Classics in Total Synthesis-I
Prof. Krishna P Kaliappan
Department of Chemistry
Indian Institute of Technology, Bombay

Lecture - 24
Gibberellic Acid (Corey)

Good morning everyone. Welcome back to the NPTEL lecture series on Classics in Total Synthesis part I. So, today we will continue our discussion on total synthesis of terpenoids and we will focus on 2 total synthesis of 1 complex natural product called Gibberellic Acid.

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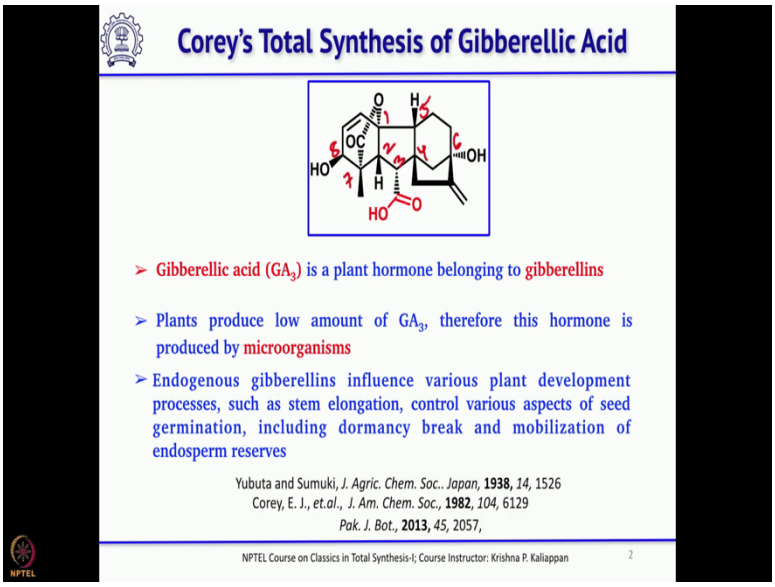

So, this gibberellic acid as you can see here it is quite complex. It has about 5 rings and several chiral centers and this plant hormone belonging to called gibberellins, and it was produced by plants. And from synthetic point of view when you look at this molecule, it poses several challenges. It has 8 stereocenters, you can see here – 1, 2, 3, 4, 5 that means, all the 5 carbons of the middle 5-membered ring are chiral centers ok. Then you have one here, 6, 7, 8 ok. So, there are 8 chiral centers in this molecule.

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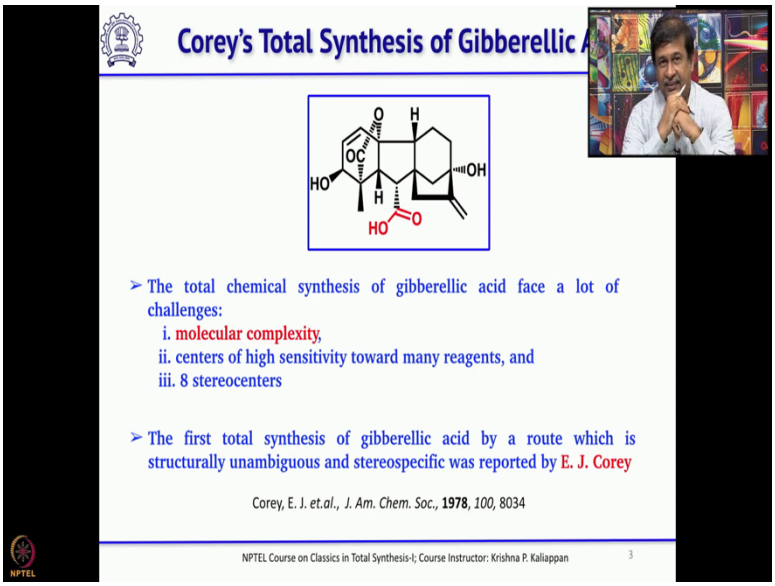

And more importantly it is not only the chiral centers, 8 chiral centers which can create trouble as such this molecule is very sensitive towards acids and bases ok. So, that is another reason why synthesis of this molecule created a lot of challenges to synthetic chemists. Nevertheless, the first total synthesis of gibberellic acid was reported by none other than Nobel laureate E. J. Corey and his synthesis involved Diels Alder reaction, intramolecular Diels-Alder reaction, iodolactonization, epoxy lactonization, and radical cyclization.

So, these are the key reactions, which Corey has successfully used in the synthesis of gibberellic acid.

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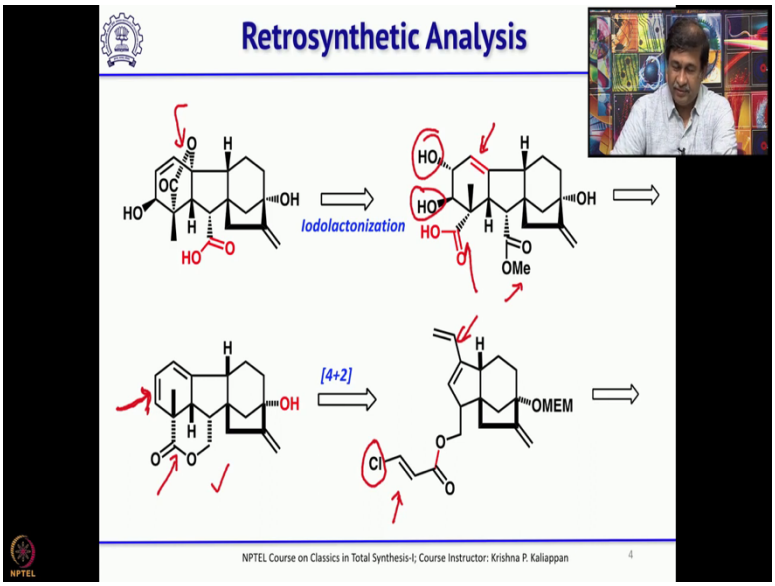

So, let us see his retrosynthesis. His idea was this particular lactone ok, this particular lactone can be made from this intermediate using iodolactonization as the key reaction ok. Using iodolactonization as the key reaction, you have a carboxylic acid here ok, and you have a double bond. So, one can easily plan iodolactonization.

I will come to that what is iodolactonization in a couple of minutes, then he thought these 2 hydroxyl groups ok, can be introduced with the help of the double bond. If you have a double bond here, then one should be able to introduce 2 hydroxyl groups which are anti to each other ok. And also you can hydrolyze this lactone and oxidize you will get this dicarboxylic acid ok. So, he thought this could be made from this particular intermediate ok.

Now, if you look at this intermediate, his idea was to use an intramolecular Diels-Alder reaction ok. So, you can see a diene here and a dienophile. The intramolecular Diels-Alder reaction 4 plus 2 and you also can see a chloride here is not it. That can undergo elimination ok, to generate one more double bond; this double bond ok. One more double bond this double bond can be generated after the Diels-Alder reaction followed by elimination ok.

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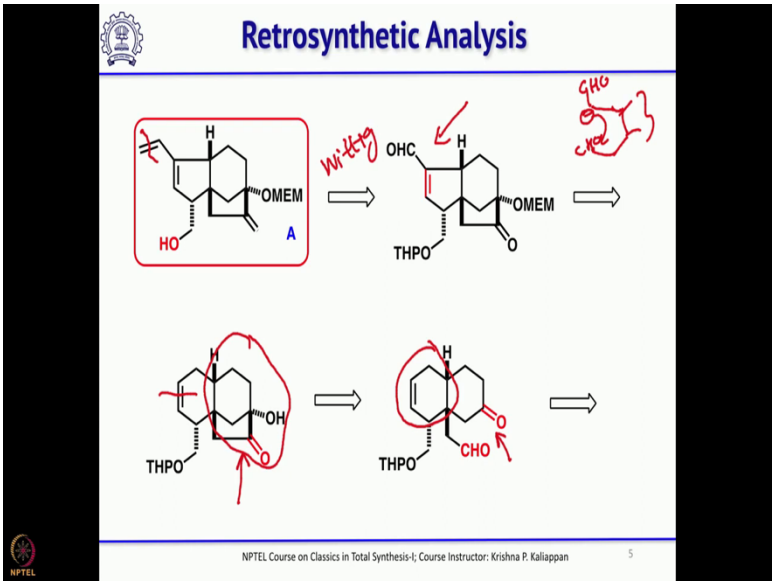

Now, this can be obtained from the corresponding alcohol ok. So, this is the key intermediate. This is the key intermediate in the synthesis of gibberellic acid proposed by E. J. Corey. How this key intermediate can be made. When you have a double bond here, one can think of using a Wittig reaction is not it.

So, by methyl Wittig it should be possible to homologate this aldehyde to the vinyl group. Now, you have an alpha beta unsaturated aldehyde ok. Wherever you see an alpha beta unsaturated aldehyde, one reaction which should come to our mind is aldol reaction ok. So, that means, if you have dialdehyde basically, if you have a dialdehyde like this; then this can undergo an aldol followed by dehydration you should get this alpha beta unsaturated aldehyde. But how do you get this 1, 5 dialdehyde?

You can do a cleavage of the double bond. You can do a dihydroxylation followed by cleavage with sodium periodide one can get the corresponding 1, 4 dialdehyde. Next, when you look at this molecule carefully, you have this bicyclic [3.2.1] system. Bicyclic [3.2.1] system and this he wanted to cyclize ok. This is through the keto aldehyde ok.

One can cyclize to get the corresponding alpha hydroxy ketone ok. Then closer look at this molecule, one can see cyclohexene, one can see cyclohexene. When you see cyclohexene in any compound, obviously, 4 plus 2 cycloaddition reaction should come to your mind, is not it.

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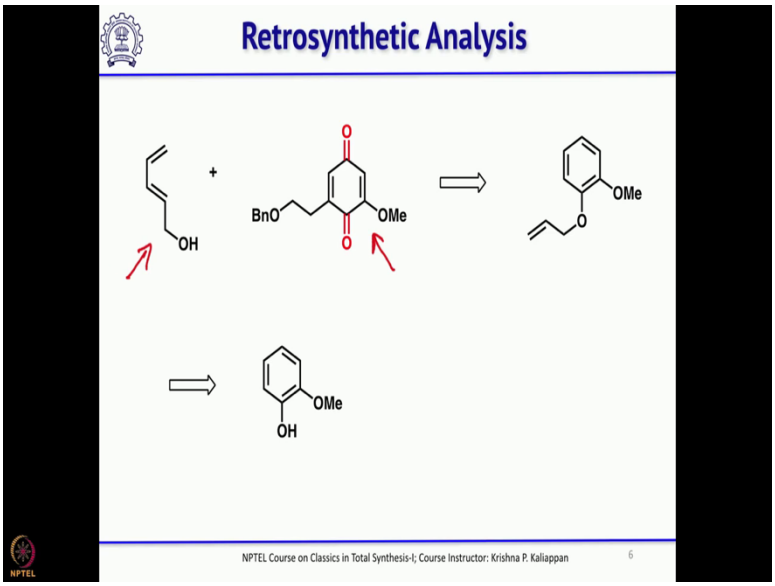

So, he thought he can use an intermolecular 4 plus 2 cycloaddition to get that intermediate ok. This is a known compound and this he thought we can prepare from this O allyl that is 2 ortho O allyl anisole, which can be prepared from guaiacol, which is commercially available ok.

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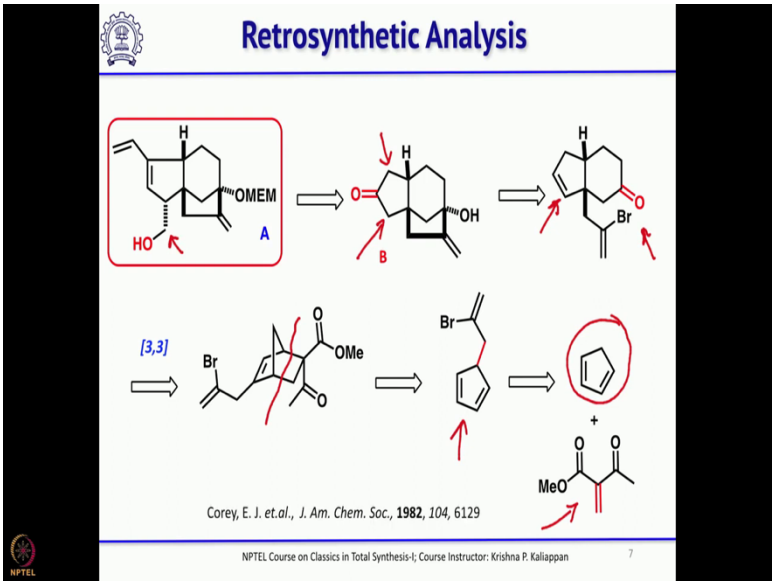

So, this is the first retrosynthesis. And he also proposed another route for the key synthesis of the key intermediate A, and that he thought he can make it from intermediate B by two alkylation ok. One alkylation will lead to the CH_2OH the other

alkylation will give an aldehyde, which can be homologated. So, this ketone can be obtained by a radical like reaction here, and hydroboration and oxidation regio selective hydroboration and oxidation should generate the ketone.

And this double bond you can see here, this could be obtained by a 3, 3 sigma tropic rearrangement ok. I will come to that when I talk about the real synthesis and this intermediate can be obtained by an intermolecular Diels-Alder reaction ok. By an intermolecular Diels-Alder reaction you can see if you cleave this, this is the dienophile and this is the diene ok. That diene can be obtained from cyclopentadiene.

So, these are the 2 pathways Corey had proposed to synthesize gibberellic acid and let us see how he executed the total synthesis of gibberellic acid.

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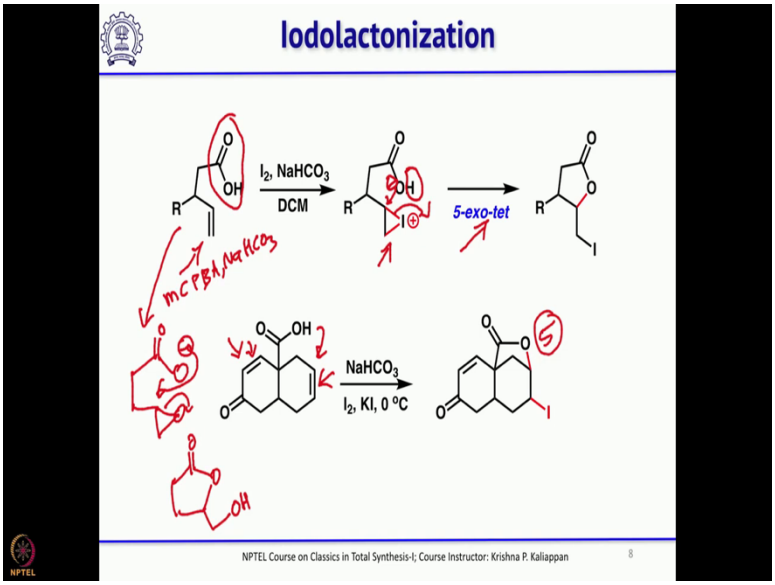

Before that as I said this synthesis as well as the next synthesis of gibberellic acid by Yamada both involve iodolactonization as the key step. So, what is iodolactonization? So, if we have a carboxylic acid, if you have a carboxylic acid and a double bond in the same molecule at appropriate place ok; then when you treat with iodine when you treat with iodine, the double bond first it will form the corresponding iodonium ion ok.

Now, if you can deprotonate this hydrogen of carboxylic acid using mild bases like sodium bicarbonate ok; then the COO minus which forms immediately can open this to give iodo lactone. Usually, the 5 membered lactone is preferred ok, and this goes through

what we call it as 5-exo-tet cyclization ok. This is another example, you can see there are 2 double bonds, one here and one here.

And if it cyclizes here it will form a 5 membered ring, and if it cyclizes this side it will form 4 membered ring ok. So, obviously, 5 membered is more favoured. So, you get 5 membered iodo lactone, likewise one can also do if you have epoxide say for example, the same thing if you use mCPBA and base like sodium bicarbonate. What will mCPBA do? mCPBA will epoxidize the double bond, then sodium bicarbonate will generate carboxylate that can open up ok, you can get intermediate like this ok. That will open up and you will get a 5-membered lactone with CH_2OH ok.

So, iodolactonization you can do, epoxy lactonization you can do. In fact, one can also use phenylselenyl chloride; if you use phenylselenyl chloride you can call this as phenylseleno lactonization, all are possible ok. What you need is a double bond and carboxylic acid, which are separated by 2 carbons ok.

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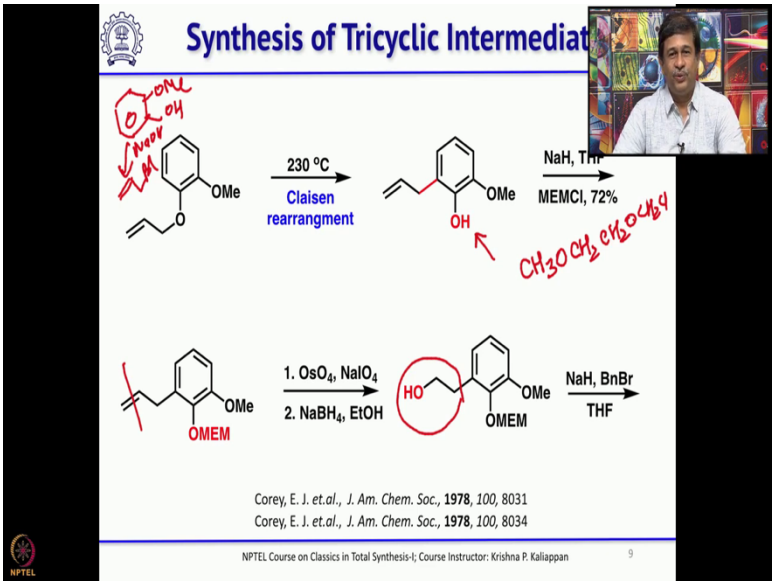

So, that you can get a 5 membered ring. Now, let us see how he synthesize the tricyclic intermediate. So, he started with guaiacol. So, that is this compound ok, OMe and OH and one can use sodium hydroxide and allyl bromide, you allylate the free phenolic hydroxyl then you heat it. So, you heat it at 230 degree Celsius it undergoes Claisen rearrangement ok, as you know.

Allyl phenyl ethers undergo Claisen rearrangement to give the corresponding allyl migrated product ok; if we protect this hydroxyl as MEM ether ok. Now, you can do a dihydroxylation ok, and followed by periodate cleavage. You get diol and cleave it, you get the dialdehyde then that you reduce it you get the corresponding CH_2CH_2OH.

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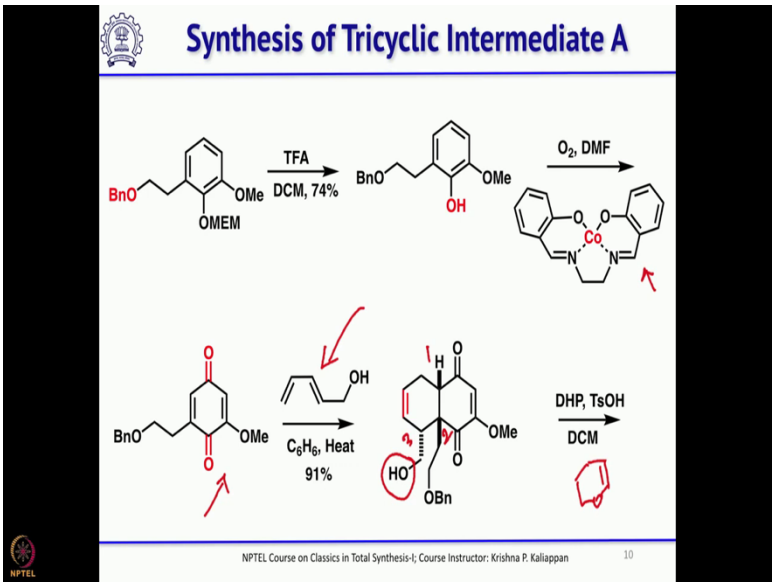

If you look at the dienophile required for the Diels-Alder reaction you need a 2 carbon unit here, is not it. So, that is done. Now, you can protect that hydroxyl as benzyl. So, you deprotonate that hydroxyl group with sodium hydride and quench with benzyl bromide, you get the corresponding benzyl ether. Then comes the removal of MEM group. So, that you can do with trifluoroacetic acid and followed by oxidation of this phenol to the benzoquinone ok.

So, that can be done with this catalyst. So, oxygen as the oxidizing agent and with this cobalt catalyst one can oxidize this phenol to corresponding benzoquinone ok. Once you have this, then you do the Diels-Alder reaction. So, this is a known compound that is a diene and this substituted benzoquinone is a dienophile and then do the Diels-Alder reaction you get the corresponding bicyclic compound ok.

So, now how many chiral centers are fixed? Of course, it is racemic. So, 1, 2, 3. 3 stereo centers are fixed. Then protect the free hydroxyl group as THP ether. So, dihydropyran and treat with para toluene sulfonic acid, you protect the primary hydroxyl as THP ether.

Now, before we move further, I will just briefly explain how the Diels-Alder reaction gave these 3 stereo centers ok, stereo selectively ok.

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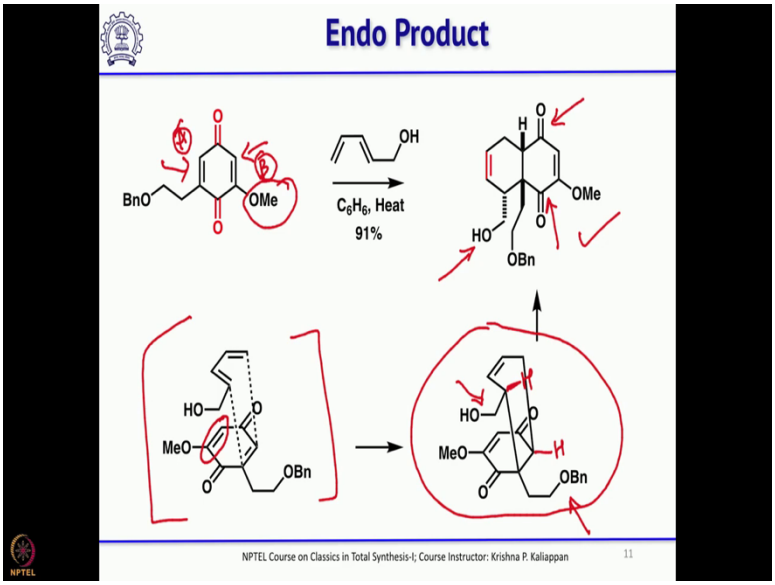

So, this is the transformation and as you know Diels-Alder reaction gives mainly the kinetic endo product as the major product. So, you can draw like this transition state. You can see in this case, you keep the diene like this and the dienophile comes from the bottom dienophile comes from the bottom and this double bond is below the diene, if it is away then it is exo, this is below. So, that is why you get the endo product, because of the secondary orbital interaction.

Now, after the Diels-Alder reaction can you draw this structure; just to connect these 2 bonds ok. And here also between these two double bonds ok, that is double bond A and double bond B, only double bond A acts as dienophile and double bond B does not. Because the double bond A is more electron deficient than double bond B ok. The double bond A is more electron deficient than double bond B, because of the presence of electron donating methoxy group ok.

So, this can be rewritten like this ok. I will keep it for 30 seconds. So, that you know you should be able to draw the conformation properly, so that you will arrive at this particular structure ok. So, it is like this now if you do it, then you will know this will be beta and this hydrogen also will be beta. So, both are cis to each other and here this hydrogen you can see that also will be beta that means this CH_2OH will be alpha ok,

done. Now, you have made the bicyclic compound. So, what is next? You have to reduce these two and before that you have to protect the primary hydroxyl.

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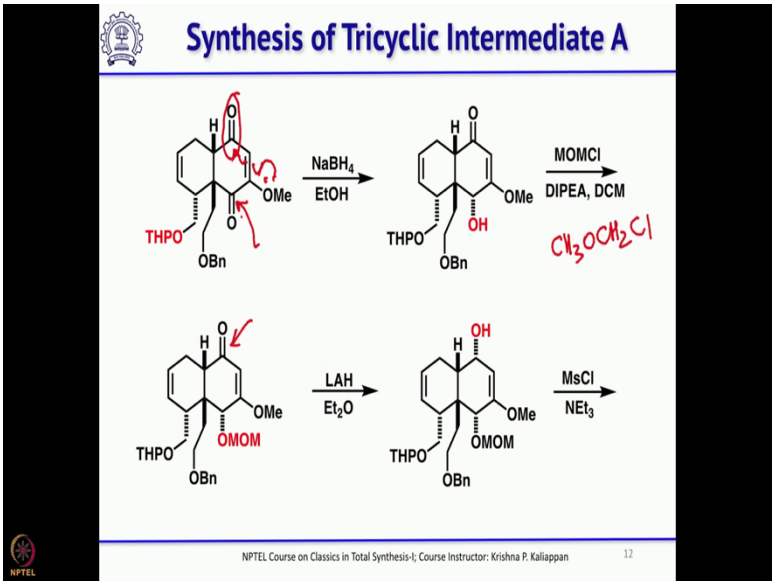

So, as I said the primary hydroxyl group was protected as THP ether by treating with dihydropyran and PPTS. Then you can reduce this ketone selectively over the other ketone; because of the presence of lone pair of methoxy group, this carbonyl is more electrophilic ok. So, that it can attract hydride faster than the other carbonyl. So, one can easily reduce. Now, also the structure is like this, is not it.

So, the hydride will come from the top that will lead to alpha alcohol ok. Then protect the alcohol as methoxy methyl chloride that is CH_3OCH_2Cl, then reduce the enone at low temperature that is alpha beta unsaturated ketone. So, reduce that at low temperature to get the corresponding allylic alcohol. Now, the allylic alcohol if you mesylate ok. So, allylic alcohol if you mesylate you get the corresponding mesylated product.

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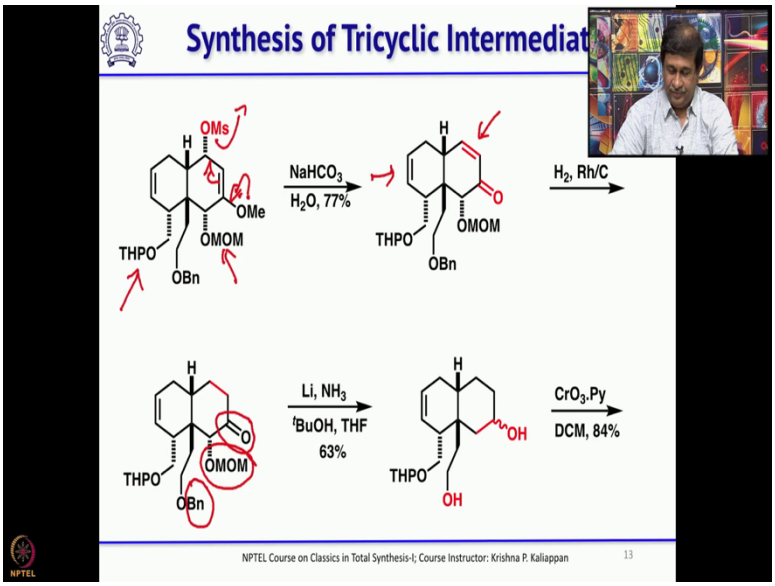

When sodium bicarbonate you know its a good leaving group. So, you can use this lone pair on the methoxy group to eliminate that and in the process what you get is corresponding enone ok. So, this could have been easily done on the alcohol with acid, but as you know this THP and MOM both protecting groups are sensitive to acid that is why he has to convert that alcohol allylic alcohol to mesylate and then use sodium bicarbonate that is base mediated hydrolysis to get the corresponding cyclohexenone.

Then you have isolated double bond, then conjugated double bond, conjugated double bond is selectively reduced under rhodium catalysed condition. Now, if you use lithium and ammonia ok. So, lithium ammonia is known to remove benzyl group ok. So, the benzyl group is removed, but at the same time you have a ketone also, is not it. When you have ketone lithium ammonia also will donate electron to the carbonyl group.

So, as a result the carbonyl group will become ketyl radical ok. Then that will eliminate this OMOM group and you will form enolate, you will form an enolate that will become ketone then that ketone also will be further reduced. So, what lithium ammonia does here is 3 things. One it removes the benzyl group you get the corresponding OH, then it adds one electron to the ketone first.

So, that removes the MOM group and in the process it forms enolate and enolate becomes ketone and then ketone is further reduced to corresponding hydroxyl group.

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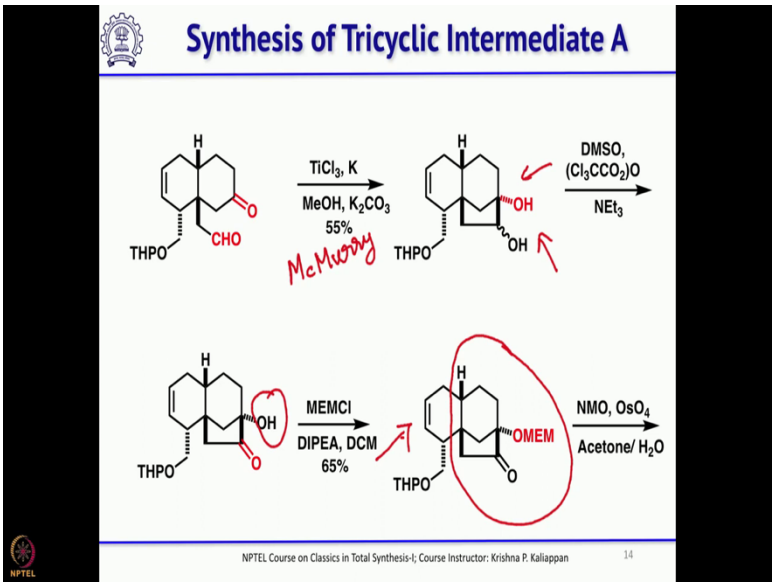

Then oxidation of the diol with chromium trioxide pyridine you get the corresponding keto aldehyde ok. Now, you carry out this McMurry coupling. So, the McMurry coupling on this keto aldehyde gives the 3rd 5-membered ring. 3rd ring which is 5 membered ring ok. Now, this is tertiary alcohol, this is secondary alcohol ok. So, secondary alcohol is oxidized under modified Swern condition to get the alpha hydroxy ketone and again this bridgehead hydroxyl was protected as MEM ether ok.

So, now this whole side is taken care. So, what we need is modification on the left hand side ok. So, you have a double bond, if you treat with osmium tetroxide in the presence of stoichiometric amount of NMO, you get a diol and that diol, if you cleave with lead tetraacetate you get that di aldehyde ok.

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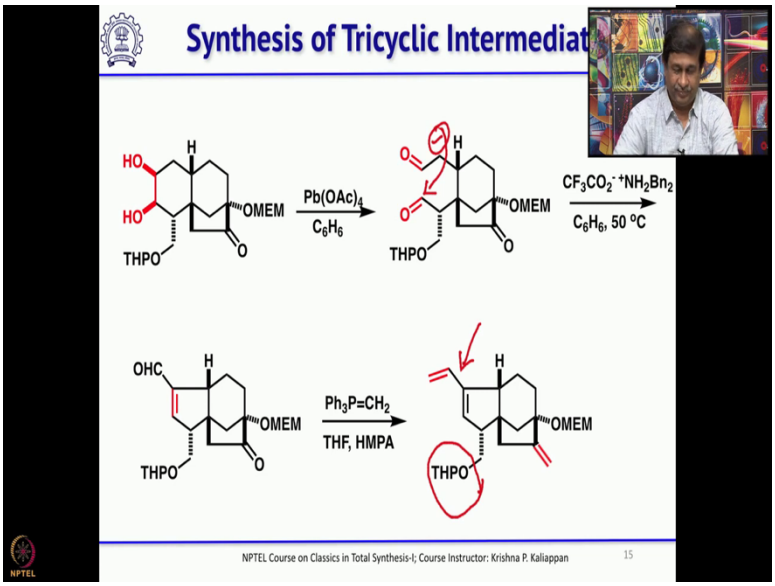

So, as we have noticed in retrosynthesis. So, this is one of the key precursor for making the key intermediate A. So, once you have this then one can carry out an intramolecular aldol reaction with bases like dibenzyl ammonium trifluoroacetate. So, that gives the corresponding alpha beta unsaturated aldehyde. So, once you have that alpha beta unsaturated aldehyde simple Wittig reaction will give the corresponding double bond. So, now, you have the diene which is ready for undergoing intramolecular Diels-Alder reaction ok.

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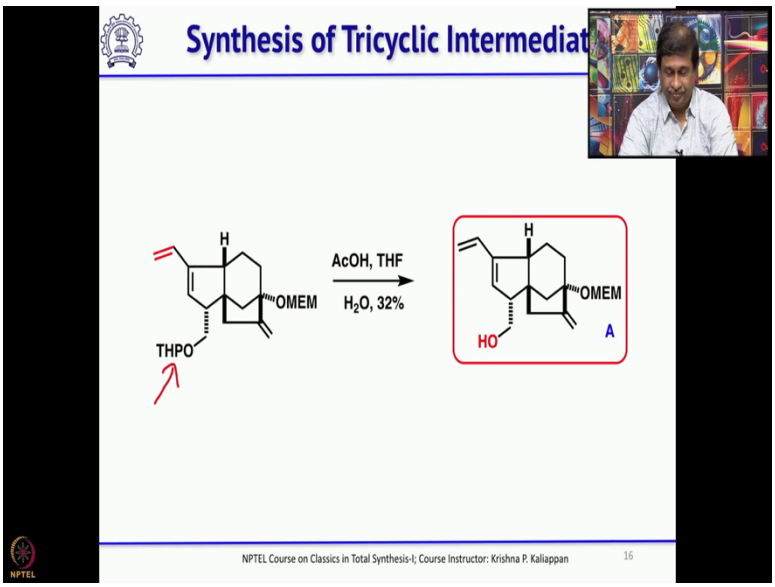

So, what we need is you need to remove this protecting group and attach the dienophile for the intramolecular Diels-Alder reaction ok. Once you have the THP ether treat with acetic acid you remove the THP and you get the key intermediate A.

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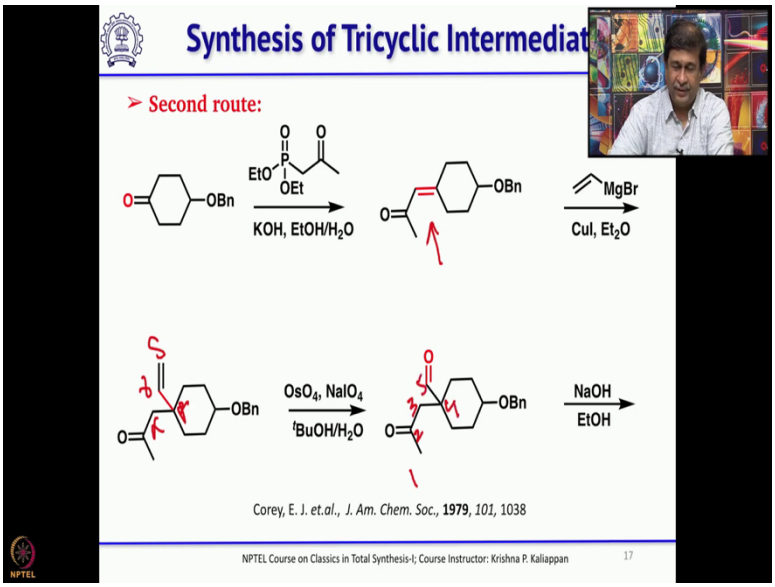

The same intermediate he has prepared by 2 more methods. The second method he started with 4 benzyl oxy cyclohexanone; 4 benzyl oxy cyclohexanone, then Wadsworth Emmons modification. So, he did this Wittig modified reaction he got the alpha, beta, unsaturated ketone and then vinyl 1, 4 addition to this enone, you get gamma, delta, unsaturated ketone. The same thing one can also think about using a Claisen rearrangement to get gamma, delta, unsaturated ketone or aldehydes. We will come to that when we talk about Claisen rearrangement.

Then the double bond is cleaved, the double bond is cleaved with osmium tetroxide and sodium periodate. So, this upon aldol reaction, this upon aldol reaction you can see 1, 2, 3, 4, 5. So, it will form a 5 membered ring ok.

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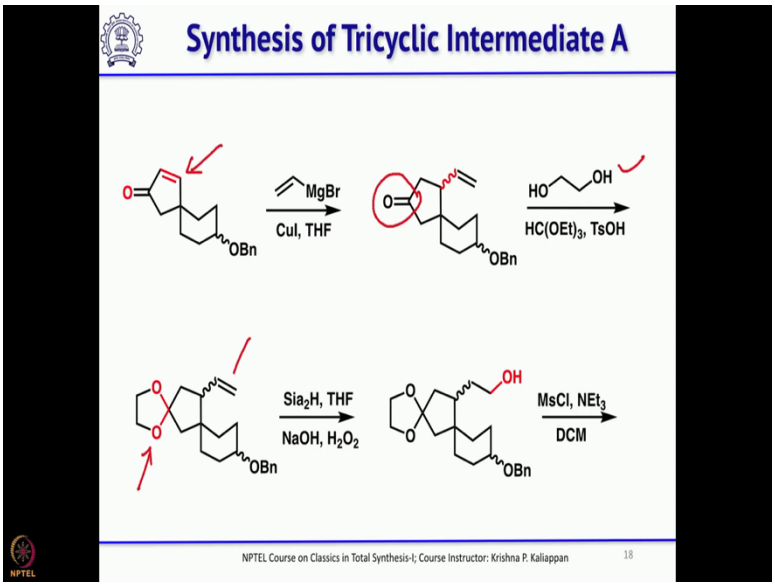

So, now you have here spiral system ok. 6 membered 5 membered both are fused through spiral fusion. Then one can think about adding a 2 carbon unit. So, that is what he did a vinyl magnesium bromide along with cuprous cyanide, it underwent a 1, 4 addition. And then with triethyl ortho formate and ethylene glycol, he protected the ketone as the ketol, then he did a selective hydroboration ok, on the double bond to get the primary alcohol that alcohol was mesylated to get the primary mesylate.

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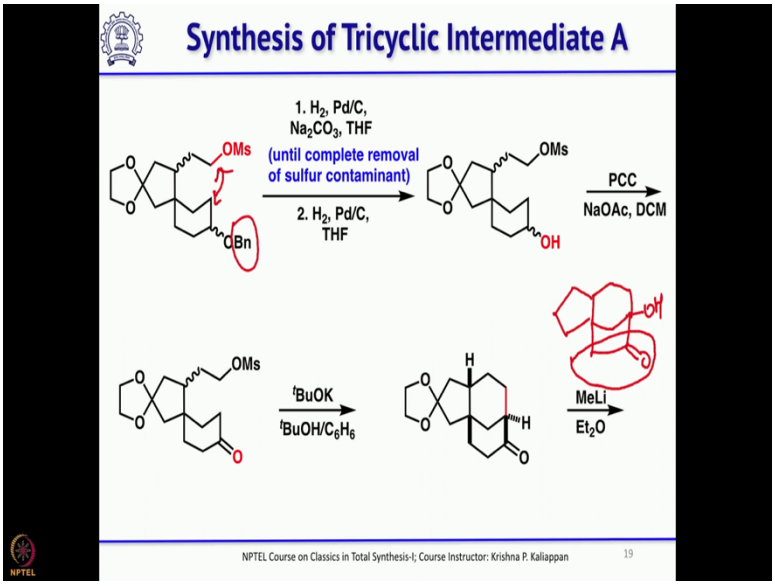

So, now what he needs is he have to remove the benzyl group, oxidize the alcohol to ketone, then connect this ok. So, the benzyl group was hydrogenolysis to get the alcohol ok; then PCC oxidation gave the ketone. Then treat with potassium tertiary butoxide to give the corresponding tri-cyclic compound. If you look at this tricyclic compound, you will see there is one carbon extra ok.

What you need is, what you need is this, is not it. So, this particular ring instead of 2 carbons, you have 3 carbons, am I correct. Instead of 2 carbons, we have 3 carbons; so, the 2 carbons, how you can get it from 3 carbons. So, you do treat with methyl lithium, then dehydrate to get the corresponding alkene ok.

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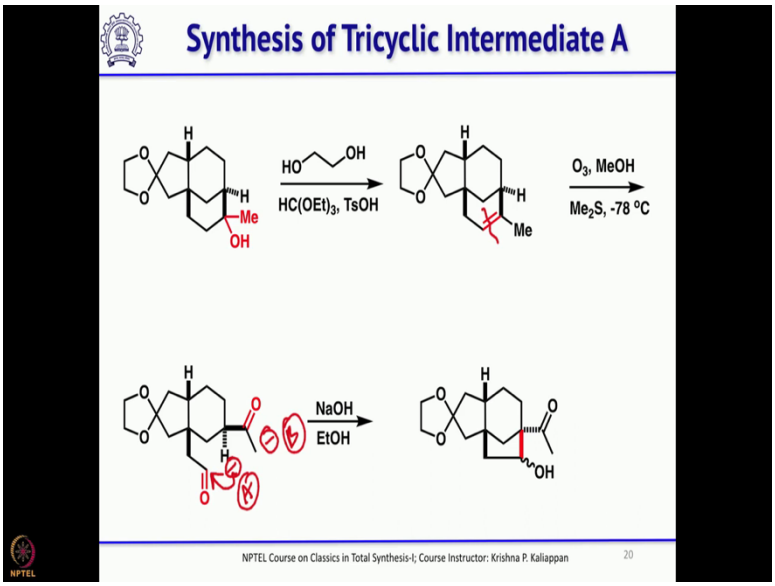

Then what you will do? You can do a ozonolysis to get the corresponding ketone ok. Now, if you treat with base, there are two places it can generate anion one here another one here. If this adds here you will get the 5 membered ring. Whereas, if B adds it will give 7 membered ring ok, but with sodium hydroxide and ethanol one could get predominantly the 5 membered ring and once you have this aldol ok, then you can carry out a Baeyer-Villiger oxidation ok.

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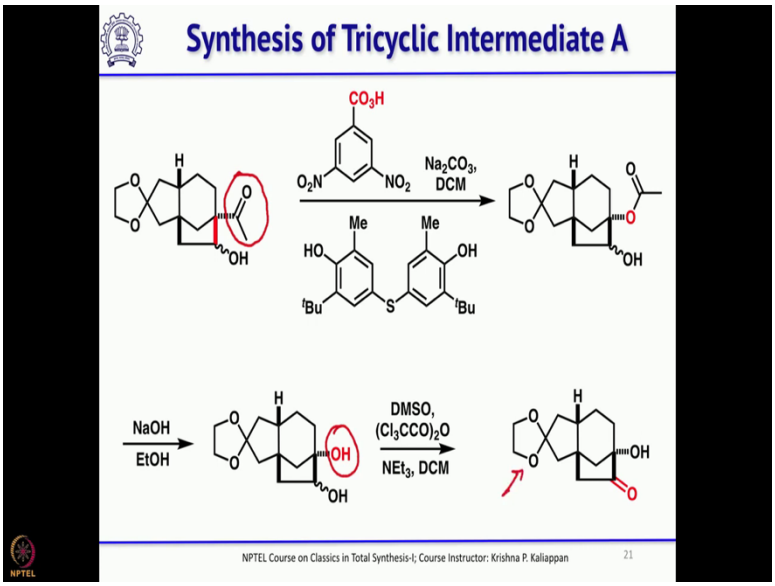

So, the Baeyer-Villiger oxidation you can see the acetyl group $COCH_3$ will become OAc ok, then hydrolysis of OAc will give the bridged hydroxyl and oxidation under Swern condition you get the ketone and remove the ketal ok.

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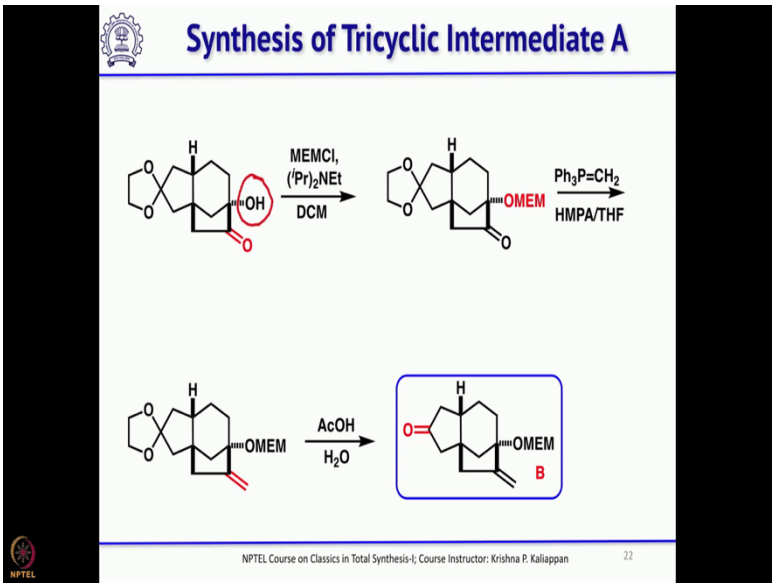

Before that of course, you have to protect the bridgehead hydroxyl as MEM ether, then do the Wittig on the ketone and remove the ketal you get tricyclic intermediate B, which has already been converted into intermediate A ok.

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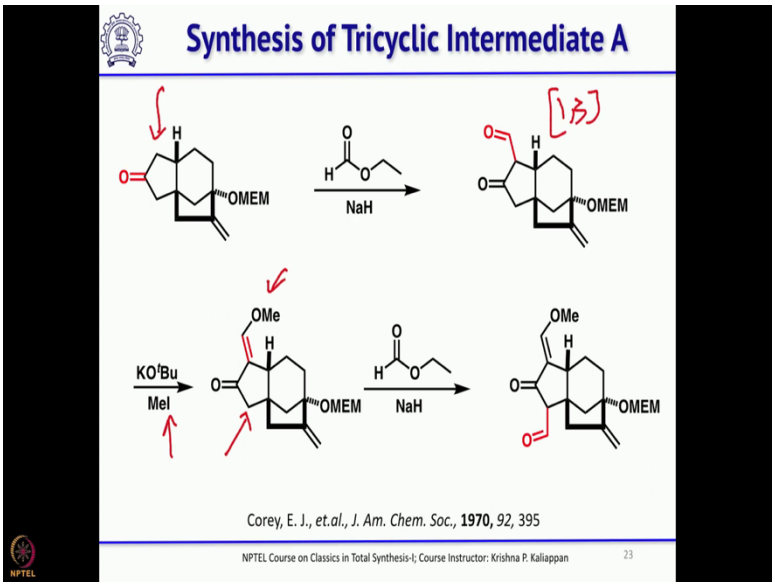

So, how did you do that? Now, if you treat with sodium hydride and quench with ethyl formate you can introduce an aldehyde on this side ok. Now, this on treatment with potassium tertiary butoxide and methyl iodide; so, this is 1, 3 carbonyl is not. It this is 1, 3 carbonyl. So, it will exist in the corresponding enol form. So, that enol become the enol methyl ether, when you treat with potassium tertiary butoxide and methyl iodide ok.

Then you introduce another aldehyde on the other side of the carbonyl ok. Again you follow the same route sodium hydride ethyl formate you introduce aldehyde on the other side.

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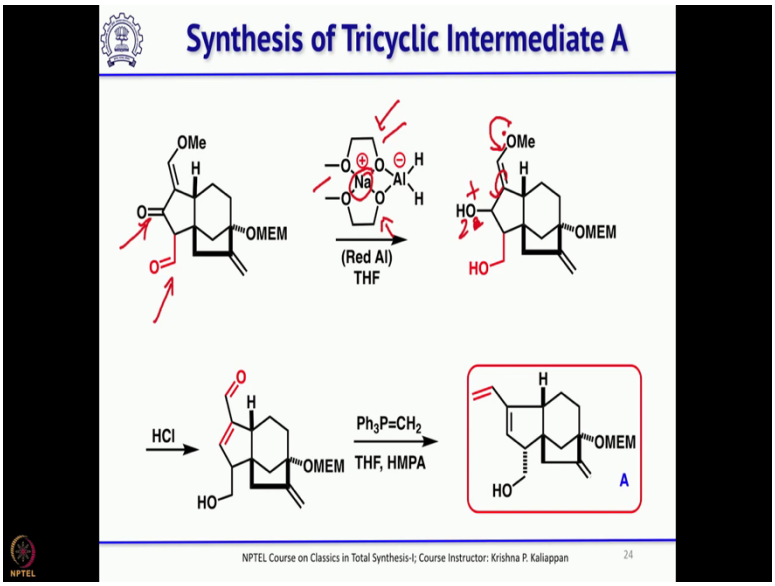

Now, you have to reduce this ketone and as well as this aldehyde. So, this is done with Red Al. So, what is Red Al? Red Al is sodium sodium bis ok, there are 2 sodium bis methoxy ethoxy aluminum hydride methoxy ethoxy aluminum hydride. So, that reduces both ketone and aldehyde to get the diol.

Now, if you treat with acid. So, what will happen? This will become protonation will take place at this OH, it will become H_2O plus then this lone pair will push this double bond here and in the end what you get is alpha beta unsaturated aldehyde which upon Wittig you will get the corresponding triene ok.

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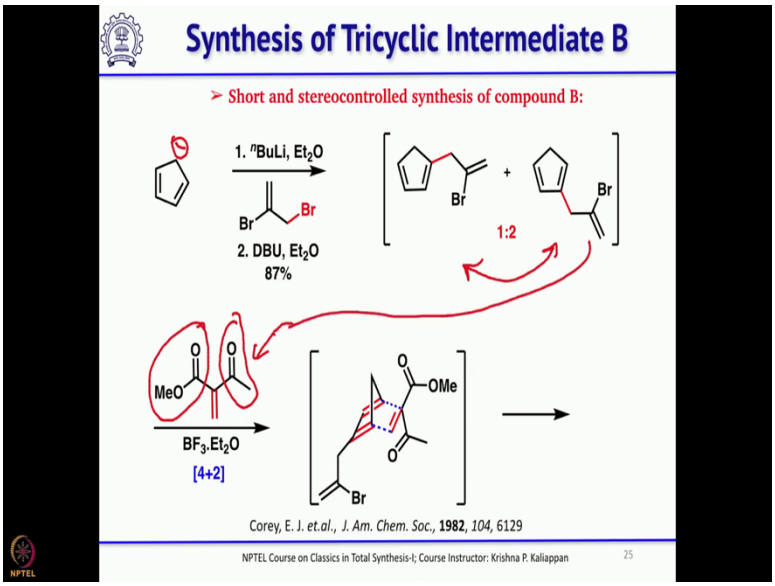

Then the third route, which is supposed to be the shortest route and here he use Diels-Alder reaction and 3, 3 sigmatropic rearrangement as the key reaction. For the Diels-Alder reaction the diene was prepared in a single step. So, butyl lithium treatment gives cyclopenta dienyl anion and quench with 2 bromo allyl bromide followed by DBU treatment gives a mixture of these 2 isomers, gives a mixture of these two isomers.

This upon treatment with this dienophile ok, between these two electron withdrawing group. One is acetyl and the other one is ester, which is more electron-withdrawing acetyl or ester, acetyl group. So, that means, the acetyl group will go to endo position. So, this upon Diels-Alder reaction with this particular diene gives the Diels-Alder product 53 percent, then there is another product very interesting product in 20 percent.

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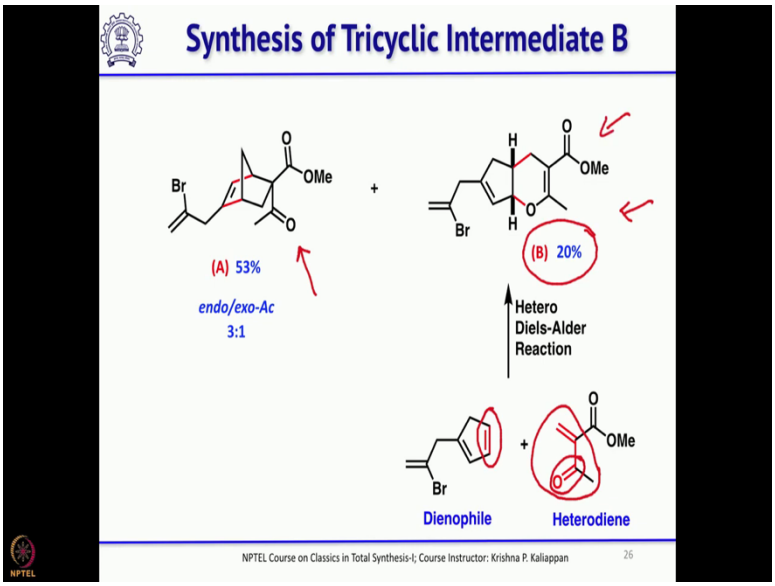

So, what is this product? How it was formed? This again was formed by Diels-Alder reaction, only difference is here this is found by normal Diels-Alder reaction and this is formed by hetero Diels-Alder reaction. So, what is hetero Diels-Alder reaction? Now, the dienophile ok, the dienophile acted like a diene ok. The dienophile acted like a diene.

Since, one of the alkene is a carbonyl group you can call this as heterodiene ok heterodiene and your original diene, now acted as dienophile ok. So, that intermolecular hetero Diels-Alder reaction gave B in 20 percent yield.

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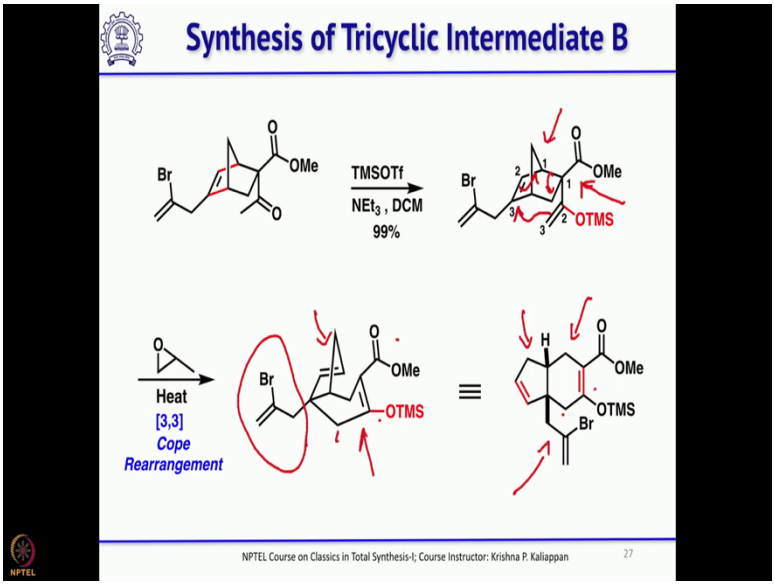

So, the major product which is obtained by normal 4 plus 2 cycloaddition this upon treatment with TMSO triflate and base formed enol TMS ether. This molecule when you look at it you can see I have given already, the number 1, 2, 3 1, 2, 3. So, that means, this can undergo a 3, 3 sigma tropic rearrangement ok. This will undergo a 3, 3 sigma tropic rearrangement to give this intermediate.

I will leave this for a few seconds. So, that you can visualize. The same intermediate can be redrawn like this the same intermediate can be redrawn like this ok. This is a 5 membered ring and you can see the 5 membered ring and this is the 6 membered ring and you see the 6 membered ring ok.

And you have the 2 bromo allyl group. So, that we have and you have CH_2. Next, CH_2 then enol TMS enol TMS, then ester ok. So, this undergoes a 3, 3 sigma tropic rearrangement to give this material ok.

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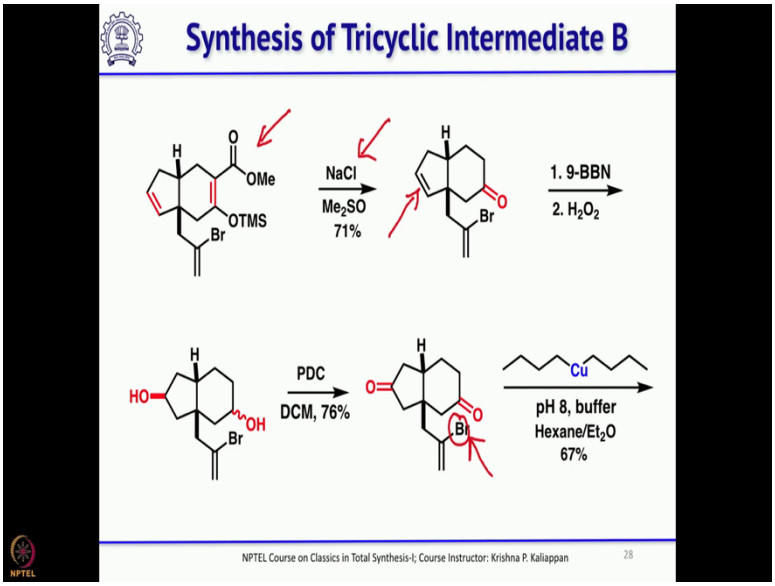

Now, if you do sodium chloride DMSO what happens this is nothing but a protected form of beta keto ester protected form of beta keto ester ok. So, the beta keto ester can undergo elimination under sodium chloride and dimethyl sulfoxide refluxing condition ok. So, that gave corresponding ketone, then one can use 9-BBN. So, that regioselective hydroboration can take place to get alcohol and that can be oxidized with PDC to get a diketone; then you carry out a di butyl copper reaction.

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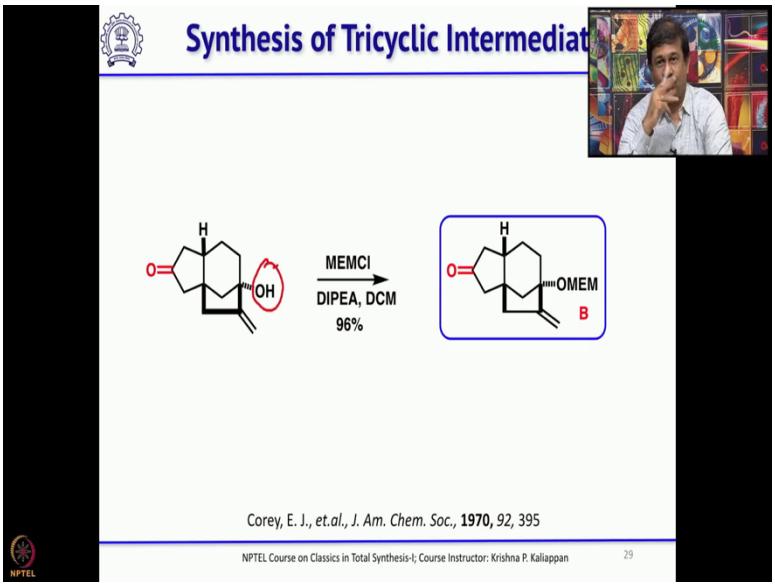

So, it exchanges with this and undergoes intramolecular nucleophilic addition to the carbonyl to form the 5 membered ring. Now, if you protect the hydroxyl group as MEM ether. So, that gives the intermediate B ok. So, what I will do, I will stop here now. Then tomorrow I will continue our discussion on the total synthesis of gibberellic acid reported by Corey starting from the intermediate A. How he accomplished the total synthesis of gibberellic acid and I also will discuss one more total synthesis of gibberellic acid reported by Yamada ok; so.

Thank you.