A Study Guide in Organic Retrosynthesis: Problem Solving Approach

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Lecture – 45
Symmetry based Strategies (Contd.)

So, welcome come back students basically in the last lecture, we have just started symmetry based strategies and we said that for symmetry based strategies.

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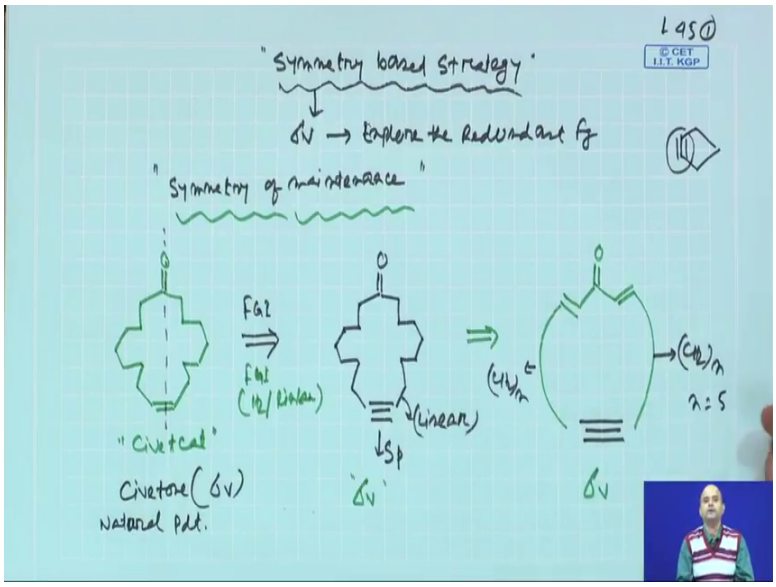

When you are trying to do a disconnection of a symmetrical molecule and mainly we said, we are dealing with symmetrical molecule which does have a well defined sigma V. Now mainly we discussed couple of designed molecule like rotane 3, rotane 5, rotane those molecules and we said in maximum cases we explore the redundant functionality, explored the redundant functionality and, also we said that maintenance of symmetry throughout the pathway is very important. And eventually we have tried to follow that guideline that symmetry maintenance.

The starting material needs to be symmetrical or if the starting material is a symmetrical it is always, advisable to use those starting materials. The symmetry maintenance is absolutely important for sigma V compound sigma V containing compound and, we said that we are not going to discuss about the symmetric controlled reaction which is the

pericyclic reaction in this particular forum, because it is not it will take too much time. So, we are not going to discuss it.

Now, now we will keep on discussing the same strategies and, now here we will be trying to take some of the natural products which does have a perfect sigma V and, how you can follow this particular guideline the maintenance of symmetry, for synthesizing those molecules, or to provide a proper guided retro synthetic disconnection for those molecules.

Very beginning will talk a talk about a natural product which is also, a perfectly sigma V containing molecule and the structure we need to be little bit careful it is a cyclic ketone and the molecules name is civetone civetone. The civetone was basically isolated from the civetcat civetcat which is normally lefts end of himalaya region, high altitude region. Now civetone the molecule name is civetone civetone is it perfectly sigma V containing molecule the symmetry is there ok.

So, now this is a basically I said naturally occurring molecule, natural product, it is a natural product. So, it is not a designed molecule, another state this molecule is a perfectly symmetrical probably the symmetry maintenance criteria, we need to fulfill. And now definitely as if you see the structural features of this molecule, this molecule is basically having a carbonyl, functionality, and now the left hand side and right hand side are basically having a equal number of methylene groups how many it is a 1 2 3 4 5 6 7.

So, 7 methylenes left hand side right hand side 7 methylenes in between you have a z olefinic unit, So, the and the all together the ring size is 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18, this is basically a large ring it is a eighteen member member ketone. The initial retro which was thought of for this molecule by doing a simple FGI and, the disconnection was proposed that the z olefin which lies in the bottom part of the molecule, can easily be constructed from the corresponding alkyne this was usually proposed. So, if you have a simple FGI by using a hydrogenation, with lindlar catalyst you will be able to do it.

Now, alkyne you may ask that say alkyne is basically S p hybridized is S p hybridized and as the ring structure is quite big enough means that this bond has to be linear, you wrote the bond in a bent fashion, but in reality this bond will be linear, to fulfill the criteria of S p and as this bond size is pretty much larger this alkyne can be

accommodated here, but for normal rings like if you have a cyclo pantene kind of ring, you cannot have a alkyne due to severe ring strain because, S p accommodation in a linear fashion cannot be done in this small ring system, but fine nevertheless we will keep on using now see, the initial static material is sigma V this 1 also, symmetry was maintained symmetry was maintained.

Now, the next disconnection which was which was proposed, or which was performed by the researchers, they proposed that if this alpha beta unsaturated ketone was used as a starting material and, then basically you can reduce this alpha beta unsaturated ketone to get this cyclic ketone.

Now, this part I would not write the CH 2 this part, I would not write the CH 2 because you know that how many CH 2s are there. So, I will just put the alkyne here this is the alkyne. So, I said that if you have this kind of fragment with this CH 2 n this is basically contains CH 2 n how many CH 2 1 2 3 4. So, now basically you are having 1 2 this CH 2 is needs to be create. So, this was done then 1 2 3 4 5, so n is now 5. So, here also you are having CH 2 n n is 5.

Now, this alkyne as well as key to olefin can be synthesized people have been though in a different way, now this molecule is also sigma V this is also sigma V.

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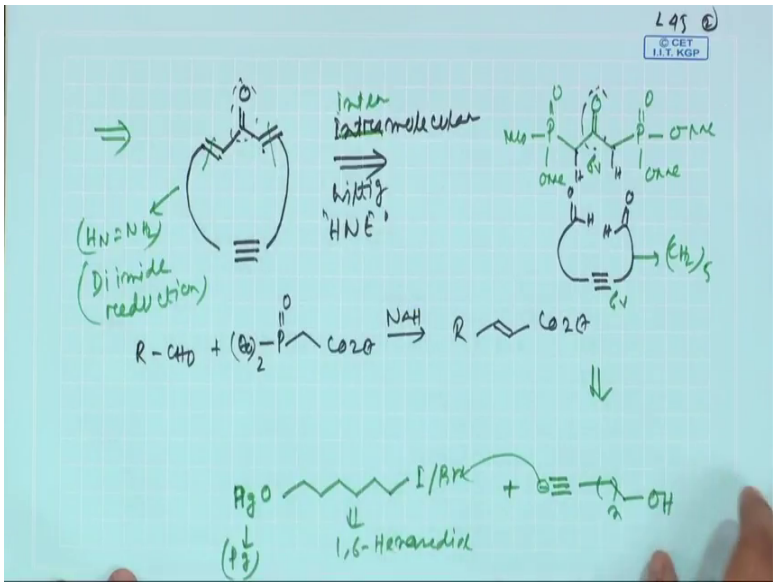

So, in the next retro which was proposed, if you see the earlier intermediate, which you basically propose it is having a we will again draw it, it is basically having a diolefinic partner and, this end and this end are basically linked you are having a asymmetric unsaturation here.

Now, I am saying that we will try to do a intermolecular Wittig reaction, intra molecular Wittig reaction to construct intra molecular Wittig, or you often talk about this reaction Horner wads worth Emmons reaction to construct this compound or. Now the Horner wads worth Emmons reaction probably all of you know you having R CHO, you react with corresponding phosphonate derivative in presence of a base, this reaction we have discussed earlier, and it is possible you can basically get the alpha beta unsaturated register, this is very known reaction well known reaction.

Now, here what I proposed? So, now if you have it is not a intramolecular Wittig actually, it is basically a intermolecular Wittig, we propose that ok. So, this part this part you will be creating and this part you will be creating. So, this particular double bond, this particular double bond is coming from a Wittig fine. So, then I say that in between if you can put this carbonyl and, then the phosphonate is basically a bisphosphonate you are using a bisphosphonate something like this meo ome now this bisphosphonates bisketo phosphonate in principle having acidic hydrogen here, which can be easily picked up by base.

Now, this central carbonyl of this ketone served as this this CH, this CH, is this CH, this CH. So, this basically gives you 3 carbon, now this carbon and this carbon is coming from the aldehyde. So, now I am saying that if you having a this alkyne aldehyde, alkyne aldehyde and this part also this alkyne aldehyde.

Now, this part basically I said is a CH 2 5 in the earlier slide. So, if you have a base alkyne aldehyd, you do a horner wadsworth emmons reaction, then you do the lindlar catalyst mediated reduction here, and then you reduce this double bond completely. So, or initially you can reduce this double 1 first and, then touch the littler 1.

So, this way basically you can do the synthesis. Now coming to your remaining part, now see this molecule is a sigma V this molecular also a sigma V. So, symmetry was maintained. So, now I am saying that probably this compound you can easily easily prepare, if you have the require this kind of this kind of propargylic alcohol.

Now, depending on the number of carbon, you can basically basically figure it out, how it can be how it can be easily easily constructed and, then for this left hand side and this is also similar kind of so, you again put a so, basically you need how many carbons basically you need 1 2 3 4 5 6, 1 2 3 4 5 6 this x iodo or bromo.

Now, this is pg stands for the protecting group. So, this kind of compound can be easily prepare from corresponding 1 6 hexanediol by using protecting group chemistry that I all know. So, what you do you just create a carbon ion, react with this electrophile, and then you get this is 6 this is also 6, then this Pg has to be removed, you oxidize this alcohol this alcohol to get the symmetrical dialdehyde fine.

Then you do the Horner Wadsworth Emmons reaction. Now once you do the Horner Wadsworth Emmons reaction, your next part is basically you have to do the first this particular double bond reduction, the double bond reduction can eventually be done without touching the triple bond mainly you can use a diimide reduction.

So, diimide is a very selective reduction which usually do not touch the triple bond and, then once double bond reduction was done, you can touch the triple bond so, in that way, but if you the take home message or the main point which were highlighting is basically a symmetry maintenance.

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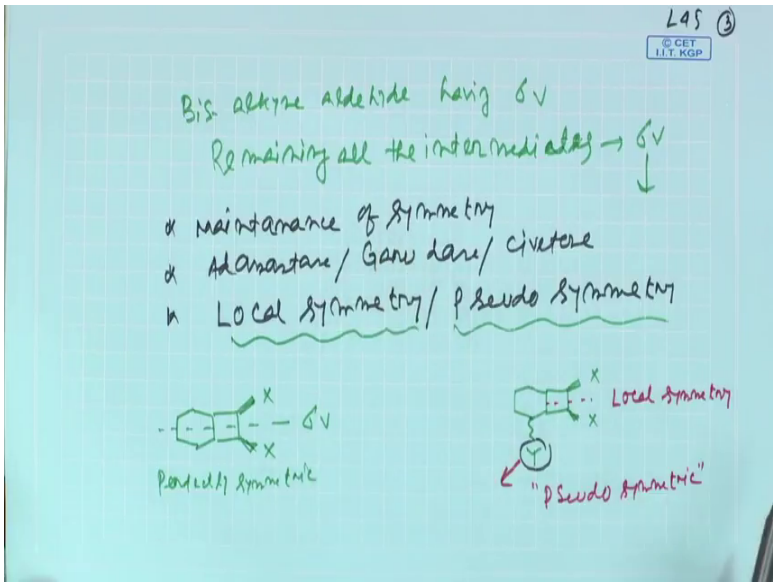

So, you see initial that bis alkyne aldehyde bis alkyne aldehyde is having the sigma V and, remaining all the intermediate remaining all the intermediate all the intermediates having sigma V.

So, sigma V was basically maintained throughout the pathway that is why you called maintenance of symmetries absolutely important. And there is also give you a good guideline that how you can make your entire pathway. Now if you go through the earlier lecture we said that under this symmetry based strategies, we will try to focus mainly 3 or 4 different topics we said, will be talking about maintenance of symmetry which you have basically discussed maintenance of symmetry and, then we say that there are examples which you kept talked about molecules like adamantane and molecule like, garudane and also the naturally occurring compound civetone.

Next we said that there will be 2 remaining points which will be need to consider, the another point which is very important the next point, it is called local symmetry and pseudo symmetry, pseudo symmetry. So, this two point now that we do discuss.

Now, this it local symmetry the name implies a molecule, or a particular segment of a molecule contains a symmetry and, that gives a local symmetry and due to presence of the local symmetry. The entire molecule is not symmetrical, but like symmetrical molecule that is why it is called as pseudo symmetry. Now if I see I will let us I will give you a very standard example, we just did not I say we have having a this kind of compound, I have drawn in a 2 dimensional way. So, I say this molecule is a perfectly symmetrical ok, that is absolutely no doubt about that.

Now, I am saying I am drawing another molecule and, then I am saying that if this cyclohexane part having a Y functionality, this molecule now does not have perfect symmetry because, the presence of this Y functional group here, makes the molecule not symmetrical, but still the cyclobutane part the cyclobutane part is symmetrical. So, now this is called local symmetry, the cyclobutane part which has the symmetry is called local symmetry. The eventually presence of Y presence of Y is basically the main disturbing factor. So, from perfect symmetrical molecule now the molecule, you can call it as a pseudo symmetry, or pseudo symmetric molecule.

Now, sometimes there are there are many natural products which will find that, they belong to this class symmetrical class and, for this the pseudo symmetrical molecule is

always always advisable, if you can disconnect the pseudo symmetrical molecule, to a called symmetrical molecule, or a now local symmetry means this part is perfectly symmetrical.

So, then our criteria of perfectly symmetrical molecule, where you say that maintenance of symmetry is the strict advisable or strict criteria; now what will be trying to do we will talk about some example and, then you will find that how this local symmetry and pseudo symmetry is a taking a lead role.

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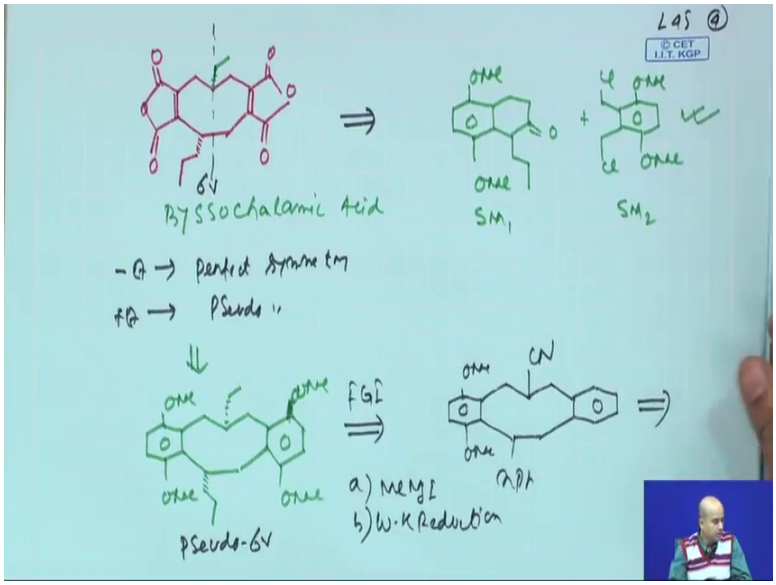

The examples will basically a natural product and this natural product name is Byssochalamic acid.

Now, you see it is structure very carefully, the left hand side and right hand side of this molecule, having a maleic anhydride part ok. And then this 2 maleic anhydride part was joined, the left hand part was joined with a 3 m threes methylene bridge and the bottom part was joined with 2 methylene bridge, in the top 3 methylene bridge in the center, you are having a ethyl functionality, in the bottom and side you are having a n profile functionality, the stereochemistry was there, but we did not discuss about the stereochemistry.

Now, this is a natural product whose name is byssochalamic acid fine. Now if you now analyze the byssochalamic acid, byssochalamic acid should be perfectly symmetrical like

this way, if there is no ethyl group here. So, minus ethyl the molecule is perfectly perfect symmetry fine. Now as ethyl is there the molecule becomes pseudo symmetry.

So, now I will try to analyze that how this molecule can be retro synthetically disconnected and, it was shown that this molecule can be synthesized by or from this 2 intermediate. So, one of the intermediate is pseudo symmetrical intermediate, and one of the intermediate is local symmetrical intermediate. Now we will explain how.

Now, this molecule I set this part this part all almost symmetrical. So, this part is having local symmetry local symmetry, the central part seems to be symmetrical except this ethyl group. So, now I am saying that you can basically make this molecule through this 2 static material, for this one is perfectly symmetrical and, this one is having local symmetrical.

So, a local symmetrical unit and a pseudo symmetrical unit contains together, to give you a pseudo symmetrical molecule. Now the disconnection part will now try to focus, at the very beginning we said that the succinic anhydride oh sorry this maleic anhydride part can easily be constructed through a oxidative ring cleavage sorry, this is oxidative ring cleavage of this aromatic nucleus like having 1 4 dimethoxy benzene.

The remaining part of this molecule will remain similar, will put a ethyl group here, will putting a end profile group here. So, this is fine so initially this mode this is again a pseudo sigma V or pseudo symmetrical right. Now I am saying that this ethyl and this n propyl. we need to introduced. So, next what retro was proposed the central thing the ethyl group will be introduced and, it has been proposed that that ethyl group can be introduced from a sign of group by a normal FGI.

Now, what are the reactions will be doing it here, sine of group reacting with a methyl magnesium iodide will give you COCH 3, then this COCH 3 will be converted to corresponding ethyl by a Wolff Kishner reduction, we are not going to discuss that the forward path as it is very straightforward. So, now the next retro which I am now proposing, it is bit different, we are now saying that that.

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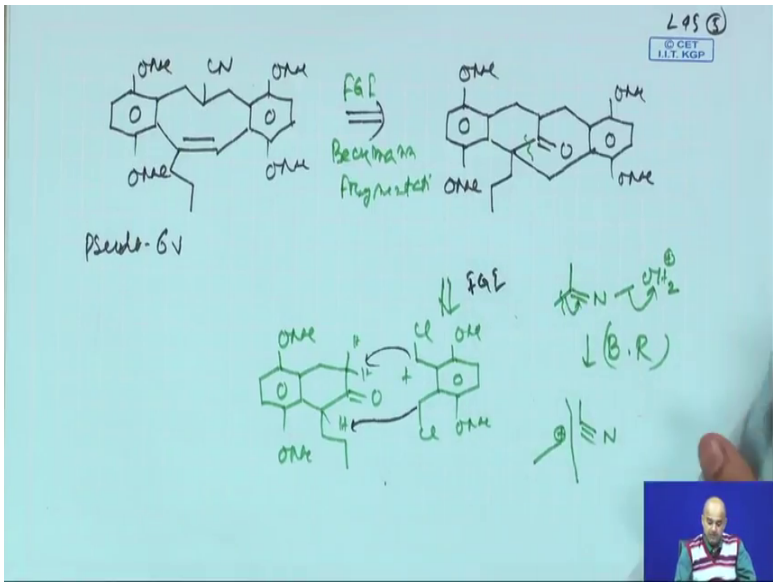

Next retro which will be now the all the other parts will be remain similar, the 2 aromatic ring is similar and, then we are saying that this CN is there and will be saying that, let us formulate this as a ring.

Now, the intermediates earlier 1 is having pseudo sigma, this is also having pseudo sigma V. So, basically symmetry was kind of maintained. And now this molecule is basically having this part is local symmetrical local symmetrical this part is pseudo symmetrical. Now why you have to this is basically a normal FGI, this is normally FGI, if we just reduce this double bond you come to the earlier intermediate.

Now, this particular fragmentation which was proposed now, it is very interesting and this is the limelight of the entire synthesis, or the main highlight of the synthesis, this will explain in detail how this mechanism takes place. So, what you say if you have this particular intermediate, which were proposing here, this intermediates can be easily converted to this intermediate.

Now, how I am saying that I am just writing in this way, that if you convert this ketone to corresponding oxime. So, oxime was means in a now you do a beckmann type of rearrangement. So, means this oxime will be first converted to corresponding this OH 2 plus and, then this will go. So, you have a electron deficient nitrogen. Now here if you see this compound you make a oxime make a oxime and, then once this OH 2 plus goes

off, you will find that this bond fragmentation will basically give you a positive carbonium ion here, like this particular bond will fragment or it. ah

So, in this way basically if it goes it puts it is charge here, to give you a nitrile and fragments in this way. So, these fragmentations are we are talking about, it is basically a Beckmann type of rearrangement, but it is called Beckmann fragmentation. Now why this carbonium ion is formed because this carbonium now which is forming here, is extremely stabilized, because it is a benzylic as well as tertiary, so, now this thing is basically cleaving and you get a cyanide here. So, this C stands for cyanide ok. So, the Beckmann fragmentation is the crucial.

So, we now say that is a very good FGI and the reaction is Beckmann type of rearrangement, you can think about Beckmann fragmentation, you can just call it fragmentation. So, now, we have to complete the synthesis, now you see the starting material can be easily correlated; now our starting material can easily be correlated. So, ome ome and the starting material which was given as the initial lead can now be linked, can now be linked.

So, these part this part you are having this corresponding benzoyl chloride. So, what you see we say that this ketone does have a this acidic hydrogen, as well as this acidic hydrogen. So, you do a successive round of alkylation 1 with this site the thermodynamically controlled, and this side the kinetically controlled, you basically get this double alkylated product through a FGI.

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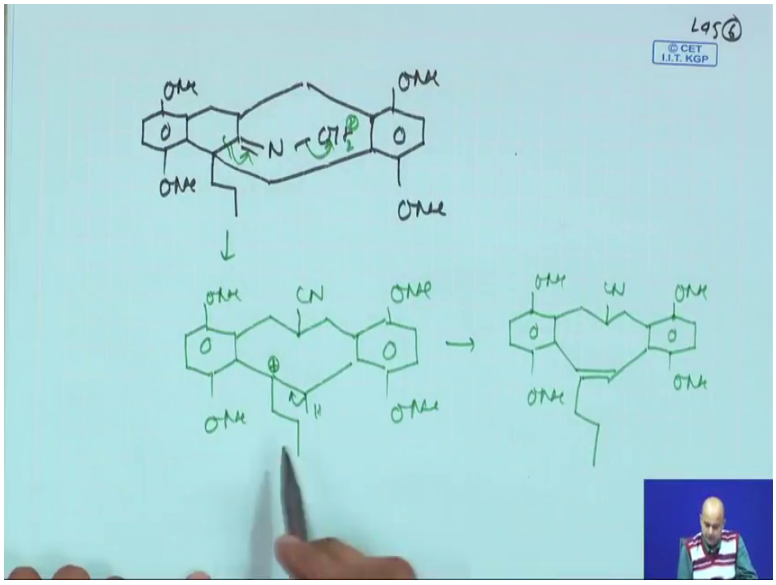

The Beckmann fragmentation was pretty important, which which will be now just giving you the mechanism just for a very simplified version. We say you have this particular compound. So, you have this Beckmann rearrangement which were proposing, or it will basically takes place and, then you have this because the drawing has to be little bit bigger, otherwise the fragmentation you would not visualize clearly ok.

So, now you say initially this goes off OH 2 plus and then once this goes off it will try to fragment in this way or this way. Now this way fragmentation give you a positive charge here, and this way fragmentation will give you a positive charge here. So, this fragmentation will basically give you ome ome, this part and then your cyanide now goes there, is not it. So, your ome ome so, fragmentation basically means this bond puts all this electrons through this double bond. So, C triple bond N is formed.

Now, you will basically having this carbonium ion, this absolutely stable carbonium ion benzylic as well as tertiary. Now you are having a hydrogen. So, this hydrogen will give you the eliminated product, which is 1 of the intermediate with proposed and, this is also the sigma V or pseudo sigma V intermediate. Now we are basically yes so, this was the intermediate which was earlier proposed in 1 of the steps.

If you see the symmetry part was strictly maintained strictly maintained. Now what you do?

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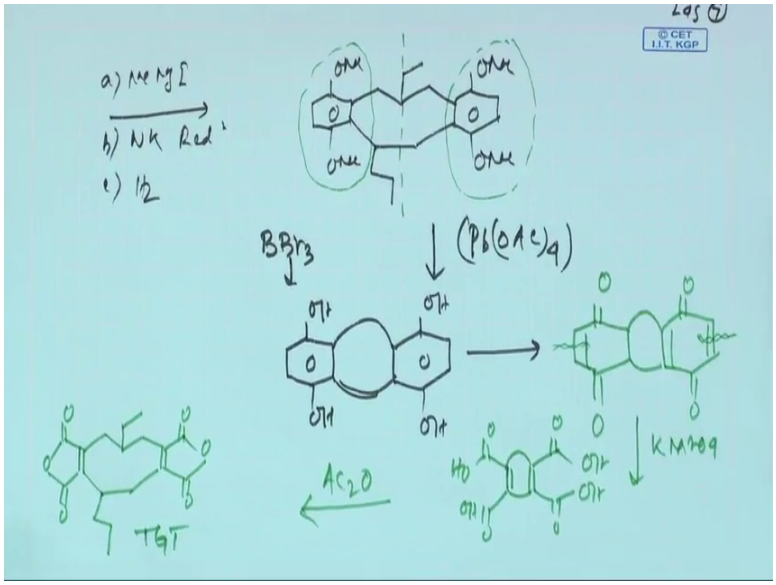

Once you have this earlier intermediate you first do a methyl magnesium iodide as I said, you do a Wolff Kishner type reduction and also you do a hydrogenation. So, once you do this 3 FGI together, you probably end up with the main core of this molecule, for only thing you need to do it, the oxidation of this aromatic electron rich, aromatic part, where you are having this 1 4 dimethoxybenzene.

Now, this intermediate is sigma b or pseudo sigma b because, this intermediate is pseudo sigma , except if this is n propyl can be removed the molecule is perfect sigma , this part I say local symmetry local symmetry, this part also I say say local symmetry. So, local symmetry element dots there ok.

Now, the remaining part what was done actually, normally this kind of transformation they used a lead tetra acetate and do a the oxidative decarboxylation first probably, initially you do a BBr 3 mediated demethylation of both the aromatic ring. So, you will be having OH OH fast, which will basically will use this one little bit later on.

So, BBr 3 first demethylate the OH this part is there and then you write this OH and OH ok. Now the oxidation part. So, oxidation you are using a lead tetra acetate to basically give you the corresponding quinine, this quinine, this quinine. So, use this quinine.

And then the reagent which was used, it is a hot KMnO 4 KMnO 4 solution to basically clip this double bond to clip this side double bond and, then cleavage of other things also

means it is like a oxidative cleavage and, then what you basically get you get this dicarboxylic acid, dicarboxylic acid, dicarboxylic acid.

So, this now undergoing cyclization basis of acetic anhydride and, then you get the parent compound whose structure is you basically have this maleic anhydride part, which you are talking. So, this maleic anhydride is you write this way, the left hand side you write the right hand side in this way ok, you have this ethyl group you have this n propyl group, and this is your target molecule.

So, the particularly this, if you do not consider the symmetry part also, the synthesis is very unique because you did couple of functional group inter conversion and, the key transformation is here the Beckmann fragmentation. It was absolutely absolutely brilliant and, the Beckmann fragmentation will definitely give you the particular a particular product what are looking for.

Now, so probably we will stop it here and next lecture we will try to continue on the similar topic and, how we can basically use the concept of local symmetry and pseudo symmetry to disconnect some of the target molecules, and a see how the guidelines, which you have earlier demonstrated, we can basically follow those guideline in a sequential manner. So, have a good time good bye.