A Study Guide in Organic Retrosynthesis: Problem Solving Approach

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Lecture – 24
Fg based Strategy based on Protecting Groups

Start coding.

Start sir.

So, welcome back students. So, basically we are discussing several strategies or several guidelines based on functional group based inter conversion.

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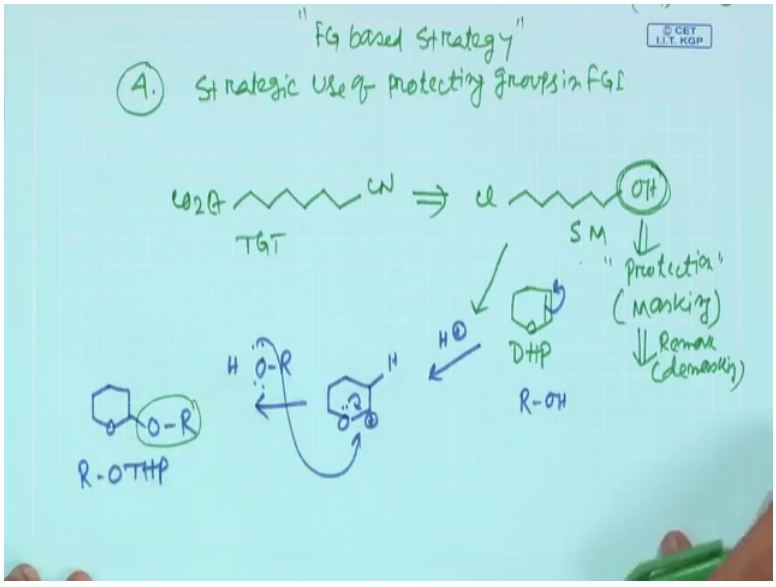

And, today, we will be trying to continue our discussion on functional group based strategies and here we will be trying to focus about our guideline – 4 and the guideline – 4, if you go back to our earlier lecture, it basically focuses on strategic use of protecting groups in functional group inter conversion. Now, in this subsequent lecture series we will try to emphasise much more on what are protecting groups then how this protecting groups will help you in designing a suitable pathway definitely as you say that our main discussion will be focused on different problem solving approach. We will try to focus on particular protecting groups and how this protecting groups will help us to design a efficient pathway. I set this particular compound which is having 1 2 3 4 5 6, 6 CH 2 or

methylene, one end is having CO 2 and CN this target molecule was given to you the starting material was something like this 1 2 3 4 5 6, I said if this chlorohydrin kind of compound one 6 this is given you the starting material and you have to basically prepare in this compound.

If you try to correlate the 6 CH 2 groups are similar in between, only thing is one end you need to have a CN and this end you need to having a CO 2 e t. Now, the straight forward way to solving this problem is basically, how you can do it? You can think about converting hydroxy to a cyano or converting the chloro to corresponding cyano and then converting this OH 2, but the main thing is this free OH probably is not comfortable with some of the reactions we will be talking about. So, free OH basically it is having a acidic hydrogen. So, you cannot use base or some other regions like you cannot generate a Grignard species from a free hydroxyl group, like I want to introduce this Grignard here you want to generate Grignard here which can be co inched with this carbon dioxide to give the corresponding carboxylic acid and then you can commit come of here, but the point is, if you have a free OH you cannot generate a Grignard because the Grignard will be immediately quenched by this alcoholic acidic hydrogen.

So, in those cases whenever you have a labial group labial functional group which can be easily reacted under acidic condition or basic condition or other conditions then you need to make this functional group as inert as you can. Now, inert means the functional group is active, you need to basically put some protecting group here. Now, that is why the need of protection group was failed or required. In reality protection group is basically nothing you are putting a mask or called a masking, basically, you are masking the alcohol functionality with a protecting group and once the synthetic transformation or FGI was done, you basically remove the protecting group which is also can called as a demasking. So, this terminology sometimes helps. Now, coming to this particular problem I said that is the alcohol is free, so, you need to use a protecting group.

Now, alcohols normally was protected as it is corresponding tetrahydropyranyl ether by a suitable reagent named as DHP now DHP is this reagent and DHP if you are having a react with DHP which alcohol in presence of a catalytic amount of mineral acid or paratonic sulphonic acid initial thing is you get a positive charge here. So, DHP in presence of acid basically gives a positive charge here, because this positive charge is stabilised by this oxygen and hydrogen is attacking adding here. So, basically is like this

you get a positive charge here now this positive charge is now quenched by this corresponding oxygen loan pair of this alcohol. The alcohol is now protected as it is tetrahydropyranyl ether is called R-OTHP. So, dihydro dihydropyran has now protected now this compound is basically nothing is like a cyclic acetyl. So, cyclic acetyl is a basically acetyl.

So, now your free alcohol is now masked and this compound is normally inert under certain conditions definitely, it will be clipped under basic condition. So, we will talk about some other aspects of protecting group, but before that we try to solve this problem which was given to us.

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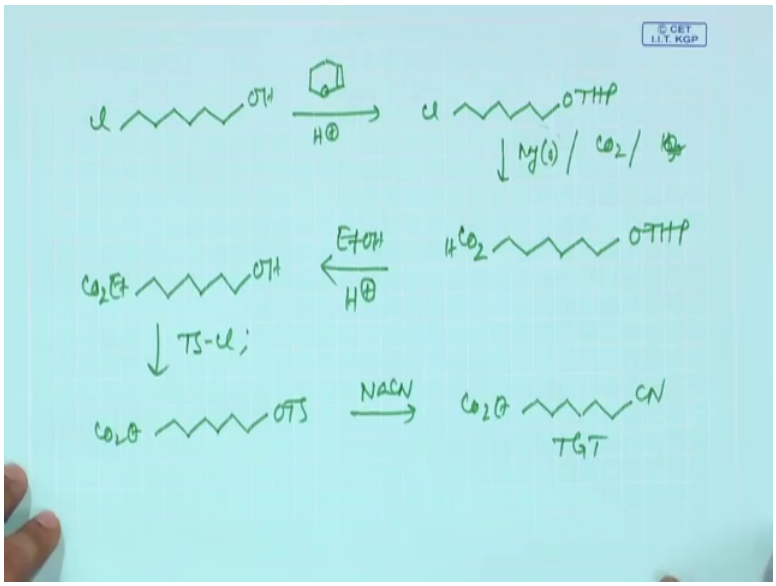

So, the initial compound which was given to you is a Cl 6 methylene between 1 2 3 4 5 6 OH we said is supported as a it is dihydropyran ostitate with H plus, we basically will get first it is THP. Now, we said will do the next FGI, we are doing a magnesium treatment, magnesium metal that will give you MgCl then you react with carbon dioxide followed by H 3 O or simple H plus treatment that will basically give you a CO 2 H means initial magnesium chloride reacts with carbon dioxide it remain similar. Now, next your carboxylic acid needs to be converted to the corresponding ester which was required.

Now, you react with ethanol and H plus strong H plus. Now, this strong H plus will form a ester bond with this acid as well as will remove the THP. So, basically what will get you get CO 2 Et in between 6, 1 2 3 4 5 6 OH. So, THP is now removed, free alcohol is

now demasked. So, only thing is for Grignard reaction the free alcohol was not recommended that is why we protect it as which is corresponding to THP ether. So, next what we need to do, you need to convert this alcohol to its cyanide. You can basically do it by standard as in to reaction treat with tosyl chloride first. So, you will get simple SN 2 displacement you get tosylate ester and react with sodium cyanide, you get the corresponding CN, this is your target molecule. So, only thing is the free alcohol was not recommended that is what you are using a protecting group chemistry. Now, the point is protecting groups are always not recommended because if you are trying to use a protecting group your synthesis would not be stay economic because 2 steps you are adding extra.

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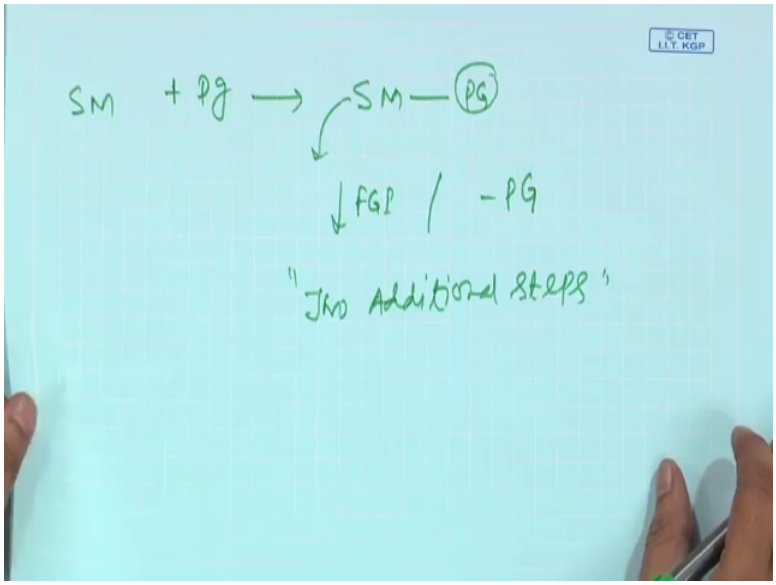

First, you have to add your protecting group to the starting material to get a starting material with a protecting group as a coherent attachment, then you do some reactions here do some FGI and then finally, you have to remove the protecting group. So, two additional steps are often required in any protecting group whenever is used in your electro synthetic pathway, that is basically the main drawback for protecting groups, but never the less protecting groups are widely used. Widely used because you will find that sometimes the target molecule. So, complex and it contains multiple functional groups which is having similar activities, we will discuss some activities little bit later on.

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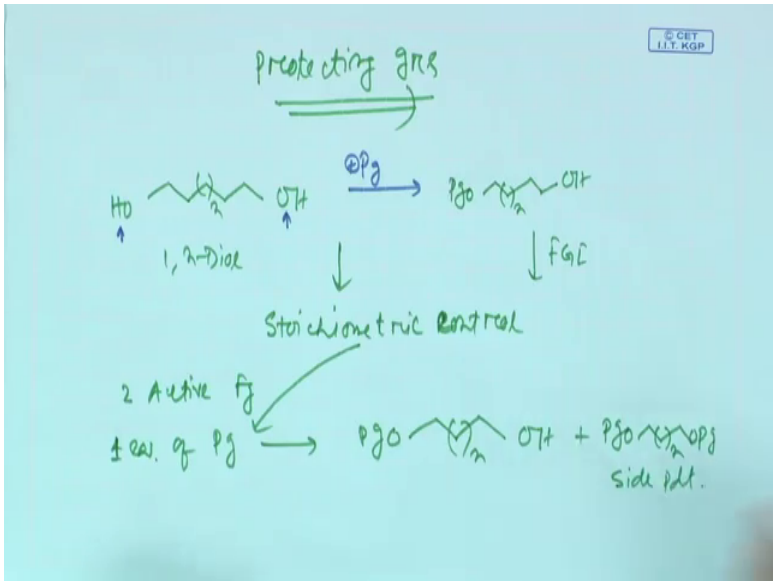

Before that, we will try to use a general conceptual analysis how protecting group have been dealt with. In reality, I will give a compound something like this I say you are having a 1, n diol one n diol and both the alcohols are having similar reactivity because both are primary alcohol having similar reactivity, but selectively you want to use FGI on these end by keeping this an intact, then basically you need to use a protecting group by masking here. So, basically what will need to do you can use a simple protecting group by masking this end then you do remaining FGI whatever is required in your synthetic transformation. Now, the point is a both the groups are having equal reactivity how we can selectively put it with one functional group. Here, basically you have to use a stoichiometric control means that, as both the groups are equally reactive you are having 2 active functional group 2 active FG.

Now, use one equivalent of Pg or the protecting group. So, make sure the Pg basically blocks one end of the active functional group remaining one end remains intact. So, this stoichiometric control builds your 2 equivalent is the 2 active part and you are using only one equivalent. Sometimes definitely you are having little bit of di protected compound as your by product, that is a side product. But, nevertheless this kind of reactions are very useful and if both the protecting groups or both the functional groups are having equal chemical reactivity like this case you are having both the case primary alcohol.

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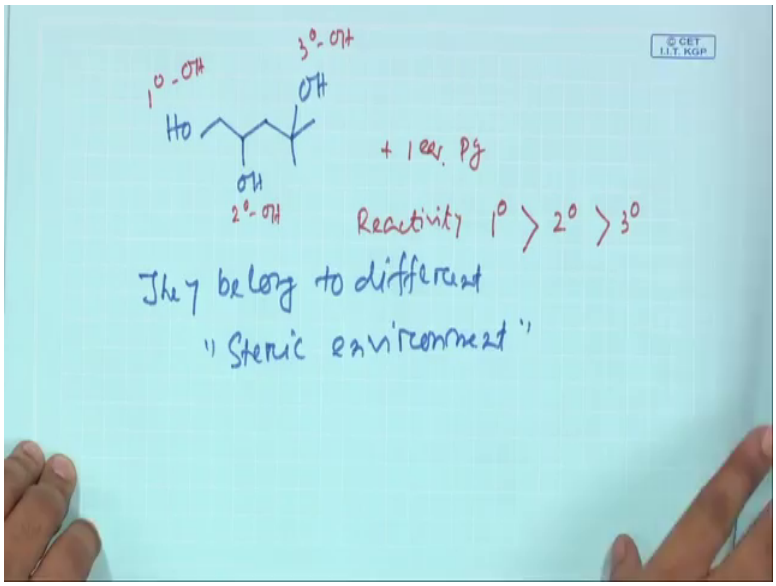

Things will be little bit simplified if you are having a compound like this. I will give you compound, let say, now this compound if you see this compound is having 3 active functional group, is a 1 degree alcohol, 1 degree OH. This is a 2 degree OH and this is a 3 degree OH. Now, 1 degree alcohol are sterically less crowded, 2 degree little bit sterically crowded, but not as like 3 degree and 3 degree alcohols are sterically highly crowded.

So, in principle if you use 1 equivalent of protecting group, the reactivity pattern or reactivity is one degree will react first then 2 degree, then 3 degree. So, if you use one equivalent protecting group first primary will be reacting first and then if you use another protecting group you have a now 2 free either secondary or tertiary. Now, I said secondary is sterically less crowded then the tertiary. So, next protecting group will attack the secondary and then tertiary will be effected. Now, depending on which functional group you want to use in your next FGI, you can basically selectively tune that which protecting group you can use. If your 3 functional groups are having similar environment like all are 3 are primary they you have to choose stoichiometric control and if the protecting groups are different like one is primary, one is secondary, one is tertiary their steric environment is different they belong to different steric environment and in those cases you can basically control it to the steric crowding. As I said the primary alcohol is protected first then secondary then tertiary.

So, we will try to figure it out the some of the chemistry of the protecting group and we are not going to do a very general discussion during the problem analysis whatever protecting groups are coming to our discussion will talk about only those protecting groups

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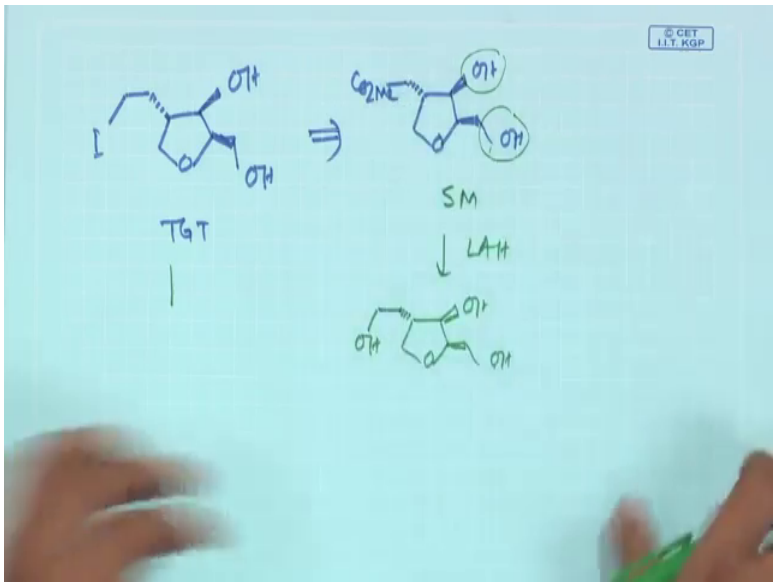

So, next problem which was given here is basically a target molecule is given to you having something like this. Now, if you see this molecule is basically a target molecule was given to you and the starting material which was also supplied to you is now, this is a very it looks a very simple transformation. What you need to do? You need to really do the CO 2 Me and CH 2 CH 2 I, if you reduce this CO 2 Me it will give you CH 2 CH 2 OH. Now, this primary alcohol you can easily convert to it corresponding iodo by apple reaction the point is there are other OH group in between.

So, if you just simply react with a lithium aluminium hydride, what we will end up? You will get OH, CH 2 OH, CH 2 CH 2 OH. Now, there are 3 hydroxyl group; 2 primary, 1 secondary and selectively your target molecule contains only one iodo group at this primary. So, it is very difficult scenario you cannot use simple apple reaction because then this will be also reacting this also may react, but this is primary and secondary probability is less, but this will be definitely not that much chemo selective. The only solution you are having that in the initial part if you can protect this primary and secondary by some selective protecting group and then do the reaction here.

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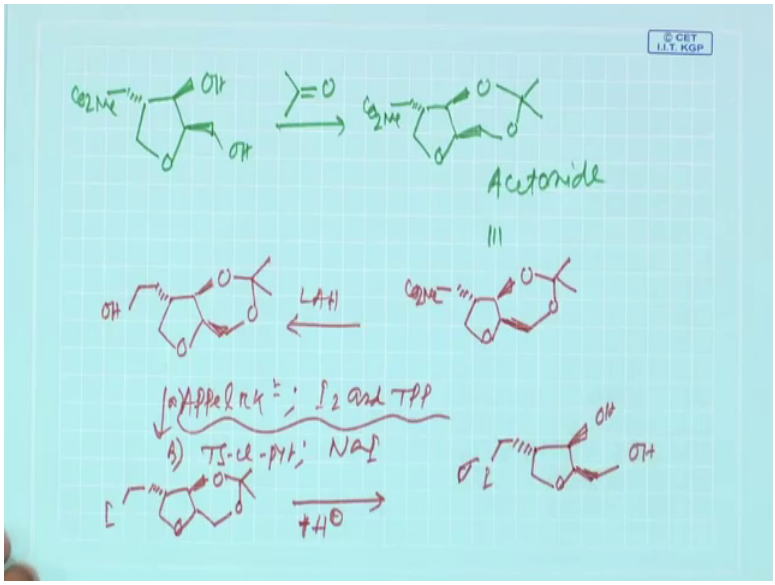

So, the solution which will now provide is, based on something like this; you have a primary hydroxyl group, you have a secondary hydroxyl group and this part you know through the reaction. Now, the primary and secondary this is basically diol this is come, but 1 2 3 is a 1, 3 diol. Now, your job will be quite simplified if you have a single chemical reagent which can protect both the primary as well as secondary will be using a reagent very simple acetone. Now, acetone as I know as you know all of you know acetone can easily form ketals with 2 equivalent of alcohol. Here, the 2 equivalent alcohol; one is primary alcohol, one is secondary alcohol.

So, what acetone will do? It will basically forms the cyclic ketal which is now named as acetonide. It is named as acetonide in terms of chemical terminology. It is basically nothing is a you can write this as acetonide structure in little bit more convenient way which looks much more easier is basically in reality say 6 member thingm now get the 6 member thing and then your this part remains.

So, what strategy you have observed here we basically use a one equivalent of chemical reagent which can react with the secondary as well as primary and then use LAH. LAH would not affect this acetonide protecting group. So, basically you have to make sure the protecting group does not affected by the reagent which will be using for your FGI. So, get the reduction and then next you do a apple reduction which you have discussed many a time apple reaction you basically use iodine and triphenylphosphine or eventually, if

you do not use apple reaction you do it a different way, you can do either apple reaction or you can do a tosyl chloride pyridine and then you can use 2 step sodium iodide that also will give you your iodide thing. So, now, you are get iodide your acetonide protection will be remain here next you just need to remove this acetonide by treatment of H plus.

So, next basically what will get? You get this part will remain similar and the alcohol will be now as it is and your acetone will be removed. So, we have used a acetone as a strategically protecting group to mask the primary hydroxyl as well as secondary hydroxyl. So, that these 2 hydroxyl group remain inert during our functional group transformation. So, in this way particularly you will be using several protecting groups and our next example will be focused on a similar kind of protecting group.

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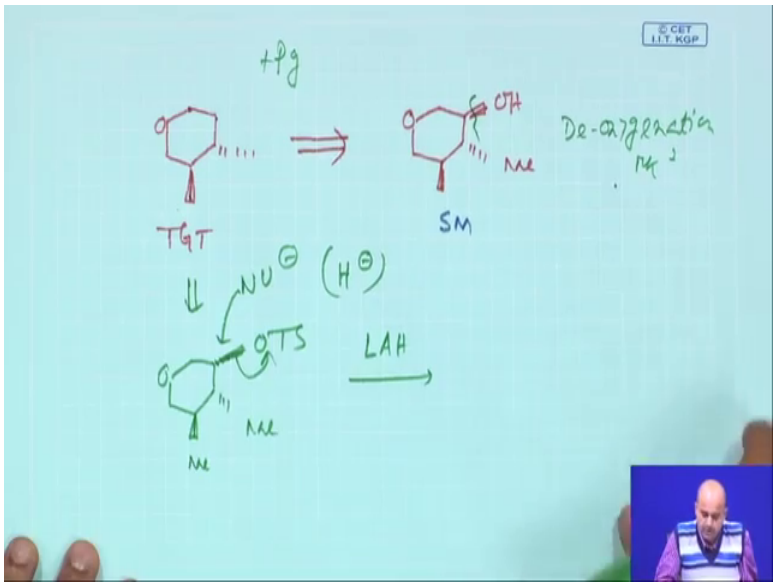

And, they are will be using some other chemistry you will just to observe how we will do it. We say target molecule is something like this and the starting material which was given to you now, the initial target is basically does not have a active functional group it is having a oxygen ring or tetrahydropyranyl ring is having a 2 methyl untie to each other.

The starting material which was also supplied to you having a alcohol functionality here. So, this alcoholic you can remove that will basically give you the carbon hydrogen. So, basically in reality you need to do a deoxygenation reaction which was basically required

from you. Now, as I said we will be using a protecting group based chemistry. So, deoxygenation this kind of reaction will be discussing when you talk about redundant functionality. So, for the time being will be using a different strategy. What will be doing the retro? The retro now will be based on a very conventional classical retro. We will say that will try to bring some functionality here based on this alcohol. We say that OTS- O tosyl; tosyl is a very good living group fine and if you can replace this OTS through a suitable living group now here you need to do a this as I said it may undergo nucleophilic displacement reaction. Now, if you bring some nucleophile here it goes off, is a very good living group.

Now, what nucleophile we have to use here because you need a carbon hydrogen bond. So, hydride might be a good nucleophile and we all of you know that lithium aluminium hydride is a good source of a hydride.

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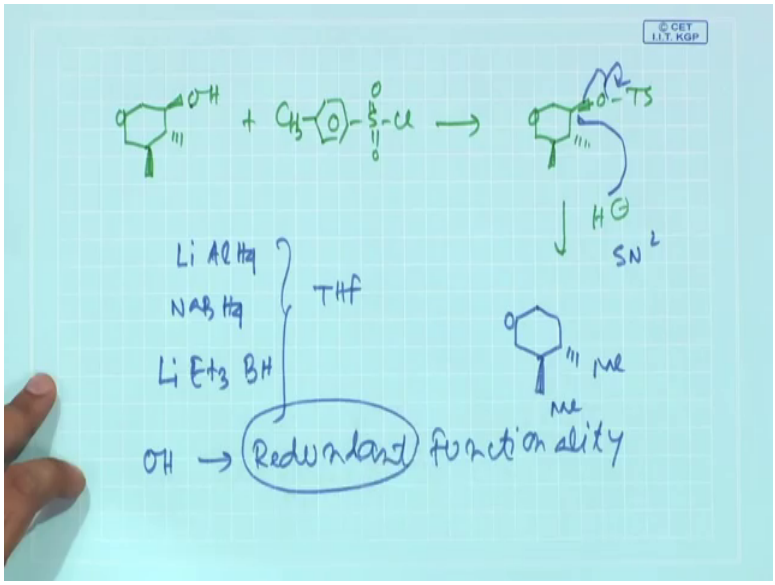

So, eventually your forward pathway will be now having the chemistry which is now we can formulate in this way. So, you are having this OH you react with tosyl chloride is this compound Cl and actually by reacting with tosyl chloride the alcohol is basically protected. Is it not? The alcohol is protected. Now, what you do? You put a H minus this H minus basically attacks to this tosyl and it goes up, entire tosyl goes up and basically you get a methyl, methyl using SN 2 reaction. We basically using a hydride source of nucleophile and this is also very nice demonstration. Now, if you cannot you can use it

very source of nucleophile, you can use lithium aluminium hydride, even you can use sodium borohydride as a hydride source, you can use super hydride lithium triethyl borohydride. This is a very good hydride source and in general, the solvent was chosen as a THF you can use it.

Now, in terms of another useful conceptual analysis this hydroxyl group is now termed as redundant functionality, because the target molecule the functional group hydroxyl was not required, but it was introduced to being a hydrogen-carbon bond and the those kind of functional group which was in reality not required in the final target and has to be removed prior to access the target molecule is named as redundant functional group or redundant functionality. We will explore this redundant functionality little bit later on.

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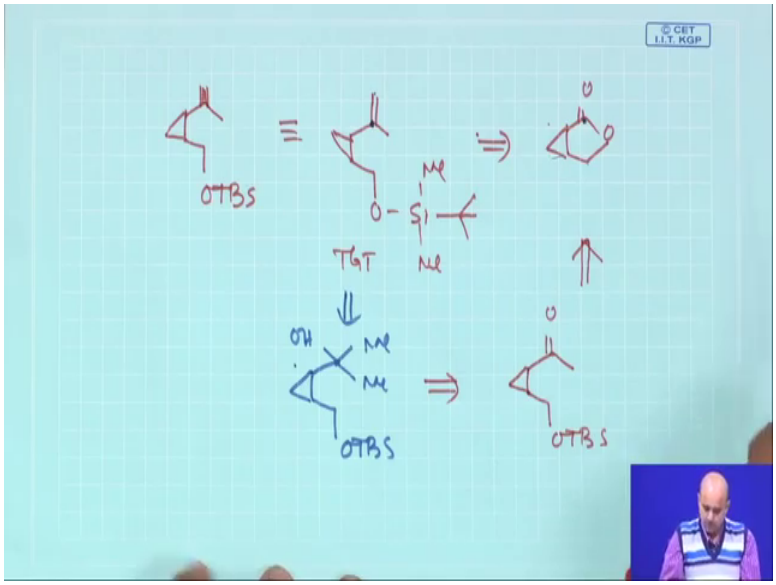

And so, in continuation of this protecting group chemistry will now try to give you a very simple problem. Now, this is basically a double bond, this is double bond will again rewrite the structure. You put a cyclopropane here and is OTBS, TBS is basically a alcohol protecting group which is tertiary butyl dimethyl silyl.

The starting material which was, this is a target molecule, the starting material which was given to you, this lactone. Now, if you see the cyclopropane part was there, cyclopropane part was there. This part is CH 2 O protected CH 2 O. Something you need to introduce a extra group extra group here you need to do introduce, that is the only thing. Now, how many carbons you need to increase? You need a basically one carbon is already there,

you need 2 extra carbon. If you try to go back the retro pathway, we say that this compound can be prepared starting from if you have this tertiary alcohol you can simple do a elimination reaction. If I say this compound can be easily prepared if you have this compound is fine and then now I say this will try to correlate with this. Now is lactones this is ester basically lactone or ester if you react with 1 equivalent of methyl lithium it will give you ketone.

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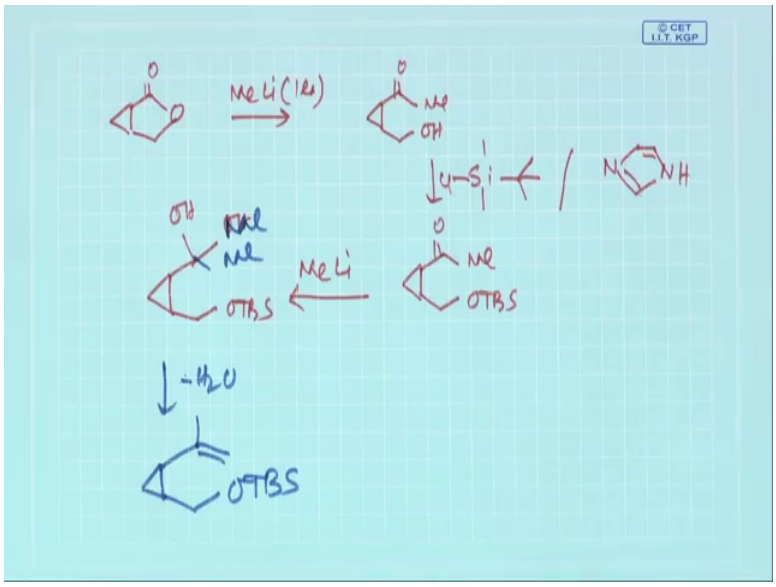

Now, we will try to explore the entire synthetic pathway. We basically having a lactone here, we react with one equivalent of methyl lithium and you say initially you will be getting this methyl and CH 2 OH. Now, this CH 2 OH needs to be protected that is why I put a TBS group, this is Cl and tertiary butyl dimethyl silyl chloride. This reagent which was used as protection purpose is a base which is basically a imidazole which was used and you will get this as a OTBS and CO Me. Then you use another equivalent of methyl lithium, that will basically give you OTBS is there and you get this tertiary alcohol OH sorry this is the methyl part the methyl remaining methyl.

So, actually you basically need to protect this CH 2 OTBS to make sure that this methyl lithium is acting as a base. So, whether the this base can do some disturbance here that is why this free alcohol need to be protected now here you can basically convert this alcohol to this corresponding tosyl or mesylate or just do a simple water elimination may it tertiary alcohol. You will find that you get the target molecule quite easily.

So, basically by simple using of properly chosen protecting group, your synthetic pathway can be very nice and very demanding. The only thing is your protection has to be completed and you need to remove the protecting group at a proper stage. So, 2 extra stages basically you are required.

We will continue our discussion based on the protective group chemistry when you come back in the next week, trill then, goodbye.