

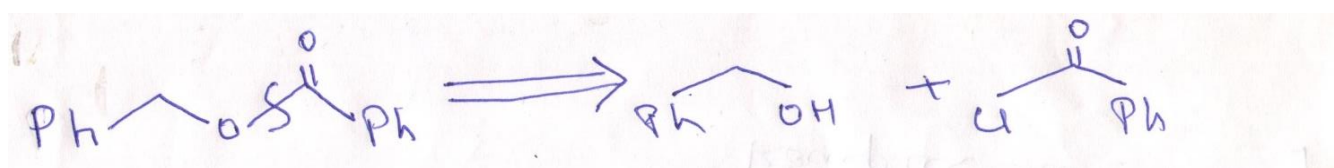
Disconnection Approach

Disconnection approach or retrosynthetic analysis

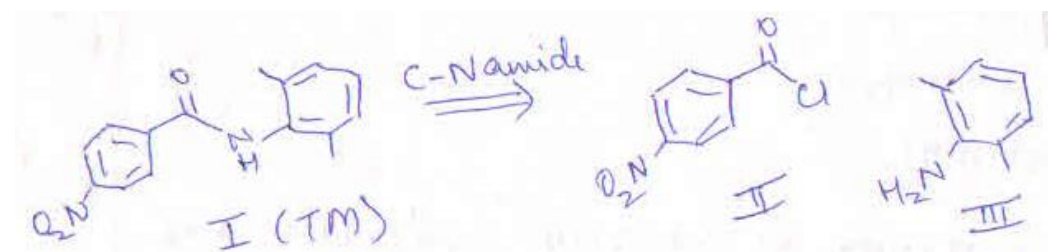
An approach for designing organic synthesis which involves breaking down of target molecule into available starting material by imaginary breaking of bonds (disconnection) and/ or by functional group interconversion (FGI) is known as disconnection approach or retrosynthetic analysis or retrosynthesis or synthesis backward.

This is the process of synthesis design which starts with the product and works backward towards the starting material.

Eg. Ester can be prepared from benzyl alcohol and benzoyl chloride. Thus we can represent this using a retrosynthetic arrow (\Rightarrow) which is commonly used to indicate a reaction written backward.



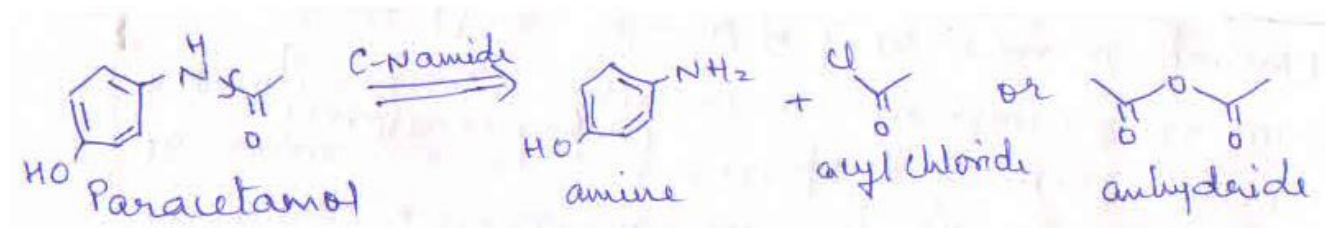
Disconnection must correspond to the reverse of real and workable reactions.



Amide (I) C-N bond was chosen to disconnect because this disconnection corresponds to the reverse of a real and workable reaction i.e. formation of the amide (I) from the amine i.e. 2,6 dimethylaniline (III) and acyl chloride i.e. p-nitrobenzoyl chloride (II)

Synthons and Synthetic Equivalents

Synthons are idealised fragments (reagents) usually cations or anions resulting from a disconnection.



Synthons need to be replaced by reagents (synthetic equivalents) in a suggested synthesis.

Eg. Paracetamol which is an amide and can be disconnected either to amine + acyl chloride or to amine+anhydride.

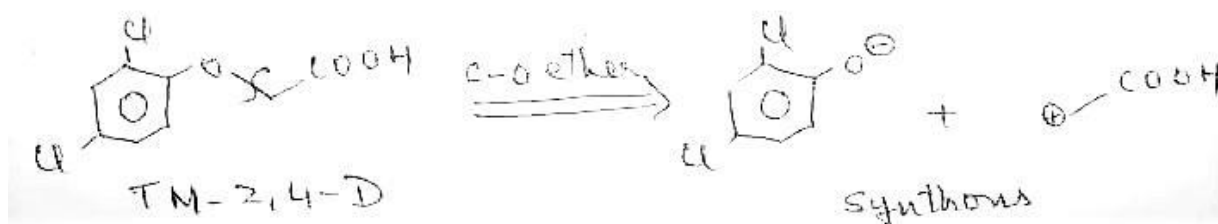
Commercially paracetamol is prepared from p-aminophenol and acetic anhydride largely because byproduct acetic acid is easier to handle than HCl.

Which reagent is best can be determined by experimentation.

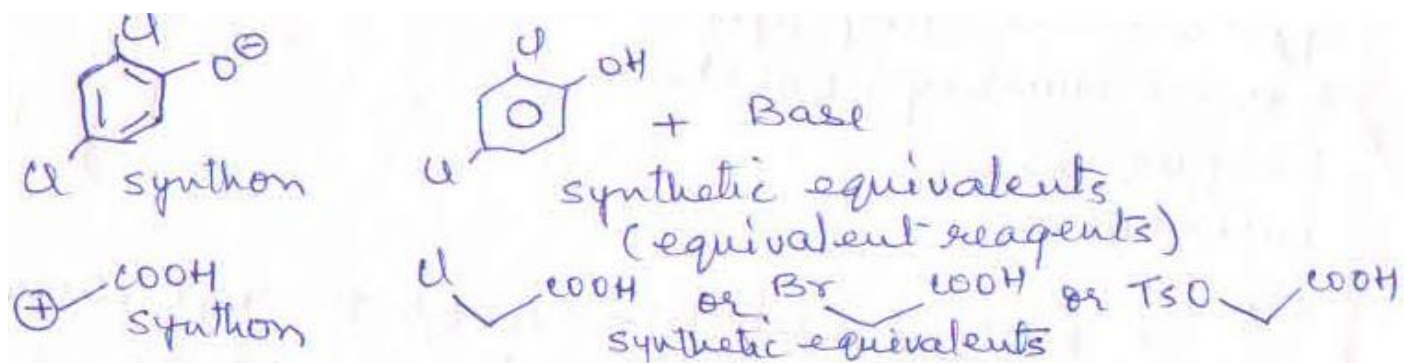
Synthons are not themselves reagents. They may occasionally be intermediates in the reaction pathway. By disconnecting bonds to synthons rather than to actual reagents (synthetic equivalents) we can indicate the polarity of bond-forming reaction we are going to use without specifying the details of the reagent.

Eg. 2,4-D (2,4 DICHLOROPHENOXY ACETIC ACID)

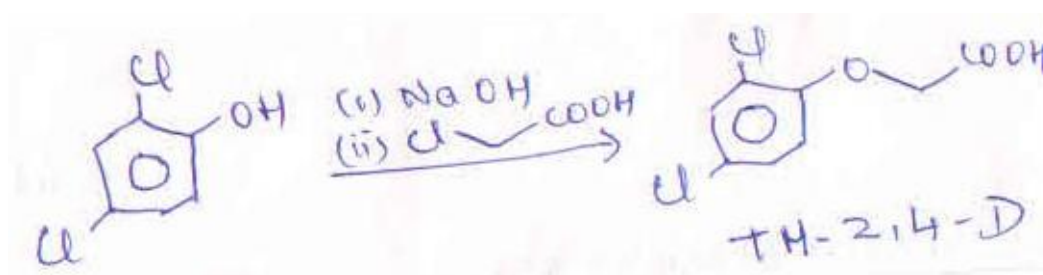
This most reasonable disconnection of an ether is C-O bond because we know that ethers can be prepared from alkyl halide by substitution with an alkoxide anion. At this stage we need not to decide exactly which alkyl halide or alkoxide to use.



To think of reagent corresponding to these synthons we need to use the knowledge of chemistry. Synthetic equivalents are real chemical compounds (reagent) carrying out the function of a synthon.

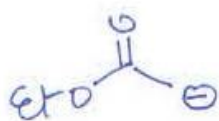
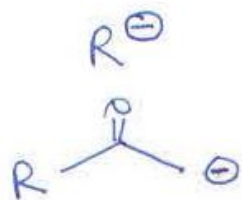
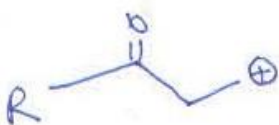
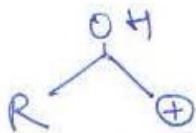
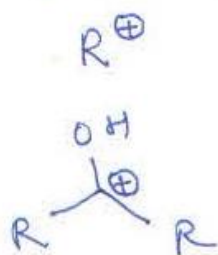


Suggested Synthesis



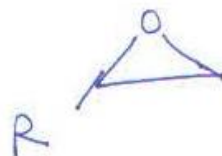
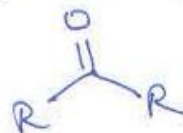
Synthons and their synthetic equivalents

Synthons

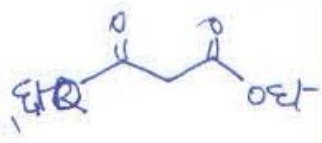
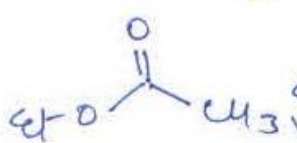
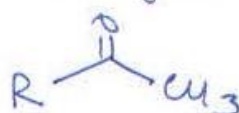


synthetic equivalents

$RBr, RI, ROMs, ROTs$
($R = \text{alkyl not aryl}$)



$RMgBr, RLi, LiCuR_2$



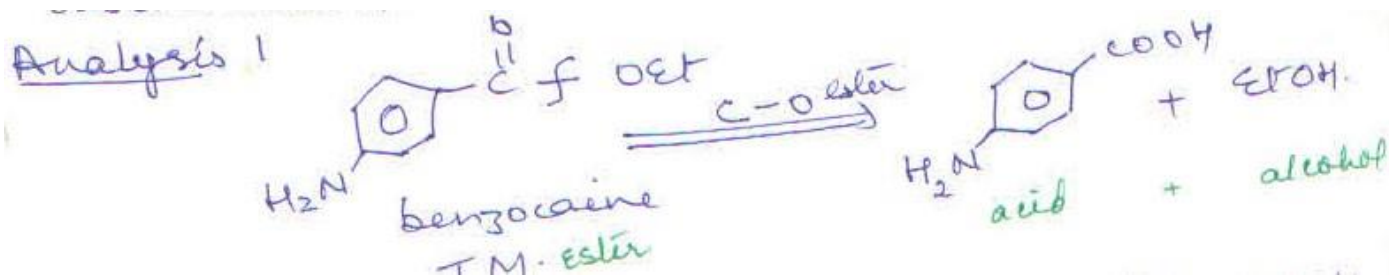
Functional Group Interconversion (FGI)

Functional group interconversion is the process of converting one functional group into another during retrosynthetic analysis. FGI mostly involve oxidation, reduction, and substitution.

It is applicable where we do not have real and workable reaction reverse to a disconnection.

Eg. In designing a synthesis of a local anaesthetic benzocaine we know that esters are made from alcohols and acids so we can write a C-O disconnection.

Analysis I

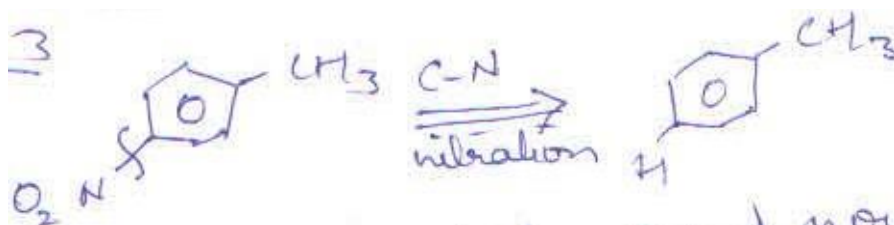


Analysis 2

We should now like to disconnect either $-\text{COOH}$ or $-\text{NH}_2$ from the aromatic ring but we know of no good reactions corresponding to these disconnection. We must therefore go for FGI to change these functional groups into another which can be disconnected. Aromatic acids can be made by oxidation of methyl groups and amine group by reduction of nitro group.

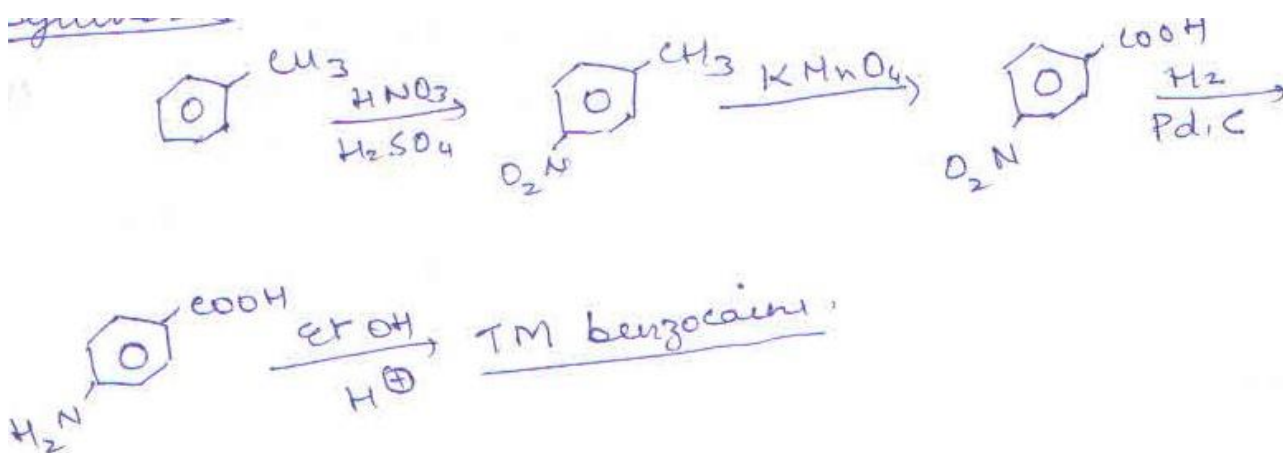


Analysis 3



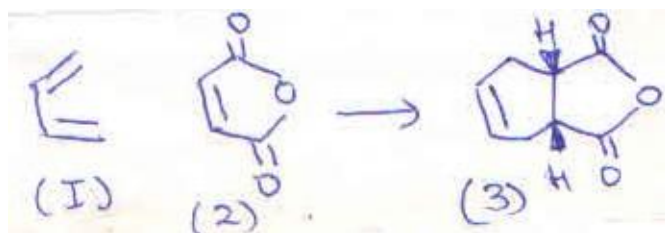
This completes the analysis and now the synthesis can be written with suggested reagents

Synthesis

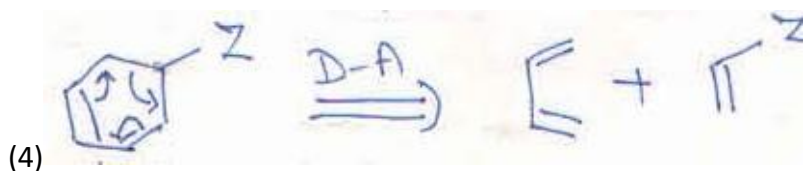


Two-Group Disconnection I: Diels Alder Reaction

The Diels Alder is the most important reaction in the synthesis because it makes two C-C bonds in one step and because it is regio and stereoselective. It is pericyclic cycloaddition between conjugated diene (1) and a conjugated dienophile (2) forming a cyclohexene.



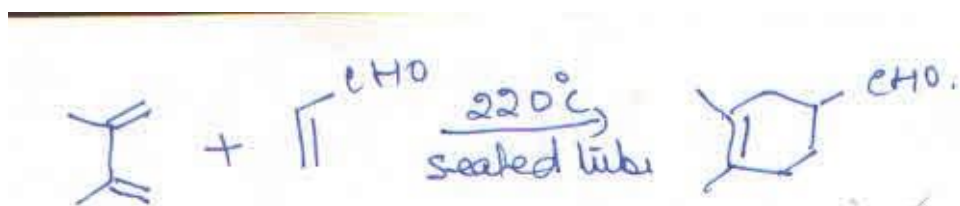
The corresponding disconnection is often best found by drawing the reverse reaction mechanism when a cyclohexene (4) with at least one electron withdrawing group (Z) on the far side of the ring is made, three arrows round the ring is made in either direction, starting from the double bond.



Aldehyde can be made by Diels Alder reaction easily discovered by this method. No special solvents or conditions are needed as no ionic intermediate are involved. The two components are simply mixed together and heated.

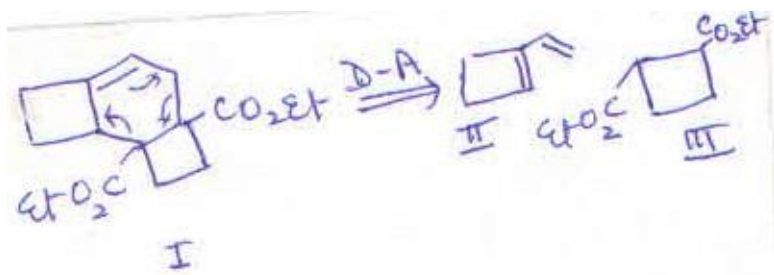


Synthesis

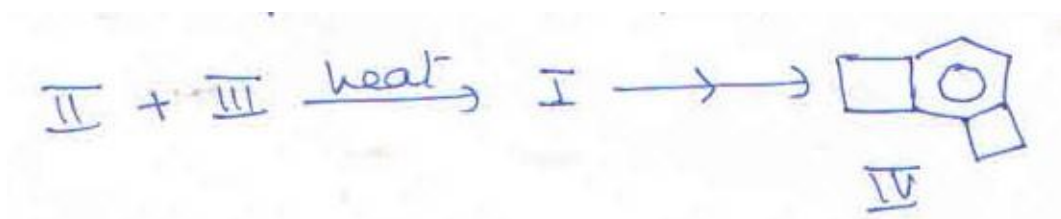


This is a two group disconnection because it can be carried out only when both features cyclohexene and electron withdrawing group are present and the relationship between them recognized.

In case of complicated molecule if it contains cyclohexene and an electron withdrawing group in the right relationship, a Diels Alder disconnection is worth trying.

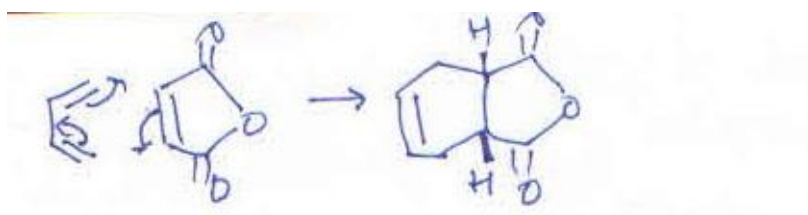


Synthesis –Benzene (IV) with two fused four membered ring is formed by using I (II&III fragments prepared separately)

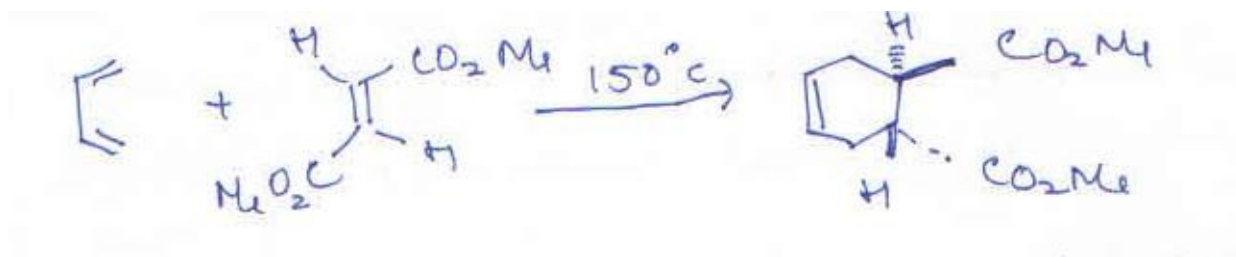


Stereospecificity and Stereoselectivity This reaction occurs in one step so that neither diene nor dienophile has time to rotate and the stereochemistry of each must be faithfully reproduced in the product. Cis dienophile give cis product.

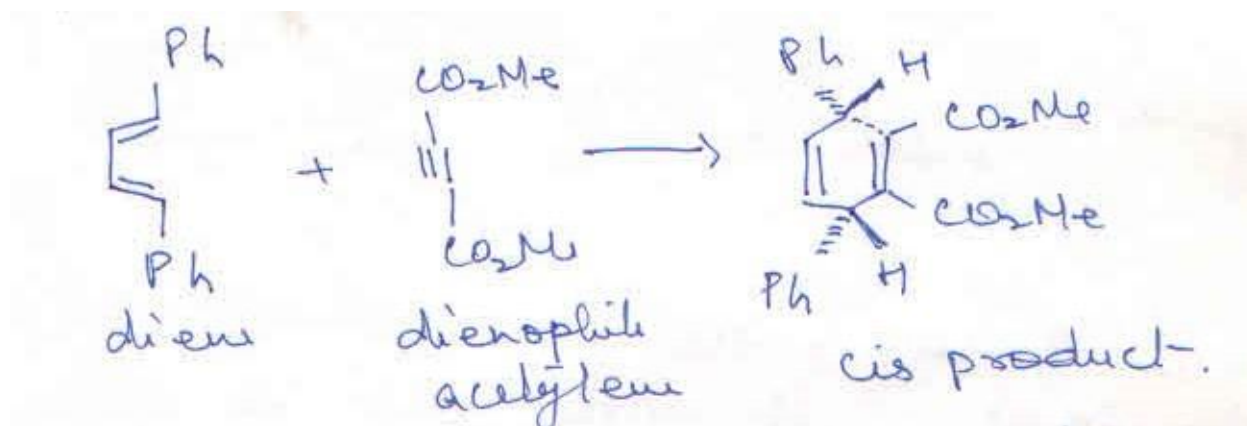
Eg



And trans dienophile gives trans product.



The stereochemistry of diene is also faithfully transmitted to the product. Diene adds to an acetylenic dienophile to give the cis product.



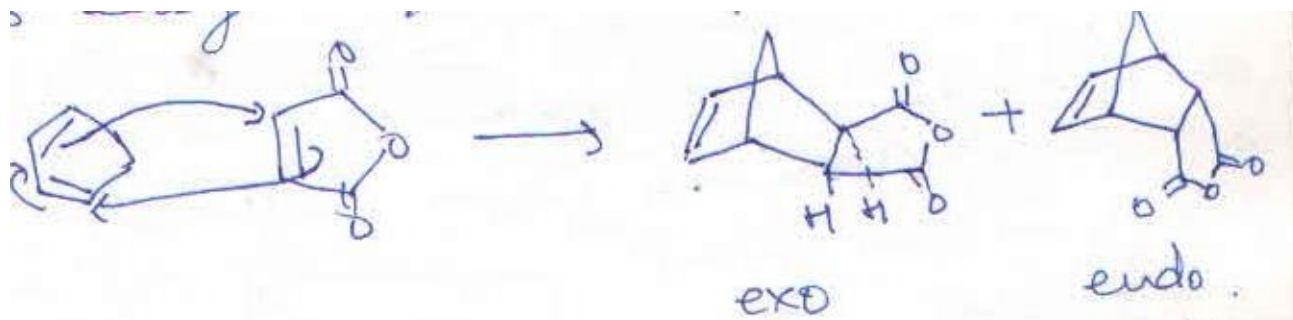
This is because the two reagents approach each other in parallel planes so that the p-orbitals overlapping to form the new σ bonds are as nearly coaxial as possible.



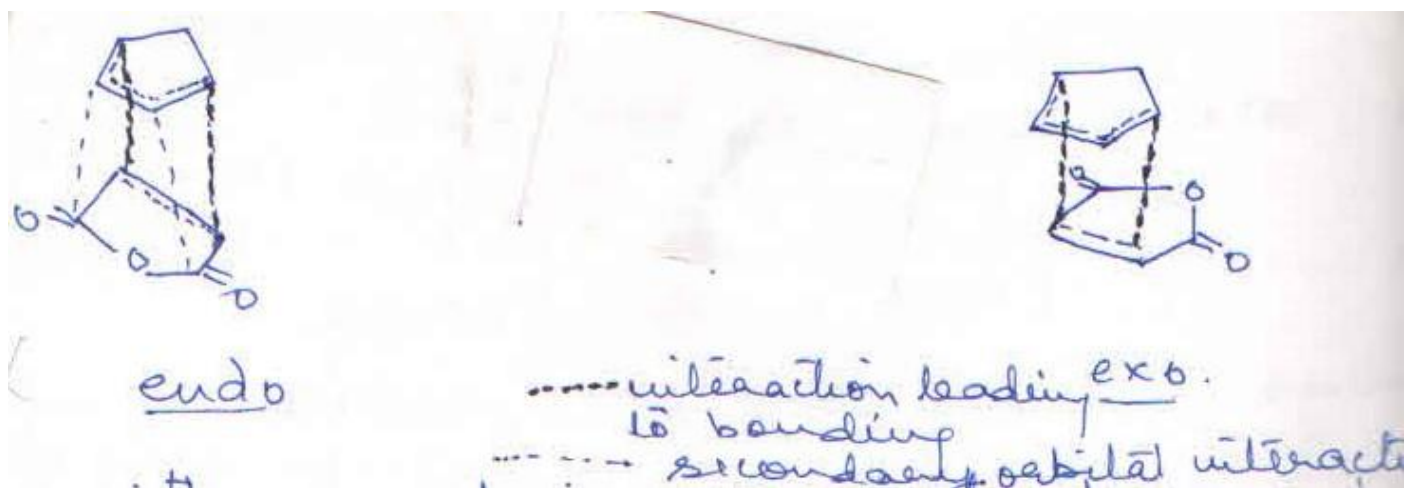
The two aspects of the Diels Alder are both stereospecific in that the stereochemistry of the product is determined simply by the stereochemistry of the starting materials and not at all by how favourable one reaction pathway may be. There is one more stereochemical aspect of the Diels Alder reaction -endo selectivity and that is a stereoselective aspect.

Endo Selectivity

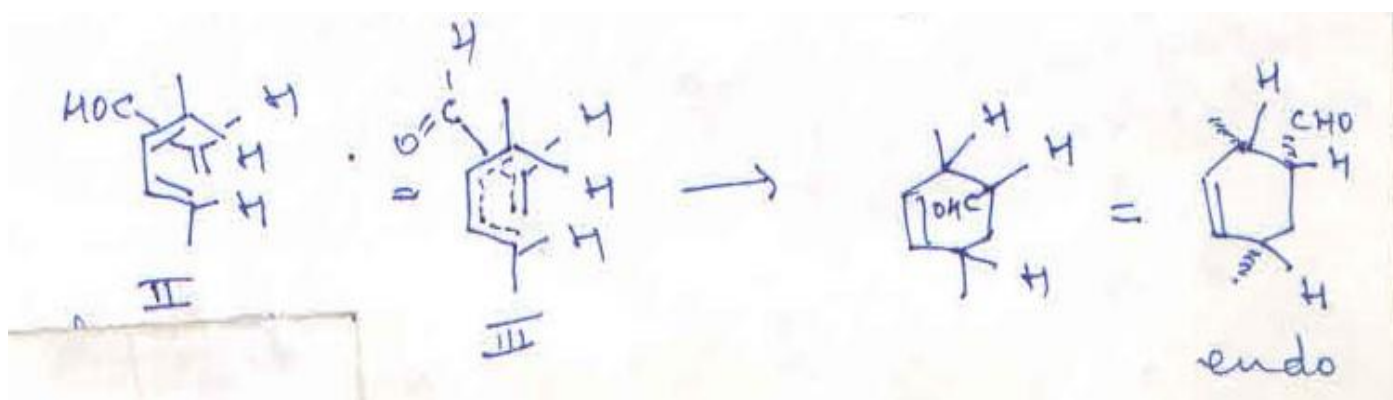
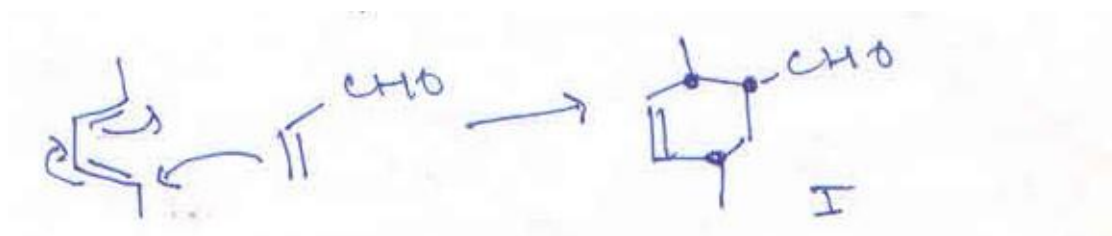
Though the stereochemistry must be preserved in many cases two products can still be formed. This is easy to see in cyclic systems.



The two products are called endo and exo. These terms refer to the relationship between the Z-group of the dienophile (here CO) and the double bond in the new cyclohexene ring. In practice endo form is favourable as it is the kinetic product, though the exo is usually more stable. The role of electron withdrawing group Z in dienophile is to attract the diene through space in the endo transition state. This is a secondary orbital interaction which does not lead to bonding but which does help to hold the transition state together.

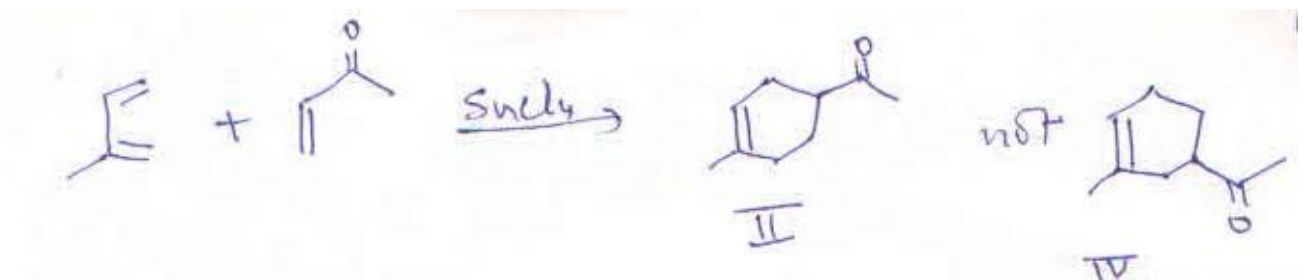
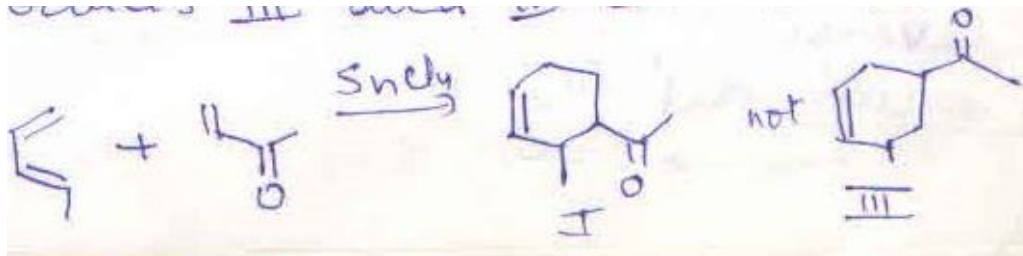


With open chain compounds it is easier to work out the stereochemistry of the endo product if molecule is drawn one on top of the other. A simple eg, would be the synthesis of I. Three new chiral centres (.in I) are introduced in the reaction. Drawing the diene on top of the dienophile (II) with the hydrogen atoms at the developing chiral centres marked and the carbonyl group arranged so that the secondary orbitals interaction can occur (III) gives the right stereochemistry for endo (I)

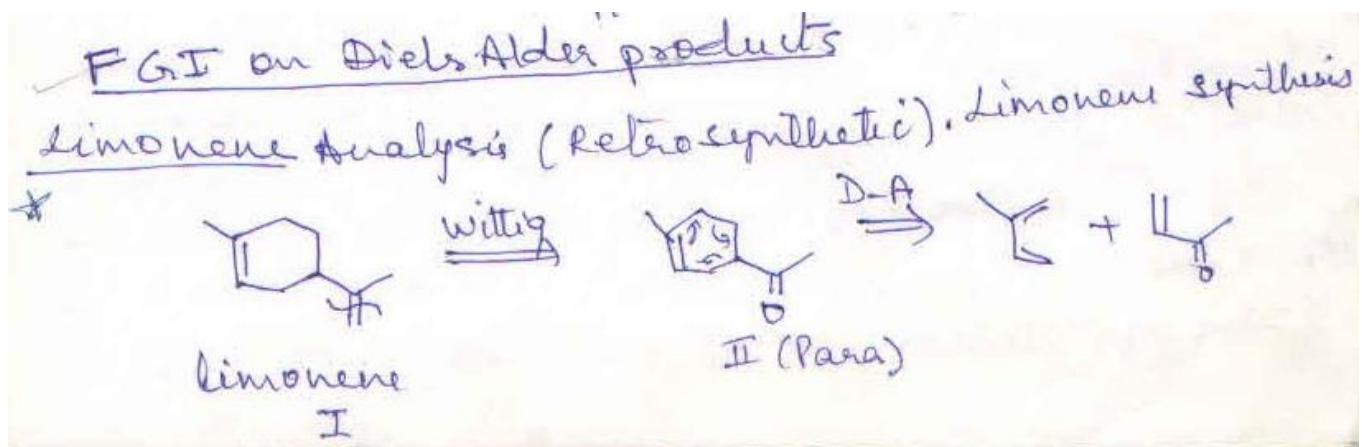


Regioselectivity of Diels Alder Reaction

Reaction between unsymmetrical diene and unsymmetrical dienophile are also regioselective. The Diels Alder reaction is ortho and para directing. Thus 1-substituted butadiene give ortho product I and 2-substituted butadiene give para product II particularly under Lewis acid catalyst. The meta product III and IV cannot be made.



FGI on Diels Alder products



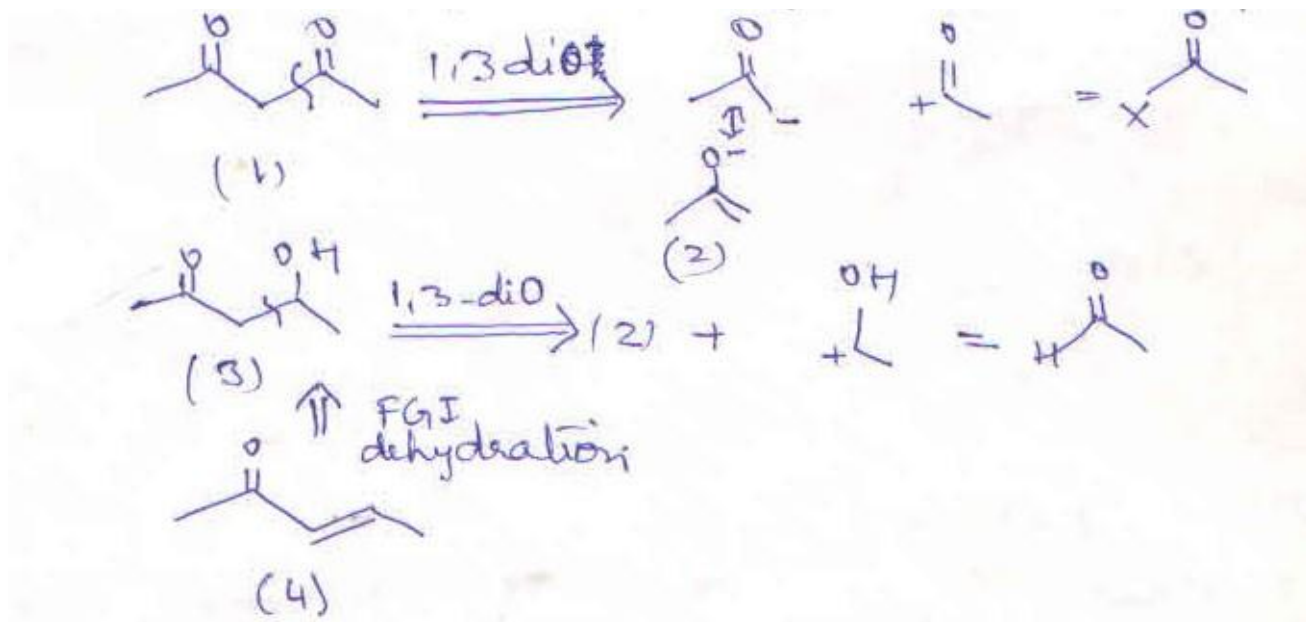
Synthesis



Vig. chose to disconnect limonene (I) (a natural odour principle found in most citrus fruits) by one carbon Wittig step because that revealed a para Diels Alder product II

Two Group Disconnections II: 1,3 Difunctionalized Compounds and α,β - unsaturated carbonyl compounds

Direct disconnection of this group of compounds is possible at two oxidation levels-dicarbonyl (1) and β - hydroxyl carbonyl (3). Enones (4) are usually made by dehydration of 3.



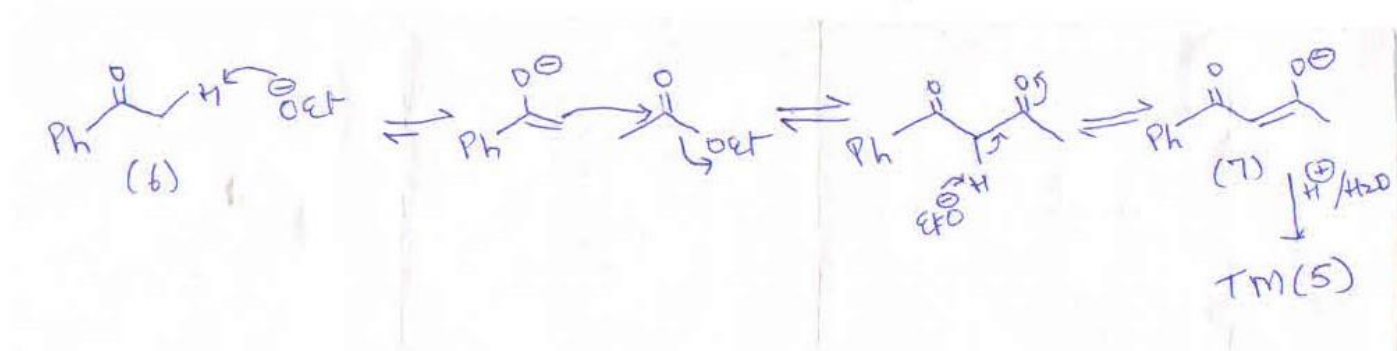
1,3 -Dicarbonyl compounds

Disconnection (1) means that we are looking for a reaction which is the acylation of an enolate anion (2). This is possible with esters ($X=OR$) or acid chlorides ($X=Cl$). The perfluorinated compound (5) can be disconnected to the enolate of a ketone and ester.

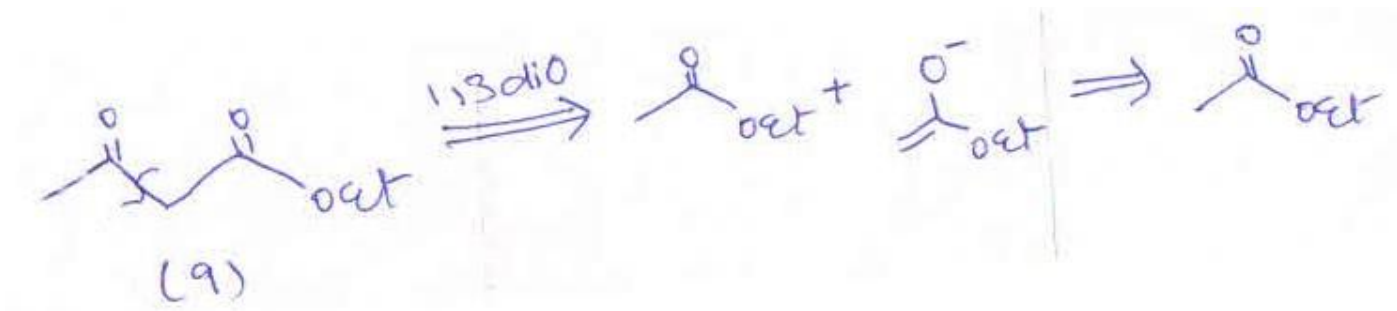


TM (5)

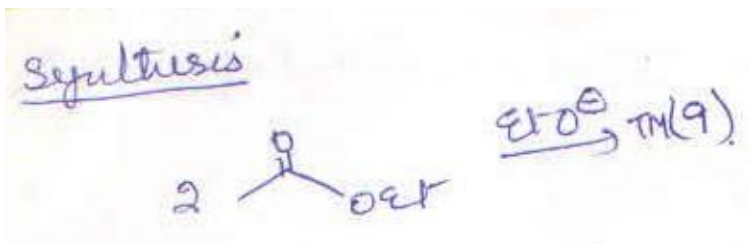
The reaction can be carried out by combining ketone (6) with the ester and a base strong enough to produce only a small conc. of the enolate, often EtO^- . The reaction is therefore in equilibrium and it is driven over by formation of the stable delocalised enolate (7) of the product. In the last step the acid releases TM (5). This last step applies to all reactions of this type but not usually written down.



This synthesis was carried out by Claisen and the reaction is known as Claisen condensation. Ethyl acetoacetate (9) is also made in this way. In this case the starting material are two molecules of the same ester and the synthesis is known as Claisen ester condensation.



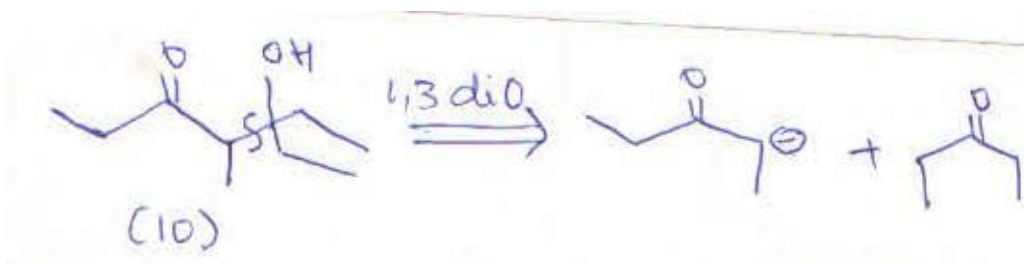
Synthesis.



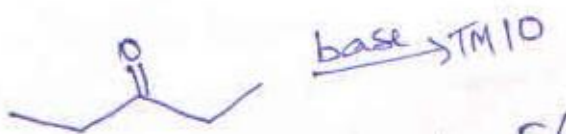
B-Hydroxy carbonyl compounds

This is the same disconnection at a lower oxidation level, the ester being replaced by an aldehyde or ketone. The compound (10) may look complicated but only one disconnection is possible and the starting materials are two molecules of the same ketone.

Analysis

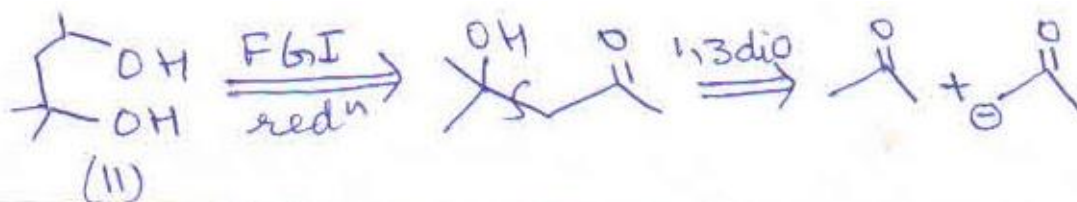


Synthesis

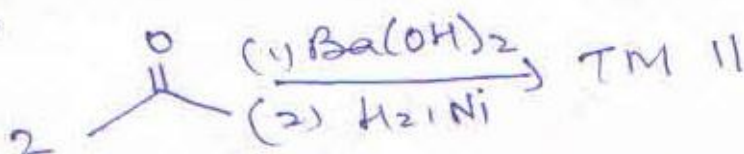


Other compounds need FGI before disconnection Eg. Compound (11)

Retrosynthetic analysis.

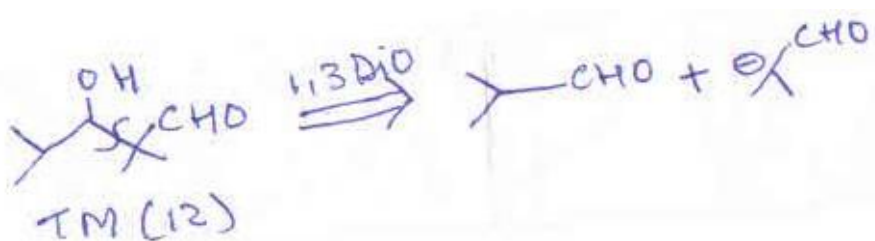


Synthesis

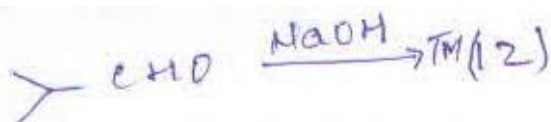


The condensation of an aldehyde with itself is an aldol reaction.

Retrosynthetic analysis

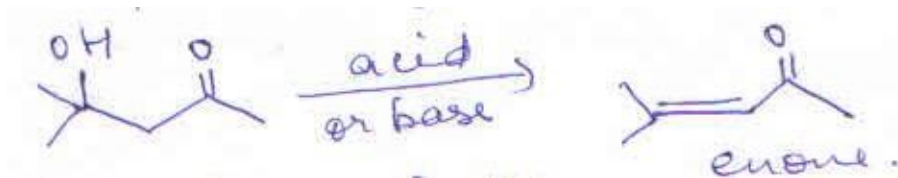


Synthesis



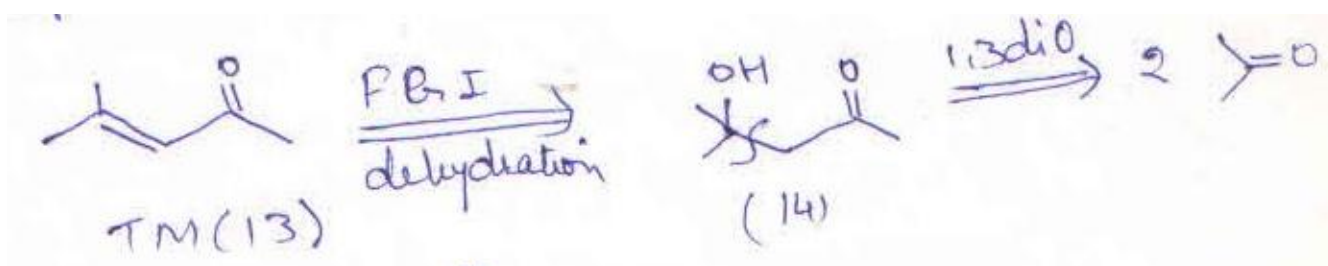
α β Unsaturated carbonyl compounds (enones)

Dehydration of β - hydroxyl compound is very easy because proton to be removed is enolic and the product formed is stabilised by conjugation.



The full retrosynthetic analysis of an enone or α, β unsaturated carbonyl compound should be an FGI followed by a 1,3 diO disconnection. The dehydration often occur during the condensation so that the aldol need not be isolated. Therefore the disconnection of the enone is directly written to the two carbonyl components.

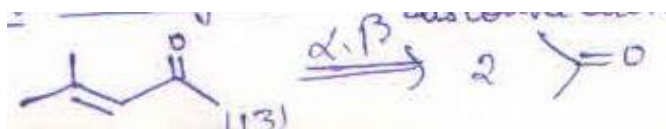
Retrosynthetic analysis



Synthesis

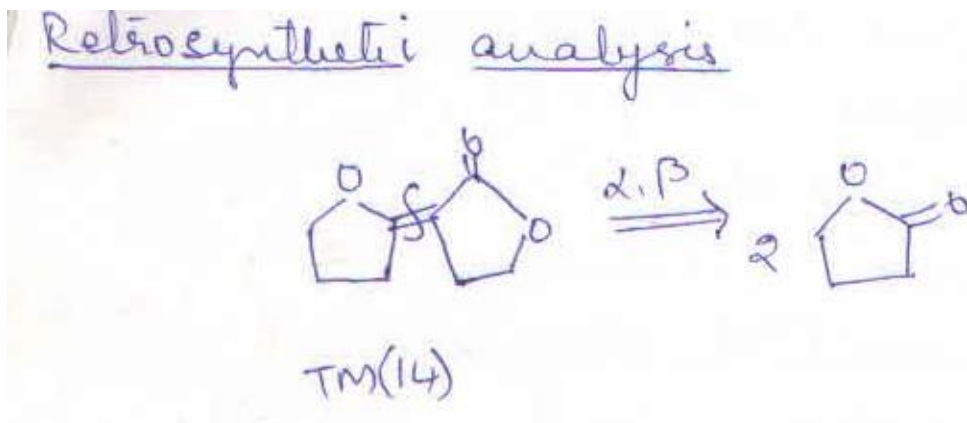


Retrosynthetic analysis

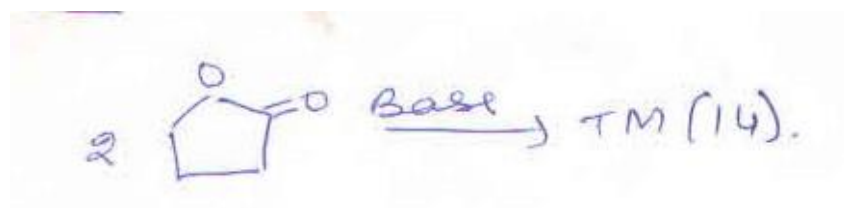


This is very important disconnection. We simply disconnect the double bond and with a carbonyl group at the β -atom. Eg. the disconnection of (14) gives two identical lactones.

Retrosynthetic analysis



Synthesis



THE END

