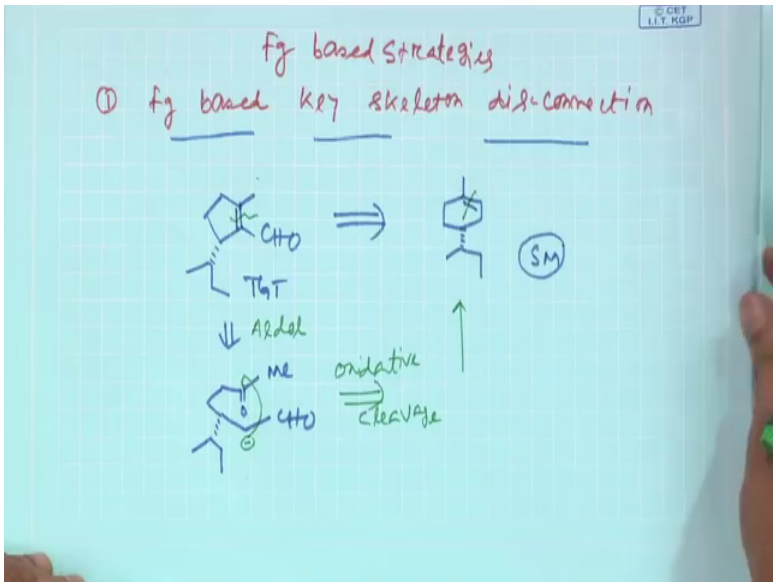
A Study Guide in Organic Retrosynthesis: Problem Solving Approach

Prof. Samik Nanda
Department of Chemistry
Indian Institute of Technology, Kharagpur

Lecture – 21
Functional Group based Strategy

Welcome back students. So, last lecture we basically discussing a several functional group based strategies and I have given you 6 particular points.

(Refer Slide Time: 00:29)



That functional group based strategies will be mainly focused on this particular 6 points. And if you remember the 6 points we have started the point number one were we have discussed functional group based keys skeletal disconnection means; a skeleton of a given molecule was given to you and you have to disconnect the skeleton by having a clear look on the molecular structure.

And then you can try to find it out what are the possible transformation you can think of to disconnect the molecule to a suitable intermediate so there intermediate is commercially available. And we have discussed the complex carbocyclic molecule which can be easily accessed from a cyclohexanone to a combination of aldol and Michael reaction and finally a let stretch carbonyl reduction reaction.

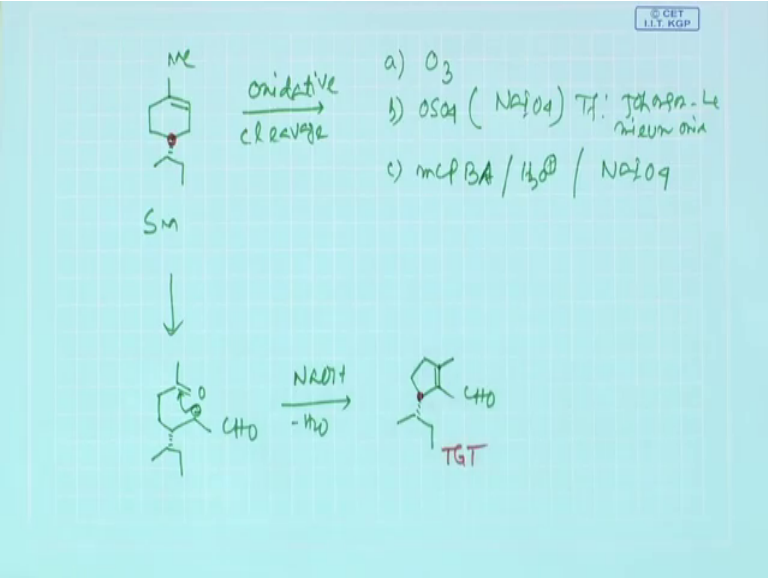
So, will try to continue our discussion on the same topic and today also we talking about this functional group based key skeleton disconnection, so will mainly try to disconnect the skeleton of a given molecule based on the functional group present in the target structure. Now particularly this particular problem which I am now going to discuss the target molecule having a structure something like this, it is alpha beta unsaturated cyclopentane best aldehyde.

And this particular centre is having a hanging appendage of a sec butyl group, though the stereo centre was given will be not discussing about the stereo centre here but the starting material which was given is a 6 member best cyclohexane. Now you target is this and your starting material is this. So this is your keys skeleton or the skeleton of the target molecule and you need to rely on the functional group present in this molecule to have a correlation that how this target molecule will be relating to this starting material through some functional group best disconnection approach.

Now, as you see the alpha beta unsaturated aldehyde probably the very first disconnection which will be coming to your mind will be something like this, you do a aldol based disconnection if you having a this compound we just disconnect this particular bond through a aldol dehydration. Now if this a purely functional group based approach as you are having a alpha beta unsaturated aldehyde here we assume that this key to aldehyde can be undergoing aldol reaction by generating this carbon ion here to go react here and then aldol dehydration.

Now, try to correlate how this compound can be correlated with this particular starting material? Now you see only active functional group bringing the starting material is a allophonic functional group and this compound does away di carbonyl functionality, so in principle if you can think about doing a simple oxidative cleavage. Now this kind of oxidative cleavage we have discussed earlier and this oxidative cleavage basically will correlate to the starting material, means that if you do a oxidative cleavage such as ozonolysis kind of thing the this double bond will be chopped and you get me co, CH2 methylene then you are hanging appendage with the perspective centre will remain unaffected and then the CH2.

(Refer Slide Time: 04:35)



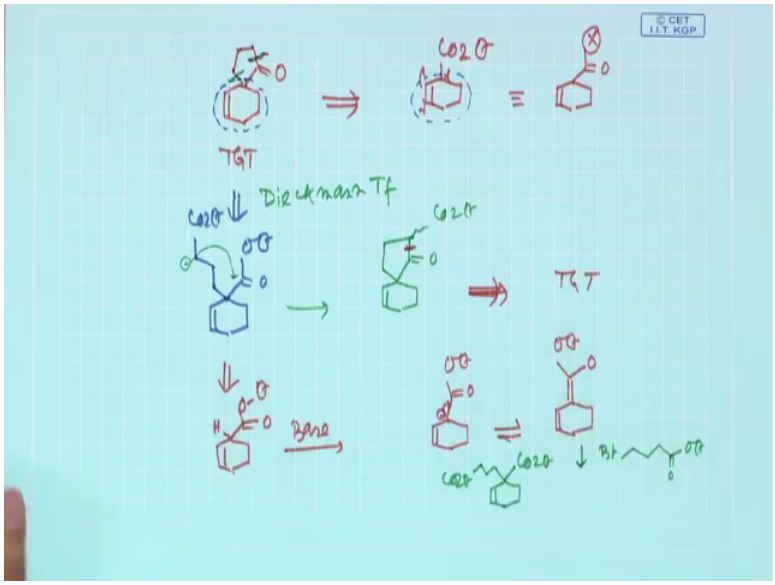
So, see then this kind of approaches are absolutely simple and eventually if I now try to analyse the forward synthesis you will see that how this forward synthesis can be effectively constructed. So, your starting material is this now I say the forward path way will first doing a oxidative cleavage oxidative cleavage of this particular double bond.

Now, you can basically think about numerous way you can continue this oxidative cleavage the pathways are you can do ozonolysis reaction, you can do a first make a diol first make a diol and then you can cleave this diol with sodium periodate the transformation which we have already set a Johnson Lemieux reaction Johnson Lemieux oxidation in addition you can also do another reaction you trade this compound with MCPB a to give you the epoxide then this MCPBA you do acid hydrolysis that will you the diol and then you cleave with sodium periodate.

So, there are many different ways you can chop or you can keep this double bond to basically generate this carbonyl compound or di aldehyde which is required for the aldol reaction. Now once you have this di aldehyde your next step is you can do a simple aldol reaction. Now here basically you are having ketone and aldehyde so you do a simple base mediated reaction to generate this carbon ion here and then this goes there you get the aldol dehydration to close the synthesis and the entire pathway is basically governed by the functional group based skeletal disconnection.

Now, important point is; whatever starting material we have taken the particular this trio centre given intact here because the stereo centre was not touched it was not touched. So, try to figure it out in these way the whenever a key skeleton was given to you can basically formulate or you can design the pathway based on your available transformation and you have to basically correlate that how this starting material which is available to you or which was given to you can basically think of that how this starting material can be correlated in a forward pathway to the design target.

(Refer Slide Time: 07:10)



On the similar line will try to do a another skeletal disconnection for a target molecule whose structure is a Spiro cycles, we are talking about the Spiro cycle ketones; a 6 member and 5 members Spiro cycle here you have a double bond and this 5 member you have a carbonyl functionality, this is the target molecule and the starting material which was given to you is a this compound a cyclohexyl based alpha beta unsaturated ester not alpha beta unsaturated alpha beta unsaturated esters sorry is a alpha beta gamma beta gamma unsaturated esters. Now try to correlate this structures this part is remained as it is in the starting material only thing is this CO this CO so basically you have to introduce this 1, 2, 3 is a kind of a 3 carbon extension you need to the so this is called a skeletal disconnection.

So, now if I do a very conventional retro probably the retro of the transformations all of you know it, if I say you are having this compound this diester basically what you are

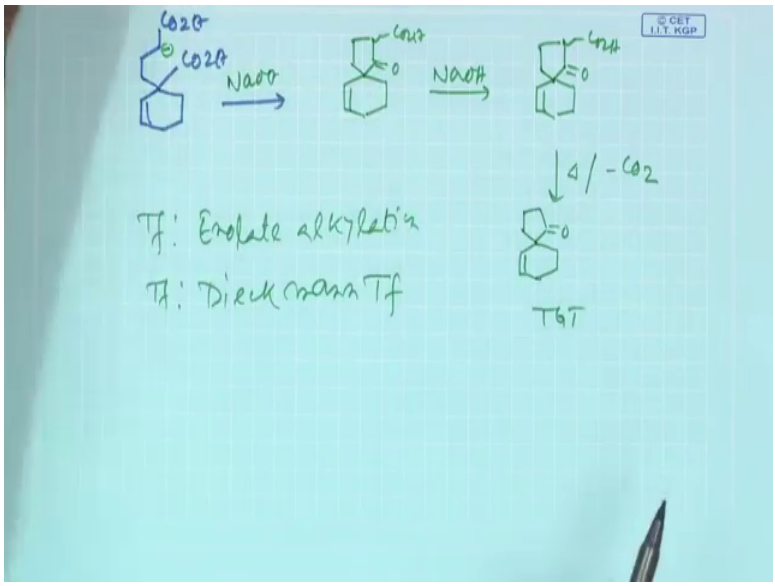
trying to do you just met this disconnection because a starting material it is already having this fame work which is C double bond do X so this what is having the starting material, so you want to make a new carbon bond here then you can close this things at this end with the living aptitude of this OET or the epoxy group.

So, basically you did to make two bonds here I this is the one bond you are trying to make it here and this is the another bond you will be trying to make it here, now if you see the disconnection which you have basically proposed here is kind of a dieckmann type of reaction is a dieckmann type of transformation which probably all of us know or all of you basically aware of, is a very standard carbon ion chemistry dried transformation and usually what happen? If you take this kind of diester you treat this generated anion which basically collapses here to finally give you a; now see you are having a basically a branching here so this gives you the Spiro thing and then your CH2 so your C double bond remains here and basically you are trying to make this CO2 ET here.

So, this is the new bond you are basically going to meet are going to prepare it is a dieckmann reaction, now next from dieckmann you basically do this hydrolysis of this beta ketone ester which give you the target molecule that is the fine the forward pathway now how to construct this intermediate which will undergo the dieckmann reaction? This is again simple we will be using a alkylation based chemistry based on enolate alkylation beside that this compound is a alylic ester the starting material means these hydrogen's are enough acidic enough acidic, so what I will try to do? If you put this compound with a base with a base you basically will be getting a enolate of this carbon ion.

Now this carbon is extremely stabilized, because this is having link to the alylic as well as this carbonyl let us make this enolate first and find that. Now this enolate you can easily trap with some electrophile, the electrophile which will be using here is basically give you this extra 3 carbon. So now based on this information you select this electrophile and you will see the electrophile which you required now having 3 carbons CH2 1 end you have you a bromo basically you need electrophile and this OET. Now if you do this alkylation which basically will now give you this CO2 ET and this CH2 CO2 ET.

(Refer Slide Time: 12:22)

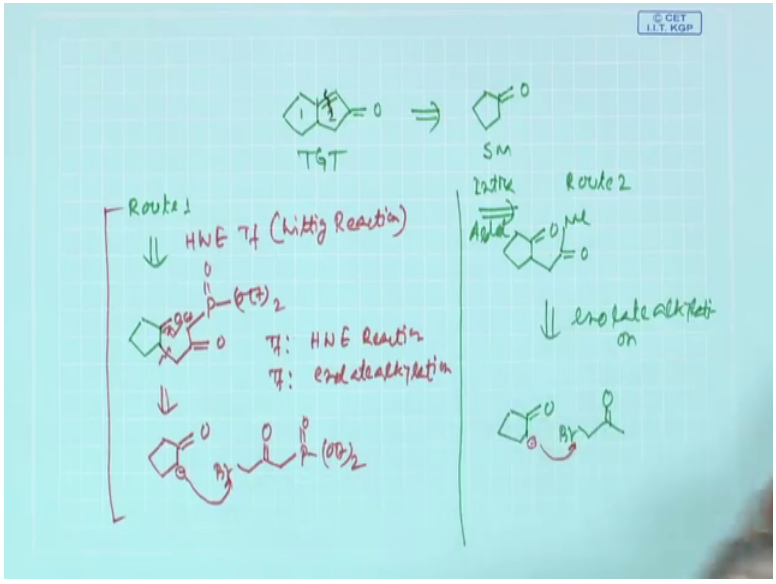


So, this intermediate is what you exactly want and now once you have this intermediate to take this intermediate as it is you take this intermediate and then subject this intermediate to a dieckmann reaction. So, dieckmann reaction normally we say the condition is you treat with a base like sodium ethoxide so initially carbonyl extraction this carbonyl will basically react with this adjacent carbonyl to give you a Spiro cycle based compound whose structure will be this, your remaining task is just to hydrolyse this corresponding ester to get this Spiro cycle beta keto acid beta keto acids are very easy for decarboxylation reaction you just heat it they will spontaneously release the corresponding decarboxylated product which is basically the target molecule which you all looking for.

So, we can see if you see the whole target and try to correlate the stereo chemical sorry not stereo chemical if you try to correlate this particular starting material will find that this is a this symbols basically two bond making you are making a new carbon bond here you are making new carbon bond here this part was given to you so this entire part this part as well as was given to you and then you make two new carbon bonds the transformations which is you basically use in the entire thing we do a enolate alkylation and in addition you do another transformation which is very important transformation dieckmann transformation.

So, as I said earlier this entire transformation based strategies, functional group based strategies, substrate based strategies all are similar. But, here basically we have tried to figure it out this transformation this disconnection is based on a functional group based approach as I put a carbonyl group carbonyl group this is the main functional group which was spread in a target and this carbonyl group was disconnected or was thought to be constructed some this starting material. And then this follows the entire retro pathway which also a simple functional group inter conversion or functional group addition kind of thing and that basically completes the entire synthesis in a efficient pathway.

(Refer Slide Time: 15:14)



In a similar way will try to now analyse a molecule whose structure is; we will be trying to synthesise this molecule as our next target which is a bicyclo compound bicyclic compound and I say the starting material which was given to you is cyclopentanone is a monocyclic compound if this compound is this compound is basically a bicyclic compound ring 1, ring 2 and alpha beta unsaturated connection here the double bond here, now the starting material was given to you for this molecule will be try to device you two pathway root 1 and root 2.

Now coming to root 1; so coming to root 1 if you do the retro what we trying to do? Will trying to do in a different way we say that will making this bond in a different way what is the different way? Will make this new carbon bond to a reaction which probably we have earlier discussed it is called Horner wads worth Emmons reaction is kind of a wittig

reaction or wittig transformation I said is a wittig reaction and this reaction if you remember we have discussed in the earlier slides fine.

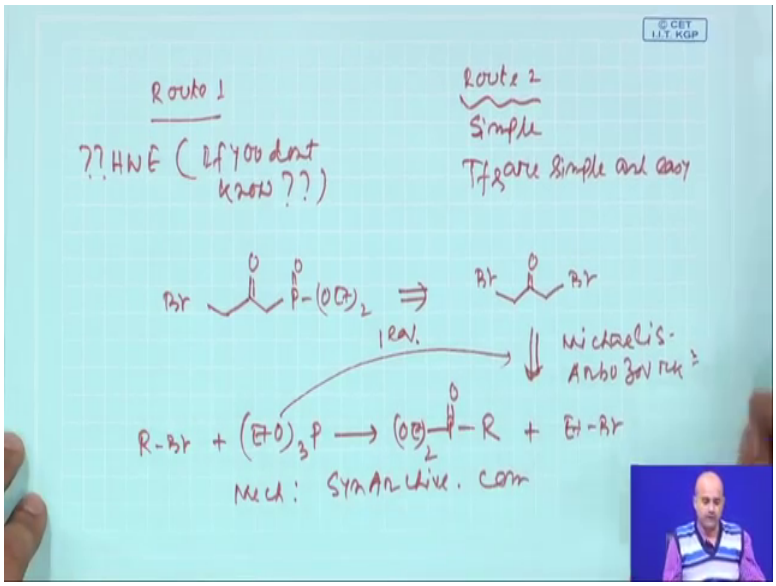
Now, next will again try to simplify the retro in this way and now you say that if you having a compound like these you can basically first do a alkylation with this electrophile, so what you need to do? You have a starting material which is given to you take a one equivalent of base that will give you the anion here you react to it this electrophile you come to here now this electrophile now wants new carbon bond all will form it is having a phosphonate.

And you are having a electrophilic carbon, so now you treat with sodium hydride as a base or other bases suitable bases for doing the intra molecular wittig type of reaction then you find this minus will go there so this is a root 1; now root 2, root 1 I say if you do not know the intra molecular Horner wads worth Emmons reaction it will be little bit difficult two transformation we have used what are those transformation what we used? Horner wads worth or Emmons reaction and we used transformation 2 is enolate alkylation.

Similarly, root 2 if you now try to figure it out would be having a simplified root, root 2 we say will be doing it a different way the initial retro was this again the same bond and then now you say; if you having a intermediate something like this, you can easily go through a intra molecular aldol reaction. So, the first retro would basically based on a intra aldol, so same bond same disconnection you can in principle construct to a two similar type of reaction, because this reaction is basically carbon bond forming reaction you can use it a through a intra molecular wittig reaction or Horner wads worth Emmons reaction or you can do a intra molecular aldol reaction. Now aldol reaction probably all of you are aware of that. So, that is why I said this root is simplified root.

Now, the next root next retro is similar is based on enolate alkylation. So, what you basically need? You basically need a; this compound is a mono bromo acetone it is mono bromo derivative. So, if you having a cyclopentane on react with mono bromo acetone through a base you do the alkylation first then you do a intra aldol.

(Refer Slide Time: 20:02)



Now, out of this root 1 and root 2 if you check it both the roots are quite feasible root 1 and root 2 both are the roots are quite feasible only thing is you can say that root 2 is little bit simple means the transformations are basically simple transformation transformations are simple and easy; where is root 1, if you do not know what is Horner wads worth Emmons reaction if you do not know then basically you cannot think about this root if you do not know then you cannot think about this transformation that is a big drawback for this root, but if you know this root there is a ample opportunity you can think about that both roots are in principle it is quite possible.

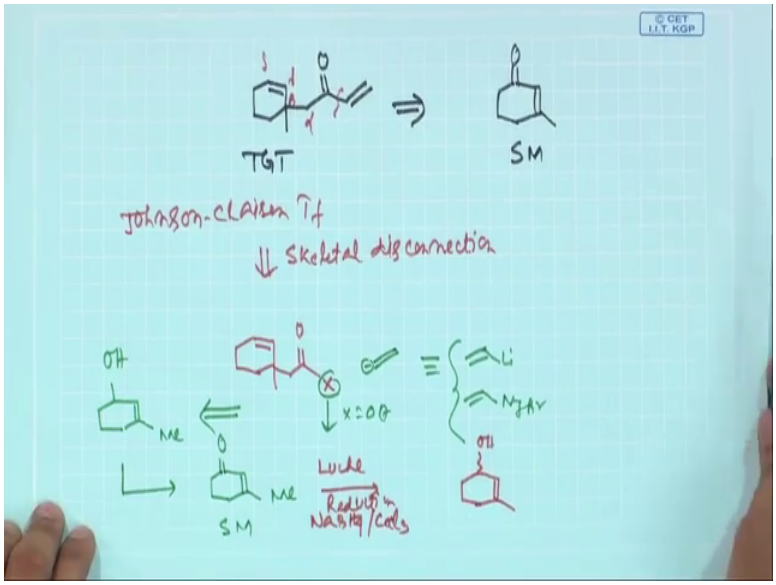
Now, next (Refer Time: 20:58) I will never ask from you people or you may ask that how this compound can be prepared? This is one of the intermediate or the starting material we have shown in the root 1 natural this can be easily prepared from this kind of compound by reaction named as Michaelis arbuzov reaction. Now arbuzov reaction is basically very interesting reaction.

If you have a alkyl bromide you react to it triethyl phosphate and then once the reaction is over you basically get this alkyl phosphonate with the loss of one equivalent of ethyl bromide the mechanism for this reaction you can basically go to the synarchive dot com the website which in the very beginning we have we have discussed synarchive dot com that will basically give you the mechanism of reaction and here. Basically, if you take this di bromo compound react to it one equivalent of triethyl phosphite one equivalent of

triethyl phosphite you will be able to get this bromo phosphonate which is serving as a alkylating agents as well as one end will serve you as a Horner wads worth Emmons reaction.

So, in this way basically you can do a keys skeletal disconnection which you also help you for your further and future synthetic challenges.

(Refer Slide Time: 22:50)



Next, will be doing a similar kind of skeletal based strategies and the reaction which you will be now discussing is already known to you; so probably I assume that, this target probably you can able to do because the information which is shared already in a transformation based approach the knowledge has been already shared with you, I said you have target molecule which was restructure and the starting material which was given is a tri methyl cyclohexanone simple starting material now the target was given to you if you try to correlate the another target and it seems to be a target which basically does have a; alpha, beta, gamma, delta unsaturated carbonyl compound at the left hand side, in the right hand side is having alpha beta unsaturated carbonyl compound

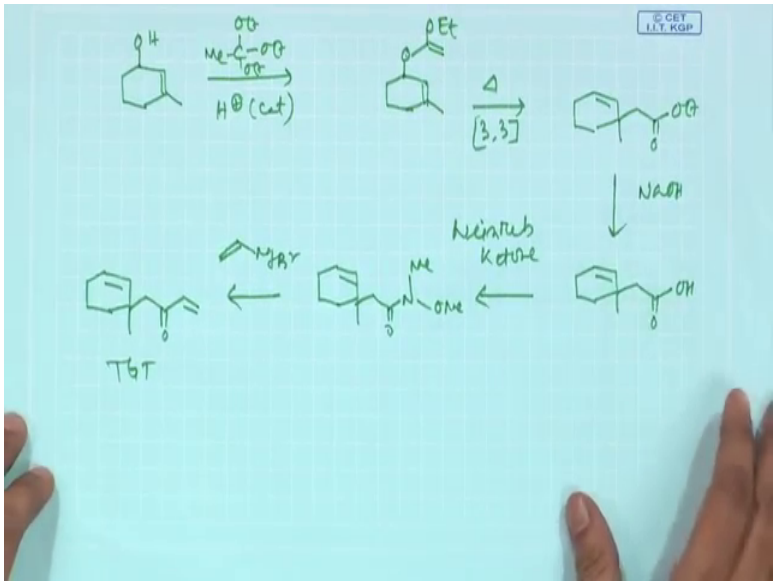
Now, we have discussed it many times whenever you find that you have a gamma delta unsaturated carbonyl compound the best reaction or best transformation will be Johnson north-western reagent Johnson north-western rearrangement or Johnson Claisen rearrangement Johnson Claisen transformation.

So, now do the skeletal disconnection we do the skeletal disconnection based on the transformation which we already know, now see the transformation we say that first we will try to introduce this vinyl group because this vinyl group can be easily constructed now I see this X should be something which will only accept one equivalent of vinyl lithium or vinyl other species basically you need a vinyl species here.

So, you basically try to have a vinyl species as you it basically could be coming from a vinyl lithium or vinyl magnesium bromide isn't it, now this is a purely alpha beta gamma delta unsaturated carbonyl compound if we put X equal to OET it is a gamma delta unsaturated ester, so next this very simple to do a Johnson orthoester claisen kind of transformation. Now I will now put that if you having this kind of allylic alcohol you do a Johnson claisen then basically you can come with this intermediate now definitely will explore the forward pathway then you will see how easy this things can be done so this is your starting material.

So, now start with the starting material first reaction is very known to us is a Luche reduction the reagent was basically use sodium borohydride and cerium chloride a combination of a cerium chloride and then basically you get 1, 2 addition of a hydride to give you this allylic alcohol, as an luche reduction we have talked it many times.

(Refer Slide Time: 26:33)



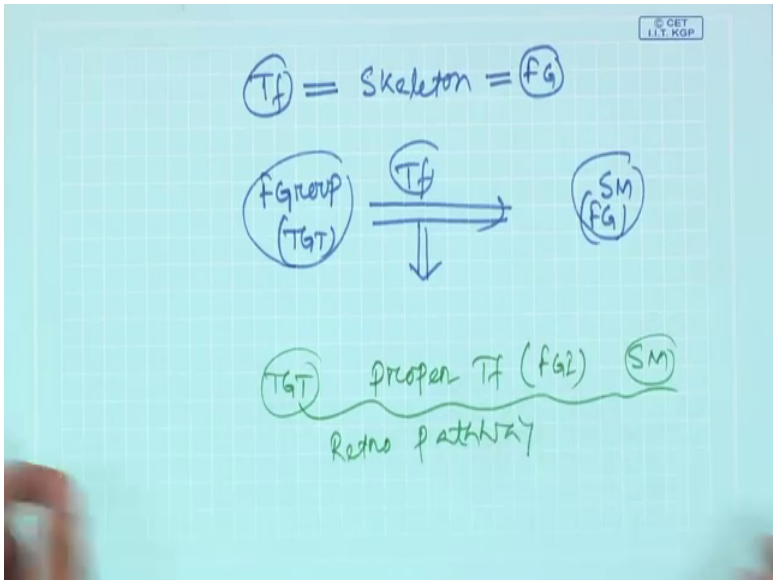
Now, once this luche reduction was done; you are basically having a allylic alcohol isn't it, now this allylic alcohol is subject to Johnson orthoester claisen rearrangement the

common reagent is tri ethyl orthoacetate in presence of a H plus source catalytic amount. Now as I said initially you will basically having a this intermediate which we have already discussed that how this intermediate was formed, now the subject is to heat is a pure 3 claisen rearrangement 1, 2, 3 and if this reagent or this rearrangement goes basically you will be now having this compound.

Now ester is a differently good electrophile and you can react with vinyl Grignard or vinyl lithium but definitely once you react to it you have to first ester will react with vinyl Grignard that will give you the ketone then ketone is again reactive so basically will end up with a tertiary alcohol the reaction would not stop in the ketone step. So, what you need to do? You basically hydrolyse this corresponding ester to stop this reaction at acid step then the transformation we have already discussed is called weinreb ketone synthesis which will basically first will prepare the corresponding weinreb amide which is very well known amide and then you react with vinyl Grignard, does not matter how much equivalent do you use the reaction will always stop at this step and basically you get this corresponding target molecule.

See if you see the retro altogether it is a purely combination of very unique transformation the point is; the skeletal disconnection is always there if you know that target molecule is having a skeleton which is nothing, but a alpha beta gamma delta unsaturated ester now this gamma delta unsaturated esters we already discussed that Johnson claisen is one of the best reagent or best transformation. So, Johnson claisen you can basically think of using it and then Johnson claisen was done you get the gamma delta unsaturated ester then you can do a simple functional group inter conversion or functional group addition eventual the initial starting material which was given to you need to just do a chemo selective reduction with the help of a luche condition which is sodium borohydride and cerium chloride to end up with the final target molecule.

(Refer Slide Time: 29:56)



So, basically pretty simple and we will try to have few more examples more things, but the take home message you can take it that transformation is always correlated with the skeleton and this is also correlated with the functional group which was present in the particular target molecule. So, initially you see the functional group which were present functional group which were present in the target molecule right, then if starting material was given to you is fine and you try to analyse what are the starting material functional groups are there? And then this functional group is the starting material and functional group is the target how they can be correlated with some transformation that should be your main approach.

Now, transformation essentially is the main key or key tool box. So, eventually as I said the transformation functional group and a starting material this 3 point is linked with a connecting thread until and unless you have these 3 points together a suitable retro pathway cannot be designed. So, your success of this entire pathway always depends on choosing proper transformation which will basically correlate the proper transformation is absolutely essential proper transformation or proper FGI is absolutely needed which is basically correlate with this target and the starting material through a common thread. So, any of this point is missing the thread cannot be competed or the entire retro pathway cannot be computed. So, the success of a retro pathway always depends how efficiently you can connect your target, the starting material through a proper transformation.

Next week will be talking about other approaches based with functional group based strategies, till then goodbye.