Classics in Total Synthesis-I
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Lecture - 58
Zaragozoic acid C

So, good morning and welcome back to NPTEL lecture series on Classics in Total Synthesis. I think we have discussed about 100 total synthesis in this lecture series and today the last lecture is going to be about total synthesis of a complex natural product called Zaragozic acid C.

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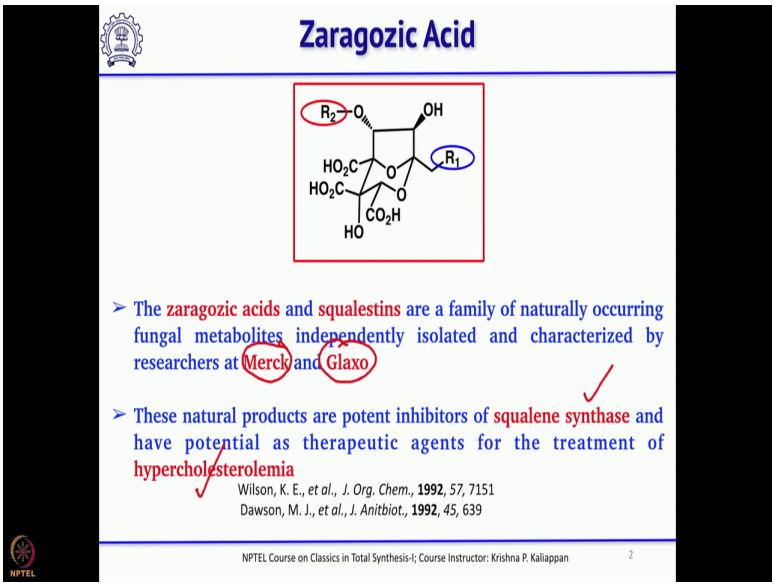

So, the zaragozic acid and squalestatins ok; so, both belong to the same family of a naturally occurring fungal metabolites where independently isolated and characterized by Merck groups and from also from Glaxo. So, these zaragozic acids and squalestins where independently isolated by researchers at Merck and Glaxo; so, they are potential inhibitors of squalene synthesis ok so; that means, you know this could be used for the treatment of hyper cholesterolemia ok.

So, those who have cholesterol problem could be potentially be treated by this naturally occurring compounds ok.

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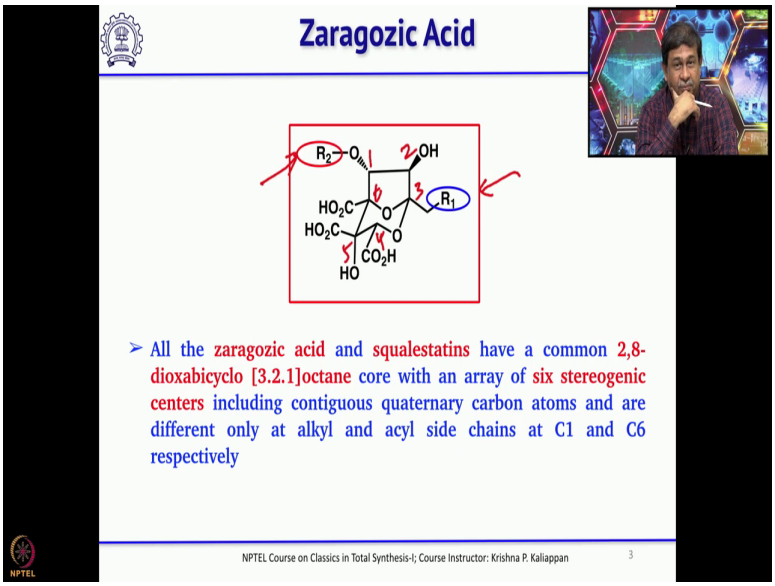

So, there are many zaragozic acids and that depends on the substituents at these two, one on oxygen that is R2 attached to oxygen the other one that is the side chain R1 ok. And if you look at these natural products carefully, you can easily find out 1 2 3 4 5 6, 6 stereogenic centers ok. And in that how many quaternary centers are there? At least 4 quaternary centers. So, it is not that easy to synthesize such complex molecule having 6 stereogenic centers and also having quaternary carbon atoms ok.

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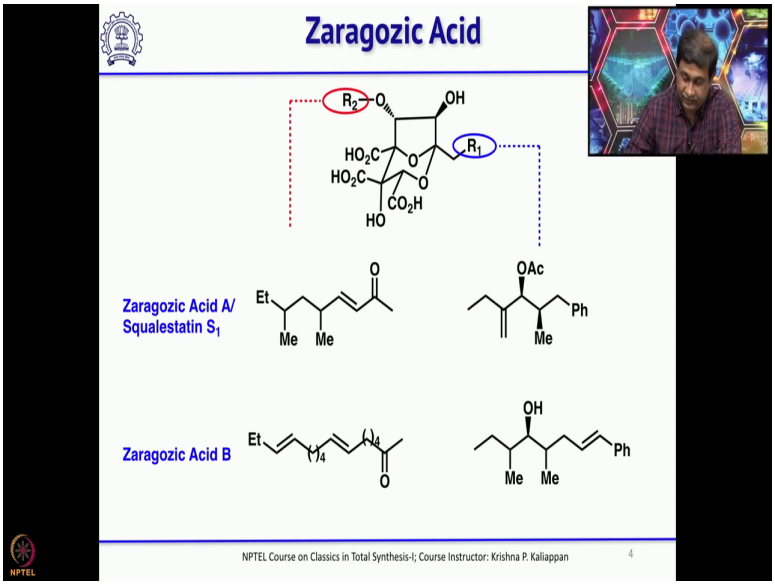

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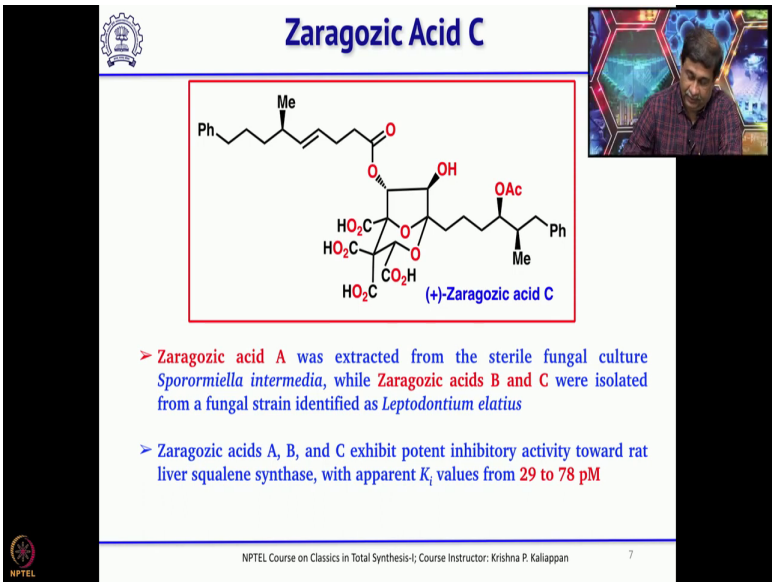

So, these are some of the squalestatin zaragozic acids isolated from the nature. And today what we will do we will talk about the total synthesis of zaragozic acid C reported by Erick Carreiras group ok.

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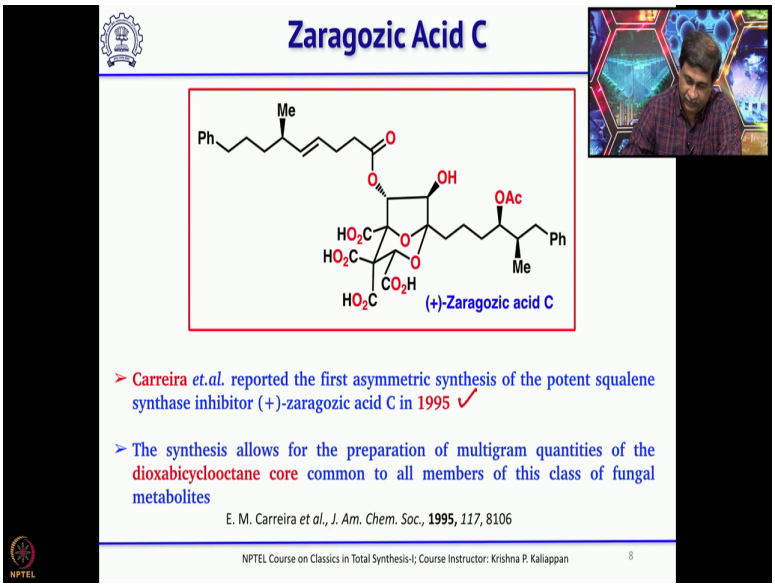

So, this was the first total synthesis reported in 1995 and his idea was to use commercially available D-Erythrono lactone as a static material and build upon the chiral centers present in Erythrono lactone.

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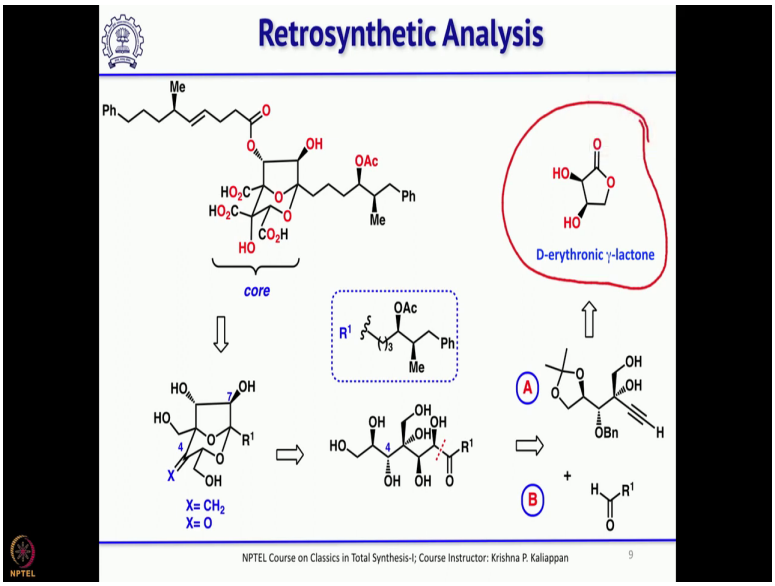

So, this chiral approach based on the retro synthesis as you can see here; so, this is the chiral starting material ok. This can be made in few steps from commercially available compound.

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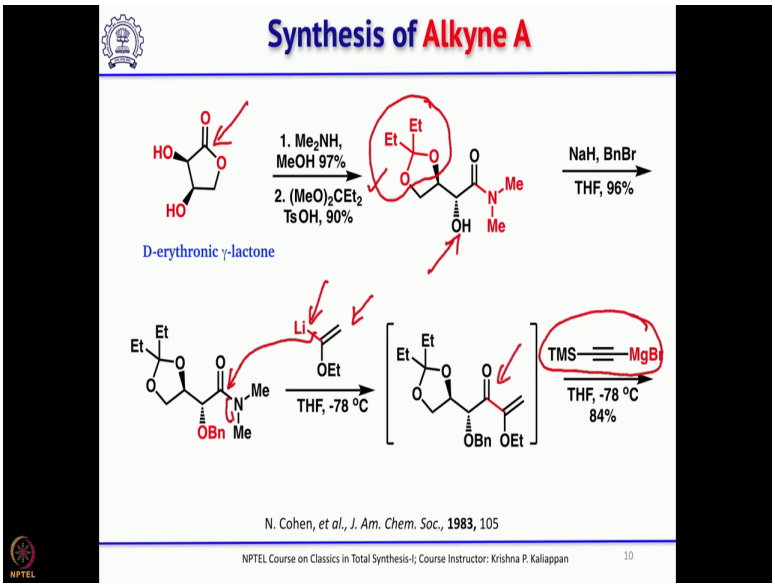

So, this upon treatment with dimethylamine and methanol, one could open these Five membered lactone to get the corresponding triol and amine. Now, the triol upon treatment with the protected three pentanone the protected three pentanone and acidic condition. So, you can see these 1,2 diol was protected as ketal ok, then sodium hydride

benzyl bromide you could remove this proton. And benzylate the remaining secondary hydroxyl group followed by treatment with two lithio vinyl ether ok.

This is a vinyl ether and at α position you can generate lithio by treating with n butyllithium or tertiary butyl lithium. So, that will add to this weinreb like amide and you will get corresponding enone ok. Then treatment of this enone with TMS acetylene Grignard. So, that will undergo highly stereo selective one two addition to the enone to give the quaternary center.

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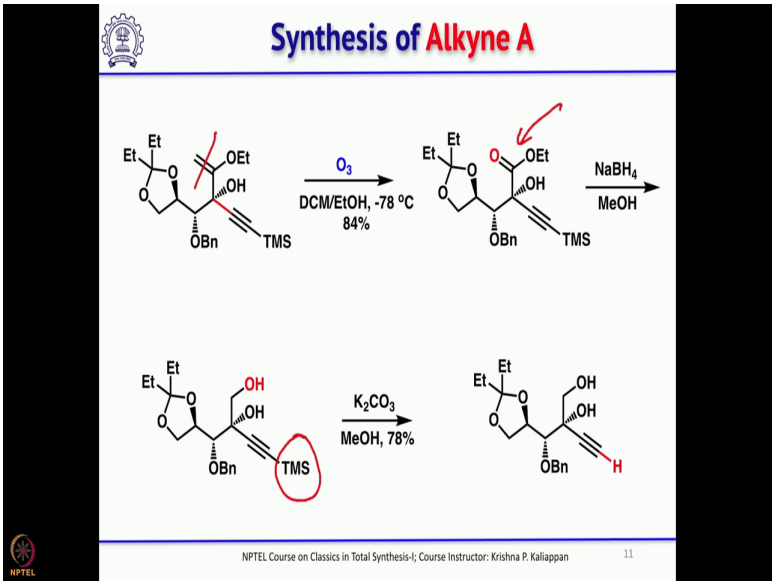

So, now if you look at there are three quaternary centers, two are carbon based quaternary center; so, that one is achieved using this addition of TMS acetylene ok. Then one can ozonolyse the double bond to get the ester that is enol ether is ozonolysed to get the ester followed by reduction with sodium borohydride in methanol the ester group is fully reduced to corresponding alcohol.

So, now, one two diol and then TMS group which is attached to the acetylene; so, these are you know this TMS group can be easily removed by treating with potassium carbonate methanol.

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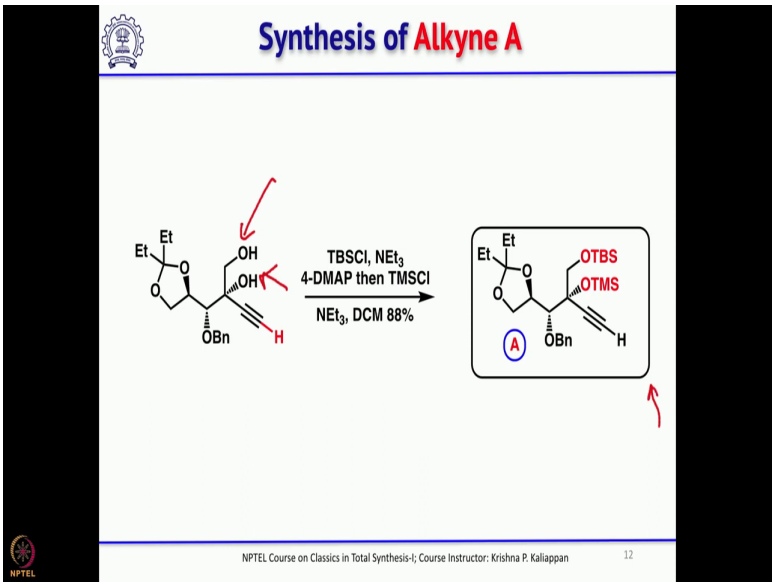

Then the primary alcohol was protected as TBS ether, then the secondary alcohol was in situ protected as TMS ether as you know between TBS and TMS. TMS is labile; so, that is how you could prepare the intermediate A required for the total synthesis of zaragozic acid C.

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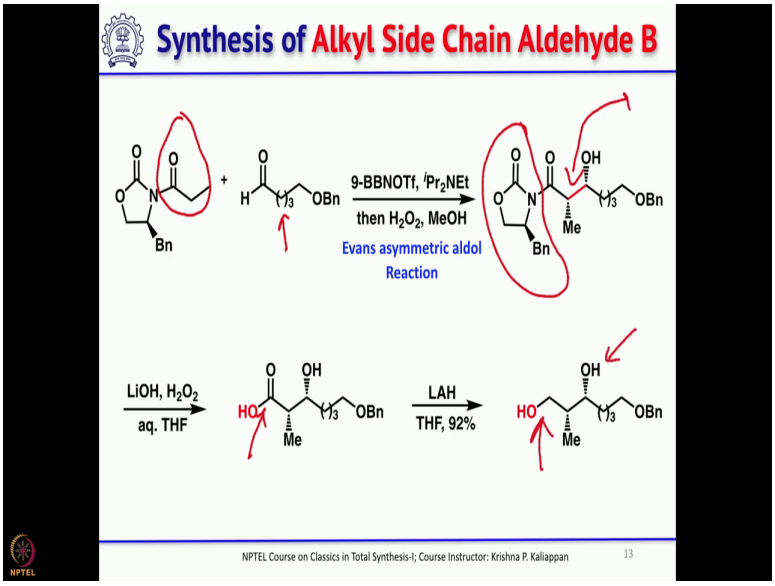

Now, for the synthesis of the other fragment aldehyde, he started with Evans chiral auxiliary and then attached the propionic acid anhydride. So, then boron enolate

followed by aldol reaction with this aldehyde ok; so, that classical Evans asymmetric aldol reaction gave this syn aldol ok.

Now, once this aldol is there then the chiral auxiliary can be removed by treating with lithium hydroxide and hydrogen peroxide to get carboxylic acid ok. What is the next step? Reduction of the carboxylic acid with LAH gave the 1,3 diol for the 1,3 diol, one is primary alcohol, other one is secondary alcohol ok.

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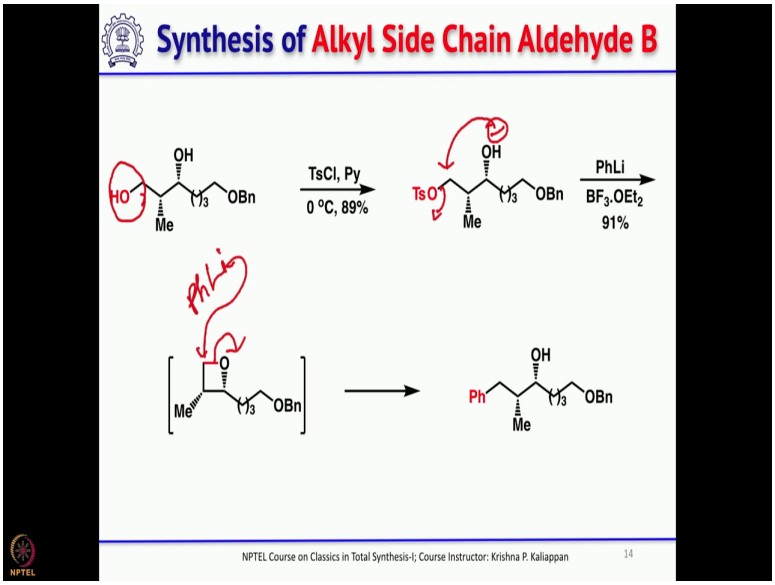

Then take this primary alcohol tosylate you get the primary tosylate; now, if you treat with phenyl lithium ok. So, the phenyl lithium what it can do? It can remove this proton and then intramolecularly attack to form oxetane ring followed by addition of another equivalent of phenyl lithium that can attack the oxetane and open the oxetane to get or introduce the phenyl group.

So, basically what has been done is to remove this hydroxyl group with a phenyl, phenyl group. So, you convert that hydroxyl group into a good leaving group followed by treatment with phenyl lithium in the presence of Lewis acid you can replace the hydroxyl group by phenyl group ok.

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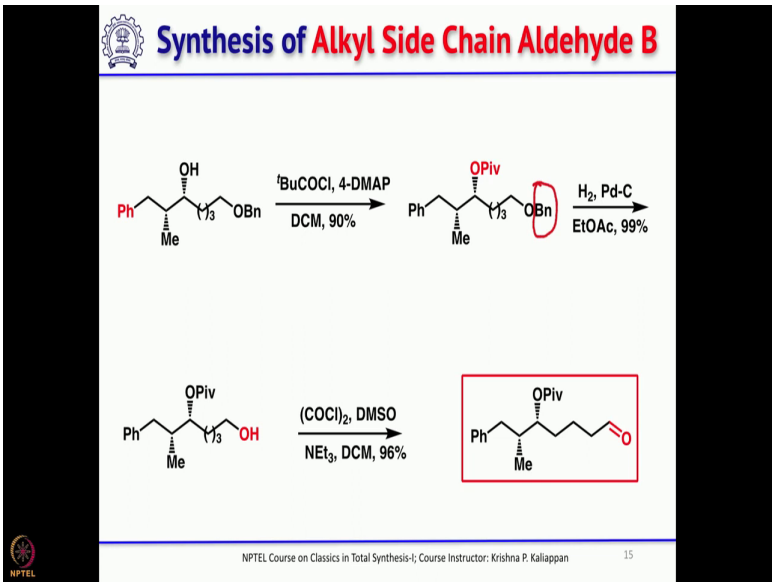

Then protect the hydroxyl group as pivalate ester, then remove the benzyl group ok, remove the benzyl group and hydrogenolysis to release the primary alcohol. This upon swern oxidation gives the primary aldehyde ok, this upon swern oxidation gives the side chain aldehyde B ok. So, now, we have seen the synthesis of fragment A and fragment B.

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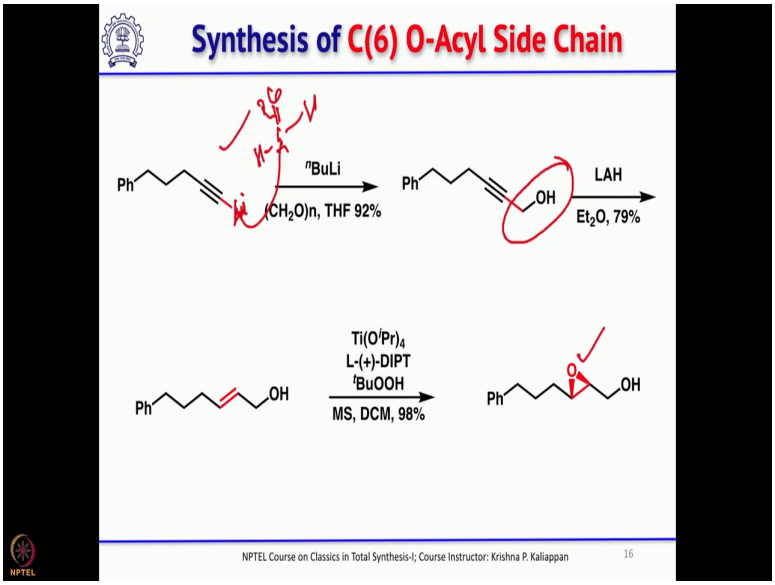

Let us see the synthesis of the other O-acyl side chain; so, for that he started with this terminal alkyne; so, this is easy to prepare in three steps from TMS acetylene. Then n

butyl lithium followed by quenching with formaldehyde one can introduce this CH_2OH. So, first you remove this proton and then quench with formaldehyde; so, that gives the CH_2OH.

Now, LAH reduction propargylic alcohol upon reduction with LAH give trans allylic alcohol. So, that was done easily and this trans allylic alcohol once you have this can undergo Sharpless asymmetric epoxidation ok. So, the Sharpless asymmetric epoxidation with L (+) Di-isopropyl tartarate gives this epoxide ok.

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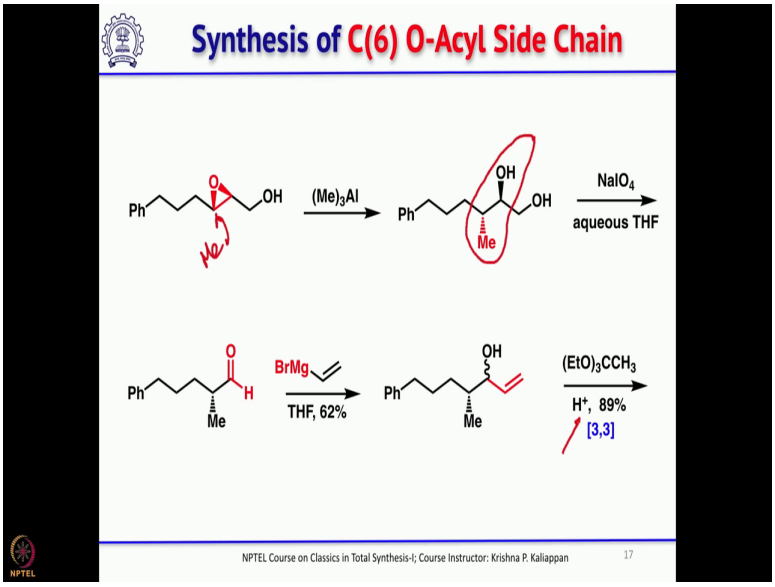

So, once you have this epoxide that epoxide can be opened particularly the epoxides derived from Sharpless condition or allylic alcohol this can be easily opened with trimethylaluminum. So, now, the aluminum will open opposite to this epoxide; so, thereby one can easily get the anti-aldol product ok if you look at this it is like anti aldol product.

Now, you have 1-2 diol, the 1-2 diol can be cleaved with sodium perhydrate to get the corresponding aldehyde. This aldehyde upon treatment with vinyl magnesium bromide; so, he got the corresponding vinyl allylic alcohol ok. So, this vinyl allylic alcohol upon treatment with triethyl orthoacetate ok, triethyl orthoacetate with the catalytic amount of acid is well known to undergo Claisen rearrangement ok.

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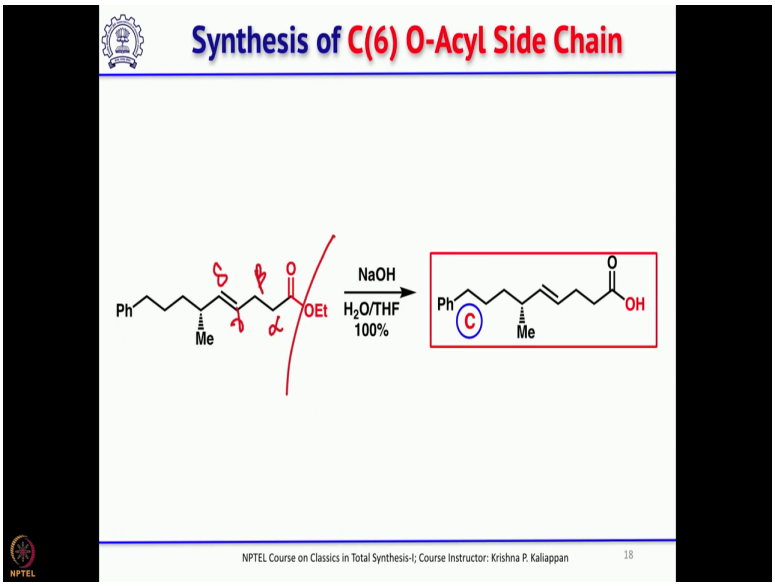

So, if that happens you get this gamma delta unsaturated ester, gamma delta unsaturated esters whenever you see or wherever you see one reaction which should come to your mind is Claisen rearrangement. So, this is what the product, this is nothing but gamma delta unsaturated ester, then simply you do the hydrolysis you get the carboxylic acid. So, now, you can see the three fragments; A B and C are ready, how these three fragments are combined to complete the total synthesis of zaragozic acid C.

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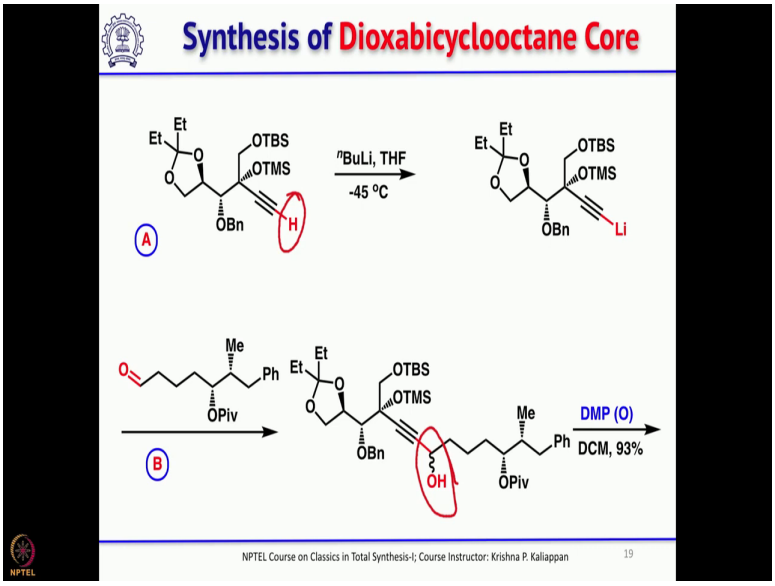

So, you start from the intermediate or the fragment A, and this fragment A upon treatment with butyl lithium or butylene this is the most acidic proton you remove that proton and then form the corresponding Lethio derivative then add the fragment B. So, fragment B has aldehyde; so, that undergoes inter molecular nucleophilic addition reaction to get this propargylic alcohol ok.

Once you have this propargylic alcohol one can easily oxidize that alcohol selectively using Dess martin periodinae reagent to get this alkynyl ketone; α–β, unsaturated alkynyl ketone.

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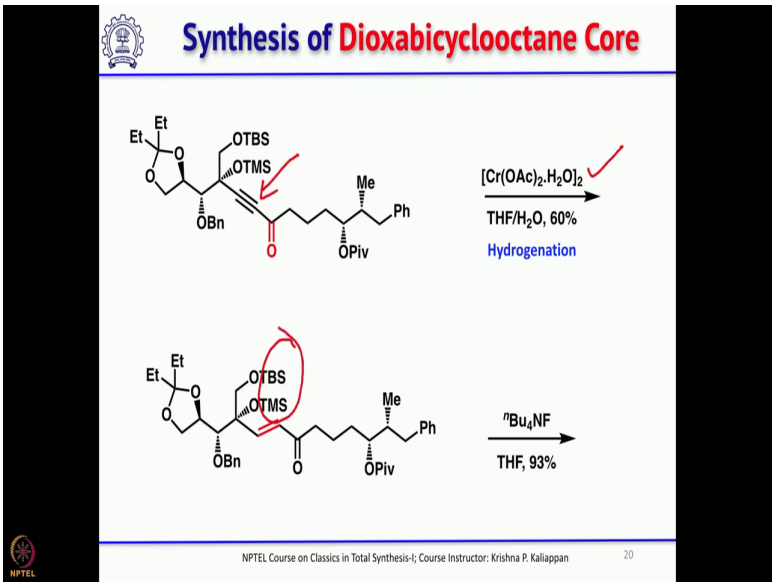

And this can be reduced the triple bond can be reduced under this condition where the triple bond is reduced to trans double bond ok, the triple bond is reduced to the trans double bond. Now, treatment with tetra butyl ammonium fluoride removes both TMS and TBS to give diol ok.

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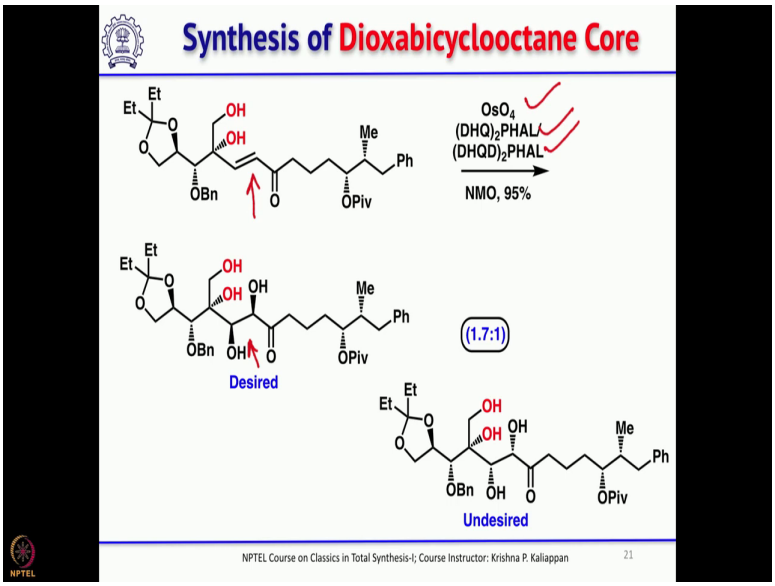

And you have this enone, enone can be subjected to Sharpless asymmetric dihydroxylation. So, the Sharpless asymmetric dihydroxylation gave this as the major product where the two hydroxyl groups are coming from beta side. And also, some amount of α which is favoring the desired beta diol was obtained the desired compound was taken and moved forward.

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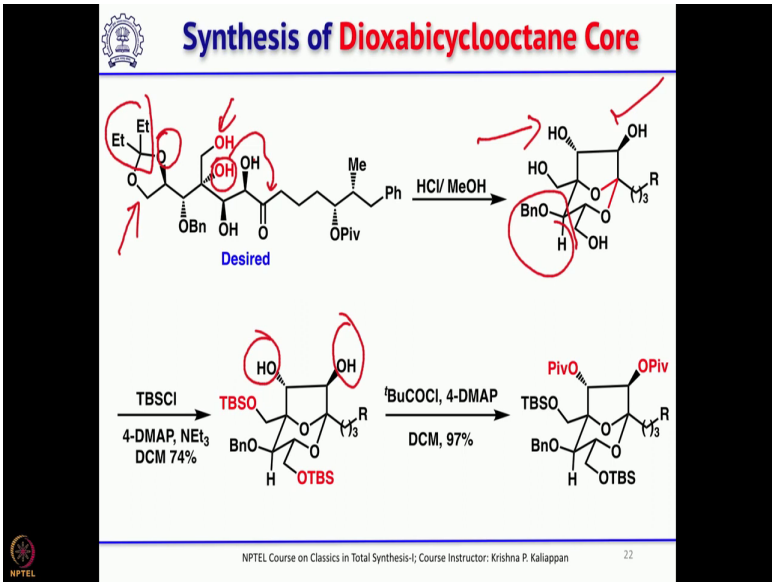

So, if you treat with HCL and methanol HCL and methanol what will happen? This whole group will go this whole group will go. So, that will form a diol ok, that will form

a diol and this hydroxyl ok this hydroxyl and this hydroxyl will form ketal with this carbonyl group to give this product. Now, you can see the core structure the core structure of zaragozic acid is formed ok.

So, what needs to be done you have to attach the side chain at this carbon and also selectively you have to remove this and then functionalize, these are two additional things to be done. So, the free hydroxyls that is the primary hydroxyl this one and this one were protected as TBS ether by treating with TBS chloride and then bases like triethylamine and four dimethyl aminopyridine.

Now, the secondary hydroxyl groups here secondary hydroxyl groups here were protected as pivalate ester by treating with pivaloyl chloride and DMAP.

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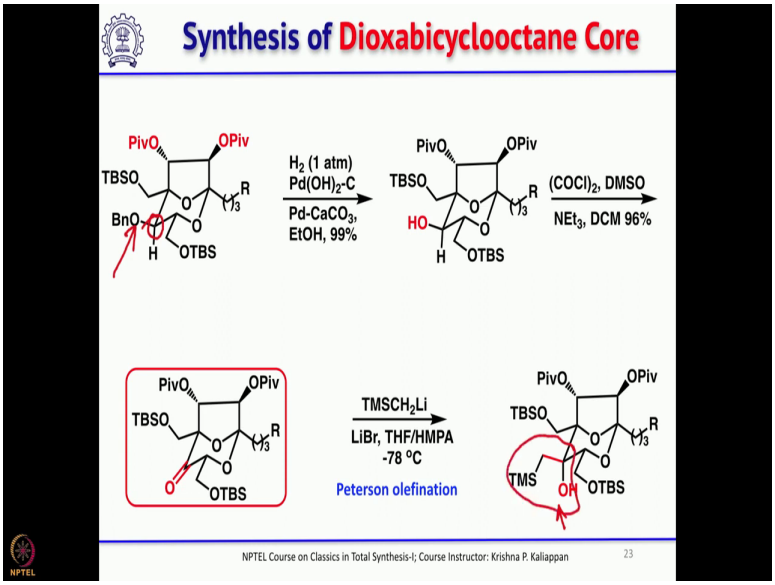

Then the benzyl group should be removed; so, that one can think about homologating at this curve. So, the benzyl group upon hydrogenolysis was removed to get the alcohol; so, an oxidation gave the ketone. Now, addition of trimethylsilyl methyl lithium gave this product, say a normally when you talk about trimethylsilyl methyl lithium or corresponding magnesium salt that is meant for Peterson olefination ok, you will get a double bond. So, now, so, the product has trimethylsilyl ethanol as the sub unit.

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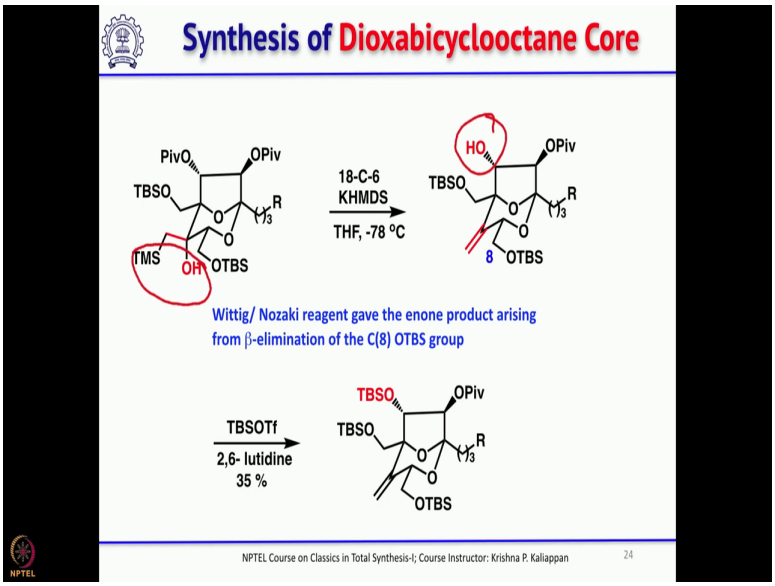

So, that compound upon treatment with 18 crown 6 and potassium hexamethyldisilazide that underwent elimination to give the double bond, basically the whole thing is Peterson olefination ok. Then protect this hydroxyl group during this Peterson olefination one of the pivalate ester also got hydrolyzed. So, you have these three secondary hydroxyl group which was re-protected as TBS ether ok.

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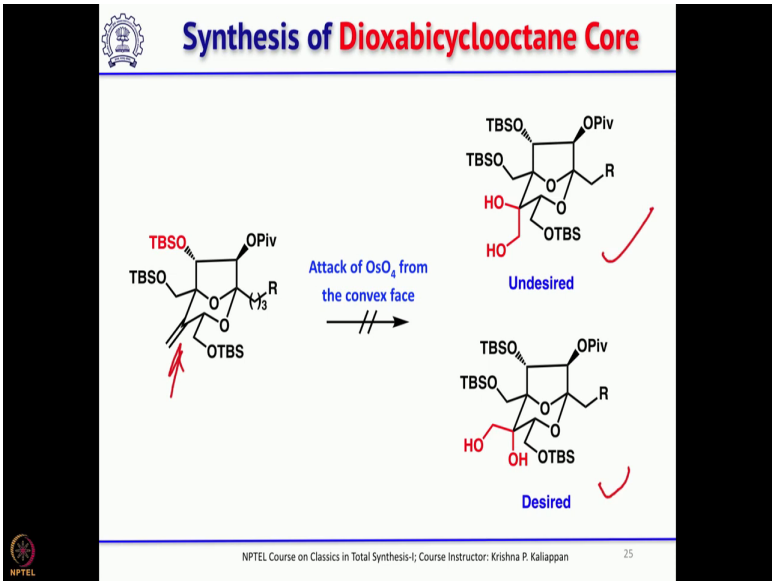

Then he needs to functionalize this exocyclic double bond ok, but all the time what he got was this undesired diol and not the desired diol. So, basically one has to do the

dihydroxylation. So, when you talk about dihydroxylation the simplest method which will come to your mind is oxabicycooctane. We tried with oxabicycooctane only the two hydroxyl groups came from the convex side ok; so, that is not the record one.

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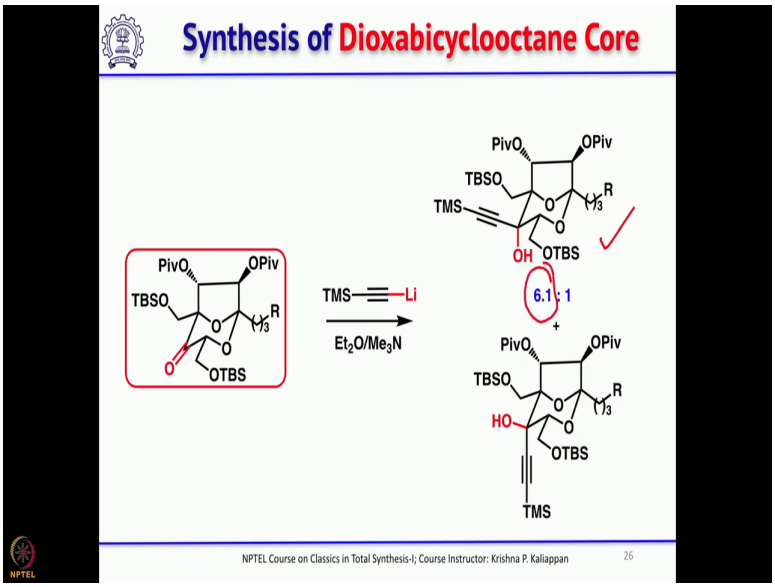

So, finally, what he did he went back to the ketone ok he went back to the ketone. So, instead of doing a Peterson olefination he added lithium trimethylsilyl acetylene to get this as the major product. Now, you can see this trimethylsilyl acetylene comes from the equatorial side and this is the major product you can see 6:1 ratio.

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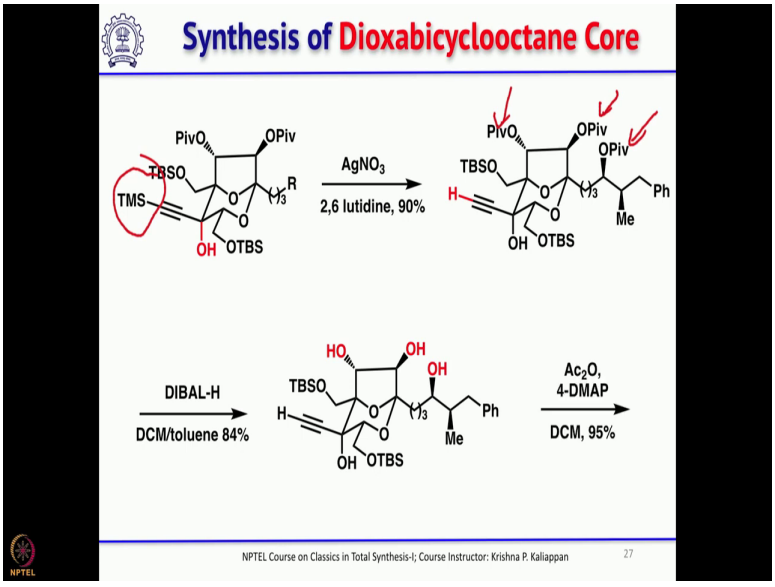

So, take this compound and then treat with silver nitrate to remove the TMS group attached to the triple bond ok. So, the TMS was cleaved to get the triple bond then dibal reduction you have three pivalate ester three pivalate ester all this can be removed by using DIBAL. Reductive cleavage of the pivalate esters done with the DIBAL to get a triol, then treatment with acetic anhydride dimethyl aminopyridine gave the triacetate ok, TBS was removed and then re-protected as triacetate.

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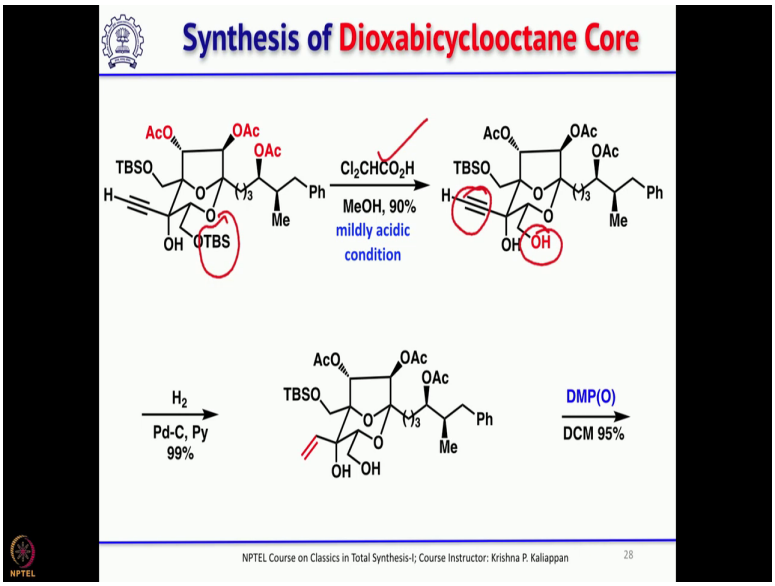

So, now you do not need this TBS group ok, you do not need this TBS. There are two TBS groups ok, this particular TBS which is less hindered compared to the other one was removed by treating with dichloroacetic acid ok. So, that primary alcohol as you can see here you have the primary alcohol and the triple bond. So, if you want to reduce the triple bond you can do it and write a generalization condition; so, that the triple bond is reduced to the double bond.

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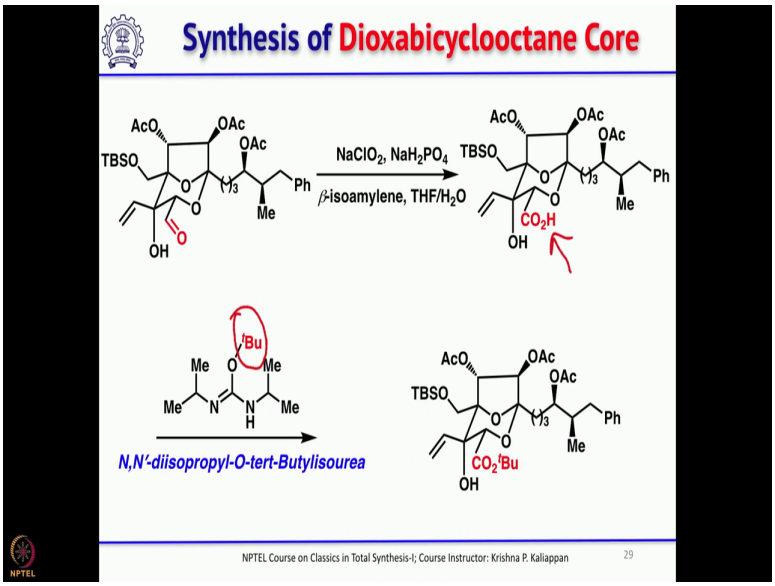

Now, Dess martin periodinane oxidation oxidizes the primary alcohol to aldehyde which upon oxidation further under pinnick oxidation condition gave the carboxylic acid. Basically, the CH_2OH is converted into carboxylic acid in two steps ok, then came the esterification this is one of the very rarely used esterification method where the tertiary butyl esters are made like this from corresponding urea derivative ok.

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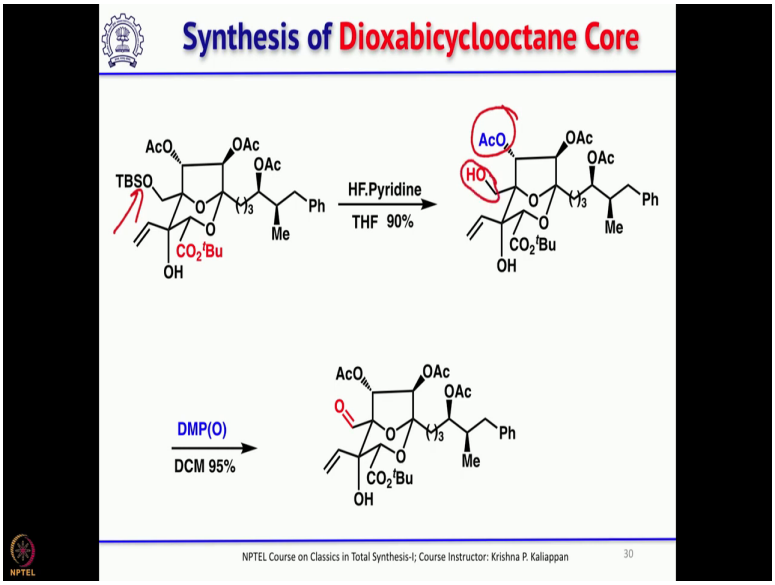

So, once you have this tertiary butyl ester, the next step is to remove this TBS group. So, that was done using HF pyridine and next what one has to do is, you have to attach the side chain here ok.

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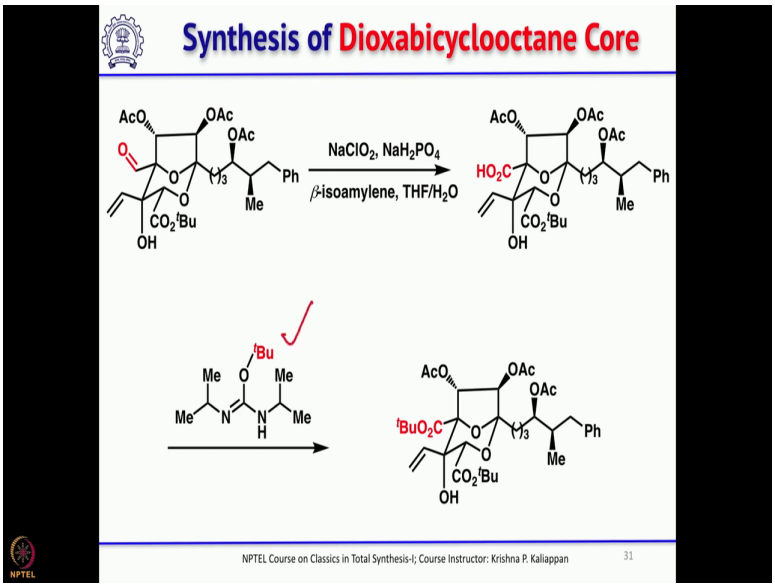

And before that this primary alcohol was oxidized under Dess martin periodinane condition to get the aldehyde and followed by oxidation and the pinnick oxidation condition to get carboxylic acid. And that was again protected as tertiary butyl ester using the substituted urea derivative.

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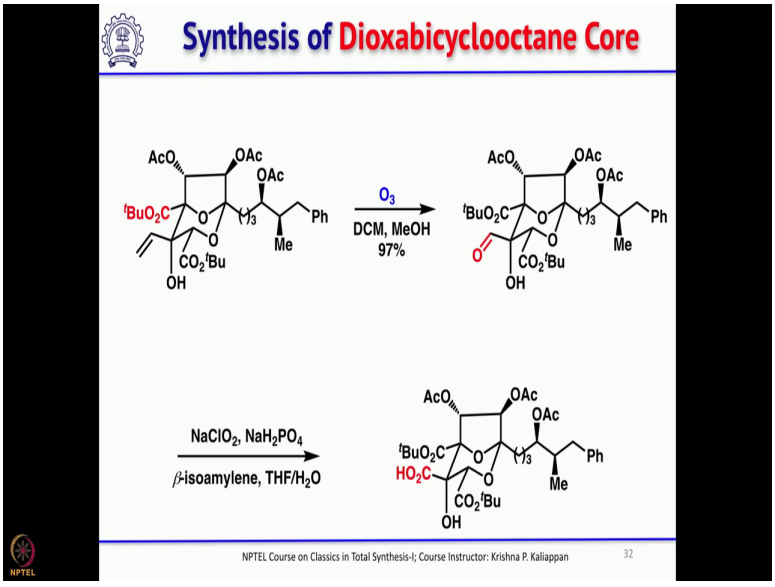

Then ozonolysis of the vinyl group gave aldehyde; so, that also was oxidized using pinnick oxidation condition to get the carboxylic acid ok.

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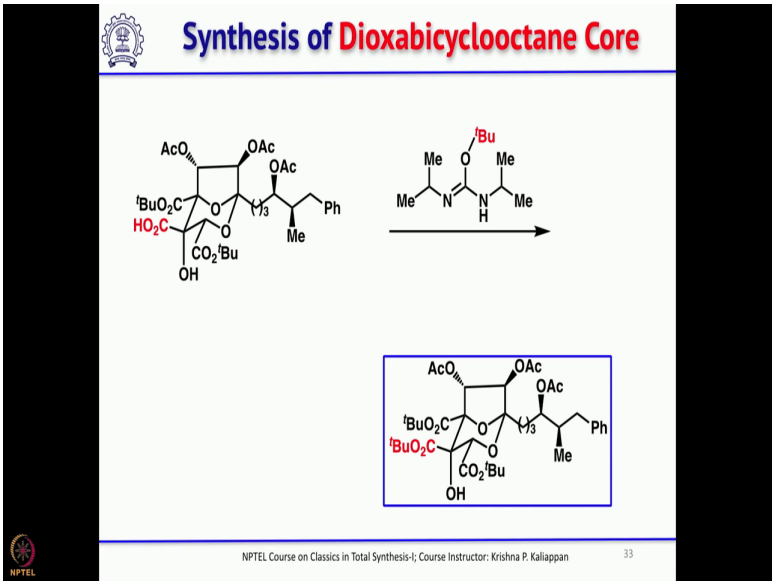

Now, if you look at this carefully the third carboxylic acid also was esterified using the same method to get the tertiary butyl ester.

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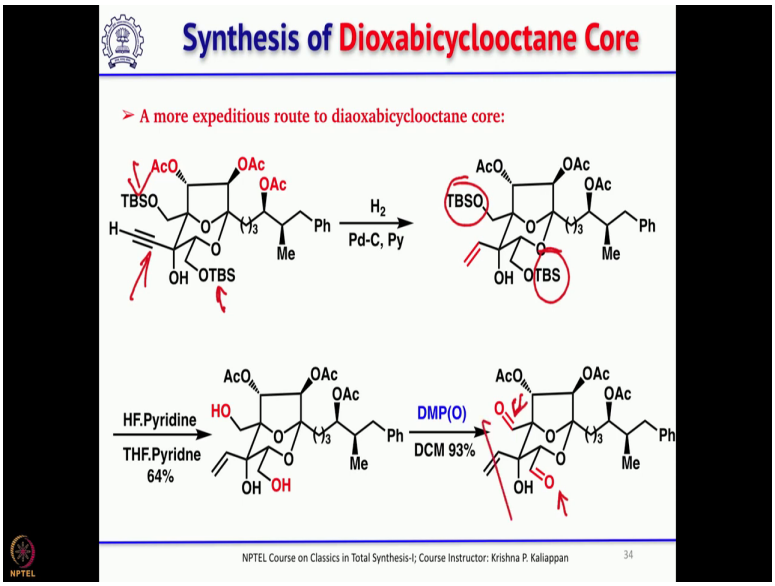

He also used another method where he could start from here; that means, he has a triple bond here and then two TBS protected primary alcohol. So, what he did, first he reduce the triple bond to double bond then the TBS groups were removed using hf pyridine to

get the primary alcohol. This primary alcohol upon oxidation under Dess martin periodinane condition you could get two primary aldehyde ok, two aldehydes.

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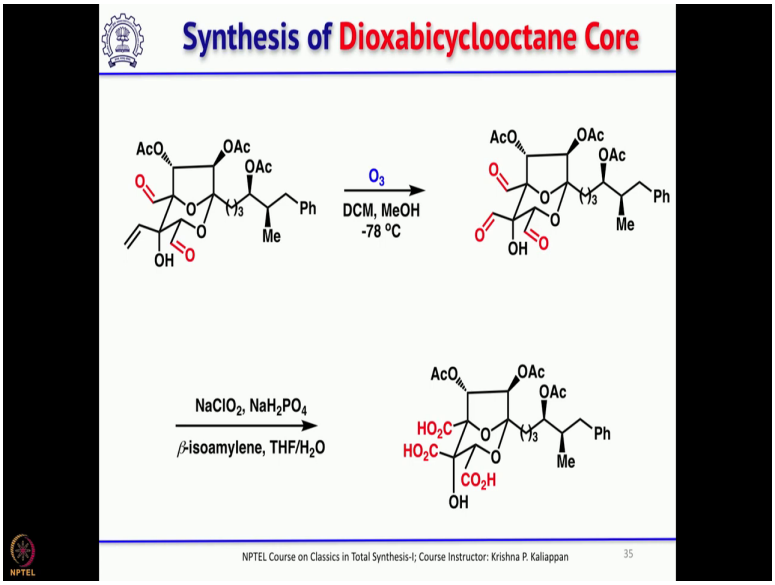

Then if you do ozonolysis, you will get one more aldehyde ok; so, you can see there are three aldehydes at the end of this sequence. Now, if you oxidize this under pinnick oxidation condition one could get the corresponding tricarboxylic acid ok.

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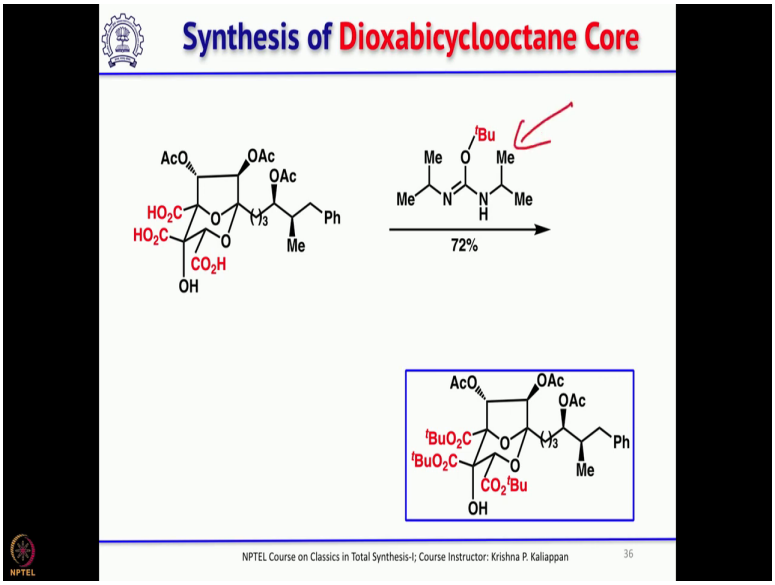

So, now you can also protect all the three carboxylic acids in one step using this tertiary butyl urea derivative ok.

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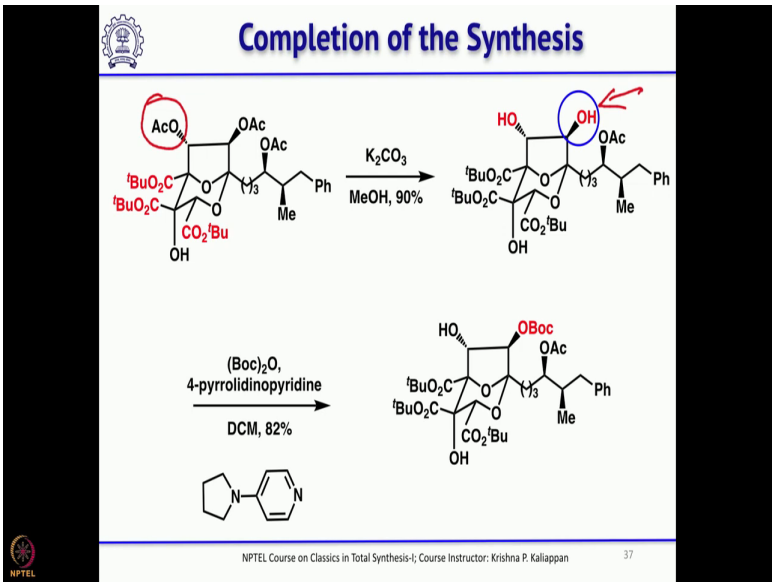

So, then what is required is you have to selectively carry out alkylation at this hydroxyl group ok. So, potassium carbonate methanol will hydrolyze both the acetates to get the diol then this particular alcohol was protected as Boc ether ok.

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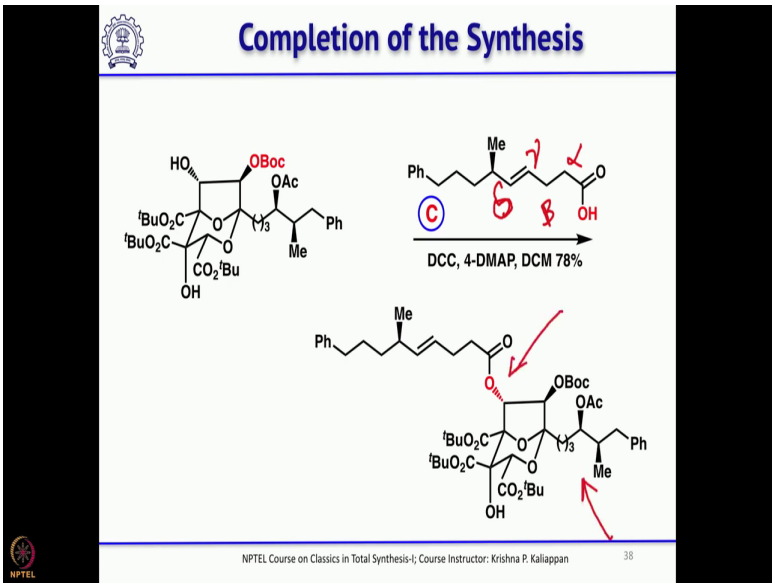

Then the other hydroxyl is free; so, that other hydroxyl group was esterified with this gamma, delta, unsaturated carboxylic acid. This is esterified with γ-δ unsaturated carboxylic acid which we already discussed how to make this γ-δ unsaturated carboxylic

acid. So, you can see this side chain was established and here also on the right-hand side chain was established; so, what is left is to remove all the protecting groups.

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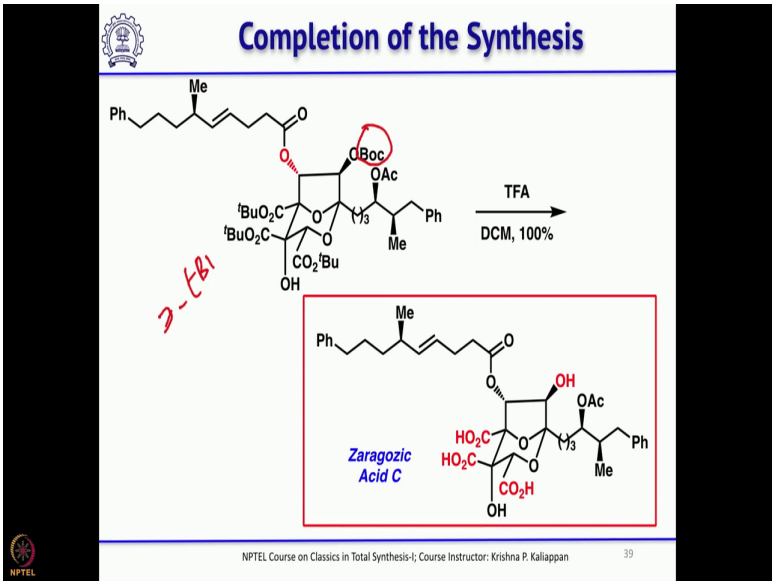

What are the protecting groups? There are three tertiary butyl group ok, there are three tertiary butyl groups which would be hydrolyzed to get the corresponding tricarboxylic acid and also there is one tertiary butyl oxy carbonyl group ok. So, these two can be easily removed using trifluoroacetic acid condition ok; so, that was done to obtain the natural product called zaragozic acid C.

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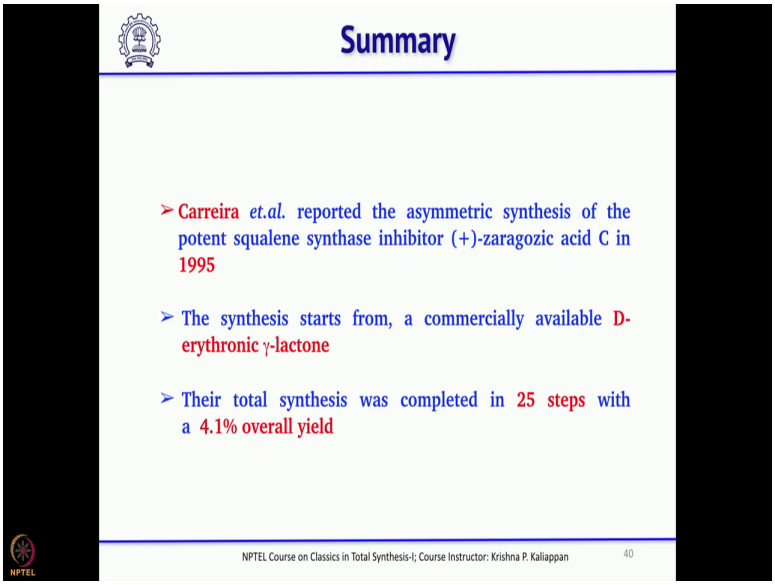

So, if you look at this synthesis, he started with commercially available to D-Erythrono lactone ok. And overall, he took about 25 steps and yield was very good considering that it is a complex molecule. And then he took he and his group took 25 steps 4.1 % overall yield is a significant method significant total synthesis among many complex natural products.

So, what I will do I will stop here and with this we have completed more than hundred total synthesis of really complex natural products starting from you know very small natural product called eluding. And we went all the way to zaragozic acid and many alkylates ok. So, the with this lecture we completed what the syllabus which I have proposed in the beginning of the course. So, the last two lectures it is basically to summarize what we have discussed ok.

I am not going to talk about any more total synthesis in the next two lectures that is the last two lectures I will focus only on the synthesis which we have discussed and that too each synthesis what are the key reactions we have discussed. So, that you will get an idea of how many reactions which we have discussed throughout this course ok. And how these reactions could be successfully used in the total synthesis of complex natural products ok.

Thank you and all the best for your exams.