A Study Guide in Organic Retrosynthesis: Problem Solving Approach

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Lecture – 32
Fg based Strategy (Contd.)

So welcome back students in the last lecture basically we were discussing redundant functional group based strategies.

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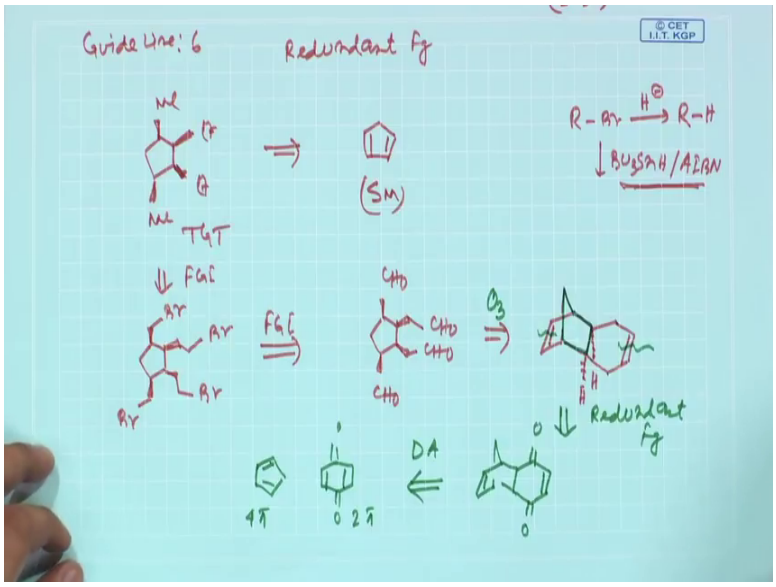

And we said that redundant functional group plays a very important role, and it is acting as a surplus functional group. In the target molecule basically you do not have that functional group which is required, but still in some cases we say that you need to introduce some functional group, which act as a redundant functionality, and you have to remove those functional group to being a inert functional group like hydrocarbon. Hydrocarbon does not have active functional group.

So, you need to introduce some alcohol also carbonyl group, and the late stage you do the de oxygenation or alcohol removal to introduce the hydrocarbon functionality. So, our next problem will be based on a similar kind of exploration of redundant functionality, and this problem was very nice demonstration of redundant functionality. Here we have given you a target molecule, which is purely a hydrocarbon, basically a tetra substituted cyclopentane there are 2 methyl groups, there are 2 ethyl groups, 1 2

ethyl one 3 methyl, and all the groups the relative stereochemistry was above the plane this 2 are ethyl group.

Eventually the starting material will also given to you the target molecule is this? The starting material was a very simple starting material cyclo pentadiene was given to you, normally I can give you a hint that whenever a starting material cyclo pentadiene was given to you, blindly you can think about this instructor or your teacher is looking for a diels alder cycloaddition reaction, because cyclo pentadiene is a very good diene a 4 pi system there is to the cycloaddition reaction.

Now, these 2 the transformation you have to use it, but before that lets go for the retro and how the concept of redundant functionality you can introduce, or you can bring it here. We say that probably if you have something like this all the things are CH 2 Br CH 2 Br.

So, basically we are trying to have a tetra bromo compound. So, this bromo compound can selectively reduced by a hydride source to corresponding hydrocarbon, this you already discuss, or if you not discussed just remember that if you use a alkyl bromide or alkyl halide react with lithium aluminum hydride, eventually you can get the corresponding hydrocarbon. Also you can use a radical mediated reaction to use BU 3 SnH and AIBN, there also is quite possible will explain this reaction it will be later on, but first remember any hydride source will be working here to give you the hydrocarbon.

So, this is basically FGI the point is you have to introduced 4 different functional groups here, our next retro was similar kind of FGI or you say that, if we are having a tetra aldehyde kind of thing tetra aldehyde. This tetra aldehyde basically can be reduced to give you the tetrol, which can be compared with the corresponding tetra bromide this is also FGI.

And now we are doing a very interesting retro. Now this retro is very interesting the retro which, now will be doing its very interesting both the hydrogenous are below the plane. So, if you closely follow this compound this basically a bicyclic compound. Now we say you will be simply doing a ozonolysis here, mean is that it will be chopping this double bond here, you will chopping this double bond here.

So, basically the core cyclopentane which is this, the core cyclopentane will be retained, and then you having CH 2 CH O bi ozonolysis CH 2 CH O, CH 2 CH O, CH 2 CH O, and this part you will be having another CH O another CH O. So, this is absolutely fine. Next I say as you have already told that you have to use a diels alder reaction the starting materials was give in a cyclo pentadiene.

Now, next retro will be based on a exploration of redundant functionality, I say that if you have this kind of compound you basically deoxygenate both the carbonyl oxygen, and you can think of having this kind of retro. This is basically that concept of redundant FG and then here is diels alder retro. So, you can basically now write a 4 pi system and a 2 pi system as your para benzoquinone as the dinophile of the dinophile.

So, now based on this will be now doing the forward path way, and will see how this synthesis can efficiently be carried out with a strategic exploration of redundant functionality.

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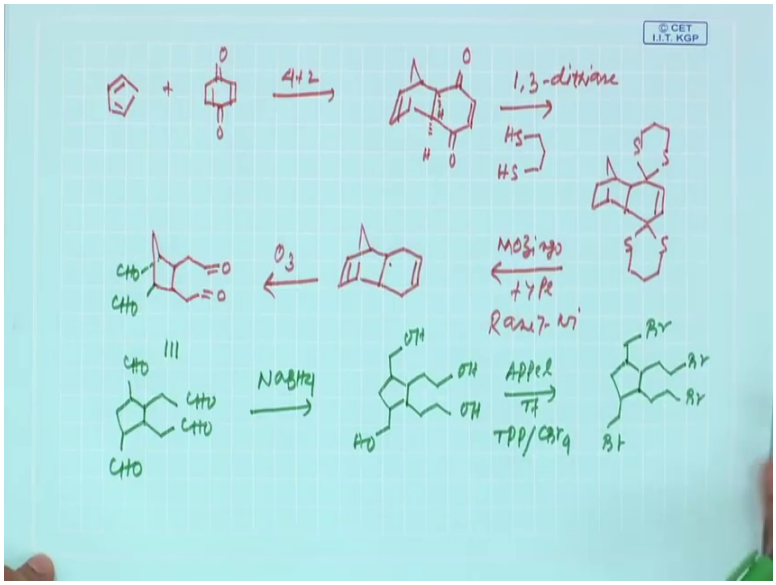

The starting material was cyclo pentadiene, and was reacted with para benzonquinone. So, initial 4 plus 2 cycloaddition you basically, normally we know the 4 plus 2 cycloaddition. The endo product was usually formed endo means this is the product.

Now, as you said this 2 carbonyl was not required. So, need to get rid of this to carbonyl. Now it will be try to remember you can do variety of reaction, but the reaction which we

will be doing, will just protect this carbonyl with 1 3 dithiane means HS, HS. So, what will get basically get the corresponding carbonyl will be portrayed as its acetyl. Now as both the carbonyl has to be deoxygenated here will be doing the mozingo type reduction which you have already explained, means you need a raney nickel. So, after this mozingo type reduction you're this part is now this.

So, basically you are now coming to this compound which is ready for the ozonolysis is not it. So, now do the ozonolysis and if you do the ozonolysis now, I will write the compound in a different way, I will write it double bond O, then this the core cyclopentane, and from here you basically getting one aldehyde, and getting one aldehyde, on this compound is basically nothing. You can just simply write that this compound is your CH 2 CH O, CH 2 CH O, and this is your CH O, the stereochemistry you can basically write it out or for simplicity simplifying the things you can omit the stereochemistry.

Now, next what you need to do all the aldehydes need to convert it to the corresponding primary alcohol. So, do it by a sodium borohydrate type of reducing agent, all are converted to the corresponding primary alcohol, then you do a appel reaction appel transformation by TPP tri phenyl phosphine and CBr 4. So, basically then you will get tetra bromo species this Br, this Br tetra bromo. Now, once you have this tetra bromo, your next job is very much similar next job is very simple.

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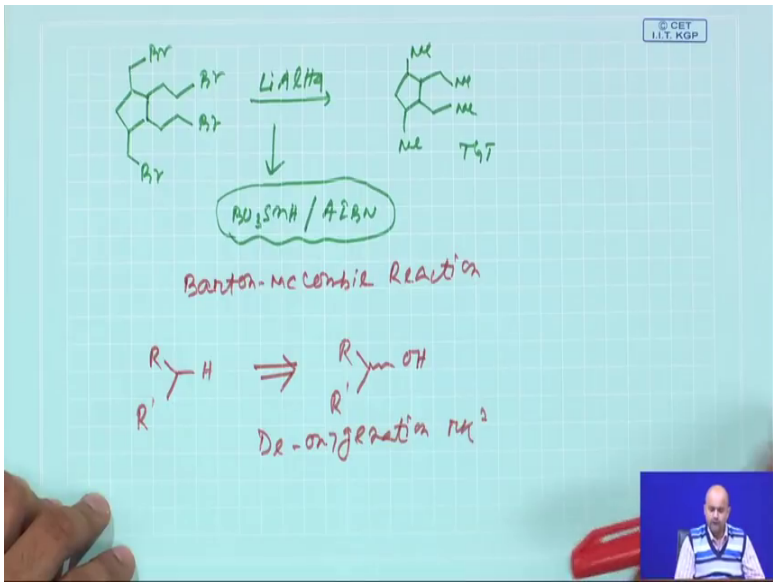

And the next job basically we said that, you have to now remove this bromo with hydrogen to achieve the target molecule. So, basically need a de hydrogenation reaction I mean, principle you can do this reaction by variety subway. I will just explain if you can take this compound use lithium aluminum hydride, you can end up with this desire product, this is the target molecule.

Otherwise there are otherwise you can also do it, this particular reaction will be explained little bit later on, if you have BU 3 S n H and AIBN a radical pathway will operate. I will explain this radical pathway little bit later on where when you explain a name reaction, which basically is very important in the context of redundant functionality.

So, if you know analyze the entire problem you will find that we explore the strategy of redundant functionality twice in the synthetic pathway. Initially we do a mozingo type of reduction, at this point you basically get rid of this tetra this 1 3 dithiane moiety to deoxygenate, this carbonyl, and then when you have this bromo you do another kind of redundant functionality exploration by using hydride source.

Now, next base from the redundant functionality will be explaining a name reaction, which is now very popular the name reaction is named as Barton MC combie de oxygenation or Barton MC combie reaction. Now in Barton MC combie reaction the basic retro synthetic pathway, you can explain in something these way, if you have to make a hydride hydrocarbon molecule, you just take the corresponding hydroxyl.

And then do this Barton MC combie reaction to access the hydrocarbon it is basically a de oxygenation reaction. Is a De oxygenation reaction is very helpful reaction very helpful reaction and Barton of MC combie reaction was used quite often. Now, in the Barton of MC combie reaction what is the main rule of a different thing.

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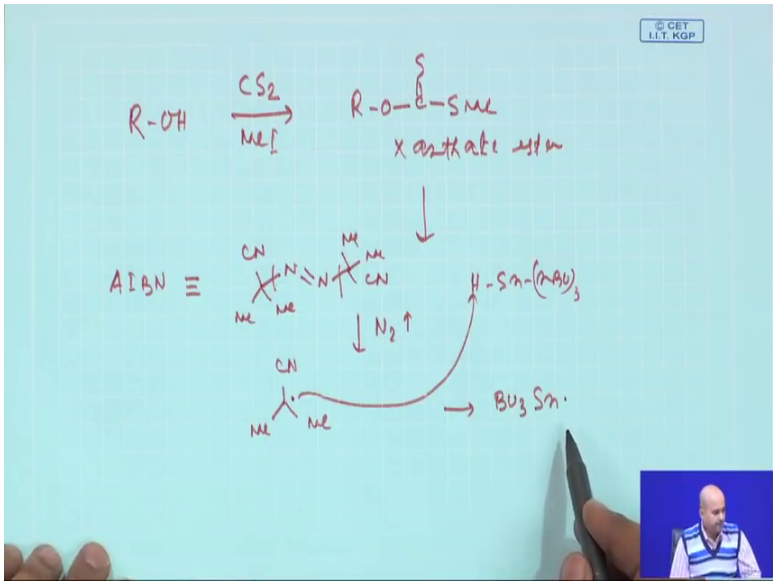

So, will find that If you have a alcohol you first react with carbon disulfide, and then you react with a methyl aldehyde. So, basically you get a this kind of xanthate ester. Now this xanthate ester was basically then subjected to your radical fragmentation. And this radical fragmentation normally we use as I said 2 reagents, AIBN which is a ja isobutyl or nitrile whose structure is isobutyro. So, me CN then this is having a ja, and then the remaining part Me Me CN and you are having BU 3 Sn H whose structure is normal BU time whole 3 Sn H.

Now, initially if you sign light to this molecule the nitrogen nitrogen born basically initially opens of and, nitrogen gas was evolved and then you get this radical, through a heterolytic cleavage to get this radical this basically this, and this because is radical on. This radical what it does it basically picks up the hydrogen from the BU 3 SnH, the basically picks up the hydrogen from BU 3 SnH, and gives you BU 3 Sn dot. Now this BU 3 Sn dot; this particular BU 3 Sn dot it is now reacting with the xanthate. So, you have this xanthate in your reaction mixture, or is a is xanthate is basically initially prepare is not it.

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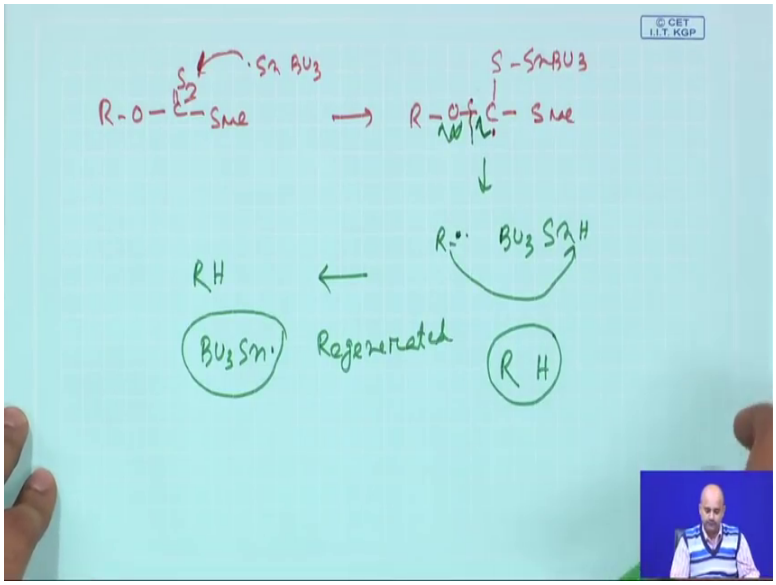

Now, this BU 3 Sn dot this BU 3 Sn dot is basically reacting with this sulfur reacting with the sulfur, through a half arrow this is a radical. So, if we always have kind of half arrow mechanism and this is also like this. And then you will find this compound will be then converted to a R O C S Me S SnBU 3. Now this this kind of things will be basically now putting a radical here.

Now, this this radical will now having a carbon oxygen. So, this heterolytic cleavage will now takes place, and you basically having this and this cleavage. So, which will now give this oxygen bond cleavage is give you a R R dot, this particular R dot. So, these things and sorry this will be like this, you have this R dot R dot and your entire other things will be dropped it here.

So, basically where this R dot, where this R dot will get a BU 3 SnH, which is in the reaction mixture, and then it will pick up the hydrogen from this BU 3 Sn it will give you a hydrocarbon which is required, and you get BU 3 Sn dot. So, BU 3 Sn dot is regenerated. Now ones this is regenerated, it can again abstract or you can undergo radical fragmentation which is xanthate again.

So, this this way the whole process basically goes on, and then you will find that finally, your hydrocarbon or de oxygenation was taking place.

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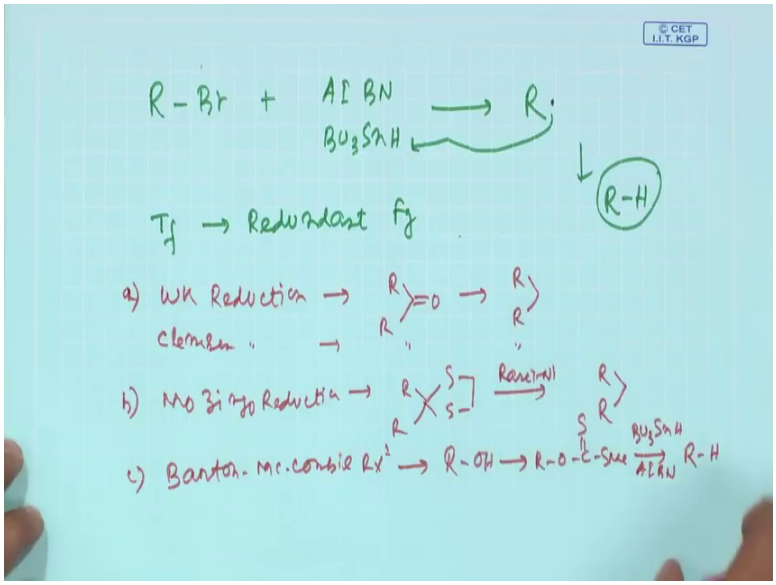

So, a similar way as I said if you are having a alkyl bromide, you can basically react with AIBN and BU 3 SnH, you can also get a similar kind of carbon bromine bond heteroatom cleavage, then get a dot radical and then it abstracts a hydrogen from this BU 3 SnH to give you a R H. So, this kind of radical immediately de oxygenation particular this a Barton MC combie reaction was one of the very well known reaction, and it was explored in the synthetic organic chemistry for a for many long time and for many years.

So, eventually for the redundant functionality you can basically now, make a note of summary. That what are the transformation we are normally using in the redundant functionality, redundant FG. The you can see the transformations are basically the reaction where a functional group has been removed, standard transformation like Wolff Kishner reduction, were basically doing a transformation something like this to de oxygen and the product. The same line you have this clemensen reduction, this is also exactly same. Is it mozingo type of reduction mozingo reduction which is also very useful?

Now, what is the exact reaction, you basically have to have a sulfur compound, and then you do the desulphurization reaction with Raney nickel, and then what you get, you get the corresponding hydrocarbon and then finally, we called a name reaction which is Barton MC combie reaction. And we say that in Barton MC combie reaction the transformation is you first convert the corresponding alcohol to the xanthate ester, and

then you sign light with BU 3 SnH and AIBN, then basically you get the corresponding hydrocarbon.

So, these 3 are the main key reaction, in this radical mediated or this kind of exploitation of redundant functionality, where you can get rid of a particular functional group to convert corresponding deoxygenated things. And these 3 transformation was often used if you want to explore the redundant functionality.

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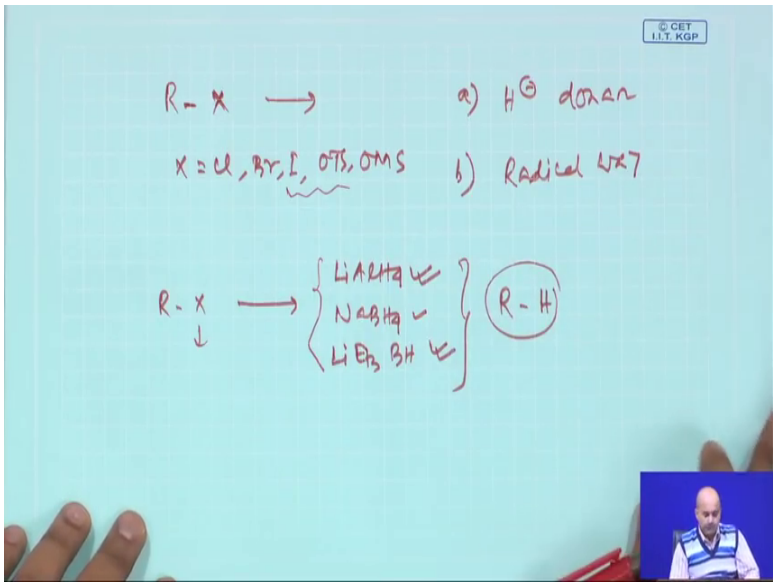

The other function transformation which we just, now said it is basically extension of these things like. If you having a R X. Now X could be anything x could be chloro, bromo, hydro, proselyte mesylate, this case also this carbon heteroatom bond cleavage you can do by different way. I said there are ways to do it if you can use a hydride donor which can act as basically a nucleophile, and you can also cleave it by radical way.

A radical way is which just explained BU 3 SnH and AIBN, and if you need the hydride donor you take the corresponding R X react which a series of hydride donor like lithium aluminum hydride strong hydride donor mainly, sodium borohydrate sometimes works, but lithium aluminum hydride is very active is sometimes, super hydrate Li Et 3 BH works very well.

So, this particular hydrides and x could be anything I mean any halogens, mainly if you having a good living group like iodine to oscillate radiation is very faster. The action is

very faster and you will always get the corresponding hydrocarbon in very good deal. So, in principle this kind of sometimes I can give you a very similar kind of example.

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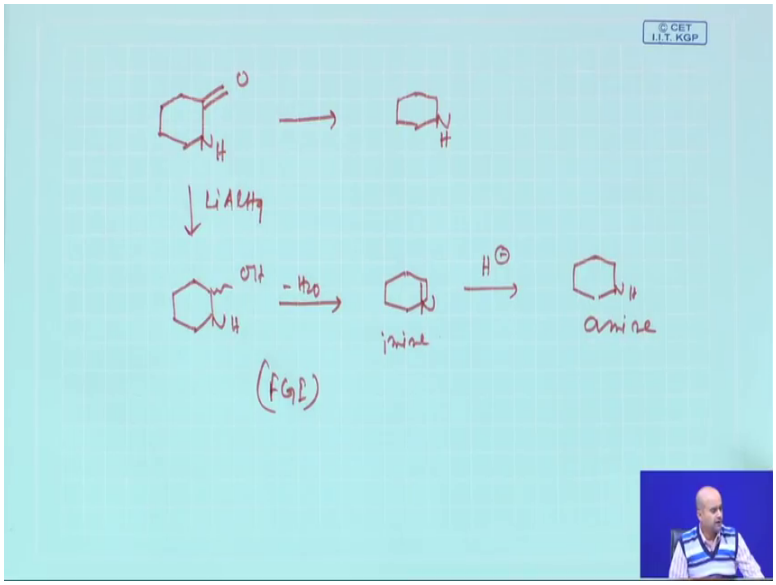

But in principle you may not call it as a redundant functionality, I will see you are having a amide, and you want to convert this amide to amine. Now, basically what you do you do a de oxygenation reaction, but in reality this is amide, amide carbonyl you cannot do a Wolff Kishner kind of reduction. So, already we have discussed it. Now if you put a reducing agent like lithium aluminum hydride. So, initially it was been known that the carbonyl reduction way takes place, and then instantly water elimination also takes place to give you a amine.

Now, this amine this amine particularly will now excess L H if you use, when a the amine will be simply reduced, amine will be simple reduce to give you the this is basically imine, imine will be simply reduced to give you the corresponding amine. This is probably all of us knowing, but this is the amine and it goes through this way. Now in 2 sense this may not be a redundant functionality basically the functional group was there, though we are doing a de oxygenation reaction still the this particular carbonyl is such a different carbonyl, probably Wolff Kishner Clemensen kind of reduction on be operating here. And other things like Barton de oxygenation you cannot do it, because for Barton de oxygenation you have to convert this keto 2 corresponding alcohol.

So, no need if you just simply subject to this amide to corresponding reducing agent instantly it will reduce to first imine, then imine will be further reduced to amine. So, it may not be a exponential of a redundant functionality, but this is a simple FGI. So, there are ways which you can basically explore certain things.

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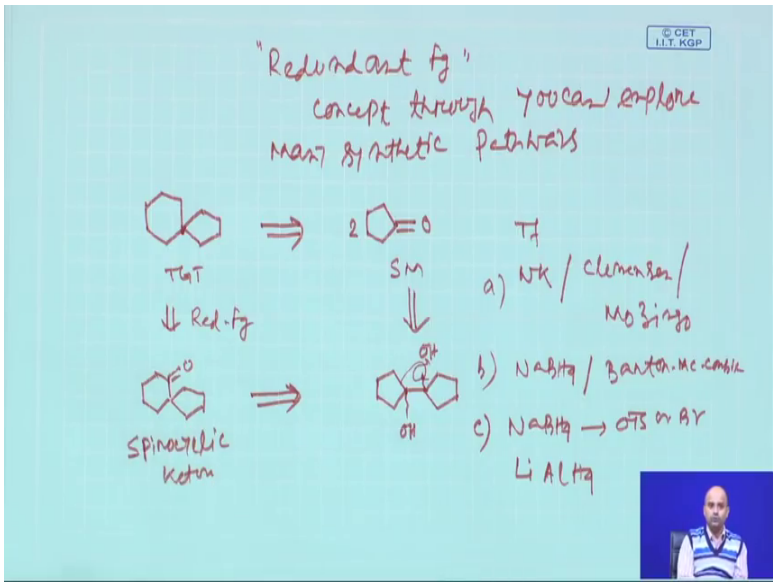

And particularly the concept of redundant functionality is a absolutely brilliant concept through which you can explore many synthetic pathways. And always try to remember let us give you a some problem like this; I said you have to make this kind of hydrocarbon. It is basically trying to refresh your memory express of redundant functionality; I say the starting material is I will give it to you a cyclo pentadiene. So, how you can approach it, I say the target molecule is this one; a starting material is this one.

Now, eventually you see that the number of carbon it is there are 5 carbons, there are 10 carbons here, 6 7 8 9 10. So, basically you need, now do the conventional retro and actually this kind of retro was turned very initially if you remember, please now try to get back to your old memories. If you are having some pinacol pinacolone type of rearrangement, this pinocol pinacol rearrangement, which basically will give you this kind of spirocyclic ketone is it pinacol pinacol rearrangement, will basically give you this then this migration takes place to come to here.

Now, these and this, the main thing is your redundant functionality. So, simple exploration of redundant functionality will basically lead you to the target molecule as I said. Now here also you what are the reaction will be doing here, you can do a simple all the wolff kishner your clemensen mozingo. All this kind of de oxygenation, you can use you can simply reduce this compound to sodium borohydride to get the corresponding alcohol, you can then do the Barton MC combie fine Barton MC combie or even you can do it other way, you can reduce it sodium borohydride, and then convert the alcohol to corresponding tosylate or bromo, and then you use the lithium aluminum hydride as you hydride source.

So, in reality no matter what are the regions you are use, but eventually the you have a much more flexibility to add up to a redundant functional group based strategies, and you see for a this transformation you have numerous ways. And depending on the resources which are available in your lab, you can basically choose any one of the regent system to get it up this target. And the only thing is the power of the retrosynthesis is very useful, you have to formulate the proper retrosynthetic pathway.

And the toolbox is as we are discussing there are toolboxes which we are basically your retrosynthetic pathway, and your transformation, your functional groups, your appendages your stereo chemical strategies those knowledge basically serve your main guidelines main toolbox. So, will continue our discussion, and till then have a have a good time will see you in the next lecture.