A Study Guide in Organic Retrosynthesis: Problem Solving Approach

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Lecture – 48
Symmetry based Strategies (Contd.)

So, welcome back students we are basically discussing desymmetrization as a useful strategies.

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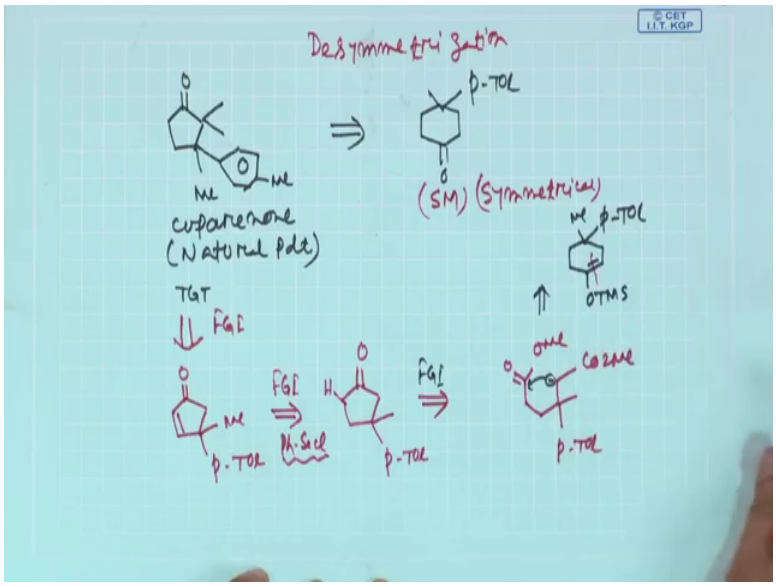

And now what I am trying to do will give you a target molecule which is basically a natural product and its structure is this compound his name is cuparenone as a natural product and I was saying that this natural product is a terpenoid molecules sesquiterpene. This is structure it basically cyclopentane based compound; cyclopentanone, you have geminal dimethyl group as well as this carbon you are having a methyl as well as a para tolyl group.

Now, the starting material; I am not I am I will be giving to you, but will be basically trying to do the retro. And then starting material which was given to you this this starting material this group is basically para tolyl group. The starting material if you see the starting material is a symmetrical starting material.

And I say that our strategy will be based on a desymmetrization strategy whether starting material is a symmetrical starting material; symmetrical starting material. The starting material is having symmetrical structure; so, you need to use a simple desymmetrization strategies to access the target molecule.

Now, before we come to a the retro which is will give you the entire structural viewpoints we will now let us do the very conventional retro that how this molecule can be constructed. So, if you are having a this particular key tone as a intermediate you can do a simple FGI to put two of these dimethyl gem dimethyl by successive alkylation.

Now, this particular alpha beta unsaturated ketone you can think about that how this can be constructed, if you have a compound like this. Now, just the earlier lecture, we talked that you can create a alpha beta unsaturated olefin adjacent to a carbonyl by a selenium based chemistry. So, if you can do a selenium based chemistry you can introduce a P h S e c l as a electrophilic reagent.

Now, here the point is if the starting material is this phenyl selenium chloride is quiet bulky group. So, expect that once LDA picks up the head unit because of this hydrogen as well as this hydrogen, but picking up this hydrogen is definitely not a favourable one as you are having a sterically bulky group at this site; methyl as well as para tolyl its huge bulk you. So, perineum is definitely a bulky reagent so expect that LDA first picks up this hydrogen create the enolate and then electrophile will be attacked in this particular carbon.

So, now how you can make this ketone? So, for making this ketone we are now do a retro which follows a very known dieckmann type of reaction. So, this FGI was saying that as a dieckmann type of reaction where you basically use these things to undergo the dieckmann cyclization fine. Now, I am coming the starting material how this starting material can be converted to here.

So, now, I am trying to do a intermediate find that; if you have this intermediate this can be easily converted to this inter diesters by a simple (Refer Time: 06:03) cleavage of this double bond here. Now from this to this this to these initial starting material symmetrical one from this to this is a simple desymmetrization reaction

Now, what we will trying to do we will now do the forward pass way and see how the synthesis can easily be carried out.

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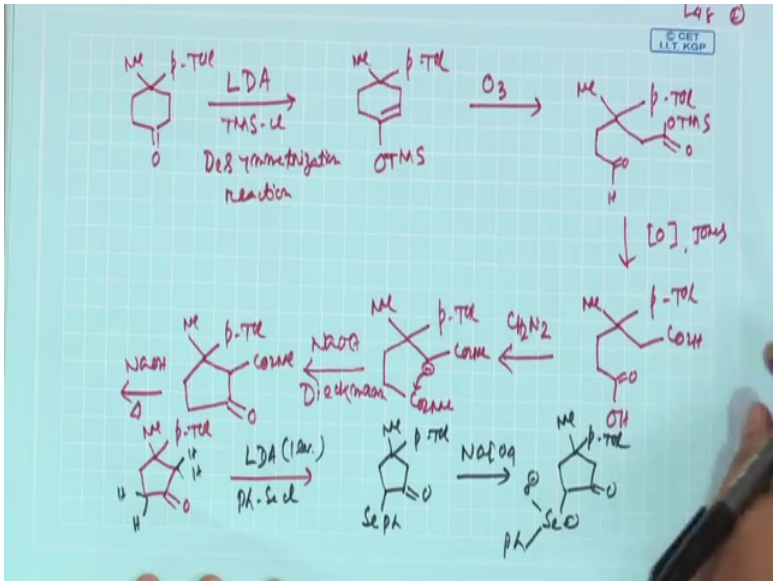

So, your initial starting material is this which is a symmetrical molecule. So, you do a LDA treatment followed by a TMS chlorite which is basically give you the desymmetrization to give you the enol ether m e para tolyl. So, this particular step is your key desymmetrization reaction.

So, I say single step desymmetrization is always preferred and you have now, accomplished this single step desymmetrization to create a desymmetric enol ether from a starting symmetrical ketone. Now as per the retro synthetic pathway if you now do a ozonolysis will basically keep this internal global bond and you get CH 2; CH 2 CH O CH 2 CH 2 CH O here and then this part will be getting CH 2 C double bond O; this OTMS ester.

So, you have a aldehyde you have acid or ester. So, what you do first? Oxidise the aldehyde; now oxidation can easily be done by Jones condition. Now Jones condition is highly acidic that will also keep this TMS ether. So, what basically you will now end up you get a para toluene here and then you get this di acid as the main product.

Now if you analyse this di acid; you basically need to convert this di acid to corresponding di methyl ester by simply treating with diazomethane. Now basic now you

will be having methyl para tolyl and CH 2 CH 2 C o 2 m e and your this is C o 2 m e. So, this is the di ester which you have earlier earlier proposed in our retro synthetic pathes one of the intermediate.

Now, I am saying you will be treating this compound with sodium ethoxide as a base to undergo this dieckmann cyclization. So, dieckmann cyclization this is first enol this carbonyl generation attack to this particular ketone. Now once this dieckmann cyclization takes place you will be getting methyl para tolyl and then you basically get the corresponding cyclic ketone. You do the basic hydrolysis with sodium hydroxide followed by heat beta keto acid which will immediately decarboxylate basically give you the intermediate methyl para tolyl.

Now, as I say you are having a carbonyl compound franked with two methylene. The most easily extractable acidic hydrogen will be picked up by one equivalent of base LDA one equivalent react with phenyl selenium chlorite. Now you see the molecule how it will react it basically give you the S e P h here this part will be remain similar. Now do the sodium periodate treatment which will give you the selenoxide; S e plus now this o minus.

And then P h; now selenoxide elimination as we discussed earlier will be now taking place and the selenoxide elimination by heating you will get a phenyl selenic acid.

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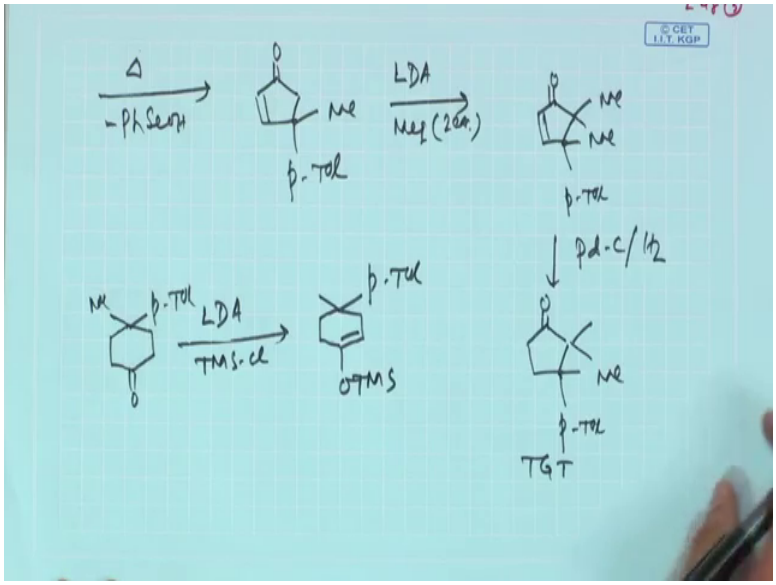

And then we basically get this alpha beta unsaturated ketone as the product. Now this intermediate we have already discussed you are having alpha beta unsaturated carbonyl to (Refer Time: 11:49), you are having this methylene group still intact. Now react with LDA excess methyl iodide 2 equivalent to introduce the gem dimethyl group here your para toluene and this methyl.

So, you are almost close now, just do the hydrogenation with paradigm charcoal hydrogenation to reduce this double bond by simple FGI. And then you can close the or you can complete the synthesis as shown here; this is your target molecule (Refer Time: 12:36) known which was initially given. The key reaction we set as the starting compound was giving to a symmetrical compound which is this compound; the main reaction we said is a enolization followed by enolizer formation which is the desymmetrization initially is required to give the cyclo hexane based enolizer which is ozonized to give you the ester which have earl earlier discussed.

So, this way a basically a very simple straightforward retro pathway of asymmetrical molecule can be easily desymmetrized. And then depending on your target structure you can complete the synthesis, but the key focus is basically desymmetrization reaction.

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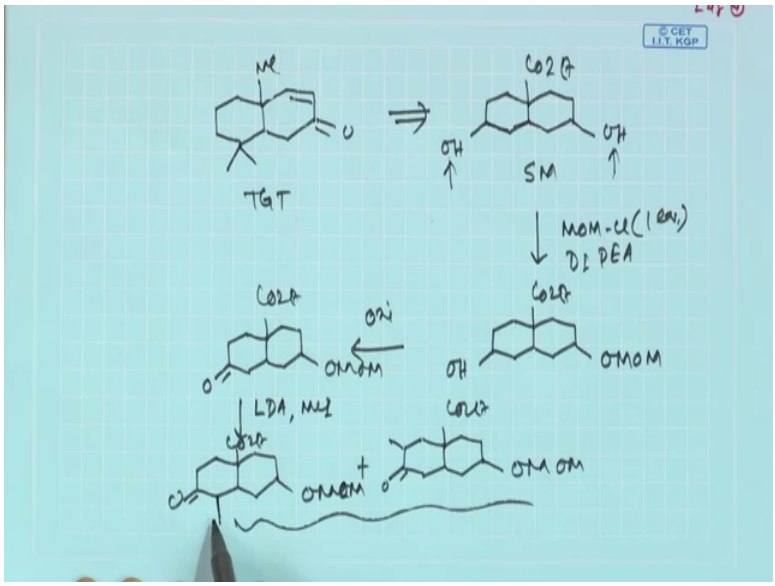

A similar line will be analysing another problem; here I am saying that the target molecule is basically having this structure.

The target molecule is having this structure we have a angular methyl. The starting material was also given to you for your better understanding the starting material now if I write I have given you this particular starting material may be see the starting material is very much symmetrical, very much symmetrical.

So, here if you now try to C o relate what are the things you basically need? You need to have a desymmetrization reaction either this end or this end. And then you need to put two extra gem dimethyl group this C o 2 et group next we convert it to corresponding methyl, you also need to alpha beta unsaturated is this carbonyl functionality.

So, initially as I said the desymmetrization is basically two type of desymmetrization achiral as well as chiral. Here as we did not mention the stereochemistry we said we will do a achiral desymmetrization and there are two OH group will seems to be having equal chemical reactivity. So, what will trying to let us do it a very simple, straight forward protecting group chemistry to desymmetrize it. We will be using a one equivalent of MOM chlorite methoxy methyl chlorite with a base di isopropylethylamine.

Now, as I see we will be doing the achiral desymmetrization; if you see the molecule this OH and OH are basically enantio topic to each other. So, in principal both the OH can be converted to O MOM and will give you a two enantiomers, but as we are focusing on only achiral desymmetrization; I will try to put only one OH group as a protected remaining part of the molecule is similar.

So, now we are protected selectively one of the hydroxyl group; now next if you see you need to introduce two gem dimethyl group. So, the best way you can do it; just simply putting this molecule through a oxidation. Now how it can be done? You simply do a oxidation by this way your MOM is remain here.

Now, I say if you use a LDA and methyl iodide. So, initial there is a there is a possibility that you get only this mono methylation; in addition you are having another carbon which also can be forms a carbon ion. So, you might have a two regioisomers this is basically a O MOM, O MOM. Now a two regioisomers either this a or this; now this steps needs to be bit carefully probably can get both of this product, you can separate them out and this particular product will be required by us as will be now doing the next round of alkylation.

Now, for the out of these two compound.

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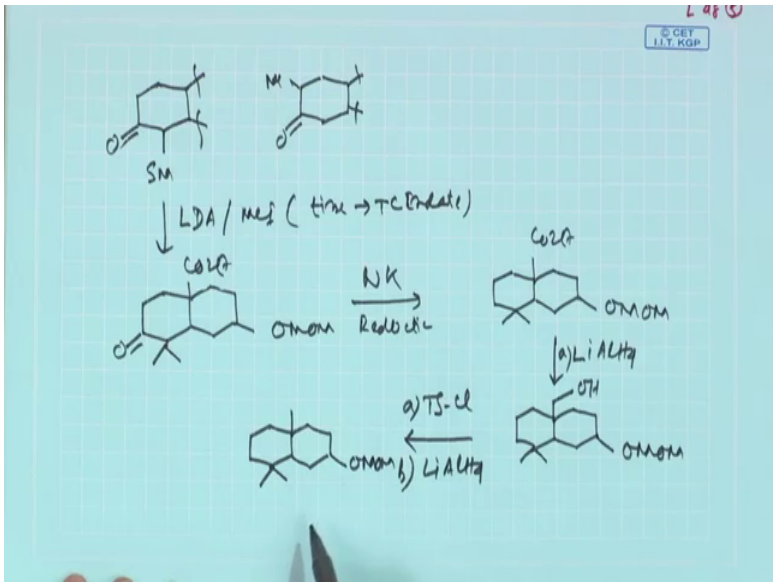

You are having a this methyl here and the remaining part it will be just we will write like this like this because those parts are similar. And you are having another methyl here; now as I said that these two compounds can be separated out if you can separate this starting material, you further do a LDA mediated alkylation.

Now, this enolate is now thermodynamically controlled. So, this enolate if you allow LDA methyl iodide little bit more time; more time is required to have the thermodynamically controlled enolate formation enolate. And then you will basically get the gem dimethyl product where your MOM is this.

Now, in reality in the final product you do not need this carbonyl group. So, what you simply do you do a Wolff Kishner reduction. So, this carbonyl now acting as a result and functionality; so, your O MOM is remains here. Now next as the target molecule having a methyl group here; so, this C o 2 e t next we converted to its so, that it can be easily converted to corresponding methyl. So, do a lithium hydride high rate reduction fast. So, initial desymmetrization is basically when you do the protection remaining steps all are basically simple FGI.

Now, you are doing a CH 2 OH here this is very simple you have to convert the corresponding alcohol to the methyl just by using a tosyl chloride, followed by lithium

aluminium hydride which will give the methyl in the angular position is will give you this compound. So, now, you are here and now only task which is remaining you have to introduce the alpha beta unsaturated ketone; this point.

So, what you now do?.

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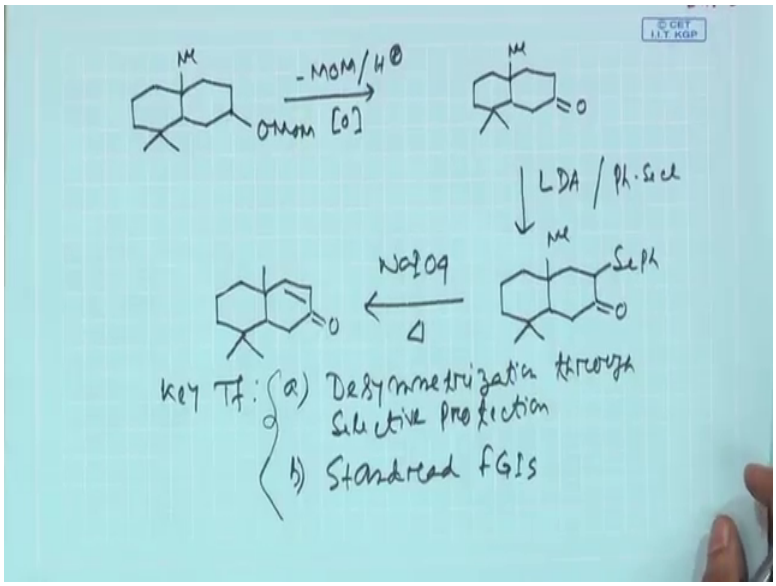

Basically now take this initial starting material methyl with MOM here; to remove the MOM which is H plus treatment do the oxidation to bring the ketone. Now if you see you will be doing a similar kind of reaction LDA; P h S e c l. This hydrogen is definitely there, but in close proximity you have this gem dimethyl group, here you do not have any such steric crowding the 1 methyl group is there little bit away.

So, now basically you will be getting this S e P h and then you follow the standard treatment sodium periodate heat will be getting the final product which is required. So, in principle what are the key transformation was used here? The first transformation we set a desymmetrization through a select trip or selective protection that was the key thing selective protection of the chemically reactive both alcohols are equally chemically reactive.

So, do the chemically protection and the remaining part is very standard FGI; we did standard FGIs. So, principle this kind of transformation can effectively be very usefully done; if you just do the selective protection of this selective protection our trying to

highlight as a desymmetrization of the equally reactive two hydroxy group which can be desymmetrized as a starting material symmetric you can desymmetrize, it through a selective protection.

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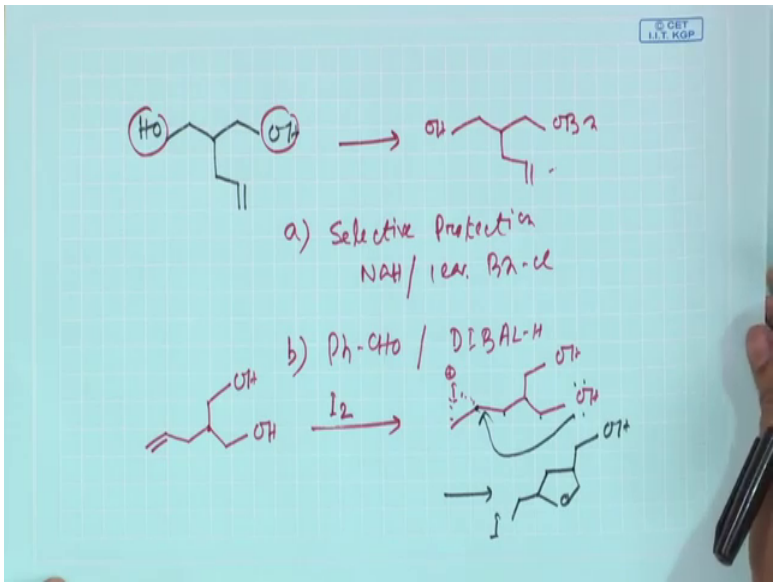

Next we will be having a the problem which probably we have already discussed. I am saying that you are having this alcohol now this particular two substituted one three propanediol; you already earlier explained as you are having a plane of symmetry here, this hydroxy and this hydroxy are enantiotopic to each other.

Now, I am saying that you need to do a desymmetrization reaction by a benzyl formation. In reality you can do this reaction by numerous way means you just do a selective stoichiometric based protection. As I said earlier if you can react with this compound is sodium hydride and one equivalent of benzyl chloride, you will get a mono protection.

And then you also explain earlier; if you go through the site to make the corresponding benzylidene acetal of this compound. And react with a hydride source like dibal; it also can be give you this cleavage of this benzylidene acetal, now this things are already known to you.

Now, what your trying to do? I will trying to give you another reaction whether this is also feasible or not. I am saying that as this compound is only having a allylic part in one

of this main functional group or appendage. So, what I do? I am just trying to see that I will be treating this compound with iodine. So, this iodine will basically give you a iodonium on first and then this compound is having two equally reactive CH 2 OH which basically act as a nucleophile.

Now, this nucleophiles will normally try to react in a intermolecular fashion to open up this a iodonium ion. And then what you get? You get 1, 2, 3, 4, 5 member ring as the main product. So, initially after this ring closing; this CH 2 OH will remain similar ok. And here you are closing this ring here 1, 2, 3, 4, 5 and basically get a CH 2 I here.

So, the molecule has been desymmetrized, but our target is you have to bring the allyl functionality back with the OBn remains. So, we will now draw the structure again.

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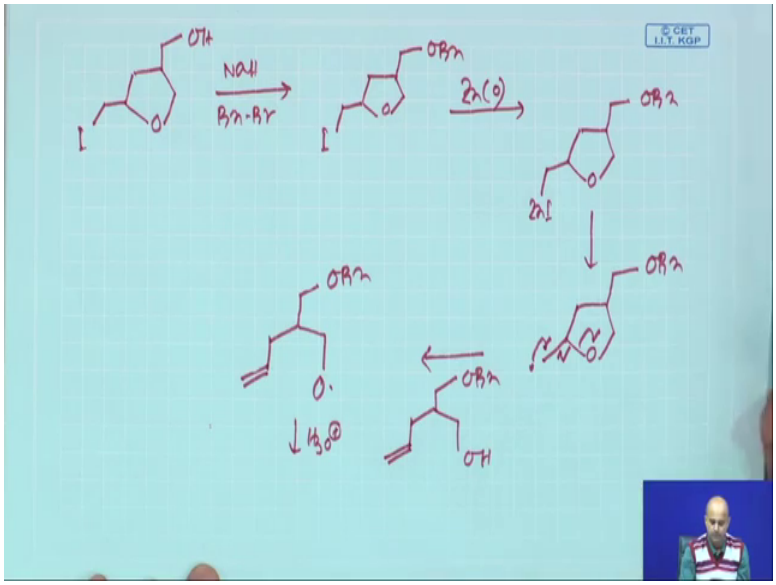

So, this compound is basically tetrahydrofuran; now I am saying that now let us do this protection benzyl bromide; now you may ask that why you require so, many long steps because this compound can be easily met through a single step as a step a and step b, but I am saying that will just explore some couple of new reactions.

Now, what I am saying? If this compounds is iodo compound if you treat with simple metallic zinc. Now metallic zinc has a strong affinity to this iodine and will takes place. Now once this de iodonization will takes place; it basically initially can give you a zinc

iodo spaces. And then it will give you a some kind of radical electron deficient spaces CH 2; CH 2 basically.

Now, this CH 2 this radical will try to fragment in a different way; now this radical will try to fragment was having a oxygen functionality in its close. So, you will get a double bond here OBn and you get these things. So, this is the reaction which were basically saying that is a main reaction which is responsible for the desymmetrization.

Now, what do you need? Simply water treatment to quench the O dot OH and your OBn so, there are though there are multiple steps involved. So, now, we will be again coming back the initial problem which was given to you.

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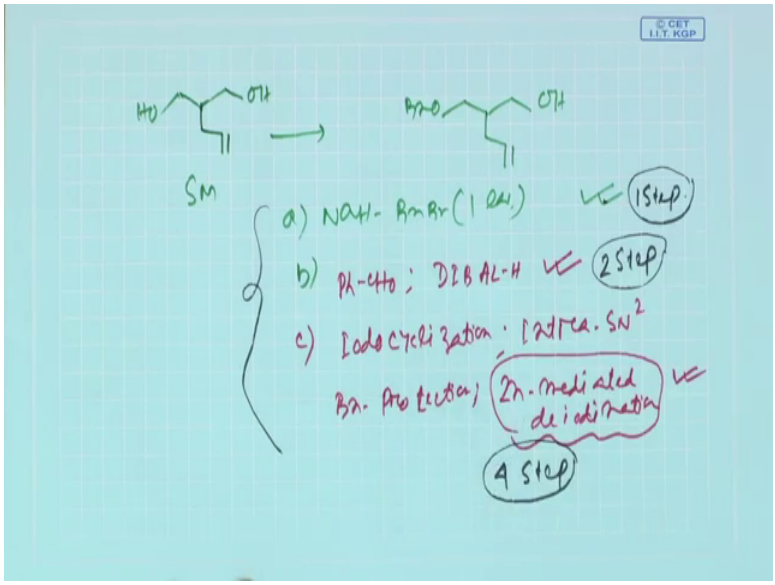

You are having this CH 2; OH CH 2 OH starting material symmetry starting material. The product which I am requiring is this one, I said you can be done by sodium hydride, benzyl bromide by 1 equivalent stoichiometric it can easily done.

Next I am saying that this one also can be done by making corresponding benzylidene acetal; followed by acetal cleavage or acetal opening through a reductive way by dibal; this is also very old feasible. The next one which I just now did the transformation which you required a iodo cyclization by basically making a iodonium ion, then you intra molecular SN 2 reaction intra molecular SN 2 reaction with one of these alcohol group one of these alcohol group.

Then we did a benzyl protection; so, this part is simple then we do a zinc mediated de iodination. So, this the fourth reaction this one probably is the most crucial reaction which gives you the thing. So, three possible pathways can be formulated for this transformation and eventually you will find that this step is probably single step reaction.

1 step only; you can have a 2 step reaction here in the step b and for this root 3 root c you have 1, 2, 3, 4; this is a 4 step. So, definitely from a cost effective manner the step 1 safer then step 2, but step four also very useful reaction and eventually this also give you the required dissymmetrized product which also is your target molecule.

So, this way basically you can think about the desymmetrization reaction and particularly the key transformation which can be thought of you can basically in principal do a different or you can use different key transformation as your main tool. And then you try to correlate this that how this target structure can be correlated back to your starting material.

We have shown that three different routes are possible and all the routes having their own key transformation. Definitely the route 1 as it is a single step it is normally preferred, but the other routes like route b where you do a reductive cleavage can also be done. And route c is unique because you have a some new reaction which will definitely give you a access of the target molecule.

Now, we will stop the desymmetrization strategies here and next we will be trying to give you a idea about the stereo chemical strategies; which we will next discuss. So, till then just go through the desymmetrization strategies lecture notes. And we will update some of the we will upload some of the assignments, try to solve those problems.

So, till then have a good time and goodbye.