A Study Guide in Organic Retrosynthesis: Problem Solving Approach

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Lecture – 30
Fg based Strategy (Contd.)

So, welcome back students, we are basically discussing functional group-based strategies and we talked about, how to introduce key appendages, which are basically hanging functional groups and, now we will trying to discuss on the same topic and the next problem, which is will be trying to analyze.

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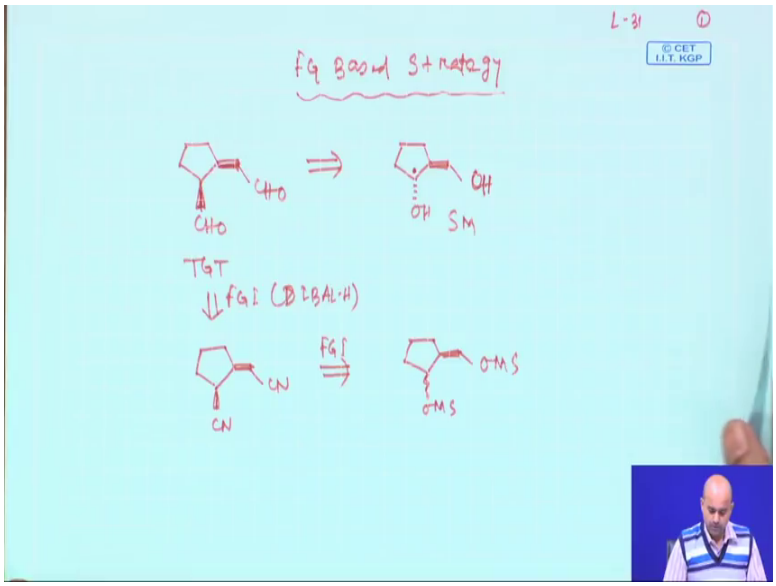

It is a simple problem, but here couple of other things also will be, discussing this compound, which was giving as a target molecule having a aldehyde, as well as another aldehyde. It is basically dialdehyde compound, the stereochemistry was given as a cs for both this want to die substitution.

The starting material which is also giving to you, having a structure up this type, this is a OH, if you analyze closely, the stereochemical point of view will be, just talking here that this particular, hydroxy stereocenter was inverted in this starting material. But the appendages have been changed, here you are having a hydroxy appendages, you are having a aldehyde appendages. So, need to do a kind of a inversion reaction to, introduce some functional groups which can be later on convert it to a CHO functional group.

Now, we do the very conventional retro, by doing a simple FGI and you already discussed that, aldehyde appendages can easily be constructed, if you having corresponding sign or compound by a, dibal reduction. It is basically reductive transformation. So, cyanide can be converted to a, dibal to the corresponding aldehyde and, if you have a dysano compound. Now, you try to correlate that, how this dysano can be converted? Or can be accessed from this dihydroxy compound.

Now, I say we will be doing a simple FGI, where if you have the O mesylate as well as this mesylate, now this we put a dotted line, we will say that this step you need a inversion because, it is a 2-degree carbon and this is a primary carbon.

Now, try to correlate that, this is a dihydroxy compound, you can easily convert to this dihydroxy compound with dimesylate. Now we analyze that, how this conversion can easily be achieved?

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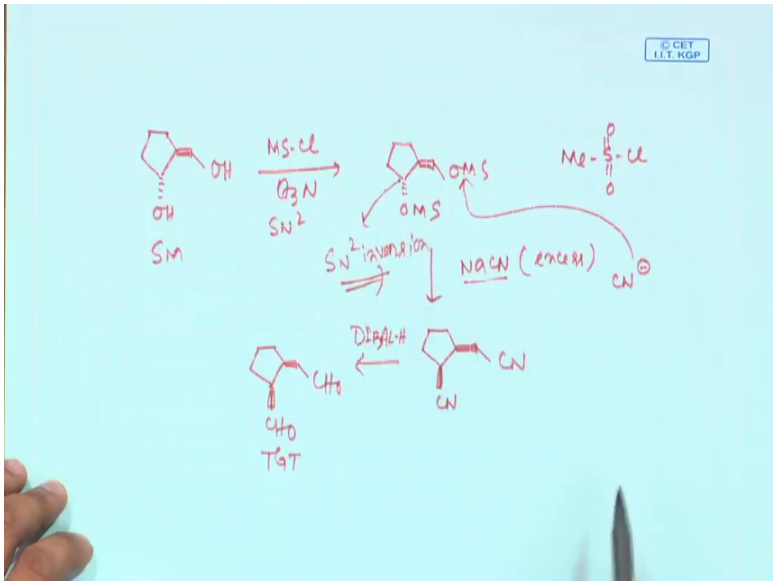

To start with the starting material, which was given to you this hydroxy was below the plane and, this primary one is above the plane, the starting material was given to you. Initially convert to this by treating with a mesyl chloride triethylamine excess, because you need to convert both the, hydroxy to it is dimesylate

Now, mesylation definitely is a SN 2 direction, but as it does not touch the carbon it will basically, the stereochemistry will remain intact, now what is mesylchloride? There is a

methyl sulfonyl chloride. And it basically, make it O minus, O minus, this O minus will now attack to this sulfur here and, you get a new oxygen sulfur bond. Now as here you did not touch this 2 center, SN 2 will be taking place, but there will be no inversion.

Now, next would be subject this molecule, to a sodium cyanide excess. Because, you need to convert both the mesylate to corresponding cyanide, now sodium cyanide basically, a source of cyanide which is also very strong nucleophile. Now this cyanide will touch here, now for this one you are now making a new carbon, carbon bond because, you are introduced the cyanide.

Now, here if I am using a strong nucleophile sodium cyanide excess, in this case SN 2 starts fine, but here also SN 2 is occurring and particularly this point. If SN 2 occurs, you have a inversion here, and this case there is no inversion. So, particularly this point the appendage when you are introducing, by a displacement reaction it undergoes inversion and, this was the main key factor and then now, as you are having this dicyanide, you do a excess dibal treatment, to complete the synthesis in a efficient way.

So, your target molecule is basically (Refer Slide Time: 06:02) it. So, whenever you have a stereo chemical issues, you can basically address it, by a standard reactions and if the reaction mechanism demands that, your inversional takes place, particularly say it here, the secondary carbon will undergo SN 2 inversion, the backside attack which is very common in SN 2 cases, anyway access the target molecule.

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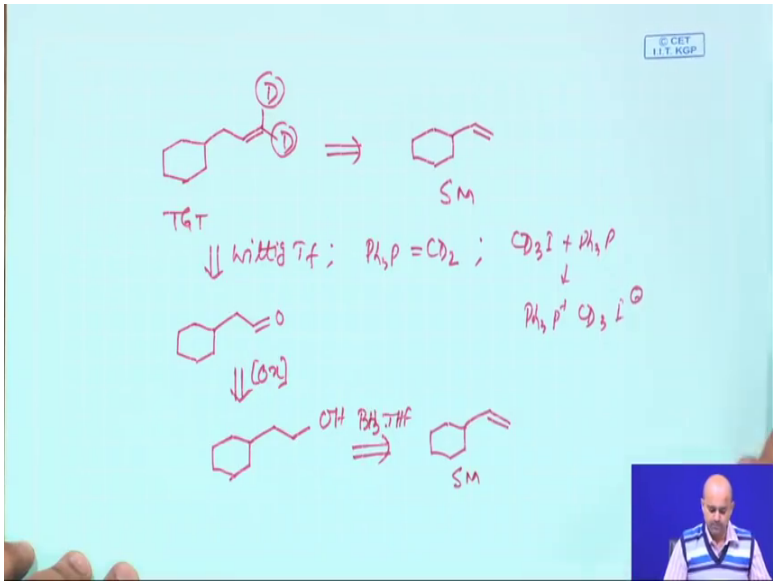

The same line, will be now discussing another related problem, based on the appendages disconnection. Give you a target molecule whose structure is this, the starting material will also give in to you, the only difference is, this starting material having a phenolic appendage, which is now converted to a allylic appendage one carbon extension and the allylic end, has been now required a deuterium, 2 of this hydrogen now have been replaced with deuterium, to give you a little bit more synthetic challenges.

So, we will now do a straight forward retro, how these things can be done. Now, I say if you do a wittig kind of transformation, based on this functional group or the appendage functional group which is present.

Now, what kind of wittig ylide you will be using here, as deuterium is require the final compound, you can probably think about. If you use this wittig ylide, which is having deuterium here. Now, this wittig ylide, you can easily prepared if you have CD3 iodide, in presence of in a like, similarly earlier problem we have talked about, if you have a methyl iodide. Now, here you replace hydrogen with deuterium and react with triphenylphosphine, to get a wittig salt and then you, try to it base to compute the wittig transformation.

So, basically you need to now convert this aldehyde and, try to correlate how this aldehyde can be accessed from the starting material. Now, this aldehyde can be constructed if we have primary alcohol, now here this is a oxidative based transformation, any oxidation suitable oxidizing agent and then here, you now try to correlate the starting material, if you do a hydroboration reaction with borane THF.

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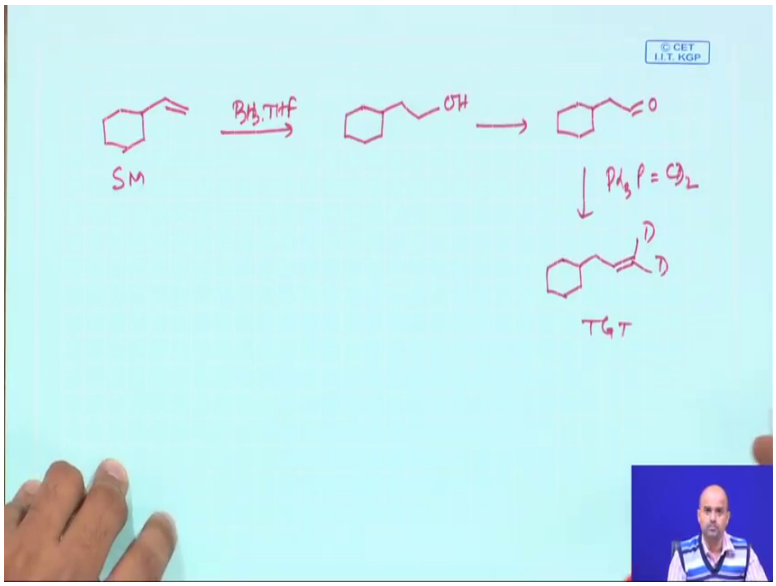

So, you can now come to your starting material. So, the forward synthesis which will be very simple, you start with the starting material l which is having the vinylic appendage. Do the hydroboration with borane THF and then, you find that this hydroboration will give you the primary alcohol.

Next, as you shown in the retro, convert this compound to this corresponding aldehyde then, your wittig reaction will be in action with this deuterium based ylide, which you already prepared from CD3I and triphenylphosphine. Now, you see you will be able to construct the target molecule, with the required allylic appendages and the allylic appendages having deuterium add it is final terminal.

So, this way you can basically simply construct the appendages, based on your requirement and simple transformations, will be always preferred the next problem which will be now discussing, it is a little bit tricky, we have given away lactone as a target molecule.

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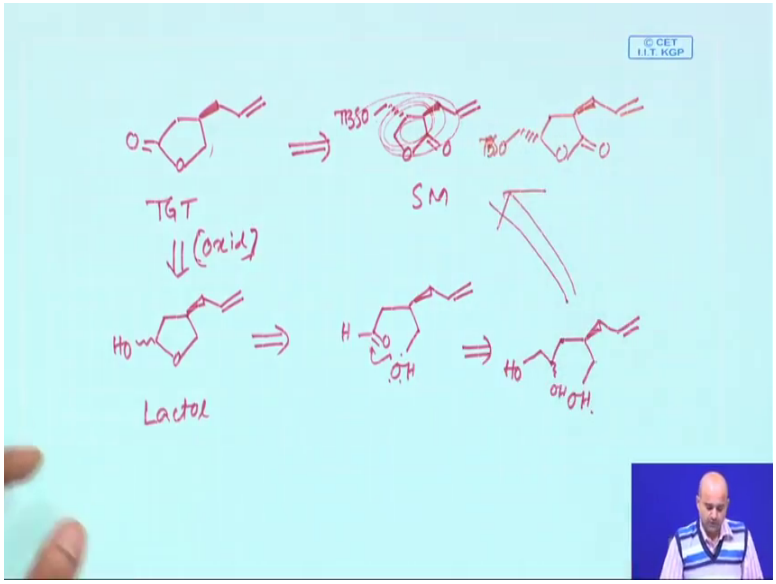

So, this lactone basically having a 5-member lactone, which allylic appendages, stereochemically pure allylic appendages, but the starting structure, if I give it to you then, you will be little bit perplexed or little bit confused, that how this starting material will be converted to this target, I say the starting material which I will be giving to you is this starting material.

Now, you try to correlate, that the starting material is having some extra group or a extra additional appendages, like this TBS group which was not present in the target molecule, as well as you see, this ketone having a allylic appendages here, but in the final product this allylic appendages, somewhere one carbon away from this ketone.

Now, you first take the target molecule and try to figure it out, how this target molecule can be retrosynthetically disconnected? Will say, the retro will be if we having a compound something like this, which is basically nothing it is called lactol or basically hemiacetal. Now, this is a hemiacetal where you have a secondary hydroxy group. So, if you have this intermediate, you do a simple oxidation here to give you the lactone with this require allylic appendages.

Now, this lactol you need to construct, how this lactol is correlated with your starting material? Now lactol are also basically nothing is a hemiacetal, as I already said and then now, you will just do a simple FGI based things, the allylic appendages is here. Now see if you having a hydroxy aldehyde, hydroxy aldehydes are basically this kind of

compound, hydroxy aldehyde will undergo lactol formation by just, this kind of attack will give you the lactol.

Now, this hydroxy aldehyde which was proposed as one of the intermediate, now we have to quarrel with the starting material, the hydroxyl appendages. Now we need to focus it out, how this hydroxyl appendages will be now? We now, come to intermediate which is a little bit unconventional, but we said that, if you have this kind of compound, where is it want to diol functionality is there, the want to diol functionality, you can definitely do a oxidative cleavage, by Johnson Lemieux reagent to give you this hydroxy aldehyde.

Now, there are 3 hydroxy group, this is the isolated primary 1, this is 2 or 1 2, normally for this Johnson Lemieux oxidative cleavage, only 1 to dihydroxy compounds are clip. Now, why we drawn this intermediate? Basically, now if you count the number of carbon is 1 2 3 4 5 the target molecule also is given 1 2 3 4 5.

So, basically trying to analyze that, how this particular carbon or this particular intermediate is linked with this starting material? And then, now you try to figure it out, how this intermediate is related to the starting material? We say that if you have the starting material, you just simply do a reductive cleavage, reductive cleavage means you do a reduction, now this reduction will basically give you, a allyl here, a allyl here, this is basically carbonyl group, which will be reduced to alcohol, then here you are having this CH2 OH and this, TBS group also can be thought that, it can also give you a particular OH by TBSD production.

Now, you compute the synthesis through a forward pathway, now start with the starting material which was given to you, the starting material which was given to you is having this structure TBSO.

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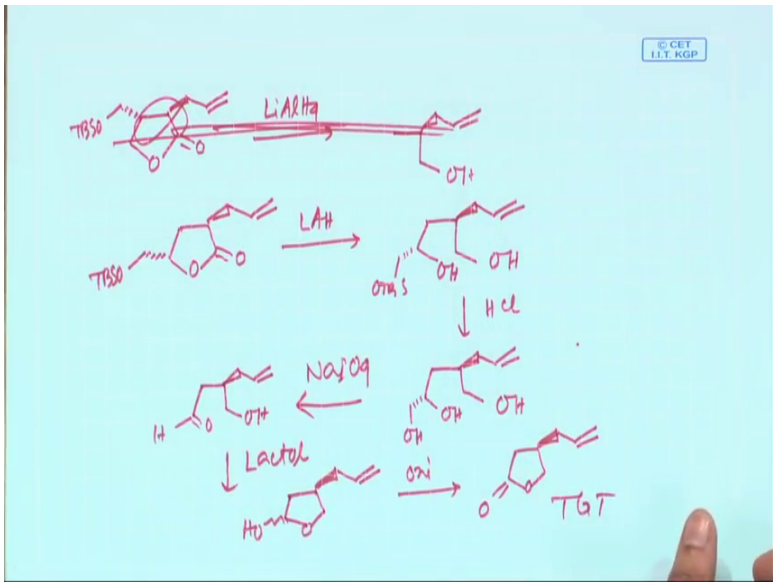

So, first we will be using lithium aluminium hydride, which is a strong reducing agent. Your allyl will be here and, you will be having a OH here and then, basically I think the starting material was that, the initial starting material which I have earlier drawn is actually, little bit wrong starting material was given. You can actually the starting material was that is, why the retro was not coming, properly it will be particularly this starting material.

So, now this starting material, which is we will just draw the starting material again and then, we will find the starting material was this one and, you are having this TBS here. So, do a lithium aluminium hydride reduction and, then you will find that this allelic group will be there and you are having this primary hydroxyl.

Now, this is after cleavage, will give you this OH and this OTBS, the TBS can selectively be clipped by HCL treatment that, will now give the diol, which is next require for this oxidative cleavage. So, allylic appendage is there and you are having this CH 2 OH.

Now, what you do you just try to it sodium periodate, it is a want to diol, want to vicinal diol which is now going to be, cleaved to give you a aldehyde. Your allyl things are remaining here and, you have this CH 2 OH, other see we have drawn the intermediate correctly, but as a starting material was not given correctly in the initial drawing, it was bit difficult to the, now you can basically visualize this starting material.

So, now we are here after this chopping of this diol, now basically what you need to do you just this ring will be automatically closed, because this is a hydroxy group and aldehyde group is their. So, lactol formation or hemiacetal formation, will take part with this, alcohol and this will get this OH. So, basically one carbon was removed by this diol chopping.

Now, see you do a oxidation, which will now complete the synthesis, as desired. This is the now the target molecule. So, as a initial drawing was a little bit wrong, you just try to get the correct structure of this particular starting material, which is now the this starting material.

So, eventually on this kind of functional group adjustment and a how this particular appendages are linked, will give you a clear-cut idea that, how the pathway can be eventually generated.

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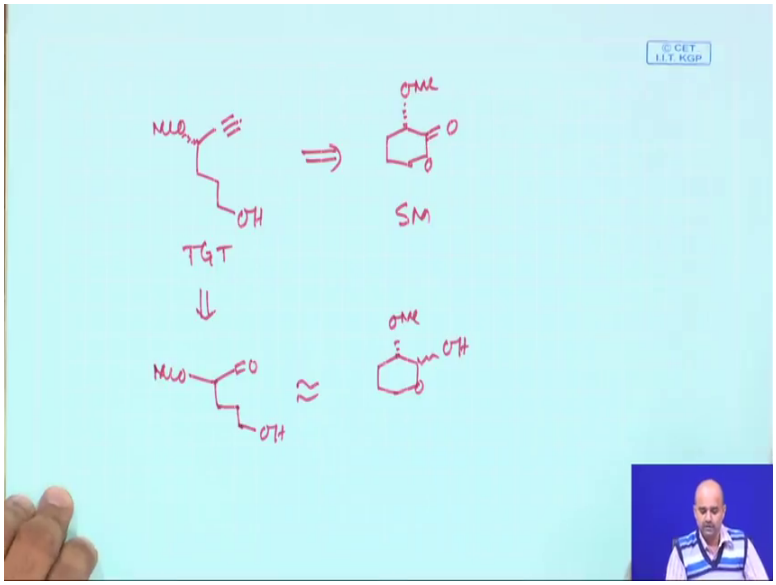

A similar kind of analysis will be now next doing, whether target molecule was you are having a alkyne functionality, you are having a methoxy here and, then you are having this 4 CH to OH group, we will just now give you the target molecule having CH2 CH2, CH2 OH.

This is the target molecule which was given to you, the starting material, was a lactone which was given to you, starting material. We try to count the number of carbon, this is a

1 2 3 4 5 the O methoxy is there, now in the target you are having 1 2 3 4 5 6. So, basically you need to introduce one carbon extra and, you trying to having a alkyne functionality act one of the terminus.

So, this basically gives you a some thought that, how this alkyne functionality can be created at one end? Let us take the starting material first and, if we try to do the target in this way, that we say this compound, we will write in a the different way, that 3 carbons CH2 CH2 is there and, you are having this OH and somehow, if you having a aldehyde functionality here, aldehyde functionality now this is, 1 2 3 4 5 which is execute the starting material.

Now, this kind of hydroxy aldehyde, normally do not exist as a linear form, they will seem to be occurred in this lactol form or a hemiacetal form. So, lactol is basically nothing but when it is open up, it gives you a hydroxy aldehyde. So, only thing is you need to know, convert a synthetic or you need to think about the synthetic transformation, where you will get a alkyne functionality, starting from a aldehyde.

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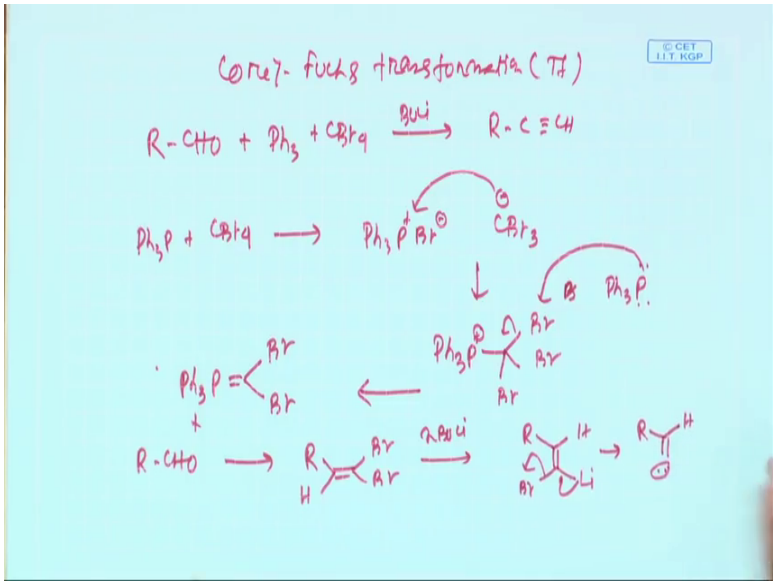

Now, for that we will talk about a transformation, which I am sure we have not discussed the transformation is basically named as, Corey Fuchs transformation is a basically named reaction. Corey Fuchs transformation is a unique transformation, the synthesis synthetic steps which you can think about, for this Corey Fuchs transformation you react

this thing with triphenylphosphine and CVr4, in pins of the aldehyde and, react with butyl lithium, you basically end up with this alkyne.

So, other transformation now we will be talking about, now how this reaction takes place. So, initially it is a wittig type of reaction, initially triphenylphosphine CVr4 react basically, give you Ph3 P plus Br minus and CVr3 minus is also generated. Now this CVr3 minus attacks to this, phosphorus positive thing and basically now, you are getting Ph3 P plus and this Br Br and Br.

Now, the remaining triphenylphosphine is there, and this triphenylphosphine is now attacking, to one of these bromine to give you a intermediate, which is now formed as a something like this. And actual in principal, this is nothing a wittig type of reaction, you remember in wittig case we treat with triphenylphosphine with any of these alkyl halide or alkyl bromide or alkyl iodide to get this kind of ylide, this is basically nothing the kind of a ylide, which you generate from triphenylphosphine CVr4. Now react with this aldehyde, with this ylide by a similar wittig mechanism, you basically will get this dye bromo species; means dye bromo normally was not isolated, to react with n butyl lithium. One of this lithium will be exchanged, with this bromine to give you the vinylic lithium species, now this vinyl lithium species on basis ideal, it basically try to react in this way, with the loss of this bromine, to give you a carbonyl kind of intermediate, where you have this negative charge.

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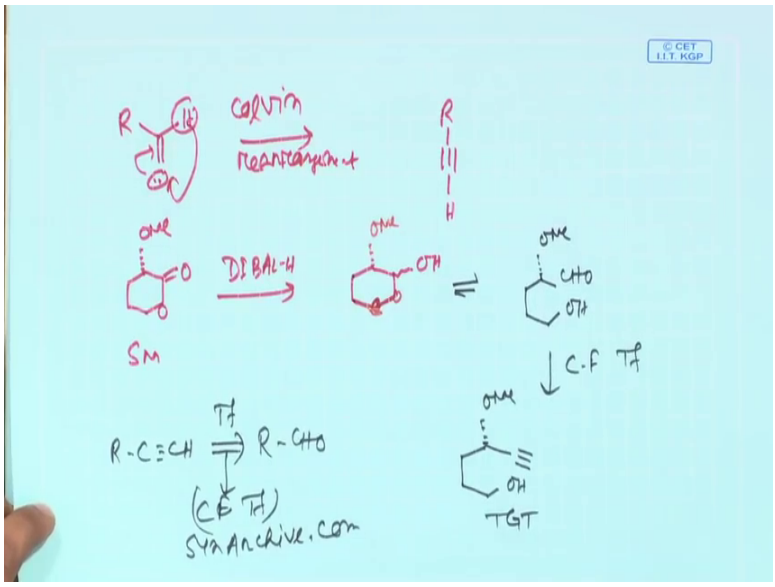

Now, this carbonyl intermediate we will then undergo a rearrangement, I will again draw this thing. This particular intermediate it is now try to give you a hydrogen migration and this rearrangement is named as colvin rearrangement, colvin rearrangement to give you a alkyne, which was the main reaction.

So, now try to figure it out the how this transformation can be carried out, to start with initial this compound which was giving to the starting material, first react with dibol. Dibol is a selective reducing agent, that will basically reduce only the lactone to lactol, the oxygen is here this is a carbon. So now, this lactol basically try to open it up, lactol is basically nothing it is a hydroxy aldehyde. So now, if this opens up you are basically getting this three CH2, CH2 CH2 CH2, we will have CH2 CH2 CH2 CH2 CH2 OH and this aldehyde.

Now, do the Corey Fuchs reaction, the Corey Fuchs transformation, which have just now discussed, basically now get these things as a alkyne and your CH2 CH2 CH2 OH. So, this is the target molecule we have initially set up.

So, in this transformation we will find that, a particular alkyne appendages or alkyne functional group, was introduced and the retro synthetically any alkyne of this kind of structure, you can basically construct from a corresponding aldehyde in a one-step transformation, by using a Corey Fuchs reaction or CF transformation.

Now, for little mechanism of this step, you can basically go to synarchive dot com, which we have told you in the beginning, that synarchive dot com will give you a list of name reaction and based transformation and Corey Fuchs is very important reaction. So, in this way basically, you can try to get access of a alkyne, starting from a aldehyde. So, will it keep on discussion of our appendage, based strategies or functional group-based strategies in next week also, until then we just study and go through the assignments, we will we will again catch you later on in the next week, bye.