A Study Guide in Organic Retrosynthesis: Problem Solving Approach

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Lecture - 27
Fg Group based Strategy

So, welcome back everyone.

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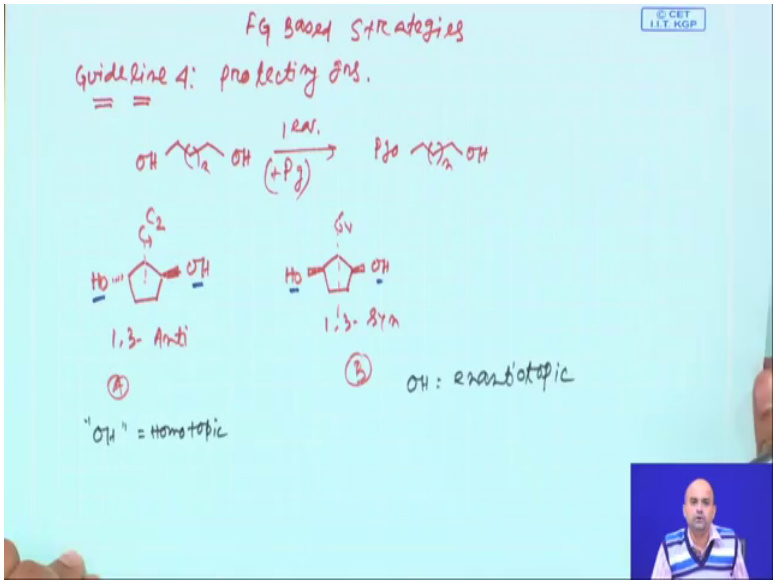

We were basically discussing functional group based strategies for a given target. And we are basically following 6 different guidelines and the last couple of lectures we talked about this guideline 4 which you said that there are several strategies where you need to use protection and de protection.

So, if you are having a some chemically labile functional group which needs to be protected, you do that protection with suitable protecting group and then do the FGI with the remaining functional groups and then at the end of this synthetic strategy; you just d block or remove the protecting group.

Now, we are already said that if you having a two equally reacting or equally reactive functional group; you can basically use a one equivalent of protecting reagent which will selectively protect one end or one particular protect functional group and this is basically you can do a stoichiometric control.

Now there are situations where you might have a difficult scenario. If you remember the last week we talk about the some molecule where you are having this situation are giving a molecule where the stereo centre of this molecules were actually given; that this OH is basically 1, 3 and anti. So, this two H are 1, 3 anti and this molecule is basically inertia pure.

Now, there are another isomer for this molecule another stereo isomers or find that the structure is this molecule is a anti as I said this is 1, 3 syn or sys. Legacy the right hand side molecule will not be having chirality because is a having a mirror plane of symmetry sigma V, but this molecule is chiral, but this molecule we said is having a C 2 axis of symmetry.

Now, we explain that when you are trying to do the protection of this kind of compound; this kind of compounds are very good building blocks for synthesis of natural products or other molecules. Now said compound A and compound B. As a compound A there are two OH OH 1, OH 2 and compound B also there are two hydroxy groups.

If you remember last week, we said that if you have this kind of compound where you are having a C 2 axis of symmetry the OH group or the similar kind of functional groups will be homophobic. So, now I say these two groups are homotopic; now homotopic means they are basically equivalent equivalent. And for this group as they are related with the molecular symmetry are, now enantio topic.

Now what implication this topic secure homotopic enantio topic will lead you for the protecting group chemistry; we will now demonstrate with this particular example.

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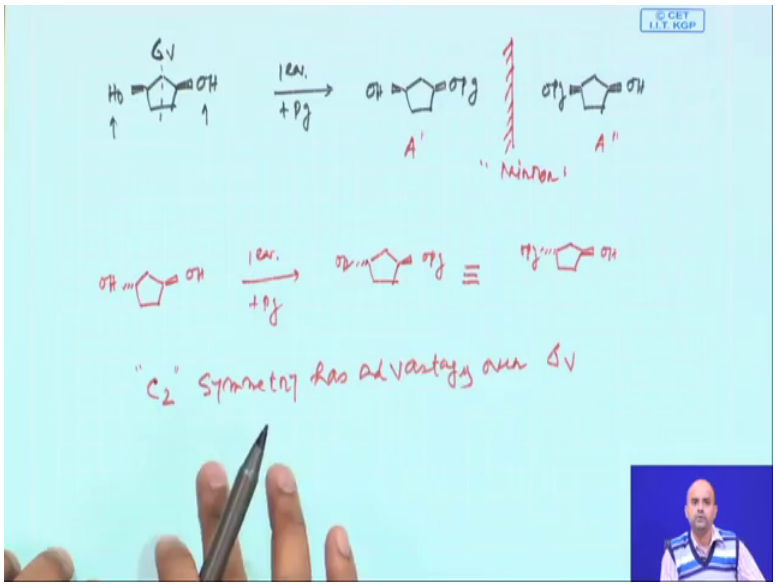

Now, say we will take this particular compound, the second compound which is having sys relationship with this to hydroxy group and we say this molecule is having a sigma V

Now, what is it we will be doing a one equivalent of protecting group. Now a principle this protecting group can come here as well as can come here. So, let us first see that if the right hand side OH is protected, you basically get this. And now if the left hand side is protected you get this compound.

Now, what you do? You basically put a mirror and then you see these two compounds are now enentiomers to each other. That is why I said these two hydroxy groups of enentio topic and as this two groups are enentio topic selective protection of any of this group over the other, we will need you an enentiomers.

Say compound a prime and compound a double prime are basically enetiomers to each other. Now in these cases if you are not careful about these particular aspects if you do some protection of this starting material; you will basically end up with two enantiomers. So, you need to be very careful, you need to be very careful.

On the contrary and the other example which we have earlier expressed or explode if you take this compound; this will be basically leading you only one compound. And the in principle if you have this pg and this OH this compounds are essentially equivalent

same; that is why always C 2 symmetry; if you molecule a C 2 symmetric; C 2 symmetry has advantage and advantages over sigma V.

And happen there are many times; your starting material or your intermediate order p concert having C 2 symmetry. We will be discussing particular this points or we talk about stereo chemical strategies between later part of our discussion.

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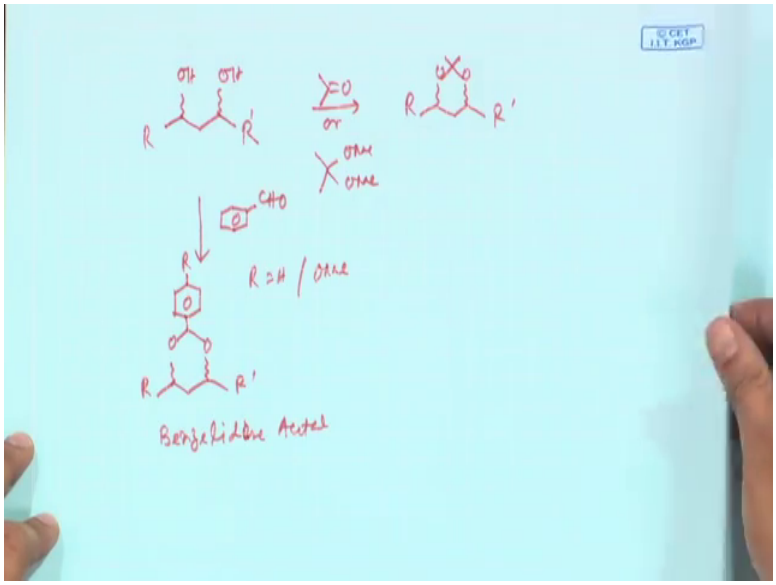

Now, in continuation with this a protecting group chemistry; next we will try to figure it out how 1, 3 diol of this kind of compounds can be selectively protected.

Now 1, 3 diol we have we have already talked that you these compounds you can be easily protect with the help of corresponding acetonite by making its acetonite derivative when you treat this compound with acetone or a two two rimsoxy if open which is basically ketalog acetone to do a trans ketalizational reaction its fine this already we have exported.

Now there are other ways you can protect this compound, you can do a simple protection of these compounds by making corresponding bengaline acetyl. The chemistry is basically similar instead of your acetone you are now using a benzyl dehide as the main reagent or that is called bengilidene acetyl; bengilidene acetyl. Even you can take another aldehyde where R could be anything.

If R is H you get the bengilidene acetyl if R is OH methoxy you get the parameter of bengilidene acetyl. Now this acetyl, this acetyl is a good protect invoice is absolutely fine no issue, but normally as I said the acetyls are basically acid labile and then if your reaction conditions are strongly acidic or even a let will be; the acidic the acetyl tend to open it up.

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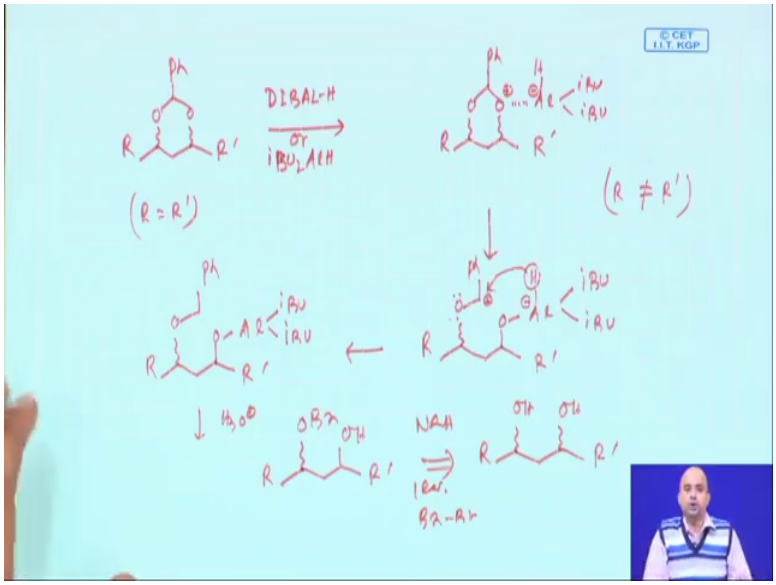

So, these acetyl you can basically do some different protection by using; you take the classical take this acetyl I said Ph and then subjected to a reagent which we already talked let us say DIBAL di isobutyl aluminium hydride.

Which is basically a bulking reagent; bulky hydride source; now if you subject this acetyl with the DIBAL or what should happen? DIBAL is basically a loose acid loose acid. So, you will find that initial stage; this DIBAL will be now we say that R equal to R prime means this two groups are equivalent.

So, we will talk about this symmetrical acetyl then we are saying that this loose acidic side of oxygen is going to coordinate with this DIBAL and this isobutyl iso butyl and you have a negative charge on this aluminium fine. Now as I said R equal to R prime there is absolutely no issue.

Sometimes it happen R and R are not equal or there is a huge stage differences. If R is pretty bulky pretty bulky then your initial coordination will takes place this side. If R prime is pretty bulky the initial curvature will take part in this side.

We will have some example when you talk about a non symmetrical residual how they are clipped with or how they are treated with DIBAL and what exactly happens.

Now once this initial coordination takes place next basically this particular bond is kind of polarized and you will find that it will open up in this way to give you a benzyl kind of cation. As all of us know that benzyl cation is quite stable so benzyl cation will be generated here. If R equal to this phenyl; it could be simple benzene ring or it could be paramethoxy phenyl.

now this is benzyl cation which is basically step by this by this phenyl the ingredients as well as this oxygen lone pair. Now, this hydride from this DIBAL is not transferred and now you see; you are basically now getting a the benzyl derivative; benzyl derivative of one of the alcohol.

And now just simply clip this aluminium oxygen bond by some hydrolysis and then basically we will end up with OBn. Now this is basically a simple mono protection of a 1, 3 diol

But without using a base and sodium hydrate it principle this reaction also you can do, if you have this diol by using sodium hydride and one equivalent of benzyl bromide which you earlier said that if you have a similar kind of functional group, which you are chemically equally reactive you can do it.

(Refer Time: 12:59) If the base is you are not using you can also have the same kind of protection by using a different region system you make the bengilidene acetyl and actually this kind of 1, 3 diol, when these are not symmetrically substituted; you can basically basically protect them with the help of bengilidene acetyl or corresponding paramethoxy bengilidene acetyl.

And then cleave the acetyls in presence of hydride donor like bulky hydride donor DIBAL and you get the unsymmetrical opening, the mechanism which we have just now shown here. So, our next problem is basically based on that.

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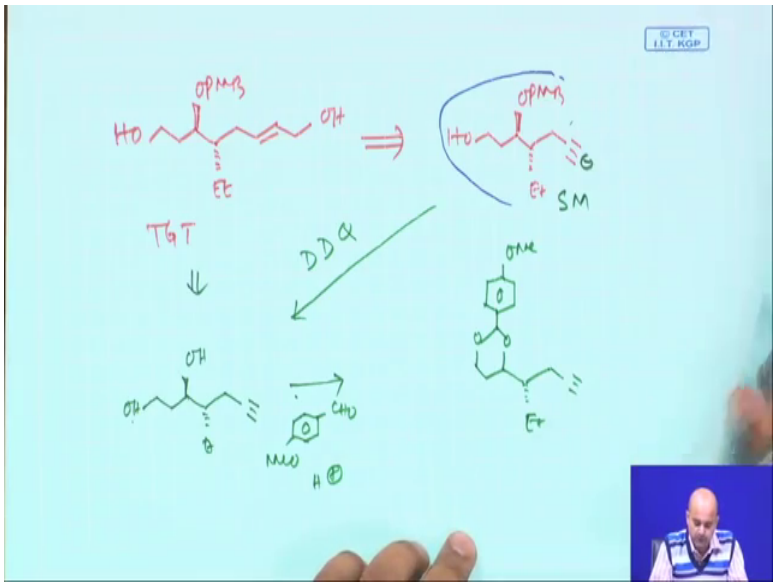

The next problem which I am going to talk about the target molecule which was given is having this structure. If you are doing a purely functional group based analysis, you see that this compound one and having a hydroxyl, one in having a hydroxy. So, there at many hydroxy free hydrosphere there in the target molecule.

So, definitely if you are doings FGI this hydroxy group should not be free; should not be free. The starting material which is also given to you is something like this which is supplied to you that this ethyl is there and basically you are having a triple bond.

So, if you now closing the analyze; this part of this molecule is exactly the resembles with this part. So, only thing is you need be day one carbon extension here with basically you can do by simple chemistry you can generate this an ion here and treat with formaldehyde then you can read with this double bond.

So, now, do the simple straightforward retro. And also you need to protect this; this hydroxy group as well as this hydroxy group. Now we say that if you have this intermediate which is something like this; you will be having a very easy job class symbol their molecule.

Now what is this? This is basically close it is related with the starting material when the starting material you are having a secondary hydroxyl group is protected. Now we take this compound; now this compound is basically what this computed having primary

hydroxy and secondary hydroxy. So, is a 1, 2, 3. So, it is basically 1, 3 diol; 1, 3 diol one is primary one is secondary.

Now, we will; so, initially we take this starting we take this starting material PMB group you can (Refer Time: 16:02). Last class you talked about you can just treat with DDQ; you basically come to this diol. Now if you see this compound we now reacted with tablet paramethooxy benzyl dehyde in presence of H plus.

So, now, you see this is oxygen; this is oxygen so basically we will be having this paramethooxy bengildene acetyl. So, now, here you are having this ethyl group and then you are having this alcohol. Now if you see the earlier one this is basically a non symmetrical acetone, because this group is having a bulky group and this group is having only hydrogen. Now if you; subject this acetyl will again write this acetyl in the next page.

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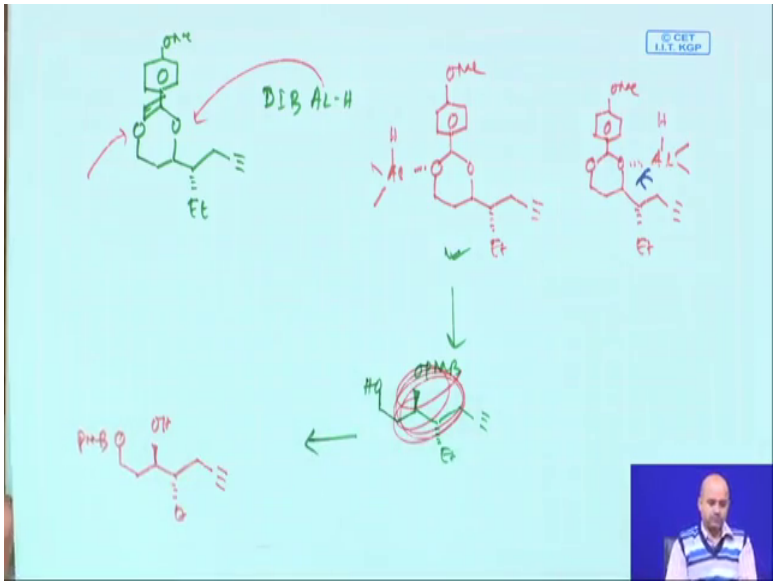

And then we will see how this acetyl will react methyl group is there now you say sorry this acetyle will now this is basically the o n e this is now reacted with DIBAL DI BAL.

Now this is a bulky reagent this aluminium will tend to coordinate this with side or this side. May be you find it statically this side is too much congested where this side is not. So, what will be happening? Your initial coordination will expert in this side aluminium

your hydride is here and your isobutyl group is there. Now this side coordination I said is satirically much more favourable.

You can have another coordination on that side which I am also writing for your better understanding; aluminium hydride isobutyl isobutyl. Now you see this side is absolutely crowded because you having a very bulky group. So, this is absolutely crowded that is why this is the main product which will be formed. And as this is formed now basically your similar kind of mechanism how these acetyls are opened up; once it opens up you basically generate now this compound. The stereo chemistry we did not mention, but will be remain same this part will be your OPMB; PMB is parametoxy benzyl.

And then your ethyl is here; so, this is the initial molecule which you can get after this acetyl cleavage; you will not get this side you we will get this side because this acetyls is a symmetrical e; it is not symmetrically substituted is basically unsymmetrical.

So, next your synthetic scheme what is the next you will be doing? You now see you will having a typical this no; we are little bit wrong here sorry your acetyl will be opened up on that side; your acetyl will be opened up in CH 2 OH 1 1 minute yeah. So, we are basically your O CH 2 yeah. So, you will be now getting this o this OH ethyl yeah OPMB.

So, this things; you basically now got and then what next is required? What next is a required from you?

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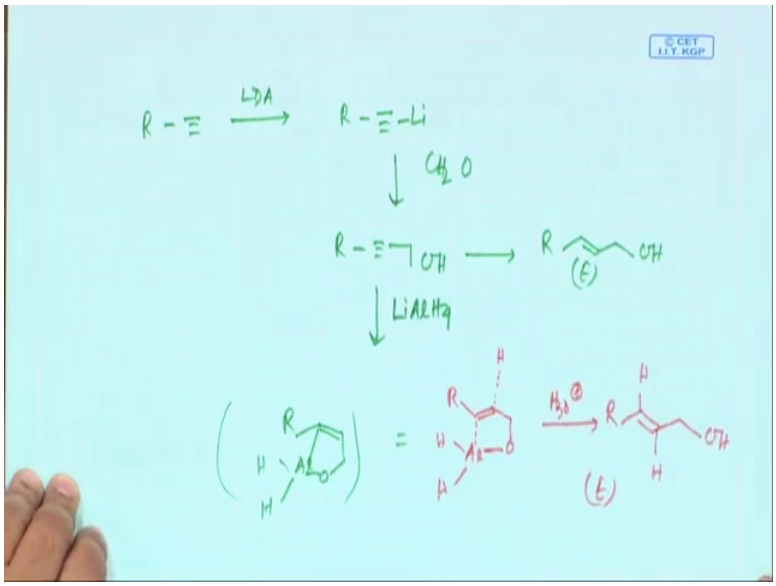

Is you just do a, you have a triple bond compound. So, you subjected to a base normally LDA is preferred. And you will find that the triple bond will the acidic hydrogen will be now given the acidy light.

And these acidy light you can basically quench with formaldehyde, you can basically get this corresponding propargyl alcohol. This propargyl alcohol; that the two way the final product which we have seen it is basically having this E geometry; E geometry.

Now this is a very important reaction; if you subject this propargyl alcohol with lithium, aluminium hydride we basically end up with this e E geometry of this particular double bond and you just subject this propargyl alcohol with this aluminium thing; the reaction is supposed to be takes place in favour of some of this cyclic alien kind of intermediate or you can write in a better way just change this intermediate yeah hydrogen hydrogen.

So, basically initially lithium aluminium hydride will transfer one hydrogen from here. And then this oxygen basically with basic side it will coated with this aluminium and then it will it is giving this cyclic aluminate ester and now, this carbon aluminium bond; it will basically hydrolyzed it will be hydrolyzed by whatever electrophile you can use; you can just use simple water because you need two hydrogen.

Now see this hydrogen is already here and so, this carbon bond and this hydrogeneretic trans to each other trans to each other. Now this bond cleavage will takes place if you do

a aquas workup, you basically end up with this aloylic alcohol where this hydrogen are E E or trans to each other with to the.

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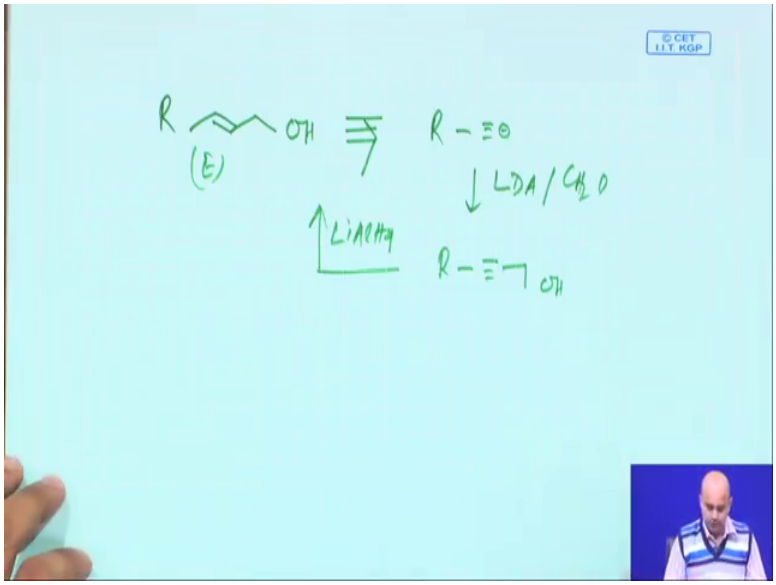

In principle the last reaction is also a very important reaction. If I give you a some retro something like this that how you can make this molecule with a triple bond. So, you can basically start with this triple bond using a base; we generate acidy light and react to it formaldehyde to get this propargylic alcohol.

Now this propargylic alcohol you react to it lithium aluminium hydride to give you the E aloylic alcohol. And this is a very simple and straightforward reaction which will solve your problem.

So, this kind of functional group assembly and this kind of particular selective protection and the protection of this acetyl cleavage which the problem which we have just explained; gives you a nice demonstration and how this protection group can be can be easily created and then you do the FGI and finally, this protection groups needs to be blocked.

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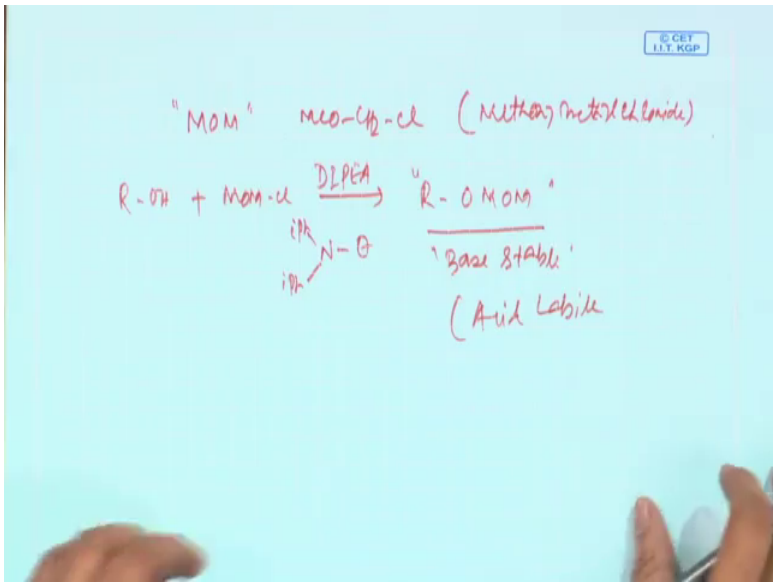

Talking about another simple protection group, which is abbreviated as MOM. MOM basically stands for this compound methoxy methyl chloride methoxy methyl chloride is basically a ether, you take the corresponding alcohol, react with this MOM chloride with a base.

Normally base which is preferred deeper which is this structure di isoprophile ethyl amen isoprophile ethyl amen or a unique base and get the corresponding MOM ether. MOM ether are exceptionally stable in base; exceptionally stable in base base stable, but they are very labile in acid we have base stable.

But they are acid labile acid labile. So, next one we will just discuss similar kind of problem where you can use this particular concept.

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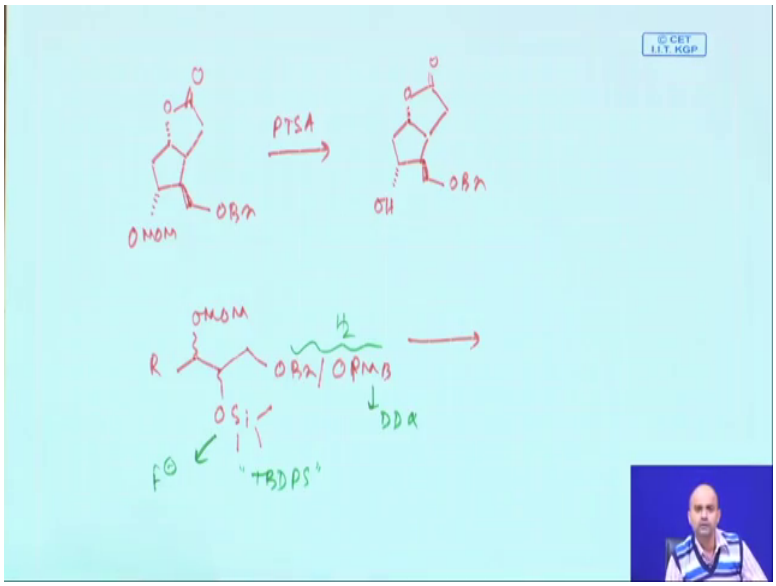

I will say we will be having a structure something like this bicyclic keton. And then I say you have to convert this compound is a MOM and you say benzyl. Now we said moms are usually labilin MOMs are usually labilin acid. So, if you see the other protecting movies is a benzyl and you have a lactone.

Now lactone can be in principle clip by acid, but you need a stronger acid condition. So here if you use a very mild acidic condition like rare paratoral suphonic acid, you can be able to selectively cleave this MOM group for the benzyl group will remain; unaffected remain unaffected.

Even if you are compounds having a MOM group; let us say then you are having a silicon containing group any silicon containing group, then say you are having a benzyl or the PMB containing group. Now here you have to see whether these 3 groups are orthogonal to each other or not.

Now silicon silicon can be easily cleaved by provide source other two groups only touched. Benzyl and PMB; PMB can be cleaved by DDQ others groups will not be affected. Benzyl and PMB boat can be cleaved by hydrolysis with simple hydrogen palladium charcoal other two groups were not affected.

Now, there if you having a MOM and TBS or this; TBS is also acid labile, MOM is also acid labile. So, then there is a little bit difficulties, but in the seloil group if we having a

TBDPS which is not acid labile, you can easily control the selective removal of MOM impedance of TDB place. So, this kind of orthogonal strategy we will find a very interesting and we will discuss those strategies little bit later in the next week. So, till then have a good time.