A Study Guide in Organic Retrosynthesis: Problem Solving Approach

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Lecture – 47
Symmetry based Strategies (Contd.)

So, welcome back students this particular lecture we will be trying to focus you a another new concept which is named as Desymmetrization.

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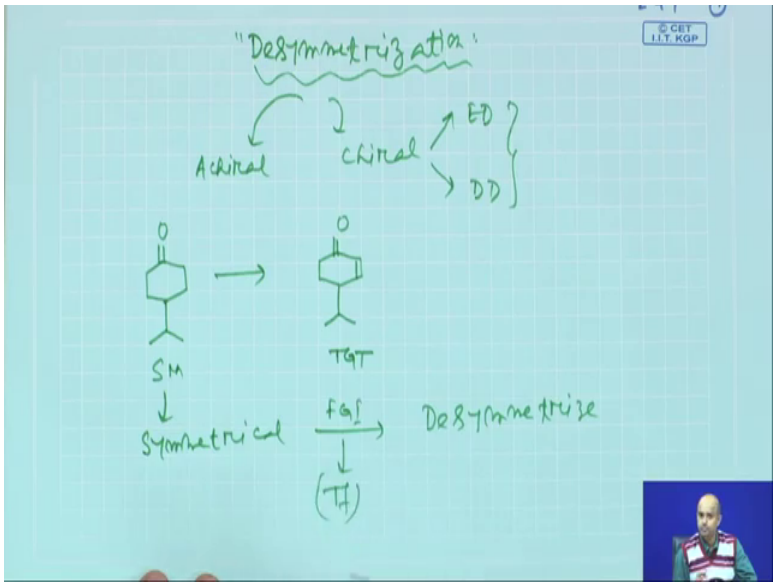

Now, desymmetrization often plays a very important role in designing a synthetic strategies. And basically we will be trying to focus on a normal desymmetrization; desymmetrization can be of two different type. We can call is achiral desymmetrization or chiral desymmetrization as a name implies achiral means the desymmetrization of this kind of strategy will give you a achiral molecule and this case will be give you a chiral molecule.

Now, in case of chiral desymmetrization there are different desymmetrization is called enantioselective desymmetrization or diastereoselective desymmetrization. But again things will be little bit complicated, we probably we will talk about few examples of ED and DD later on, but now if you consider what is exactly desymmetrization; then I will say that I will I will talk about a very specific example I am saying that you are having this compound.

Now, this is starting material you target which I am giving you that you please convert the starting material to this target. Now initially do not focus about the functional group base inter conversion definitely; that is your main key point. But as I said initially try to have a visual communication with the target molecule. The only difference is the initial molecule is symmetrical having a sigma v; this part is basically you create something which makes the molecule pseudo symmetric or the molecule has been desymmetrized.

The pseudo symmetry and desymmetrizations are kind of similar thing; basically the symmetry of the starting material has been removed or you disturb the symmetry. Now in principle probably I can give you a series of problems or I can just ask you that is symmetrical starting material is symmetrical starting material was given to you; symmetrical starting material was given to you and you need to do some FGI; some FGI to desymmetrized the molecule to desymmetrized the molecule.

Now, how you do the FGI? This FGI is are basically we have already discussed couple of key transformation which is required to a symmetrical molecule the FGIs are very simple; the same FGIs which you have already learned will use those things, but the concept is the starting material will be giving a symmetrical starting material, you basically need to do it in a straight forward simple way. And normally when we talked about that this particular desymmetrization will talk about it either if single step desymmetrization or a multiple step desymmetrization.

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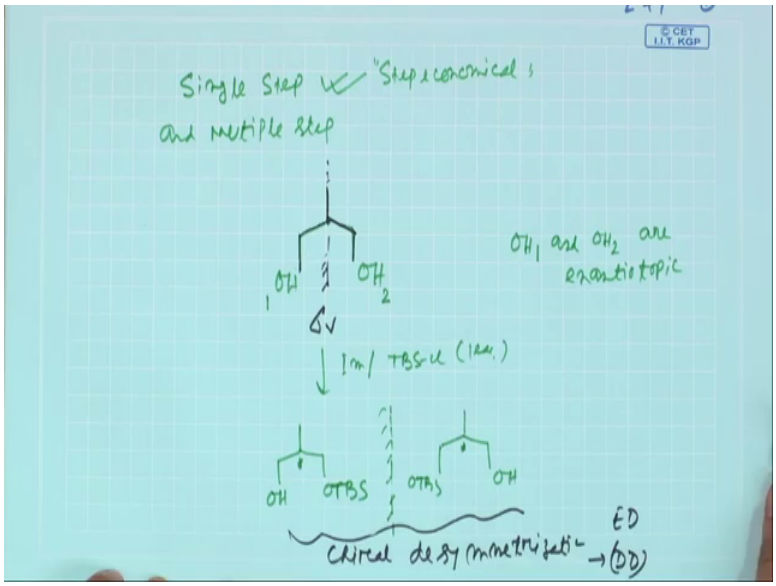

So, there are definitely two different ways single step and multiple step. When in principle single step is always safer because this is step economical and you are cutting down the cost step economical; muls multiple step also sometimes you have to use it based on your prior prior requirement.

In addition as we talked about the other things the the second part. So, this all these things come into the achiral desymmetrization; now I just try to give you a information what is chiral desymmetrization? Now take a molecule something like this this molecule is basically 2 methyl 1 3 propanediol; this molecule is having a nice mirror plane of symmetry ok.

You can basically put a mirror in between which basically cuts the molecule into equal halves. So, sigma V fine and the planes of the sigma V basically makes OH 1 and OH 2 are enantiotopic to each other OH 1 and also OH 2 are enantio topic enantio topic fine.

Now, I am saying that is there a way you can desymmetrize the molecule? You said the definite is I have say possible; you have both the OH why did not you do a selective protection of one of the OH. The protection group chemistry all of you have already learned; so, what you do is stoichiometric imidazole and let us say TBS quite you are using it one equivalent.

So, in principal you are doing it you say I am having 2 TB OH group. So, one of this thing is protected now the big question mark is these compounds have equal reactivity under this condition. Now I say that you are only touching OH 2 why not OH 1? Now seeing is after the desymmetrization you will see that this molecule is no longer achiral, the center is now stereogenic center. Initial this is a prochiral center because CH 2 OH and CH 2 OH are same. Now once you convert this OH one of the OH to o TBS, you basically bringing a stereogenic center. So, things become little bit complicated.

Now, I I am saying that you have all only consider about OH 2 what about the OH 1? Now I am saying that; so, now, you convert the OH 1 also which will be giving you this OTBS where OH 2 is remains similar. Now you analyze these two compound; these two compounds are what? These two compounds are basically mirror images compounds are mirror images though the absolute configurations was not given here.

So, desymmetrization which lead you enantiomers or diastereomers or a stereogenic center a particularly you can call stereoisomers. These are basically falls in the class of chiral desymmetrization chiral desymmetrization. Now in this case as enantiomers will be generated you can have you can call this as a enantio selective desymmetrization. You can also have a diastereo selective desymmetrization if the final products are diastereomeric to each other. So, this is a very simple and straightforward way, but I am saying simple, but is in real it is very difficult.

So, probably will have some examples where you can find it out. Now will try to explore the concept of desymmetrization with some very simple examples; I am trying to give you couple of starting materials one by one.

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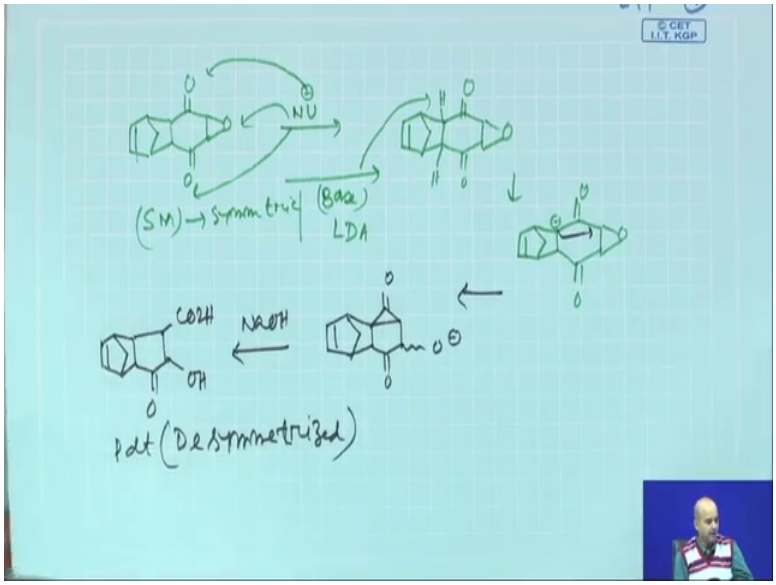

And what I am asking that please try to do the desymmetrization of this given molecule. So, that the symmetry is getting disturbed the symmetrical molecule this is symmetrical molecule.

Now, in principal as I said you can do a single step transformation, you can do a multiple step transformation. Or sometime if there is a very key transformation is available which people often used is very unique transformation will try to use those transformations. Now in principal if you see this molecule this molecule what are the functionality is having a double bond here, you having a ketones you having a epoxide those of the things of there.

Now, in principle basically you can do any kind of reaction which basically you can do epoxide hydrolysis with some nucleophile not water nucleophile, you can just a unsymmetrical nucleophile like sodium azide that gives you OH and N 3; the molecule is desymmetrized. So, like this you can basically put a nucleophile here, but now the point is if you do a nucleophile nucleophile can attack here, nucleophile can attack here it can attack epoxide; so, regio selectivity is a big issue.

So, the particular reaction which I am now trying to draw here we will take this compound and subject it to one equivalent of base. Now base I am using a sterrically bulky based like lithium diisopropylamide.

Now, you see the structure of this compound LDA is non nucleophilic base; it basically having two of these hydrogens which are extremely acidic, now these are symmetrical in nature ok. So, in principle initially if you think that you have a base; this base will abstract this hydrogen and they will basically will give you this carbonium; sorry carbon ion. Now is like a favorskii kind of reaction may take place because you have a electrophilic quencher in form of epoxide. So, this reacts here to basically give you a will give you a basically will give you a basically give you a this things.

Now, eventually if you now treat with sodium ethoxide or sodium hydroxide; this OH minus now attack this cyclopropene ring because it is strain. And if favorskii type of ring opening will takes place which probably I am sure all of you know it. And then you will see that this compound is now converted to a compound like this. Now this starting material and this product are completely different structure; now this is the desymmetrized structure.

Now, now you may also what is the basic things you are trying to say? I am basically trying to say that this is very simple transformation. The transformation is a well known transformation only thing is this symmetrical starting material is desymmetrized that is the only thing.

Now, if I give this molecule as a target molecule this molecular as a starting material probably if you do not mention the desymmetrization term is fine because is not required a in the sense. But a structural features give a sense that the starting material is this and your product is having this things, where the only difference is the symmetry of the starting material has been lost or destabilized.

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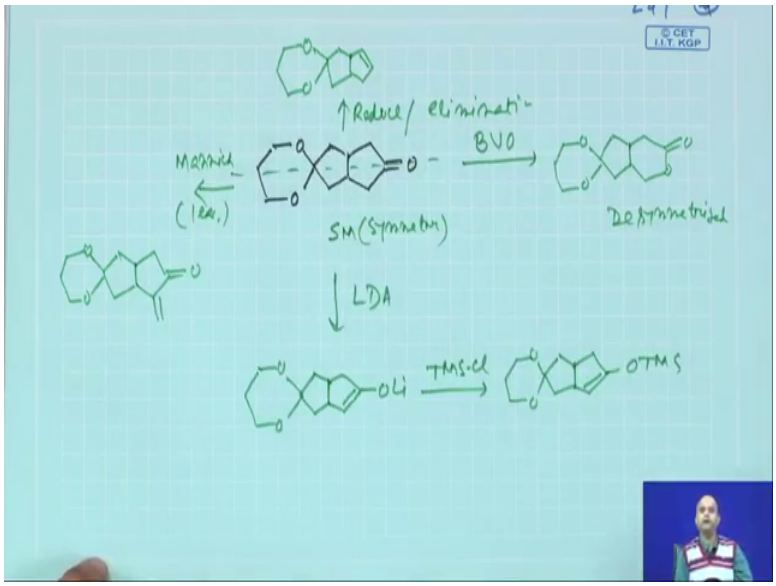

Now, next we will try to figure it out a cup a series of or a set of example where you see that how this particular compound can be desymmetrized with the help of many reactions. I say in principle you can think about many reaction. Now probably I will try to put you very simple reactions now this compound is basically a symmetric compound this compound is a symmetric compound right.

So, what exactly can you thought about; in principle you can thought about any transformation which will basically desymmetrize the molecule. Simple transformation like Baeyer Villiger Oxidation now if you do the Baeyer Villiger Oxidation of this molecule and find that the left hand side wont to be touched and the right hand side a basically now having a lactone.

So, the symmetry is now desymmetrized is nothing new is always known actually. Now I am saying you treat with LDA this molecule LDA will abstract this proton acidic proton to basically give you a OLi.

Now, now also this thing is desymmetrized or OLi normally is not a stable form you can treat this compound with TMS chloride the enol silyl ether you basically get the corresponding OTMS OTMS; so, in this way the desymmetrization was done. Now let us see whether you can do any other desymmetrization reaction you think about doing a mannich type of reaction with 1 equivalent of reagent.

Then you see you basically get this compound which is also a desymmetrized reaction. The initial starting material you can simply reduce do the re reduction followed by simple elimination, you can create the alpha beta sorry this unsaturation at this point or this point. So, this is the OH basically you can take a symmetrical starting material and you can the just disturb its symmetry through a proper synthetic transformation.

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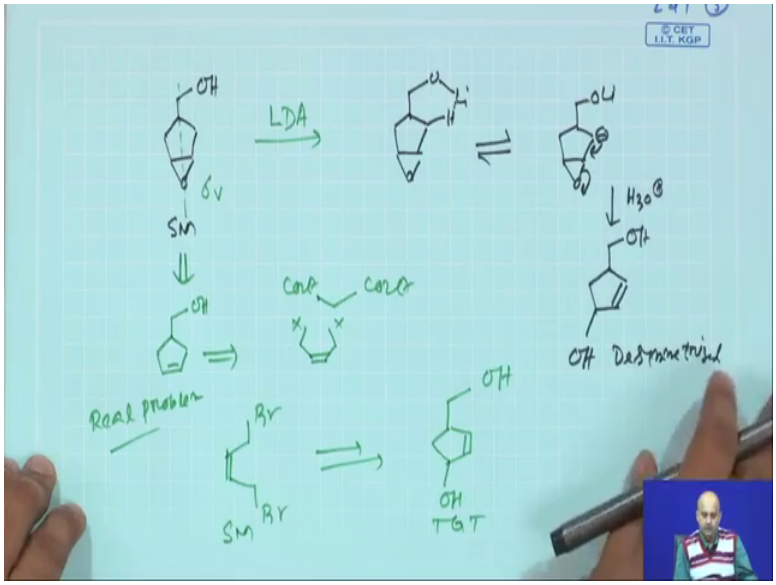

Now, I will be giving a example I am saying that I am giving you this compound. I am saying that this compound is symmetrical starting material is absolutely no issue because if you consider its 2D structure this having a perfectly sigma V I am saying that this molecule is reacted with LDA. Now LDA in principle is a very strong base, but it is the nucleophilic base.

Now, if this compound was stirred with the LDA it has been found that this oxygen l I is coming from this LDA, it also picks up this e naught carbon as it is in close proximity. So, then it basically gives you a OLi and a negative charge here. Now this negative charge now have a electrophilic epoxide hand at the one end, it basically opens up the epoxide; this is also very useful transformation for epoxy alcohol.

Now, you quench this things with H 3 O plus. So, basically get a allylic alcohol now starting material is symmetrical; the final product is desymmetrized. So, now, if I give you this particular problem that I say that this starting material was given to you or you or I can I can say that how you can make this starting material? The retro for this starting

material probably then I am saying a typical diethyl malonate can react with this compound followed by decarboxylation and this things.

So, for a real problem based on this desymmetrization would be something like this; I say you start with this bromide this bromide how you can make this particular compound starting material and your target. So, now, if this was given to you; you basically have to follow the pathway which I have just now discussed.

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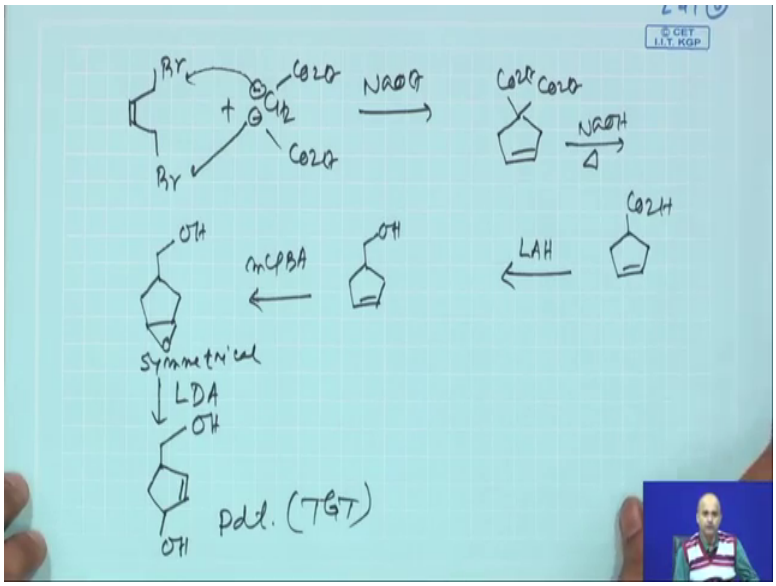

Take this dibromide react with diethyl; malonate now diethyl malonate is having active methylene group, you treat excess base let us say sodium ethoxide. Now two hydrogen principle can be abstract buy excess of ethoxide and then this is a minus and this minus by abstraction of this hydrogen will basically give you reactive this way.

So, what will be getting you get this Co 2 e t C o 2 e t; now do the base hydrolysis followed by heat. So, decarboxylation will takes place with one carboxylic acid will be remaining. Now this one you basically convert to corresponding alcohol by lithium aluminum hydride that will basically give you CH 2 OH. Now this CH 2 OH; you now convert to corresponding m C P B A to basically give you the epoxy alcohol.

Now, you treat your desymmetrization reagent or the LDA; now this epoxide is initially symmetrical which we said your desymmetrization reaction. So, now, here if you do this desymmetrization as done earlier is basically come to this compound which is your

product or target given to you. So, reactions are in principal very simple only thing is we need to have a desymmetrization concept properly exploited.

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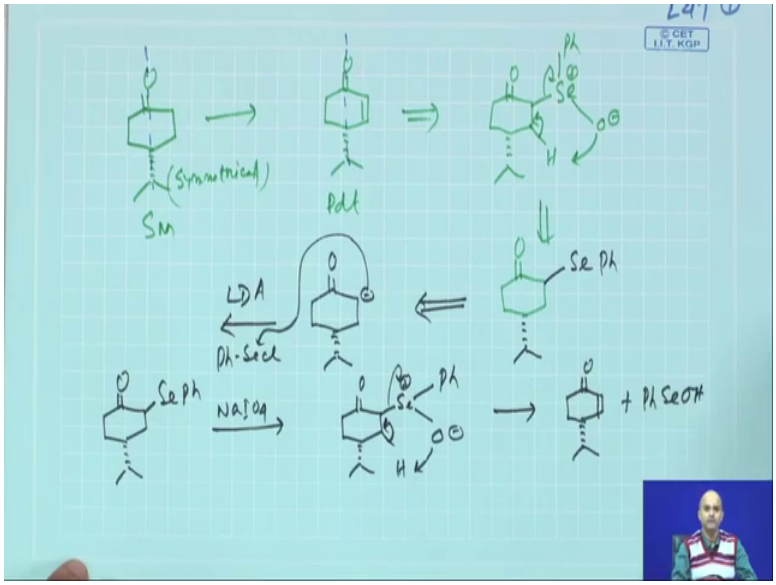

The same line will try to give you. another assignment probably all of you as you. Now I say you are having a starting material of this structure and I am looking for this product; this product.

So, this one basically you can easily do the retro probably the chemistry was already explained to you. I am saying that I will doing a selenoxide seen elimination, what is basically nothing it 2 3 sigma tropic rearrangement. So, this is O minus picks up this hydrogen hydrogen gives here P h S c OH in all together is living.

Now, how this you can make this compound; so, initial molecule is symmetrical this molecule is symmetrical if you consider only this part now this molecule is not symmetric. So, in this way basically we are trying to do it; so left have a right have is not symmetrical. So, fine now I say that this compound you can basically easily make from this S e P h, this also you can easily make from the starting material like this. So, yours forward synthesis now starts with LDA and P h S e c l the electrophilic reagent.

So, initial is we are anion generation which will attack to S e c l to basically give you double bond ketone and S e P h. Now, as I said you need to convert this S e P h to selenoxide, you treat with sodium periodate. So, which basically will oxidize the S e plus

O minus. Now this selenoxide it is basically acting as a base to abstract this hydrogen; in reality it is basically a 2 3 sigma tropic rearrangement 1 2 and 1 2; 1, 2, 3. So, this goes like this and it goes like this; it comes basically you will get the desymmetrized product with the P h S e OH phenyl selenic acid.

So, in this way basically you can do a very nice desymmetrization concept and similar kind of thing if I give you a another example.

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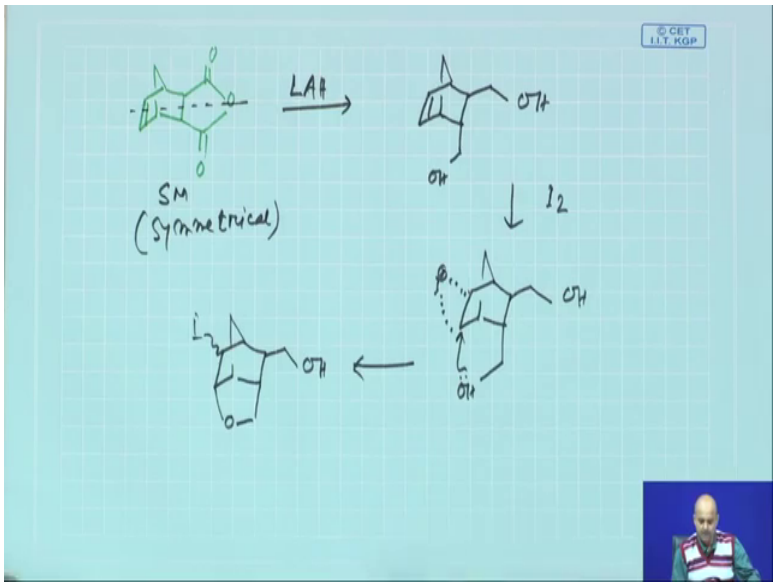

I say how you can desymmetrize this particular compound. Now saying that you are having a compound something like this which looks to be a perfectly symmetrical compound, if I do not talk about the stereochemistry fine. So, as a starting material which is symmetrical, which is symmetrical; now what I am saying?.

That reactions you need to think about some reactions which will destabilizer or which will remove the symmetry. So, I said fast will beat reducing this a nitride because a nitrides are not good functional group to deal with. So, I said first we reduce this things to corresponding OH OH ok.

Now, we see OH are nuclephilic nature and you have a electrophilic double bond. So, any day any principally unique reactions you can think about. So, let us say you will be doing a simple iodonium ion chemistry treat with a iodine, you convert this corresponding iodonium ion and then make this CH 2 OH and the CH 2 OH.

Now, one of the CH 2 you undergo this iodo verification reaction and there are find that your final compound basically having this kind of structure this is now this molecule becomes desymmetric. So, in this way the symmetrical structures can be very nicely desymmetrized; if you try to follow certain very key transformations which we already already discussed ah; probably we will stop with a very simple example.

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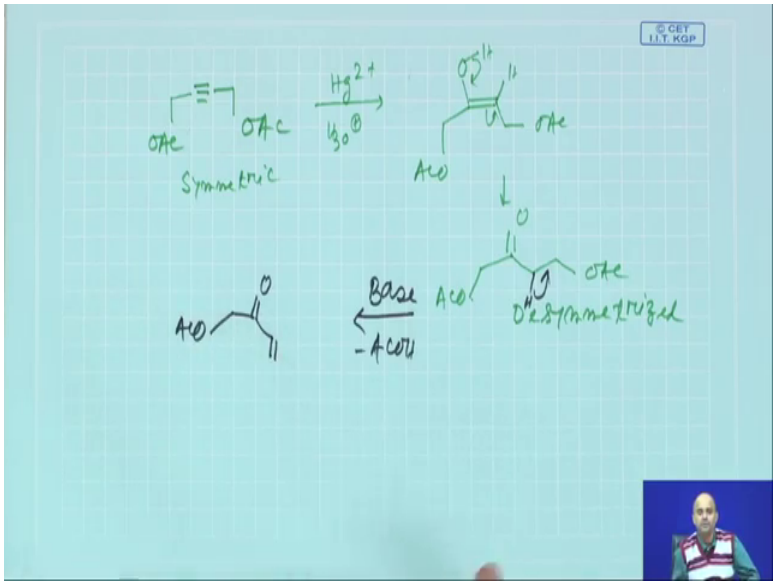

Let us talk about this a cyclic example; I see you are having this example; how you can desymmetrize it. Alkyne you all know; if you react with H g 2 plus in acidic medium; hydration of alkyne takes place to basically give you the moroconic of fashion. So, in a symmetrical alkynes; so, you are having this OH CH 2 ACO; hydrogen attacks here having a CH 2 O A C.

Now, this basically vinyl alcohol undergo tautomerization basically give you ACO double bond Ol CH 2 CH 2 O A C. Now see this starting material was symmetrical very much symmetrical; symmetrical alkyne. You do a simple mercury mediated immediated hydrolysis; you basically get a ketone which is know desymmetrized. So, this is the main reaction which I am trying to focus and eventually this kind of reactions plays a very unique role in eventually.

Now, this particular particular sequence of reaction where from I took it it also gives you a another thing if you treat this compound with a strong base a acetic acid one two elements and takes place, you are having these acetic acid. This compound does not have

a 1 2 eliminations place. So, basically you will be now having this alpha beta unsaturated compound.

So, this way the any principal unique reaction or any standard FGI is able to do the desymmetrization reaction on a given symmetrical molecule. So, we just need to focus is on the structure of the molecule and probably the next lecture we will give you a demonstration of such strategy for the disconnection of a of a natural product. And we will see how this natural products can effectively will be constructed with the help of desymmetrization strategy by applying standard FGI.

So, we will talk those things in the next lecture. So, till then goodbye have a good time.