Classics in Total Synthesis - I
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Lecture - 25
Gibberellic Acid (Yamada)

Yeah, good morning and welcome back to the NPTEL lecture series on Classics in Total Synthesis Part I.

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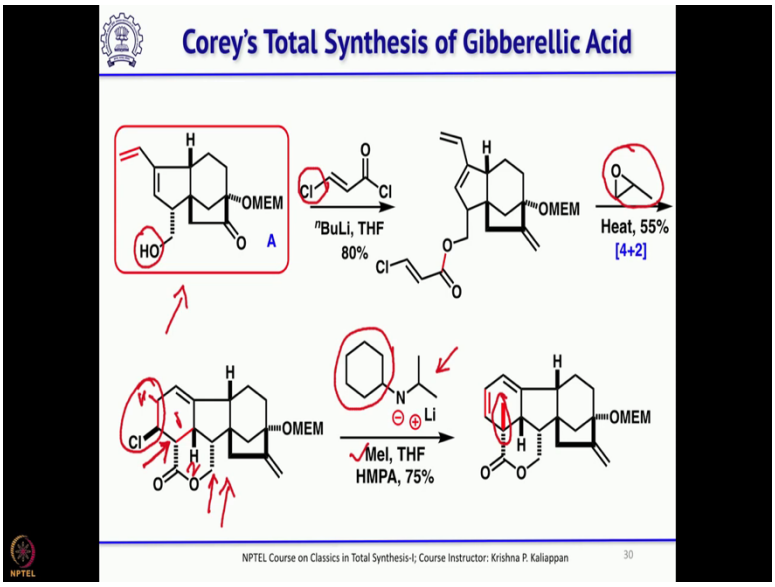

So, yesterday, we were talking about total synthesis of Gibberellic Acid by E. J. Corey and that time, we discussed up to the synthesis of this key intermediate by three different routes. So, now, we will discuss further reactions towards the completion of the total synthesis of gibberellic acid ok.

So, if you look at the molecule A, you can see already there is a diene. So, what one has to do is you have to attach the dienophile. So, how Corey has done? So, he added this acid chloride and having a chloride at the beta position, first he deprotonated this OH with butyl lithium and then, carried out this acylation ok. So, now, the key intra molecular 4 plus 2 cyclo addition reaction was done in the presence of propylene oxide.

So, which is normally you know proton sponge that gave you know very good yield of this pentacyclic compound ok. So, how many rings are formed? Two more rings are

formed. Normally, Diels Alder reaction gives one ring, but when it is intramolecular reaction, then you can get more than one ring. So, you could construct two rings; 1 and 2 using this key 4 plus 2 cycloaddition reaction ok.

So, if you look at this molecule, so what is missing is in gibberellic acid, you need one methyl group here ok. Then, this CH_2O should be oxidized to COOH ok. So, for that, first he treated with LDA equivalent. LDA is lithium diisopropylamide right. So, now, instead of one isopropyl group, if we replace the isopropyl group with cyclohexyl group. So, then you get this amide ok. This amide generates anion here ok; generates anion here and then, upon quenching with methyl iodide, you introduce this methyl group ok. So, that was the idea.

So, the methyl group was introduced. As well what happened? You can see this HCl ok. There was also an elimination of HCl because of the presence of base like lithium isopropyl cyclohexyl amide ok. So, that generated a diene and also, you could introduce the methyl group at that required position.

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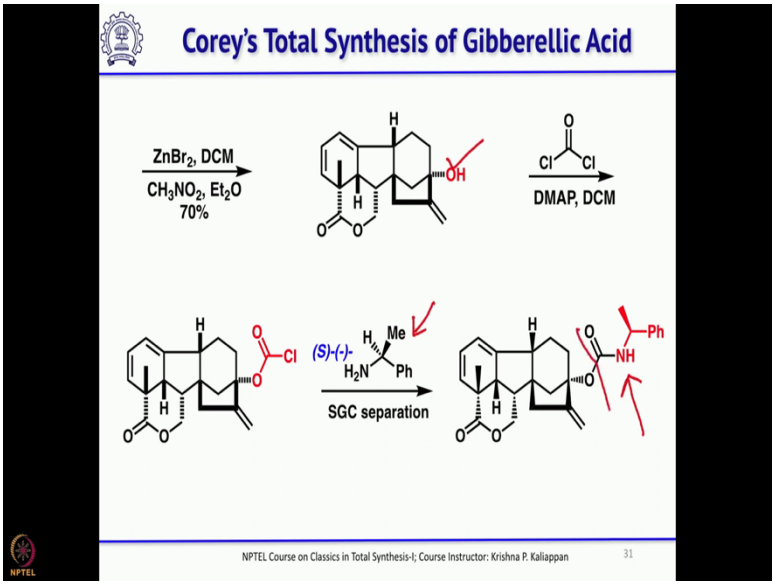

So, the next step is to remove the MOM group ok. So, you have a MOM group here; that MOM group was removed using zinc bromide. Then, if you use phosgene, it can form half ester ok. So, one equivalent of phosgene and then, this hydroxyl group, you form the half ester that on treatment with phenyl methyl amine ok. This is a good chiral resolving agent.

So, now, you form this carbamate and one can resolve two diastereomers ok. You resolve two diastereomers and these two diastereomers can be easily separated. This diastereomers, if you hydrolyze the required one, you get the corresponding hydroxyl group ok.

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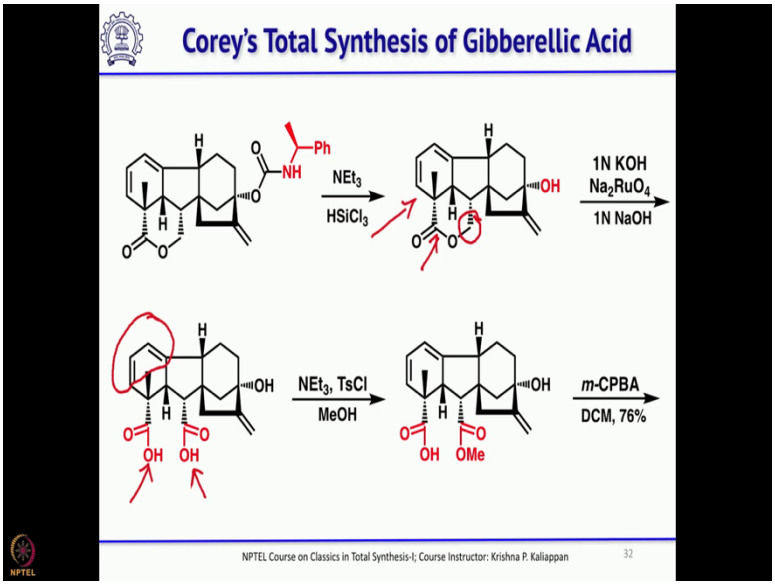

So, and till the bridged hydroxyl group, all the compounds which we discussed are racemic. After forming the half ester and then, treating with alpha methyl benzyl ammine and the resolving. From now onwards, you can see all are chiral; real chiral centres ok. Then, what you need to do? You need to oxidize this CH_2O to COOH as well as hydrolyze this. So, both were done in one step by treating with potassium hydroxide and sodium ruthenate. So, it cleaved and then, you got a dicarboxylic acid ok. There are four rings.

Now, you need only one more ring that is lactone. This diene should form a lactone and one hydroxyl group, then the total synthesis is accomplished. So, before that if you have to do iodolactonization with this carboxylic acid, then the other carboxylic acid should be protected ok. So, that was selectively done by treating with triethylamine tosyl chloride and methanol ok. Just think about mechanism. So, what happens? It involves two reactions ok; think about and then, write the mechanism for this key reaction.

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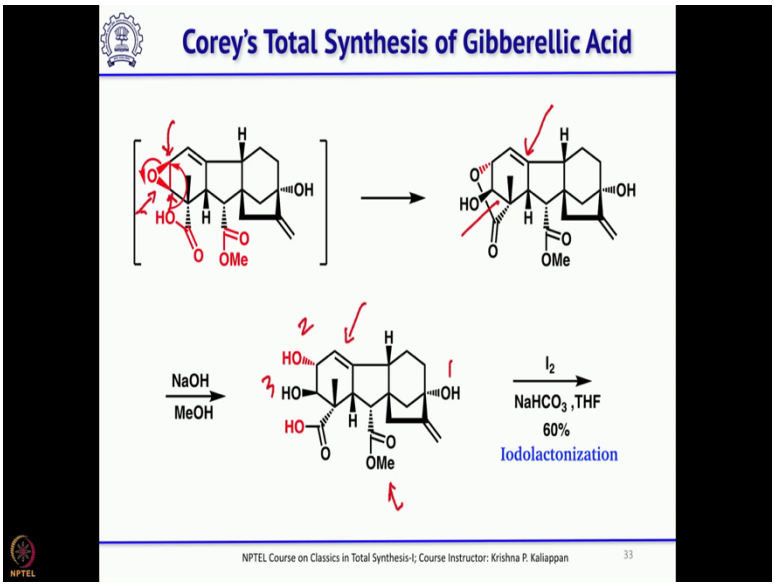

Then, m-CPBA, so you have diene; this on treatment with m-CPBA if this double bond forms epoxide, then it can open the epoxide. If it opens from this side, this will be four-membered ring. But if it opens from this side that will be five-membered ring. So, the five-membered is better than the four-membered ring. So, 5-exo-tet opening of this epoxide gives the corresponding five-membered lactone ok. But what we need is lactone here. You do not want lactone here, but this is important. So, what happens?

Now, once you have this, you treat with sodium hydroxide methanol. Basically what you do? You hydrolyze this lactone. Now, you got tri hydroxy carboxylic acid; 1, 2, 3 tri hydroxy carboxylic acid having an ester here. Four functional groups ok along with two double bonds; quite sensitive. Then, he carried out the key iodolactonization ok. You have double bond and treat with iodine in the presence of sodium bicarbonate, it forms the iodolactone ok.

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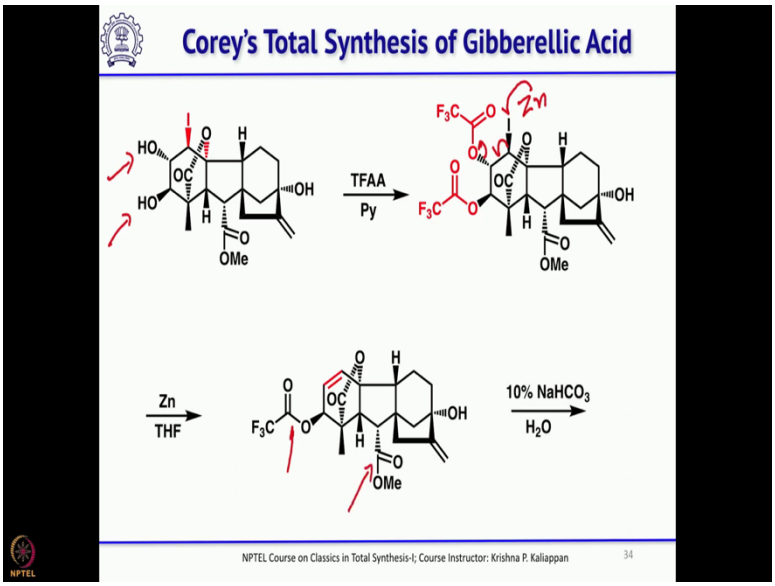

Then, what you need? You need to get a double bond for gibberellic acid ok. Protect these two hydroxyl which are trans to each other as trifluoroacetate, then treat with zinc. So, when you treat with zinc as you know zinc will give 1 electron and it can eliminate to give corresponding double bond. So, the lactone is formed and then, you have the O acetate, what you need is the ester should be hydrolysed. So, 10 percent sodium bicarbonate water.

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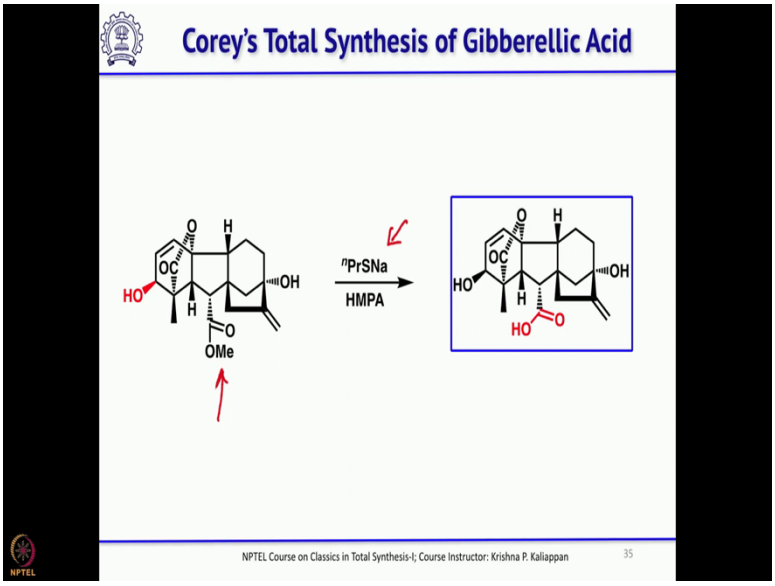

The trifluoroacetate could be hydrolysed to get the corresponding allylic alcohol. Then, the methyl ester, the hydrolysis of methyl ester is quite difficult. Because that is very unstable. The carboxylic as soon as the COO minus is formed, it is quite unstable. So, he has to use sodium thio propylate to hydrolyse the methyl ester to get the natural product.

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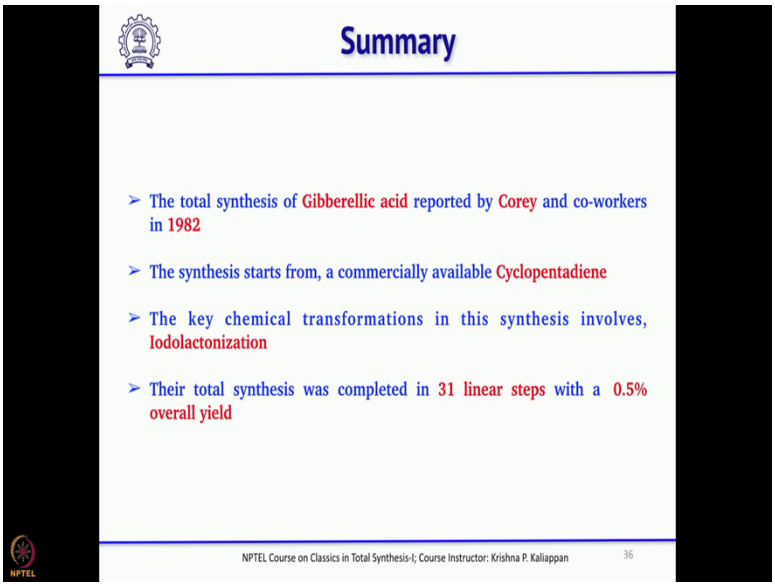

So, this is how E. J. Corey could successfully accomplish the total synthesis of gibberellic acid in almost 40 years ago and the starting material was from cyclopentadiene in one case and so, butadiene in another case; butadiene having a CH_2OH in another method.

The key reactions used by Corey in the synthesis gibberellic acid of 4 plus 2 cycloaddition, iodolactonization, epoxy lactonization and McMurry coupling. So, these are four key reactions which we use in the total synthesis of gibberellic acid which involved 31 longest linear steps and with an overall yield of 0.5 percent.

Such a complex molecule, he could successfully accomplish synthesis and that was one of the classical and most difficult synthesis reported in the literature.

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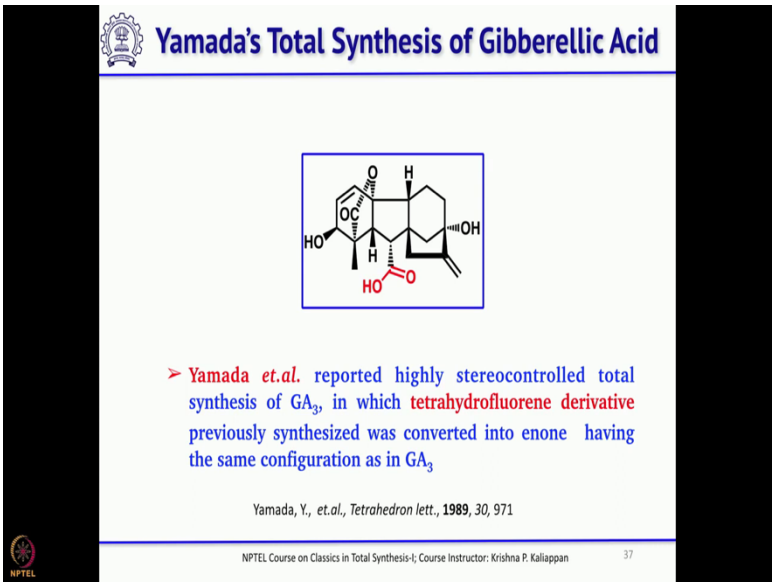

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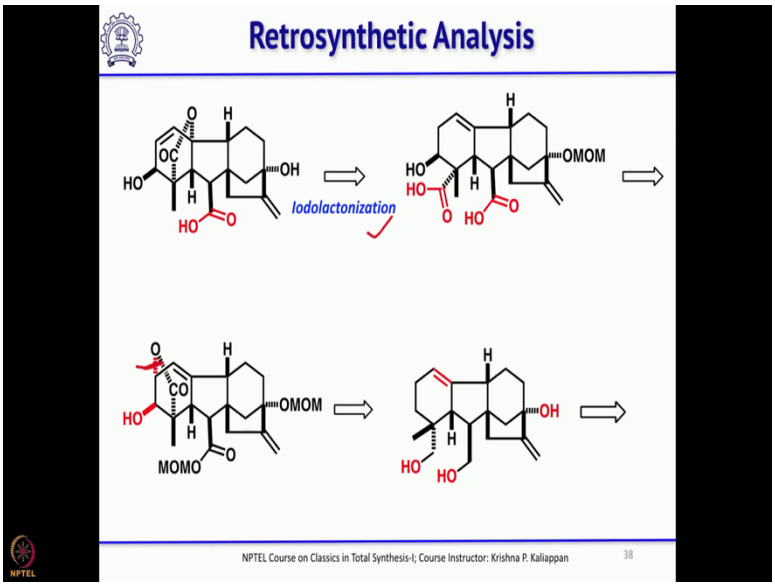

So, now, we will move to the second total synthesis reported by Yamada on the same molecule and what are the key reactions he has used in the total synthesis of gibberellic acid? Of course, once you have a lactone, one reaction which will be common is iodolactone ok. So, he used again the same idodolactonization as the first key disconnection to get the gibberellic acid, then he wanted to cleave this bond.

If you have an allylic ester, allylic carbonate, one can cleave that under either palladium catalyst condition or metal ammonia condition to get the corresponding double bond. So,

he thought he can use that to get the corresponding double bond. This of course can be obtained from this alcohol.

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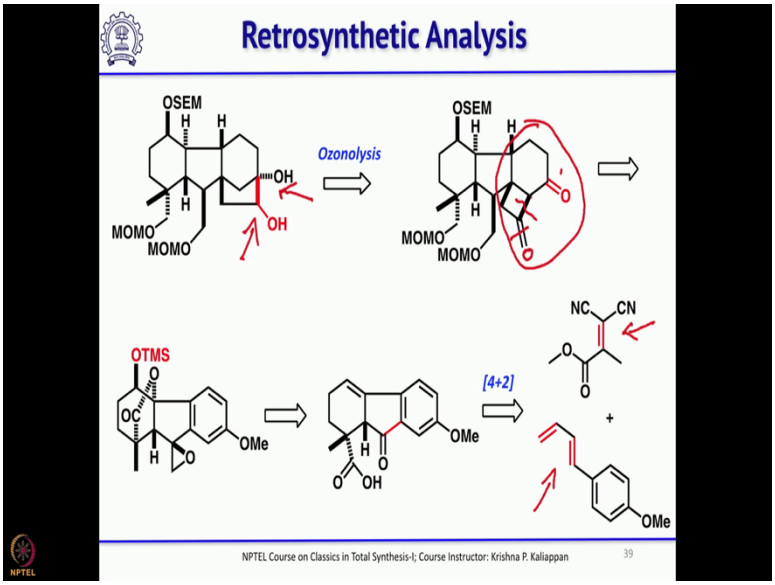

Then, his idea was to do like this, if you have a bicyclic compound ok; if you have bicyclic compound his idea was if you do ozonolysis, you get 1, 1, 2, 3; 1, 3-diketone, then you can open this four-membered ring ok. So, you can open this four-membered ring and then, cyclize that will give this five-membered ring.

Opening followed by McMurry type coupling, you will get the diol ok. So, that was the key reaction and this, he thought can be obtained by metal ammonia and some functional group transformation ok. So, that actually took him all the way to this diene and this dienophile.

So, there are few reactions which are common between E. J. Corey and Yamada's total synthesis of gibberellic acid. One Diels Alder reaction, two you can you could have seen already that iodolactonization and three, he wanted to use a coupling reaction to form this five-membered ring. In the case of Corey, he used McMurry coupling and let us see what Yamada has used to make this five-membered ring.

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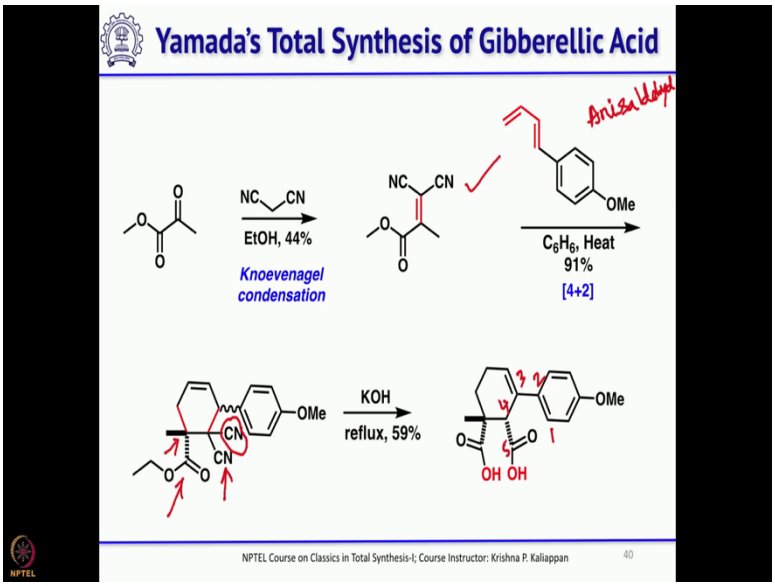

So, his total synthesis started with methyl pyruvate and knoevenagel condensation with maleononitrile gave the dienophile ok, the dienophile is ready and the diene is very easy to make from anisaldehyde. If you have anisaldehyde, then you can make this in one step and once the diene is ready, do the Diels Alder reaction ok. So, when you do the Diels Alder reaction, you can see the quaternary methyl group, quaternary methyl group is fixed and what you do not need is one extra cyanide ok.

You have to hydrolyse this cyanide to ester; at the same time, you have to remove the extra unwanted cyanide so that if you treat with potassium hydroxide. So, what will happen? The cyanide will be hydrolysed to carboxylic acid. Since, it is dicarboxylic acid, one will be de-carboxylated; at the same time, this ester also you know during hydrolysis, ester will be hydrolysed. So, you get directly the dicarboxylic acid ok.

And once you have this dicarboxylic acid, you can see here 1, 2, 3, 4, 5 intra molecular Friedel Craft's acylation may be possible on the aromatic ring, did he do that? Let us see ok.

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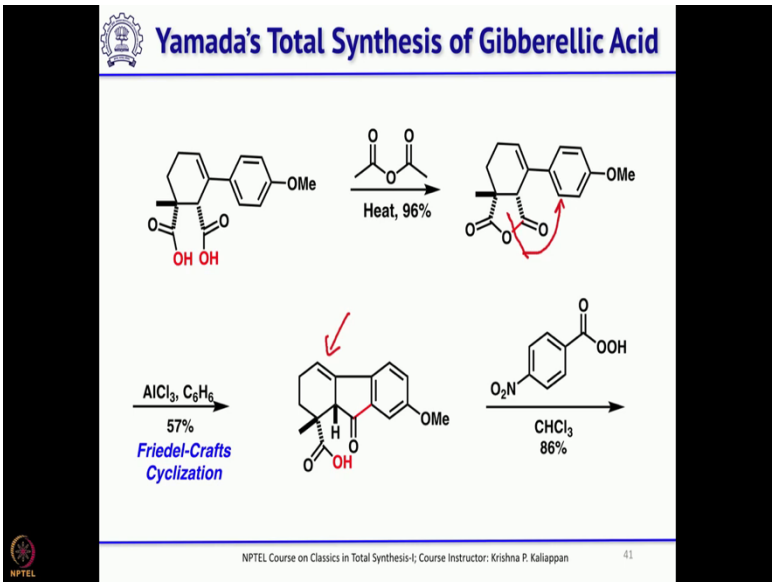

So, before that, he made anhydride. He made anhydride of this dicarboxylic acid. Then, he tried this Friedel Craft's reaction ok. So, if you have anisole and treat with acetic anhydride ok. So, that can undergo Friedel-Crafts reaction at para position. So, same thing here, he carried out the Friedel-Crafts reaction and then, cyclized here to get the corresponding five-membered ring ok; five-membered ring and carboxylic acid ok.

Then, you treat with para nitro perbenzoic acid; para nitro perbenzoic acid; what it can do? There is only one possibility that is if you have double-bond, the double-bond will be epoxidized ok.

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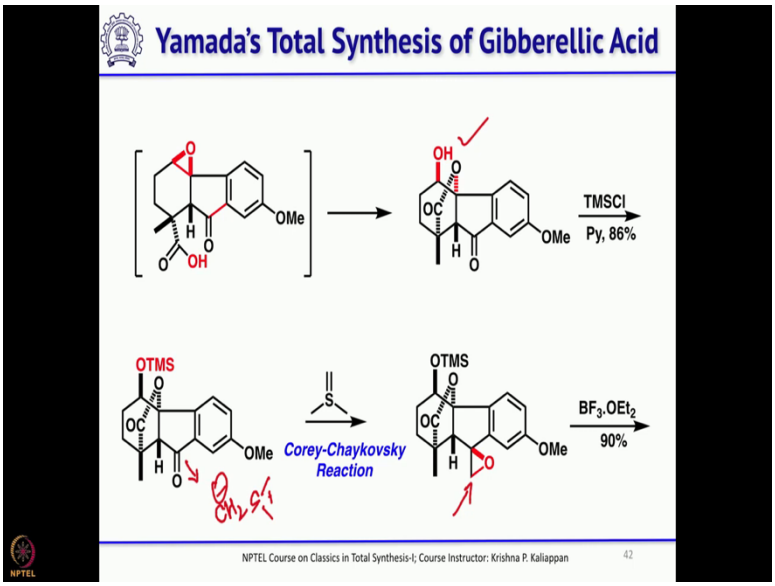

So, you get the epoxide and the epoxide will not be like that, since you have carboxylic acid. So, that will open the epoxide and you get hydroxy lactone ok. Then, protect the hydroxyl as TMS ether. It is a transient protecting group and you cannot use it for a long time because TMS is a very labile protecting group ok. So, you protect that hydroxyl as TMS ether, then carry out a Corey-Chaykovsky Reaction. That means, you convert this CH2 into an epoxide with one carbon extra ok; CH_2 minus and ok.

So, Corey-Chaykovsky reaction gives the epoxide ok. Basically as you know in this place, what you need is COOH ok; COOH. So, this epoxide when you treat with BF_3 etherate, it will undergo rearrangement. So, epoxide will open up and it will form enol and that enol is nothing but corresponding aldehyde ok.

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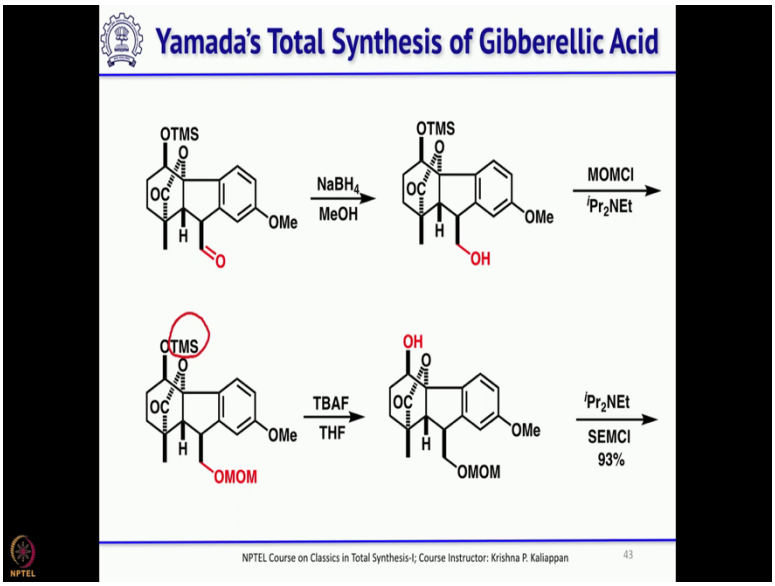

Then, reduce the aldehyde to corresponding primary alcohol with sodium borate methanol and protect that as MOM ether; protect that as MOM ether. Now, the transient protecting group that is TMS is cleaved with TBAF to get the secondary alcohol and protect that as SEM ether with treating with Hunig's base and then, SEM chloride.

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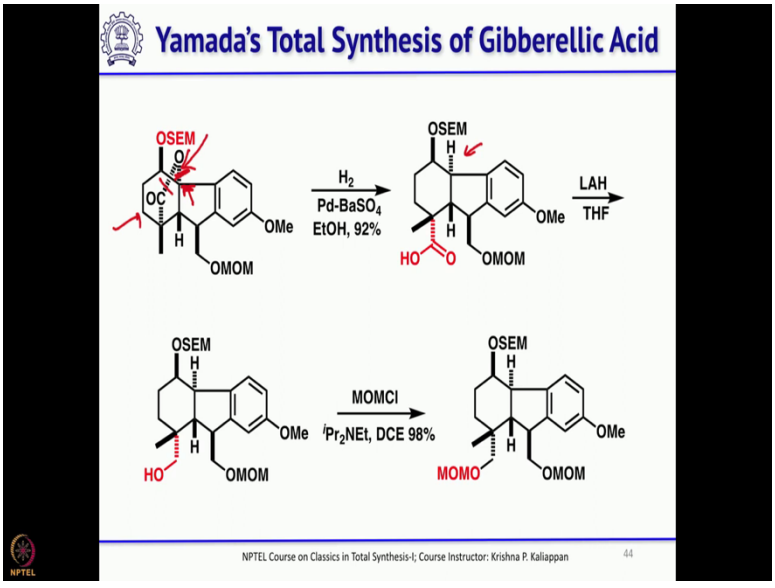

Now, you have protected the SEM and you have protected the primary hydroxyl as MOM, what you need to do is hydrolyse the ester ok. When you do that, you can get the corresponding carboxylic acid. But at the same time, what you do not need is this

oxygen. If you hydrolyze you get only carboxylic acid and hydroxyl group. When you do not need the oxygen, then you have to do hydrogenolysis. The hydrogenolysis, suppose if you have a benzyl ether, what will happen? You will remove the oxygen; is not it? $ROCH_2$; $ROCH_2$ phenyl group, what will happen? The CH_2 phenyl will go.

Likewise, so this is the benzylic carbon ok; hydrogenolysis will cleave this. So, you get hydrogen here and this whole thing will come out as carboxylic acid. The cleavage of the lactone was done under hydrogenolysis condition to get carboxylic acid. Now, reduce that with LAH to get the primary alcohol and protect that as MOM ether. So, you get di MOM.

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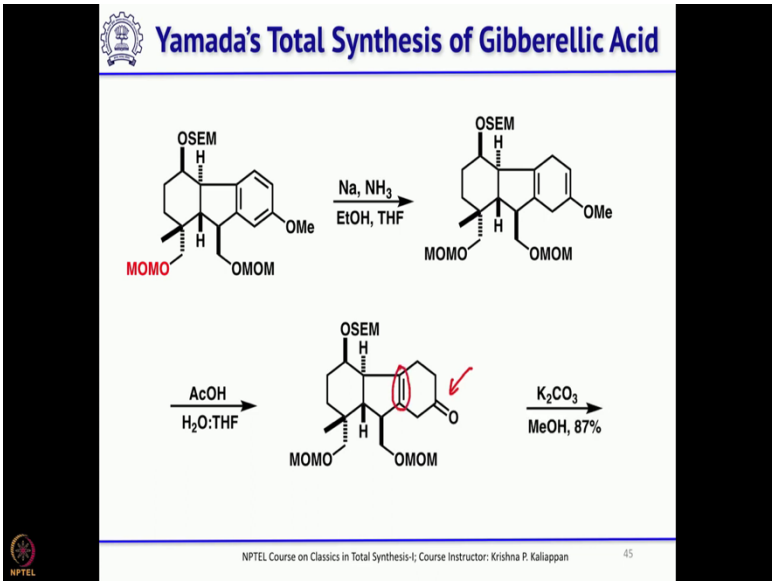

Then, you have aromatic ring ok, that aromatic ring should be reduced to get the ketone. So, metal ammonia reduction gives diene and this diene upon hydrolysis, you get the corresponding ketone and this double bond is still intact ok.

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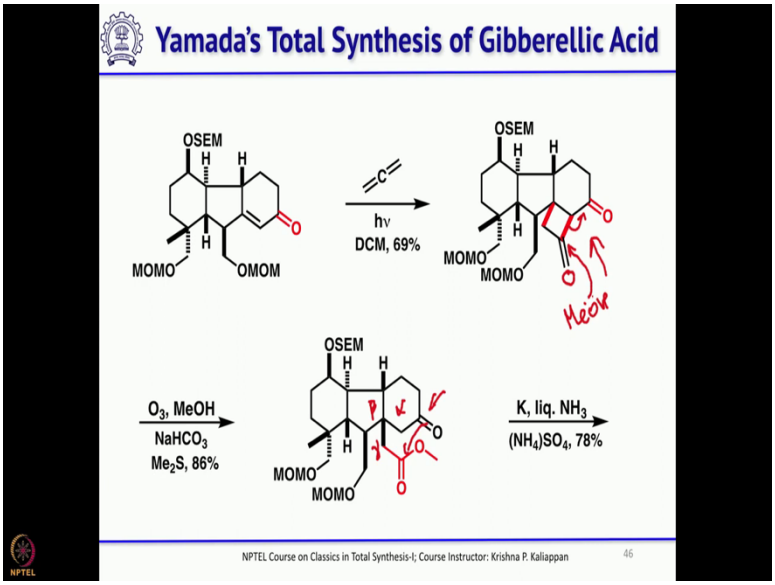

Then, potassium carbonate methanol isomerises the double bond to give alpha beta unsaturated ketone, then carry out intermolecular 2 plus 2 cycloaddition with allene ok. So, that gives this bicyclic compound. Ozonolysis gives ketone. This while doing ozonolysis itself in the presence of methanol and sodium bicarbonate, it gives alpha beta gamma ok or you can write the other way ok alpha beta gamma. The keto ester, it forms. How it forms?

Once you have this diketone, ozonolysis will give the diketone; is not it? That opens up because this four-membered ring is strained. So, this attacks this carbonyl and it can open up. So, that will give the corresponding keto ester. Once you have the keto ester, again you reduce with potassium and liquid ammonia. Potassium and liquid ammonia, it will give 1 electron. So, that 1 electron will go to ketone, then that ketone can cyclize here to give the corresponding hydroxy compound ok. So, dihydroxy compound.

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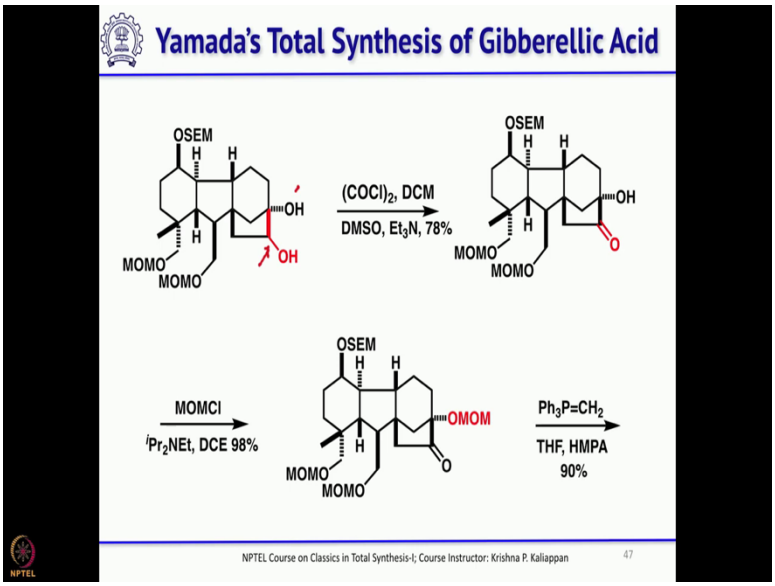

First, it will form hydroxyl here and then, here it will be ketone. That ketone also further reduced under the potassium liquid ammonia condition to get the diol. Swern oxidation will give ketone, then protect the bridgehead hydroxyl as MOM ether, then do the witting to get the corresponding exocyclic double bond ok.

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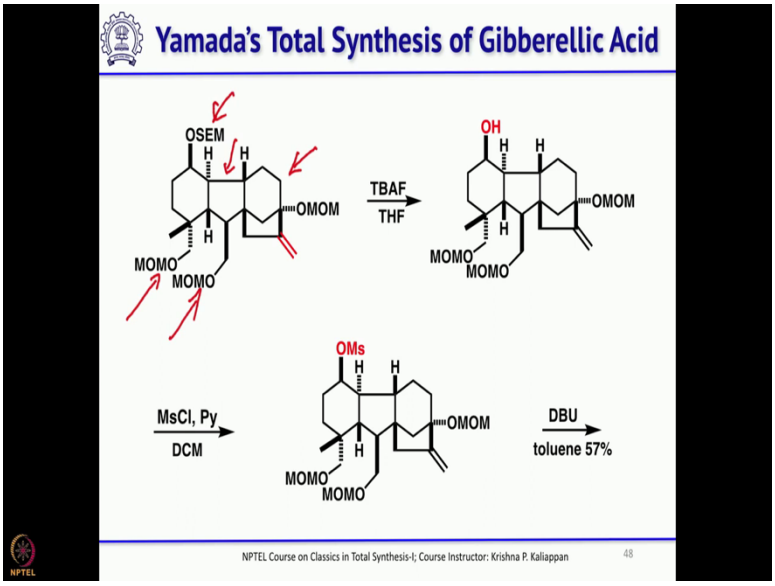

Now, you can see this two rings are done, the third ring is also done; what you need? These two should become carboxylic acid ok. Then, the iodolactonization has to be done and also, you have to introduce a hydroxyl group on this particular ring. So, TBAF, it

will remove the SEM group ok; you get a hydroxyl group. That SEM is nothing but a trimethylsilyl ethyl methyl chloride ok. So, mesylate, then do the elimination with DBU to get the double bond ok.

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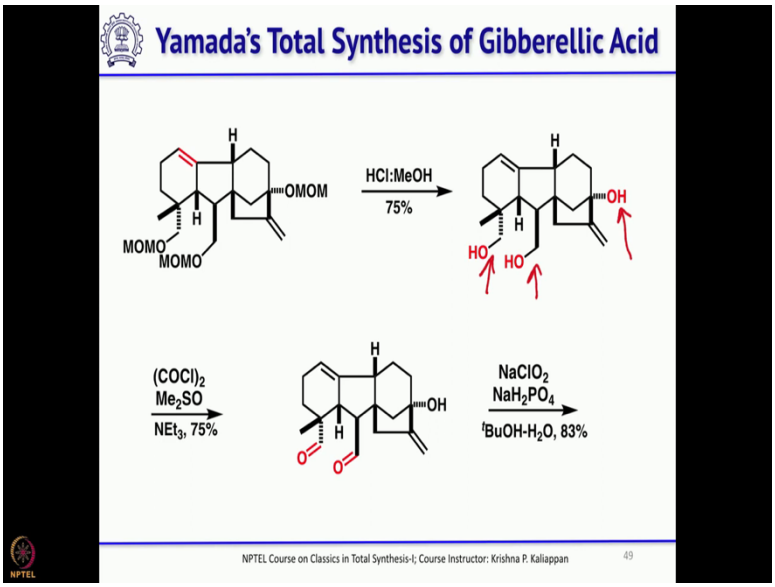

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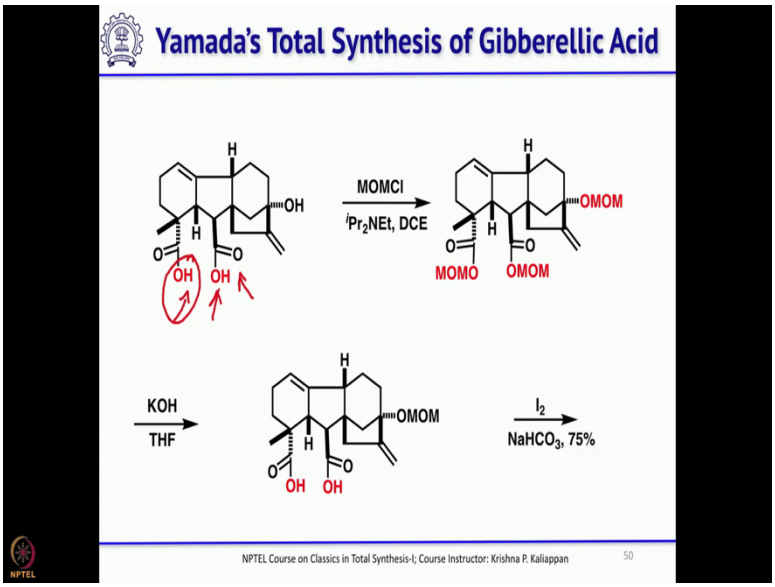

Then, remove all the MOM groups with HCl methanol you get the triol. One is tertiary alcohol, other two are primary alcohols. So, you can oxidize the primary alcohols under Swern condition to get the aldehyde. Then, further oxidation under Pinnick condition, you get the dicarboxylic acid. Then, you carry out the iodolactonization; but before you

do iodolactonization as you know you have two carboxylic acids, only this hydroxyl group of carboxylic acid should undergo iodolactonization; that means, you have to protect this.

So, selective protection is difficult. So, all three were protected; the hydroxyl and then, two carboxylic acids were protected as MOM ether, then hydrolyse. So, what happens? You get back the dicarboxylic acid.

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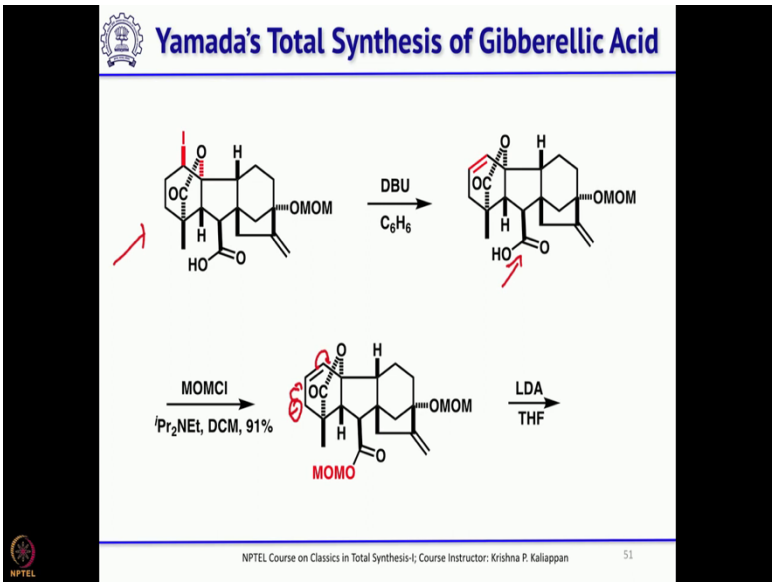

Then, you treat with iodine and sodium bicarbonate and that undergoes iodolactonization to give this iodolactone. Then, treat with DBU you introduce the double bond. Now, you protect the carboxylic acid as MOM ester because having free carboxylic acid is not good because free carboxylic acid can create more trouble. So, you protect this as MOM ester, then treat with LDA. So, what does LDA do? LDA, it can generate anion and opens the carboxylic acid to get a diene ok as well as carboxylic acid.

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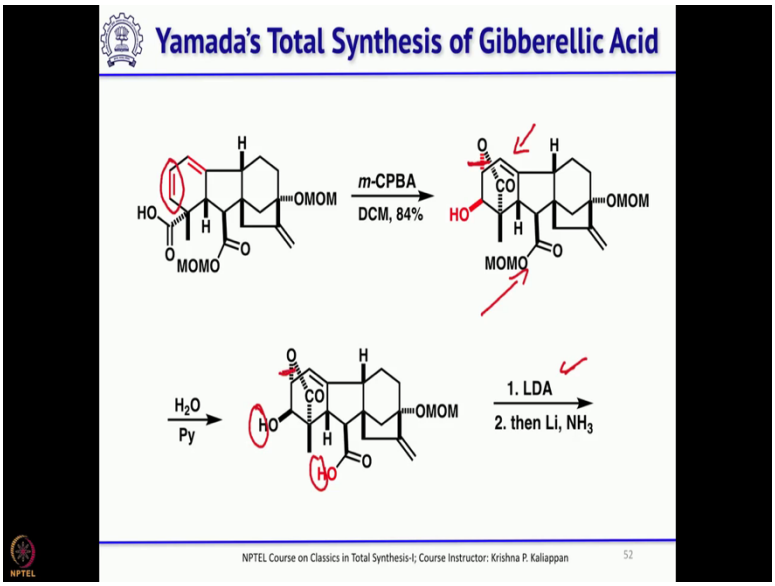

Now, if you treat with m-CPBA ok. This will undergo epoxidation and followed by opening of the epoxide, you get hydroxy lactone ok. Then, the hydroxy lactone, if you can cleave this bond, if you can cleave this bond, you will get the carboxylic acid. At the same time, the double bond should be intact ok; cleave the CO bond as well as the double bond should be in same place. How these two can be done? If you have a close look at this molecule that is nothing but allylic acetate ok.

So, such allylic acetate can be cleaved under hydrogenolysis condition ok. Before that, you hydrolyze the MOM group ok; simple water pyridine MOM group because it is ester ok. So, ester hydrolysis give carboxylic acid, then as I said you can use hydrogenolysis condition or equivalent to that is metal ammonia ok. So, before you do the metal ammonia, treat with the LDA because you have two hydroxyl group; this and this. So, that will become corresponding O-Lithium derivative.

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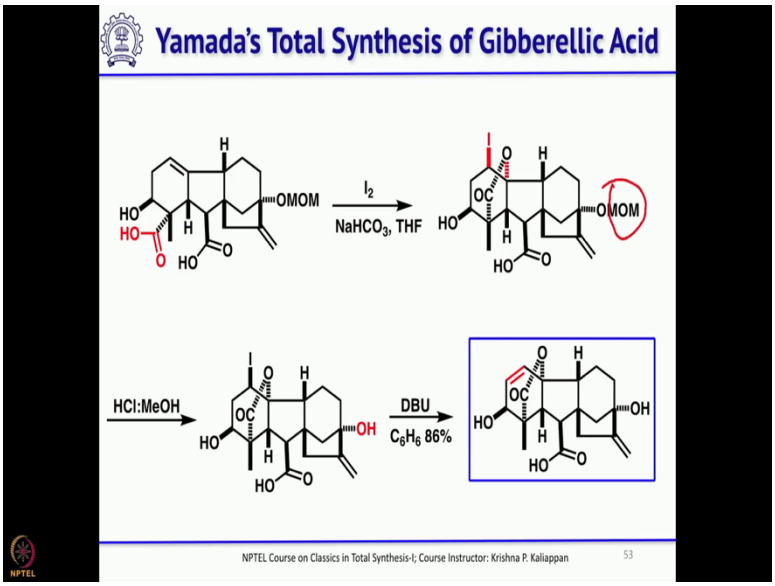

Then, you do metal ammonia that will cleave the CO bond; followed by acidification, you get this compound ok. Now, you do the iodolactonization once again, you get this and remove the MOM group with HCl and followed by treatment with DBU ok. So, DBU will eliminate the iodide to get the double bond and that is how Yamada completed the total synthesis of gibberellic acid.

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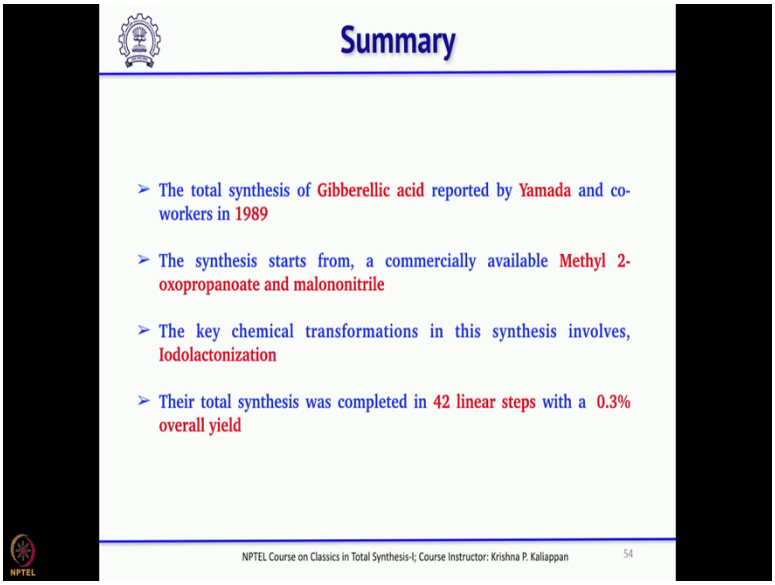

To summarize, so total synthesis of gibberellic acid was accomplished by Yamada and his co-workers in 1989 and his total synthesis was started from Malenonitrile and Methyl

pyruvate to prepare the dienophile ok and the diene was prepared from anisaldehyde and intermolecular Diels Alder reaction was the first key reaction and he also used ozonolysis, he also used iodolactonization epoxy lactonization as key reactions to complete the total synthesis of gibberellic acid.

So, overall, he took about 42 steps to complete the total synthesis of this complex molecule and the overall yield of this synthesis is 0.3 percent. Considering the complexity as well as sensitivity of the natural product, 42 steps is ok and overall yield 0.3 percent is also acceptable ok.

So, now, we will move to total synthesis of other natural products in the next lecture ok. Today, we completed two total synthesis of very complex natural product called gibberellic acid ok.

Thank you.