A Study Guide in Organic Retrosynthesis: Problem Solving Approach

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Lecture - 26
Protecting Group based Strategic Disconnection

So, students welcome back we will basically discussing several strategies and our main focus is how you can use a particular protecting group based strategies to functionally manipulate a given target molecules.

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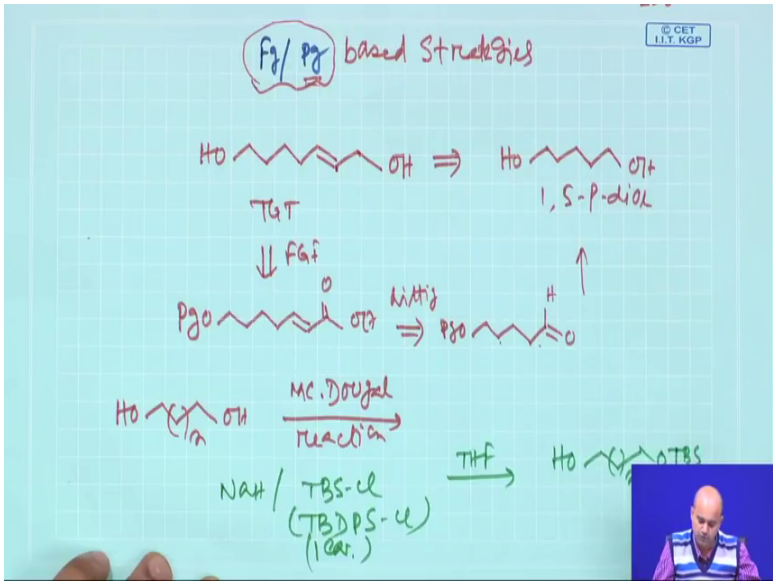

And if the starting material is given how your strategies should look like; we are trying basically focusing on functional group and Pg based strategies Pg stands for protecting group

Now, this particular lecture will try to emphasize couple of problems which selectively deals with a; if you have a target molecule something like this and I will give you a starting material 1, 2, 3, 4, 5. So, I say I give you this target molecule and the starting material is 1, 2, 3, 4, 5; 1, 5 pentene diol 1, 5 pentene diol now you have to see what do you exactly to do?

You just need to put a new carbon carbon bond here and two carbon extension; simple two carbon extension. In reality this was done by I put a Pg here to be on the safe side,

but if you have something like this you can just do a simple FGi through a functional group reduction.

Now these things can easily be done; this is a aldehyde you can simply done by a wittig olefination kind of thing. Now try to correlate it this is a 1, 2, 3, 4, 5 1, 2, 3, 4, 5 if this one type pentene diol you protect this one of the height of the hydroxide this mono protection group and a I do a oxidation it will be coming of here.

Now, earlier we explained that if you having a similar kind of one and diol were both the dials are having similar reactivity; you can basically protect one hydroxide group selectively by doing a stoichiometry control. Now here we will try to give you a name reaction is called Mc. Dougal reaction.

The Mc. Dougal reaction is says that if you have a diol you react with one equivalent of sodium hydride and tebeoscoride. Tebeoscoride structure was already discussed to you even you can use Tebeoscoride it does not matter what is the protecting group TBDPS structure we have not discussed and it says it is a one equivalent.

You need one equivalent only you react in a THF solvent and you can basically get a nice mono silyl ether either TBS or OTBDPS based on the reagent which you use. So, I say this is this protocol is named as Mc. Dougal reaction.

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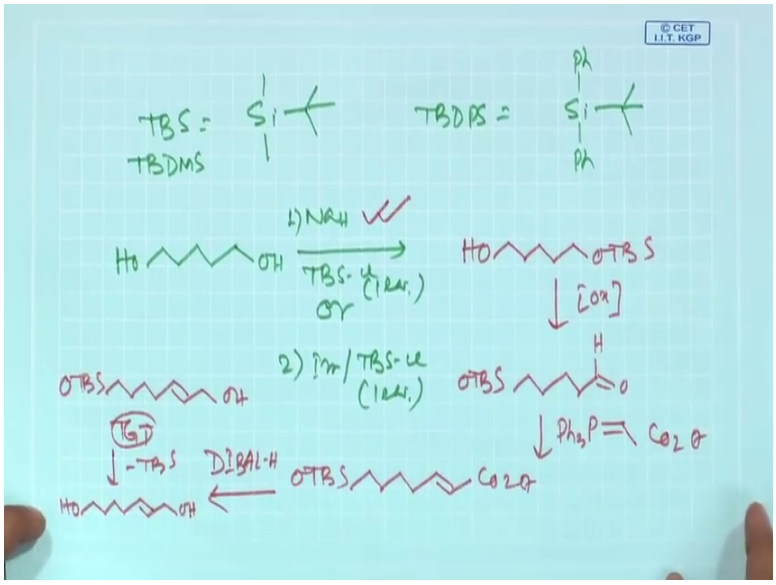

Now TBS the structure which we have already explained earlier methyl methyl this is called tertiary butyl dynamical silyl, sometimes you have also named as TBDMS as a TBDPS the structure is a silicon is there is tertiary butyl dyphenyl silyl. So, two final groups are there and you have a tertiary butyl fine.

So, now, you start with your 1, 5 pentene diol 1, 2, 3, 4, 5 1, 5 pentene diol.

So, first do the Mc. Dougal protection or Mc. Dougal reaction sodium hydride TBS scoride. Even you can do the same reaction if you use emedagol and TBS square that is all the fine. So, you might have a group one to they might have TBS scoride or we use Imedagol TBS TBS scoride.

Both the cases you need one equivalent of TBS scoride, one equivalent of TBS scoride, but usually the yield for this reaction or the optimization is pretty good. So, you basically get this mono TBS 1, 2, 3, 4, 5 mono TBS things things.

Next to job is absolutely simple you need to oxidise these things compound with this with a oxidizing agent; any oxidizing agent will does the job 1, 2 3, 4 you basically get the corresponding aldehyde.

Next your wittig reaction your wittig reaction will be basically will be done and you will get C o 2 et. This is alpha beta also seen in a register and next as I said this can be easily reduced by a mild reducing agent DIBAL which went as in the double bond; only reduce the corresponding ester. And basically we get your target molecule which was allylic alcohol.

So, here basically use this and then you just remove the TBS group. So, we have this is on the target molecule, you have to remove the TBS group to get your target molecule. So, your target molecule is these things. So, in synthetic experiences if you have a similar kind of functional group which whose chemical reactivitys are almost similar; you need to protect or either to mask one of the functional group through a suitable product reagent; the choice is yours.

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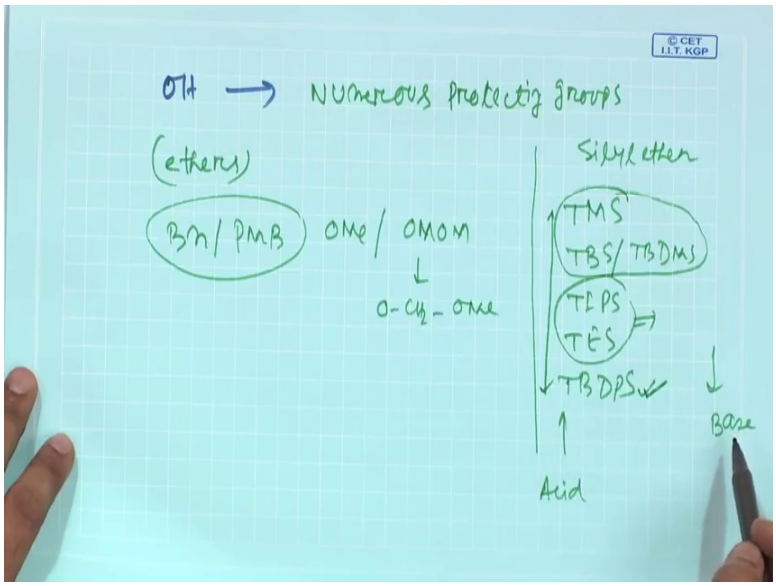

Now as I said alcohols can be protected through a. numerous protection groups.

Numerous protection group; mainly you will find that alcohols are the most actively explore functional groups in the protection group chemistry numerous; protecting groups can be used protecting groups can be used.

Mainly alcohols have been protected as their corresponding ethers ethers and find ethers like benzyl ether, PMB ethers; the most widely known I am saying simply ethyl like methoxy ether then called OMOM ether OMOM is that nothing is a methoxy methyl chloride O CH 2 ome.

Then your silyl ether; so, silyl ether you are having many silyl protecting group; you have a TMS tri methyl silyl, you have TBS or TBDMS as I said you have tips tri isopropyl silyl tri isopropyl silyl we have tast tri ethyl silyl, you have TBDPS.

Now this protecting group was basically chose based on their stability under certain conditions. Like this way the the groups have been written in this way; normally is found TBDPS was normally very stable under acidic condition very stable under acidic condition. And the groups like TBS or TMS seems to be seems to be too much active under acidic condition.

This groups TIPS and TES seems to be having a metal activity; they are kind of reactive impedance of acid, but not as much reactive as like TMS or TBS. But TBDPS is somehow a cd naught, but things will go completely reverse.

So, acid reactivity is this way and the base reactivity is this way. So, we treat with this now where TBDPS is very fast will be deep protected, but in in contradiction TMS and TBS are normally stable under basic condition.

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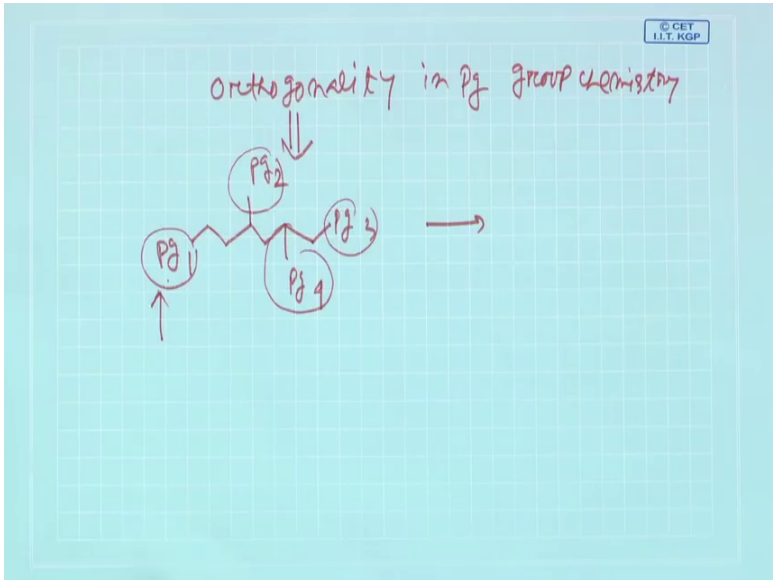

So, in that way we often use a term mamed as orthoganility in the protection group chemistry; Orthogonality in Pg group chemistry or protection group chemistry.

This orthoganality basically means that you are how you can manipulate your different; let us say you are having several protection groups here in the molecule Pg 1, Pg 2, Pg 3, Pg 4. Now whenever you are doing some reaction on any of this reacting side, in principle all the protecting group should be inert isn't it?

Then I say that you want to selectively remove Pg 1; to do some FGi on this reacting site. Now under this reaction condition; your Pg 1 should only be cleaved Pg 2, Pg 4 and Pg 3 must remain intact that is the orthoganality.

That your have reagent system should only target Pg 1. Now if I say you have to d block only Pg 2 and you want to do FGi here you need to find a reagent system which will only

cleave Pg 2. The remaining Pg 1, Pg 4, Pg 3 will remain intact; so that is the main beauty or main challenge to find a the orthogonality in the protection group chemistry.

Now it happens sometimes if you are dealing with a very complex molecules, you might have a 10, 12 protecting groups in a given intermediate and that is very difficult often to find out what are the optimum condition to be block or to remove any particular protecting group.

And those cases you basically you have effort will be mainly optimizing the reaction condition or to find what is the best orthogonal condition to the block these things. Similarly on the similar way we will be trying to use another problem.

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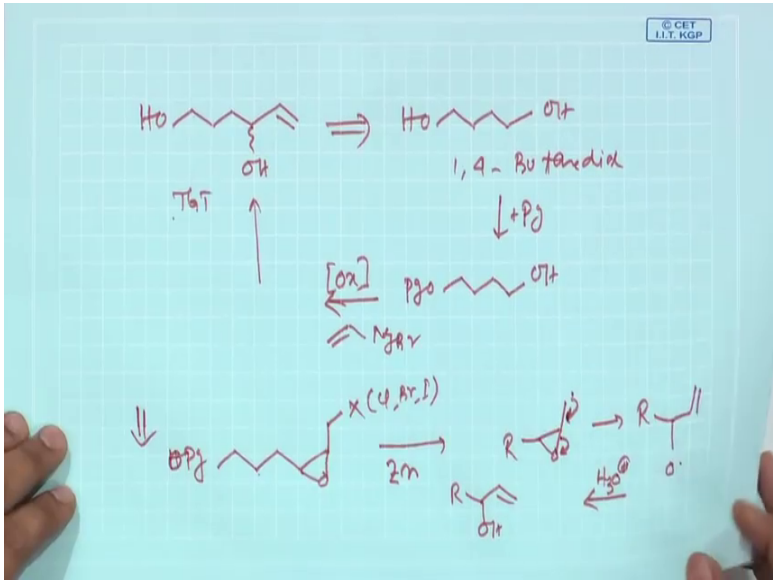

Which is now based on something like this; a problem which was given to you is a target molecule and a 1, 4 butane diol was and this one you can simply do it by using a very conventional reaction. You will be a mono protection mono protection; so, basically you will be OPg 1, 2, 3 O H.

Now what you do? You do a oxidation and then you do a vinyl magnesium gummite to get the target molecule; this is as simple as that fine. Now if there is any other way to do it?

I say let us try to formulate if there is the other way take this target molecule and do a retro I put a O Pg here sorry O Pg and then I say if you have something like X try to count the carbon 1, 2, 3, 4, 5, 6 1, 2, 3, 4, 5, 6 I say X is a cloro, bromo or ardo.

And there is a very nice interesting reaction if you take this kind of epoxy cloro or bromo epoxy bromo compound you react with zinc, you react with simple metallic zinc does not found that this zinc reacts with this epoxy cloro or epoxy bromo compound and normally gives you a radical species here.

Now then if you have a radical species there this is basically R; I keep it as it is and this radical tend to trip this epoxide in this way and it basically will give you a o dot and a double bond here and this o dot is basically abstracting a pro.

Come from either acid source or solvent it basically give you a allylic alcohol. This is the another alternative way it is basically a d halogenation reaction that is basically favoured by a epoxy system if you are having a epoxy system here.

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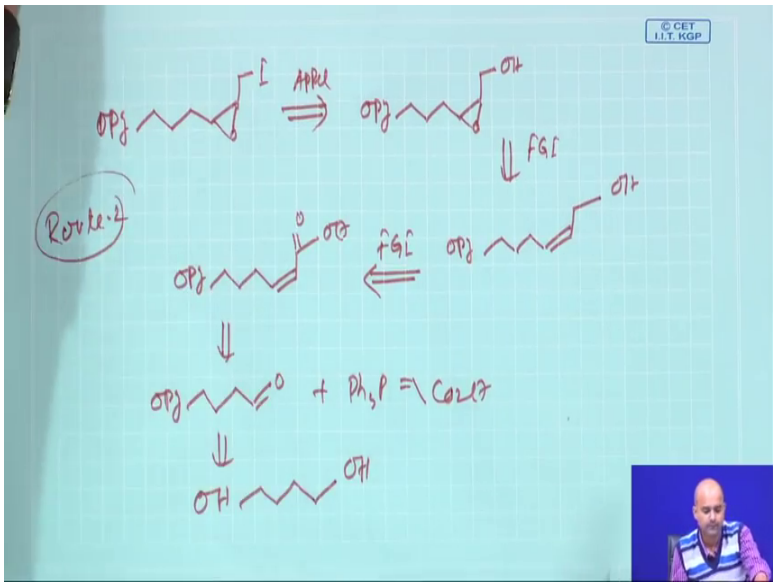

So, now, trying to formulate the entire path way. So, you are having OPg the epoxide which I am now saying O CH 2 I now try to do a retro this ardo compound, you can simply make it or access by corresponding alcohol through apple reaction; through apple transformation.

This epoxy compound; now, you can basically make if you have a suitable allylic alcohol right. Now these are allylic alcohol call just now we have prepared if you have the corresponding ester to a dibal mediated FGi.

So, this is also FGi now see this one we just need for the one five pentene diol, if you know having this OPg 1, 2, 3 with a wittig reaction. Now in principle and this can be easily made from the starting 1, 4 butane diol 1, 2, 3, 4. Now this is route 2 route 2 under route 1 which is pretty simple the route 1 is absolutely simple route 1 is this one.

Route 1 route 1; we say you take this corresponding butane diol, mono protect oxidation vinyl magnesium romide addition this is very simple four step, but the other pathway also very interesting, but this is little bit more step; how many steps? To start with alcohol first, then you mono protection oxidation two step wittig, three step.

Then you do a dibal four step you do epoxidation five step apple reaction six step then your d ordination through epoxide opening epoxide opening which tell tours now saying then finally, you have to get rid of this protecting group. So, route 1 and route 2 both are in principle possible.

And both the routes in case of route 2 having you are having much more steps and route 1 is little bit less step, but route to the chemistry little bit new chemistry unconventional chemistry which we have we have not discussed earlier and that is why you thought that let us talk about this particular chemistry. And here also use the particular predicting group.

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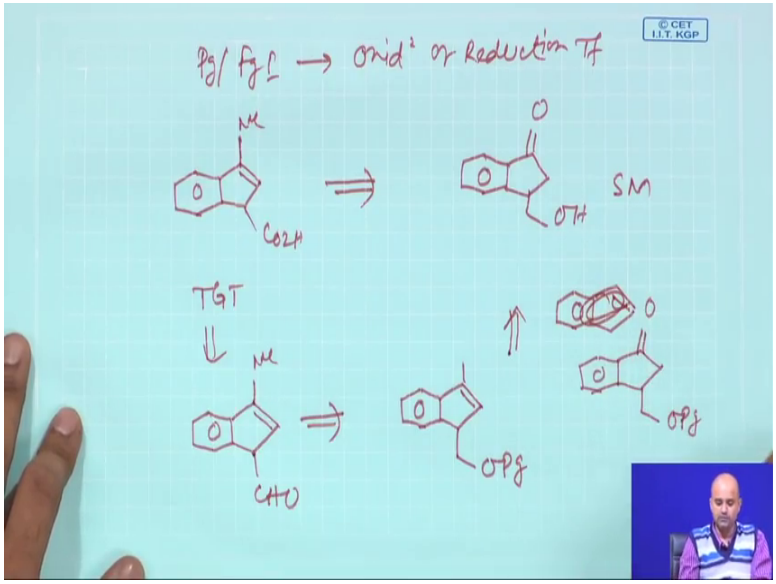

Now we will talk about a simple protection group and functional group based strategies which normally involve oxidation or reduction based transformation. So, basically these are similar just now we talked about similar kind of problem.

Now this particular problem was framed in this way; the compound which was given to you as a target molecule, you see the structure this is the target. And the starting material which is also given to you is basically having a kitu alcohol kitu alcohol.

Now what exactly you need to do? You basically need to oxidize this alcohol to acid and then somehow here you need to put a methyl group with a olefinic unsituration here. So, basically you need to selectively react I this ketone functionality as well as alcohol functionality. So, it means that we will now try to do a retro based on this thing which say. Now first if you put these things and you put a aldehyde can easily be converted to acid then we say.

So, now, these things can you used a protecting group chemistry for the free alcohol because you have a free alcohol. And then you see if you can now make a intermediate something like this or sorry if you have a intermediate something like this, where these free hydrox is protected and you can do a methyl given an addition do a elimination.

That was the simple transformation which was proposed. Now try to find it out how with this entire thing was done; how this entire thing was done. So, we will now go to the forward path way.

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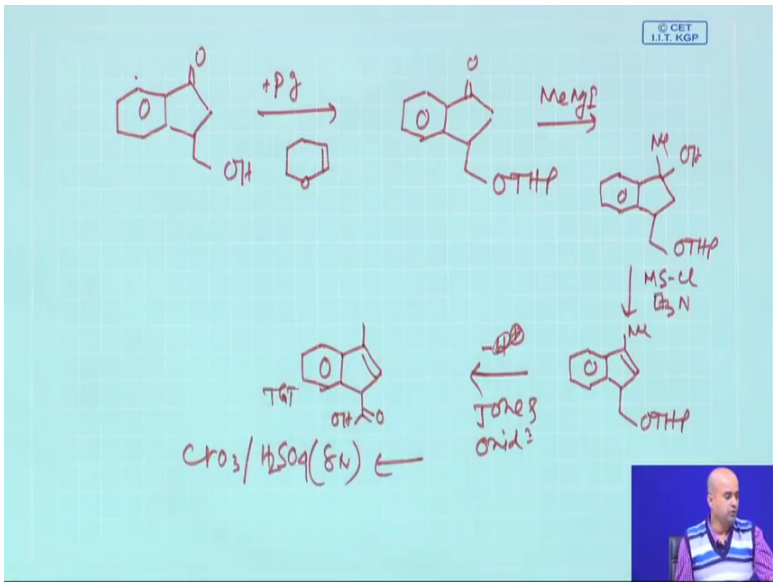

To start with the starting material whose structure was given as it is now for particular protection group of this hydroxy group you can use any protection group. Let us we use the simple protection group which you earlier used dihydropyridine group.

Dihydropyridine group was used and then the primary was protected as a OTHP our next reaction which you are earlier explained should be a methyl group addition one carbon needs to be added and then basically you will be getting a tertiary alcohol with this part remains similar.

Now you need to do a simple elimination; the elimination based to you can do it convert this corresponding alcohol to mesylate and heat with tri ethyl amen that will basically give you a kitu elimination.

And methyl is now; so, you are almost completing the steps. Now the top part was done, now you remove the thp group by h plus treatment, but in reality it was done through a condition whose name is Jones oxidation is a called Jones oxidation.

The Jones oxidation is basically a chromium trioxide based oxidizing system which was used in a considering sulphuric acid 8 normal was used. It is a very strong oxidizing

sorry strong acidic condition. So, what happened first if you treat this compound with Jones region OTHP removal takes place?

An OTHP removal takes place at the initial and then subsequently this alcohol was oxidized to corresponding acid. So, this is the target molecule which was initially given to you. So, this kind of simple transformation often is helpful to give you a particular design synthetic target which was often desired.

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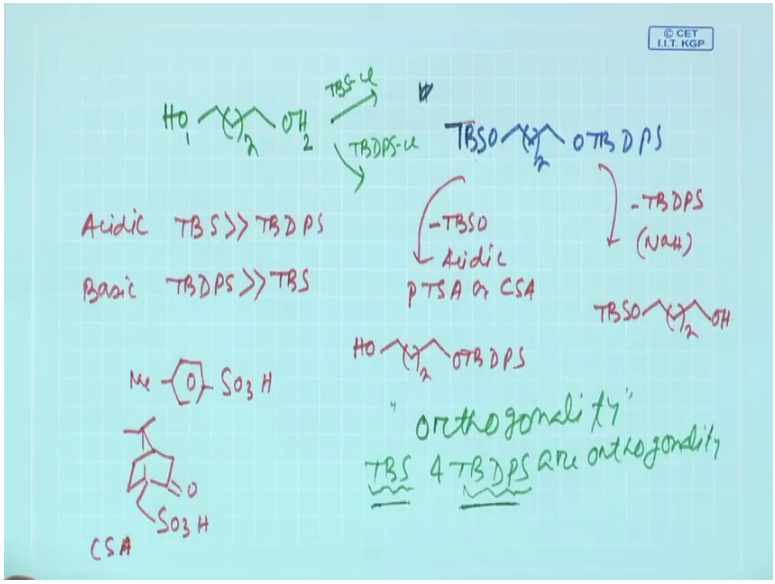

Now next I will try to give you a very simple. that one one all one and diol problem I said you are having this diol and is a OH 1, OH 2. Now there are different OH you can basically do this reaction as a OH 1, you first react with TBS chloride followed by TBDPS chloride both the reagents was used together.

And then what product you will get? One end is TBSO and another in this O TBDPS. Now we will explain the, consider an orthogonality now I said we will be using both the protecting group as our next FGi. We need to first remove TBS in payments of TBDPS do a FGi here, then TBDPS we will be removing in presence of TBS do FGi here. So, you basically need a selective TBS group reproduction method.

And selective TBDPS group the protection method the selective TBS I said TBS are much more acid level they are basically acidic reactivity acidic reactivity TBS are much

more reactive than TBDPS and basic reactivity I say TBDPS are very labile towards base TBS is not that much.

So, means that now if you selectively try to remove the TBS you need to use a acidic condition. And the acidic condition which was preferred basically by using a simple sulphonic acid paratolan sulphonic acid or camphor sulphonic acid. Now this condition PTSA is all of you know a structure is SO 3 H.

Camphor sulphonic acid a similar kind of sulphonic acid it is basically having structure. So, 3 H CSA now this compound can be selectively used to remove this TBS group. So, now, basically you are having O TBDPS; now you can selectively do whatever reaction you want to do on this end.

Now here you can remove this TBDPS by simple treating with sodium hydride which is a base and this condition will now not touch the TBS part and we will basically give you this OH. So, eventually you can this is a very nice demonstration of orthogonality of this two protecting group.

Now, I say that TBS and TBDPS are orthogonal to each other means that these groups can be selectively the product rate or removed in presence of one another. So, TBS can selectively removed in presence of TBDPS or vice versa means that TBDPS can selectively removed in presence of TBS.

That is what if your reaction condition allows the orthogonality your synthetic pathway is much more efficient. And in that way you can basically fine tune the entire reactivity. And similarly I will talk about another two orthogonal protecting group those are not very orthogonal in the true sense.

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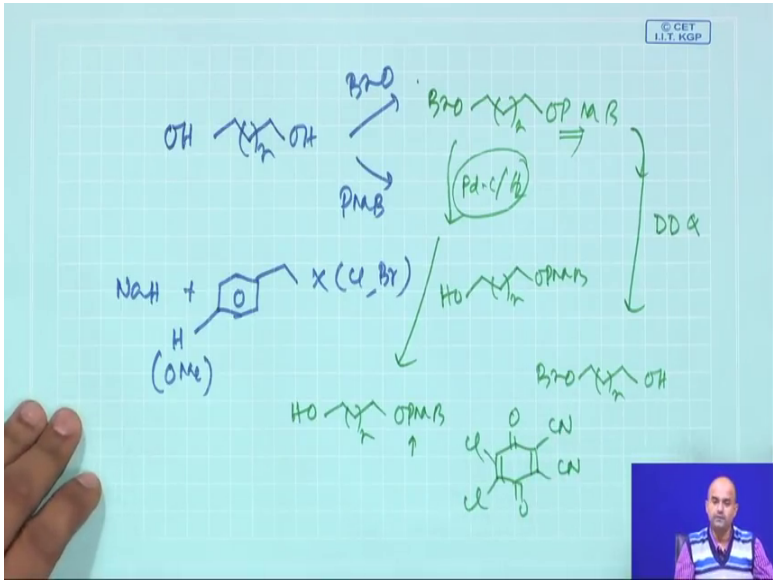

Like if you have a similar one end diol; you react with protection group called benzyl and PMB. Normally this protection was often done by treating the corresponding alcohol with benzyl chloride or benzyl bromide.

If you having a hydrogen here that is give you OBN derivative if you have the methoxy that give you PMB derivative. In reality you will basically get Bno OPMB. Now I say I need two conditions whether this group as a orthogonal to each other I need one condition where OH can be selectively removed to give you OPMB and another condition where OPMB can selectively removed in presence of bezoil.

The answer is yes basically you can do it in case of benzyl and PMB; both are basically can easily be cleaved if you treat this compound with palladium charcoaler hydrogen. Well normally this hydrogen melon is very faster if you have benzyl, but you probably cannot get 100 selectivity because PMB also undergoes cleavage with this palladium charcoaler hydrogenation.

Well palladium charcoaler hydrogen is usually faster with benzyl. So, if you had this palladium charcoal hydrogenation condition; you will definitely get this product, but some portion of PMB might get affected. So, PMB and benzyl in true sense benzyl is not exactly orthogonal to PMB.

But the other way whether PMB can selectively removed this is with 100 percent position. If you use a reagent called DDQ; DDQ structure is this. If you use DDQ this is a basically a single electron transfer reaction takes place.

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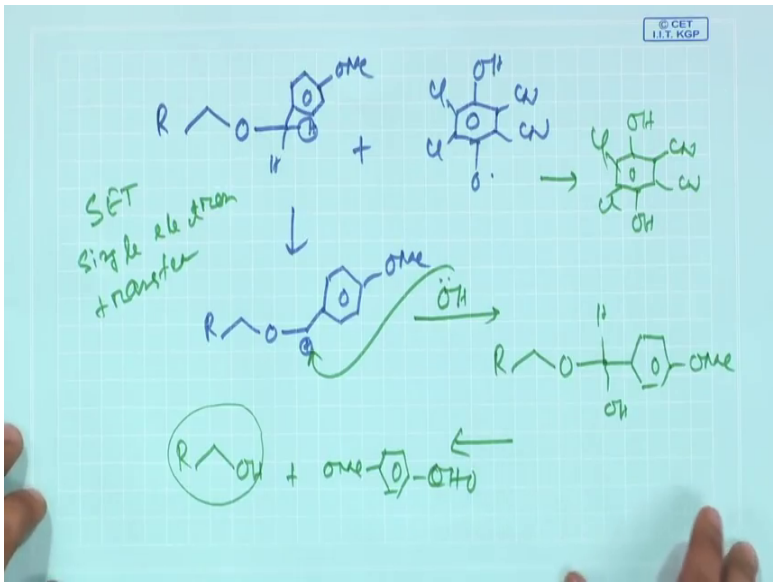

When in reality what happens? If you treat DDQ you have a RO PMB right; it react with DDQ, DDQ is this aromatic compound this particular hydrogen one of the hydrogen is basically transferred to the DDQ to give you the this. And then when this hydrogen goes up you will basically get a corresponding PMB caton which is stabilized by this paramethoxy group. So, water now attacks.

Water now attacks here and basically what we will get? We basically get a hemiacetal; we get a hemiacetal hydrogen is there we get a hemiacetal, which is simply collapses to give you the RCH to OH and your and its aldehyde and its aldehyde ome CHO.

And this also the hydrogen source is converting this corresponding this quinol radical to the corresponding quinol. So, this is a nice acidy reaction acidy means basically single electron transfer mechanism takes place.

Single electron transfer mechanism takes place and find that these now the driving forces is the presence of this mythoxy group which helps the selective removal of PMB in presence of benzyl. And some process it happens that DDQ also removes benzyl in very harsh condition.

Suppose you can keep on our discussion on this particular topic that how selective protection group and how they are manipulation can effectively be tuned up to get the desired target? We catch you in the next week; till then goodbye have a good time.