Classics in Total Synthesis-I
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Lecture - 05
Total synthesis of FR900848

Yeah, good morning everyone. Welcome back to NPTEL lecture series on Classics in Total Synthesis - part I and we just started discussing about total synthesis of natural products having 3-membered ring. And in the last lecture we talked about total synthesis of illudin and there we talked about the utilization of carbonyl ylides in making 5-membered ring as well.

Today we will continue our discussion on the total synthesis of natural products having 3-membered rings. And in that we will talk about total synthesis of a natural product called FR-900848, this is a very interesting natural product isolated and reported in 1990 by Yoshida.

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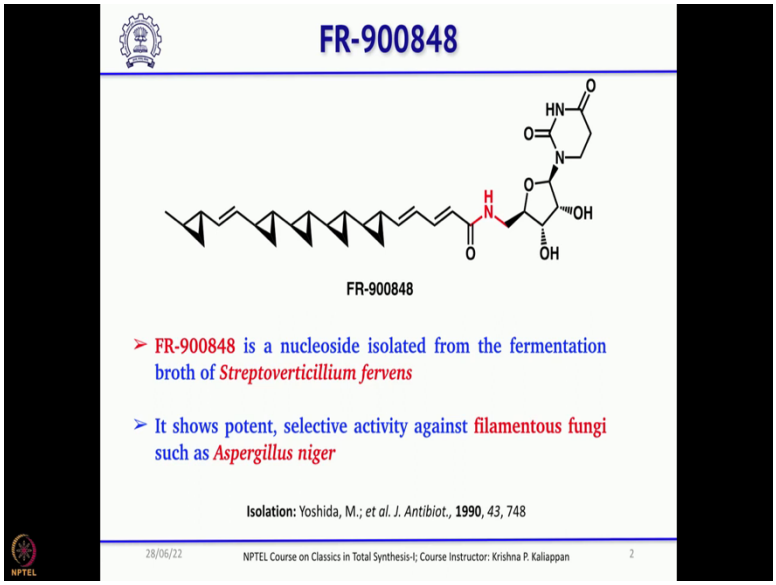

And his group and if you look at this molecule you can see there are 5 cyclopropanes. So, its indeed a complex natural product, its a nucleoside having a long chain and then the long chain has 5 cyclopropanes and 3 double bonds and this was isolated from the fermentation broth of streptoverticillium fervens. And it also showed a exceptional activity against filamentous fungi, such as aspergillus niger.

So, because of this structural complexity and also due to the biological activity a many synthetic groups were interested in the total synthesis of this natural product.

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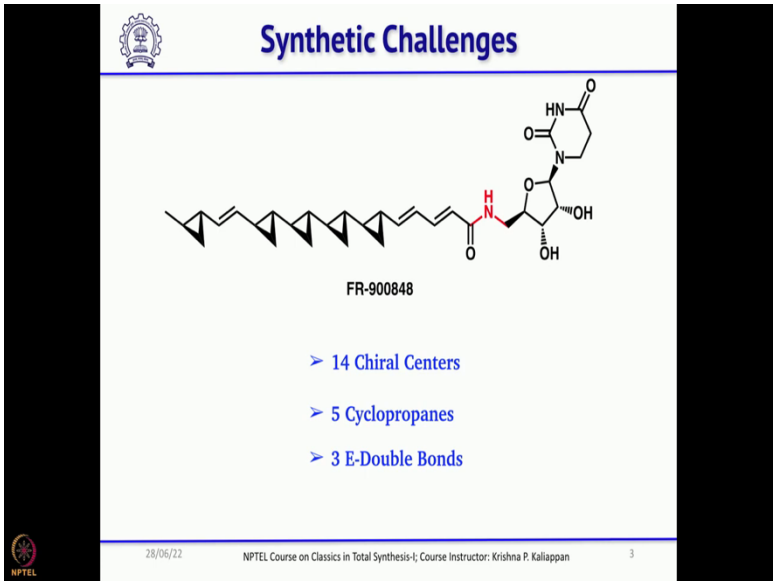

And 5 years later the first total synthesis was reported by Tony Barrett and if you look at this molecule as you can see it is indeed a complex natural product. The major challenges posed by this molecule or one there are 14 chiral centers in this molecule ok. Of course, so you can say four are from sugar unit. So, that can be easily you know obtained from commercially available starting material.

But the remaining one ok they are not easy to you know make it and there are 5 cyclopropanes which I already mentioned and there are 3 E-double bonds ok. So, these are some of the major challenges one has to think about while planning a proper retrosynthesis.

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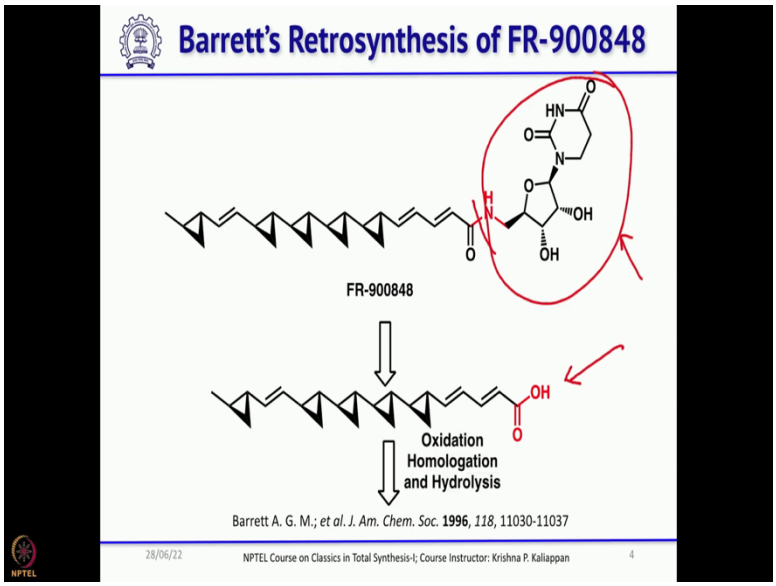

And according to Barrett, this can be first disconnection can be done by just cleaving this amide bond, say that is a obvious disconnection when you have an amide and the easiest bond to cleave is the C N bond, ok. So, that cleavage will give you the corresponding carboxylic acid and the nucleoside the whole nucleoside is the other fragment.

So, that actually simplify the retrosynthesis of FR-900848 to making only this carboxylic acid if we can develop a good method for making this carboxylic acid and this is a known compound or it can be easily made, ok. And just coupling these two should give the natural products.

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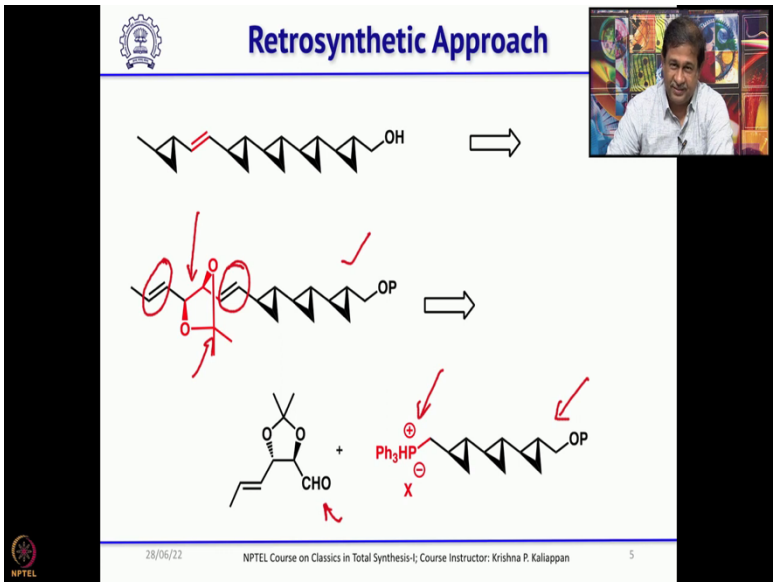

So, with that he further did retrosynthesis and this carboxylic acid can be made from this alcohol by oxidation and homologation using you know Wittig type reaction to get the corresponding dienoic acid ok. And this if you look at his original idea was, if you have this material then one can do bis-cyclopropanation here and here and followed by converting this diol into double bond, ok.

So, you have two double bonds and the two double bonds you do cyclopropanation, then the diol which you get after removing this acetonide you can convert that into a double bond. So, that was his plan and that in principle can be obtained from this aldehyde and this Wittig salt, ok. So now, you should have a proper method to make this particular fragment with 3 cyclopropanes ok. And if you look at the literature, what are the methods available for cyclopropanation ok?

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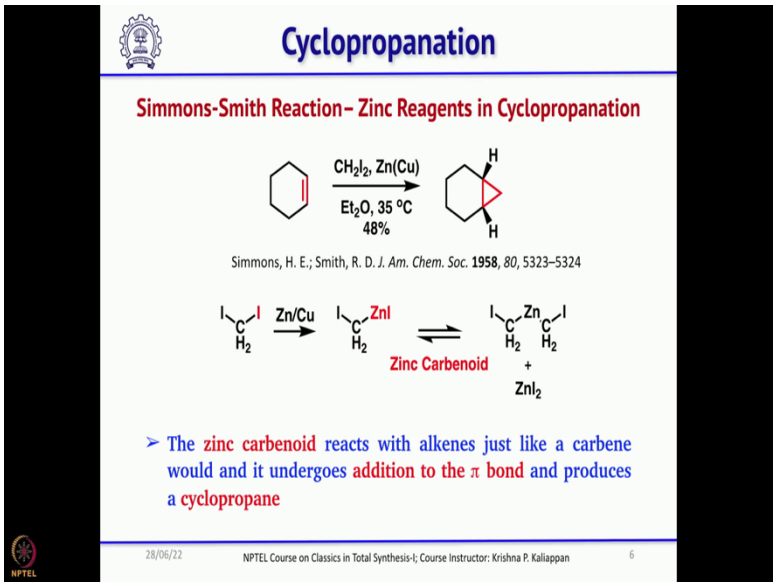

There are few methods, but one method which should come to your mind immediately is Simmons-Smith cyclopropanation. So, Simmons-Smith cyclopropanation is nothing but if you take an alkene and treat with diiodo methane in the presence of zinc copper couple, at ambient temperature you can easily cyclopropanate an alkene, ok. And this was reported way back in 1958. It is believed that it goes through a zinc carbenoid like mechanism ok.

So, like how, if we have a carbenoid how it can undergo a cyclopropanation, the same way when you have zinc as a metal. So, the zinc carbenoid you know you know undergo cyclopropanation of an normal double bond.

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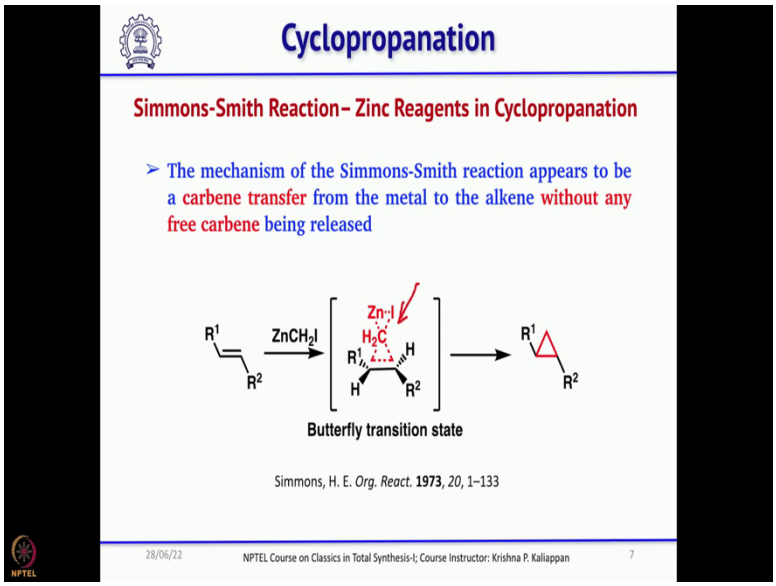

And this is the mechanism so it goes through the 3-membered transition state and followed by removal of zinc iodide. So, in the process zinc iodide comes out after delivering the CH2. And based on the evidence based on the products based on the mechanistic studies there was no free carbene involved in this reaction, always the metal was involved, the carbenoid was involved.

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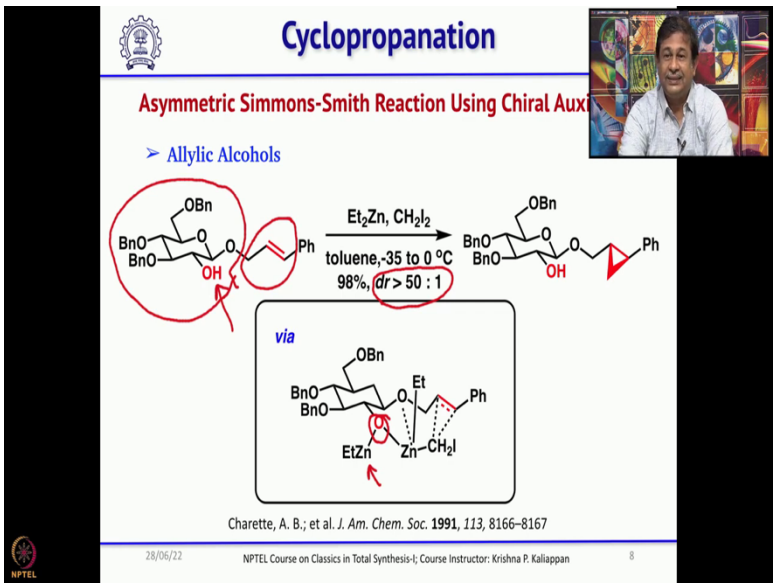

Later so once you introduce the cyclopropane ok, later many people were interested in introducing this cyclopropane asymmetrically because when you do your

cyclopropanation you introduce two chiral centers So, if an asymmetric method can be developed, then it will be very interesting so that is how many people were interested in developing asymmetric strategy for cyclopropanation.

The first method which was reported by Andre Charrette. So, what he did he used allylic alcohol and also a chiral auxiliary. So, he started with a sugar unit ok. So, you can see you have a sugar portion ok and then allyl group and this hydroxyl group actually helped in directing the cyclopropane.

So, he took this compound and then treated with the same combination, that is you know CH2I2 and diethyl zinc which in situ prepares you know CH2Zn and I I 2, ok. So, this gave about 98 percent yield with a diastereomeric excess of 50 is to 1. So, this was a very very interesting method and this is the mechanism and this is how the free hydroxyl group, ok. So, first it the it forms a bond with zinc, then it coordinates with zinc and CH 2I and then intramolecularly the CH2 is delivered to the double bond, ok.

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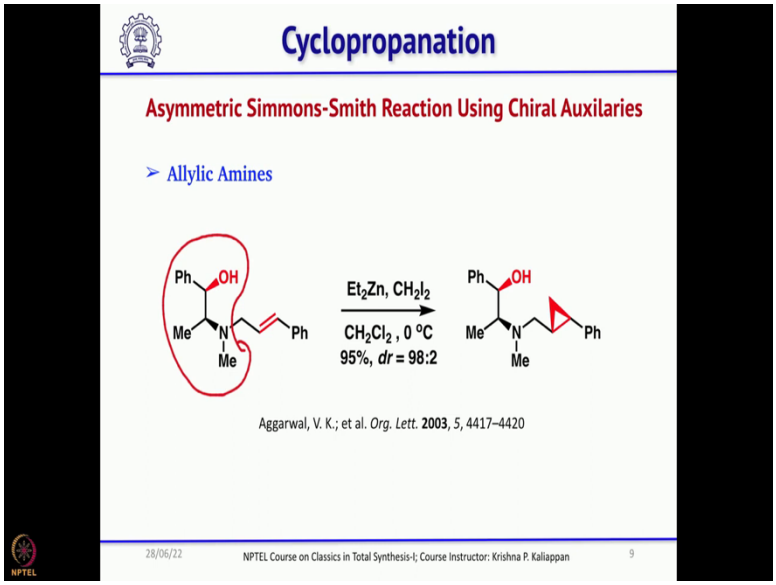

And Varinder Aggarwal in 2003, he reported another asymmetric Simmons Smith cyclopropanation using ephedrine-type amino alcohol and here also it gives a very good diastereomeric ratio, 98 is to 2 and exactly following a similar pattern. So, in these two cases what we have seen is we need a chiral auxiliary you can see that this is a; this is a chiral auxillary and you attach the allyl group then do the cyclopropanation.

So, it will be nice if you do not have to use chiral auxiliary and if you have to use a chiral promoter or chiral controller or chiral catalyst, then this reaction will be much better.

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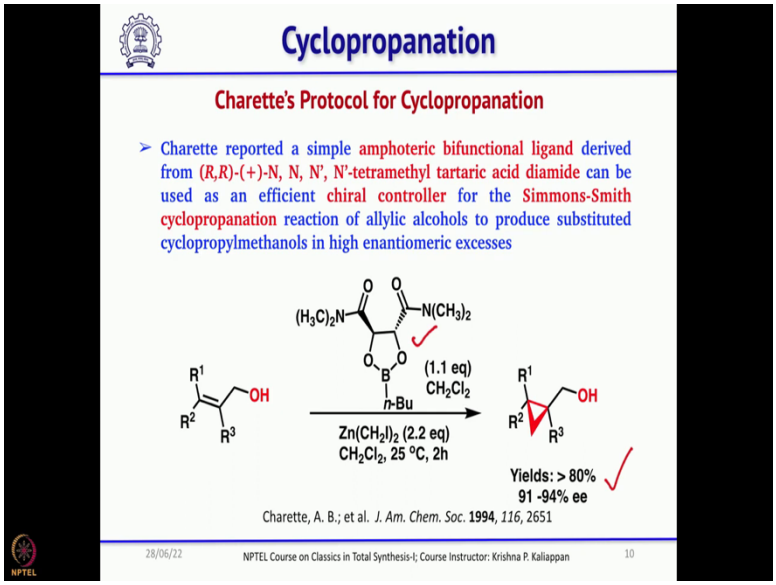

So, with that charrette prepared a very interesting you know you can call it as chiral controller, dimethyl tartaric acid ester was used and he prepared this boron boronate ligand ok. So, this was used almost you know a stoichiometric amount, nevertheless what you can see is the main difference is, this is not attached to your allylic alcohol, this is not attached to your double bond, ok.

So, you can add separately and then recover it if you want ok. So, that way this reaction also gave very good ee, 90 to 94 percent ee. So, this reaction has been successfully used in many such cyclopropanation reaction where you take simple allylic alcohol and as usual zinc iodide and then diiodo methane and add this ligand that gives very high ee of this cyclopropane methanol ok.

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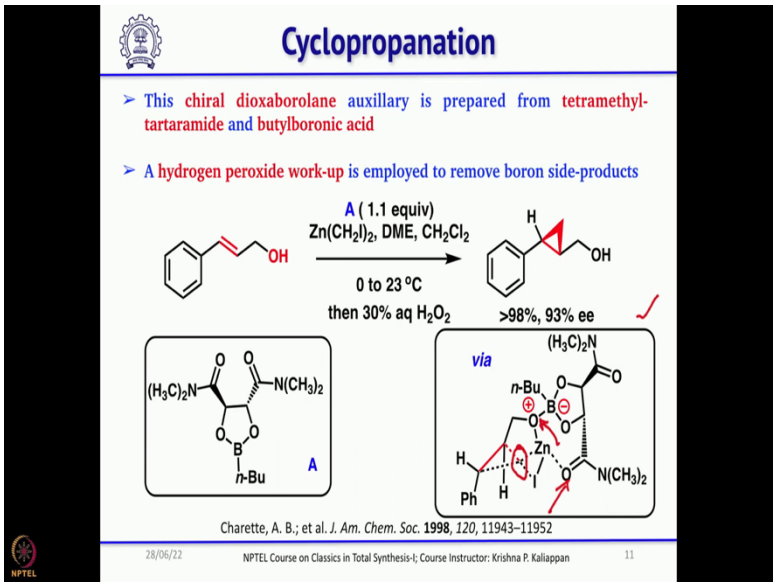

And when you do this reaction, you can also use hydrogen peroxide because why you have to use hydrogen peroxide is as you know you use boronate ester. So, to remove the side, you know side products from boron you will always use hydrogen peroxide workup to get the corresponding cyclopropanated methanol in good yield as well as in good ee. So, this is the mechanism.

So, I will not go into the details, as you can see here the boron coordinates with oxygen and it later it forms the covalent bond with zinc and zinc also forms coordinate bond with oxygen of the amide. Then it transfers the CH2, transfers the CH2 from the same side. So, that you get higher selectivity ok.

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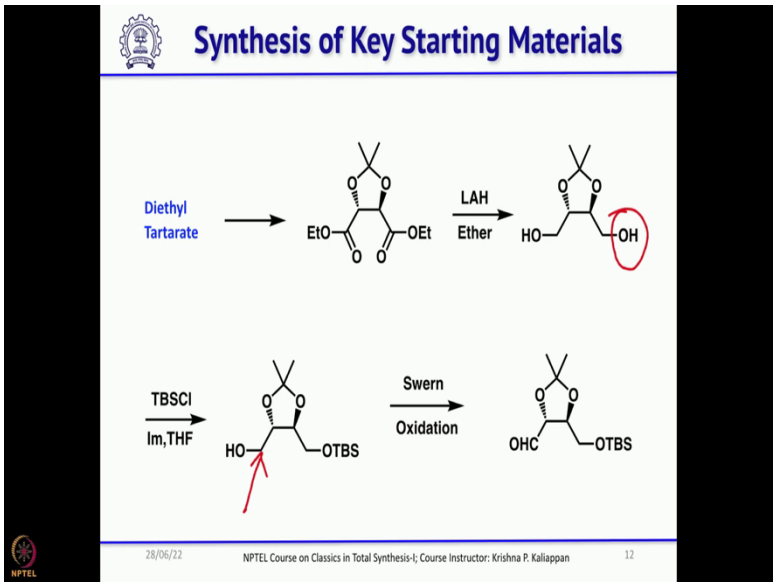

And then since it is a chiral controller or chiral promoter you can reuse this. Now, coming back to the total synthesis of FR-90048. So, ee also started with diethyl tartarate, the starting material for one of the fragments is diethyl tartarate and protect the hydroxyl groups to hydroxyl groups as acetonide. Then reduce the ester esters as a diol and protect one of them as it is symmetrical, one of them can be easily protected as TBS ether.

Then oxidize the other alcohol, other primary alcohol under one condition to get the aldehyde.

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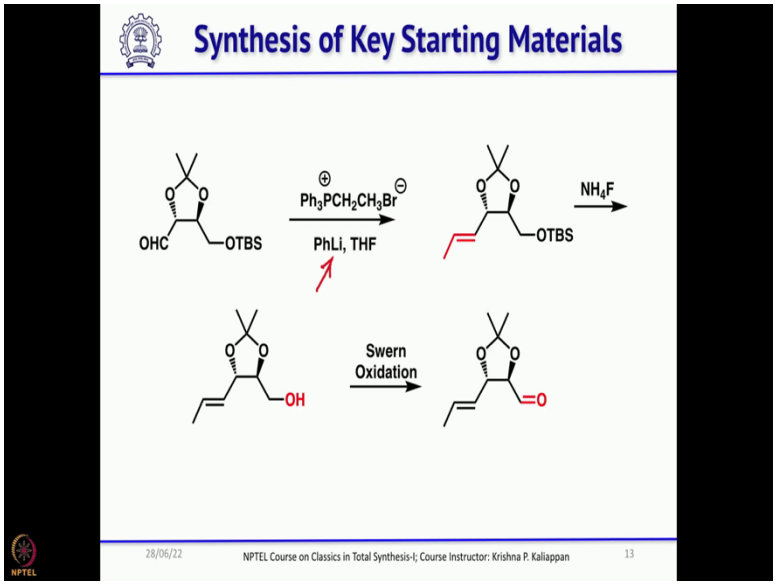

Once you have this aldehyde, then you can do a Wittig reaction with ethyl bromide derived Wittig reagent and then use Manfred Schlosser's condition that is you have to use excess phenyl lithium. So, that gives a trans double bond E-double bond, then remove the TBS group and oxidize. So, you get one fragment which is required for the total synthesis of FR-900848.

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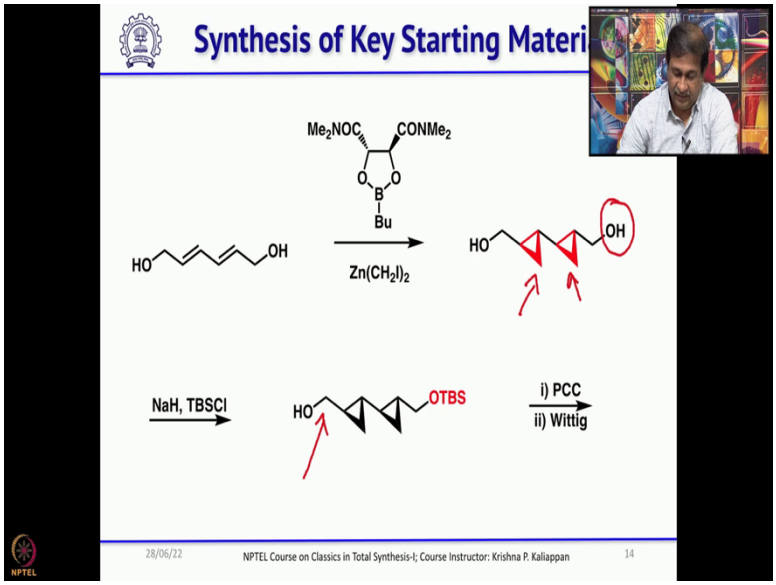

Then the other fragment is started with this dienediol and used Andre Charrette's cyclopropanation and you could introduce these two cyclopropanes in one step ok, it is a symmetrical compound. So, then protected one of the hydroxyl group. So, it is since it is symmetrical one can easily protect one of them as TBS ether. So, you could protect successfully one of them as TBS ether, then the other alcohol was oxidized to aldehyde with PCC, then a stabilized Wittig on that aldehyde give the corresponding alpha, beta unsaturated ester.

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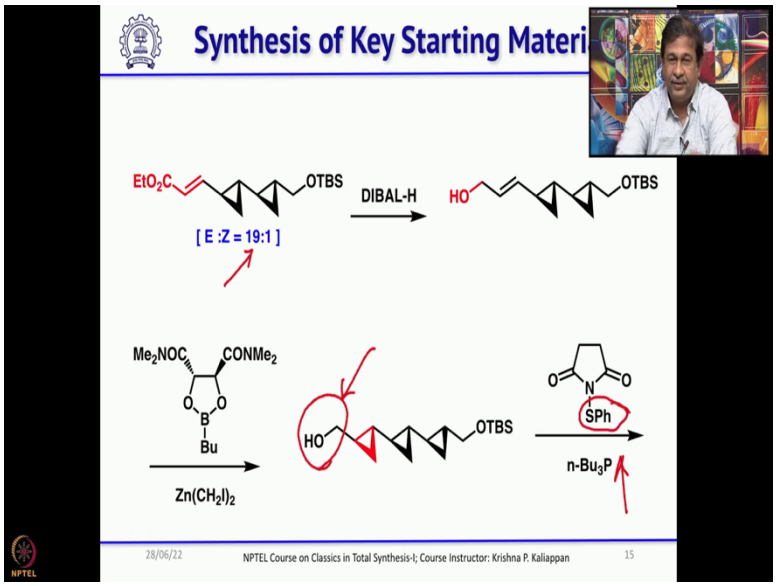

Here the E-Z ratio is 19 is to 1 which are separable then you reduce the ester to alcohol. Normally, one can use LAH rarely use DIBAL and do another cyclopropanation using same Charrette's protocol ok. So, now, the next step is to convert the CH2OH into CH3. So, first he wanted to convert this CH2OH, into corresponding sulfone and then do reductive removal, removal of the SO2Ph.

So, first the alcohol was converted into SPh using a Mitsunobu type reaction by treating with tributyl phosphine and N-phenyl sulfide ok.

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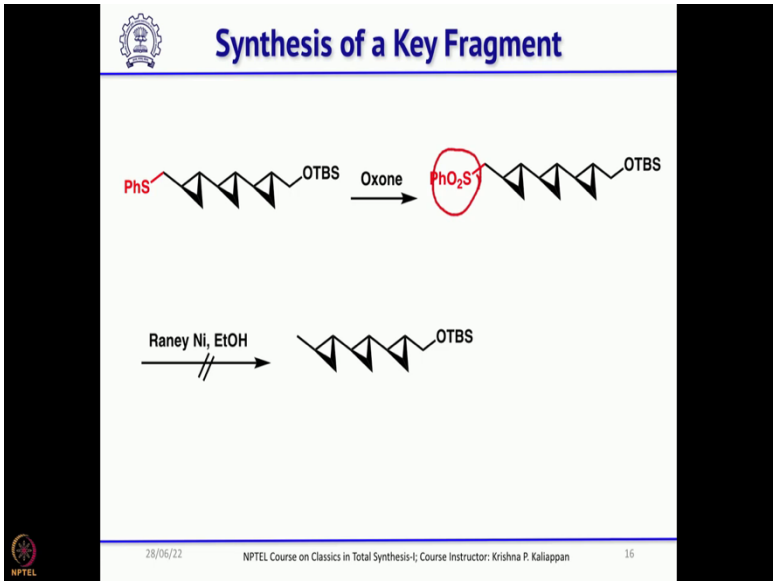

So, you could convert that OH into corresponding SPh, this was oxidized with oxone to get the corresponding sulfone, but what you could not achieve was the removal of this sulfone to get the methyl. So, you tried several conditions one of them is Raney nickel and ethanol and you could not get the corresponding methyl group.

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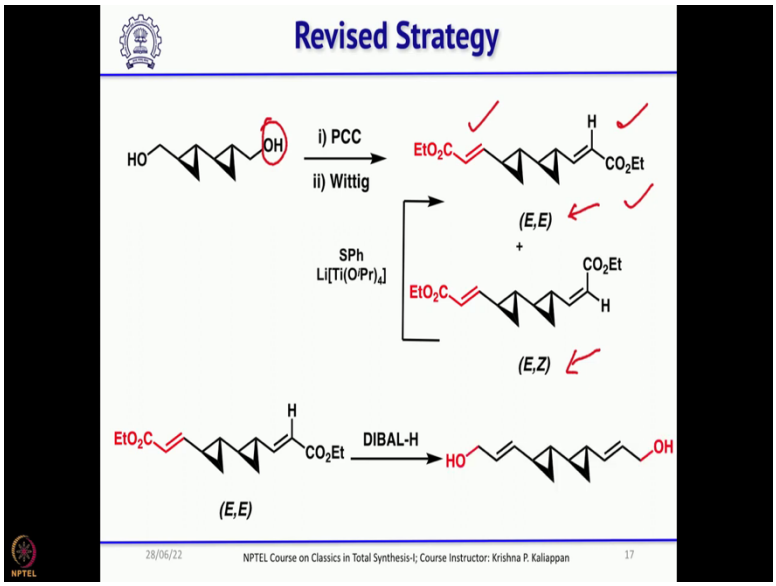

So, then he thought this may not be the right strategy so he revised the strategy and for that he started with this diol which he already prepared ok. So, he took the diol, then he did the Wittig reaction oxidation with PCC then did the Wittig reaction that is the stabilized Wittig. Only difference is in the earlier, earlier case he protected one of the alcohol as TBS ether then oxidize the other alcohol to aldehyde.

Here he oxidized both the alcohols with PCC to get the dialdehyde and the dialdehyde he treated with the stabilized Wittig reagent to get bis ester, bis alpha, beta unsaturated ester. So, here he got a mixture of both required E, E and E, Z of course, this is a major isomer, but this minor isomer also he could convert into the major isomer by treating with phenyl thiol or benzene thiol and titanium tetra isopropoxide and butyl lithium, ok.

So, this is a nice reagent combination which isomerises the cis or Z isomer to E isomer ok. So, since he needs only the E isomer. So, the E isomer was taken and he has taken it forward reduction with the DIBAL, with excess DIBAL gave the diol.

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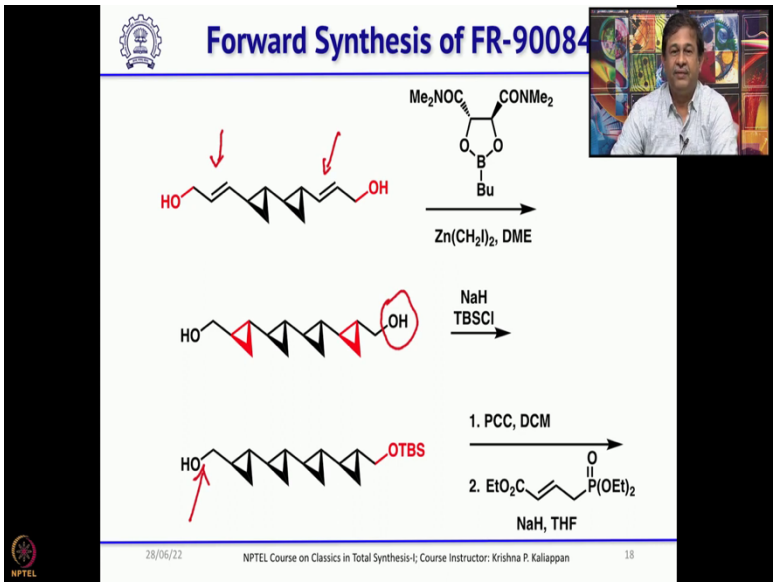

Once you have the diol, here you can do 2 cyclopropanation, here and here. So, now, you can see he has introduced 4 cyclopropanes. Overall, how many cyclopropanes he has to introduce? 5. But these four are contiguous, then you have a double bond in between followed by another cyclopropane and methyl group. So, this diol then he selectively protected one of them as TBS, ok.

So, since this is symmetrical you take this alcohol and protect it, as TBS ether then oxidize the other primary alcohol then do the Wadsworth Emmons Wittig reaction to get the corresponding diene ester.

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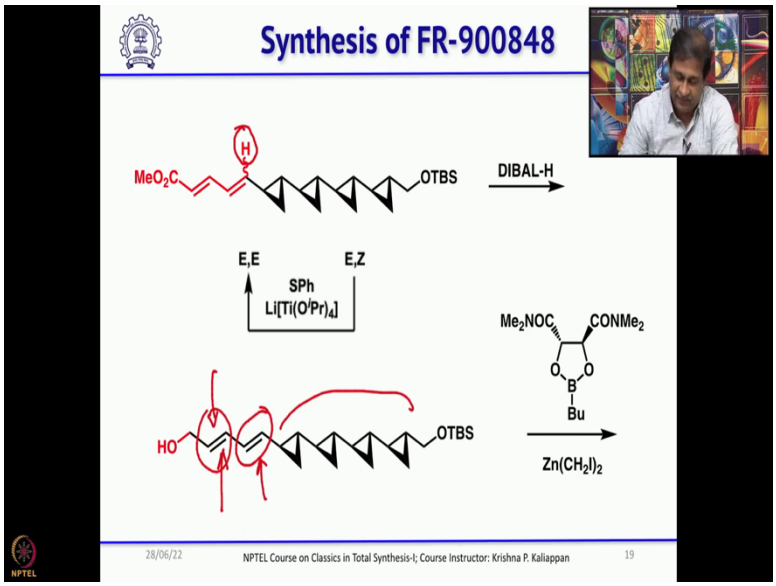

Again, he got a mixture of E, E and of course, E, E and E Z, that E Z can be converted into E, E by following the same process which I had already discussed. And this upon further reduction with DIBAL-H, he got the diene alcohol ok. So, this is again now it is full E, E ok. Then this allylic alcohol you could successfully selectively do the cyclopropanation.

As I said what you need is another cyclopropane, another cyclopropane and these four cyclopropanes and this cyclopropane should be linked through a double bond, ok. So, you could selectively do the cyclopropanation on the terminal double bond which is now allylic alcohol.

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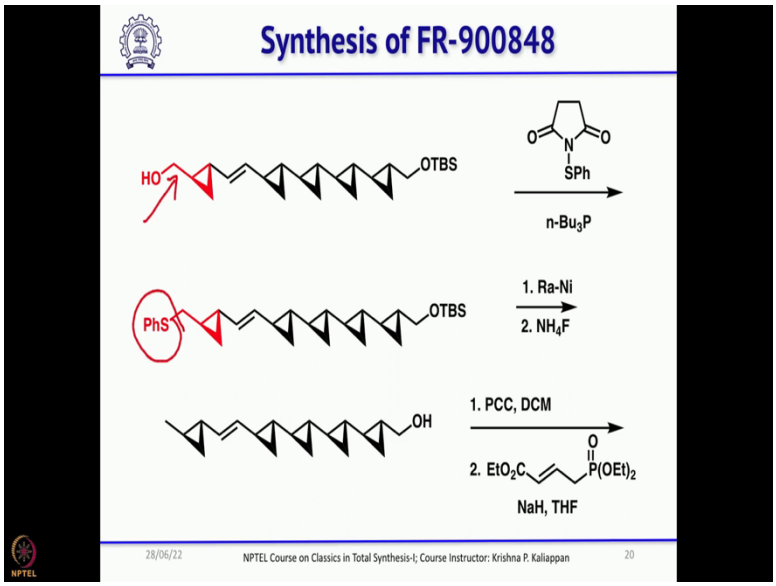

So, you could successfully do. So, you can see all the 5 cyclopropanes required for the synthesis of FR-900848 or that. Then, now he tried this conversion of CH2OH to corresponding SPh. So, this reaction worked and at this stage he removed using Raney nickel ok. Then that SPh was removed and then we got the methyl group, then ammonium fluoride removed the TBS, he got the alcohol and oxidation of this primary alcohol with PCC, he got the aldehyde and again a Wadsworth Emmons modification of this Wittig reaction.

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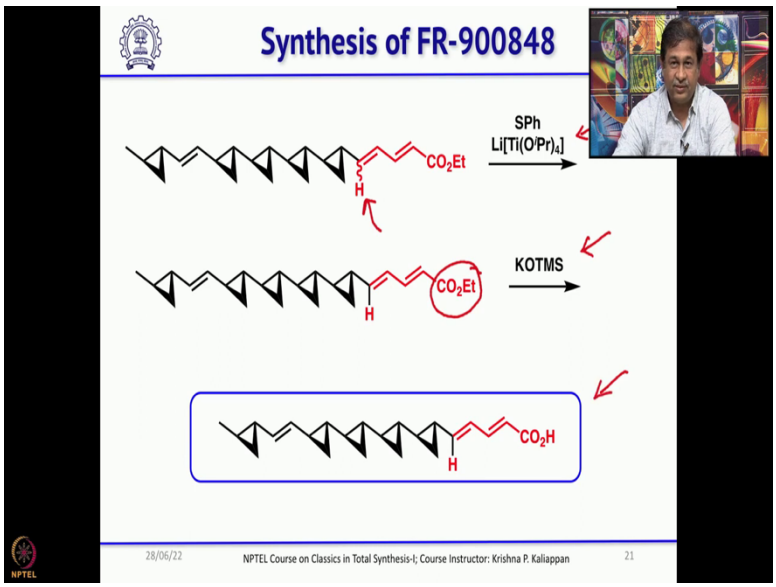

And gave the diene ester ok and again you got a mixture of E and Z, that was converted into E, E using the conditions which he already used twice, then he tried to saponify this ester to carboxylic acid. So, all the conditions gave decomposed product. So, finally, used a simple KOTMS hydrolyse the ethyl ester to carboxylic acid. So, now, if you look at the structure of FR-900848. So, this is the side chain which should be attached to the nucleoside, the side chain is prepared.

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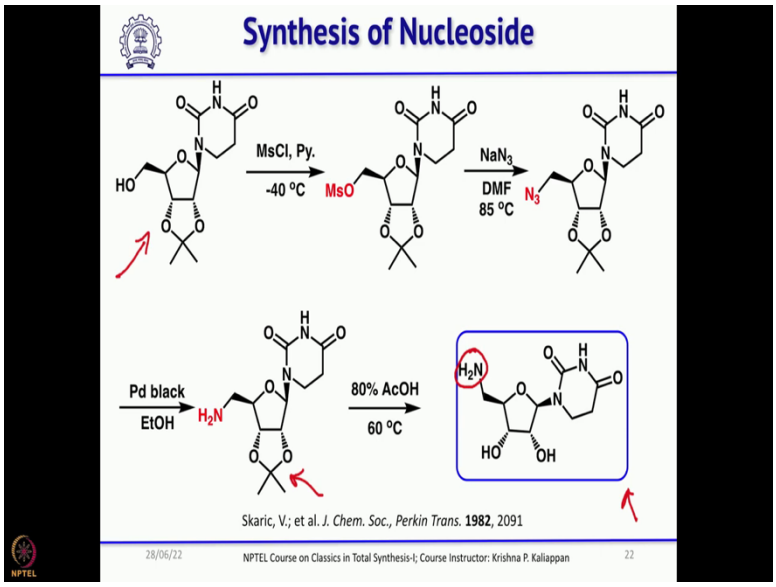

Now, let us see how the nucleoside is prepared. So, the nucleoside is here then what he has to do he has to combine this amine with the carboxylic acid to make the natural product. So, he took this commercially available alcohol ok, this is made in three steps from D-ribose in you know in kilogram scale, this primary alcohol was converted into mesylate and then mesylate underwent an SN2 reaction with sodium azide to get the corresponding N3.

Then N3 is reduced to get the corresponding NH2 and the acetonide ok, the protected acetonide was cleaved with 80 percent acetic acid to get the nucleoside which is required for the DCC coupling with the carboxylic acid.

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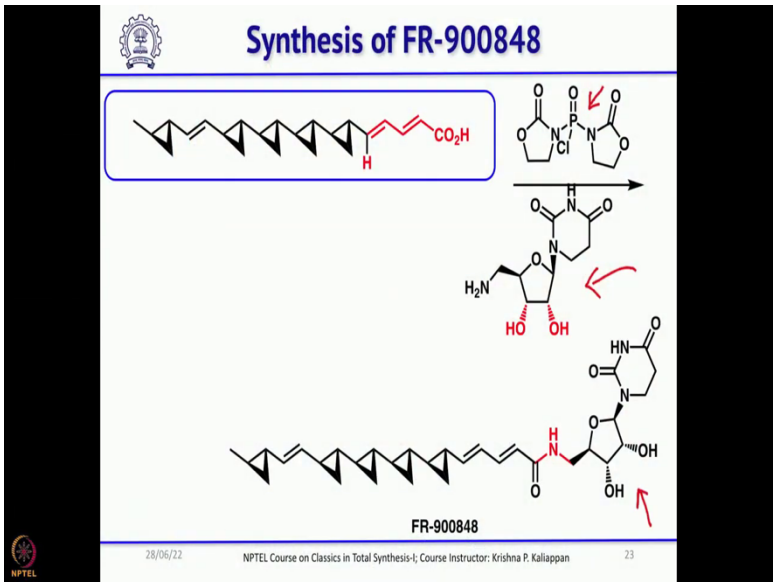

So, what he did? He did not do the DCC coupling, he took the carboxylic acid and then treated with this phosphoryl chloride. So, this is called BOPCl ok, then added this amine ok. So, that gave directly this FR-900848. So, if you look at this whole synthesis, the key reaction is nothing but introduction of cyclopropanes. There are 5 cyclopropanes, he could successfully introduce and also, he established three E E-double bonds. And of course, he did not face much problem in making this nucleoside.

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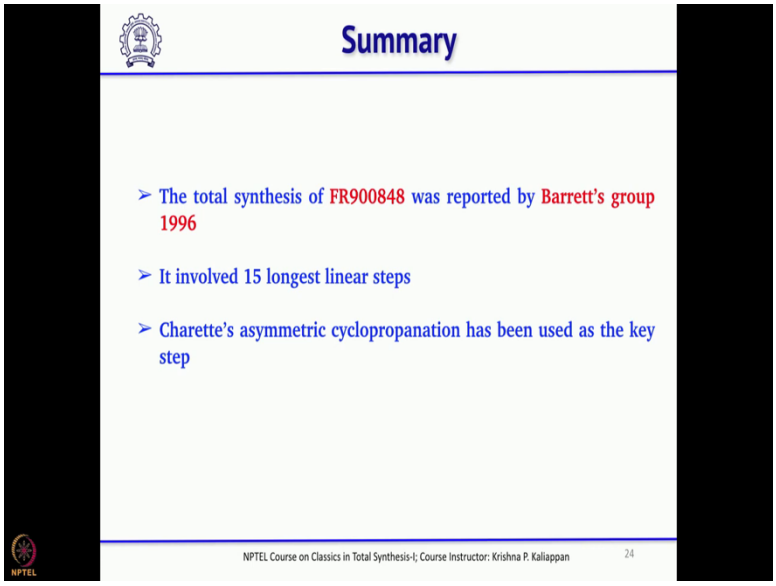

So, overall are the total synthesis of a FR-900848 was accomplished in 15 longest linear steps by Barrett's group. And Andre Charrette's asymmetric cyclopropanation was used as the key step in introducing all the 5 cyclopropanes, ok. So, with this now we have discussed total synthesis of two natural products having cyclopropane. Now, we will move to a natural products and non-natural products having 4-membered ring as the key substructure ok.

Thank you.