THE LOGIC OF ORGANIC SYNTHESIS
SEMESTER – IV
CBCS SYSTEM

PRESENTED
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THE LOGIC OF ORGANIC SYNTHESIS

SYLLABUS

Retrosynthetic analysis: disconnections; synthons, donor and acceptor synthons; natural reactivity and umpolung; latent polarity in bifunctional compounds: illogical electrophiles and nucleophiles; synthetic equivalents; functional group interconversion and addition (FGI and FGA); C-C disconnections and synthesis: one-group and two-group (1,2- to 1,5-dioxygenated compounds), reconnection (1,6-dicarbonyl);protection-deprotection strategy (alcohol, amine, carbonyl, acid).

Strategy of ring synthesis: thermodynamic and kinetic factors; synthesis of large rings, application of high dilution technique.

Asymmetric synthesis: stereoselective and stereospecific reactions; diastereoselectivity and enantioselectivity (only definition); diastereoselectivity: addition of nucleophiles to C=O adjacent to a stereogenic centre: Felkin-Anh model.

The logic of Organic Synthesis

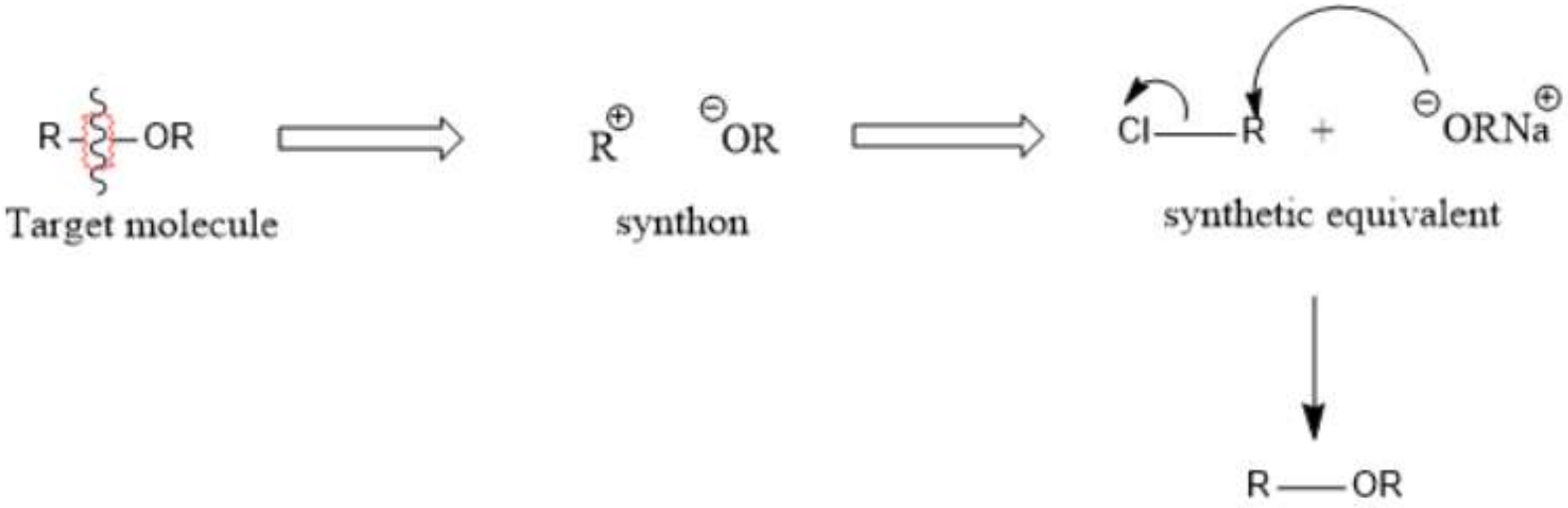
Retrosynthetic analysis: Retrosynthetic analysis is a technique for solving problems in the planning of organic syntheses. This is achieved by transforming a target molecule into simpler precursor structures.

Disconnections: A retrosynthetic step involving the breaking of a bond to form two (or more) synthons.

TARGET MOLECULE (TM): The molecule whose synthesis is to be planned by retrosynthetic approach is the target molecule.

Synthon: Fragments after disconnections

Synthetic Equivalents: Molecule that gives the requisite synthon.


R—OR
Target molecule
R⊕ ⊖OR
synthon
Cl—R + ⊖ORNa⊕
synthetic equivalent
R—OR

Natural reactivity and *Umpolung*

Umpolung or **polarity inversion** in organic chemistry is the chemical modification of a functional group with the aim of the reversal of polarity of that group.[1][2] This modification allows secondary reactions of this functional group that would otherwise not be possible.[3] The concept was introduced by D. Seebach (hence the German word *umpolung* for reversed polarity) and E.J. Corey. Polarity analysis during retrosynthetic analysis tells a chemist when umpolung tactics are required to synthesize a target molecule.

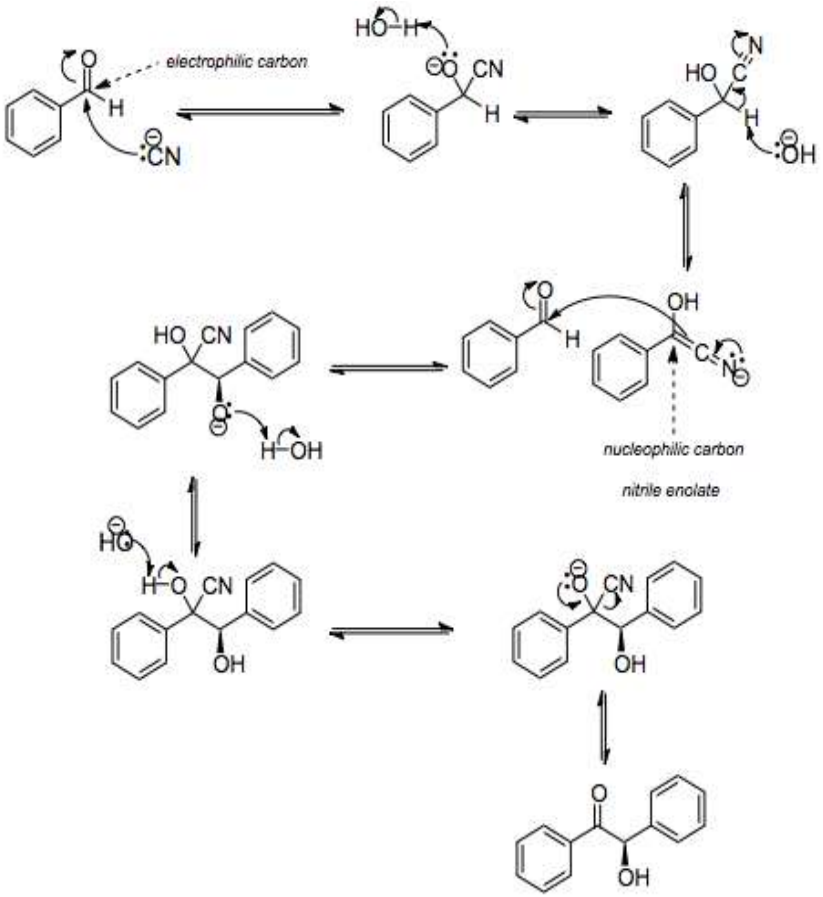
The vast majority of important organic molecules contain heteroatoms, which polarize carbon skeletons by virtue of their electronegativity. Therefore, in standard organic reactions, the majority of new bonds are formed between atoms of opposite polarity. This can be considered to be the "normal" mode of reactivity.

One consequence of this natural polarization of molecules is that 1,3- and 1,5-heteroatom substituted carbon skeletons are extremely easy to synthesize (Aldol reaction, Claisen condensation, Michael reaction, Claisen rearrangement, Diels-Alder reaction), whereas 1,2-, 1,4-, and 1,6- heteroatom substitution patterns are more difficult to access via "normal" reactivity. It is therefore important to understand and develop methods to induce *umpolung* in organic reactions.

Cyanide-type *umpolung*

The canonical umpolung reagent is the cyanide ion. The cyanide ion is unusual in that a carbon triply bonded to a nitrogen would be expected to have a (+) polarity due to the higher electronegativity of the nitrogen atom. Yet, the negative charge of the cyanide ion is localized on the carbon, giving it a (-) formal charge. This chemical ambivalence results in umpolung in many reactions where cyanide is involved.

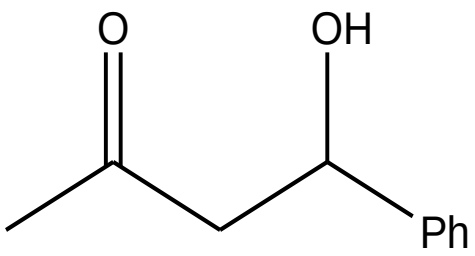
For example, cyanide is a key catalyst in the benzoin condensation, a classical example of polarity inversion.



Latent polarity in bifunctional compounds

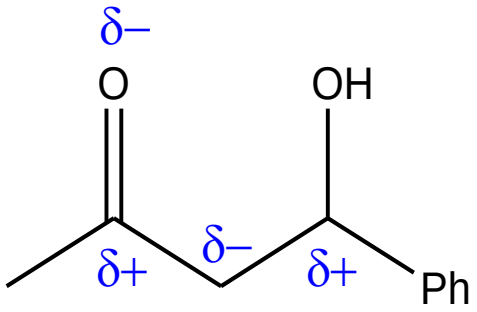
Latent polarity concept is the imaginary pattern of alternating + and – charges in the target skeleton, used to help in the identification of the disconnection and hence the synthons of a target molecule.

Consider a 1,3-disubstituted molecule, e.g.

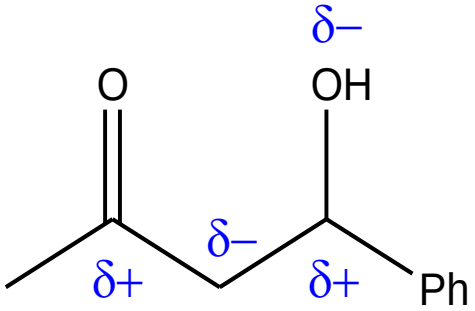


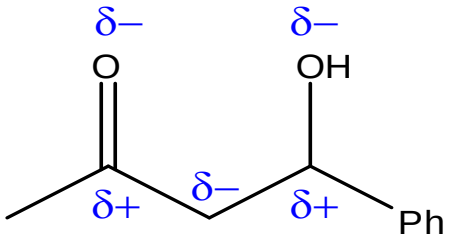
Latent Polarities:

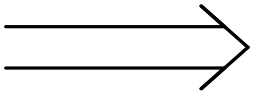
starting from C=O

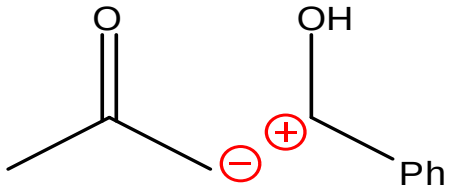


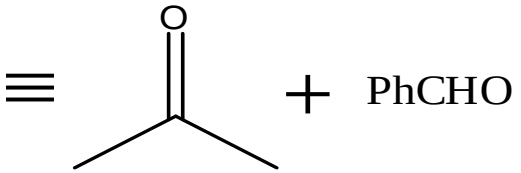
starting from C—OH



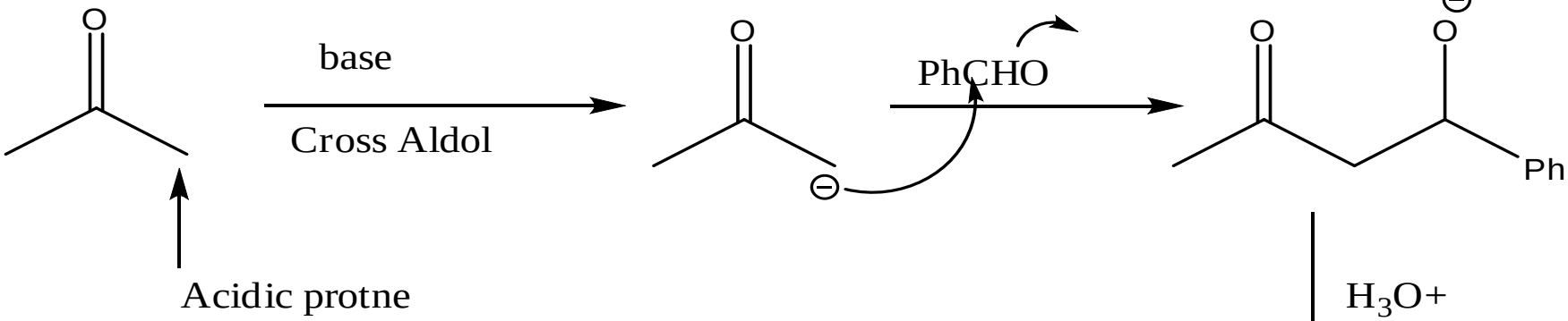

δ–
δ–
O
OH
δ+
δ–
δ+
Ph



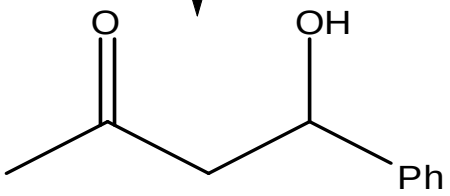

O
OH
Ph


O
PhCHO

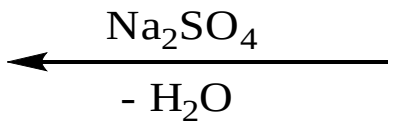
Thus

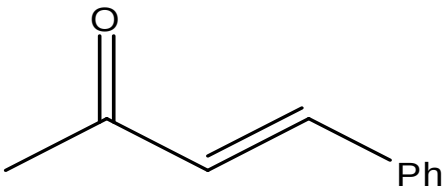

O
base
Cross Aldol
PhCHO
O
O
Ph
Acidic protne

H3O+


O
OH
Ph

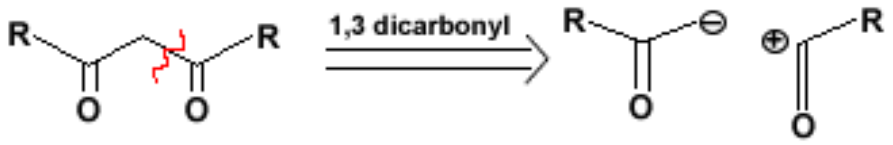
TM


Na2SO4
- H2O

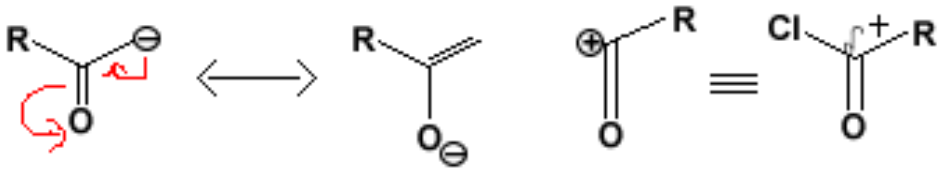

O
Ph

TM2

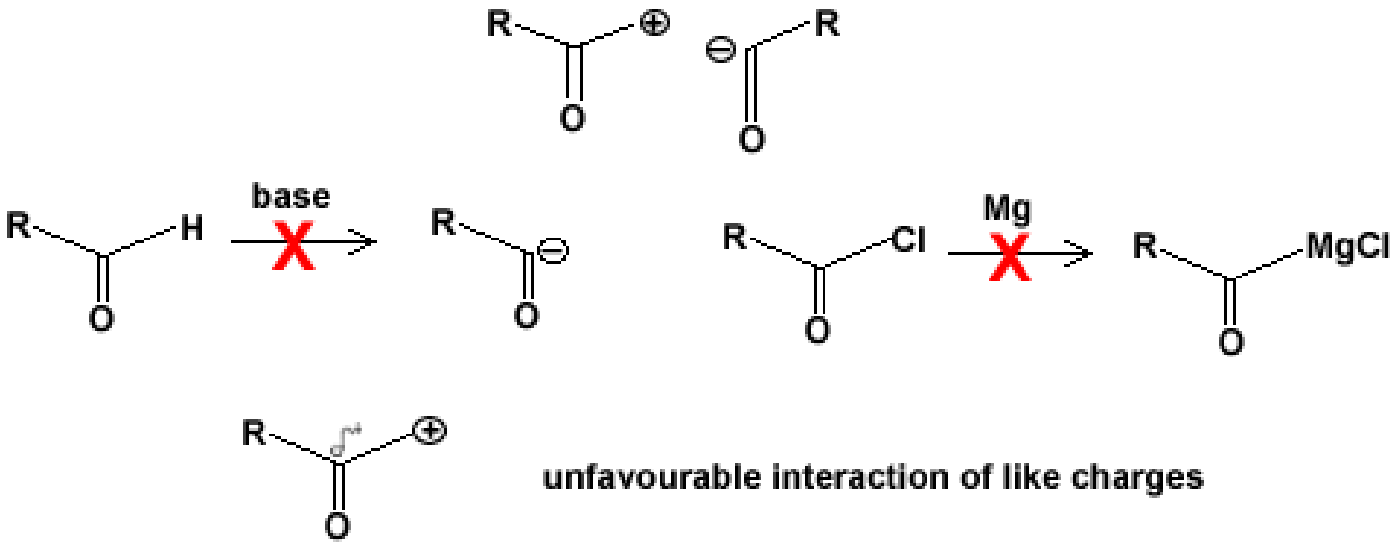
Illogical electrophiles and nucleophiles



These are logical synthons due to the favourable interaction of charges with functional groups:



However, if the charges were swapped around, the synthons would be "illogical" because of unfavourable interactions:



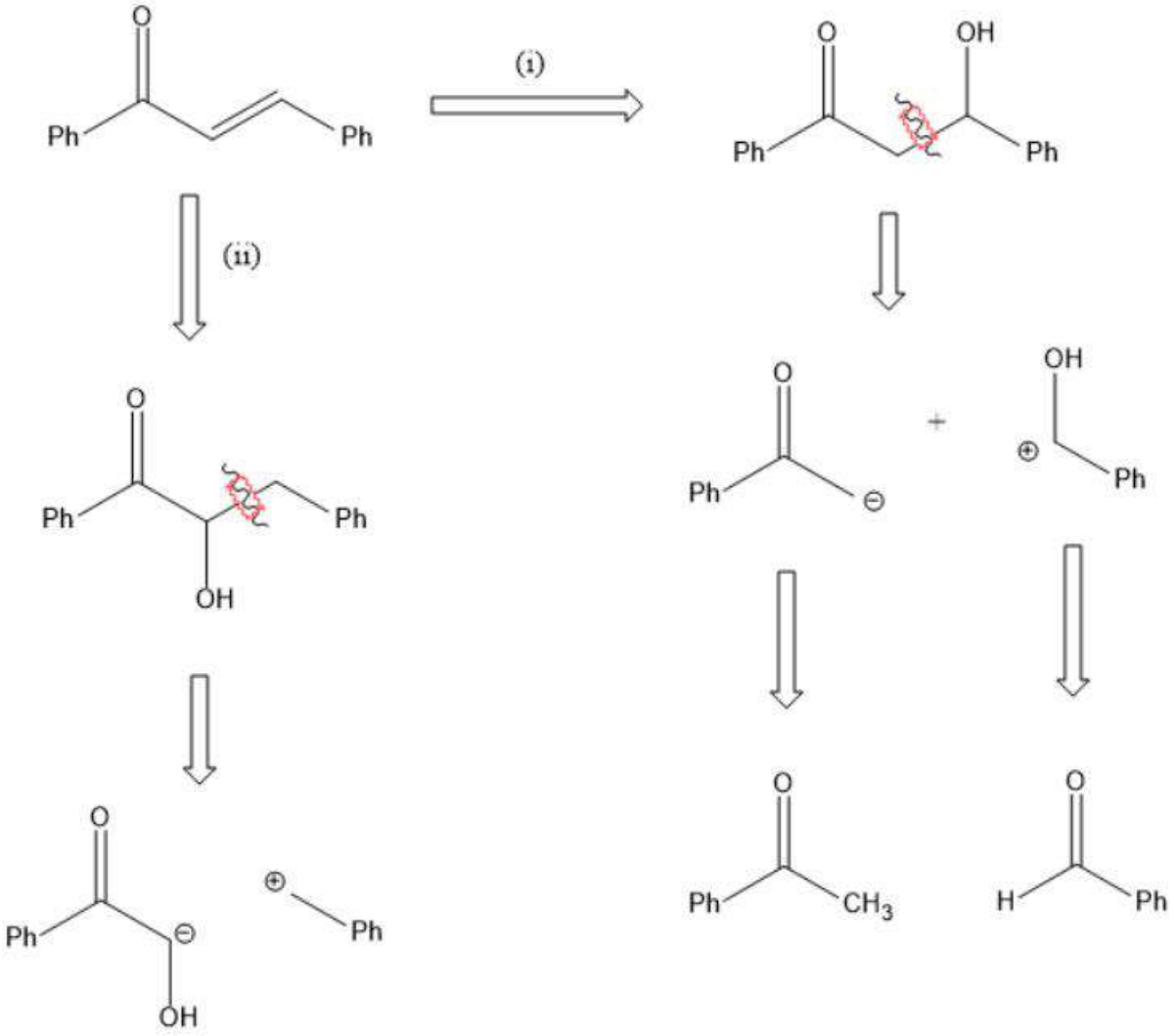
Functional Group Interconversion (FGI)

writing of one functional group for another so that disconnection becomes possible to get a starting material available in the market. FGI can be done by substitution, addition, elimination, oxidation, reduction etc.

Why FGI is needed?

During the synthesis of a target molecule containing more than one functional group, one functional group may interfere in the desired synthesis of the other. This could be overcome by protecting that interfering functional group or by changing the synthetic strategy, which is called FGI.

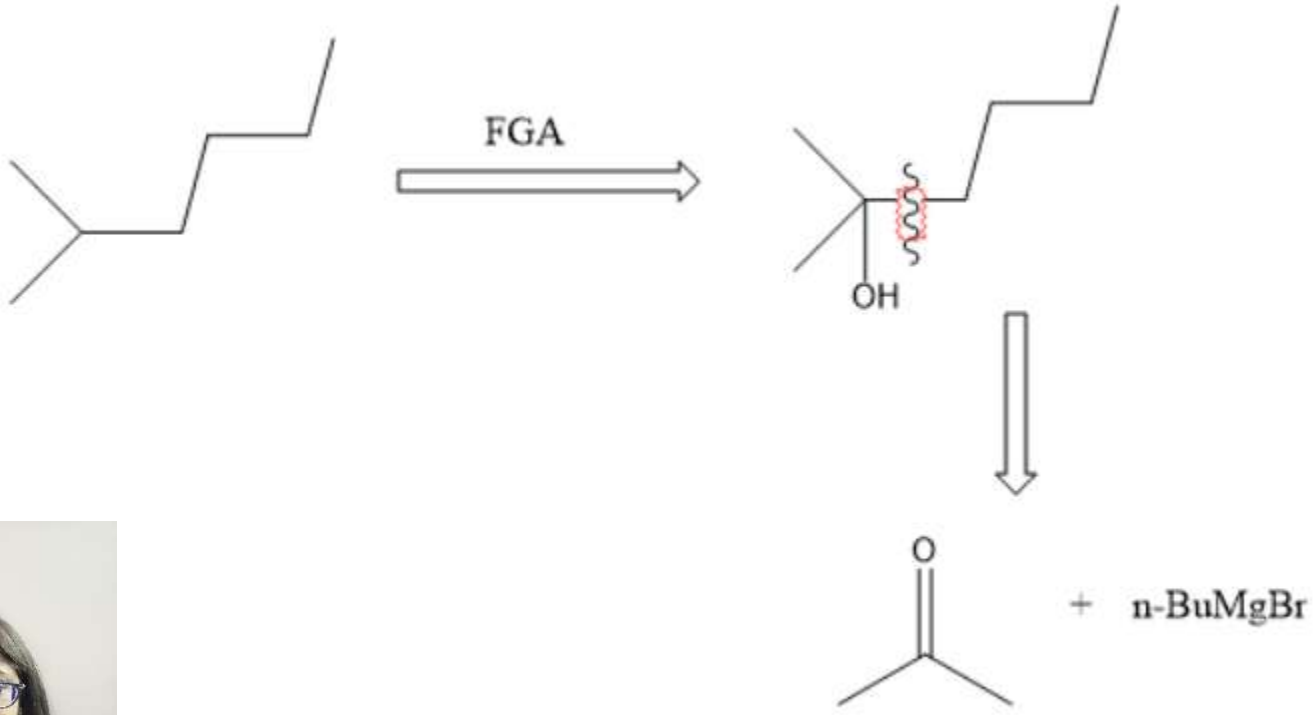
Example of FGI



Synthetic equivalent not available

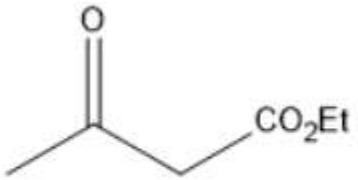
Functional Group Addition (FGA)

Sometimes it becomes necessary to add a functional group during analysis so as to make the disconnection easier. The same functional group is then removed during synthesis.

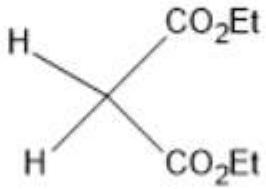


C-C disconnections and synthesis:
one-group and two-group (1,2- to 1,5-dioxygenated compounds)

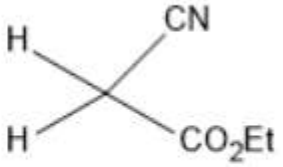
Use of active methylene compounds :



ethylacetoacetate (EAA)



diethylmalonate (DEM)

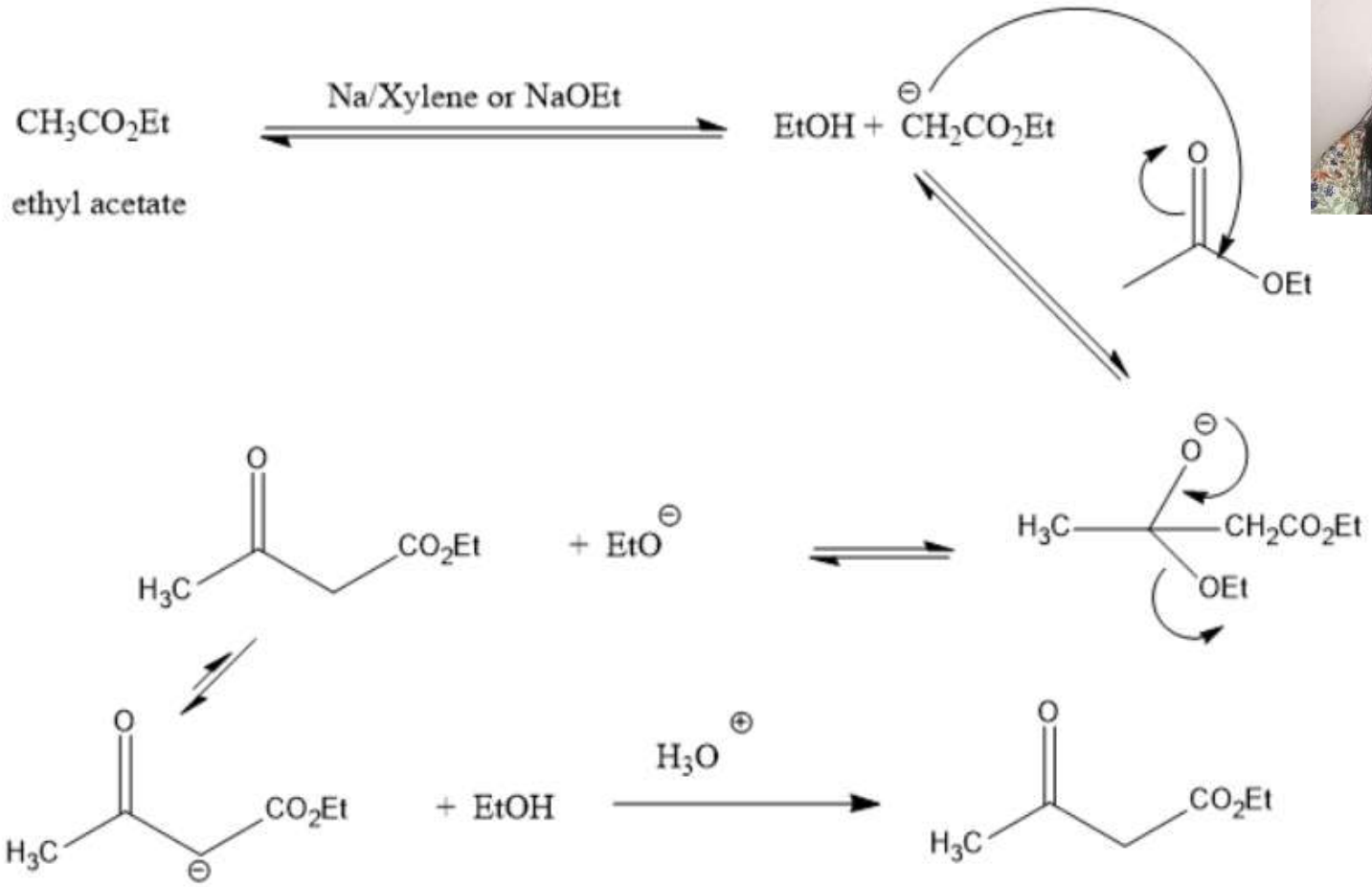


ethylcyanoacetate (ECA)

Q. Carry out the disconnection and synthesis of EAA -

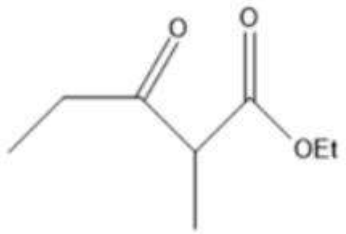
Retrosynthesis

Forward approach (Claisen Condensation)

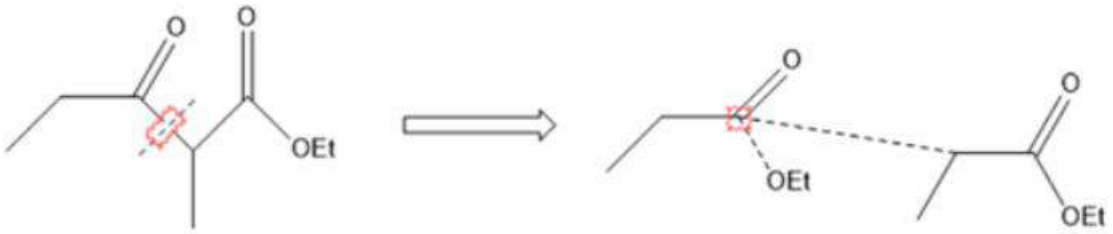


Though EtOH is stronger acid than ethyl acetate, the EAA formed is much more stronger acid than EtOH.

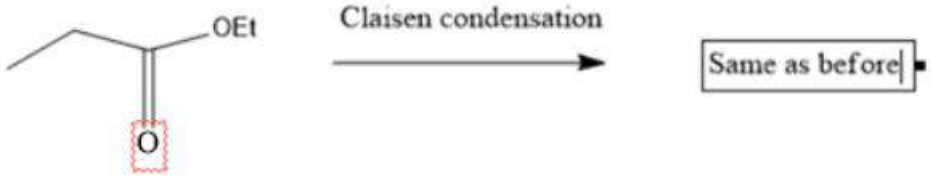
Q. Carry out the disconnection and synthesis of the following compound -



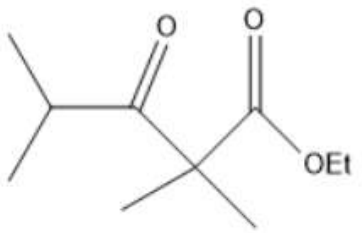
Backward approach



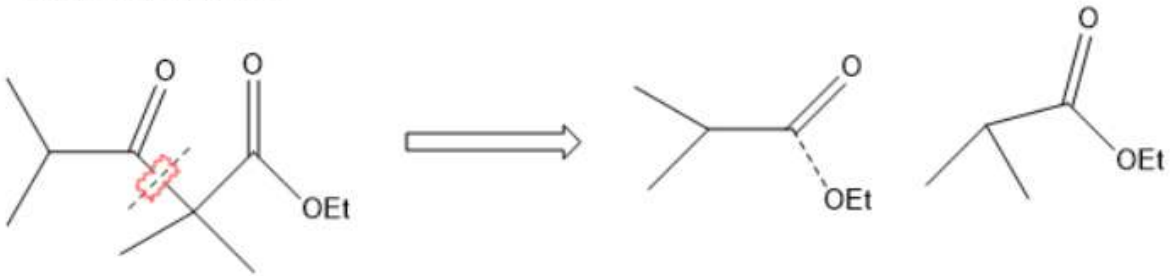
Forward approach



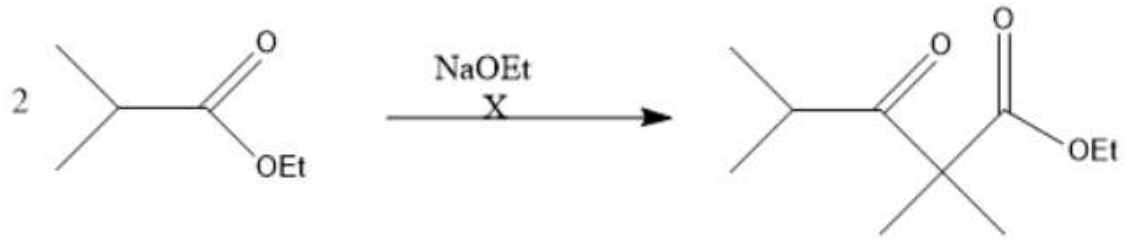
Q. Carry out the disconnection and synthesis of the following compound -



Backward approach

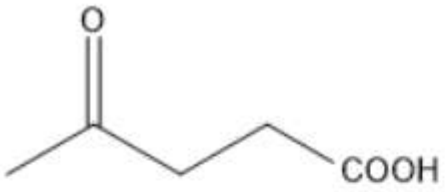


Forward approach

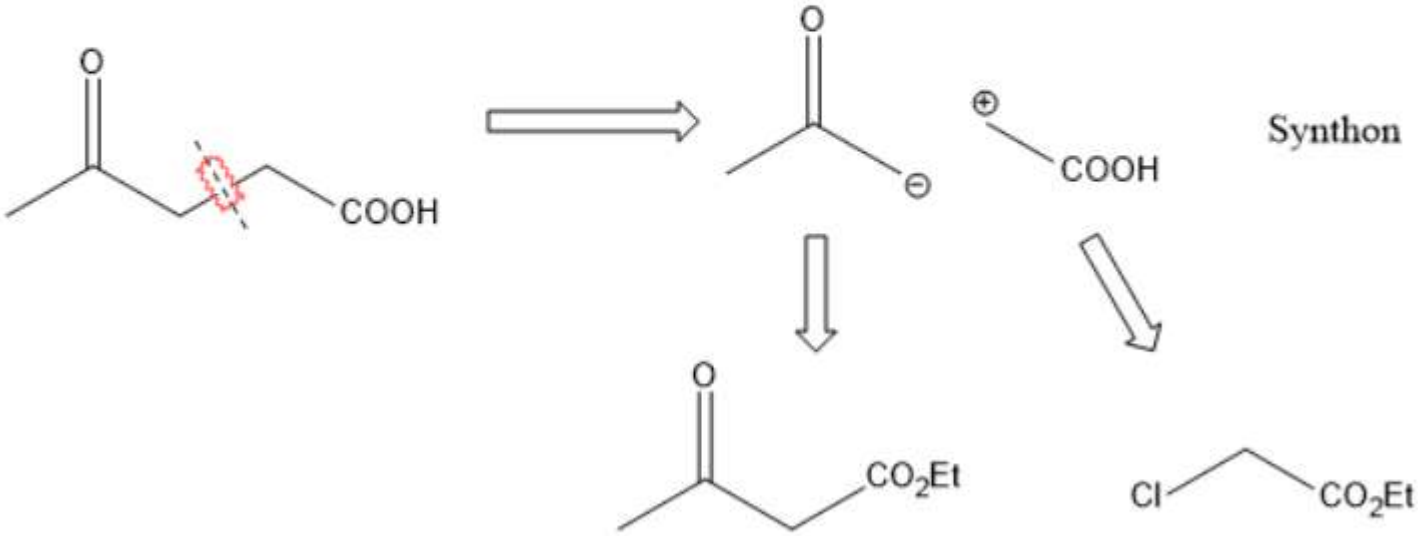


Because of steric crowding, here we have to use $Ph_3C^-Na^+$, $NaNH_2$, NaH i.e. a very strong base.

Q. Carry out the disconnection and synthesis of the following compound -

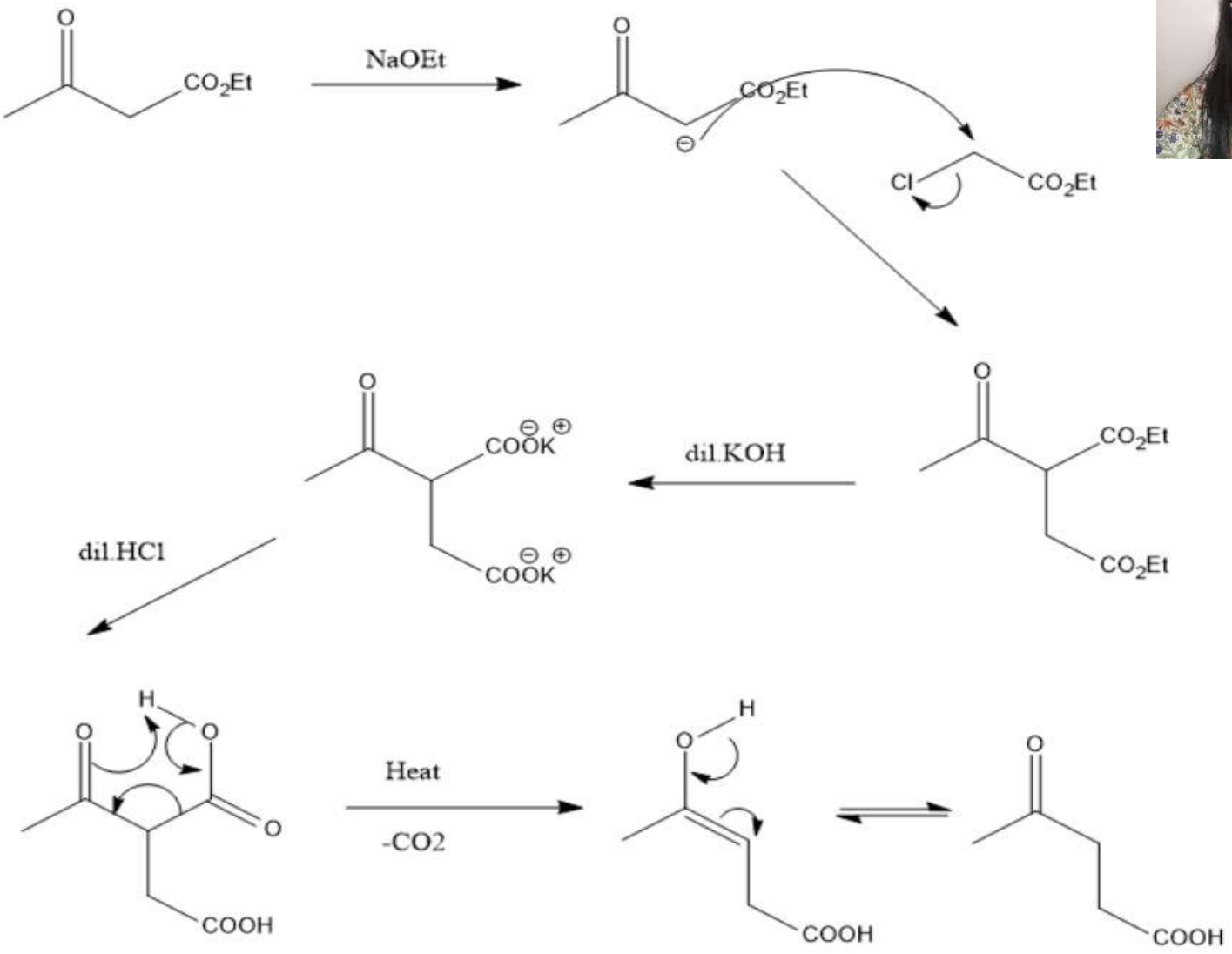


Backward approach

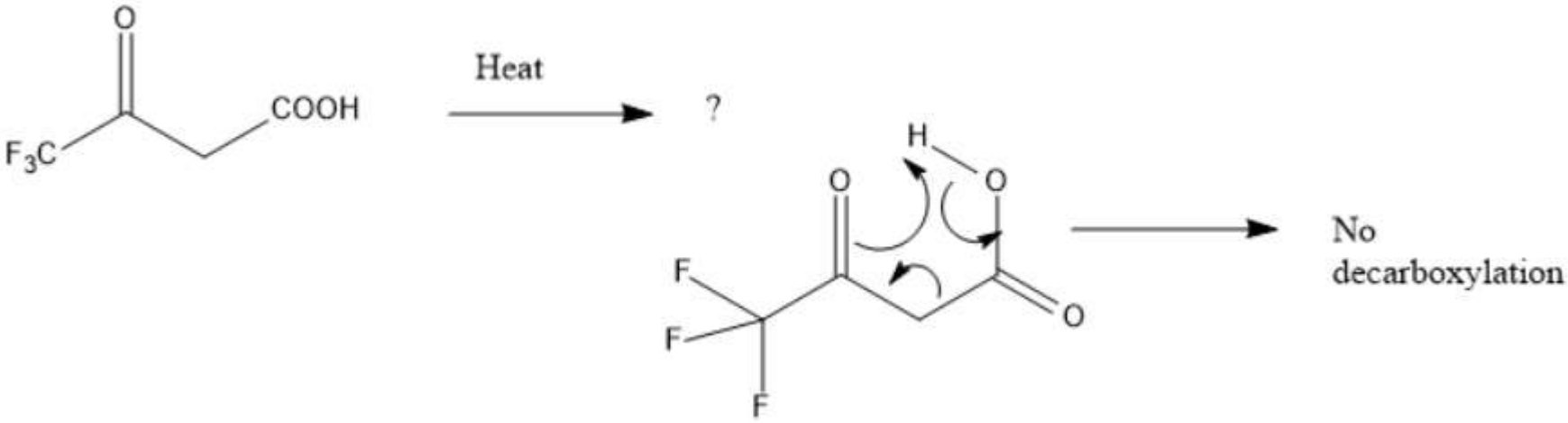


Synthetic equivalent

Forward approach

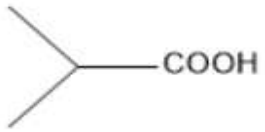


Q. What happens when -

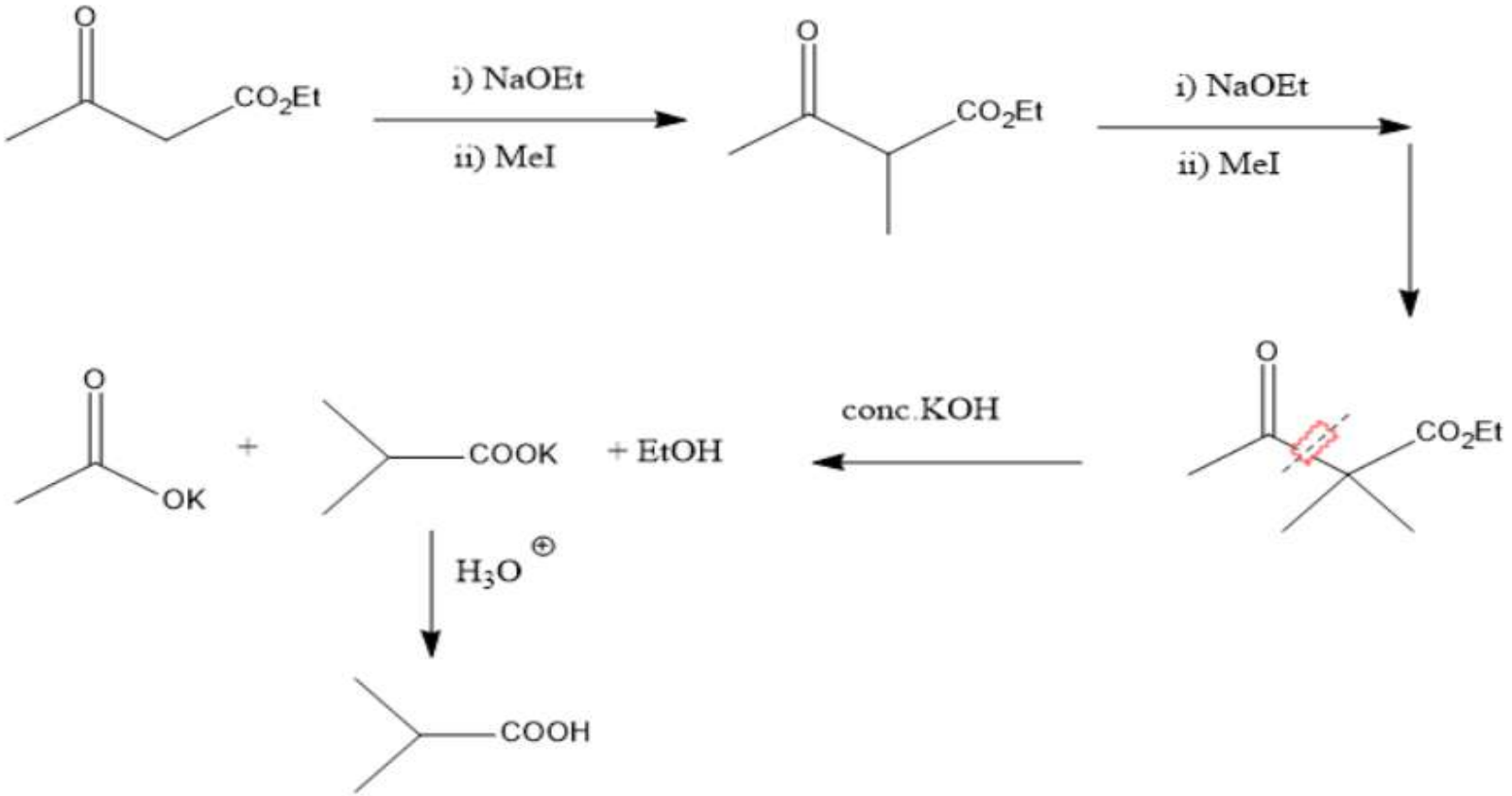


The highly electronegative F atoms doesn't allow this type of rearrangement. Therefore, no decarboxylation occurs.

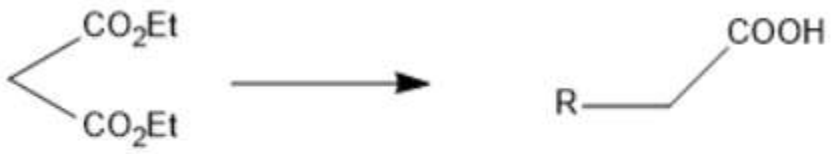
Q. Carry out synthesis of the following compound -



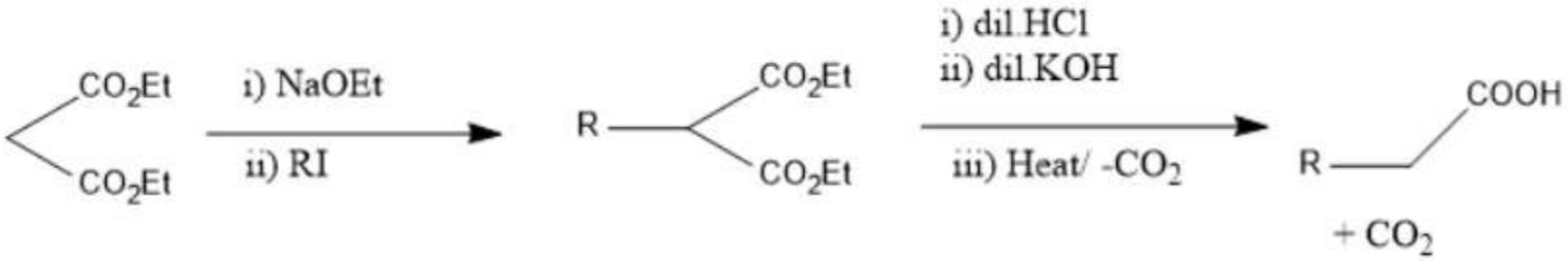
Forward approach



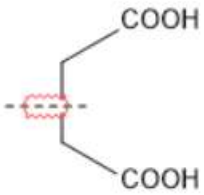
Q. Carry out the following conversion -



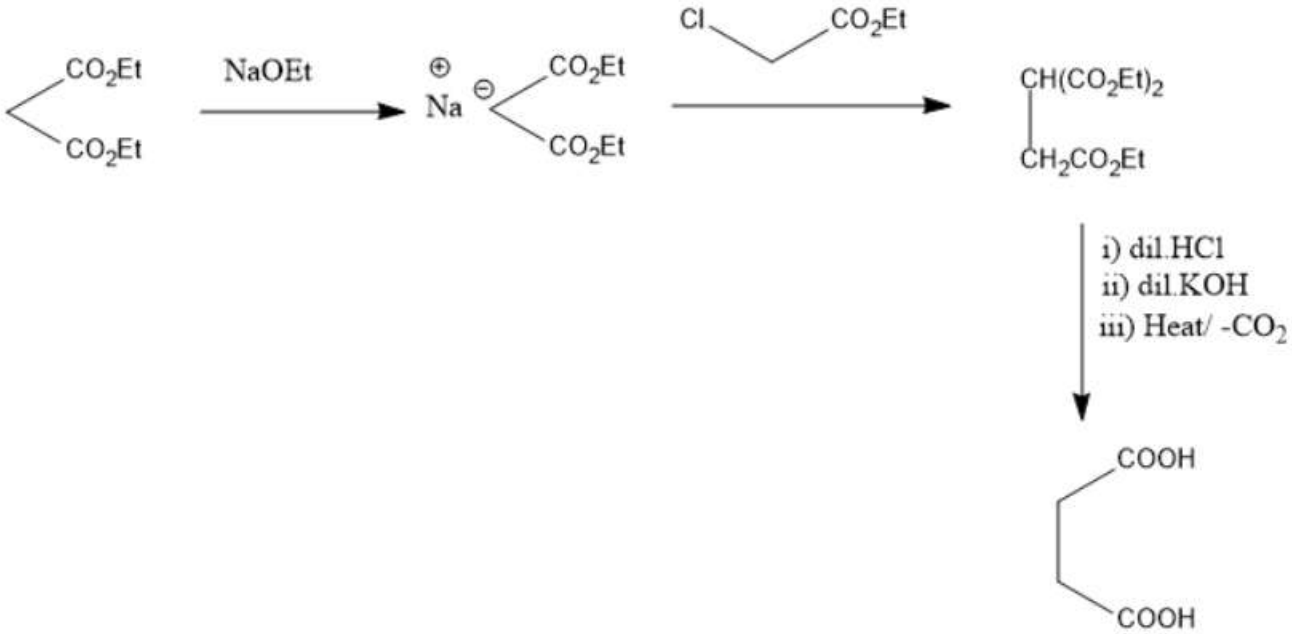
Forward approach



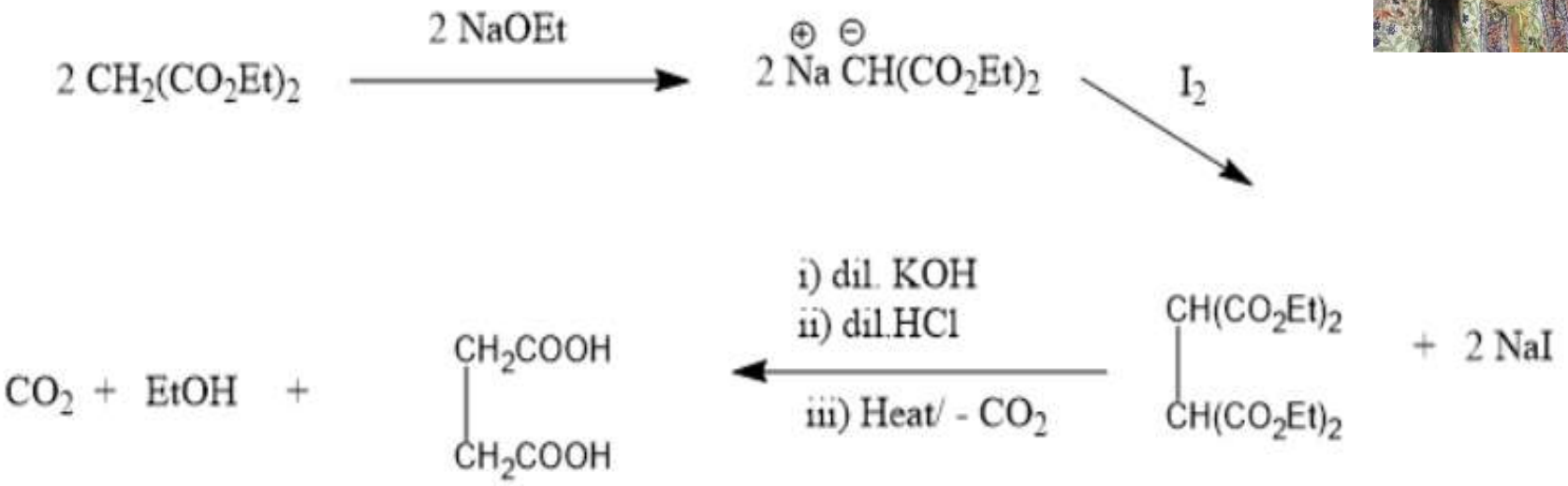
Q. Synthesise the following compound -



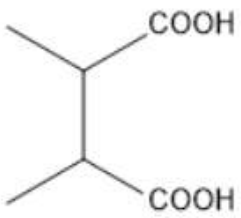
Forward approach



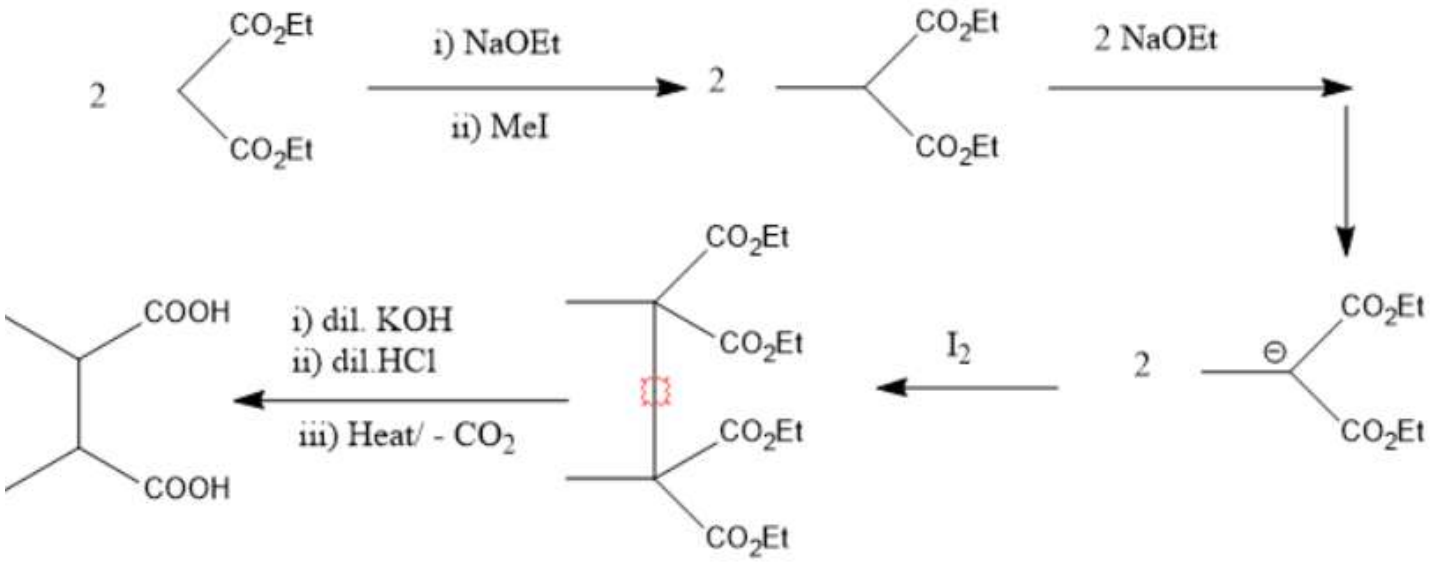
Alternate way



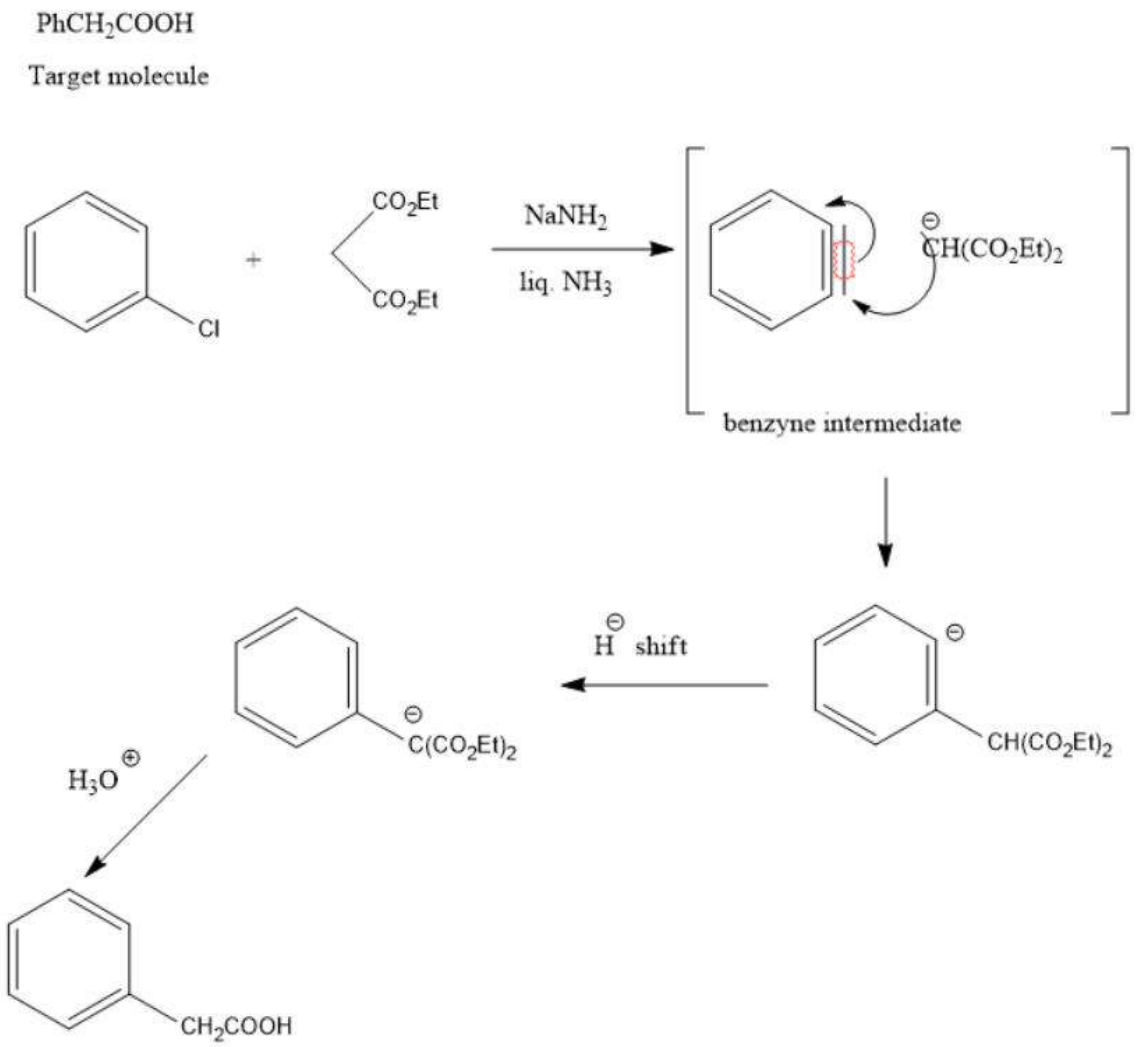
Q. Synthesise the following compound -



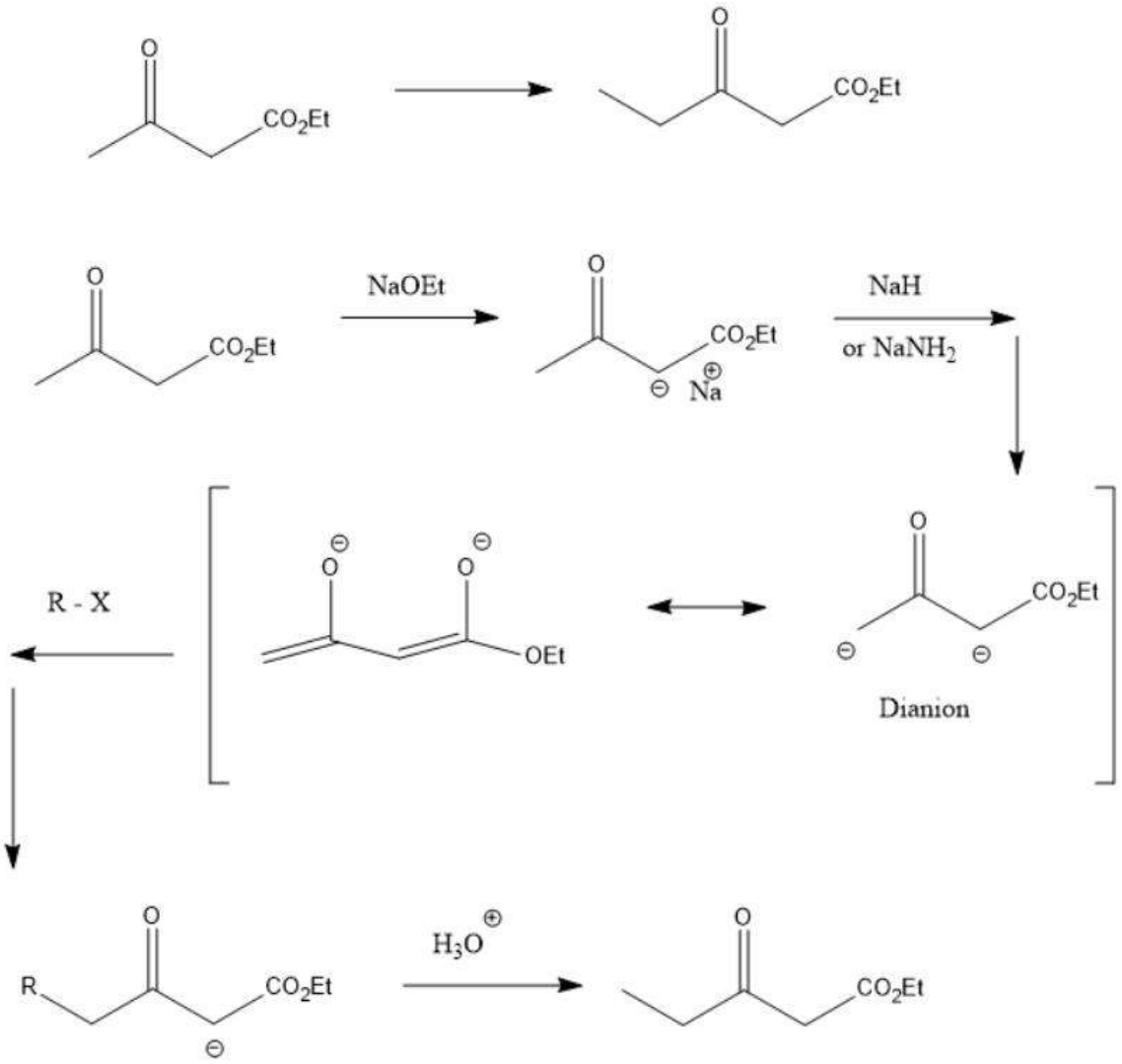
Forward approach



Q. Synthesise the following compound -



Q. Carry out the following conversion:

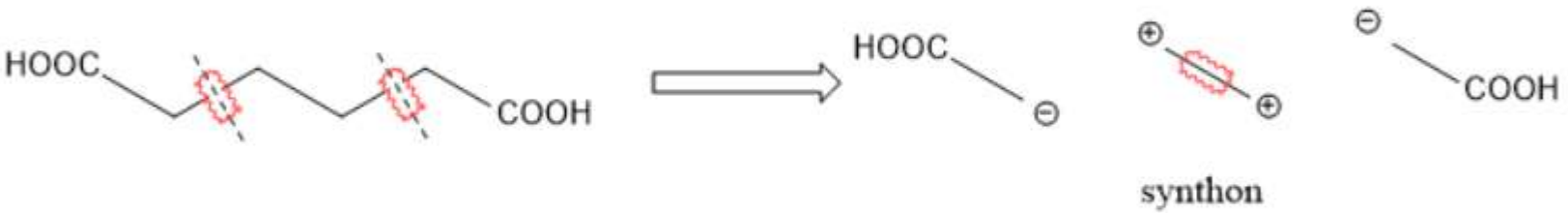


Q. Synthesise the following compound -

$COOH(CH_2)_4COOH$

Target molecule

Backward approach

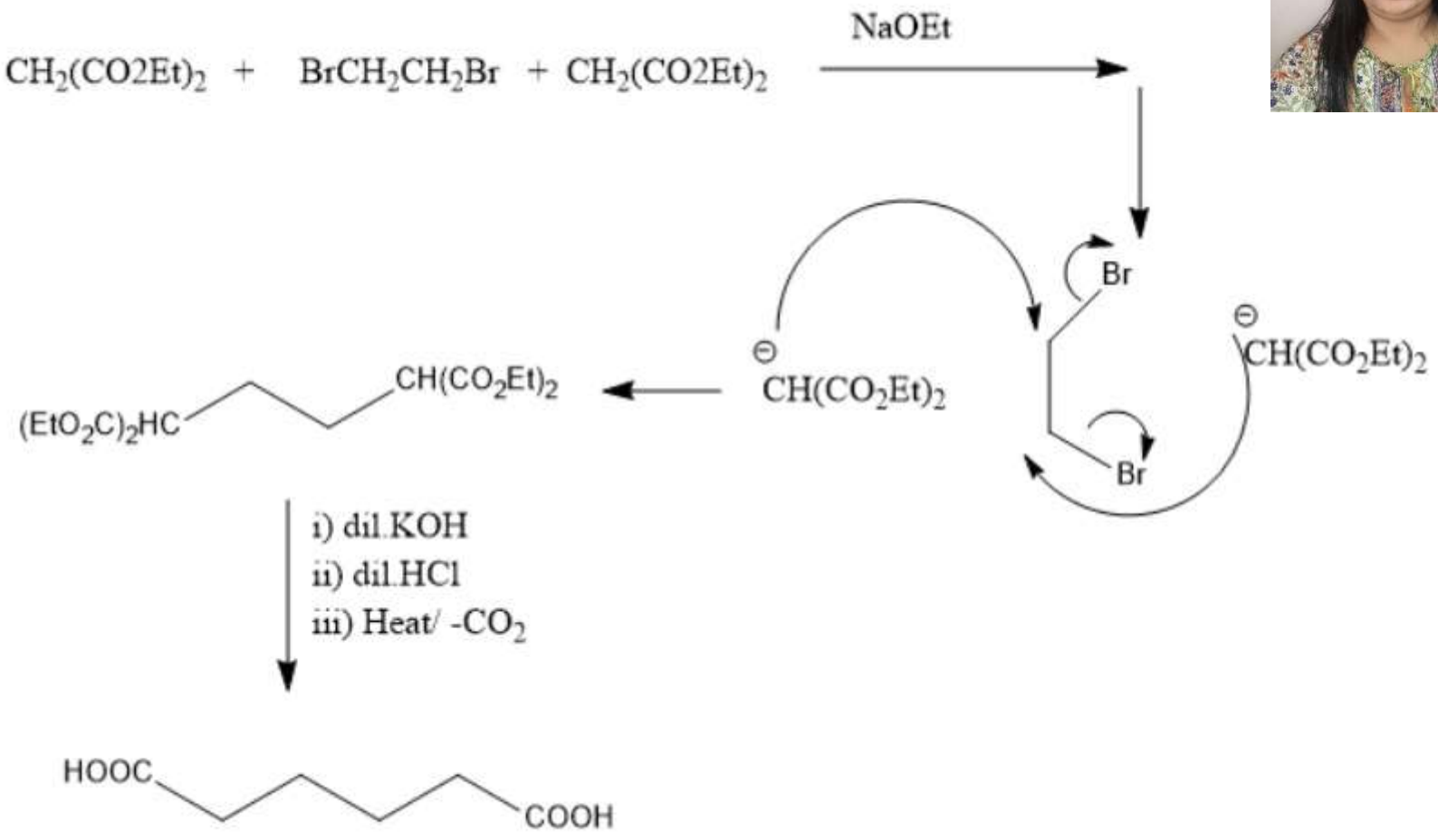


synthon

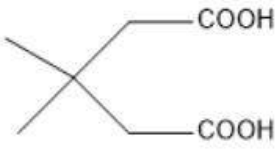
$CH_2(CO2Et)_2$ + $BrCH_2CH_2Br$ + $CH_2(CO2Et)_2$

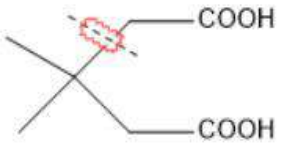
Synthetic equivalent

Forward approach

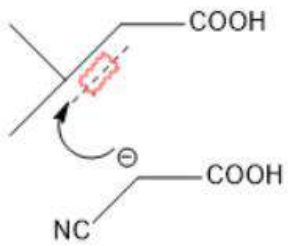


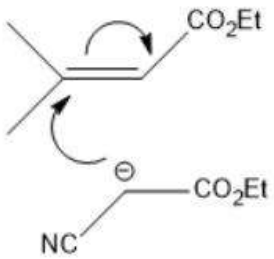
Q. Synthesise the following compound -



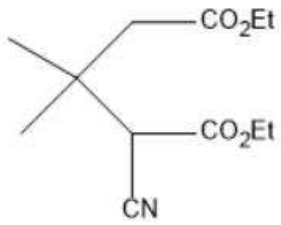


Process 1

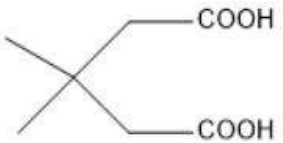


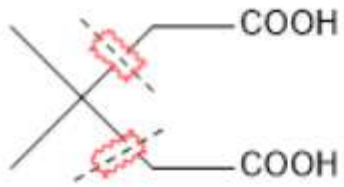


Michael reaction

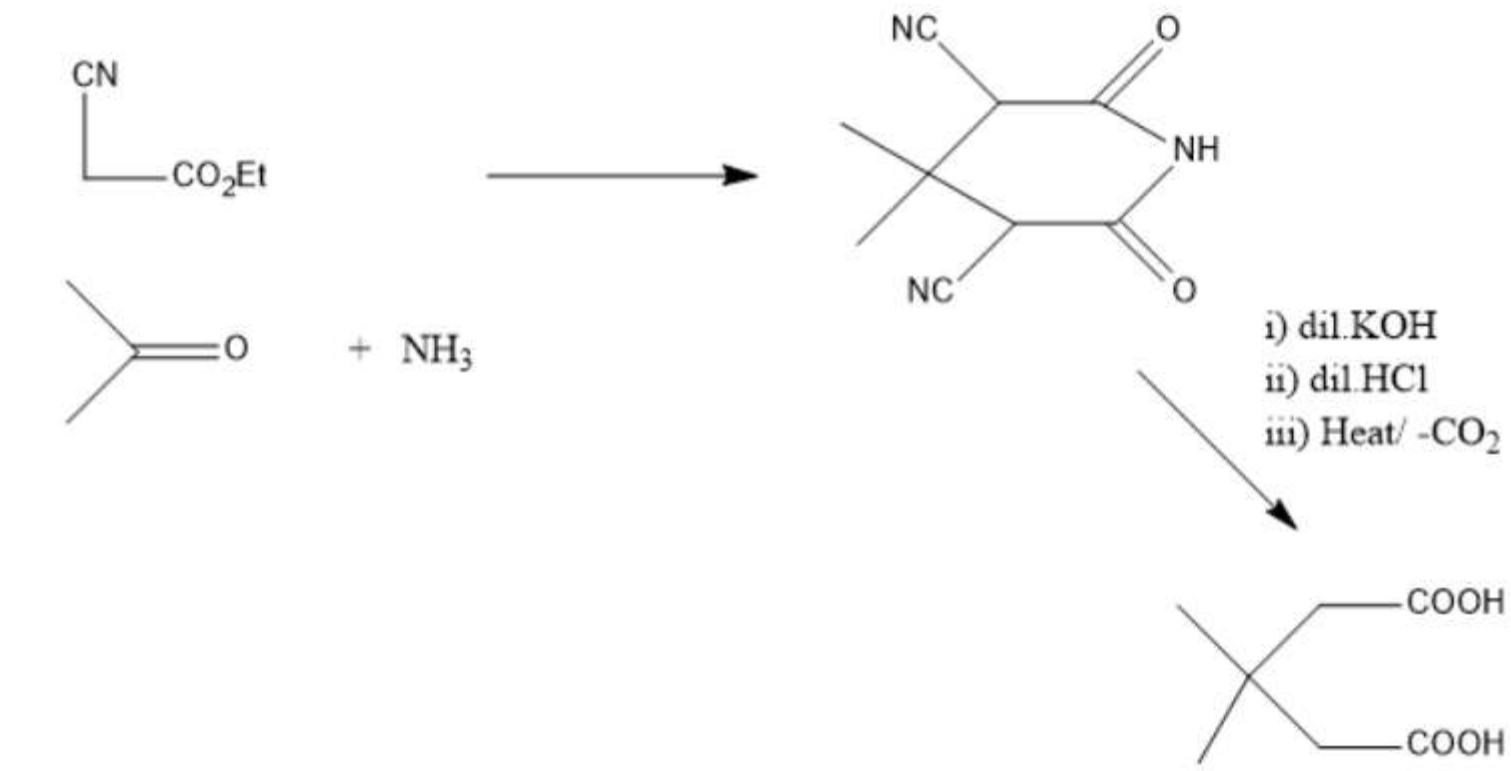


i) dil.KOH
ii) dil.HCl
iii) Heat/ $-CO_2$

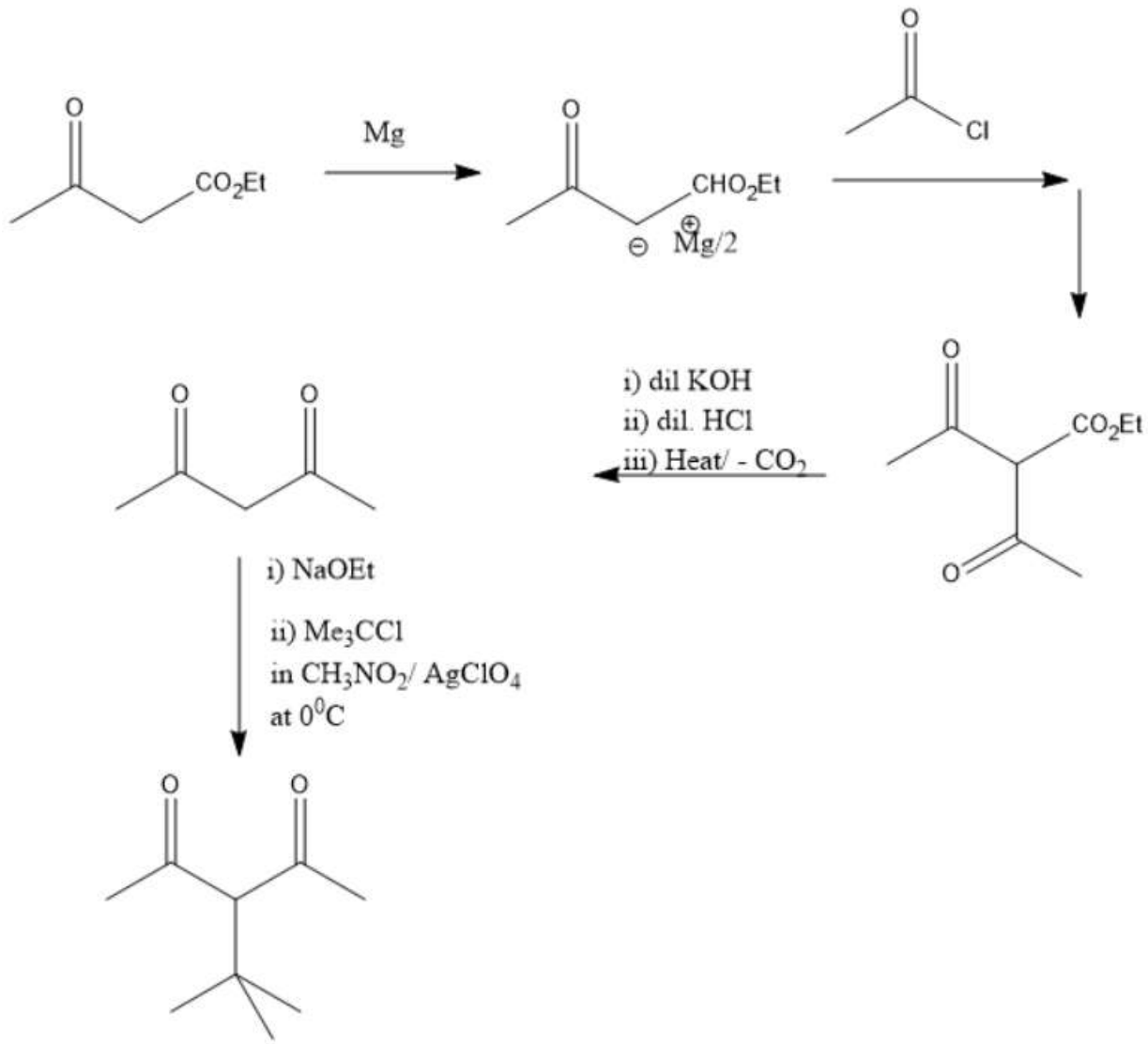



COOH
COOH

Process 2


CN
CO2Et
O
+ NH3
NC
O
NH
NC
O
i) dil.KOH
ii) dil.HCl
iii) Heat/ -CO2
COOH
COOH

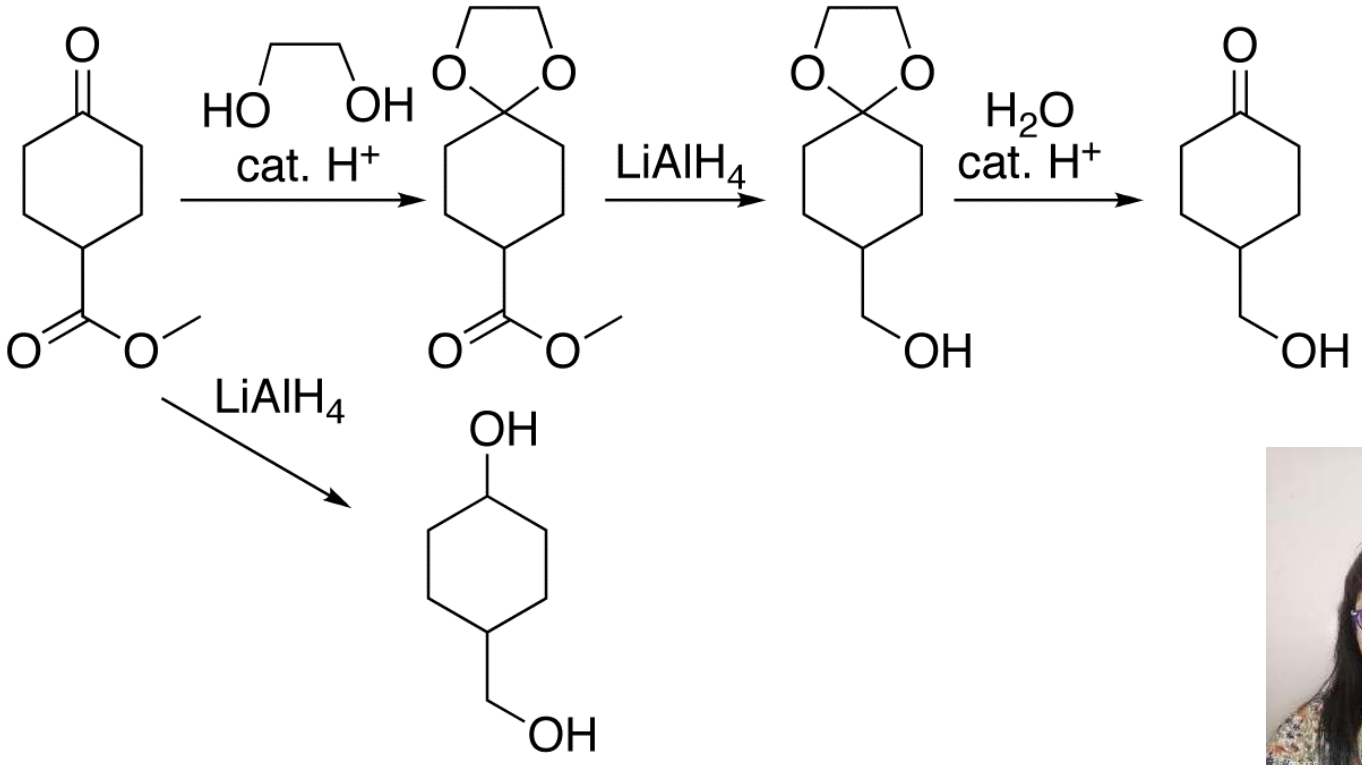
Q. Carry out the following conversion:



Protection and Deprotection Strategy (alcohol, amine, carbonyl, acid)

A **protecting group** or **protective group** is introduced into a molecule by chemical modification of a functional group to obtain chemoselectivity in a subsequent chemical reaction. It plays an important role in multistep organic synthesis.

Protection of carbonyl group by acetal formation



Protection of amines:

1. Carbobenzyloxy (Cbz) $PhCH_2OCOCl$ group

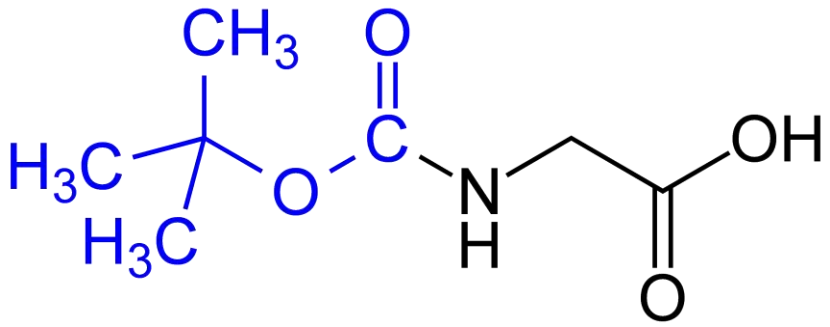
$PhCH_2OH$ + $ClCOCl$ → $PhCH_2OCOCl$

$PhCH_2OCOCl + RNH_2 \rightarrow PhCH_2OCONHR$

The protecting group can be removed very easily by hydrolysis at mild condition or without recourse to hydrolysis (H_2/Pd).

$PhCH_2OCONHR + H_2/Pd \rightarrow PhCH_3 + CO_2 + RNH2$

2. tert-Butyloxycarbonyl (BOC) group – Removed by concentrated strong acid (such as HCl or CF_3COOH), or by heating to >80 °C.



Q1. How is the $-NH_2$ group protected by its BOC derivative during peptide synthesis? Also mention its removal in the subsequent steps? 2

Protection of carboxylic acids:

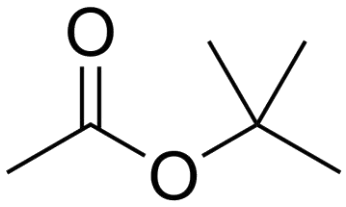
1. Methyl esters – Removed by acid or base.

-COOH + MeOH → -COOMe

2. Benzyl esters – Removed by hydrogenolysis.

-COOH + $PhCH_2OH$ → -$COOCH_2Ph$

3. *tert*-Butyl esters – Removed by acid, base and some reductants.

-COOH → 

Protection of alcohols:

1. Acetyl (Ac) – Removed by acid or base.

   -OH → -$OCOCH_3$

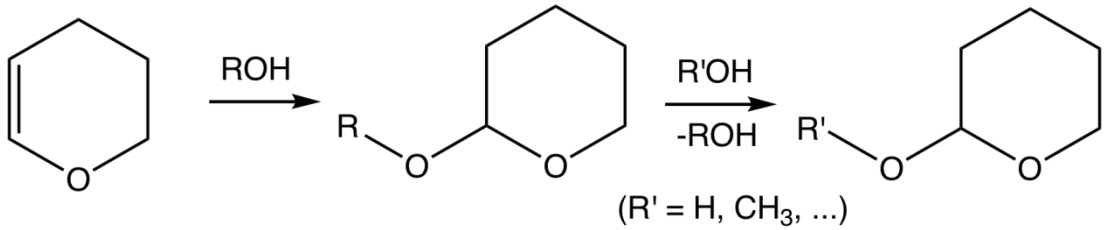
2. Benzoyl (Bz) – Removed by acid or base, more stable than Ac group.

   -OH → -OCOPh

3. Benzyl (Bn) – Removed by hydrogenolysis. Bn group is widely used in sugar and nucleoside chemistry.

   -OH → -OCH_2Ph

4. Tetrahydropyranyl (THP) – Removed by acid.



Protection of alcohol as tetrahydropyranyl ether followed by deprotection. Both steps require acid catalysts.

Strategy of ring synthesis: thermodynamic and kinetic factors

Entropy is the key factor:

1. concentration of the reaction – high dilution favours ring-closure
2. ring size formed – smaller rings favoured

$\Delta G = \Delta H - T\Delta S$

1. Ring-closure under thermodynamic (TD) control (i.e. reversible conditions):

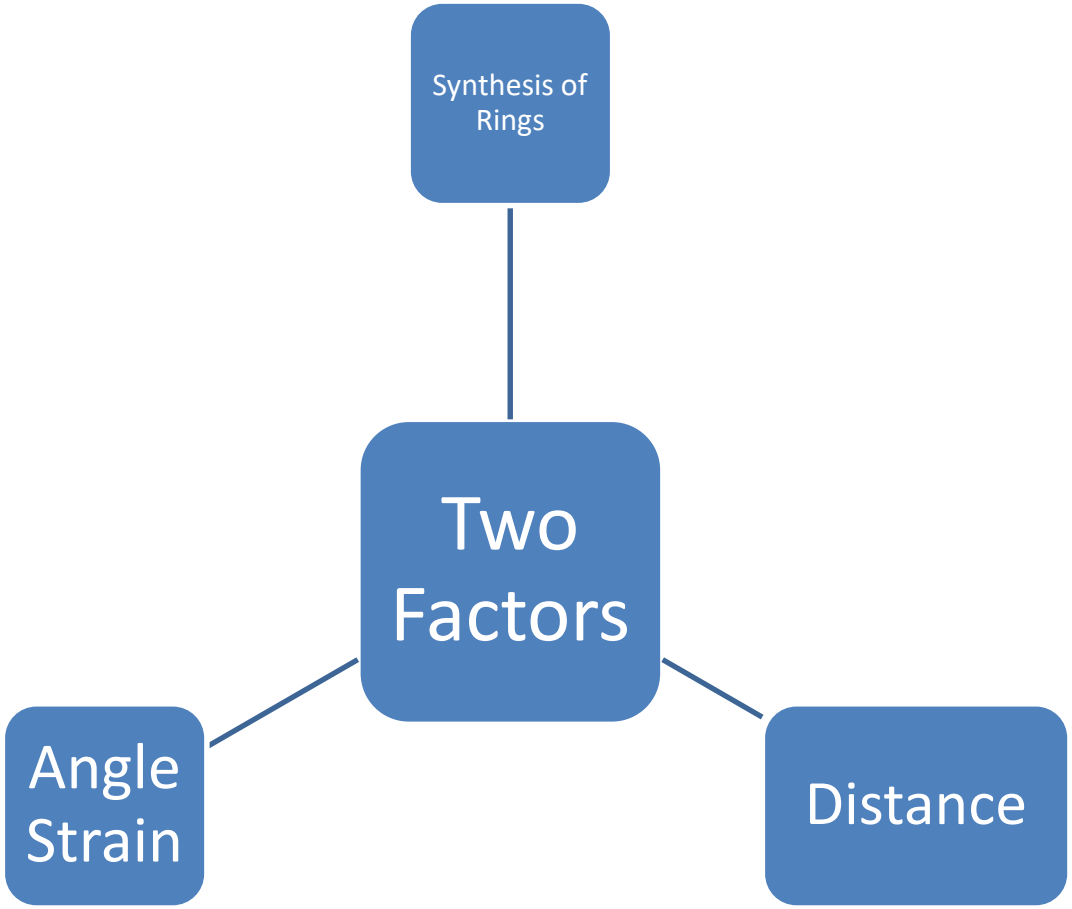
- many reactions forming heteroaromatic products are driven by:

favourable $\Delta S°$ due to loss of small molecule

- favourable $\Delta H°$ due to stability of aromatic product

2. Ring-closure under kinetic control (i.e. irreversible conditions):

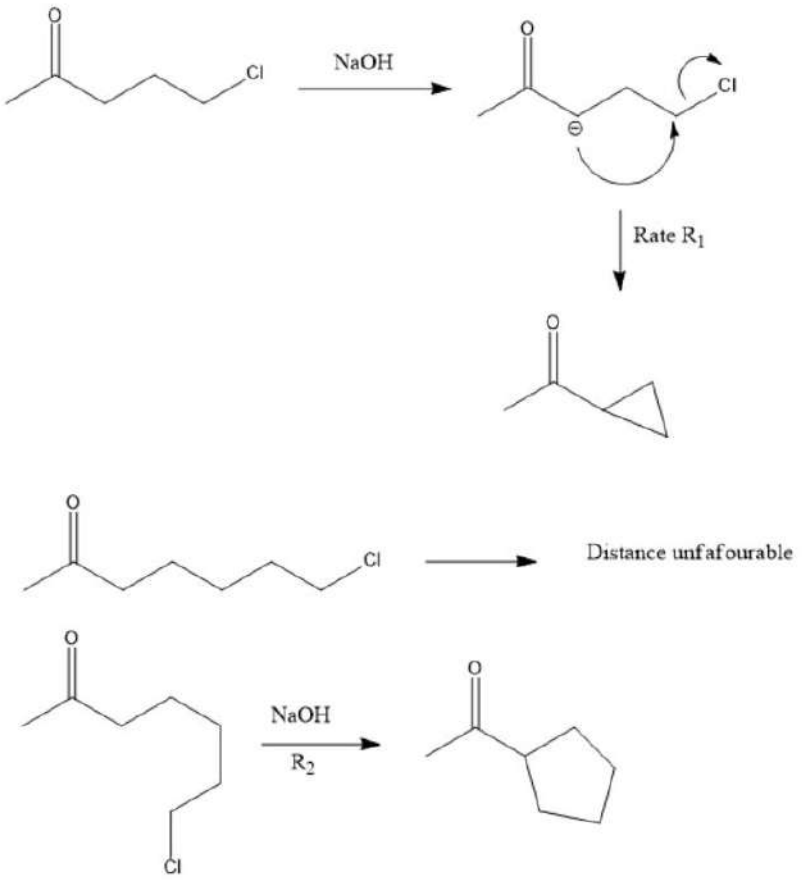
- less common when forming heteroaromatic products, but does affect the rate of TD controlled reactions:
- variable $\Delta S^{\#}$ - critically dependent on ring size & hybridisation of reacting centres - Baldwin's rules


Synthesis of Rings
Two Factors
Angle Strain
Distance

Factors Influencing the Synthesis of Rings of Different Sizes:

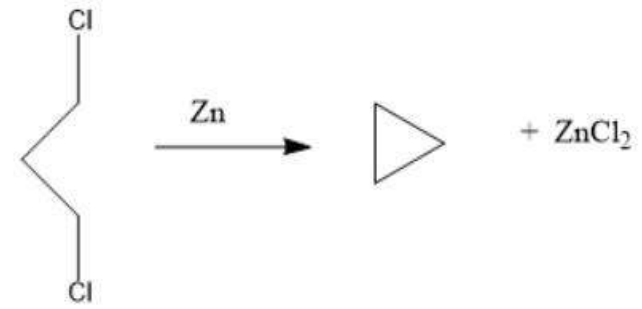
Serial No.	Ring Size	Distance Factor	Strain
1.	3-membered	Favourable	Maximum
2.	5-membered	Not too far (favourable)	Strain free
3.	6-membered	Distance is more than 5-membered	Strain free
4.	Large Ring	unfavourable	Strain absent

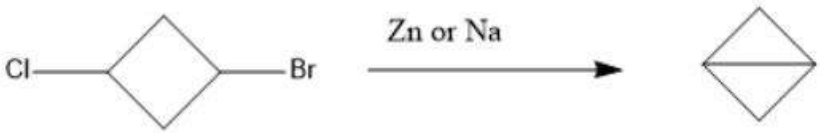
Examples:

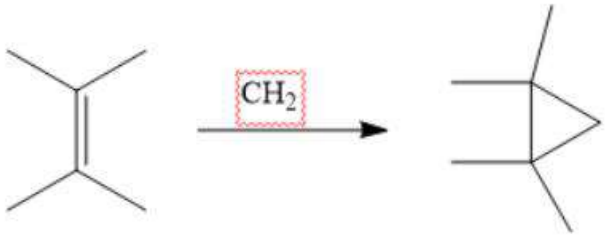


$R_1 >> R_2$

Wurtz Reaction

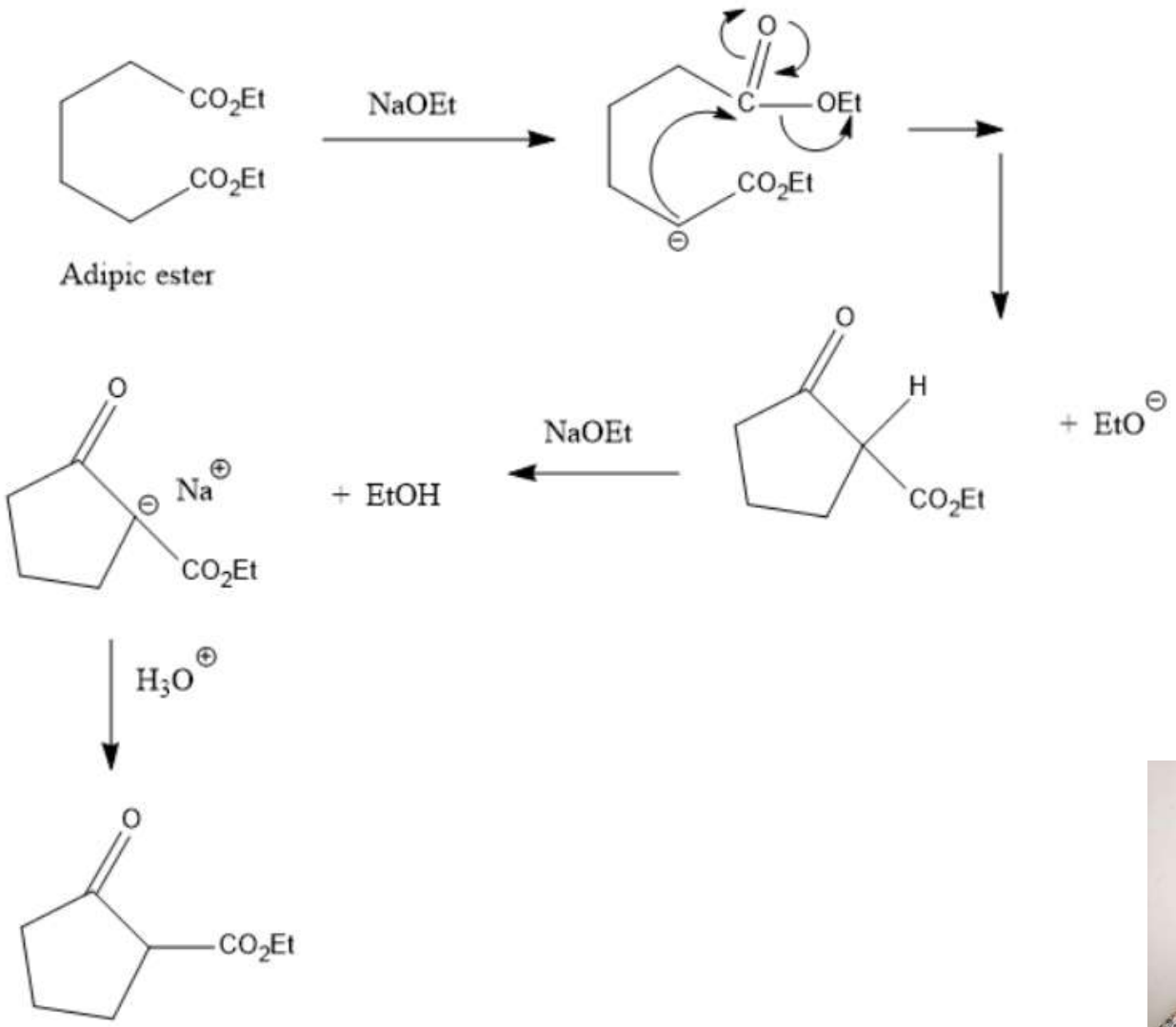




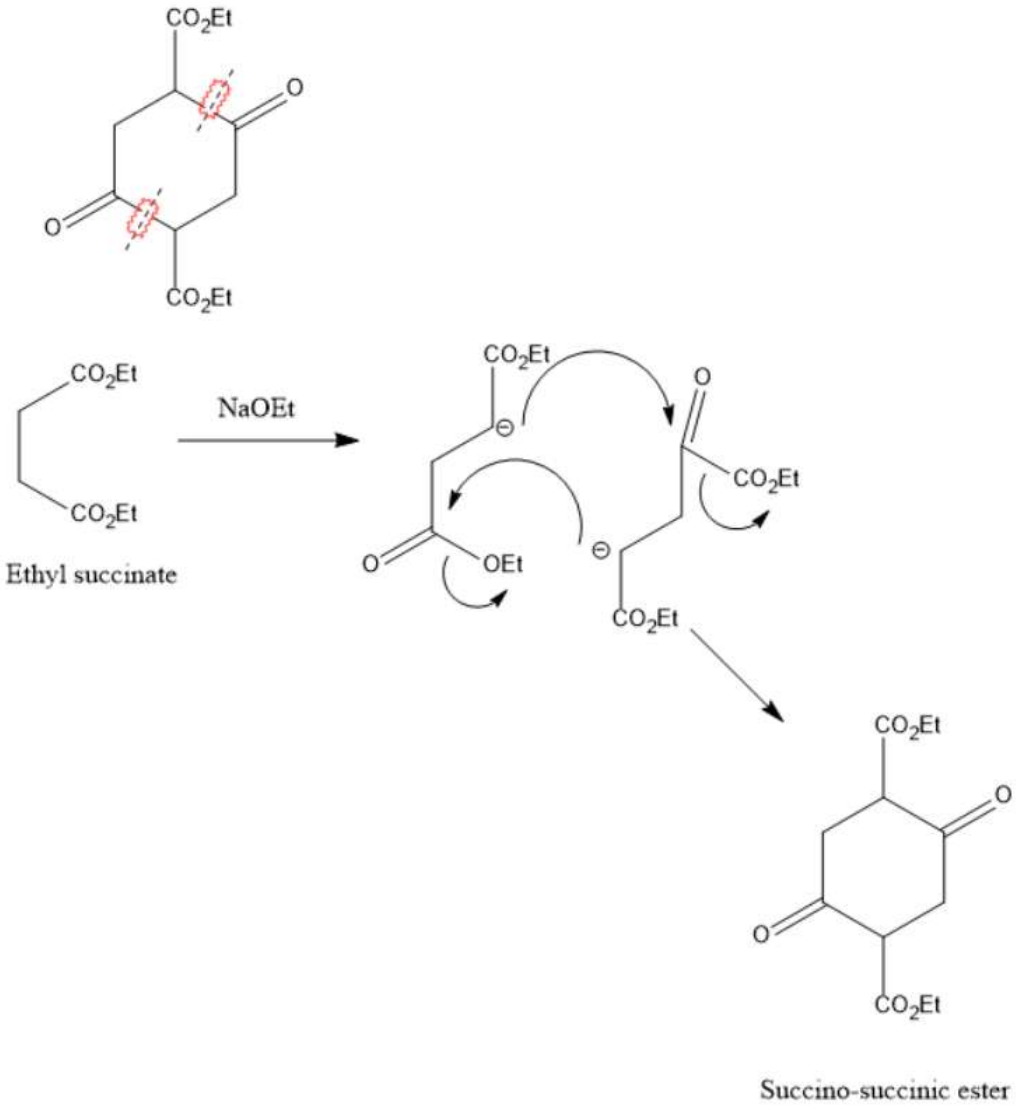


Simon Smith Reaction

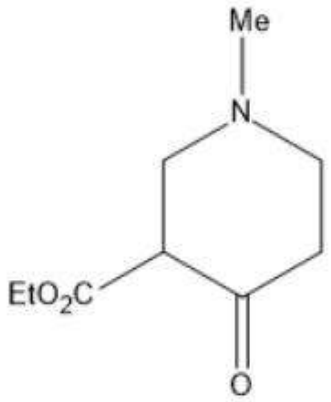
Dieckmann Reaction (Intramolecular Claisen)

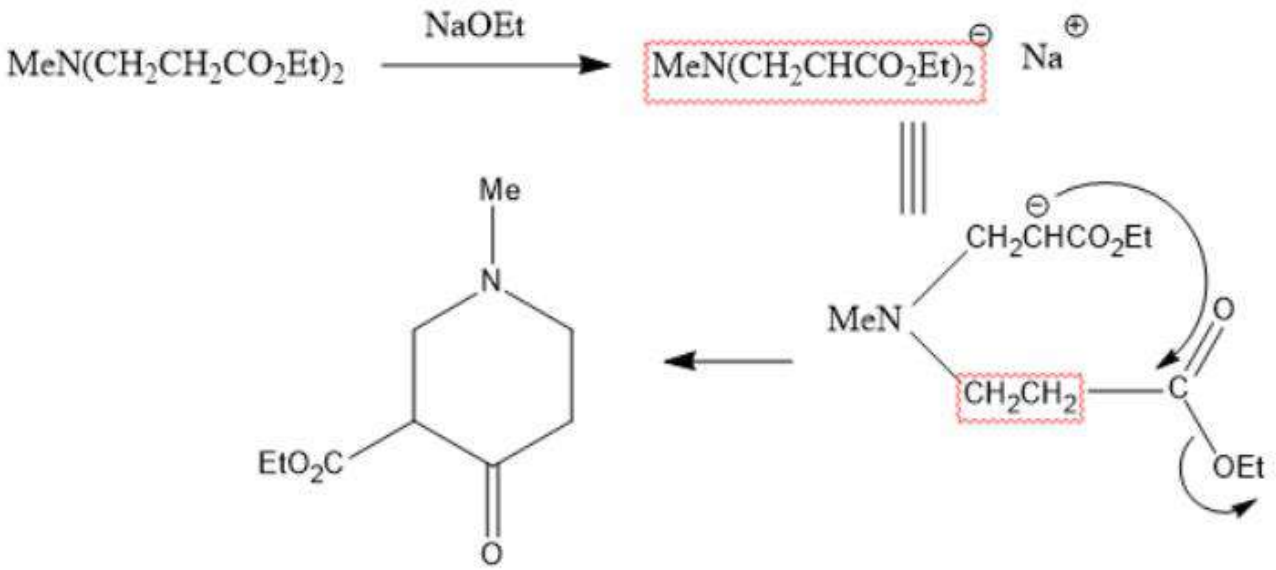


Carry out synthesis of the following compound:

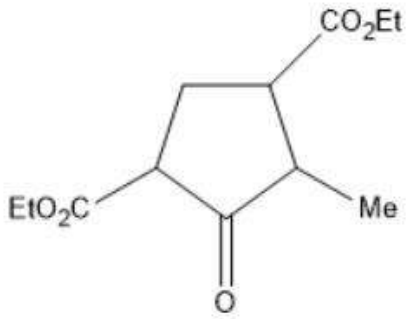


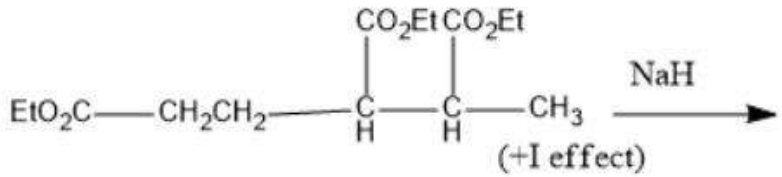
Carry out synthesis of the following compound:

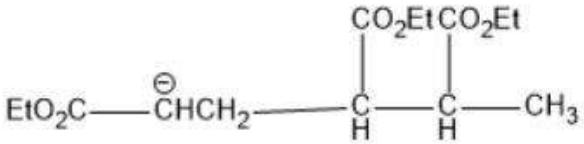


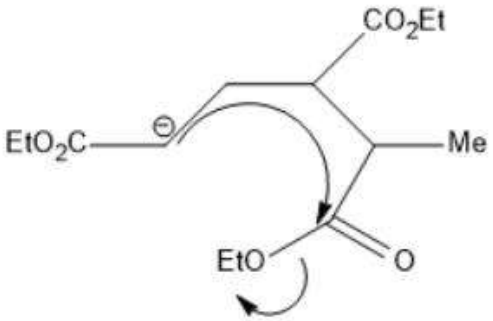


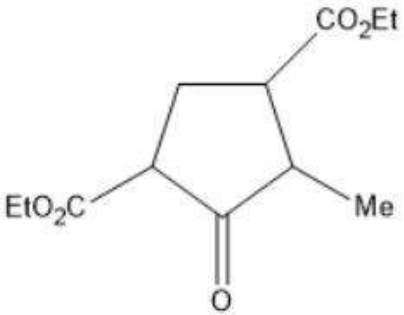
Carry out synthesis of the following compound:



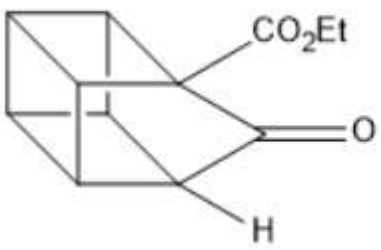


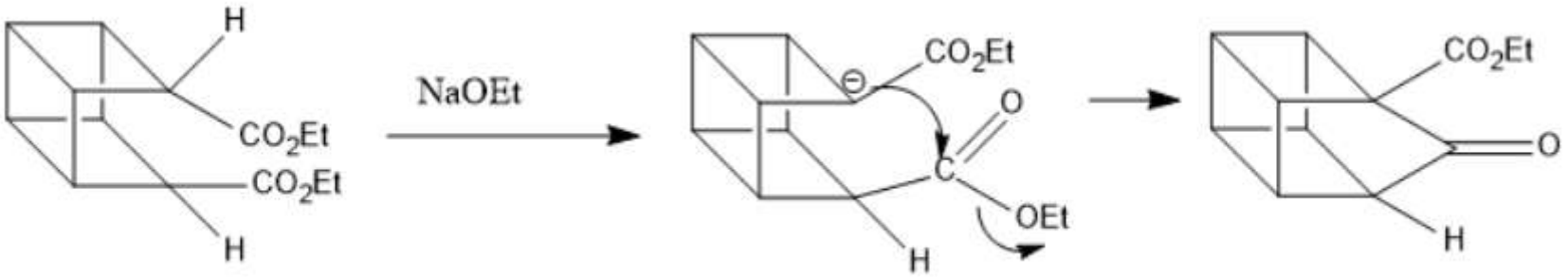




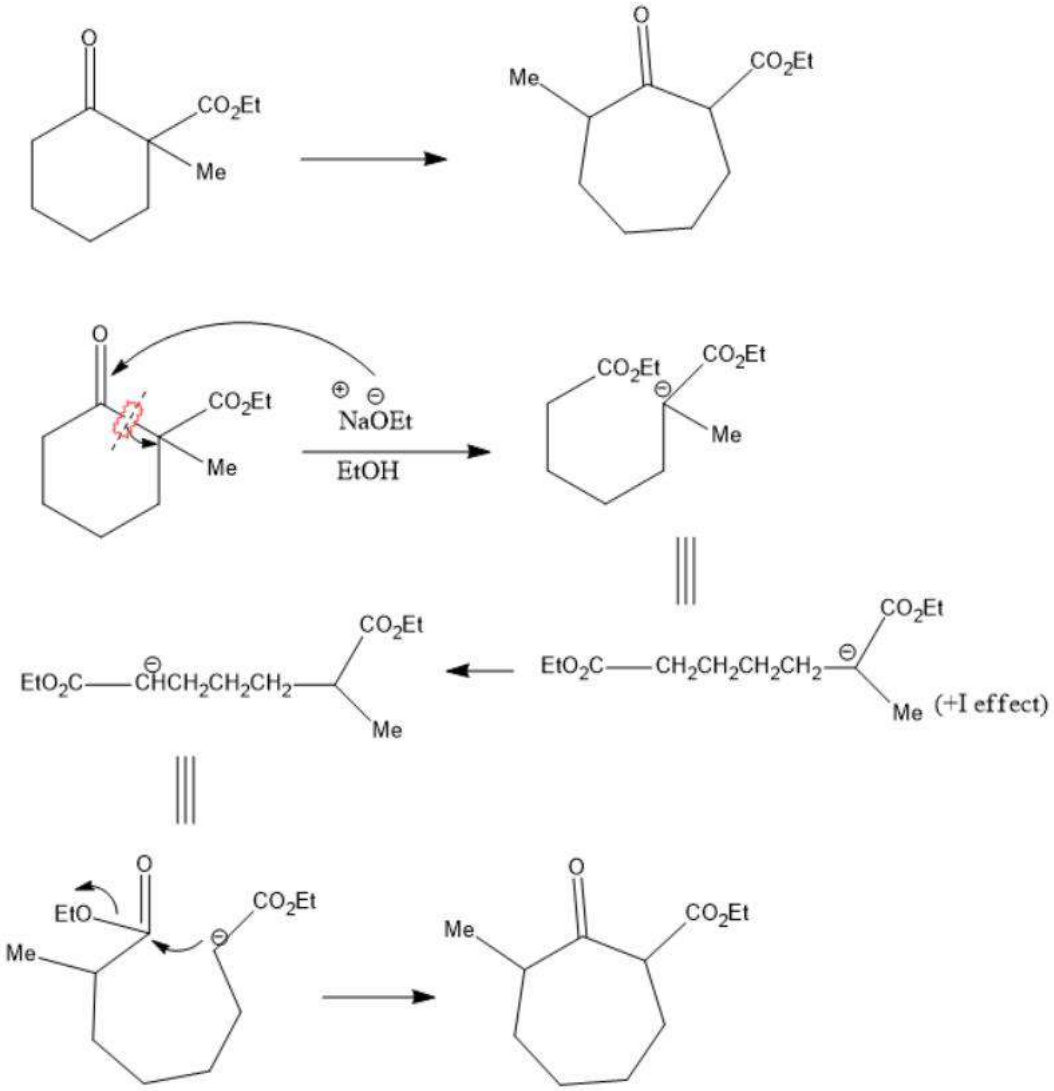


Carry out synthesis of the following compound:



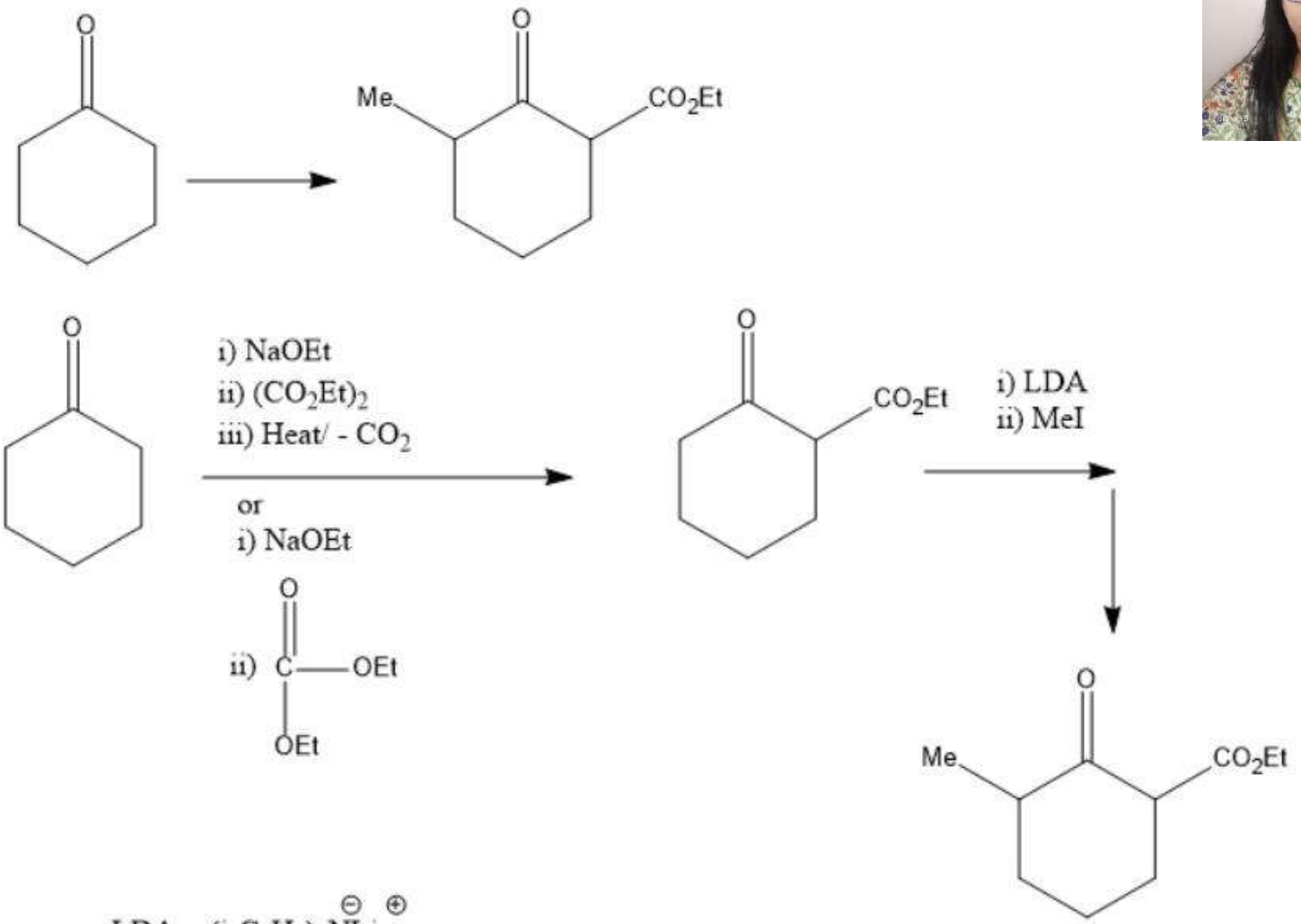


Carry out the following conversion:



This reaction is known as Retro Dieckmann reaction. Here ring expansion occurs.

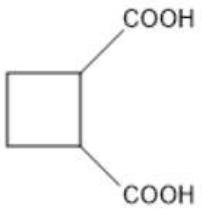
Carry out the following conversion:



LDA = $(i\text{-}C_3H_7)_2\overset{\ominus}{N}\overset{\oplus}{L}i$

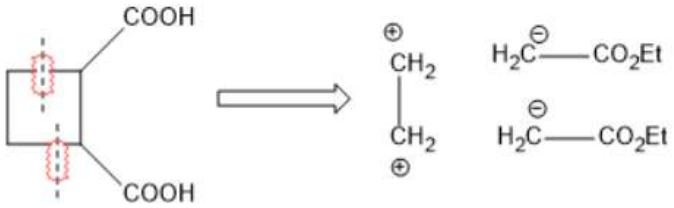
Lithium di isopropyl amide

Synthesise the following compound using active methylele compound:

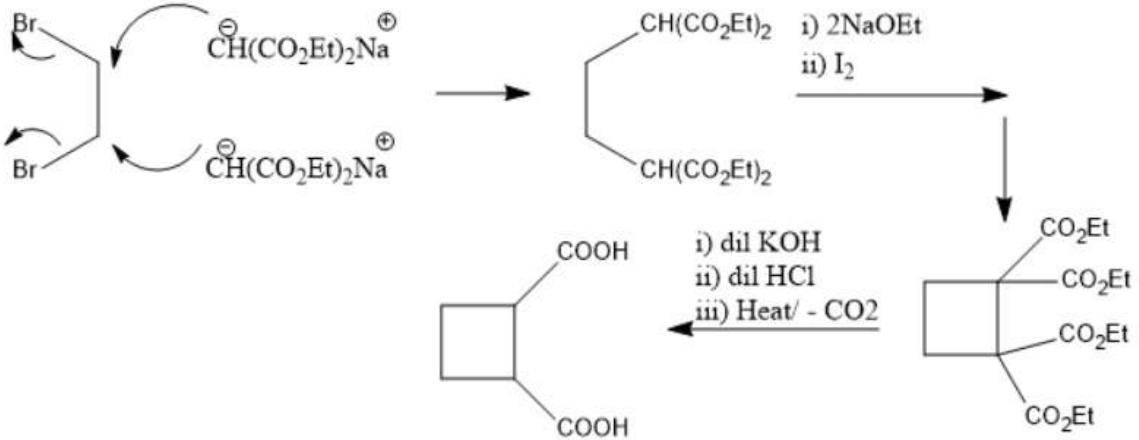


TM

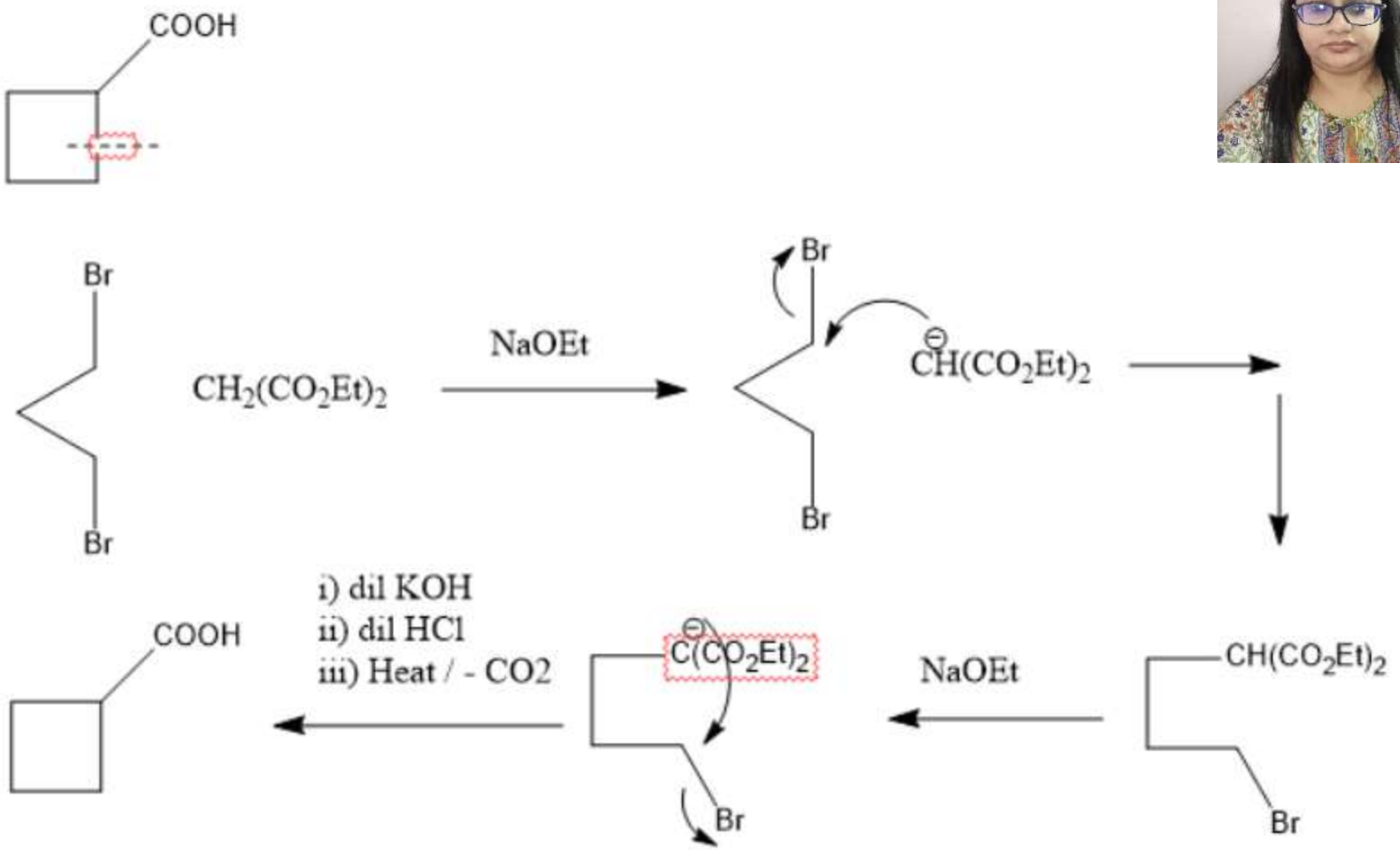
Backward approach:



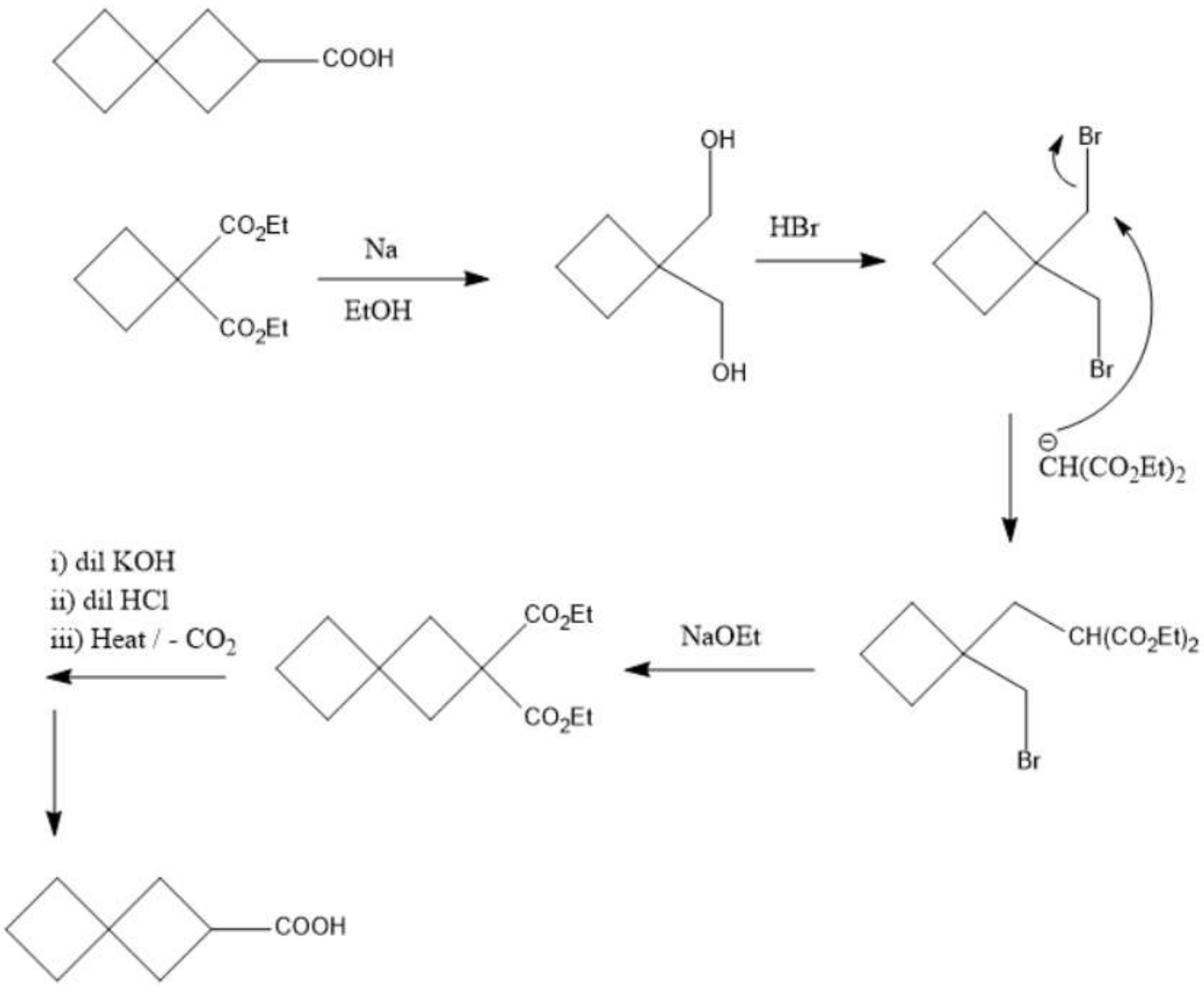
Forward approach:



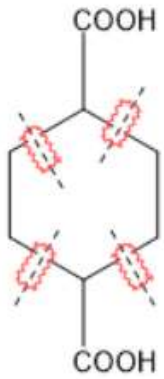
Synthesise the following compound using active methylele compound:

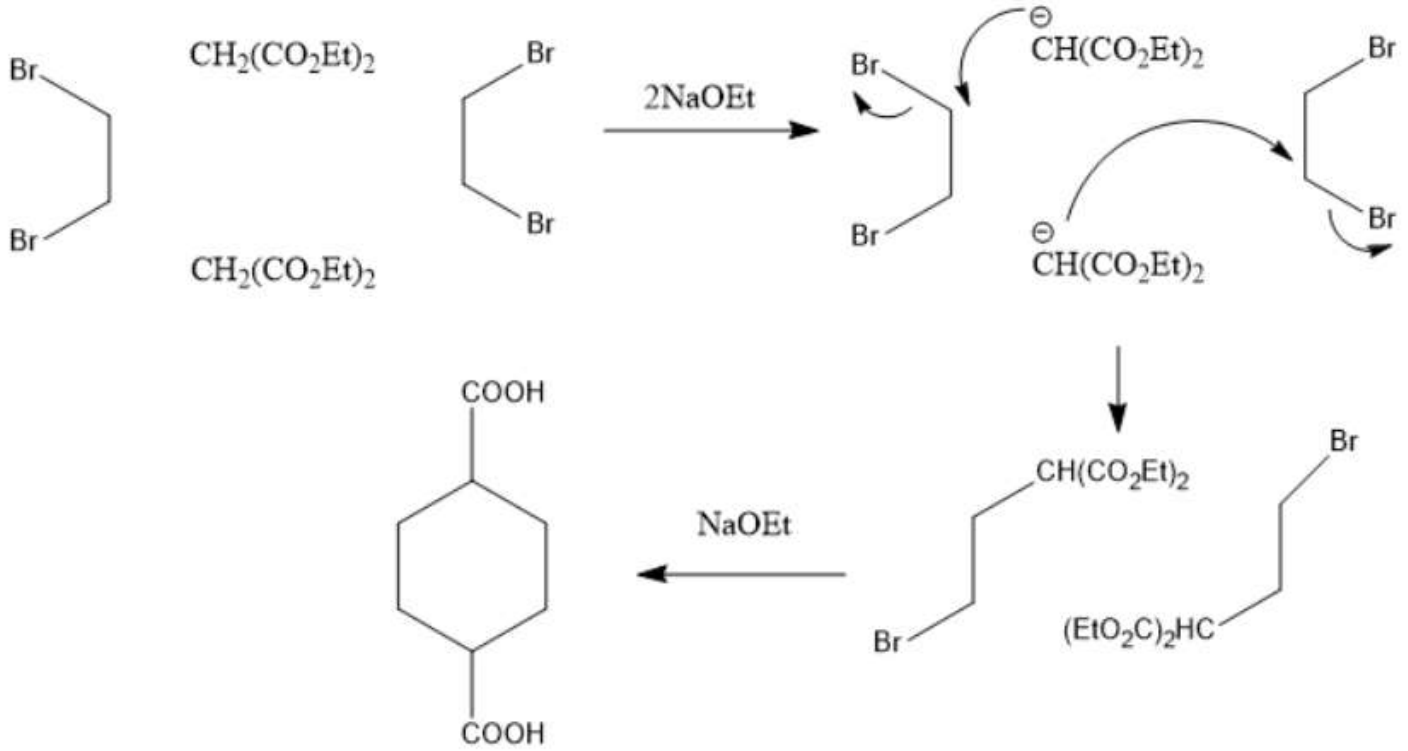


Synthesise the following compound using active methylele compound:

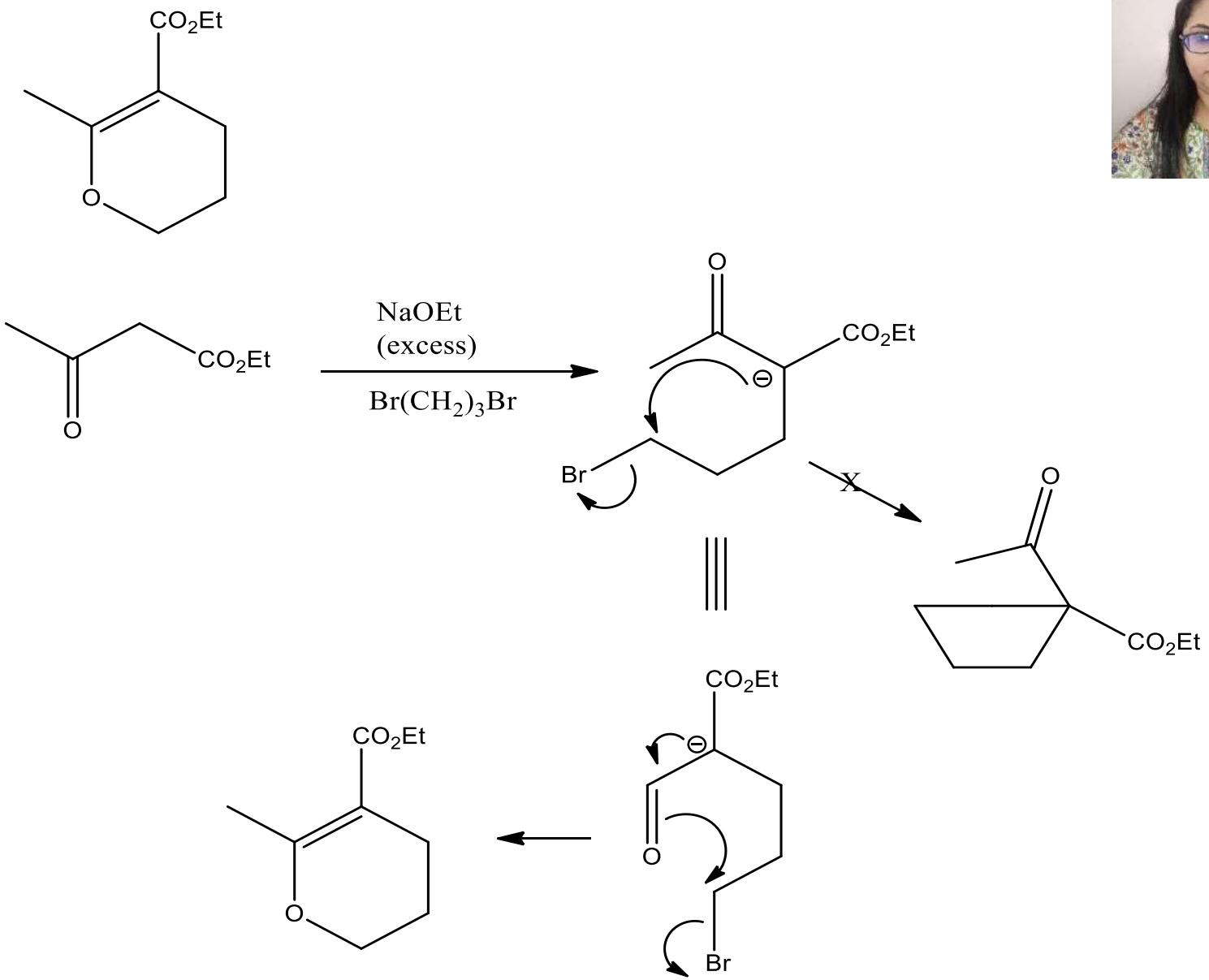


Synthesise the following compound using active methylele compound:

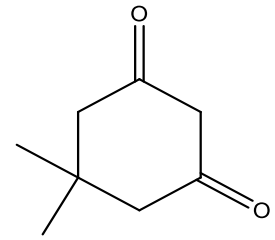




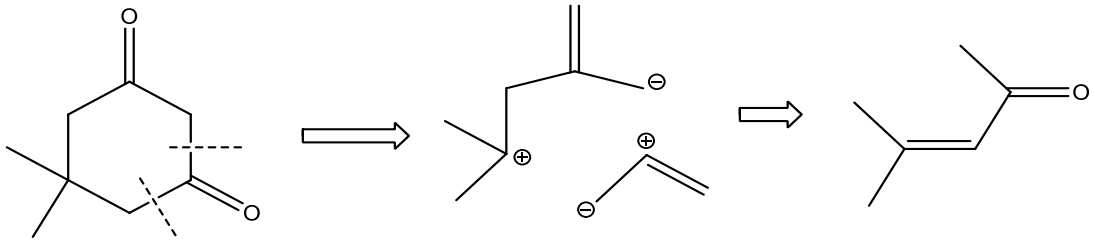
Carry out synthesis of the following compound:



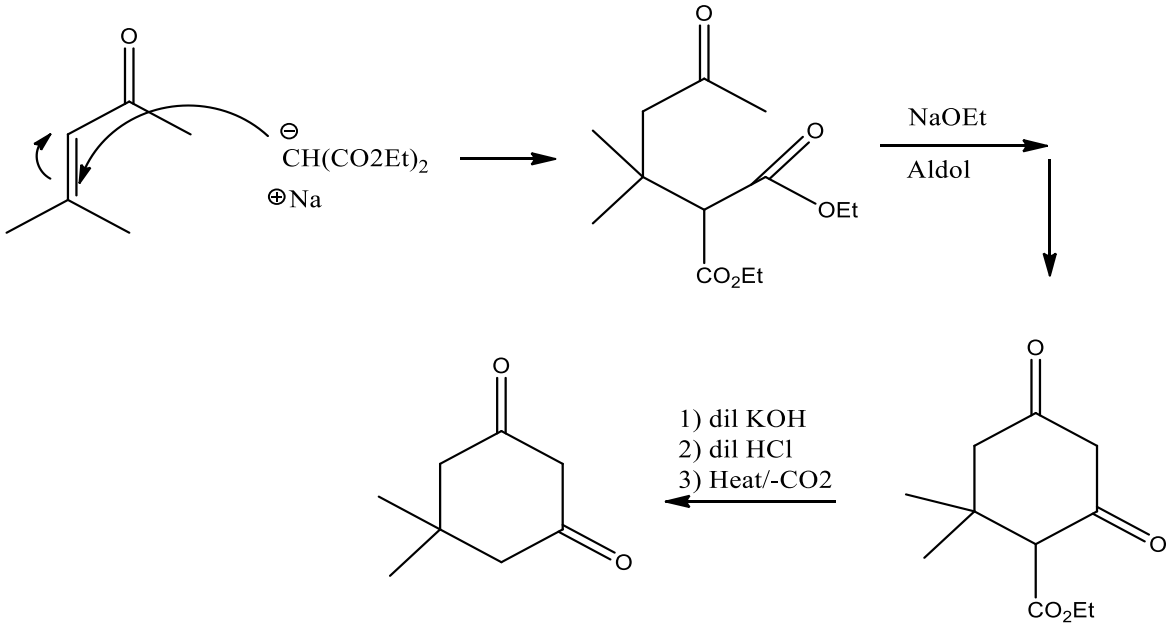
Carry out synthesis of the following compound:(Use of Michael condensation)



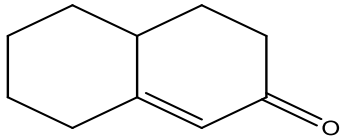
Backward Approach



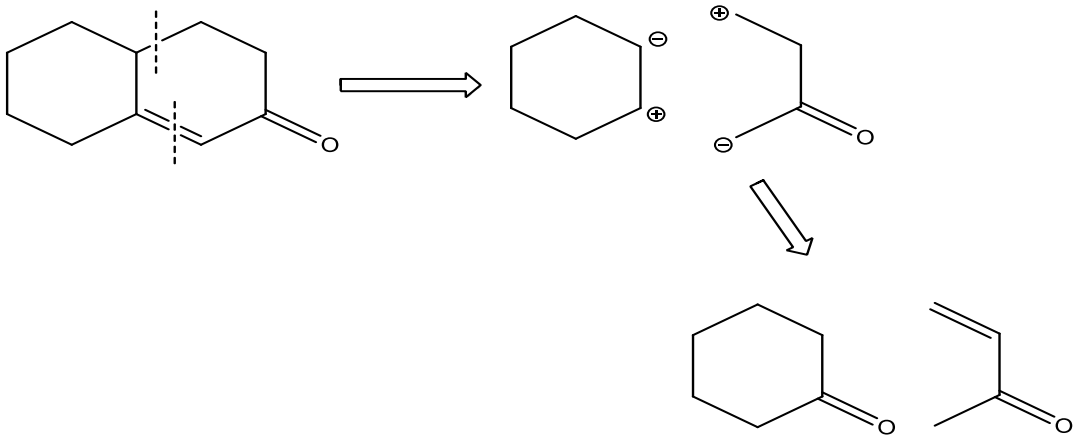
Forward Approach



Carry out synthesis of the following compound:

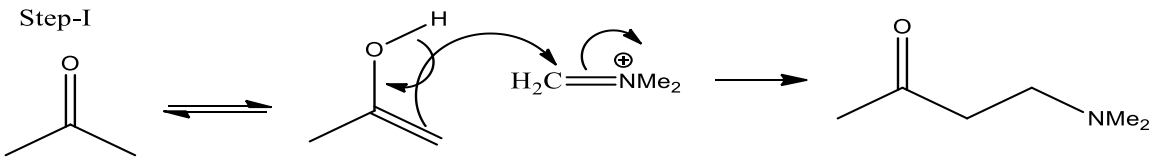


Backward approach

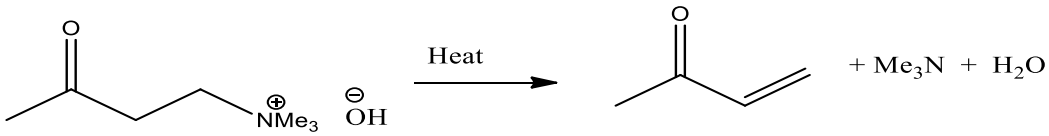


Forward approach

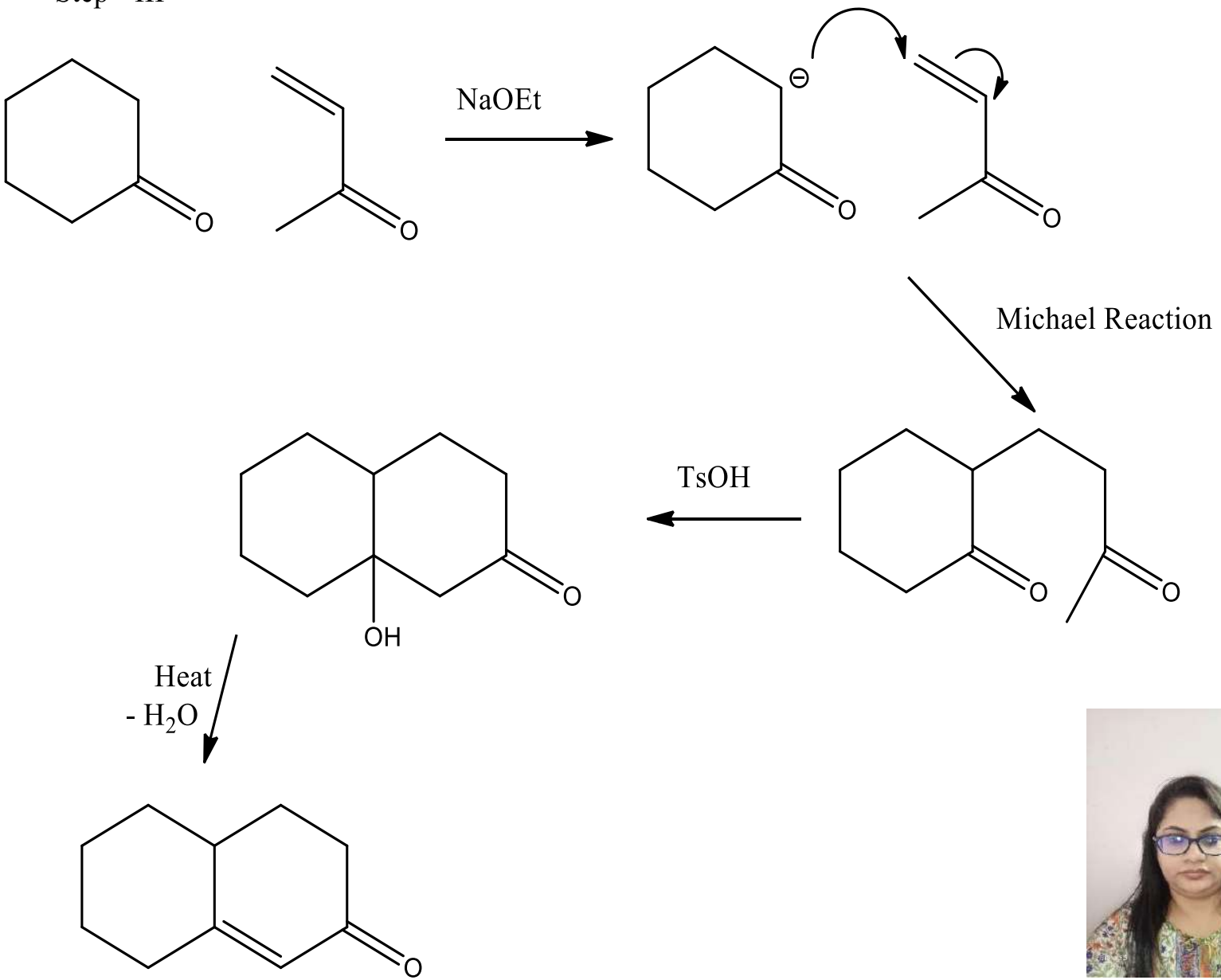
Step-I



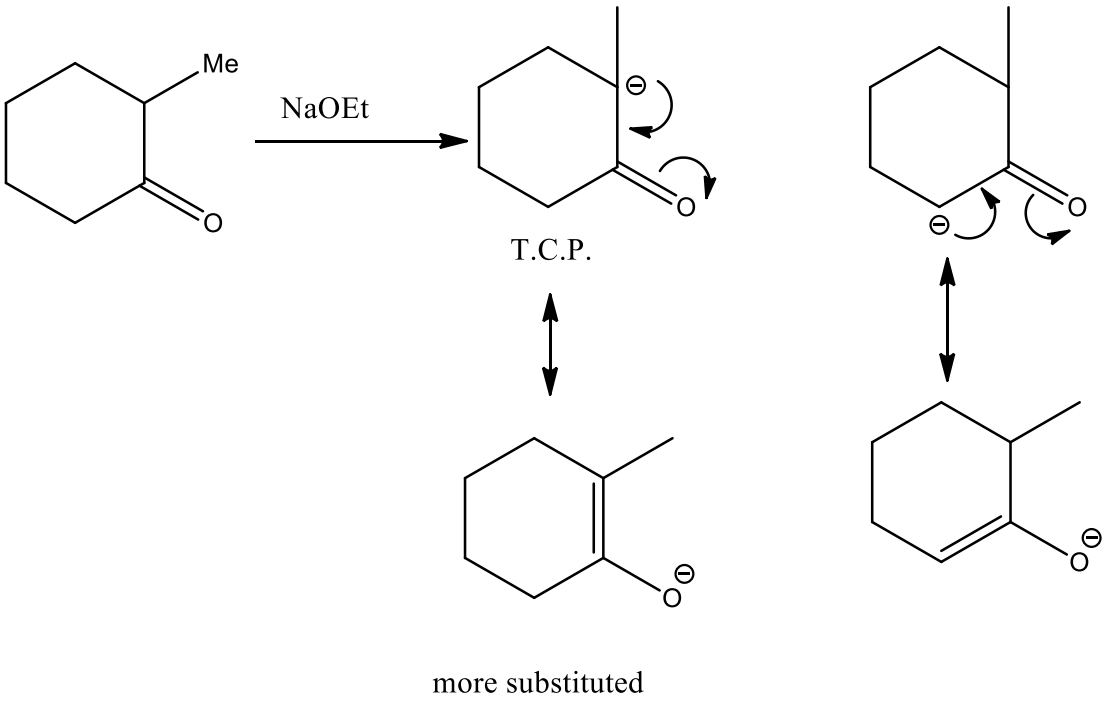
Step-II



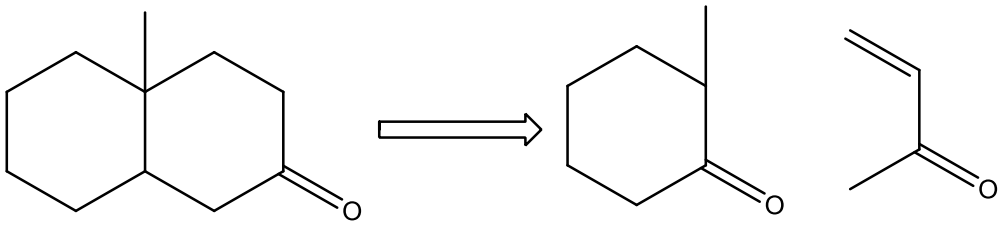
Step - III



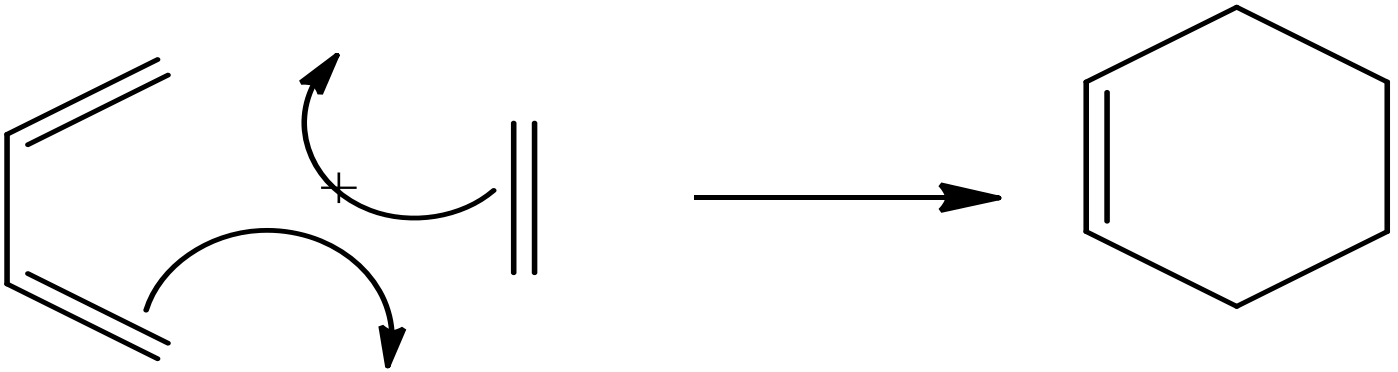
Key Point



In Michael condensation, the thermodynamically (more) stable carbanion undergoes the condensation.

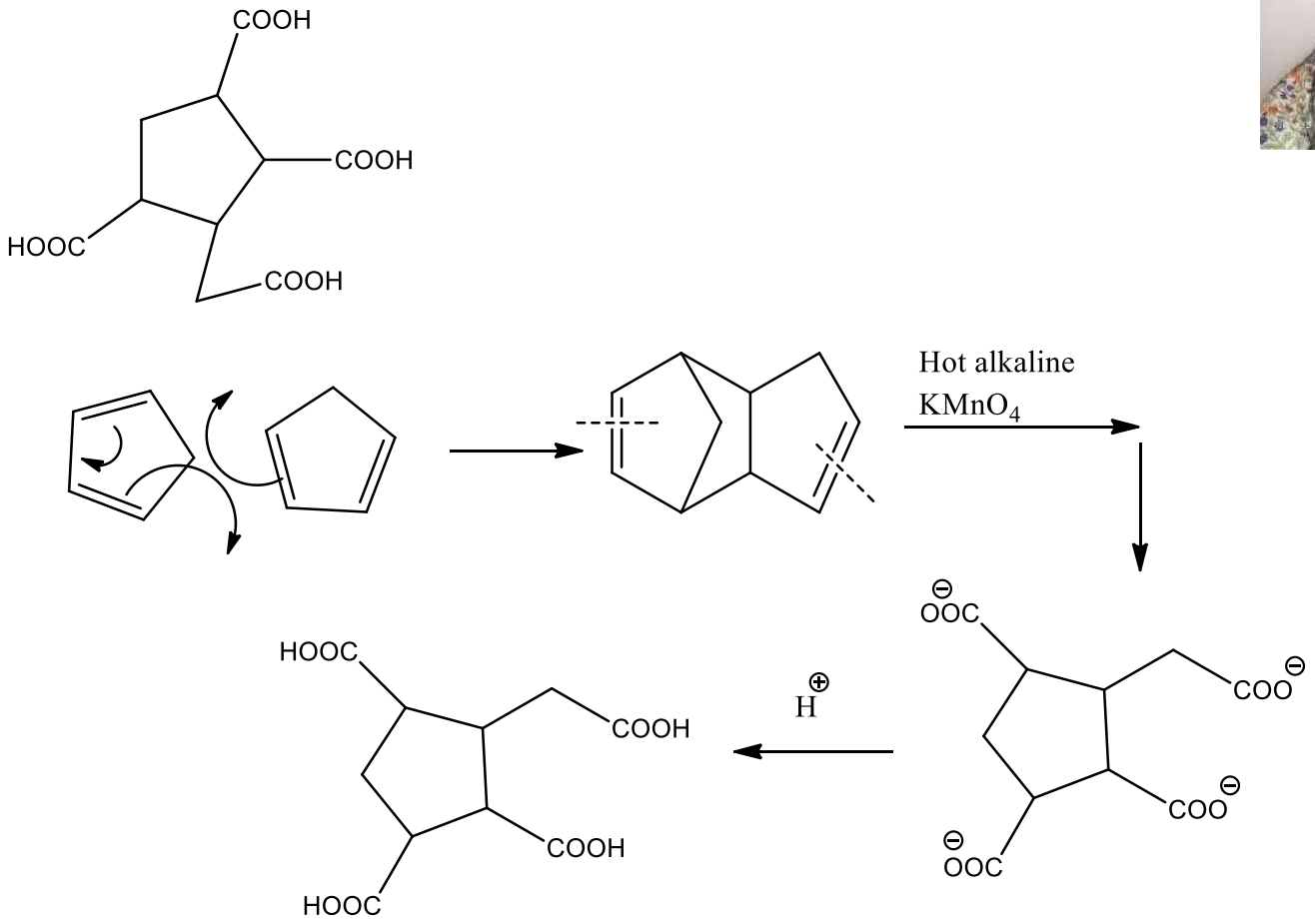


Diels-Alder Reaction:

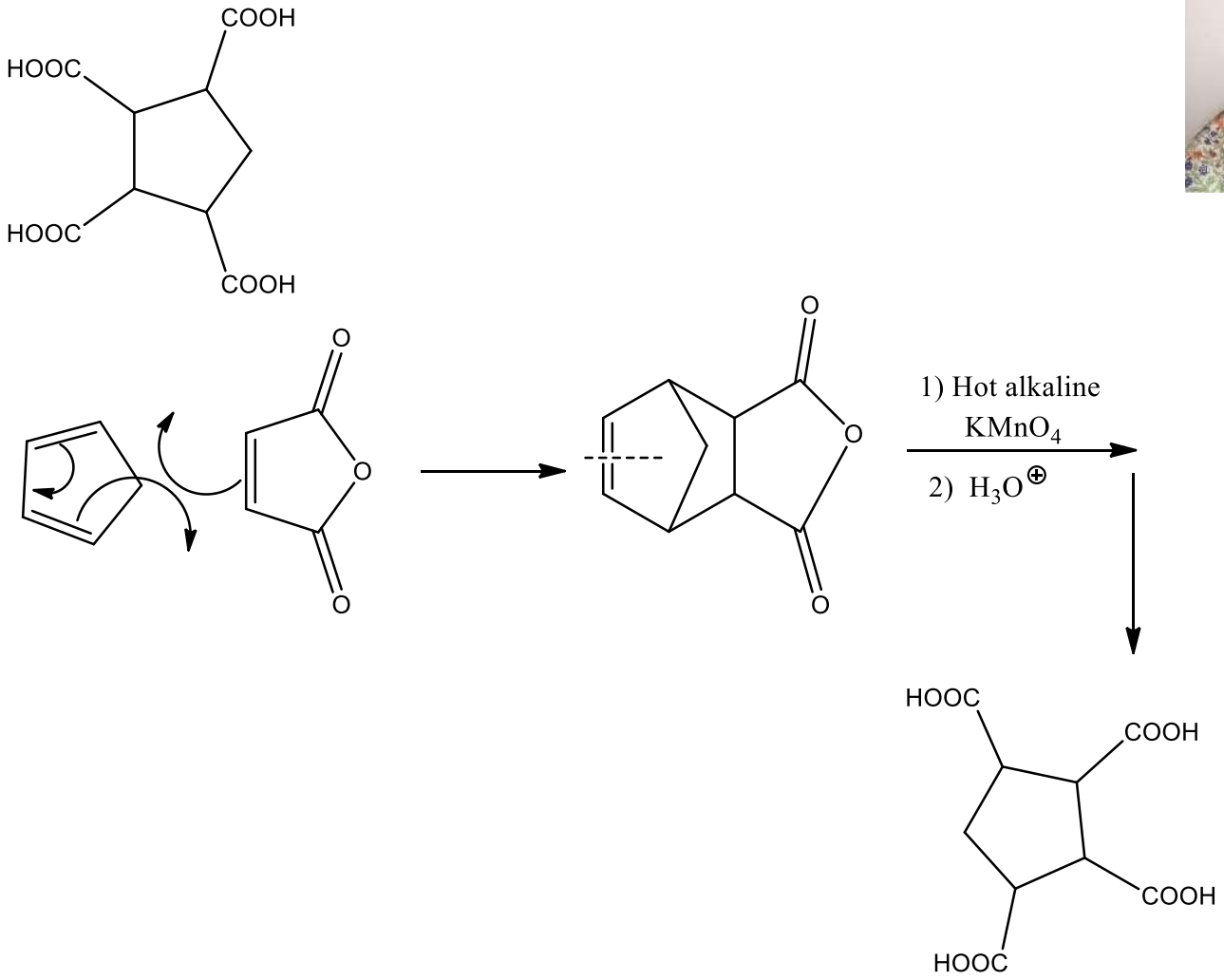


Diene Dienophile

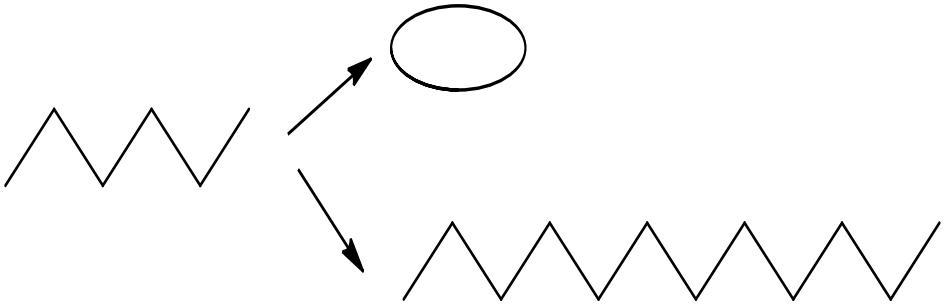
Carry out synthesis of the following compound:



Carry out synthesis of the following compound:



Principle of High Dilution:

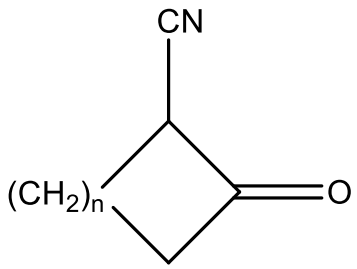


For cyclisation, Rate α [Substrate]

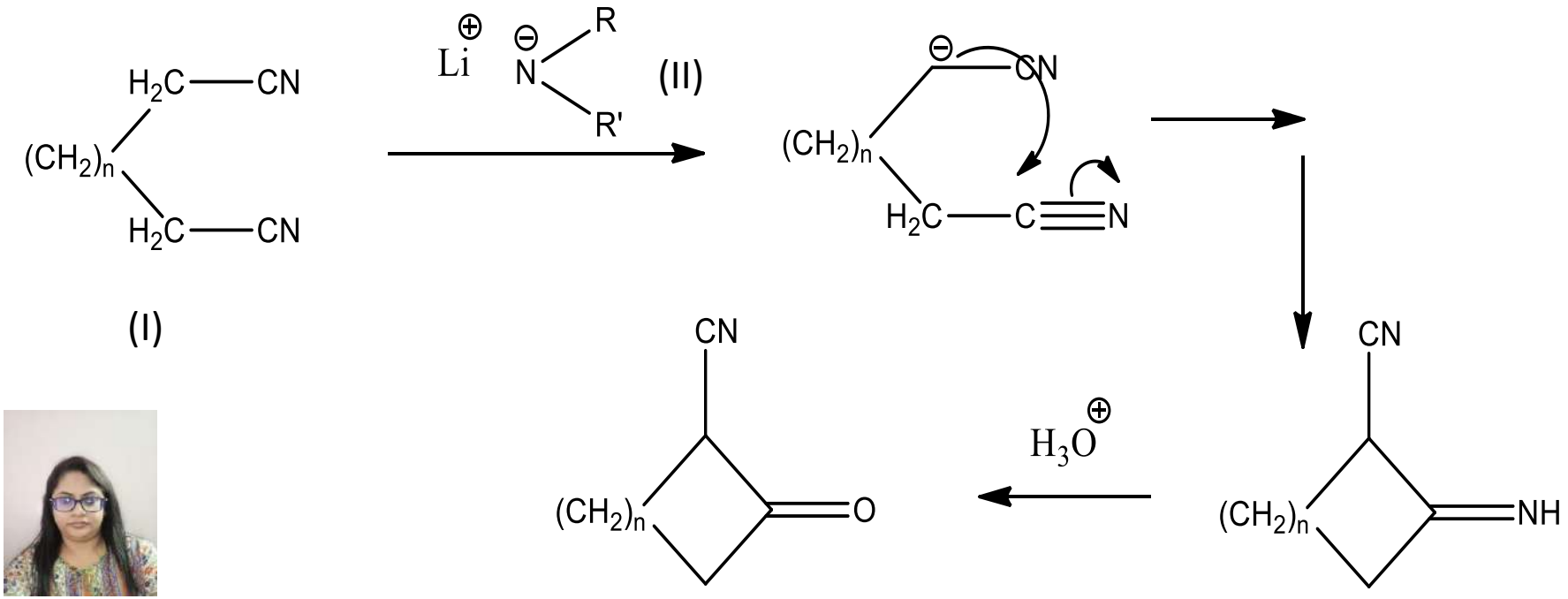
For linear condensation, Rate α [Substrate]^n

In organic chemistry, the **High Dilution Principle** is a strategy for some macrocyclization reactions, i.e. the synthesis of macrocycles. Unlike the synthesis of 5- and 6-membered rings, the preparation of larger rings competes unfavorably with polymerization reactions. Polymers arise from coupling of long chain precursors. Such reactions are disfavored when the acyclic compounds are dilute.[9] Although high dilution reactions can be conducted in a batch reactor with large volumes of solvent, a more practical implementation entails slow addition of reactants, under conditions that the reactants are more rapidly consumed than the rate of addition.

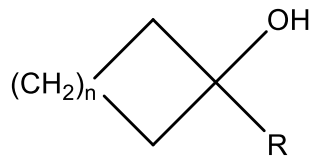
Carry out synthesis of the following compound (Ziegler):



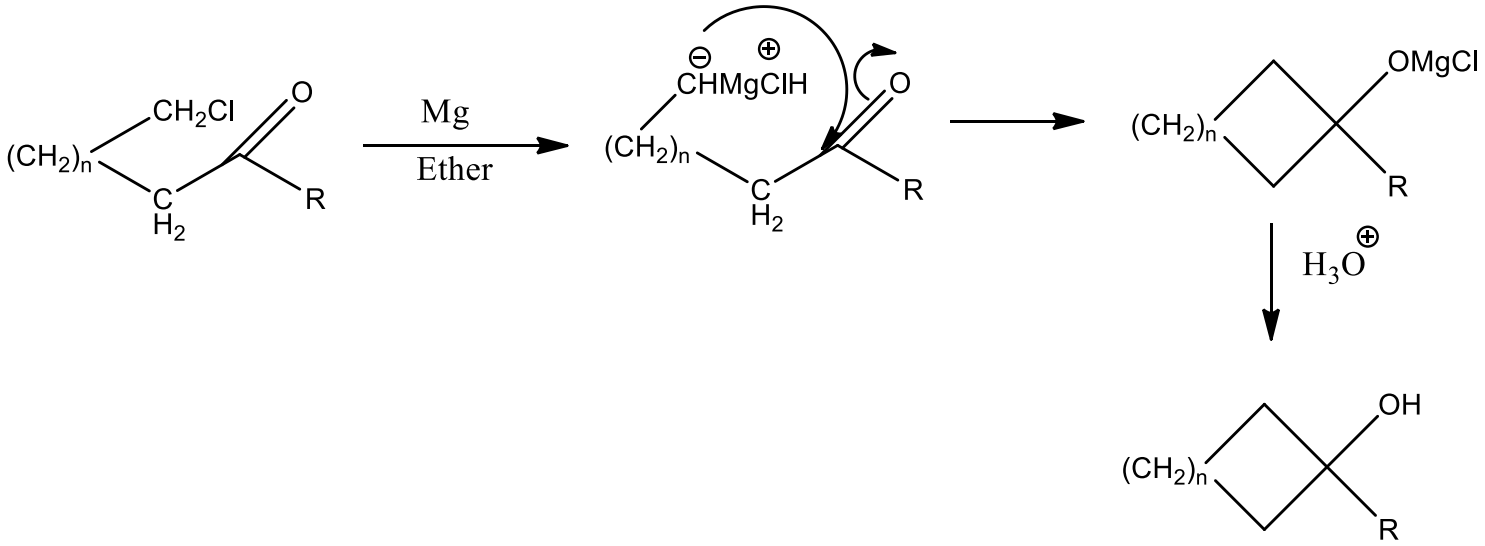
Ziegler made use of the high dilution principle, obtaining large rings by the intra-molecular condensation of α, ω – normal aliphatic dicyanide (I) in the presence of alkali derivatives of secondary amines (II). The mechanism of the reaction is not certain.



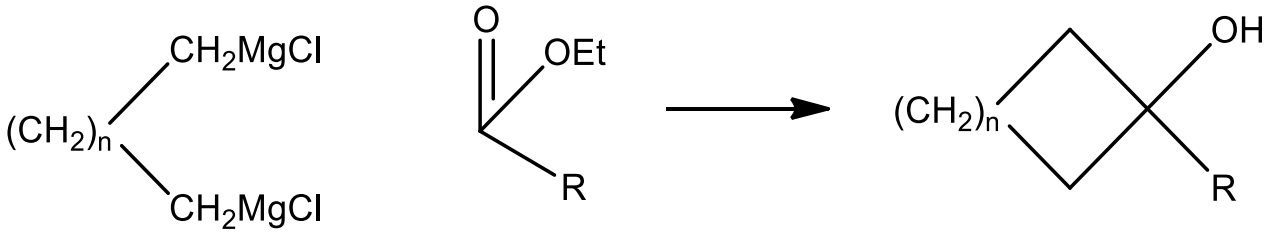
Carry out synthesis of the following compound (Grignard) :



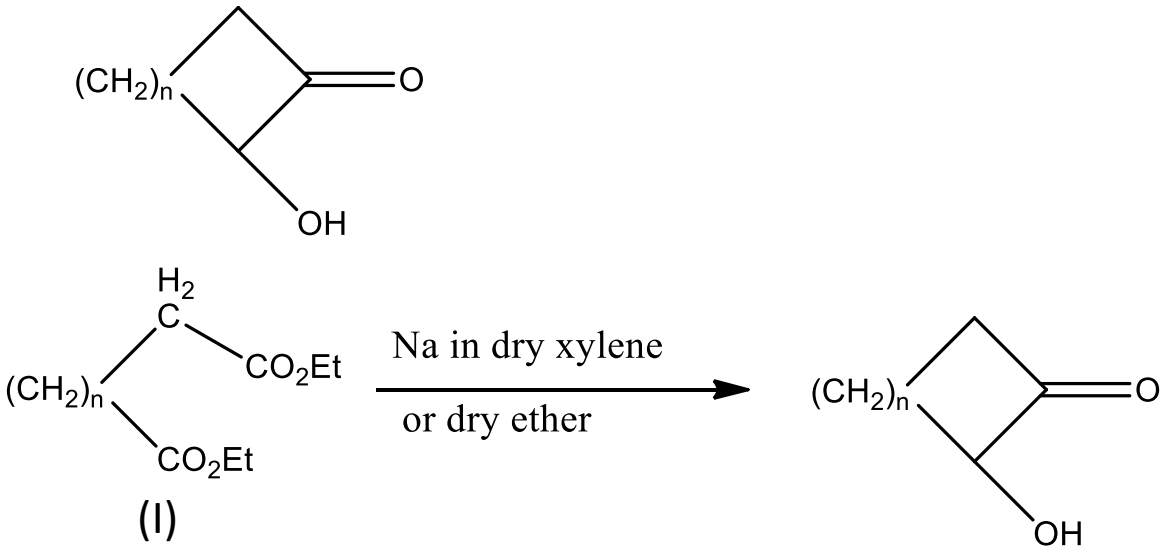
Procedure - I



Procedure II



Carry out synthesis of the following compound (Acyloin) :

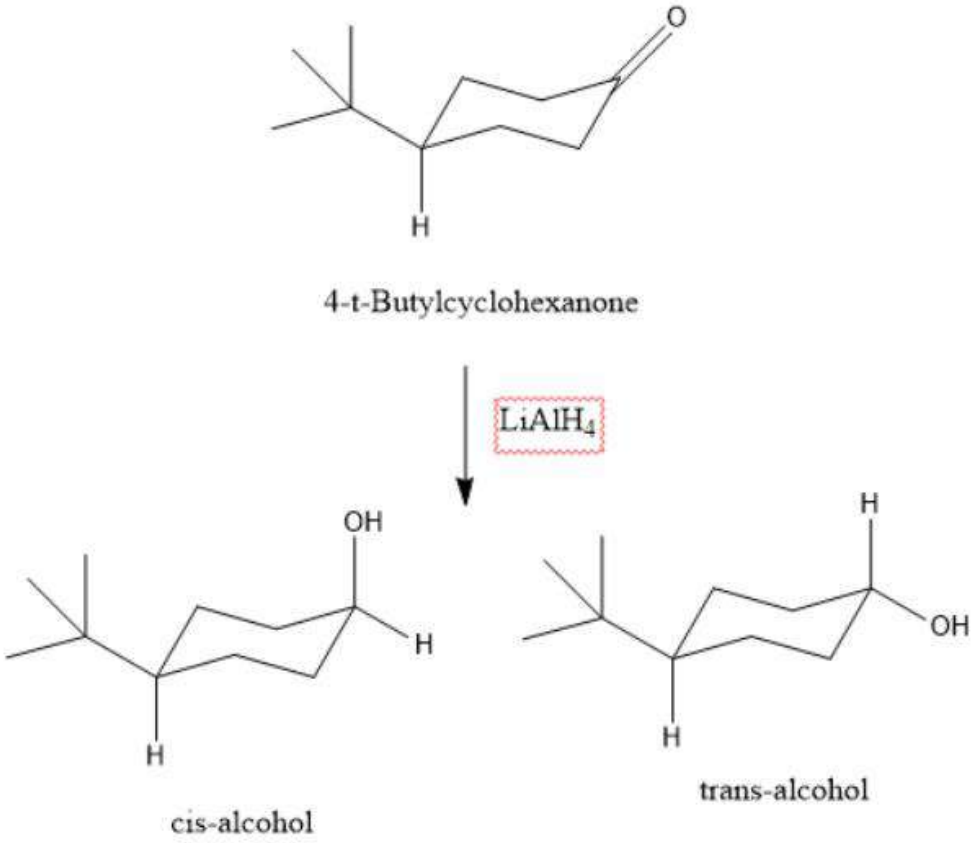


The most useful method of preparing large rings is the intra-molecular acyloin condensation of α, γ – dicarboxylic esters (I). This method does not require the high dilution technique. The corresponding cycloaklane was obtained by reduction of the acyloin by the Clemmenson method.

Asymmetric synthesis

Stereoselective Reactions

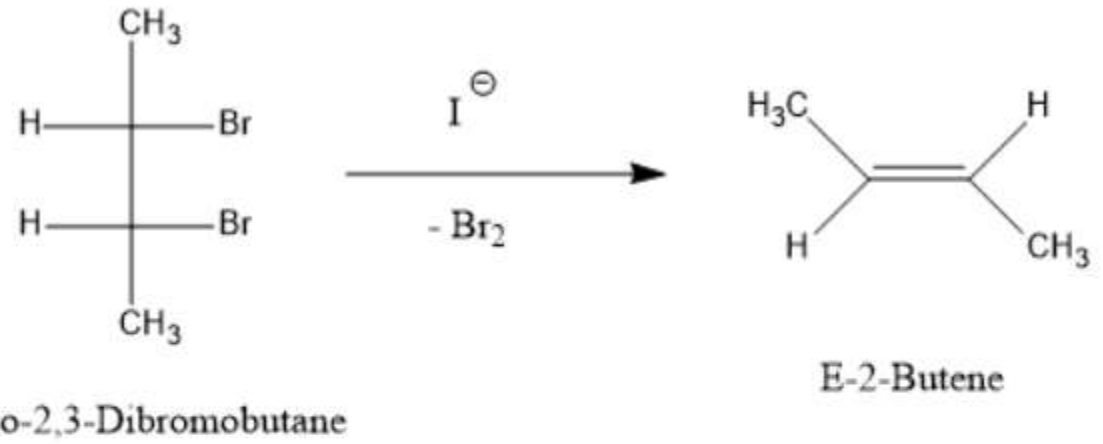
A stereoselective reaction is one, which produces one diastereoisomer in excess over the other.



major

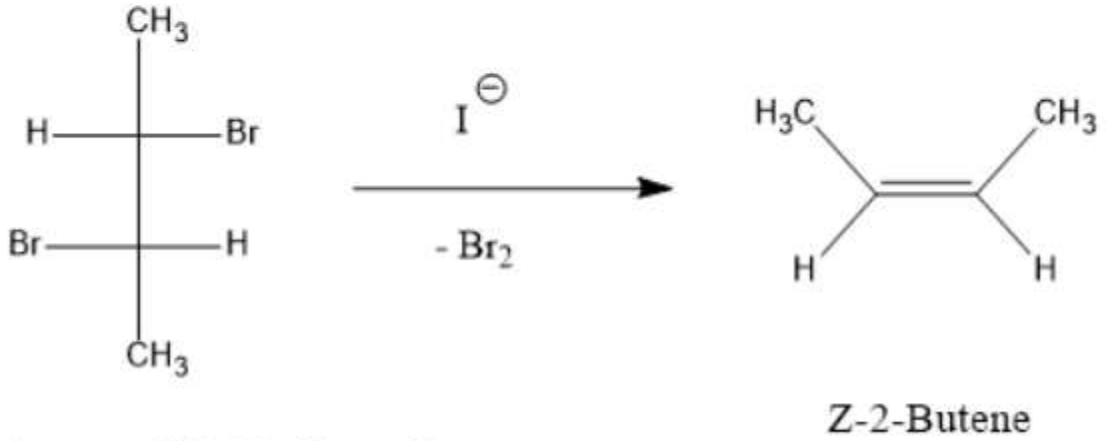
Stereospecific Reaction

A stereospecific reaction is one in which stereochemically different isomers lead to stereochemically different products.



meso-2,3-Dibromobutane

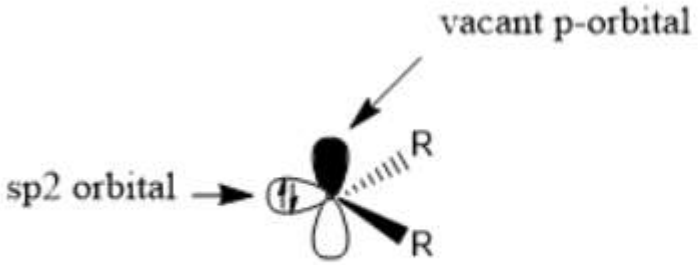
E-2-Butene



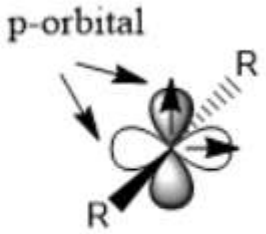
active isomer of 2,3-Dibromobutane

Z-2-Butene

Another example of Stereospecific and Stereoselective Reaction



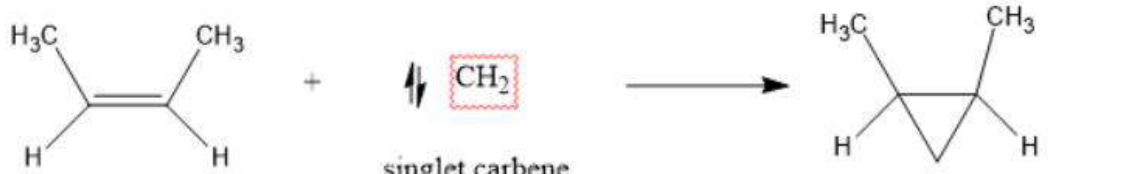
singlet carbene with sp2 carbon



triplet carbene with sp carbon

2S+1 = 2x0+1=1

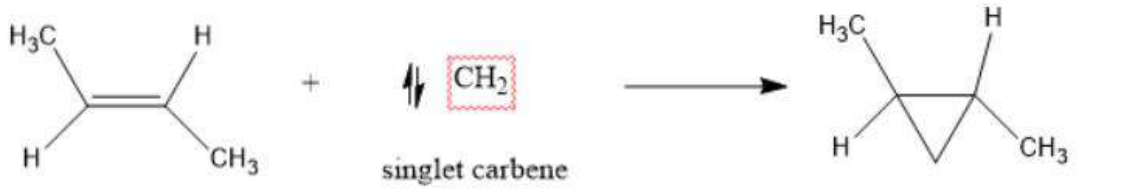
2S+1 = 2x1+1=3



(Z)-2-Butene

Methylene

cis-1,2-dimethylcyclopropane

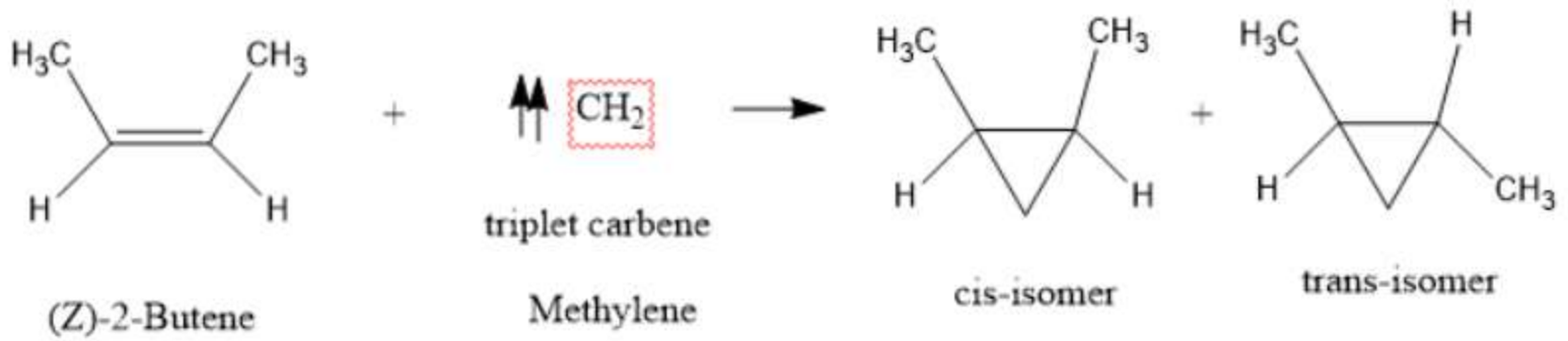


(E)-2-Butene

Methylene

trans-1,2-dimethylcyclopropane

Stereospecific Reaction



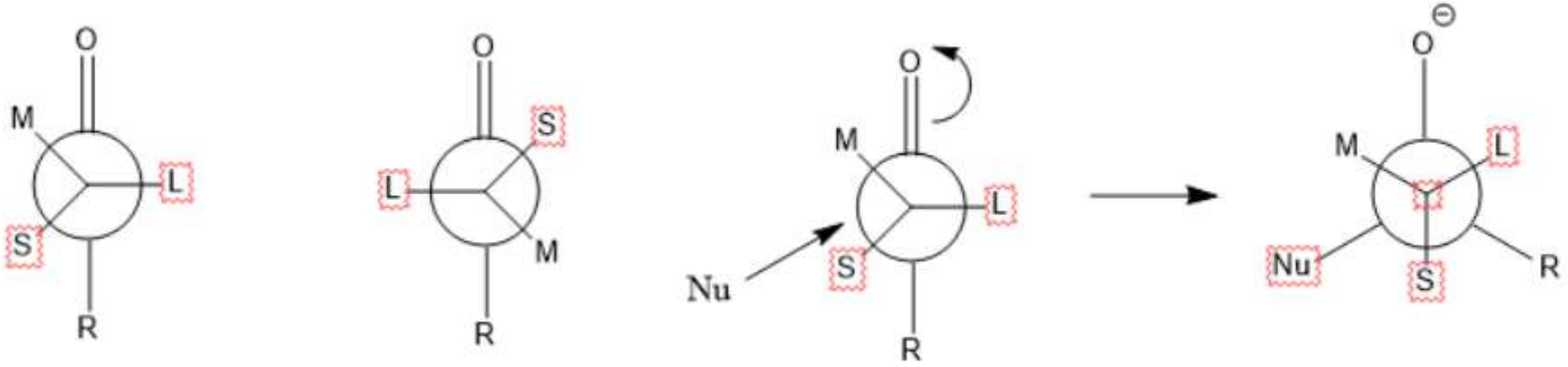
Stereoselective Reaction

If we take E-2-Butene as the starting material, the result is same.

Diastereoselectivity:

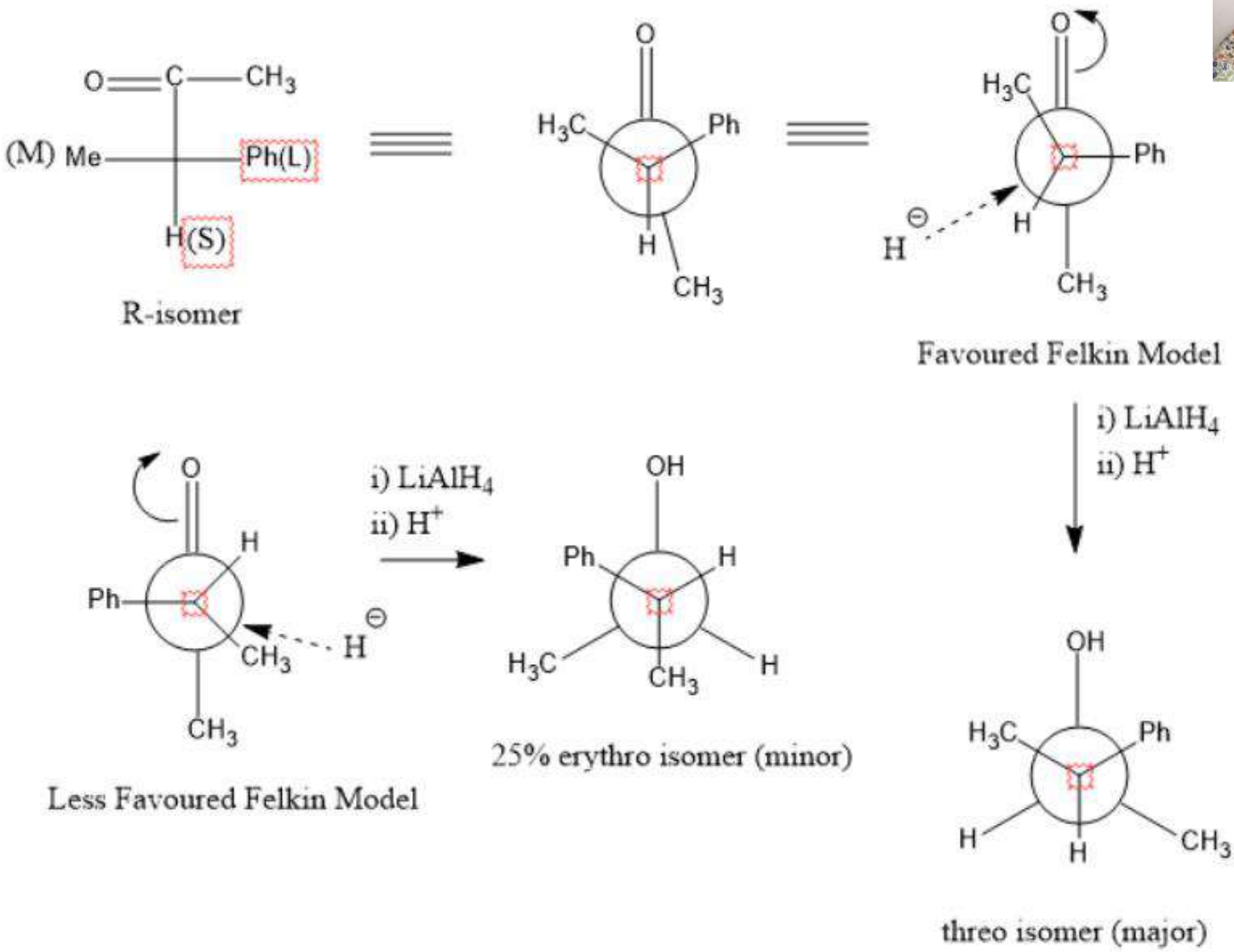
Addition of nucleophiles to C=O adjacent to a stereogenic centre: Felkin-Anh model

Diastereoselective reactions lead to the formation of diastereoisomers in unequal amounts. Most important diastereoselective synthesis is diastereoface differentiation of compounds of the type R*-CHO where R* is a chiral centre. CO group in this case represents a diastereotopic face and designated as *Re* and *Si* face. Diastereoface differentiation is also observed when the substrate is not representing a chiral system.



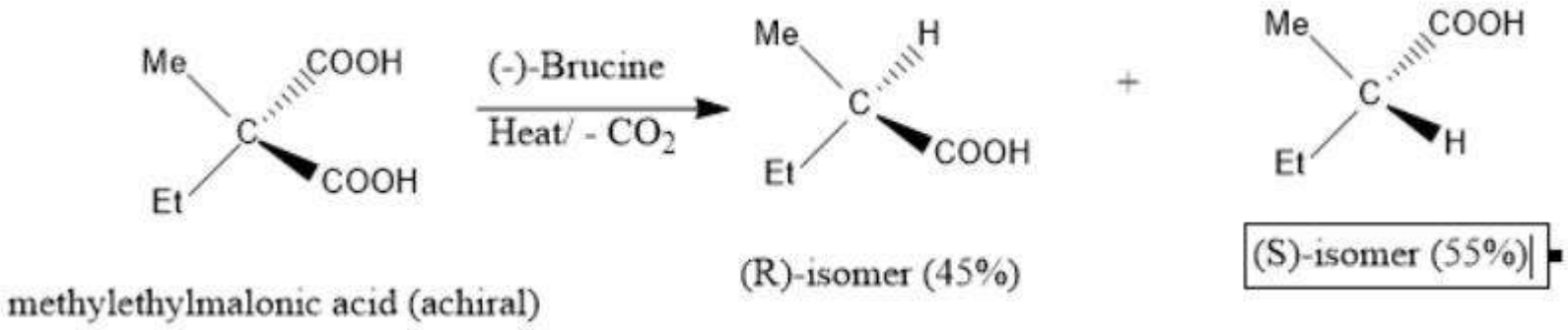
Model I Model II

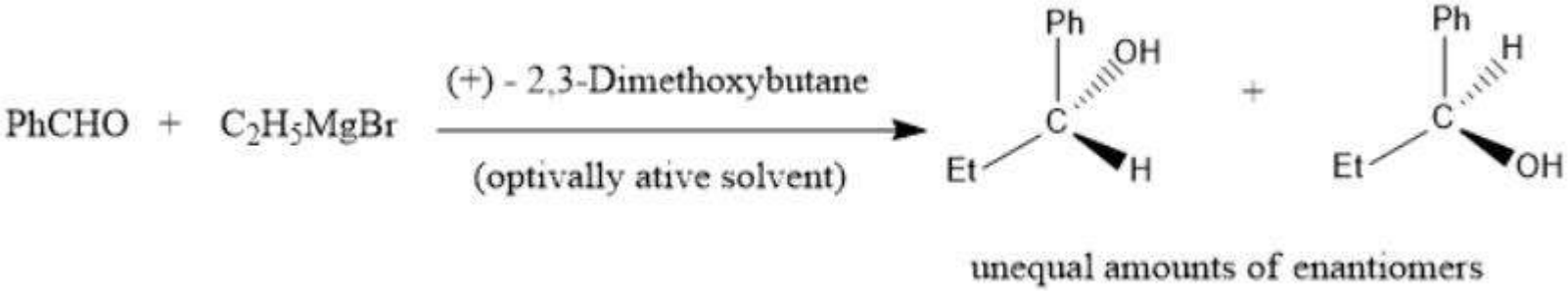
Example:


O
C
CH3
(M) Me
Ph(L)
H(S)
R-isomer
H3C
Ph
H
CH3
H3C
Ph
H
H
CH3
Favoured Felkin Model
i) LiAlH4
ii) H+
OH
Ph
H
H3C
CH3
H
25% erythro isomer (minor)
Ph
H
CH3
H
CH3
Less Favoured Felkin Model
OH
H3C
Ph
H
H
CH3
threo isomer (major)

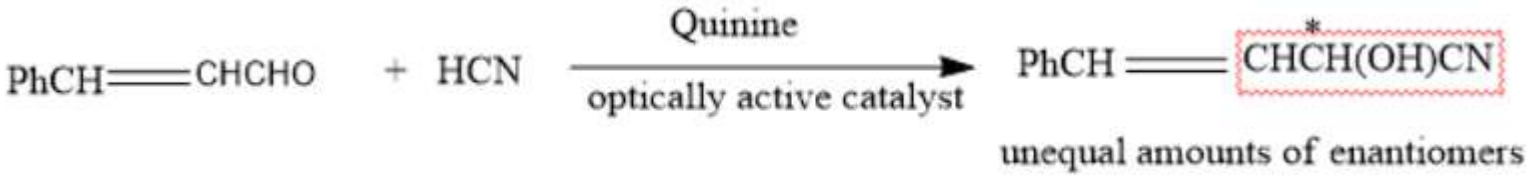
Enantioselectivity

In general any reaction that involves asymmetric induction is called asymmetric synthesis. Definition wise enantioselective synthesis also belongs to the category of asymmetric synthesis. It is now common practice to define asymmetric synthesis as a special case of stereoselectivity in which a prochiral unit (centre or face) is transformed into a chiral centre and results in unequal amounts of stereoisomers. In enetioselective synthesis, substrate is achiral but the reagents are chiral.





It is a case of enentiofacedifferentiation by a reagent in a chiral solvent.



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***2.**Gröbel, B. T.; Seebach, D. (1977). "Umpolung of the Reactivity of Carbonyl Compounds Through Sulfur-Containing Reagents". Synthesis. **1977** (6): 357. doi:10.1055/s-1977-24412.*

***3.**Seebach, D.; Corey, E. J. (1975). "Generation and synthetic applications of 2-lithio-1,3-dithianes". The Journal of Organic Chemistry. **40** (2): 231. doi:10.1021/jo00890a018.*

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5. Warren, S. Organic Synthesis the Disconnection Approach, John Wiley and Sons.

6. Warren, S., Designing Organic Synthesis, Wiley India, 2009.

7.Carruthers, W. Modern methods of Organic Synthesis, Cambridge University Press.

8. Baldwin's rules were formulated following analysis of transition state geometries: Baldwin J. Chem. Soc., Chem. Commun. 1976, 734 [DOI] & ibid 736 [DOI] & ibid 738 [DOI]

9. https://en.wikipedia.org/wiki/High_Dilution_Principle

THANK YOU