A Study Guide in Organic Retrosynthesis: Problem Solving Approach

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Lecture - 34
Fg/Tf/SM based Strategies

So welcome back student. So, we are basically discussing several strategies and in the last lecture we said that, we will be trying to discuss on the starting material based strategies, where the target will be given to you and I will also give the starting material.

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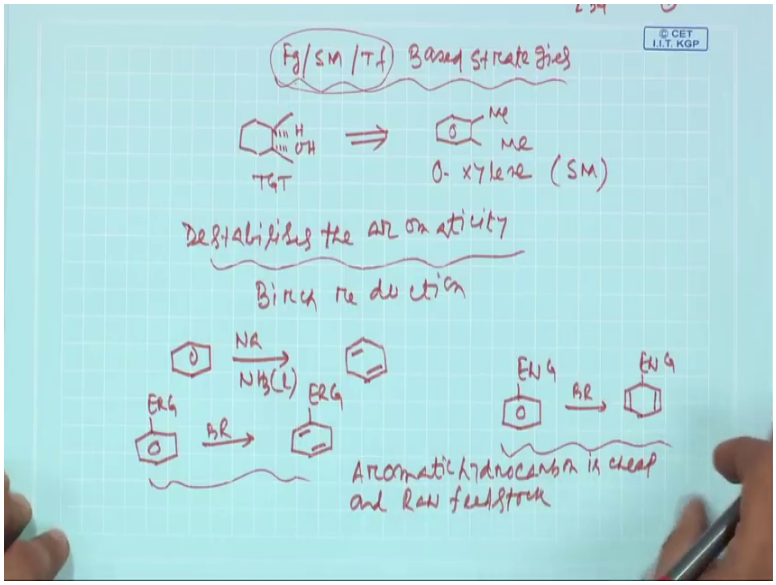

Now, actually for these strategies, we will try to have a combination of all the three strategies. We have discussed together which is functional group, starting material transformation are basically a combine, the approaches for a given target in this particular target was pretty similar.

It is a very simple, target is a cyclohexane based compound; you are having two methyl here and also a tertiary alcohol. The relative stereo chemistry of this hydrogen and OH was given that basically means that this hydrogen and OH has to be in seen phase or same phase fine. The starting material was pretty cheap, is ortho xylene. Eventually, starting material is aromatic and this product is non aromatic.

So, normally in the synthetic transformation, if I say how many reactions can you name; which basically destabilizes their aromaticity of a given aromatic nucleus? Destabilizes the aromaticity, basically there are very few known name reactions, which can allow this and one of the classic reaction is Birch reduction, which does the tricks.

Birch reduction; we have earlier explained; it is basically a radical mediated or single electron mediated reduction, when you have a sodium metal or lithium metal dissolved in liquid ammonia; you will get this kind of non aromatic hydrocarbon. Now Birch reduction has a very unique regio chemistry, if you put a electron releasing group in this benzene nucleus, after this Birch reduction, we will normally get this compound.

Now, this regio assume, regio chemistry will explain a little bit later on. And if you having a electron withdrawing group after the Birch reduction, we will basically explain this regio isomer and this two regio chemistry, I mean this regio chemical issues sometimes help to design effective synthetic pathway, that which particular aromatic hydrocarbon, will you choose to access the corresponding cyclohexa dye or now, this functional groups of these double bonds.

You can basically manipulate in such a way, you can create a substituted cyclohexane from aromatic hydrocarbons. Now, aromatic hydrocarbons, I say aromatic hydrocarbons are very cheap. They are very cheap, because they have been derived from petroleum industry. Aromatic hydrocarbon is very cheap and raw starting material or you can call them raw feedstock, these are absolutely cheap starting material. So, you can often use this as a starting material, for the synthetic pathway depending on the target structure. Now, in this particular case xylene was used as a starting material.

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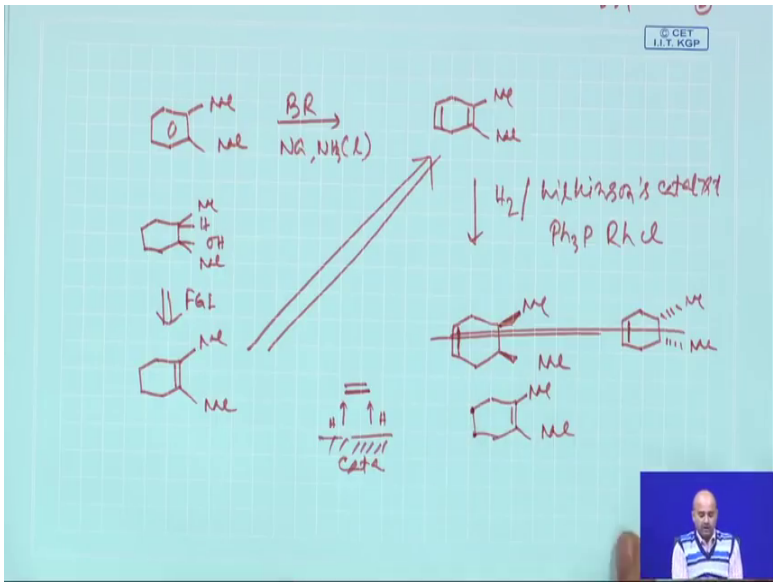

Now, xylene you see, the xylene molecule having two electron realizing group in the benzene ring. So, you do a Birch reduction by sodium and liquid ammonia. So, based on the regio chemistry, we will basically get this compound. Now, you see the target molecule. Now, we will do the retro, the target molecule is having methyl is there, here the hydrogen having OH.

Now, what we do? We now, do a retro and see how this compound can be correlated; we say if this olefin is there, you can do a hydroboration reaction. So, it is FGI by simple hydroboration reaction. Now, can you correlate with this? This means that, one of this olefinic unsaturation needs to be hydrogenated. The only difference is, this double bond is electronically rich, because is having more methyl groups and this is not like that and also it is sterically less crowded.

So, particularly this case, you can use a hydrogenation reaction by sterically bulky catalyst, which is very well known named as Wilkinson's catalyst. Now, Wilkinson catalyst, we are not going to talk about every detail in this. Catalyst is a rhodium based, catalyst is having tri phenyl, phosphine rhodium chloride. This catalyst basically helps in hydrogenation reaction, is a basically homogeneous catalyst.

Now, as this, catalyst is pretty bulky, it will tend to hydrogenate the olefin, which is sterically less crowded or less congested. Now, this olefin is very much sterically congested. So, catalyst has to up with in this particular olefinic site and it is very difficult

the catalyst also quite bulky. So, in this case the sterically less congested olefin will be hydrogenated. And now, basically we can explain, we all know the hydrogenation always is a same (Refer Time: 06:44) the basically the catalyst surface is this. This is the catalyst and your olefin is like this. So, hydrogen will be always attacking from same phase.

So, then if you reduce hydrogen in this compound, you can basically get either this compound or you can get, it is an isomer right oh sorry. So, these things are there, the things are there. No, this double bond is sorry. So, you get basically this compound and there is no chance of stereo chemistry, because this double bond is only reduced and there is a most user centered here, fine. So, now next what we are doing? Next, basically have to do a hydroboration reaction.

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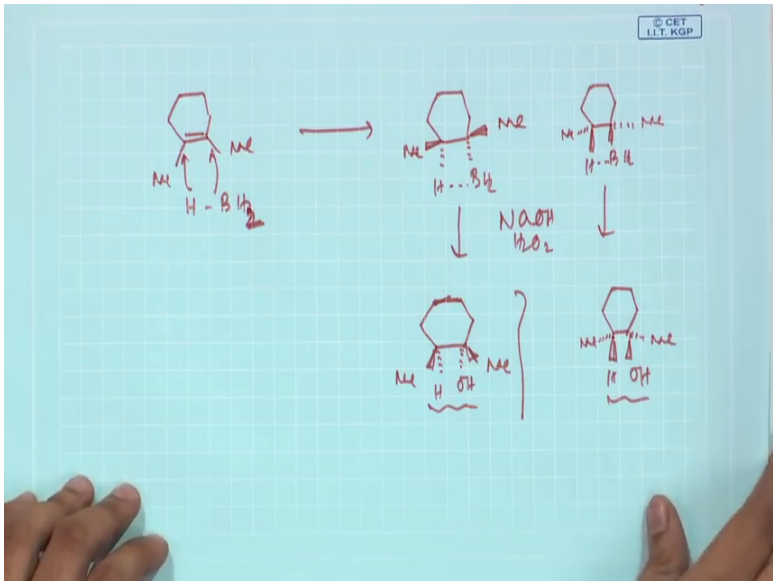

So, hydroboration, we will now try to write the olefin in this way, in the methyl. Now, hydroboration is basically addition of hydrogen and BH 2 and hydroboration will always say, is a scene addition. So, means that will basically having this isomer or you may have the other isomer, where methyl will be below hydrogen, will be here and BH 2. So, now basically you can treat these things with sodium hydroxide and hydrogen peroxide and you can basically get the product, which is given as a target molecule.

So, you can get either this product or you can get this product. These are basically an isomer to each other. Means that hydroboration, the hydrogen and OH are seem to each other. Now, any one of, this is our target molecule. So, if you can see a simple aromatic

hydrocarbon is undergoing a Birch kind of reduction and then will do a simple hydroboration reaction, which will now fetch the target molecule in a very systematic and efficient way.

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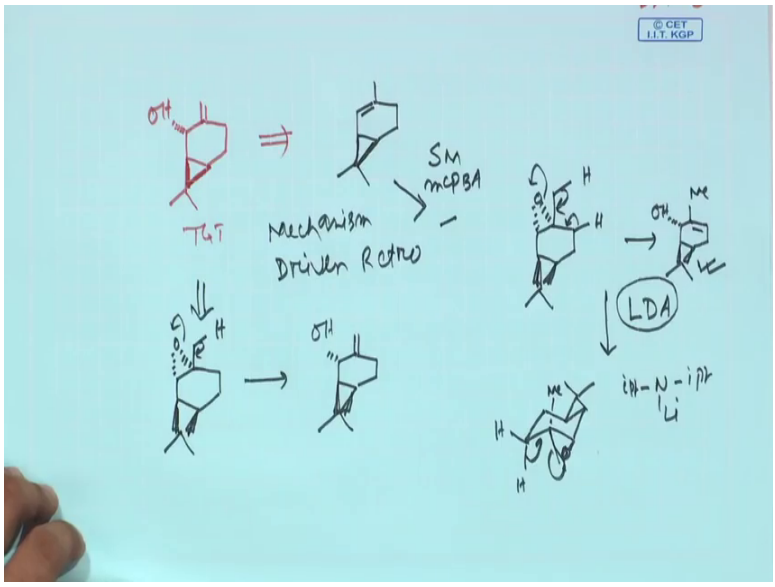

So, the same line, our next target is little bit different molecule. So, the cyclopropane is above of this plane and you have a alpha hydroxyl. This is a target molecule, the starting material which was given here, is having almost similar connectivity, but only thing is the number of carbon, everything is same. You basically have oxygen introduced here, the oxygen containing functionality in it. It is stereo selective way, I mean the particular stereo center is to be taken care of the double bond, instead of endo cycle divided, but now, we are having exo cycle double bond.

So, what you are trying to do? We will now follow the retro pathway and how it could be? This is a cyclopropane thing. And then you say, if you are having this epoxide. Now, this epoxide probably, if somehow you can abstract this metal hydrogen, by some means is it possible that you can do a little bit rearrangement. So, that the epoxide opens up to give you this target molecule. Now, eventually this obstruction of this hydrogen seems to be bit difficult, but there are ways to do it. So, now, we will try to figure it out, how the synthesis can be carried out the starting material. So, what we do now? We take the starting material, the first step we need to do, a tape oxidation. We will try to put a MCPBA meter probe, our benzoic acid.

Now, this cyclo propane group, blocks the above phase polyphen like this. So, basically a static guided or sterically directed epoxidation will takes place and we will give you the beta epoxide as the major product, means the top phase of the olefin is blocked by this cyclo propane group, as it occupies the above plane.

Now, here we see that this compound, if you can treat with a base like LDA is Lithium Dioshpoyle Amite. Now, is it possible that this base will abstract this hydrogen? It is possible, actually it can abstract hydrogen from here, it can abstract hydrogen from here also. Now, we will try to analyse, which hydrogen will be abstracted for this.

We will now write the cyclo propane in this way. It is three dimensional structure; then you see the cyclo propane is here and then you can now figure the epoxide in something like this, the epoxide and then this epoxide, you are having this particular epoxide. This particular epoxide is having this methyl, you say methyl is there.

Epoxide is below methyl, has to be up and we said that LDA might abstract the hydrogen. Now, LDA can also abstract the hydrogen from here also, because you see this CH 2 might be abstracted, this hydrogen also can be obstructed. And there is a LDA is a n isopropyl lithium. This is the real base.

Now, the mechanism, basically, if it abstracts this hydrogen, then it will be something like this open up and you get this product. Now, if it abstracts this hydrogen, this will also opens up and in reality that will give you the another rearranged product, whose structure will be something like this. Now, in reality this product also might be formed, but as we have given only one product, you can take it and if this hydrate is abstracted, but in reality there is a absolute possibility that, this product might be reformed and in my opinion.

if you see the particular stereo chemistry here, the hydrogen which is close to the oxygen, the epoxy oxygen, it is always possibility to that LDA might pick up this hydrogen and then do a this kind of thing. So, this part also might be formed, but as we did not observe it, here as the target is having this structure. So, we formulate that, if this mechanism operates were a methyl, hydrogen was removed by this. So, it is basically a mechanism driven retro and in many cases sometimes depending on the mechanism or the pathway, we can explain that how this retro might be possible.

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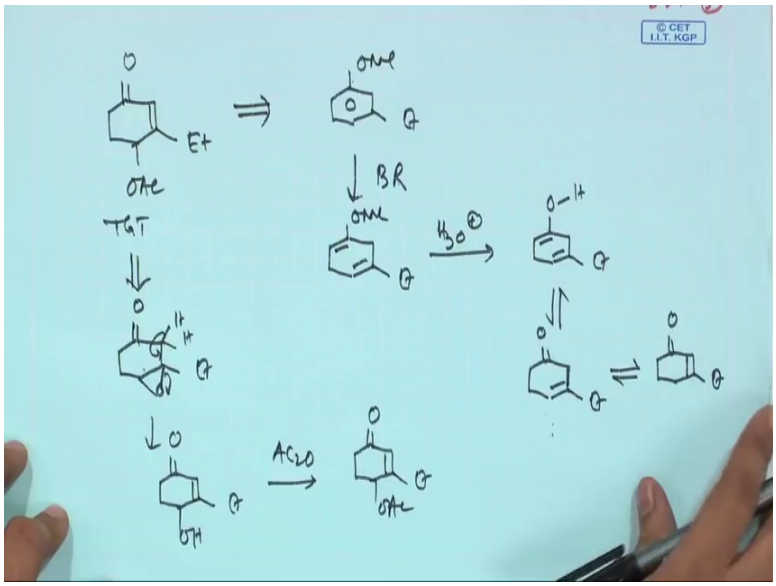

In the next retro will trying to have a little bit complicated one, not complicated the exactly, but we will explore the strategy, which you already discussed before, who is it; cyclohexanone, which target molecule was given to you, the starting material was very interesting. You are having an aromatic hydrocarbon, this three ethyl and it is shown or three ethyl methoxy benzene.

So, this was the starting material which was given to you. Now, again this will basically give you a possibility that is aromatic hydrocarbon keep starting material. So, initial step, you need to do a Birch kind of reduction. So, at the aromaticity will be disturbed. So, now, this compound has electron releasing group here, as well as here. This compound if you undergo Birch reduction, it will basically give you as this product. Now, you will find that the final compound, you have a ketone.

Now, if you have a anisole kind of compound after Birch reduction, you do a hydrolysis. Once you do the hydrolysis, this vinyl ether will undergo hydrolysis and will give you a enol. The enol can be instantly tautomerize this, to give you this compound. Now, this compound is not the conjugated ketone. It is not the conjugated ketone. It can basically in principle, they will undergo isomerization reaction to the more stable keto form, but if you see the target molecule, now the target molecule. Now, what we try to formulate? The reaction, we say that the target molecule can be accessed if you have some epoxide like this.

Now, just before this slide we have explained the epoxides can easily be opened up by treating a base. Now, here you are having these hydrogens, which your acetate due to, because of this carbonyl group. Now, if this hydrogen will be picked up by this base, you can generate a carbonyl and that can basically opened up this epoxide to actually give you the ethyl and OH, which now can be converted to the corresponding acetate by treating with the acetic anhydride. So, your entire pathway will be now formulated as this way.

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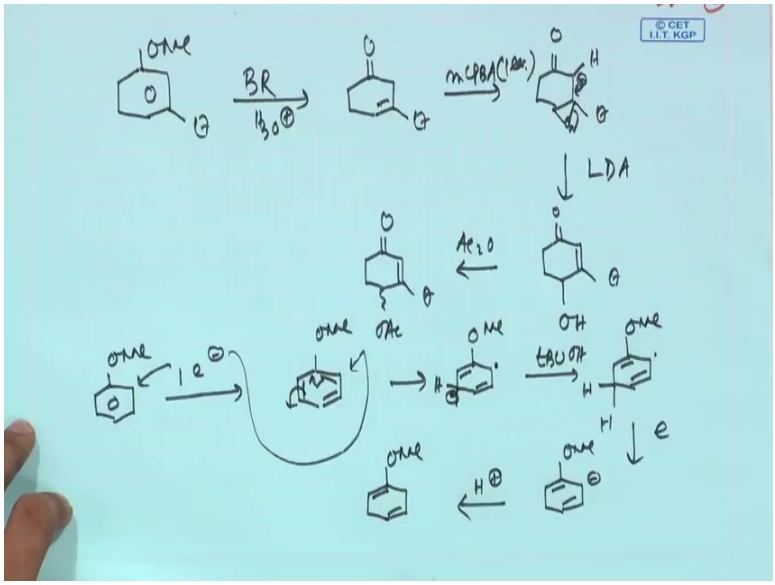

So, first take the starting material, do the Birch reduction. So, after Birch reduction, we do the hydrolysis, as explained earlier, we will basically get this compound. Now, as I said do not expose this compound for longer time. So, it will isomerise to this alpha beta, unsaturated compound. So, immediately subject it to epoxidation through a MCPBA is electron reach olefin instantly, MCB use one equivalent, other as if use X is equivalent by that higher oxidation may takes place here. So, use this one equivalent of MCPBA, you get these things.

Now, you use LDA, it will pick up this hydrogen, it will make a negative here, and then this carbon ion. We will get this electrophilic epoxide to go into the anion and then it will basically convert this to alcohol and then it can be converted to acetic anhydride by this OAC. Now, this Birch reduction as we explained, we say that if you having electron releasing group, this Birch reduction occurs in a different way.

And it gives you a very nice non aromatic hydrocarbon. Now, Birch reduction, basically single electron reduction sodium, once you dissolve in liquid ammonia, it gives you a single electron. Now, this single electron now, attacking the aromatic hydrocarbon. Now, depending on this group is the ome, though it is electron withdrawing ability, but it is also electron reducing. And it is electron reducing, capacity is much more than it is inductive effect.

So, it will not take the electron in the epso substitution. It is always taken into electron at ortho and then you will find, that once the electron has been transferred, I will write it this way. I will first try to put this benzene in this way and then I am transferring this electron to here. And then we will try to figure it out, how it is basically quenching? We will now, leave a O methyl, this is here. You get a dot here and you get a H and this is also you get a dot here.

So, you get a dot here and this electron has been basically transferred eventually. The solvent is always a tertiary butanol or ethanol, was always used. So, this basically this minus actually, this is minus, will now abstract the photon and it will give you this hydrogen. Now, this one again will accepts another electron to become again negative and this ome remains here and basically you will then take H plus from the solvent. It will give you this compound.

So, if you have an electron releasing group, it always prefers the single electron attack, it is ortho. Now, the next scenario, if you are having a electron withdrawing group like; CO 2 H or carboxylic acid, I say CO 2 H.

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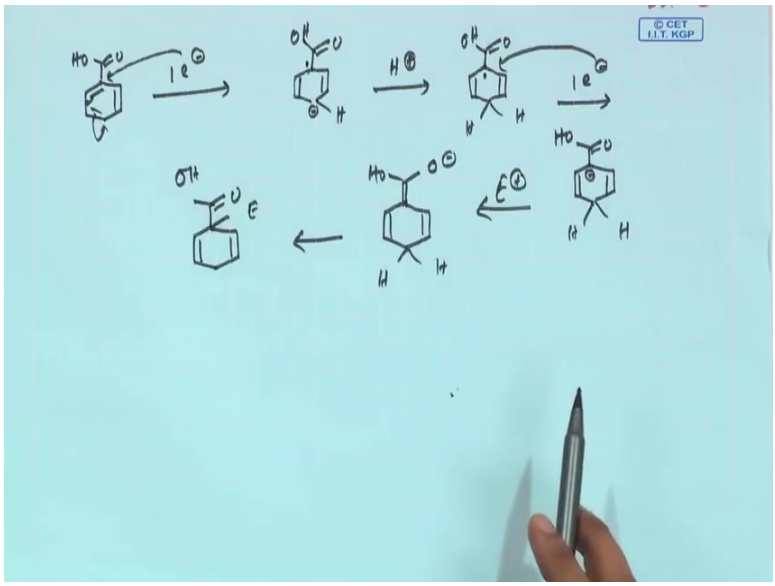

Now, what happen? You are taking 1 electron which has been generated from this. Now this 1 electron is transferred to this if so, because the electron is joined group; it can accept for that negative charge. And then you will find that it is basically will come here, will come here. You basically put a negative charge here for this hydrogen and then as a this dot. Now, this negative will be accepting H plus to basically give you this things. Now, this dot is there, another one electron will be transferring here, to give you a net negative charge on this carbon.

Now, this negative charge is highly stabilized with this resonance of this corresponding carboxylic acid, which we all know and this is the main reason. When you have electro withdrawing group, it can do this kind of regio chemistry. Now the point is as you are having a negative charge here, this negative charge can be trapped efficiently by electrophile.

Now, if it was electrophile here, you will find that this electrophile can nicely be trapped and you can get a carbon electrophile bond with this kind of structure. So, Birch reduction if you doing, do with electro withdrawing group like; carboxylic acid group and you simultaneously take with a electrophile like; methyl go halide, any alkyl halides, you can get a carbon electrophile bond here, our next problem is basically based on this particular strategy.

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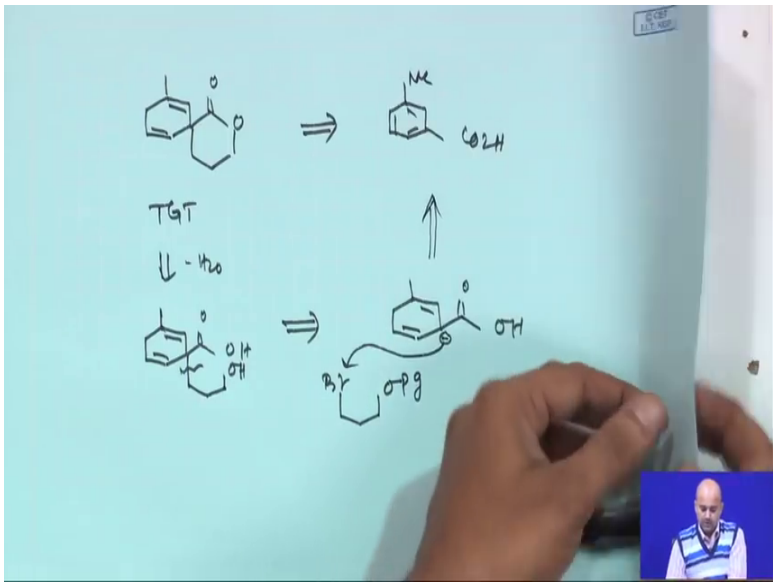

I say the next problem, which we now designed is a Spiro cycle based lactone for structure is this, and the target molecule is this and the starting material which was given to you is this. So, he is having electro reducing as well as electro withdrawing. So, now, do the conventional retro. So, I say if we do the conventional retro you can have this C double bond to O or H something, and then CH 2 O H, just do etherification reaction minus water.

Then just now, which you have explained, that if you have a Birch reduction of this kind of system and you can quench these things with electrophile; so, basically what you need? You need electrophile, which structure will be a Pg, is a protecting group and then this electrophile can undergoing a carbon bond forming reaction, then you remove the protecting group and do this esterification.

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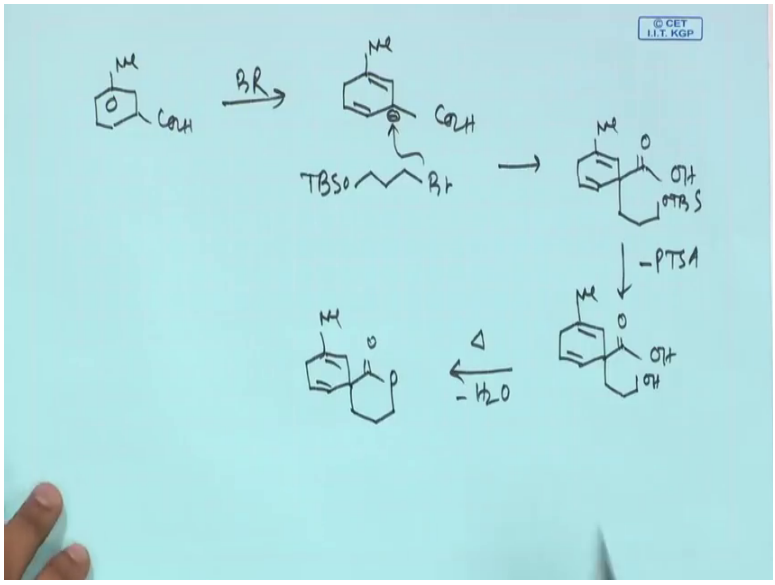

So, now we try to do the forward synthesis. Starting material is this methyl CO 2 H, do the Birch reduction first. Once you do the Birch reduction, we will basically get this compound and CO 2 H minus, we do not. Now, what we will be using? We using alcohol protected, this electrophile as a electrophile. And then you will be using this electrophile to trap this carbon ion. Now, get the compound CH 2 OTBS.

Now, we are almost close, we remove this TBS group by PTSA, which you have already explained and then you find. You basically get a hydroxy acid, you just hit it with the water, elimination will takes place, it is a condensation reaction and then basically it will give you the Spiro cycle lactone.

So, a simple structure can efficiently be constructed with the help of a Birch reduction by taking care of the proper region chemical issues. We see that body reduction; if you have electron withdrawing group, it will always give this kind of compound. In addition, this Birch reduction also having a electron reducing group. So, both the things can be coupled together, they may use a protecting group based electrophile, this compound is having a protecting group.

So, everything was basically combined together in the strategies and this kind of a strategical disconnection, based on starting material functional group at transformation, we will keep continuing in our in future lecture. So, till then just go through all the slides try to analyze the assignments; we will see you in the next class till then.

Good bye.