Retrosynthesis

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Why Retrosynthesis?

The Synthetic Route to a Target Molecule

Learning Outcomes

- After studying this module, you shall be able to:

1. Know about synthons.
2. Know about synthetic equivalents.
3. Know about retrosynthetic analysis.
4. Study the steps involved in retrosynthetic analysis.
5. Know the routine for designing the synthesis.

Retrosynthetic analysis

Definition: The construction of a synthetic pathway by working backward from the target molecule is called retrosynthetic analysis.

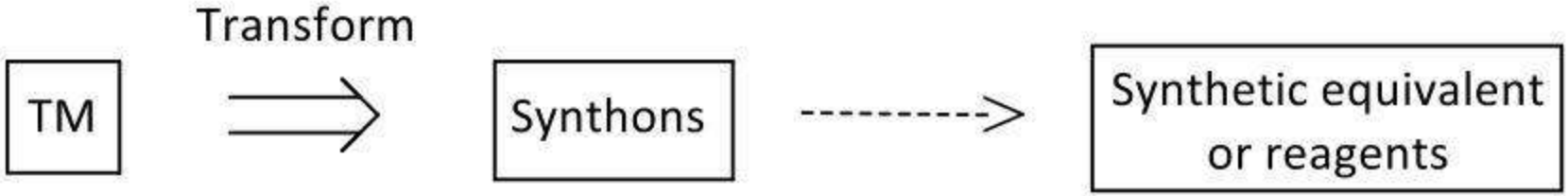
- Retrosynthetic (or antithetic) analysis is a problem resolving method for converting the structure of a synthetic target (TGT) molecule to a sequence of gradually simpler structures through a path which eventually leads to simple or commercially available starting materials for a chemical synthesis.
- This helps chemist to design synthesis. The symbol => (double line arrow) signifies a reverse synthetic step and is called a transform.
- In a reverse synthesis or retrosynthetic analysis, we move from target molecule to synthons and further to synthetic equivalents.

Important Aspects of Retrosynthesis

- **Practicability:** The methodology actually works in the experimental condition.
- **Step-economy:** In general, the number of synthetic steps must be as less as possible.
- **Atom-economy:** The yield of each step must be good to excellent.
- **Cleanliness:** The side products and impurities must be lesser amount and easily separable from the desired product.
- **Greener Approach:** The synthetic steps must follow principle of green chemistry.
- **Pot, Atom, Step Economy (PASE) :** The synthetic process must be economically viable.

Retrosynthesis

TM : Target molecule
FGI : Functional group interconversions
SE : Synthetic equivalents
IP : Inverting the polarity (Umpolung in German)



Target Molecule:

The molecule whose synthesis is being planned

Functional Group Interconversion (FGI):

Many functional groups can be interconverted into each other, e.g., oxidation of an alcohol gives an aldehyde, and further oxidation gives carboxylic acid. Many organic transformations can be used to do FGIs. Carbonyl groups are particularly useful in this respect . The reactivity of the carbonyl group can be masked during synthesis as double bond (ozonolysis for FGI into aldehyde) or dioxolane until needed.

Synthetic Equivalents, Inverting Polarity and Synthons

Synthetic Equivalents:

Synthetic equivalents are the chemical species which is used to generate synthons. They are the actual substrates used for the forward reaction and hence forward synthesis. Also, the synthetic equivalents are the reagents derived from inverting the polarity of synthons.

Inverting Polarity or Umpolung:

Inverting Polarity or 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. This modification allows secondary reactions of this functional group that would otherwise not be possible. The concept was introduced by D. Seebach and E.J. Corey. Polarity analysis during retrosynthetic analysis tells a chemist when umpolung tactics are required to synthesize a target molecule.

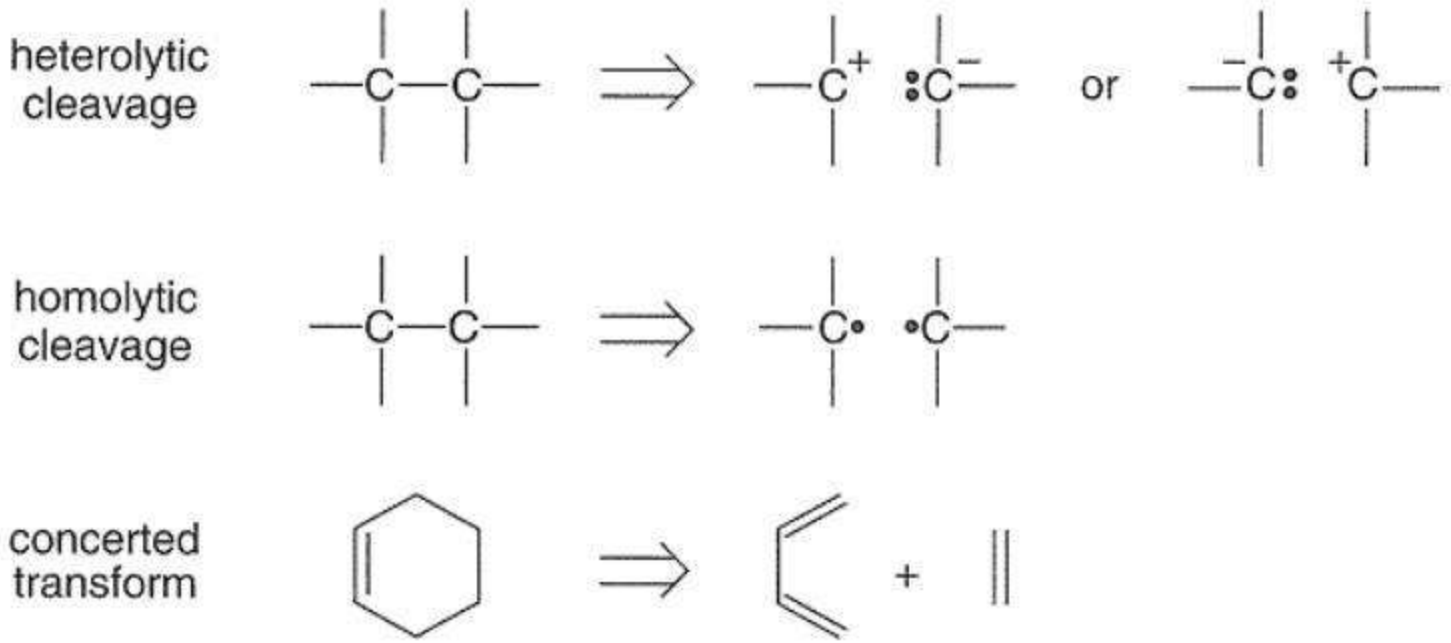
Synthons:

Synthons are the chemical fragments obtained from the disconnection of bond(s) of the target molecule.

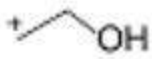
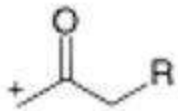
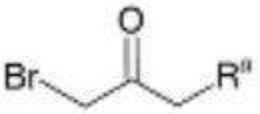
Disconnection

Heterolytic retrosynthetic tic disconnection of a carbon-carbon bond in a molecule breaks the TM into an **acceptor synthon**, **a carbocation**, and a **donor synthon, a carbanion**. In a formal sense, the reverse reaction - the formation of a C-C bond - then involves the union of an electrophilic acceptor synthon and a nucleophilic donor synthon.

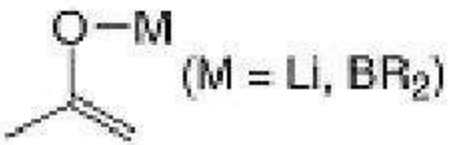
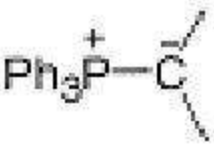
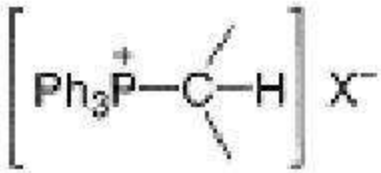
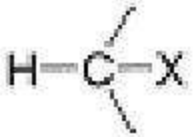
Chemical bonds can be cleaved heterolytically, homolytically, or through concerted transform (into two neutral, closed-shell fragments). The following discussion will focus on heterolytic and cyclic disconnections.



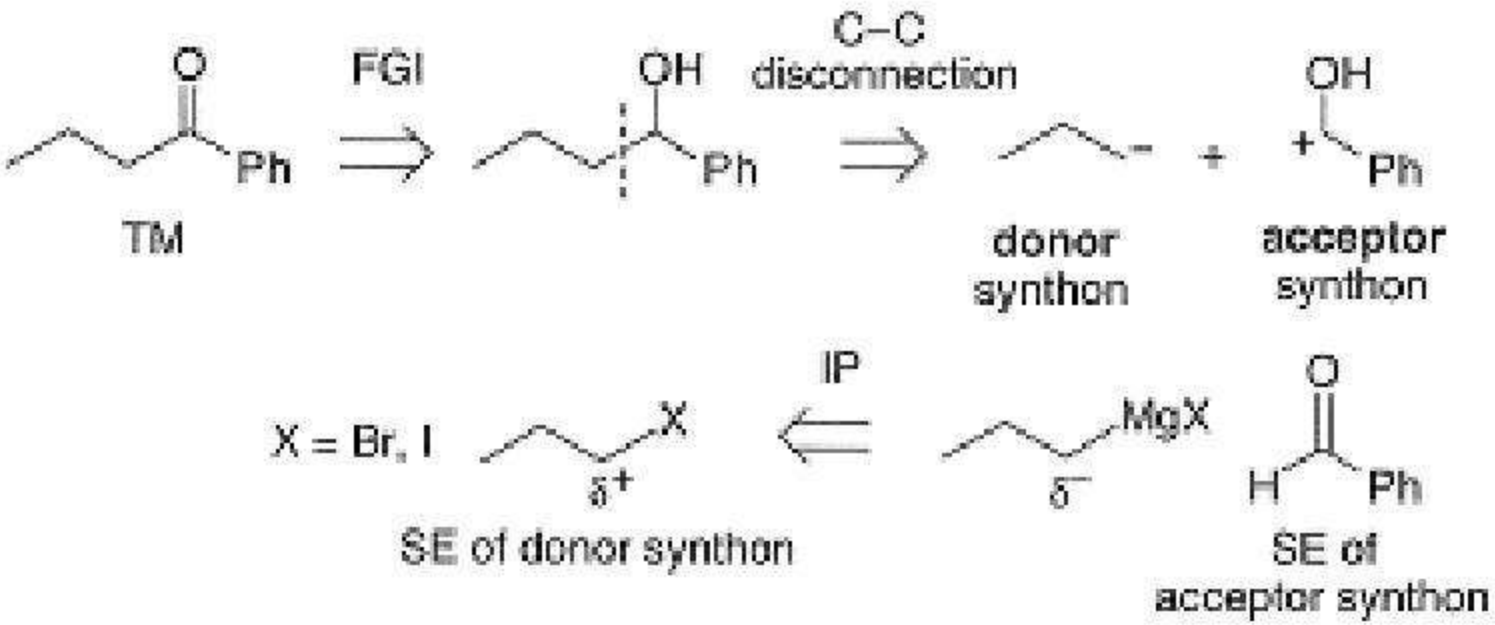
Common Acceptor Synthons

Synthon	Synthetic equivalent
R^+ (alkyl cation = carbenium ion)	RCl, RBr, RI, ROTs
Ar^+ (aryl cation)	$Ar\overset{+}{N}_2\ X^-$
$H\overset{+}{C}{=}O$ (acylium ion)	$H\overset{O}{\overset{\|}{C}}{-}X$ (X = NR_2, OR)
$R\overset{+}{C}{=}O$ (acylium ion)	$R\overset{O}{\overset{\|}{C}}{-}X$ (X = Cl, NR_2', OR')
$HO{-}\overset{+}{C}{=}O$ (acylium ion)	CO_2
$\overset{+}{C}H_2CH_2\overset{O}{\overset{\|}{C}}{-}R$	$CH_2{=}CH\overset{O}{\overset{\|}{C}}{-}R$ (R = alkyl, OR')
$\overset{+}{C}H_2{-}CH_2C{\equiv}N$	$CH_2{=}CHC{\equiv}N$
$\overset{+}{C}H_2OH$ (oxocarbenium ion)	HCHO
$R\overset{+}{C}H{-}OH$ (oxocarbenium ion)	RCHO
$R_2\overset{+}{C}{-}OH$ (oxocarbenium ion)	$R_2C{=}O$
	
	

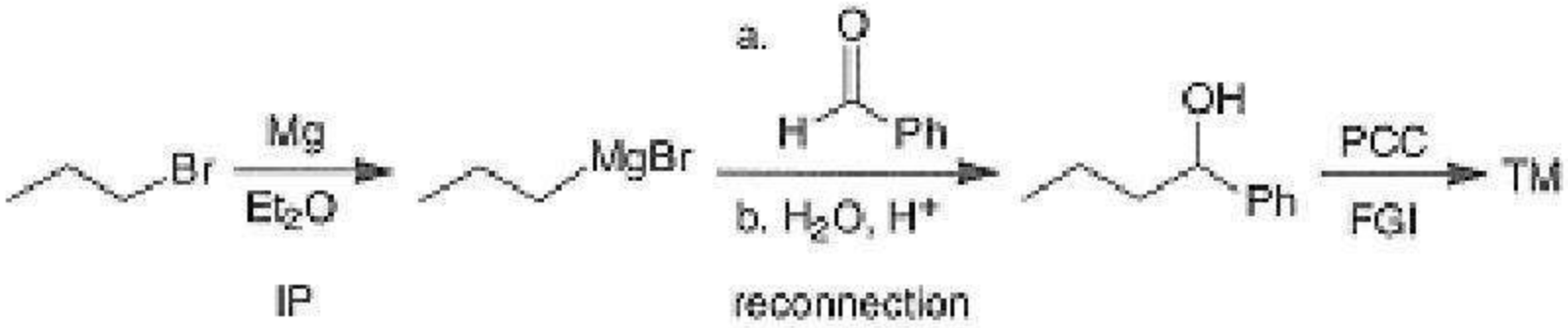
Common Donor Synthons

Synthon	Derived reagent	Synthetic equivalent
R^- (alkyl, aryl anion)	RMgX, RLi, R_2CuLi	R–X
^-CN (cyanide)	NaC≡N	HCN
$RC{\equiv}C^-$ (acetylide)	RC≡CMgX, RC≡CLi	RC≡CH
 (enolate)	 (M = Li, BR_2)	
 (ylide)	 X^-	
 (α-nitro anion)		

Retrosynthetic anaylsis A

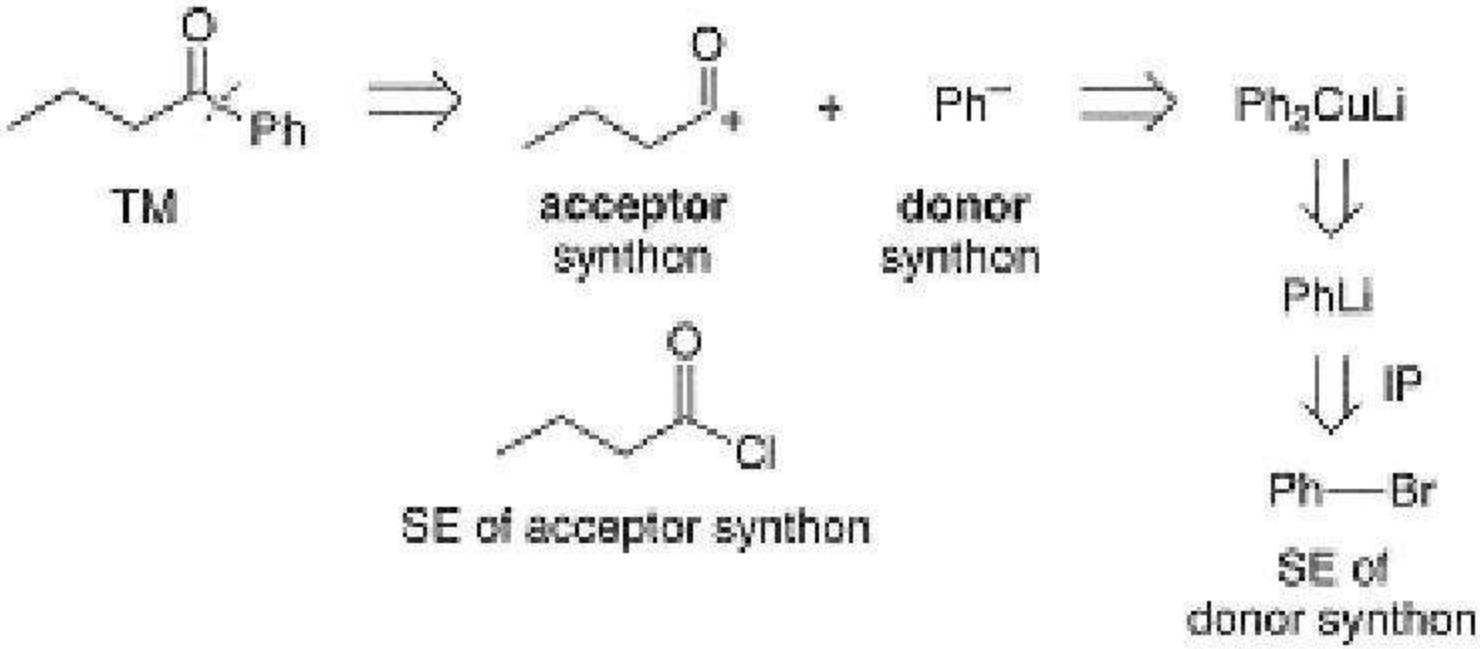


Synthesis A

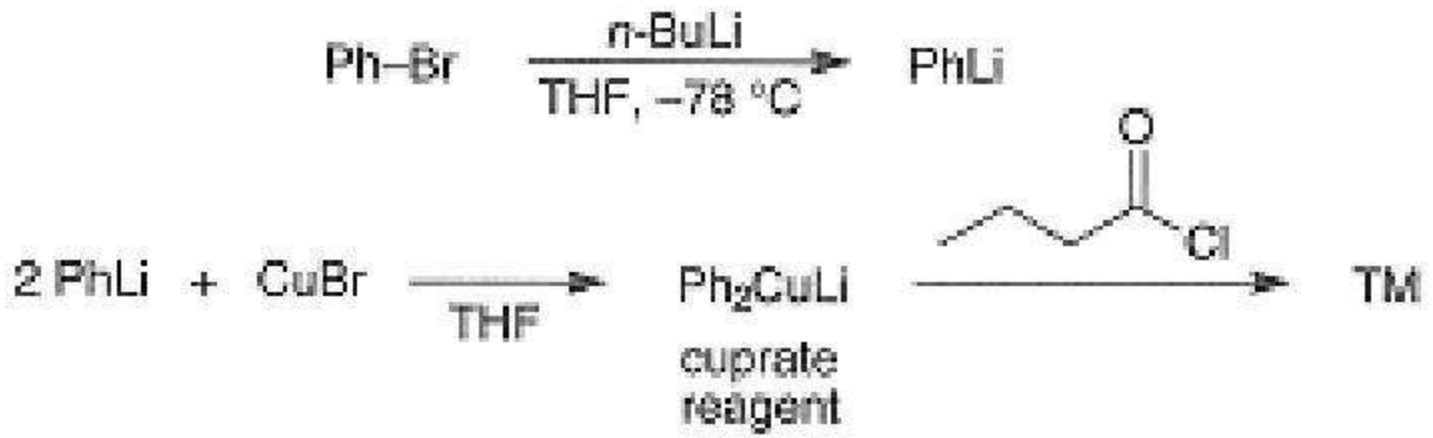


PCC: Pyridinium chlorochromate

Retrosynthetic anaylsis B



Synthesis B



Alternating polarity disconnections

Functional groups may be classified as follows:

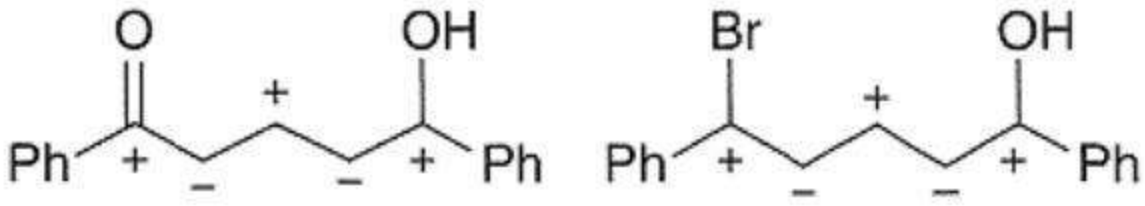
E class: Groups conferring electrophilic character to the attached carbon (+):
$-NH_2$, -OH, -OR, =0, =NR, -X (halogens)

G class: Groups conferring nucleophilic character to the attached carbon (-):
-Li, -MgX, $-AlR_2$, $-SiR_3$

A class: Functional groups that exhibit ambivalent character (+ or -):
$-BR_2$, $C=CR_2$, CECR, $-NO_2$, EN, -SR, -S(O)R, $-S0_2R$

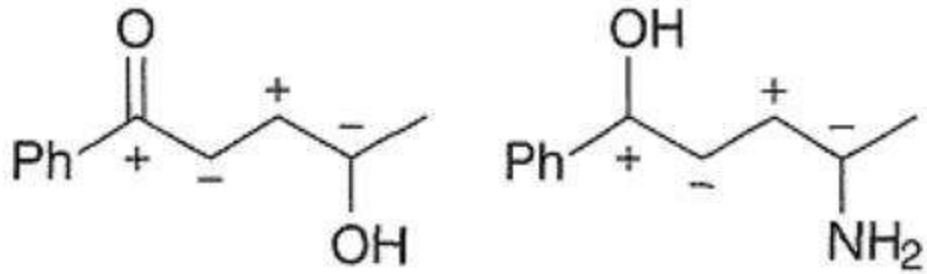
The positive charge (+) is placed at the carbon attached to an E class functional group (e.g., =0, -OH, -Br) and the TM is then analyzed for **consonant** and **dissonant patterns** by assigning alternating polarities to the remaining carbons. In a **consonant pattern**, carbon atoms with the same class of functional groups have matching polarities, whereas in a **dissonant pattern**, their polarities are unlike. **If a consonant pattern is present in a molecule, a simple synthesis may often be achieved.**

Consonant patterns



Positive charges are placed at carbon atoms bonded to the E class groups.

Dissonant patterns

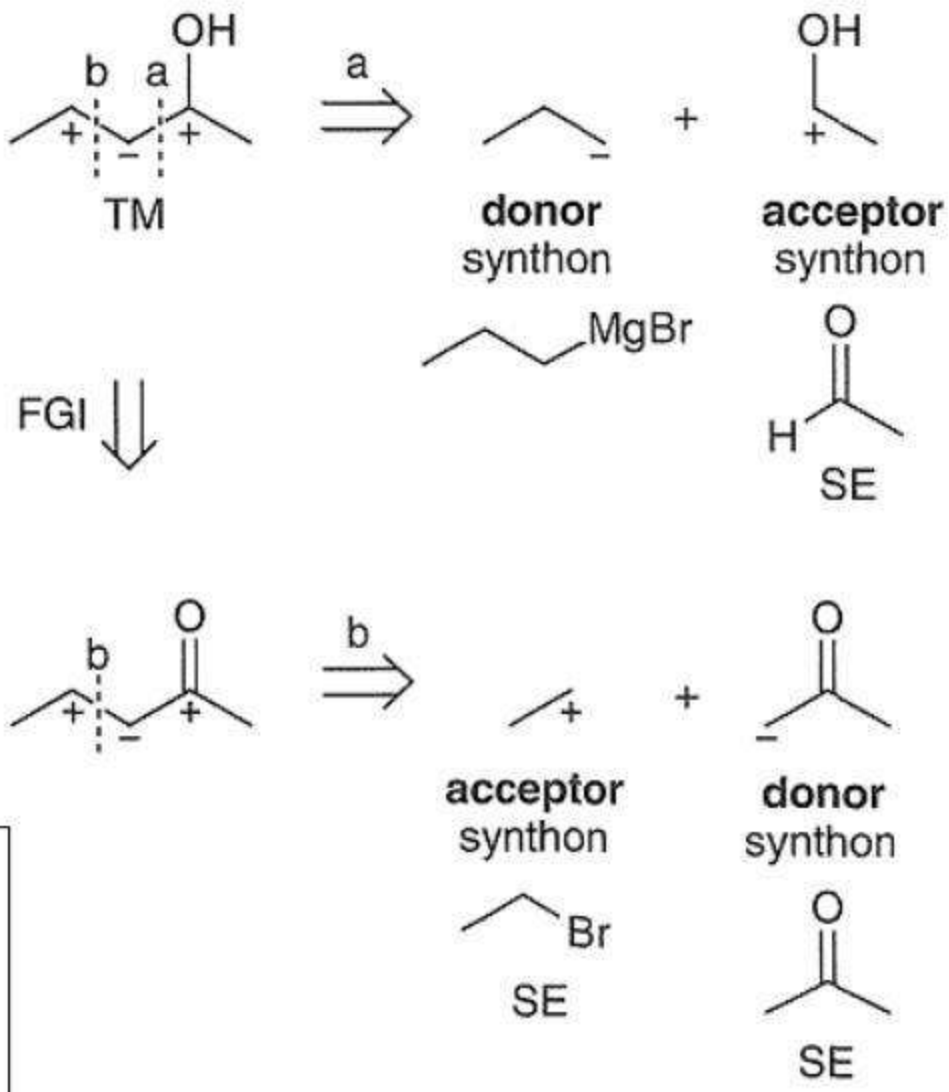


One E class group is bonded to a carbon with a positive charge, whereas the other E class group resides on a carbon with a negative charge

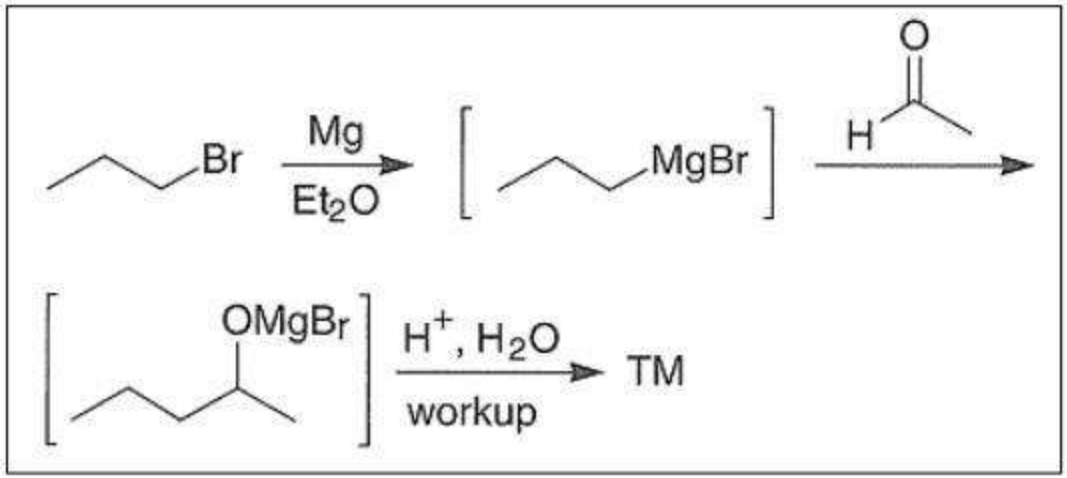
One Functional Group

Disconnection close to the functional group (path a) leads to substrates (SE) that are readily available. Moreover, reconnecting these reagents leads directly to the desired TM in high yield using well-known methodologies. Disconnection via path b also leads to readily accessible substrates. However, their reconnection to furnish the TM requires more steps and involves two critical reaction attributes: quantitative formation of the enolate ion and control of its monoalkylation by ethyl bromide.

Analysis

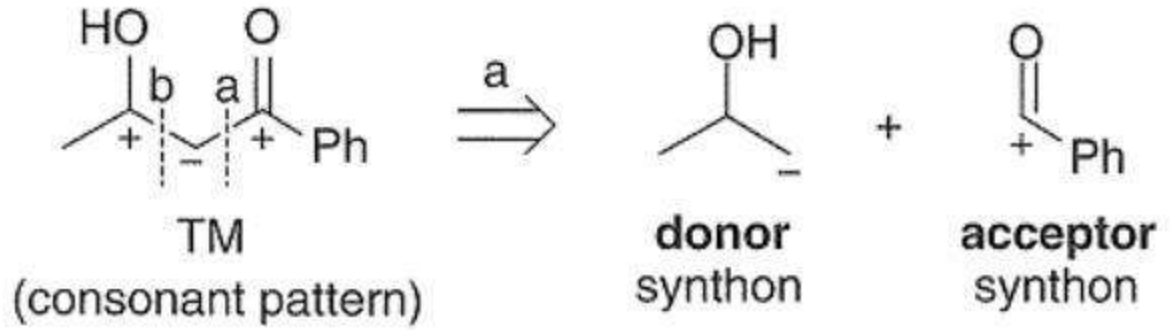


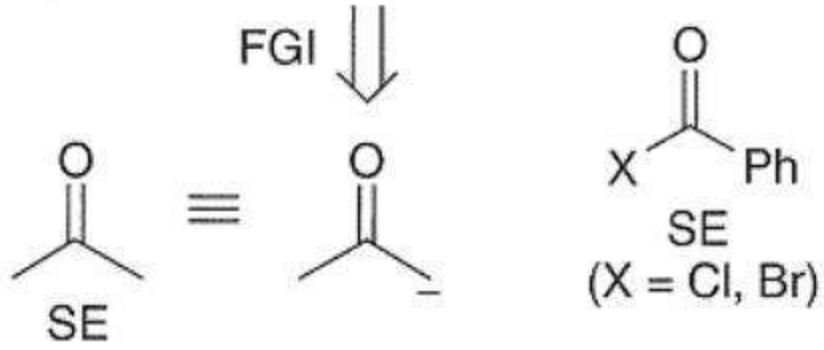
Synthesis (path a)



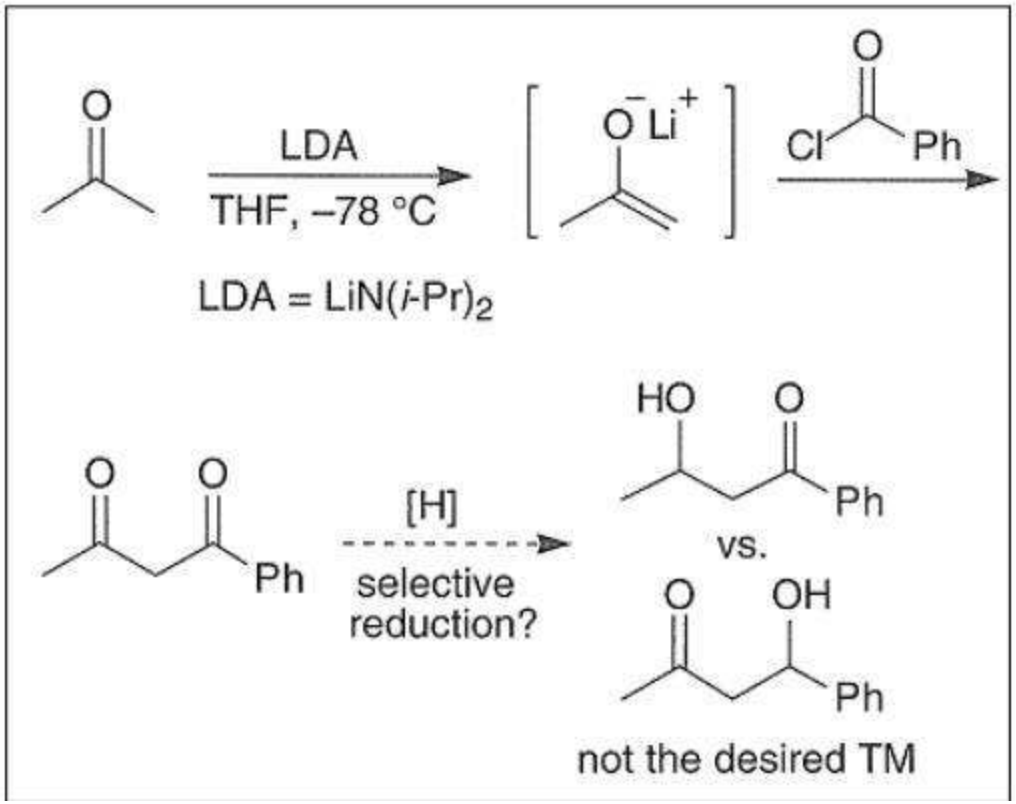
Two Functional Groups in a 1,3-Relationship

Analysis



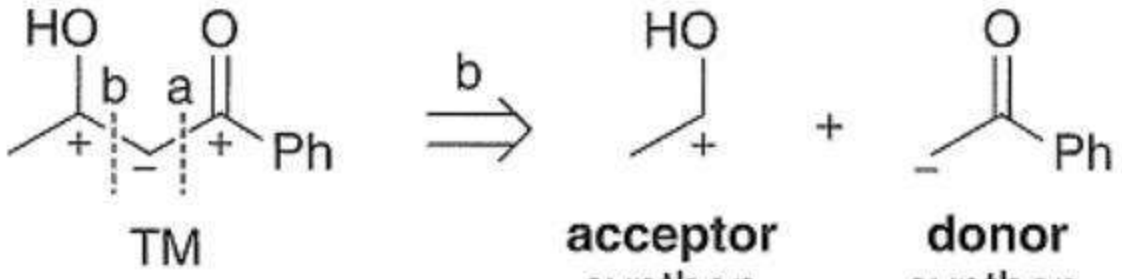


Synthesis (path a)

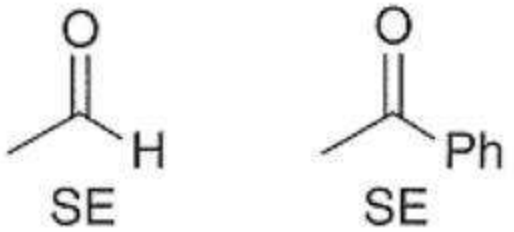


The consonant charge pattern and the presence of a β-hydroxy ketone moiety in the TM suggest a retroaldol transform. Either the hydroxy-bearing carbon or the carbonyl carbon of the TM may serve as an electrophilic site and the corresponding a-carbons as the nucleophilic sites.

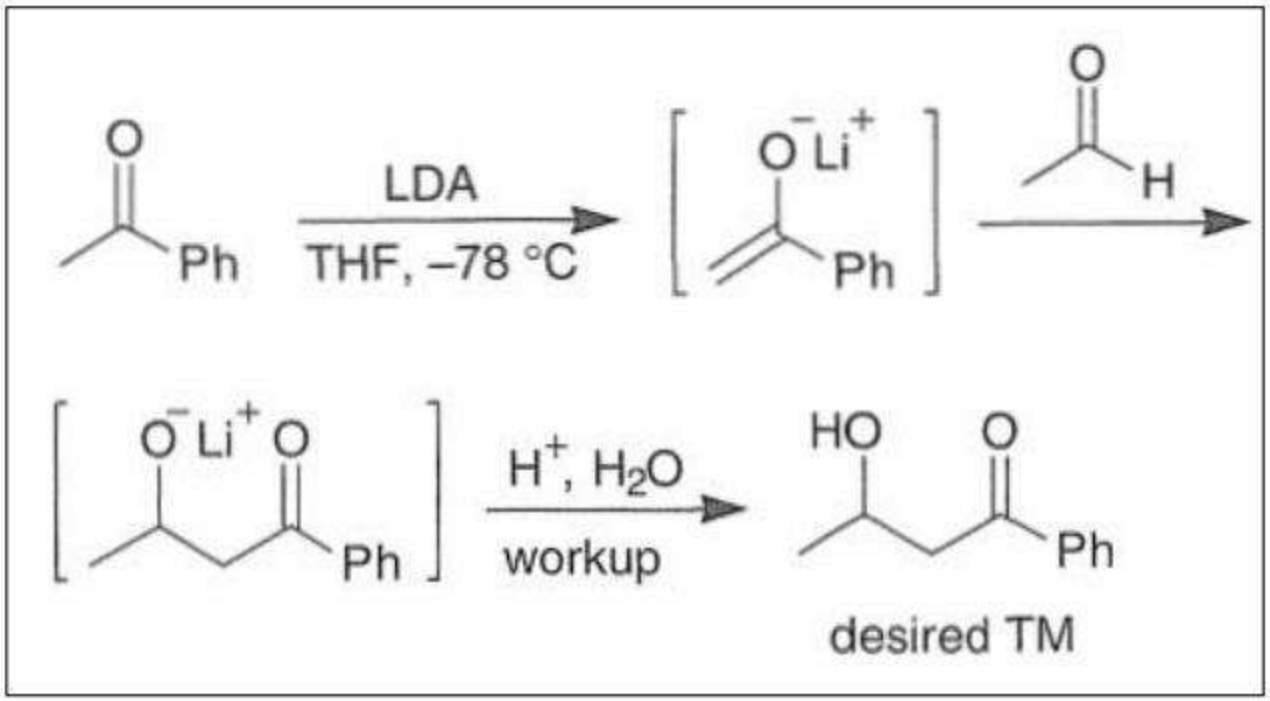
Analysis



However, path b is preferable since it does not require a selective functional group interconversion (reduction).



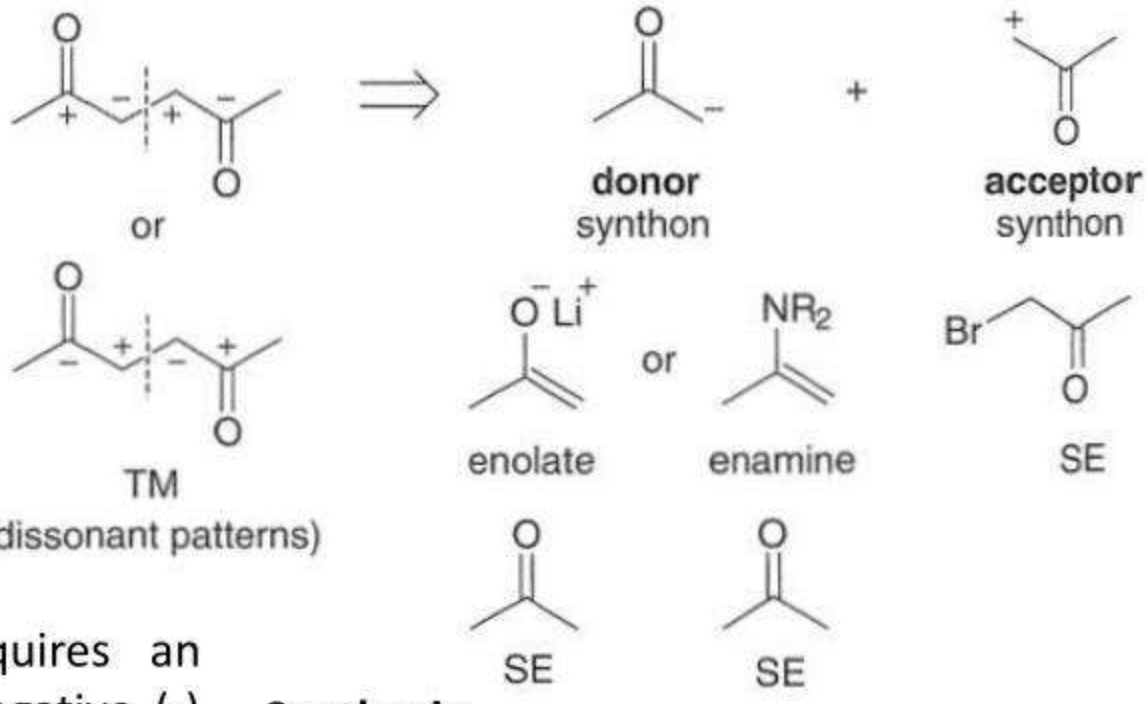
Synthesis (path b)



Two Functional Groups in a 1,4-Relationship

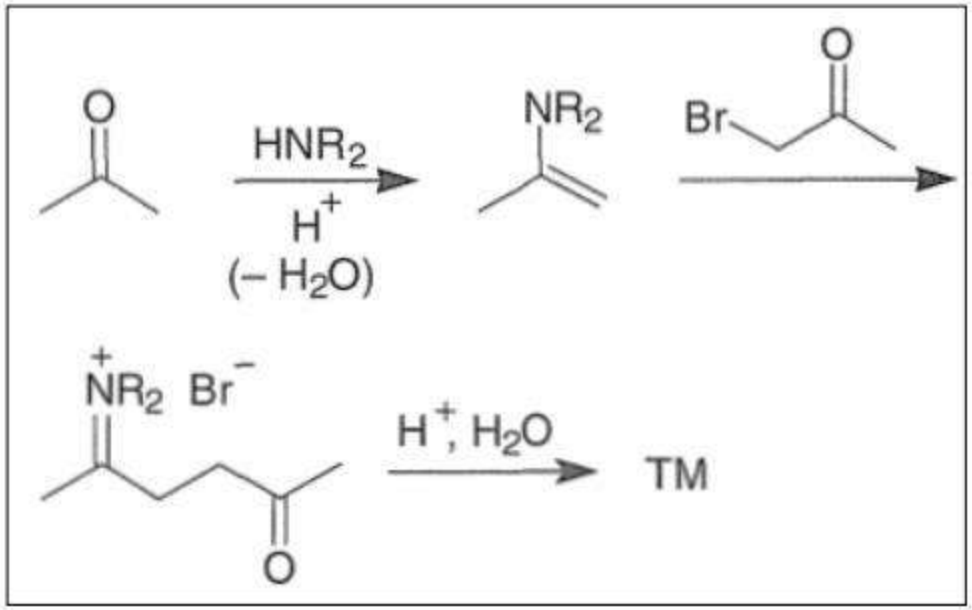
Analysis

2,5-hexanedione



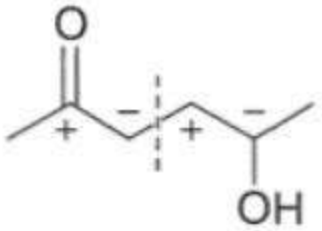
The α -carbon in this synthon requires an inversion of polarity from the negative (-) polarity normally associated with a ketone α-carbon. An appropriate substrate (SE) for the acceptor synthon is the electrophilic α-bromo ketone. It should be noted that an enolate ion might act as a base, resulting in deprotonation of an α -halo ketone, a reaction that could lead to the formation of an epoxy ketone (Darzens condensation). To circumvent this problem, a weakly basic enamine is used instead of the enolate.

Synthesis

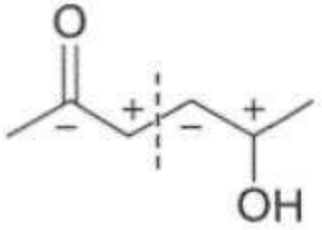


Analysis

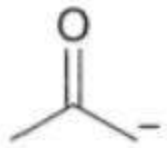
5-hydroxy-2-hexanone



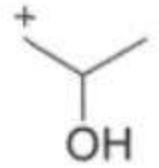
or



TM
(dissonant patterns)



donor synthon



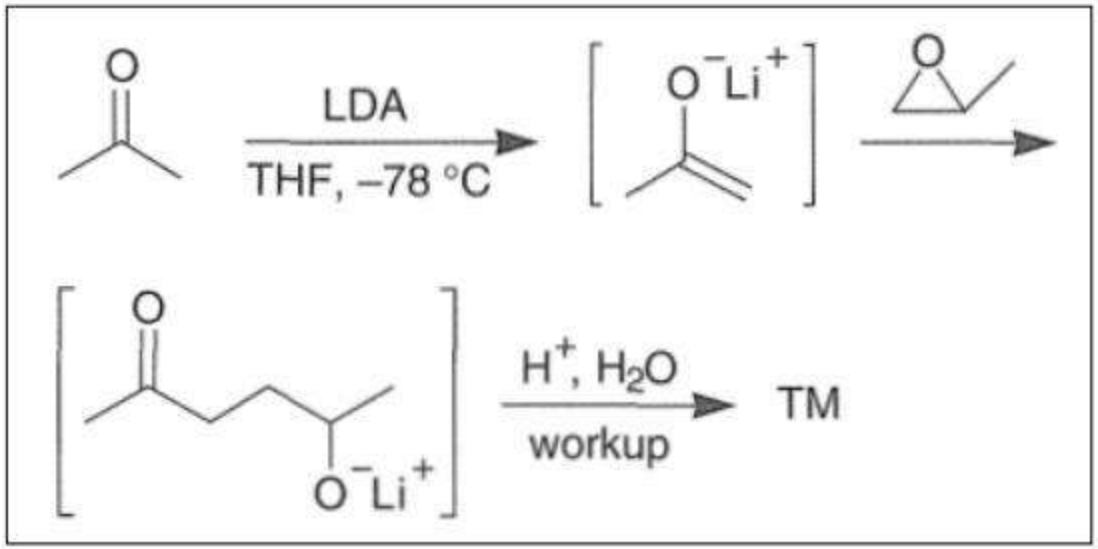
acceptor synthon

enolate

SE

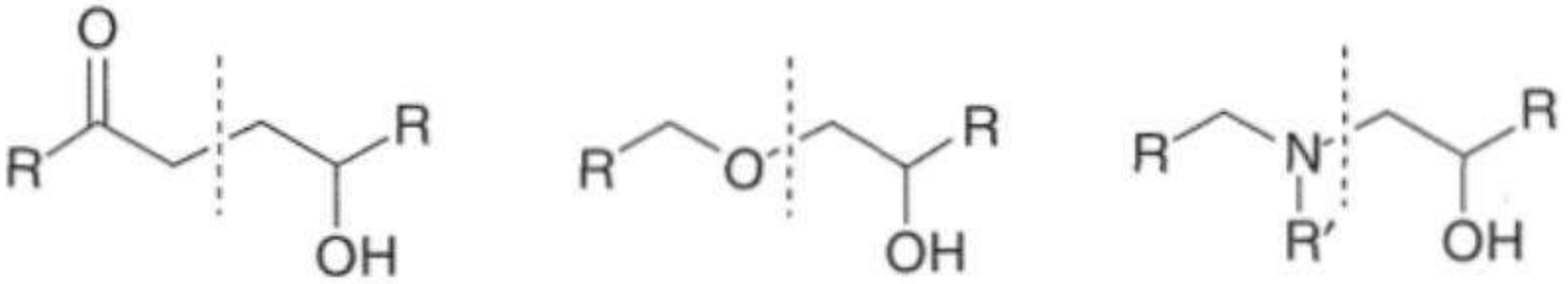
SE

Synthesis



Inversion of the polarity in the acceptor synthon is accomplished by using the electrophilic epoxide as the corresponding SE.

The presence of a C-C-OH moiety adjacent to a potential nucleophilic site in a TM, as exemplified below, points to a reaction of an epoxide with a nucleophilic reagent in the forward synthesis. The facile, regioselective opening of epoxides by nucleophilic reagents provides for efficient two-carbon homologation reactions.



Summary

- Organic molecules are diverse in nature and have applications in all fields of life.
- The synthesis of organic molecules is a challenging field.
- The synthesis requires the help of disconnection approach or retrosynthesis.
- The backward way of observing a reaction is known as retrosynthetic analysis.
- Retrosynthetic (or antithetic) analysis is a problem resolving method for converting the structure of a synthetic target (TGT) molecule to a sequence of gradually simpler structures through a path which eventually leads to simple or commercially available starting materials for a chemical synthesis.
- Through the disconnection method, we break the entire molecule into smaller starting materials on paper and then join these by chemical reactions.
- The toughest job in planning a retrosynthetic analysis is recognizing where to make the disconnections.

THANK YOU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