Classics in Total Synthesis-I
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Lecture - 54
Discodermolide

So, good morning and welcome back to NPTEL lecture series on Classics in Total Synthesis.

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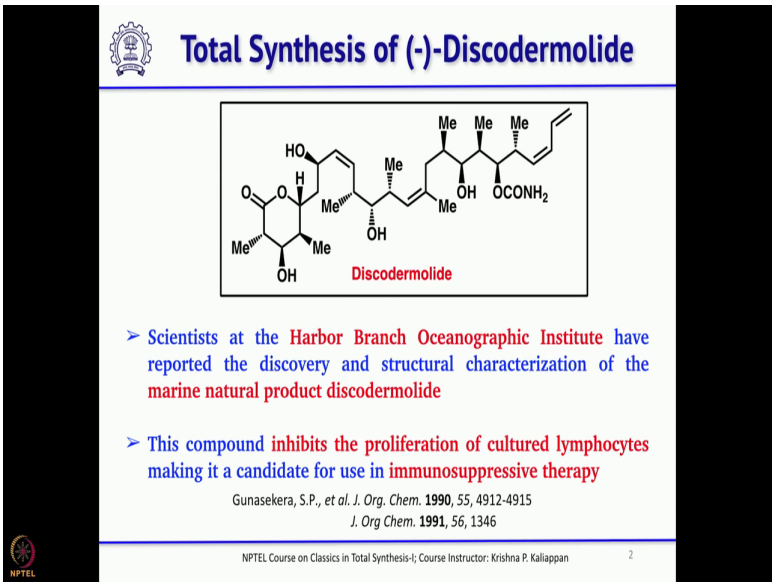

So, today, we will talk about another very interesting and complex natural product called Discodermolide. This marine natural product and it shows really excellent biological activity; particularly, it is an anti-cancer agent and also, it could be used as immunosuppression. So, that is why since its isolation many groups were interested in the total synthesis of this particular complex natural product. The first total synthesis was reported by none other than Stuart Schreiber.

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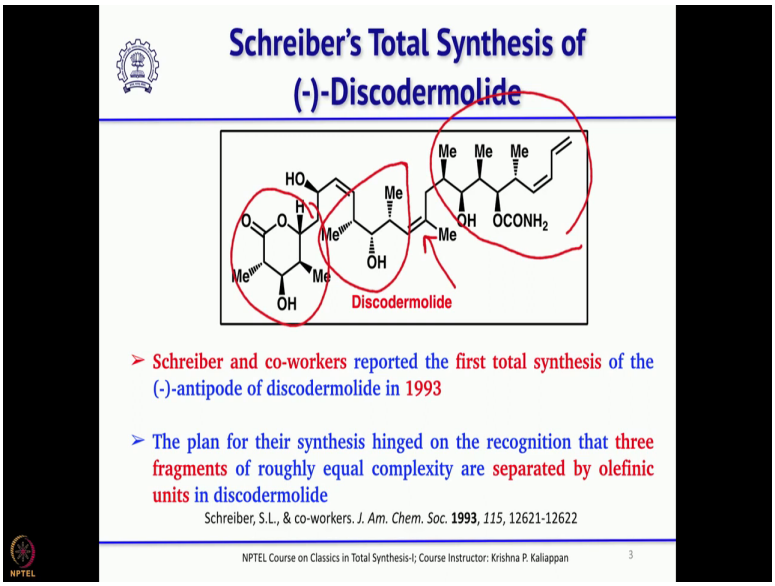

So, who reported this synthesis three years after the molecule was isolated. When you look at this molecule you can see there are many chiral centers first of all ok and you have a six-membered ring on the left hand side and you have five chiral centers on the right hand side ok. So, in between you have three chiral centers here ok. And all these are connected by a double bond ok.

So, you can easily disconnect this molecule into at least three fragments. So, that is what Schreiber and his group did. So, they disconnected this molecule into three fragments; fragment A, fragment B and fragment C. Let us see how they have done that.

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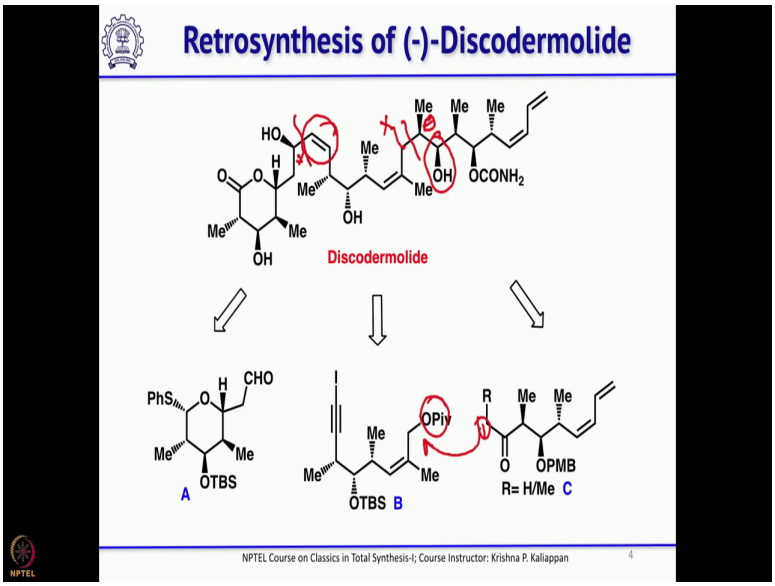

So, first disconnection on the left hand side was to break this bond. So, the idea is to use Nozaki Kishi coupling reaction ok. So, here if you have a triple bond and you can add to this aldehyde. So, you can get this propargylic alcohol that can be reduced to the corresponding allylic alcohol ok. So, that was the first key disconnection. The second key disconnection was here. The idea was to have a carbonyl group here instead of alcohol ok.

If you have a carbonyl group, then you should be able to generate an anion here and if this is a leaving group, then it is easy to do an alkylation. Later the ketone can be reduced to get the alcohol. So, the second disconnection was on that. So, you can see. So, this pivaloyl group can be removed and then, converted into a good leaving group followed by alkylation, you can make this bond. So, the first disconnection led to three fragments; fragment A, fragment B and fragment C.

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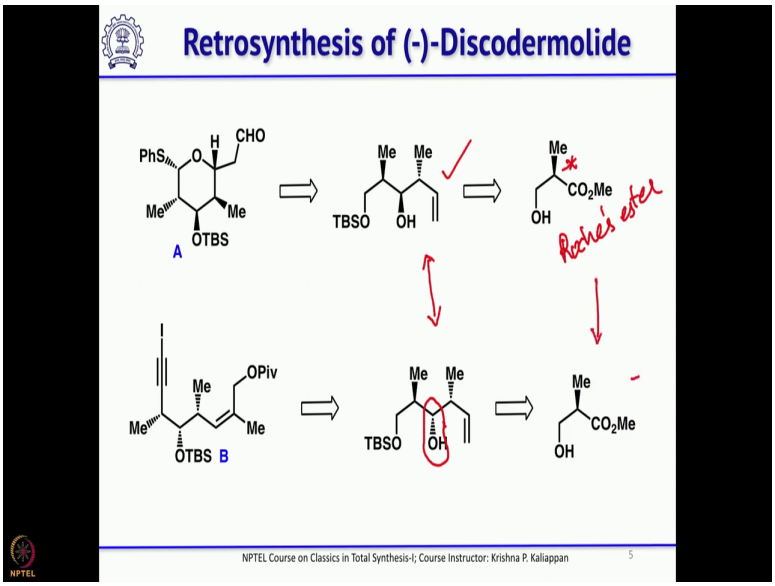

And these three fragments can be obtained for example, first start with fragment A and that can be obtained from this compound which has already three chiral centers ok. These three chiral centers were established or built upon one chiral center. This molecule is called Roche ester ok and it has one chiral center and from using this chiral center, so you could build two more chiral centers.

And for the fragment B, again if you look at it was made from almost similar starting material. If you have a closer look at this molecule, then you will see only it differs at this chiral center ok and again, the same starting material that is Roche ester.

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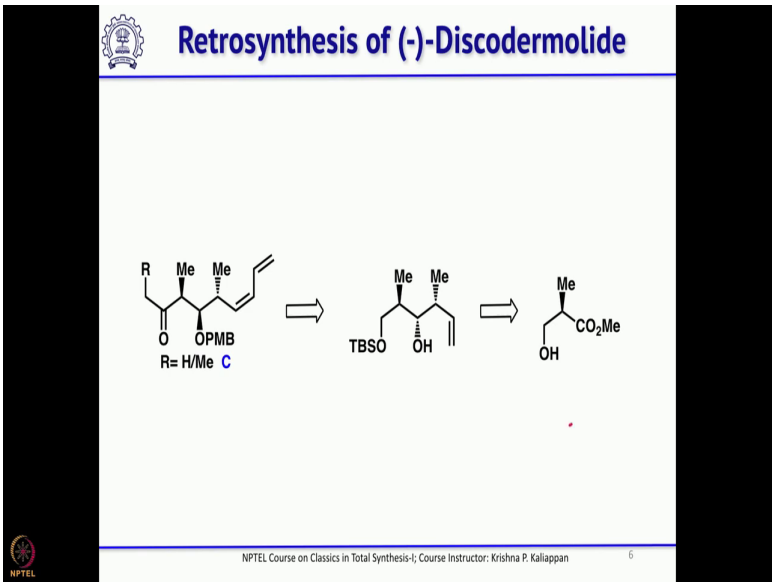

And the third fragment incidentally again comes from the same intermediate which was the intermediate for making fragment B and the starting material is same. That means, he has designed this synthesis in such a way that all the three fragments can be made from one starting material that is Roche ester ok. Let us see how he has synthesized all the fragments and then, combine to form discodermolide. So, the first step obviously, is to protect the primary alcohol and reduce the ester ok.

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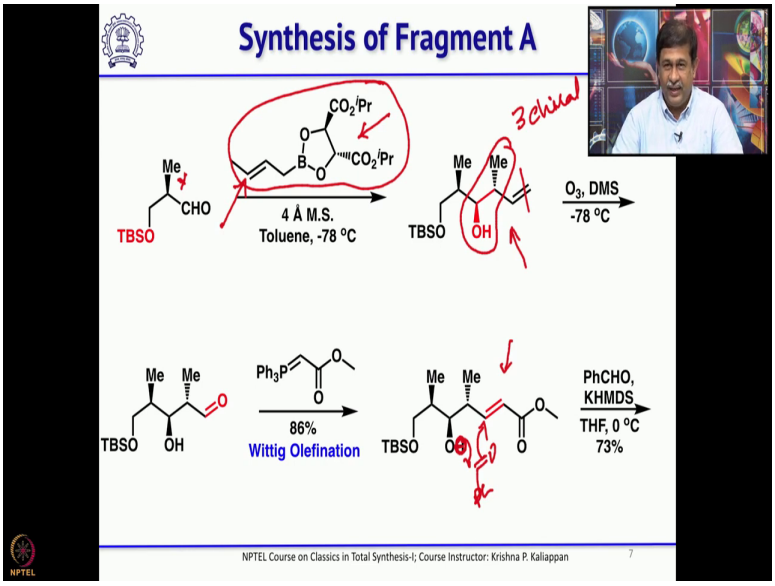

So, the primary alcohol was protected as TBS ether and then, DIBAL reduction gave the aldehyde. Then, came the first key reaction. The first key reaction was to use William Roche Crotyl Boration. So, what he has done was he has taken this chiral crotyl borane derived from diisopropyl tartrates ok.

So, it is known it was reported by William Roche that if you start with trans one, you will get this an anti aldol and if you start with cis one, if you start with the cis double bond then you will get here syn aldol product ok. This is a very established aldol reaction ok. So, you could now based on one chiral center as well as using this chiral auxiliary, you could establish three chiral centers ok.

Next the double bond was analyzed to get the aldehyde, then stabilized Wittig gave the alpha beta unsaturated ester. The second key reaction was when you have this alcohol and also the alpha beta unsaturated ester, if you treat this alcohol with potassium hexamethyldisilazide. So, what will happen? It will become O^-. It will become this proton.

Then, when you add benzaldehyde, so the benzaldehyde is like this. So, it will add to benzaldehyde and then, the benzaldehyde carbonyl oxygen will attack the alpha beta unsaturated ester and the whole process we can call it as oxa-Michael addition ok.

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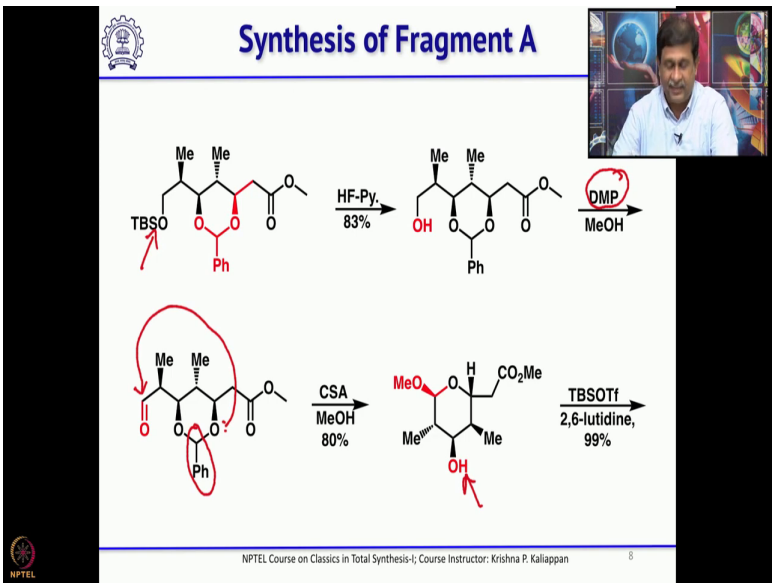

So, what you get is now you introduce the fourth chiral center and also, the two secondary alcohols are now protected as benzylidine derivative. So, this is a very interesting reaction developed by David Evan's group ok. So, now, you can remove the TBS group with HF pyridine and once you have that you need aldehyde. So, that was done with Dess martin pyridinane to get the primary aldehyde.

The idea of to form the six-membered ring is to first cleave this benzylene derivative, then this hydroxyl group should attack the aldehyde to form the six-membered ring ok. So, that was done in one step by treating with camphor sulfonic acid and methanol. So, camphor sulfonic acid and methanol first removes the benzylene derivative, then that is how the two hydroxyl groups are released.

Once these two hydroxyl groups are released, one of the hydroxyl groups will immediately attack the aldehyde to form the six-membered ring ok and since you use methanol, then in the presence of acid, it will become the corresponding lactol methyl ether ok. Then, you protect the secondary alcohol here with the other secondary alcohol which did not react to form the corresponding TBS ether ok.

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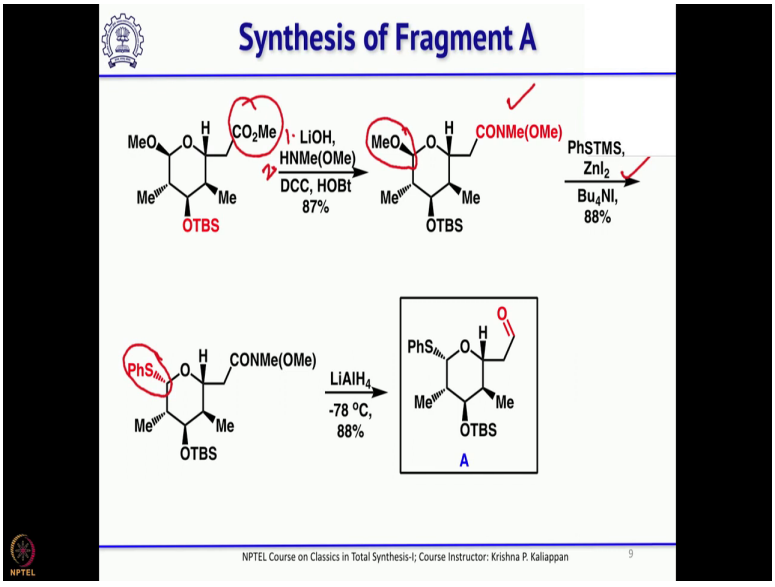

Now, the ester should be converted into aldehyde ok. So, that was first hydrolyzed with lithium hydroxide to form the carboxylic acid, then the carboxylic acid was coupled with Weinreb amine to form Weinreb amide. So, this is called Weinreb amide. As you know

when you have Weinreb amide, if you treat this Weinreb amide with Grignard reagent or organolithium reagent, you will get the corresponding ketone.

But if you treat this with reducing agents like DIBAL, Red-Al or lithium aluminium hydride,. you will get the corresponding aldehyde. So, that was the idea, he wants to get the aldehyde. Before that this -OMe group which is slightly labile. So, he wanted to convert that into -SPh that was done under Lewis acid condition by treating with zinc iodide and PhS-TMS. Then, lithium aluminium hydride reduce the Weinreb amide to get aldehyde which is fragment A ok.

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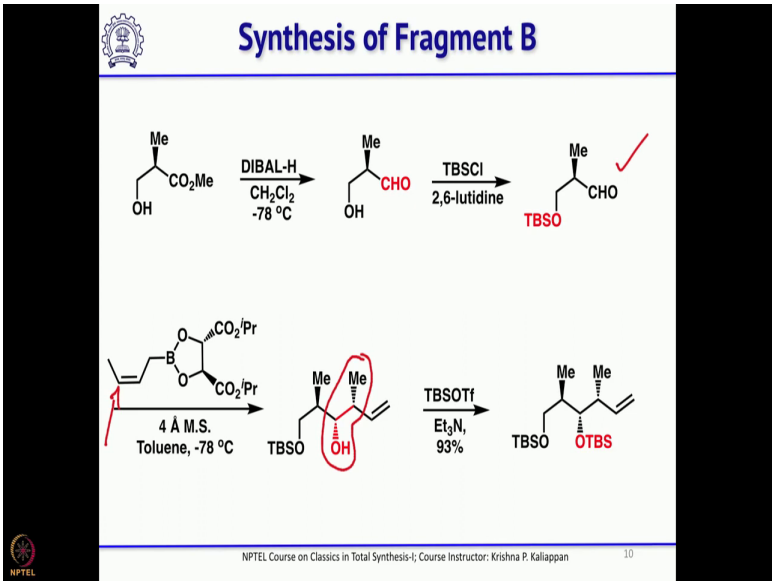

So, now, the next step is to make fragments B and C. For the fragment B, again as I said we started with the same Roche ester; in two steps, you could get the aldehyde in good yield and now, instead of trans, what he has used is cis crotyl boration ok. So, that you could get the *syn* aldol products ok.

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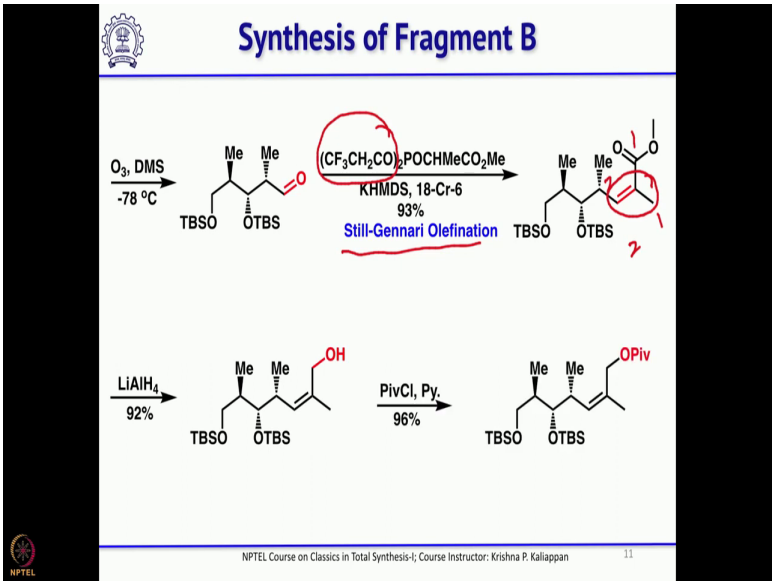

Now, once you have the syn aldol, protect the secondary alcohol as corresponding TBS ether and was analyze the double bond to get aldehyde. Then, the next step if you look at the structure of discodermolide carefully, the methyl group as well as this the double bond, the double bond which is actually connecting fragments A, B and C ok. Here, it is you know 1, 2; it is *Z* isomer ok. So, if you want *Z* isomer, then you have to use Still-Gennari Olefination.

Here instead of normal alkyl ester, the phosphonate ester, if you use trifluoroethanol ester, then that gives *Z* isomer as the major product. So, that is what he has used to get the Z isomer as a major product. Then, reduce the ester with lithium aluminium hydride to get the corresponding alcohol and that alcohol was protected as pivalate ester ok.

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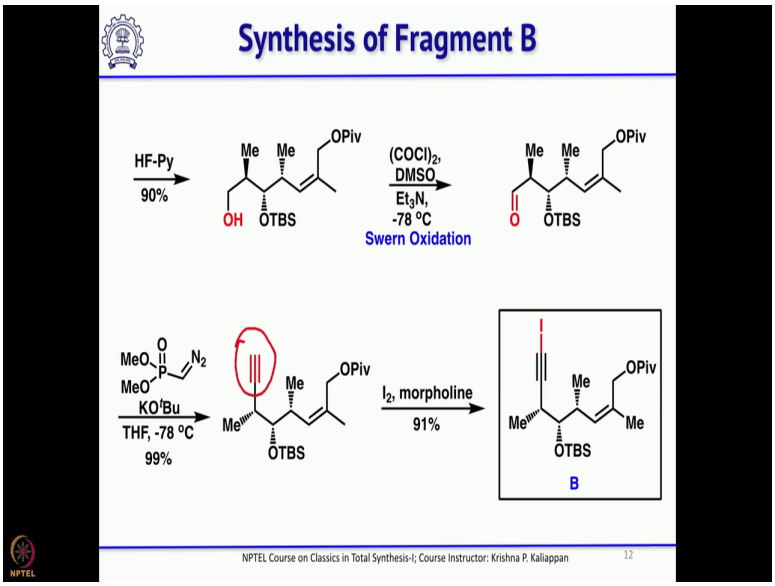

Now, remove the primary alcohol protected as TBS ether. So, you remove that TBS selectively with HF pyridine to get the primary alcohol which was oxidized under Swern condition to get the aldehyde. Now, the aldehyde is homologated using Bestmann Ohira reagent. So, you got the triple bond and the triple bond upon treatment with iodine in the presence of marpholine gave fragment B. So, the fragment A and the fragment B both are ready. The next thing is to make fragment C. But the fragment C is we already discussed ok.

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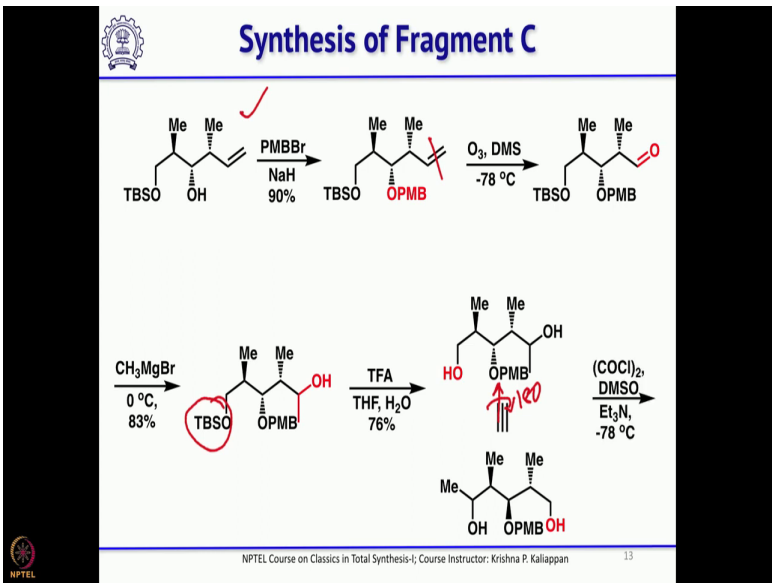

When we saw the retrosynthesis fragment B and when fragment C were made from the same intermediate ok. This is the intermediate which is common to fragment B and fragment C. So, he took this intermediate and then, protected the secondary alcohol as PMB ether because at some point of time you have to differentially remove the protecting group.

So, it is better to protect it with a different protecting group ok. So, that was protected as PMB ether by treating with sodium iodide and PMB bromide para methoxy benzyl bromide. Then, you do the ozonolysis, you get the aldehyde and treat with methyl Grignard to get the secondary alcohol ok. This also now the primary alcohol which is protected as TBS can be cleaved by trifluoroacetic acid to release the primary alcohol.

Now, you can see if you can rotate it by 180° along this axis, you will get this. If you rotate it by 180°, you will get this ok.

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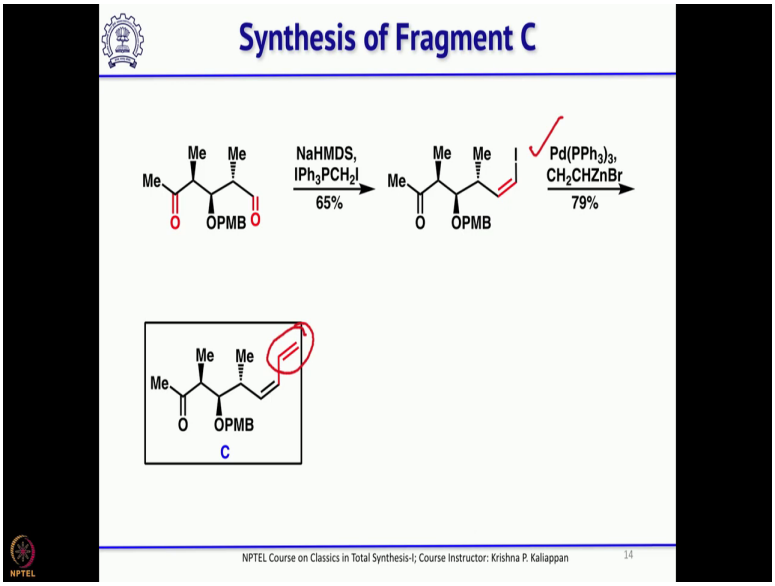

So, you have this diol, then oxalyl chloride will oxidize that is one condition will oxidize both primary alcohol and secondary alcohol to get the corresponding ketoaldehyde and the aldehyde was selectively treated with Wittig reagent derived from CH_2-I_2 ok to get the cis vinyl iodide ok. Now, the cis vinyl iodide was homologated or olefinated with -CH_2 double bond CH zinc bromide.

So, this is nothing but Negishi coupling ok. So, Negishi coupling help to introduce the next double bond. So, you have a diene at the right hand portion of discodermolide. So, this is how Schreiber introduced the diene in fragment C. So, all the three fragments are made now fragment A, fragment B fragment C. Now, how he combine all the three fragments to make or to synthesize discodermolide.

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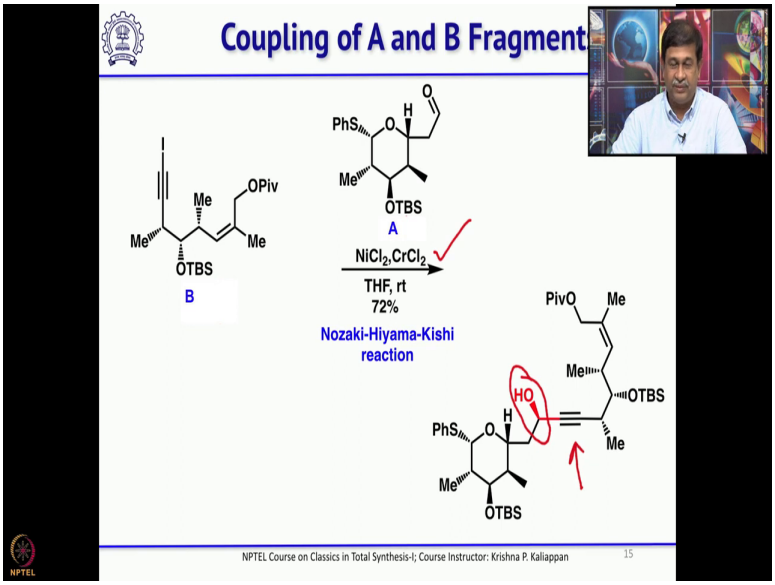

So, he took the fragment B and combined with fragment A under this Nozaki Hiyama Kishi conditions ok. So, this is well-known reaction which gives the corresponding alcohol. So, he got mainly this enantiomer and next you need a double bond. So, that can be easily reduced. If you have a triple bond and the triple bond can be selectively reduced in the presence of other double bonds ok.

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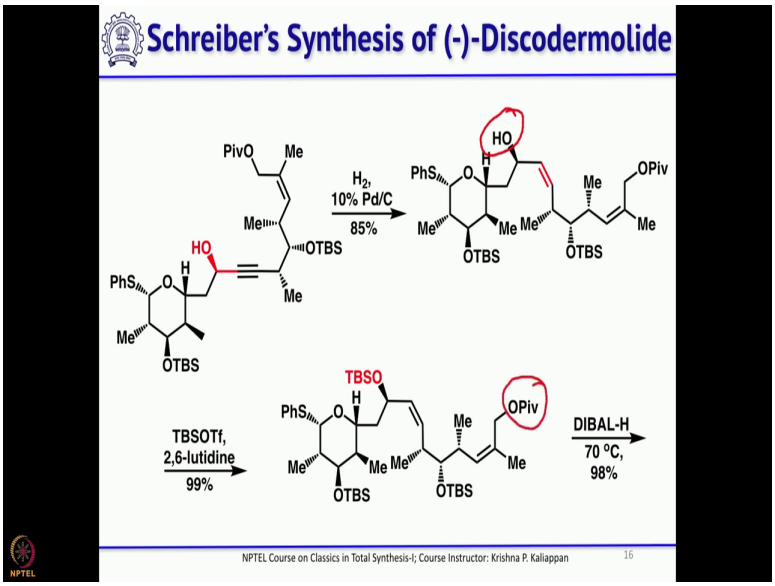

So, once you have this propargylic alcohol, reduce the triple bond to get the *cis* double bond. Then, protect the newly formed hydroxyl group ok; protect the newly formed hydroxyl group as TBS ether by treating with TBS triplet. And base like 2, 6 lutidine. Then, you reduce with DIBAL ok. So, when you reduce with DIBAL the pivalate ester will be reductively cleaved ok.

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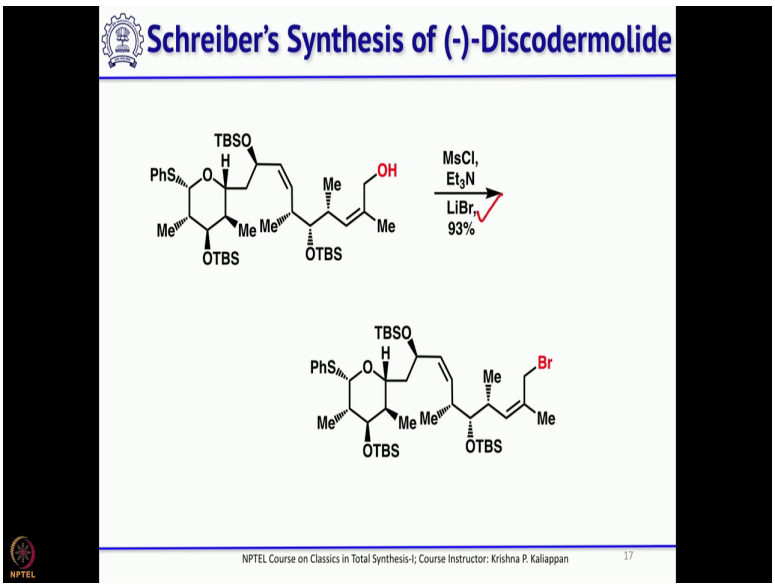

So, that will give you the corresponding primary alcohol. Then, this primary alcohol was converted into corresponding bromide in two steps via mesylate followed by treatment

with lithium bromide, you can call it a Finkelstein reaction. So, using this Finkelstein reaction, you could convert the primary alcohol to corresponding primary bromide in two steps.

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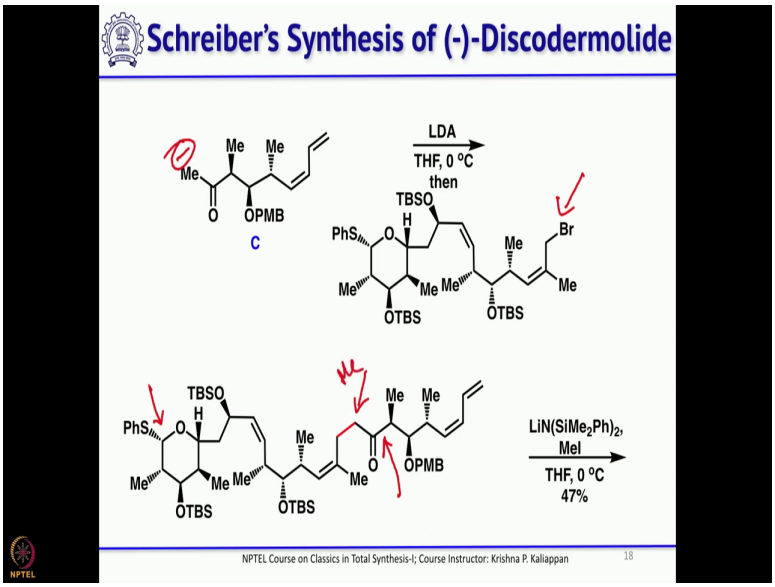

Then, you have the fragment C take the fragment C and then, treat with LDA; so, our lithium hexamethyldisilazide. So, you can generate anion selectively at this carbon, then quench with this bromide ok. It is simple alkylation, SN_2 substitution reaction. So, now, if you look at this carefully, you have the complete structure ok; you have the complete structure of discodermolide except that you need to introduce one methyl group here and you have to reduce the carbonyl group.

And of course, you have to remove the protecting groups and convert this into corresponding lactol. So, these are the steps remain to complete the total synthesis of discodermolide. So, he treated with lithium hexamethyldisilazide and quenched with methyl iodide so that he could introduce a methyl group here.

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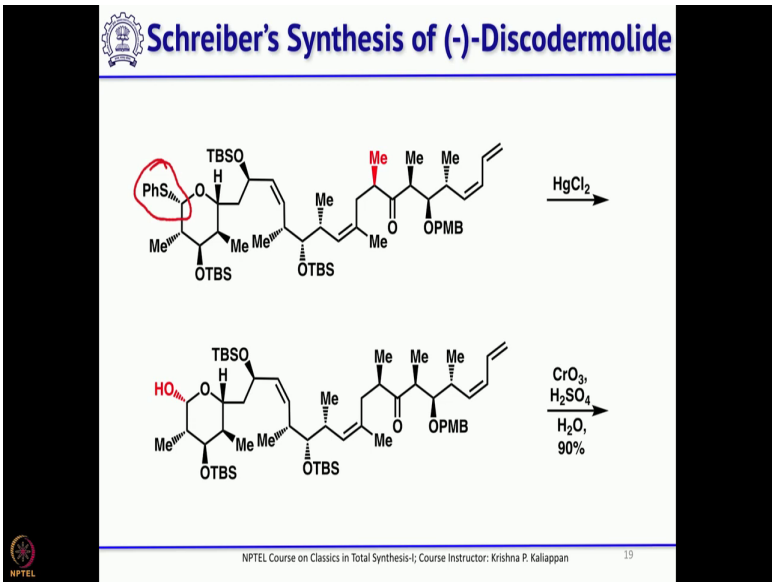

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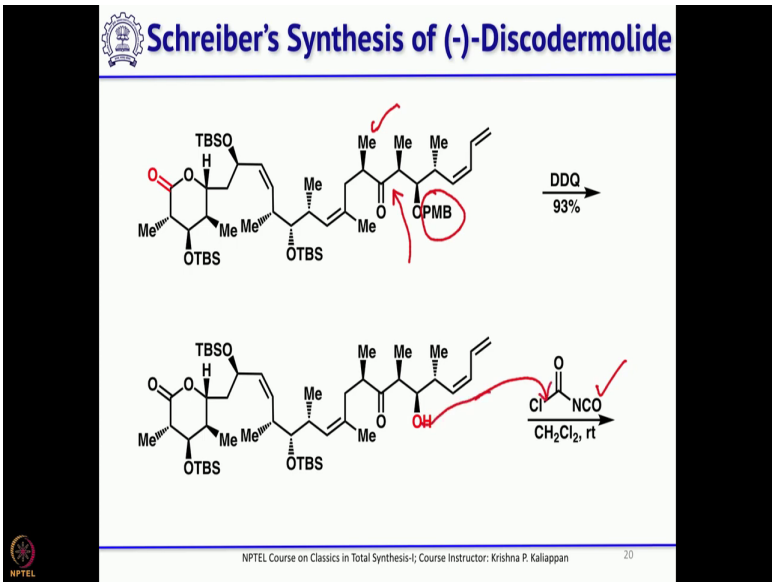

So, he could successfully introduce a methyl group, then you need a lactone here. So, the sulfur was removed with mercury chloride and oxidized with chromium trioxide to get the corresponding lactone. So, the left hand side is fine, the right hand side is fine, the methyl group also introduced. Now, only one more functional group remains to be introduced is to get the alcohol; that means, you have to reduce the ketone.

So, before reducing the ketone PMB was first removed to get the alcohol, the secondary alcohol; then, the secondary alcohol was treated with chloro isocyanate. So, here, it forms an ester ok.

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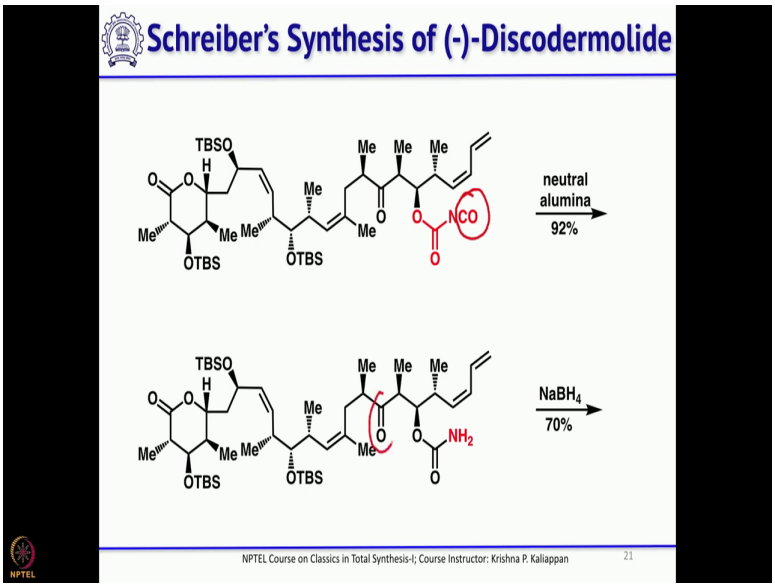

So, it forms an ester here -OC=ONCO and what you need is -OC=ONH$_2$. So, that can be easily done by simple hydrolysis. So, neutral alumina just hydrolyze the NCO$_2$ corresponding NH$_2$. Then, sodium boride reduction gave or reduce the ketone to corresponding alcohol ok.

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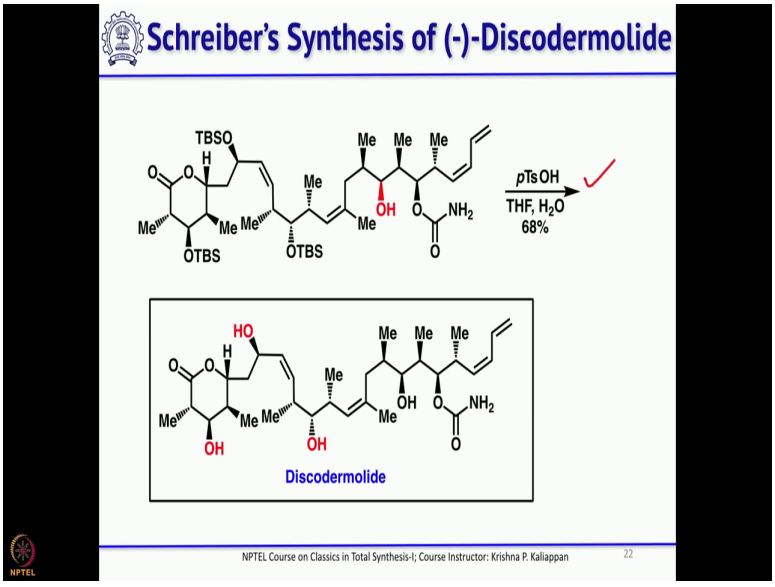

So, now only one step is remaining that is removal of all the TBS group. So, that was successfully done with *p*-toluene sulfonic acid. So, that is how he could complete the total synthesis of discodermolide and if you look at the total synthesis of discodermolide reported by Schreiber.

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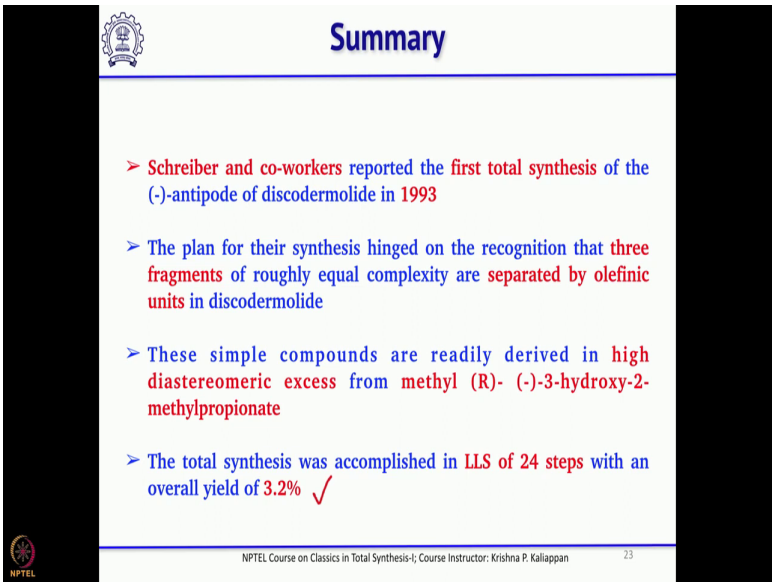

So, what are the key reactions he has done? So, first key reaction as you know is the crotyl boration; the roche crotyl boration established two new chiral centers, where it is syn-aldol or anti-aldol ok. He has established two new chiral centers using Roche crotyl boration one. Second if you look at he has used kishi coupling reaction of the iodoalkane with aldehyde to introduce one more chiral center and later the triple bond was reduced to get the corresponding cis double bond ok.

Overall, he took about 24 steps and the yield is quite impressive. So, 3.2% overall yield for such a complex natural product is really commendable ok. After this total synthesis, there are many total synthesis of discodermolide reported in literature; even no one made 60 grams of this discodermolide following different procedures reported in the literature and it is the first time such a high quantity of natural product was made in an industry following literature procedure and then, they use this for several studies biological studies ok. So, I will stop here.

Thank you.