A Study Guide in Organic Retrosynthesis: Problem Solving Approach
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Lecture – 31
Fg based Strategy

So welcome back student to this particular week, we will try to discuss couple of similar strategies which we have already talked.

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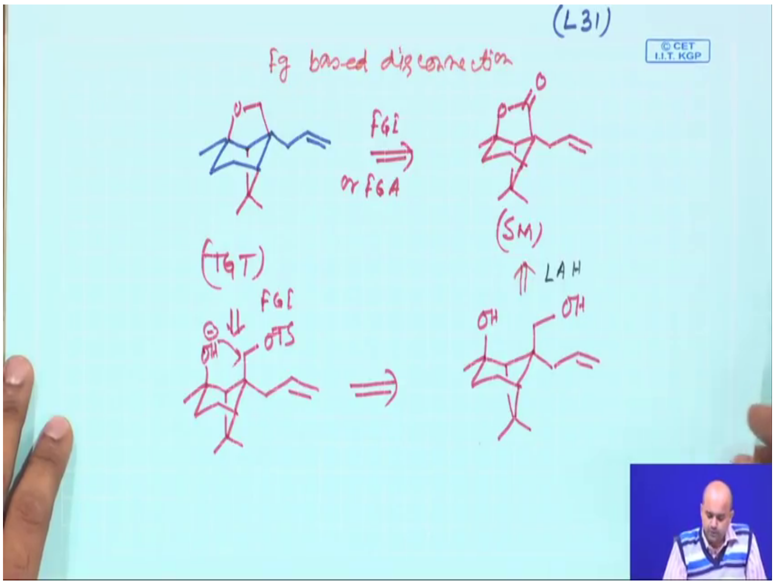

We are basically describing functional group-based strategies and the guideline 5 basically we are talking about Fg based disconnection and we are mainly focusing on how to introduce different kind of appendages or different kind of key functional group-based appendages.

Now, next particular problem is not a appendage based disconnection, but it will be relatively easier one now I am trying to give you the target structure. The structure might look little bit complex to you, but never the less we will try to draw this kind of structure a 3-dimensional form and then the target which was giving to you is having this structure.

But the starting material we are also giving, the starting material which was giving to you having a cyclohexane-based core structure, and this part we are basically having a lactone the remaining part all are similar. If you closely analyzed through a skeletal disconnection approach or any other approaches you will find that only thing is you basically deoxygenated the lactone in the starting material to complete the synthesis. So, in principle it is basically FGI or FGA you can say functional group inter conversion or functional group addition it could be based on FGI or FGA.

Now the target was given a this spot is basically ether the 5-member ether based on a cyclohexane framework, by the way it is a normality known as Tetra Hydro Furan. Now the disconnection which will be now drawing here if you have a compound something like this if you having monotosylate of this particular or hydroxytosylate, you can simply do a intramolecular SN 2 reaction by abstracting a hydrogen here to generate a alkoxide which can undergo a ring closing. So, this is basically a simple FGI.

Now, try to correlate how this intermediate can be linked to this starting material. I say this intermediate can efficiently be constructed if you have in this corresponding diol. Now this diol will be having structure of this this structure now this can be easily prepared by a reductive cleavage of this studying lactone.

So, synthesis which will be now we will go to the forward synthesis and we will see how it can be done.

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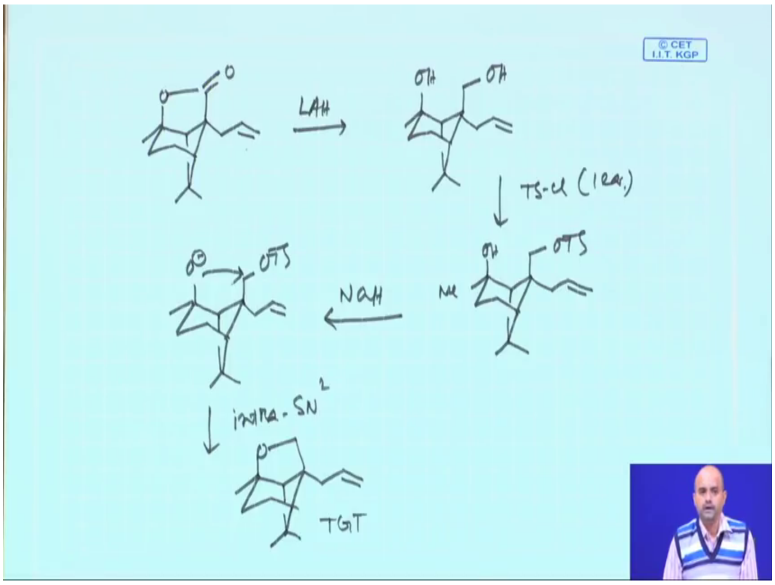

The starting material was given a cyclohexane-based lactone, the 3-dimensional drawing was basically given to give you a practice that you should start drawing, that how the cyclohexane which compounds can efficiently be drawn in a 3-dimensional pattern.

now say this compound little bit subjected to lithium aluminum hydride is a strong reducing agent and you will get the corresponding diol, diol fine, but this is a primary hydroxy and it is a tertiary hydroxy. So, you will just convert this to a one equivalent of tosylchloride to the corresponding monotosylate and monotosylate will be giving you this particular compound.

So, OTS is the primary hydroxyl group which is selectively reacting to give you the monotosylate. Now this compound if you react with sodium hydride you will basically initially generate the alkoxide. OTS and definitely the allyl group is here allyl group is here.

Now, this O minus will now attack in a SN 2 fashion intramolecular SN 2 to complete the synthesis through a simple intra SN 2 type reaction and then basically you will access the product. So, this is nothing this is just a simple FGI and this now completes the synthesis. So, what we did? We basically analyze the skeleton of the target and try to correlate with this starting material. The starting material was this one and the target was this one you basically need a deoxygenation reaction to this lactone and that was normally done through a intramolecular etherification reaction.

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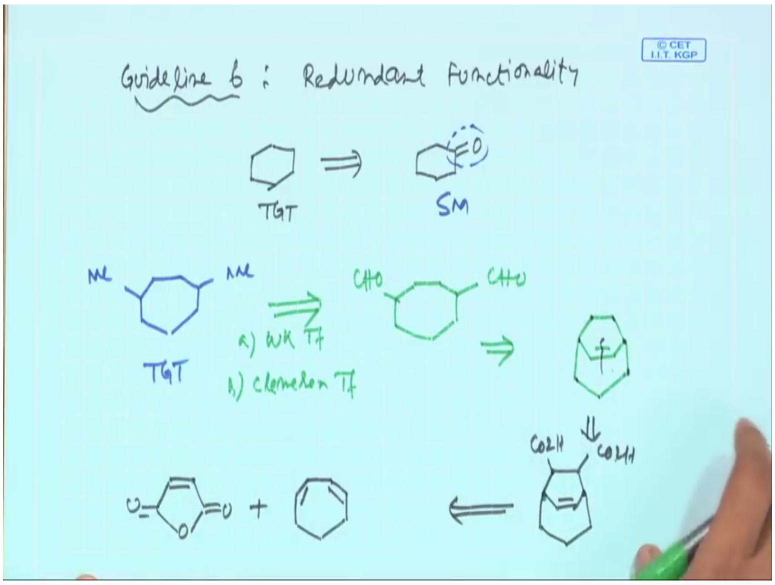

So now we will try to focus it out our final guideline for functional group-based disconnection. The guideline 6, the guideline 6 mainly focused on redundant functionality now redundant functionality we sometimes discussed, but not in detail we said redundant functionality are those functional groups which is absolutely required for a FGI, but they are not a part of the final target molecule for simplification, or simplified explanation if I say I have give you a target the molecule something like this a cyclohexane and I say the starting material which was given to you a cyclohexane 1.

Now all of you know that this reaction can be done in a single state transformation named as Wolff Kishner reduction. So, only thing is ketone group will be now the oxygenated. Now the starting material which has a ketone will be remain absent in the target molecule, because the final target does not have any active functional group.

So, wherever you would find that the target molecule does not continue at the functional group you need to introduce some functional group in the intermediate which act as a redundant functionality. Redundant means in reality to us not part of the final target molecule which basically you need to introduce for the functional group interconversion because you need some functional group for functional group interconversion. This is a considerable redundant functionality and we will try to explore it with couple of example.

The first example which we will pick the cyclohexane-based compound and normally try when were discussing this redundant functionality you always find that the final target molecule may not have a active functional group. Now this compound is a purely hydrocarbon the target molecule and see there are only 2 methyl appendages 1 4 position in a cycloheptane framework.

So, we will explore the redundant functionality by introducing to CHO group you say that the CHO group can be converted to the corresponding methyl group by the transformation which you already know. You can do a Wolff Kishner type transformation or you can do a Clemenson reduction this is already known to you Clemenson transformation fine. Now this kind of functional group now you need to think about.

Now, here as the target molecule have given the starting structure was not given is fine, we will now let us simplify it how this intermediate we can convert the next retro which we are drawing it is something like this. Now what do you say? You say if you have this kind of bicyclo hydrocarbon with your olifinic unsaturation you do ozonolysis you do a ozonolysis here now count the ring carbon 1 2 3 4 5 6 6 7. So, if you do ozonolysis this part is your CHO this part is your CHO which is act as in a appendage.

Now, why we have disconnected in this way there must be some logic that there must be some transformation which is already known to you or some kind of function transformation you already or familiar. Now still we want to discuss it further and try to focus on the remaining part, and if you see the compound here this is also a kind of there is no active functional group. So, here we bring another 2-functional group which are also a redundant functional group, which will be removed because in the target this in this is not target molecule which does not have this kind of functional group.

Now, we all know if carboxylic acids are heated under strong thermal condition they undergo decarboxylation reaction. So, in principle if you do a decarboxylation reaction you can end up it here now to formulate this one now we say we will be trying to give you a this compound as a dinene and this compound as a dienophiles which will be basically the give you this particular compound.

now initial visualization was difficult, but I say now try to visualize this in this way this is this bottom ring is basically the 7-member ring 1 2 3 4 5 6 7 you have a double bond here which basically can be coming from this diene part double bond here, and this 2 things is now these 2 things you have a maleic anhydride. So, which will basically hydrolyze to give you this carboxylic acid.

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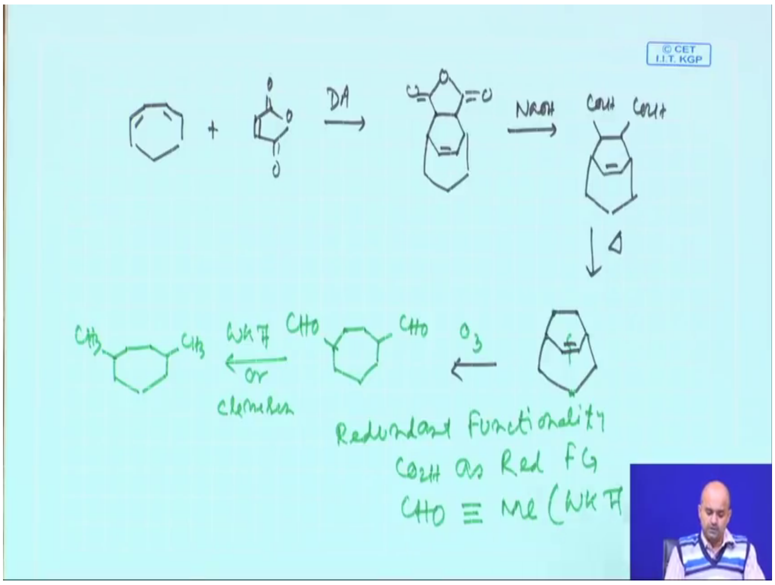

Redundant Functionality

CO_2H as Red FG

CHO ≡ Me (WK T

So now you do the forward synthesis then it will be quite clear to start with this diene, take this diene and react with maleic anhydride. So, basically what we will get I will write in a different way as given in the intermediate. I will put this double bond here which has been newly generated and then we will this is the initial intermediate which will basically get by a 4 plus 2 cycloaddition or dielsalder reaction. Now this will be just simple hydrolyze with a base and that will give you the intermediate which is our known intermediate which we have earlier drawn.

Now the synthetic step demands both this carboxylic group needs to be removed we will do a very strong heat to decarboxylate those 2 carboxylic acid groups. Eventually this 2-carboxylic acid group also serving as a redundant functionality. Now where you come here now see this 1 2 3 4 5 6 7 even the this ring also 1 2 3 4 5 6 7. Now we are doing a ozonolysis reaction. So, ozonolysis basically clips this particular bond and if it clips this particular bond we will now getting this compound isn't it?

Now, you do a Wolff Kishner transformation or a Clemenson transformation which is pretty much known to you I hope. And then you can basically complete the synthesis. So, here what we did basically we use the concept of redundant functionality. We say that redundant functionality are those functional group which in reality is not a part of the molecule, but still you need to introduce those functional group in terms of a effective FGI.

So, in this whole synthetic pathway we will find we used a carboxylic acid as a redundant functionality we can call it redundant Fg. As well as the final step we use aldehyde as a equivalent of methyl functionality we introduce a methyl group and we started from a corresponding aldehyde which we know can be done by either Wolff Kishner transformation or Clemenson reaction.

So, until and unless you know this Wolff Kishner and Clemenson you would not be able to use the consider redundant functionality for this molecule and redundant functionalities is very nice demonstration of how a typical target molecule where you do not have a active functional group you need to introduce the redundant functionality the same line we will now pick up some other examples which will basically give you a conceptual clear-cut idea of the entire topic.

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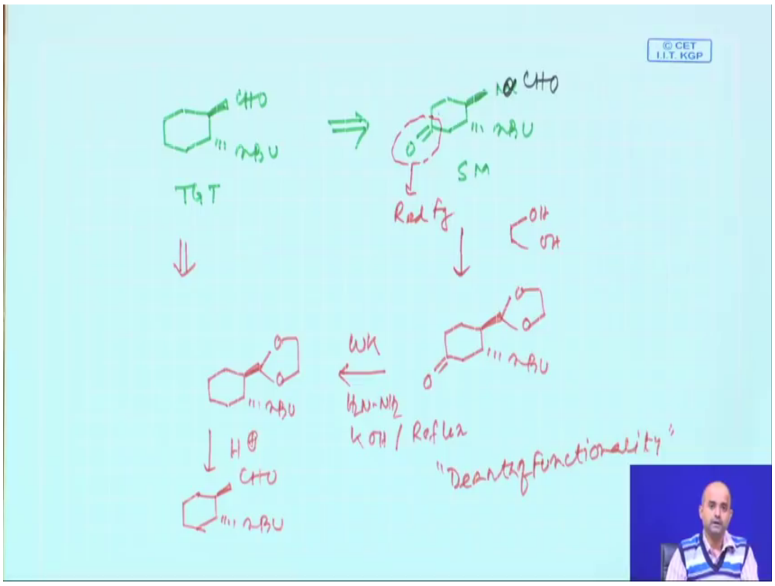

So, I say this is your target molecule. Now the earlier one we have not gave you the starting material now I will provide the starting material. Now I say the starting material is something like not something is exactly the same starting material.

So now if you basically consider you will find that the no is a little bit wrong sizes will be actually CHO yeah CHO. So, you see that starting material is a aldehyde containing group aldehyde containing molecule and the and the molecule which was giving you as a precursor was having a extra ketone group. now try to correlate this ketone in the final target has to be removed. So, here basically this ketone is serving as a redundant functionality redundant Fg.

Now, do a retro now we say that there are actually if you introduce a ketone there is already aldehyde. So now, if you try to deoxygenated by Wolff Kishner or Clemenson reduction ketone and aldehyde both can undergo such a such reductive reaction and then your target will be something different this aldehyde will be converted into methyl. So, we do not want that. So, means that you have to basically protect this aldehyde as a sum of this protecting groups. So, the aldehyde activity will be suppressed.

So, start with the starting material and you protect the aldehyde first, the aldehyde protection as we said you can easily protect the aldehyde with ethylene glycol. You do the protection. So now, the aldehyde is basically masked aldehyde you are protecting it now there is absolutely no problem in this Wolff Kishner reduction.

So now you do the Wolff Kishner reduction the region is hydrazine hydrate and KOH was used as a base and you reflux this whole thing and then you will find that this part will be now deoxygenated. There are actually other ways to deoxygenate this ketone, but is a very simple way and if you remember the earlier slide couple of earlier slides we have talked about how the alcohol can be deoxygenated.

So, in principle this ketone also can be reduced to give you alcohol then alcohol can be converted to tosylate or mesylate and then use the super hydride allyl 83BH or even sodium borohydrate that can also deoxygenated by a hydride attack. So now, only thing is you basically require the removal of this protection group. So, which can be simple done by this acidic workup and you come to your target molecule.

So, this kind of simple functional group interconversion by it taking the help of a redundant functionality often helps and whenever you will molecule there is probably a dearth of functionality which sometimes called dearth. Dearth means there is absolutely no functional group present dearth of functionality. So, in this process the redundant functionality very helpful and I will try to explore the redundant functionality with couple of more example.

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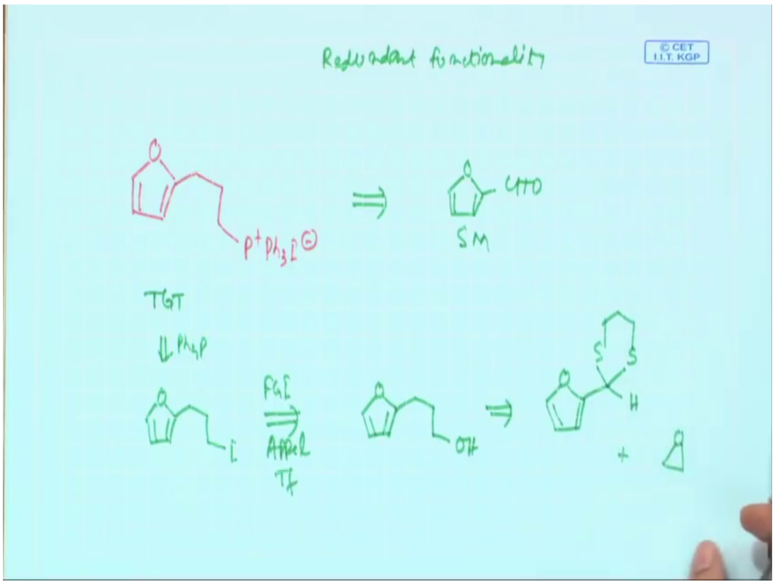

We give a target which is now physically a salt, a phosphenium salt which is often used in the wittig reaction this is your next target, and you are exploring the concept of redundant functionality. The starting material which was given to you this one now I say if you try to correlate this compound is having a furan ring and a 2 position you having a 3-carbon extra CH2 CH2 CH2 and the starting material is having a furfural 2 position of the furan you are having this aldehyde group.

The conventional retro probably will give you the first intermediate which you basically need the corresponding ardo, ardo you reflux with triphenylphosphine to get the metigilide the ardo we can easily synthesize by using a very standard FGI appel reaction which you have appel transformation which you already discussed this.

Now, try to correlate this is one carbon you need to introduce 2 carbon extra and this 2 carbon extra probably you can think about by using a umpolung type of chemistry which you have already discussed.

We say if you have this compound which is basically nothing a furfural have been protected in as this 1 3 diethane you can easily abstract a hydrogen through base now do this forward synthesis to start with the furfural.

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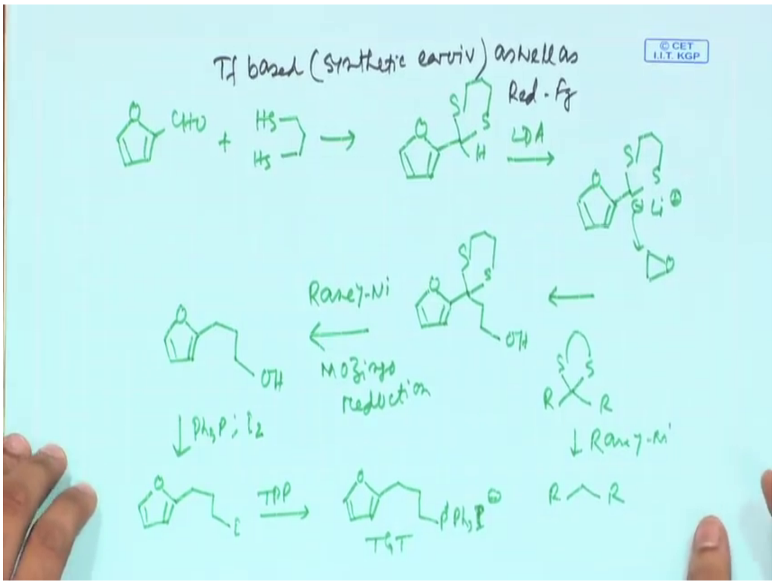

React with 1 3 diethane. So, initially the aldehyde will be basically protected as it is diethane, diethane remaining hydrogen is extremely acidic. So, react with LDA and you generate the corresponding lithiated species which is serving as a umpolung minus lithium plus.

Now, as you need to introduce 2 carbon extra you react with a epoxide as electrophile. You find that this epoxide reacts very nicely and then you make the this. So, 2 carbon extradition was done, but in the final product this 1 3 diethane was not required. So now, this once 3 diethane is surplus extra. So now, you need to remove these things with some reagent.

Now, if you remember the earlier very beginning part of our lecture we talked about sulphur can be easily desulpherized by a reagent named Reney nickel. So, Reney nickel will essentially reduce this sulphur thing and to give you a CH2. Now this particular reduction sometimes referred as mozingo reduction, mozingo type of reduction which is basically nothing if you having a diethane you react with reney nickel hydrogen you basically get the corresponding hydrocarbon.

So now see we are here now you do the appel reaction triphenylphosphine and iodine sorry we have the final component iodine yeah fine. So, then you get the appel thing and then reflux with triphenylphosphine again to complete the synthesis. So, you can basically get the corresponding phosphonium sorry phosphonium iodide as a salt and this is your target molecule.

So, here is basically a combination of transformation-based approach where you used a synthetic equivalents. The synthetic equivalence concept we have earlier explained and synthetic equivalence as well as we use redundant functionality redundant Fg. So, redundant functional group in that way is very nice demonstration whenever your molecule does not have any active functional group they can think about bringing some extra functional group in the intermediate stage.

And then are depending on your final target those functional group can be removed. Functional group can be removed because those functional groups are not required. So, the surplus, but you need to bring those functional group because without functional group we cannot think about retro.

As I said the retros always need to be based on a functional group as I discussed it functional group the retros. So, we will keep on our discussion or keep on continuing our discussion on this redundant functional group-based approaches in the next week till then have a good time and,

Good bye.