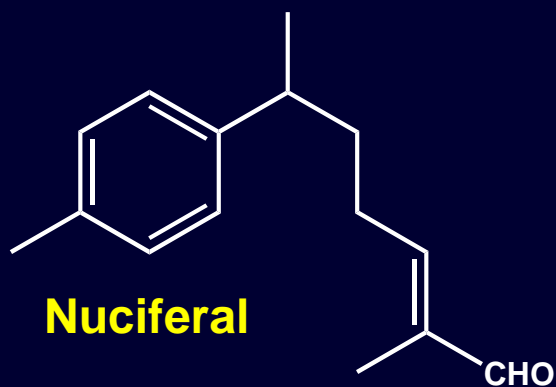


- Six-membered rings via partial Reduction



Synthesis of Nuciferal

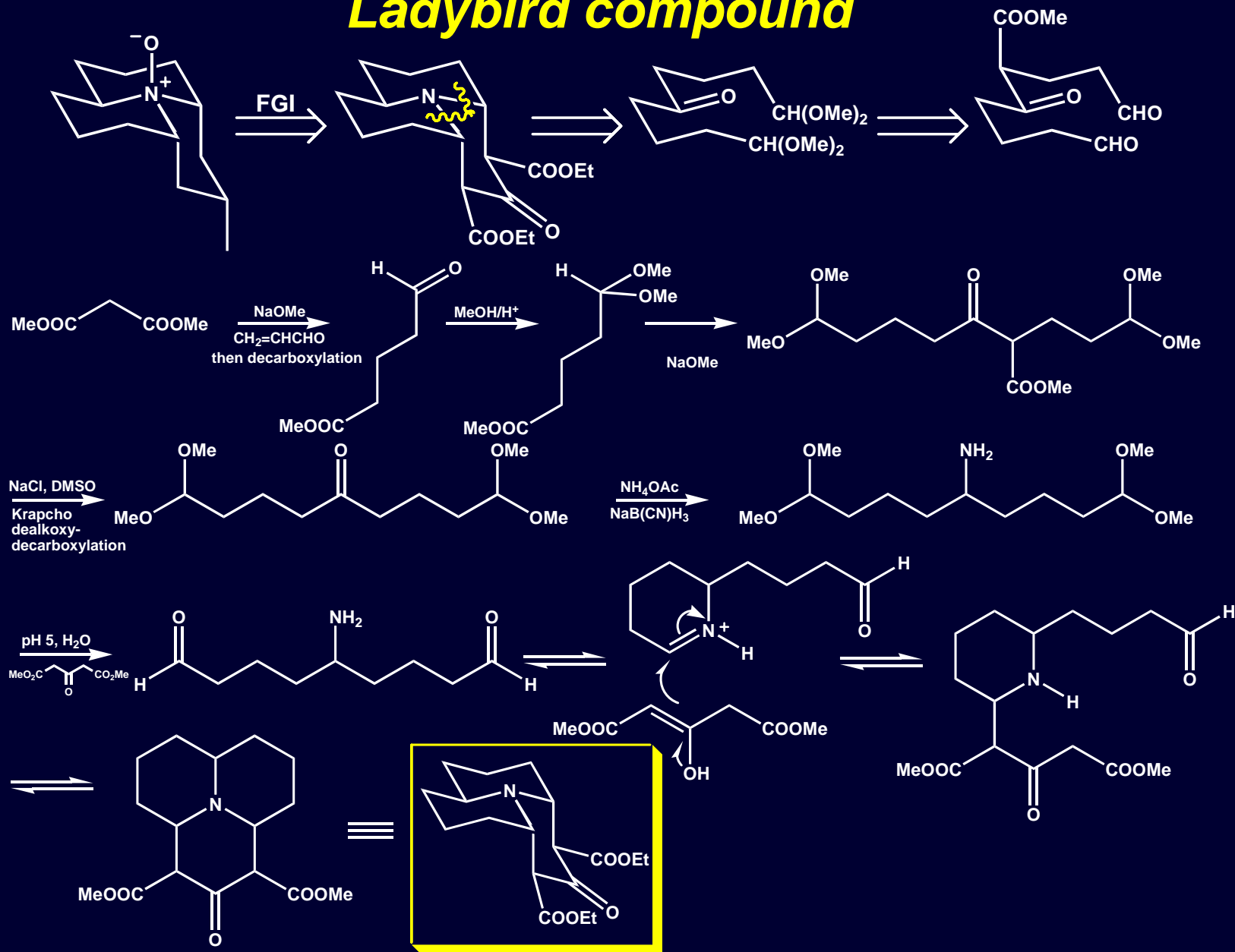
*Bisbolane type sesquiterpene isolated from wood oil of *Torreya Nucifera**



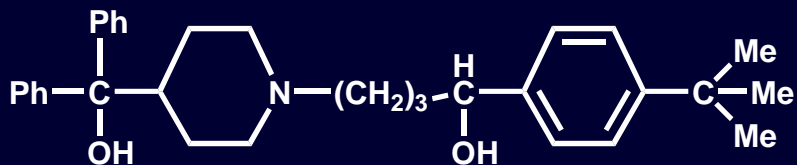
1. Suggest a synthesis for the starting material A
2. Suggest reagents for stages 1, 2 and 3
3. Draw out the retrosynthetic analysis with suitable labelling for all retrosynthetic steps
4. Which synthon does the starting material A represent?

Synthesis of Coccinelline

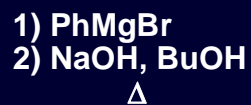
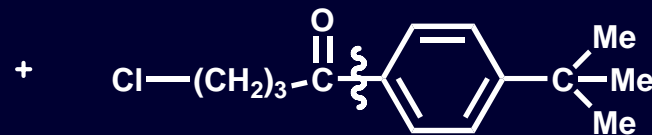
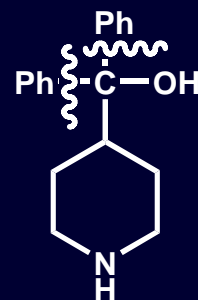
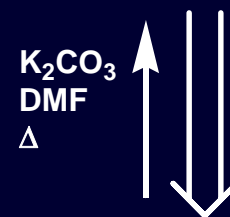
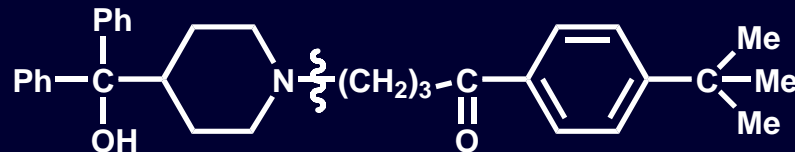
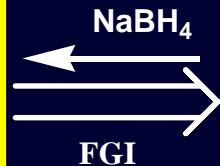
Ladybird compound



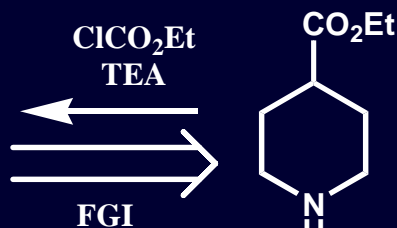
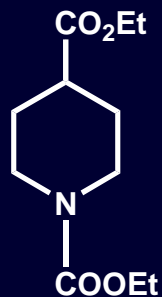
Retrosynthesis of Terfenadine



Antagonist H₁



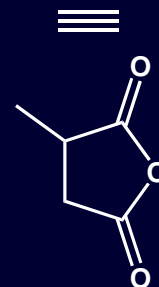
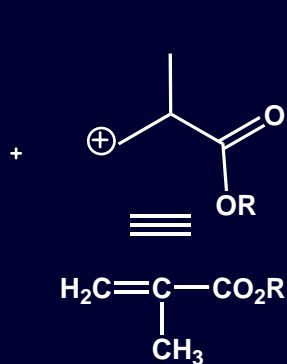
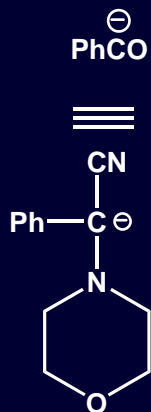
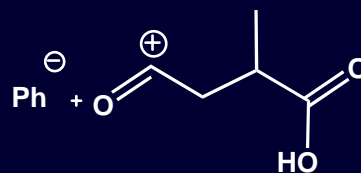
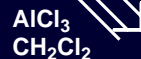
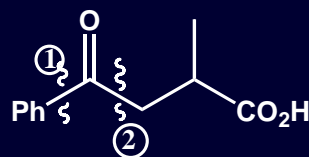
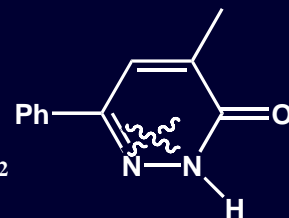
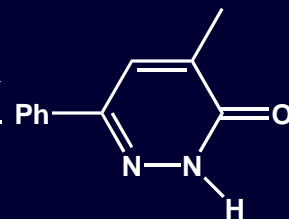
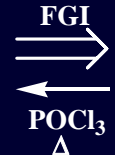
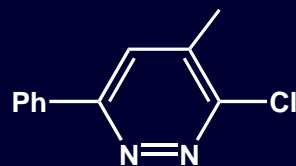
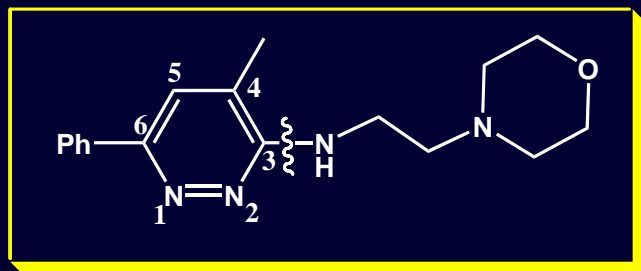
FGI,
RETRO GRIGNARD



RETRO ACILAZIONE
FRIEDEL CRAFT

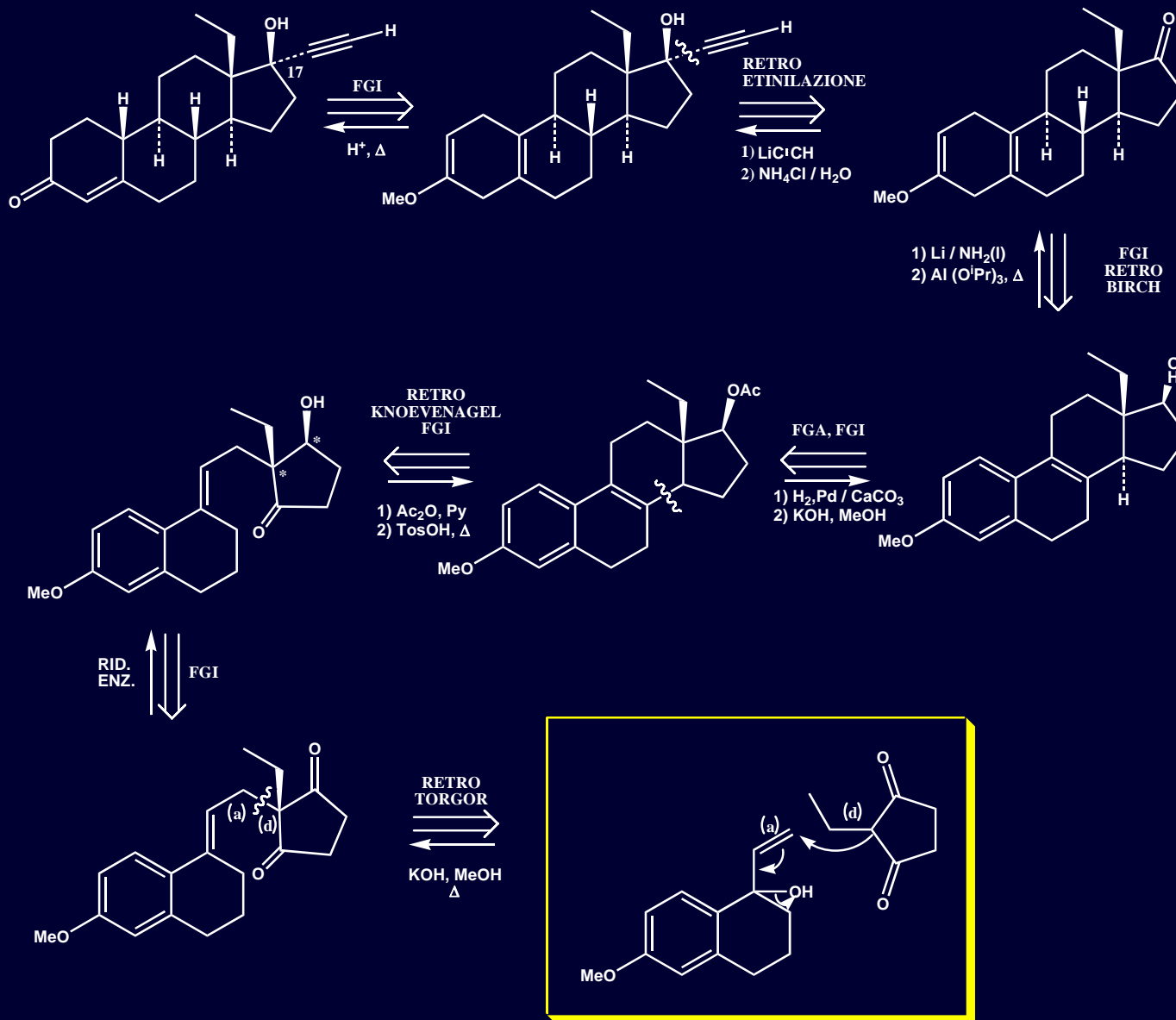


Retrosynthesis of Minaprine - Antidepressant

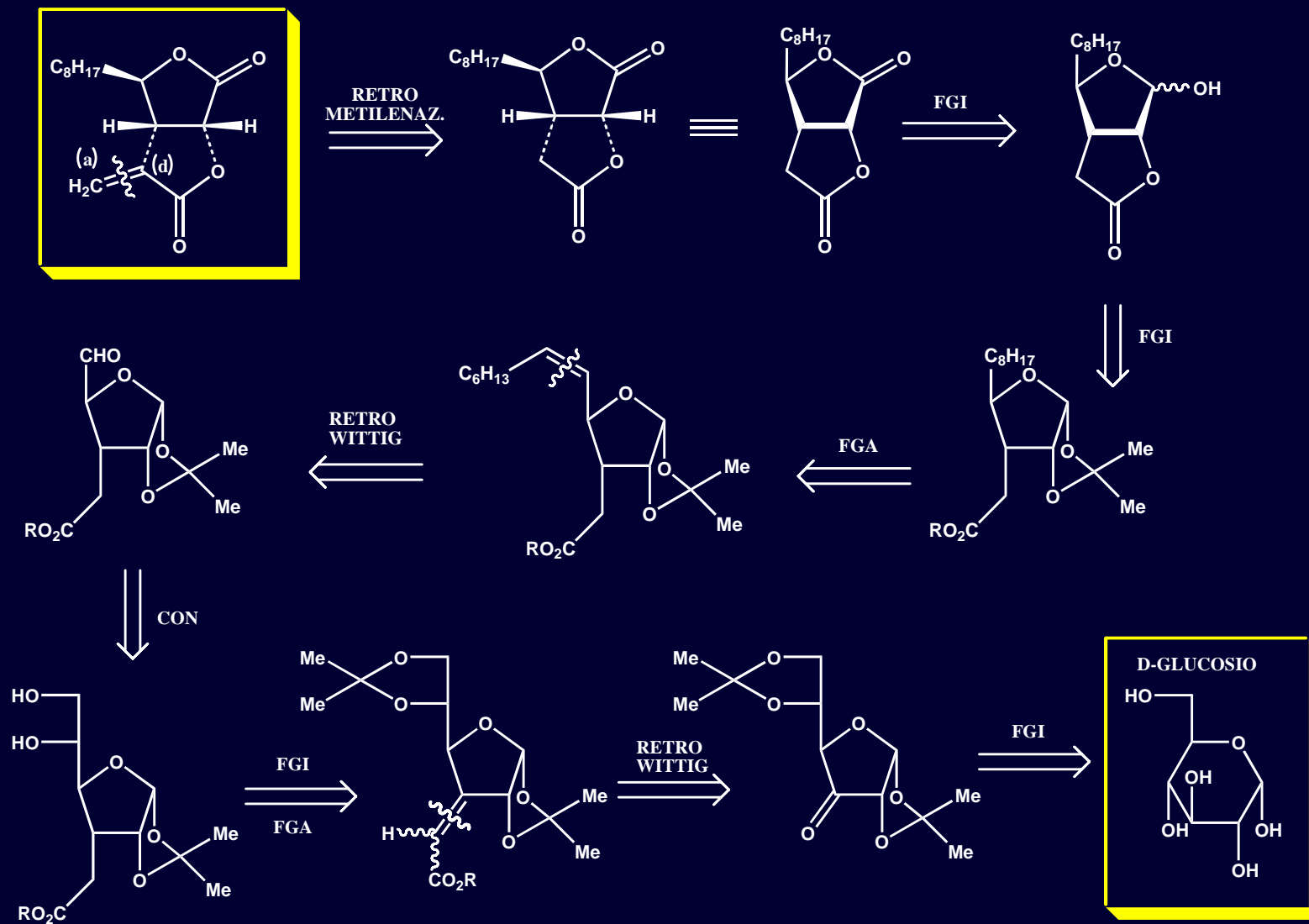


Retrosynthesis of (+)-Norgestrel

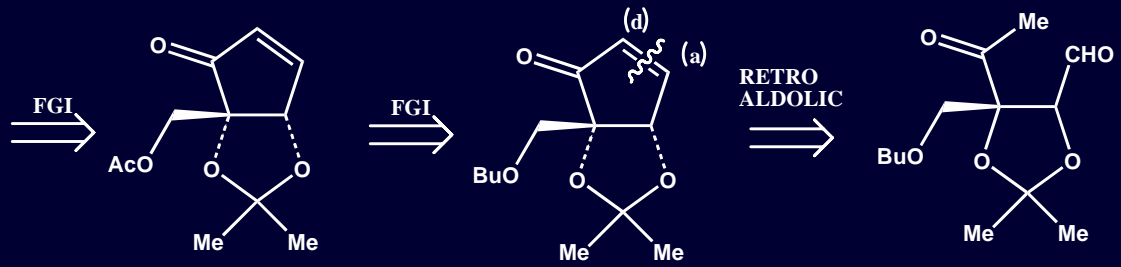
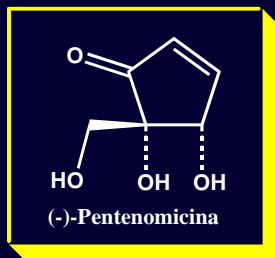
19-Nor Steroid



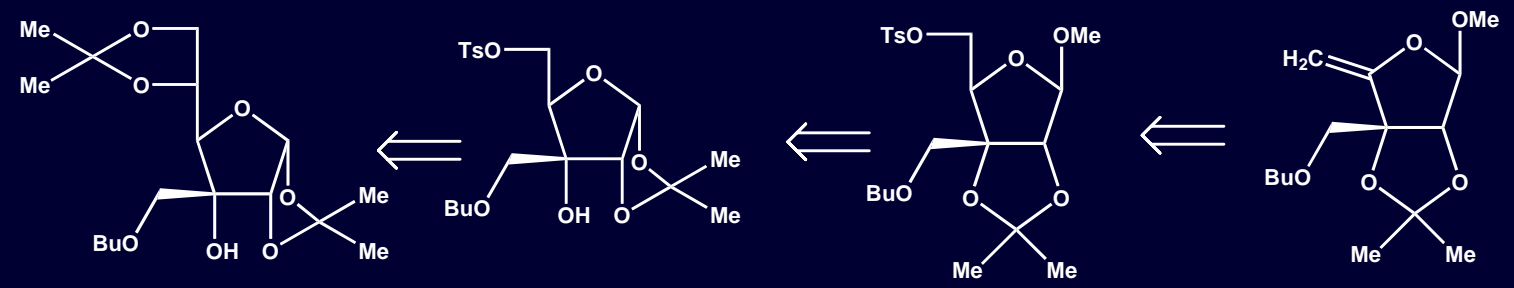
Retrosynthesis of Avenaciolide



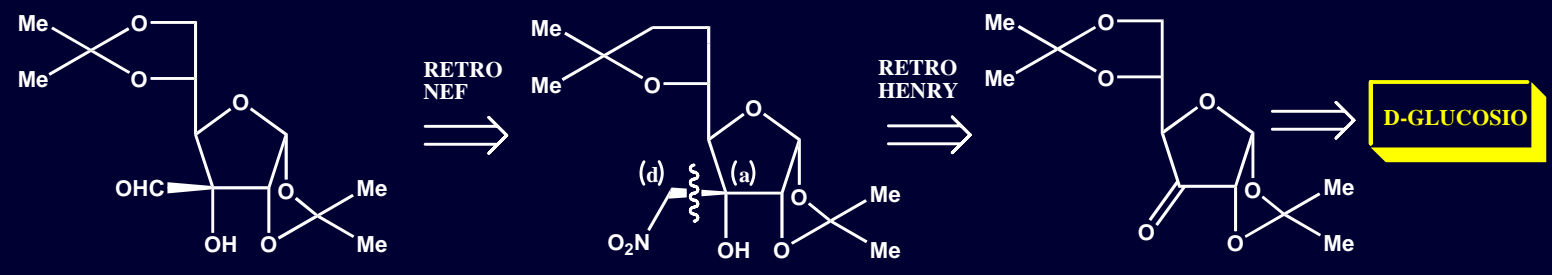
Retrosynthesis of Pentenomicina



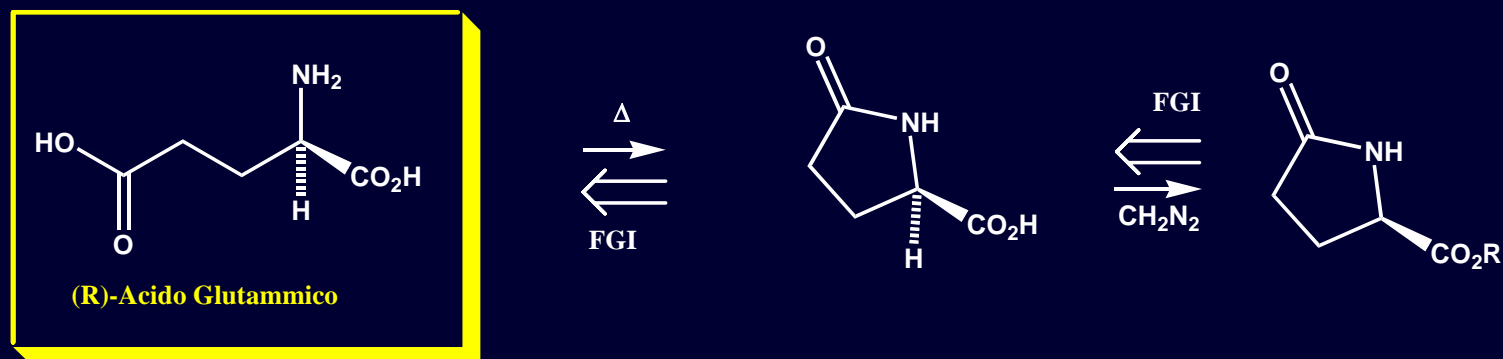
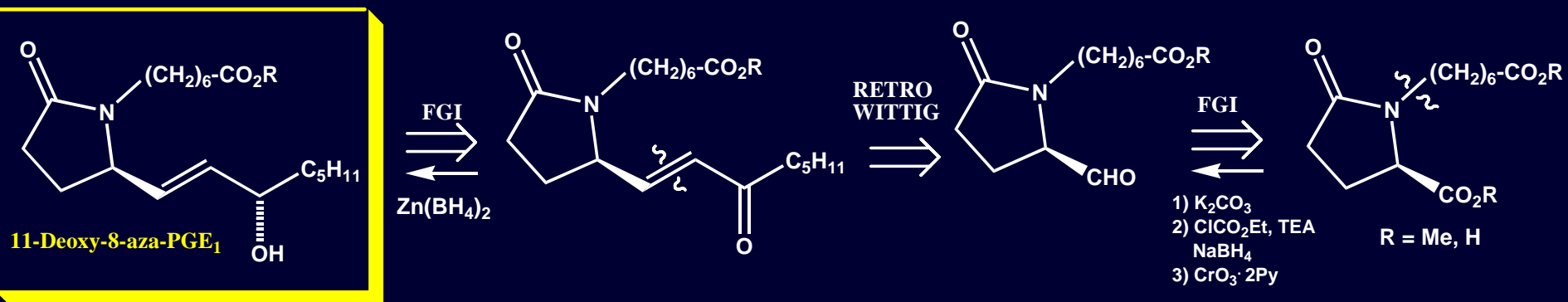
FGI



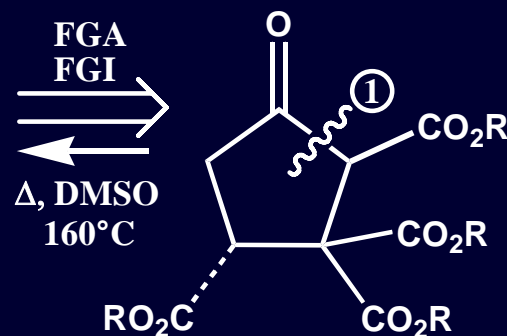
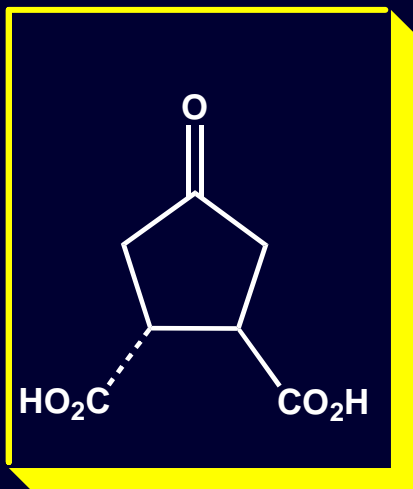
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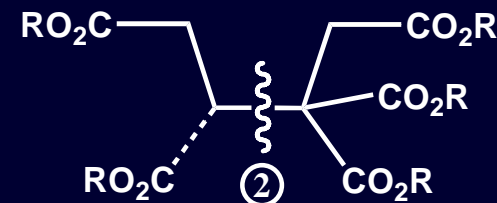
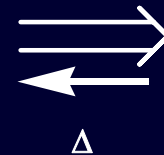
Retrosynthesis of 11-Deoxy-8-aza-PGE₁



Retrosynthesis of ± 4 -oxocyclopentane-1,2-dicarboxylic acid

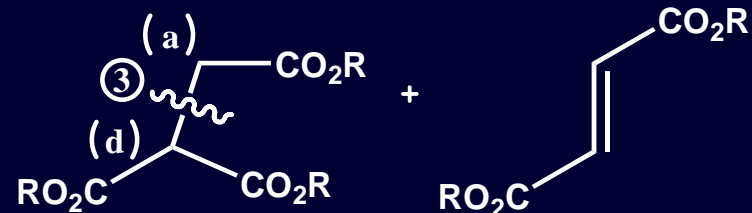
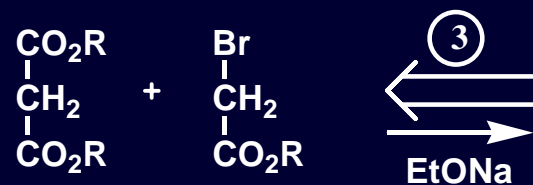


RETRO ①
DIECKMANN

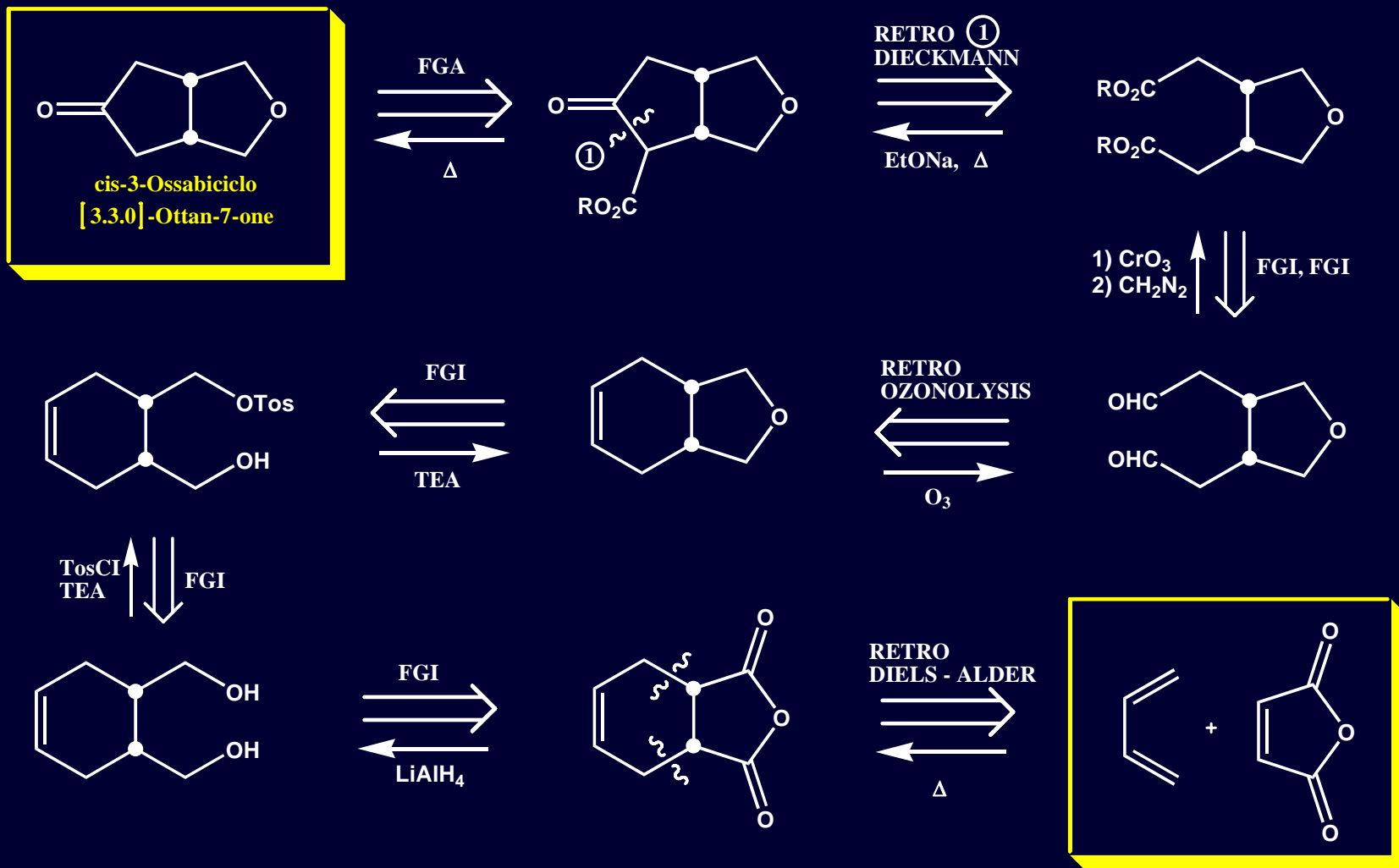


②

RETRO
MICHAEL

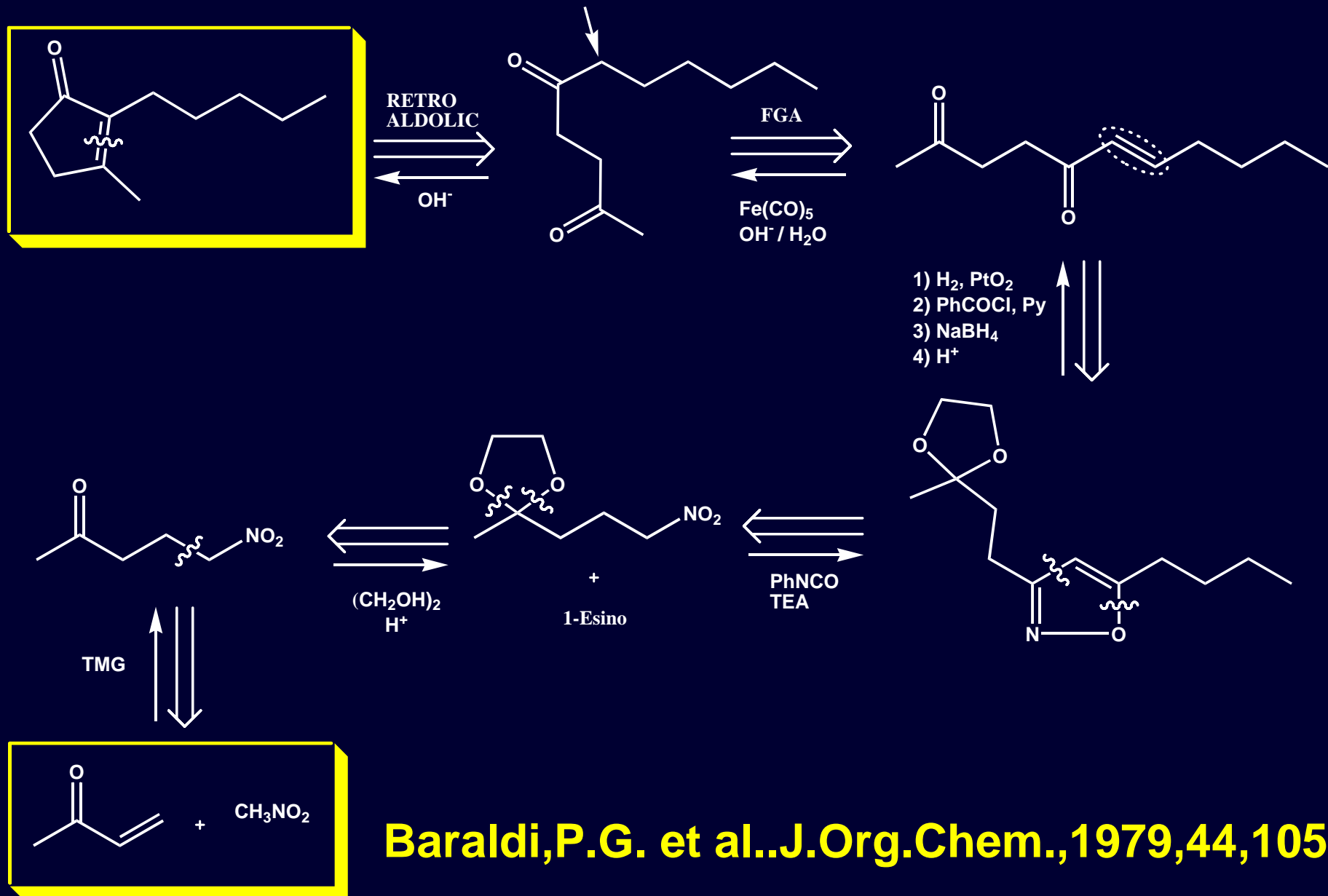


Retro-synthesis of cis-3-oxabicyclo[3.3.0]octan-7-one



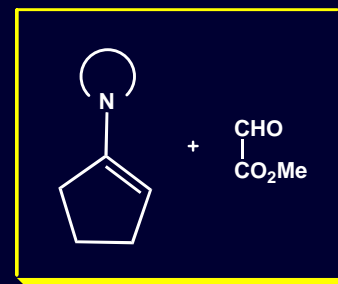
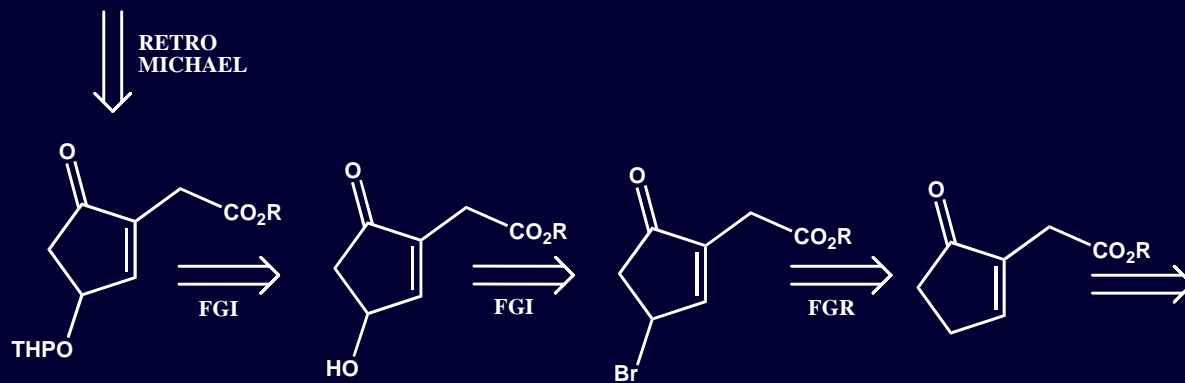
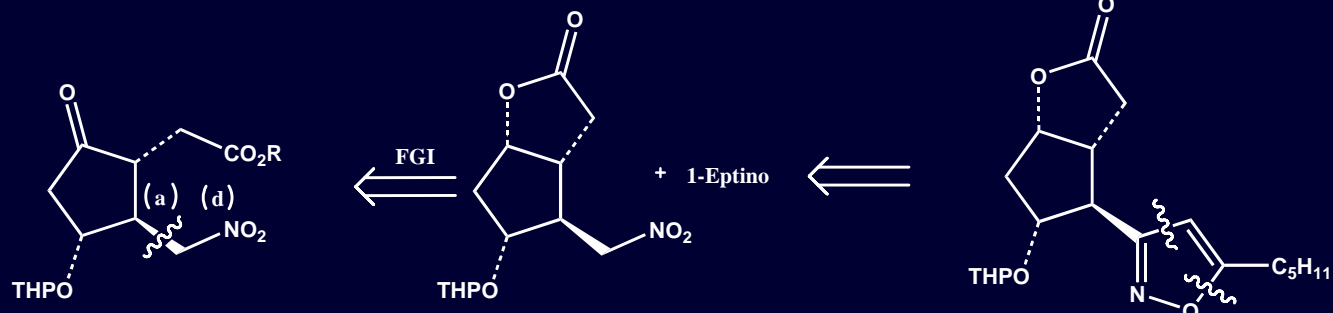
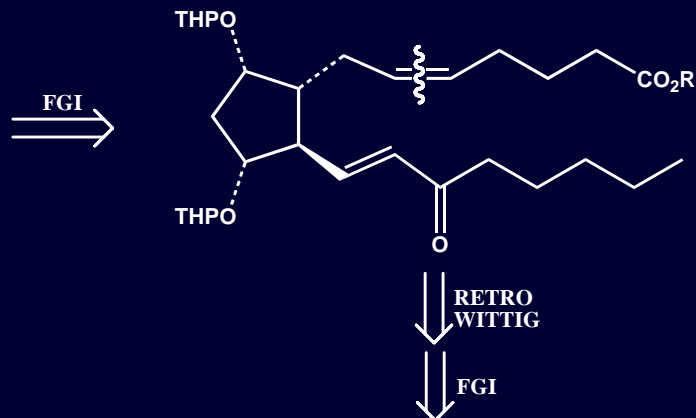
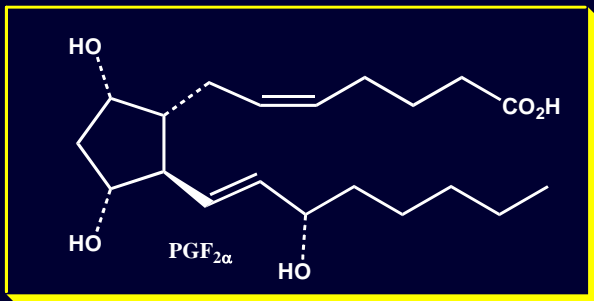
Baraldi, P.G. et al., Tetrahedron, 1984, 40, 761

Retrosynthesis of Diidroiasmone

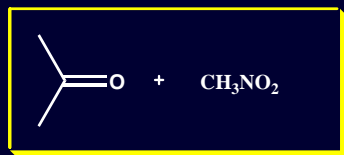
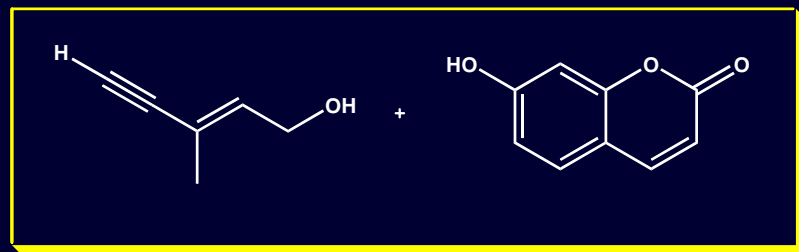
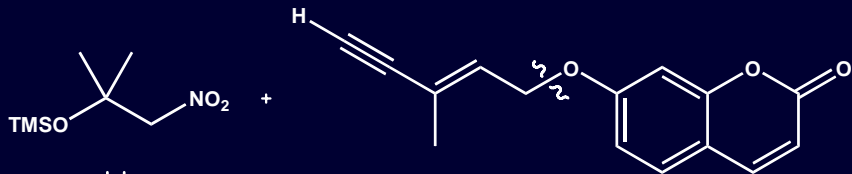
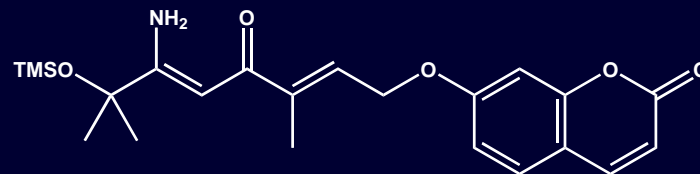
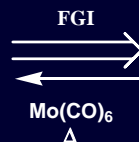
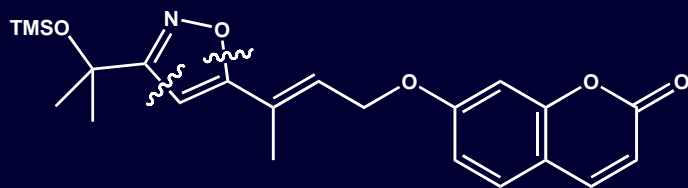
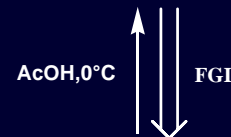
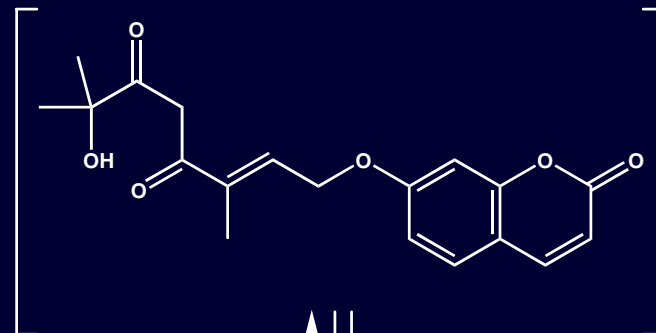
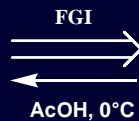
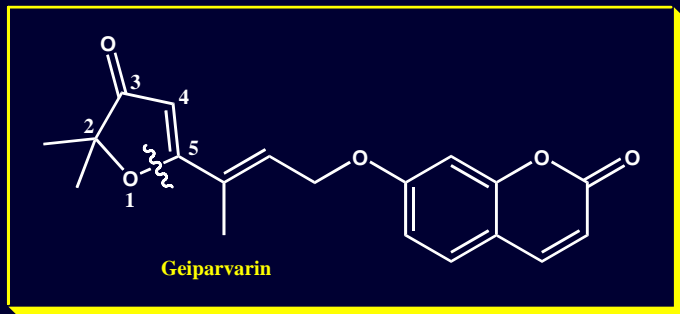


Baraldi, P.G. et al. J. Org. Chem., 1979, 44, 105

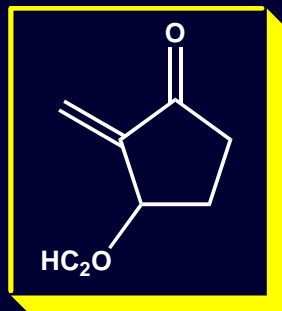
Retrosynthesis of PGF_{2α}



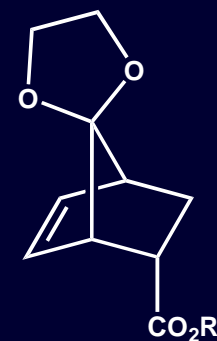
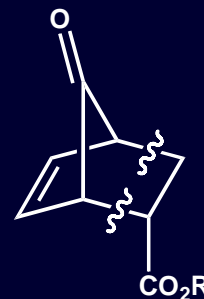
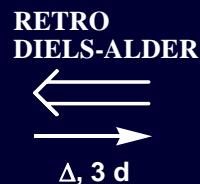
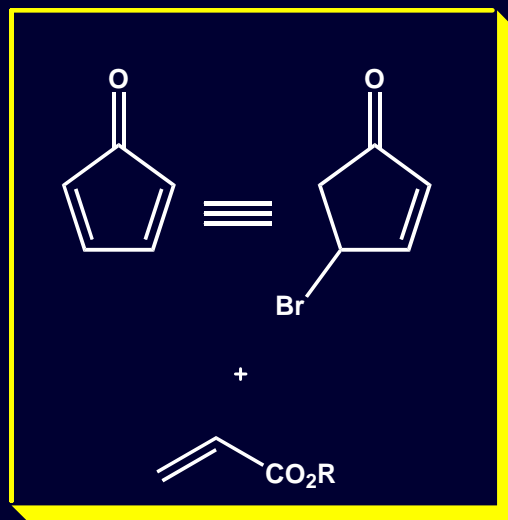
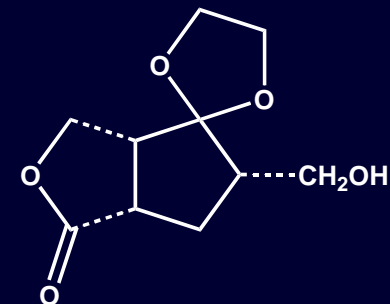
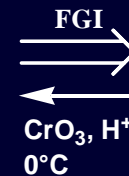
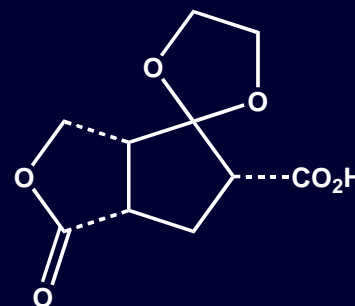
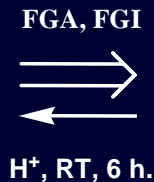
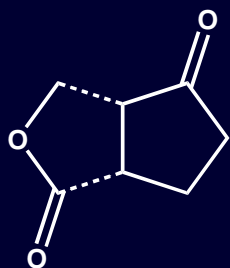
Retrosynthetic Route to Geiparvarin



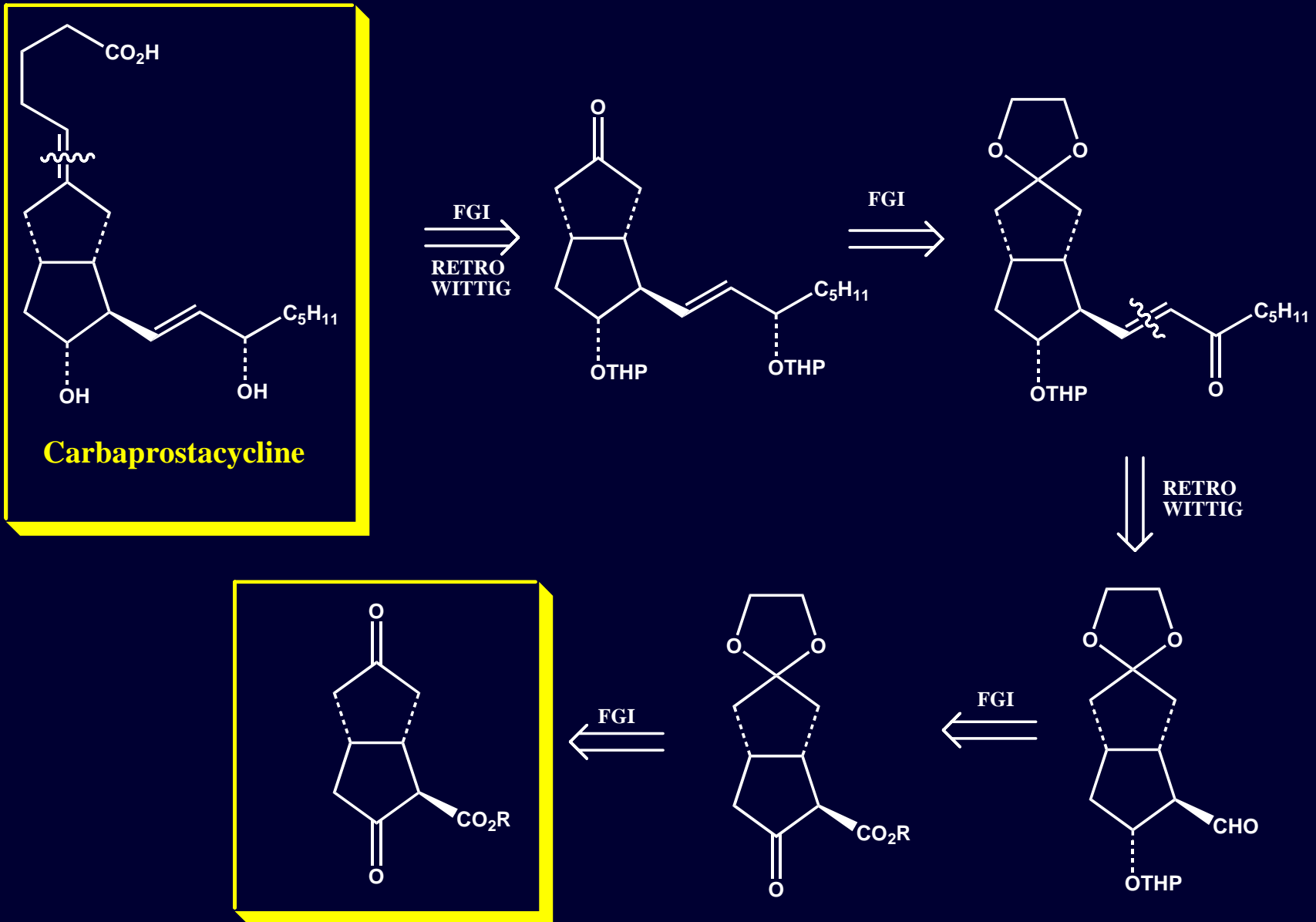
Retrosynthesis of Sarcomycin



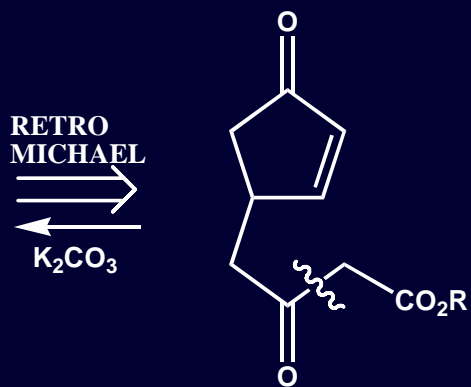
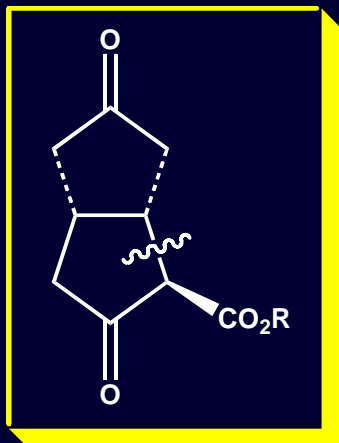
Sarcomicina



Retrosynthesis of Carbaprostacycline



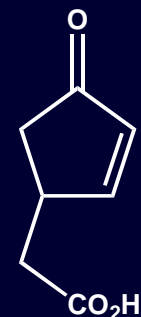
Retrosynthesis of a intermediate for Carbaprostacycline



RETRO CLAISEN



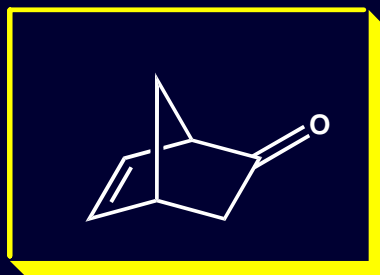
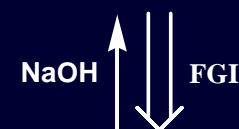
1) Im_2CO
2) CO_2Et
 CH_2
 CO_2H
 $Mg(OEt)_2$



FGI



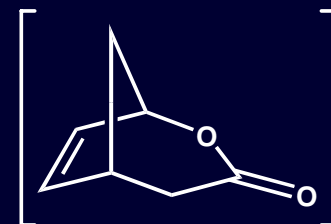
Jones



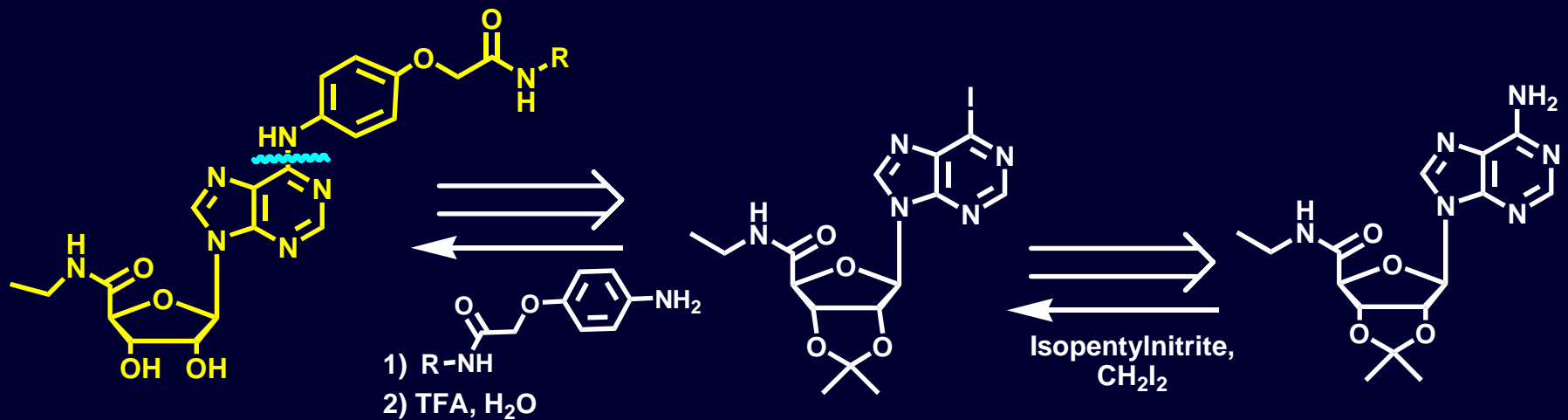
RETRO BAYER-WILLIGER



NaOH, H_2O_2



Synthesis and Retrosynthesis A_{2B} Agonists



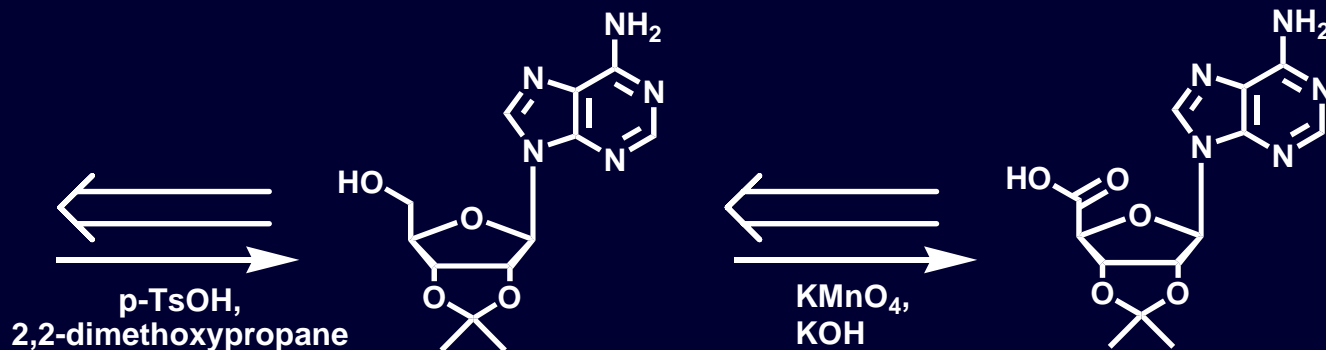
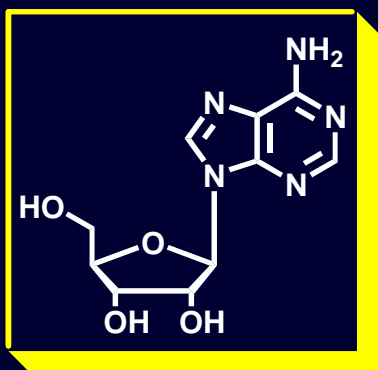
R = Ph

hA₁ K_i = 8.5 nM

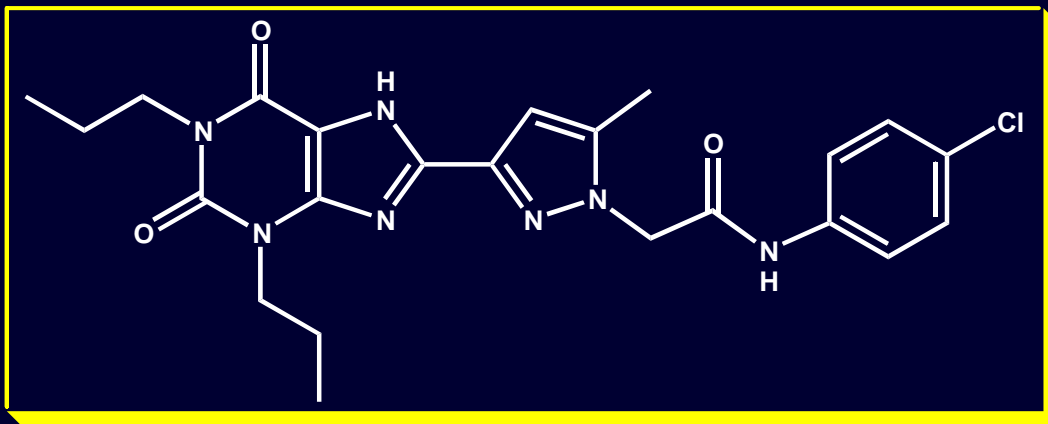
hA_{2A} K_i = >1000 nM

hA_{2B} EC₅₀ = 7.3 nM

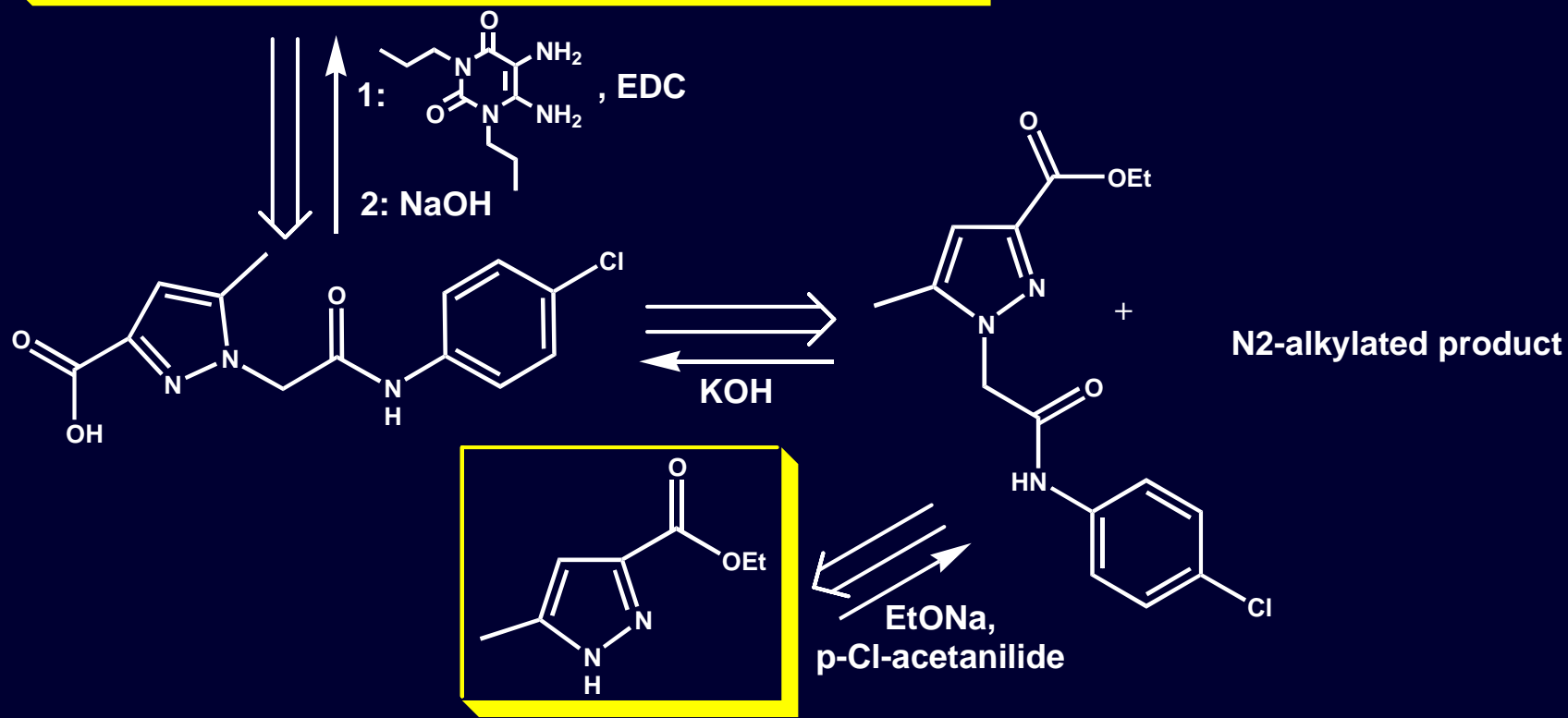
hA₃ K_i = 38.4 nM



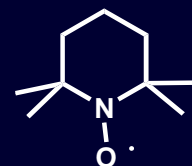
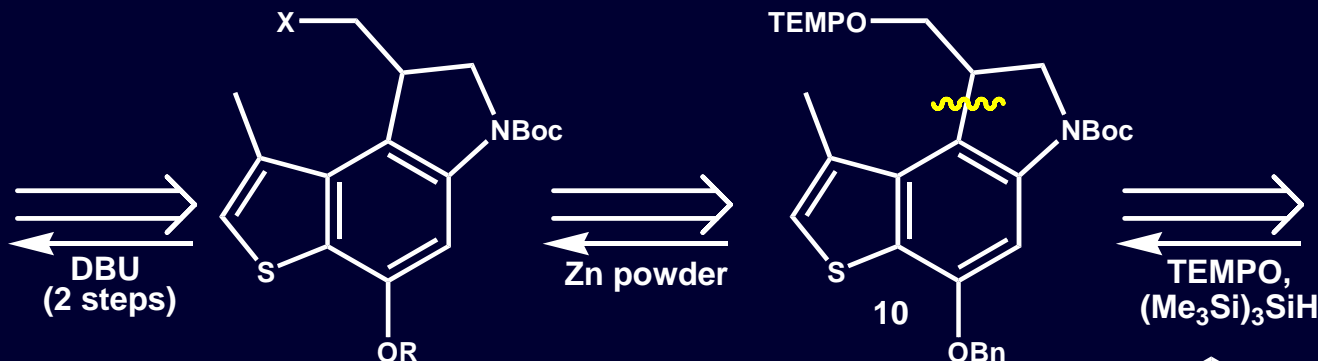
Synthesis and Retrosynthesis A_{2B} Antagonists



hA₁ K_i >1000nM
hA_{2A} K_i >1000nM
hA_{2B} IC₅₀ = 7nM
hA₃ K_i >1000nM



Synthesis and Retrosynthesis of sulphur Duocarmycins



Chiral column

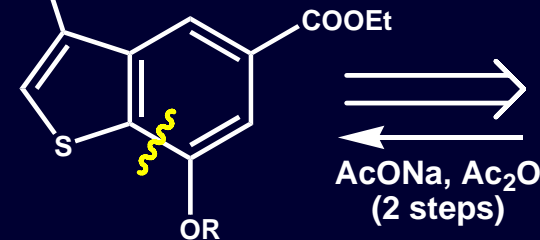
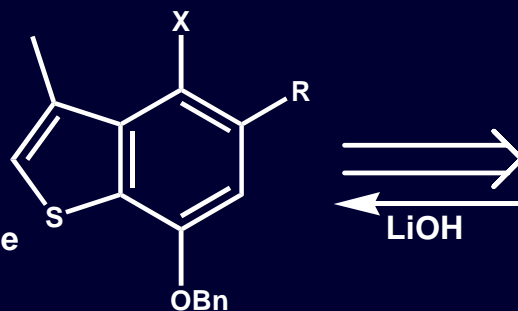
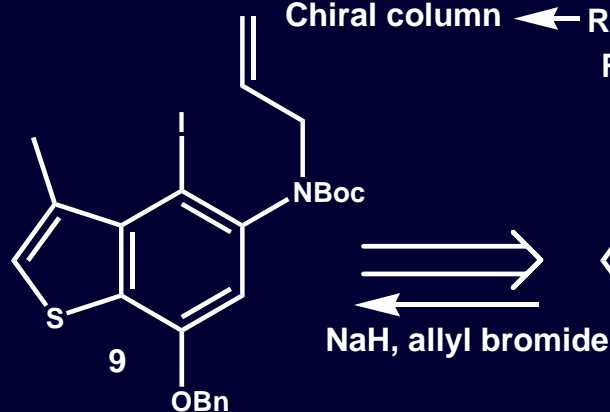
R = Bn, X = OH, 11

R = Bn, X = Cl, 12

R = H, X = Cl, 13

PPH₃, CCl₄

Pd/C, H₂CO₂NH₄



R = COOH, X = H, 6

R = NHBoc, X = H, 7

R = NHBoc, X = I, 8

DPPA

NIS

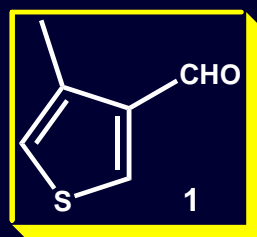
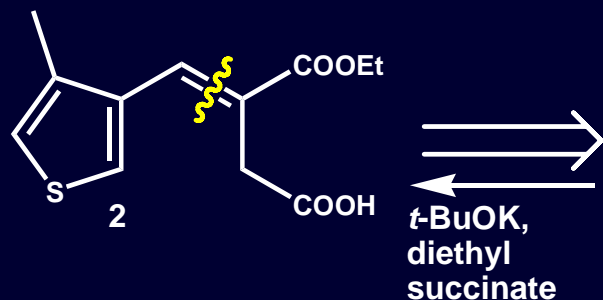
R = Ac, 3

R = H, 4

R = Bn, 5

K₂CO₃

BnBr



Baraldi P.G., Boger D.L., et al.
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