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

Lecture - 50
Eleutherobin (Nicolaou)

So, good morning and welcome back to the NPTEL lecture series on Classics in Total Synthesis Part 1 and we have been discussing total synthesis of complex natural products and in the last lecture we talked about the total synthesis of an anti cancer agent called Taxol and we will continue to discuss about more complex natural products and particularly anti cancer agents.

In 90's when we talked about Taxol I also mentioned there were other complex natural products which were used as anti cancer agents, there were at least five naturally occurring compounds which were supposed to be you know very potent against various cancers the one which we already discussed was Taxol which is quite complex.

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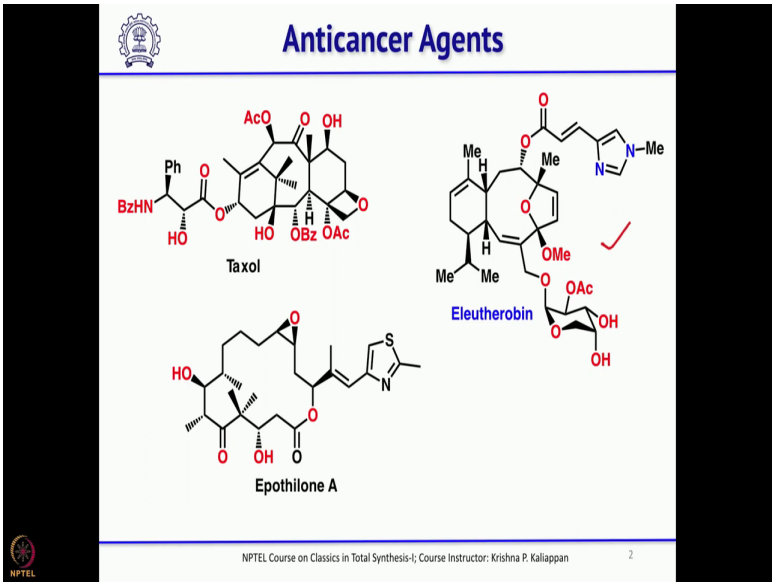

And the second one was eleutherobin which you can see that it is quite complex in structure almost similar to Taxol and the third one was epothilones here I am showing the structure of epothilones A and there are other epothilones as well. So, this is a macrolide.

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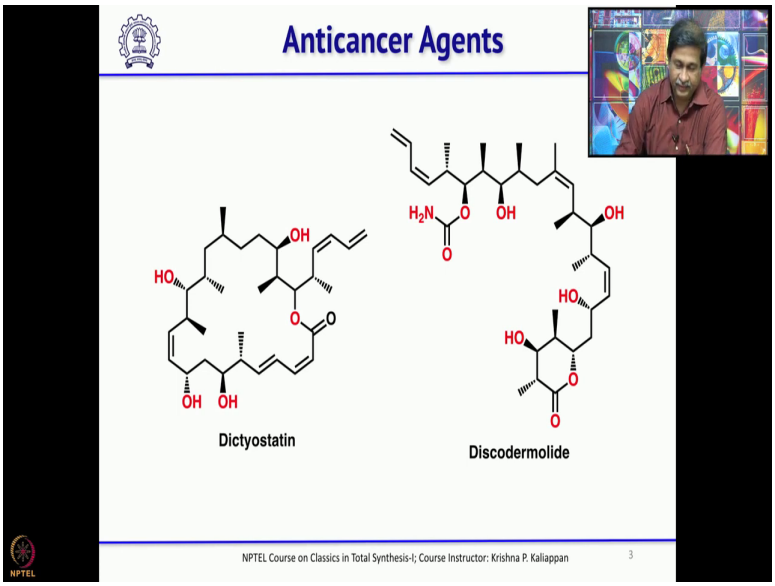

And two more natural products which were also considered to be you know very good anti cancer agents in 90's were dictyostatin and discodermolide. So, these are the 5 natural products where many synthetic groups were focusing on developing new methods, new strategies for their total synthesis ok. Today, what we will do we will focus on one of them that is eleutherobin.

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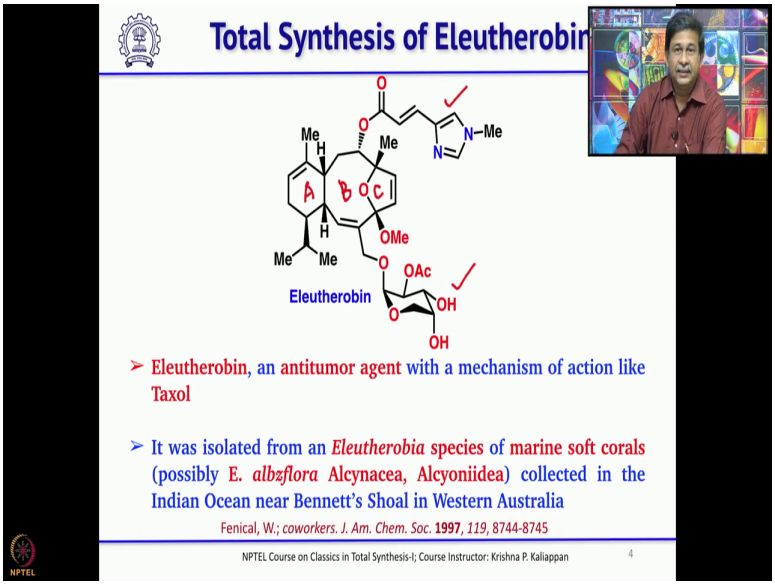

See this structure of eleutherobin if you look at it has three rings you can call it as A B C ring. And you have two side chains, one here and here ok; this was isolated in 90's from

eleutherobia species of marine soft corals found in Indian ocean ok. And it was isolated few milligram and pedicles group which isolated this compound proposed this structure ok. Of course, as you know it was through various high field NMR studies they could propose the correct structure of eleutherobin.

Nevertheless it is important from synthetic point of view to synthesize this compound and to prove the absolute configuration. Because absolute configuration was not known that time. Then the second most important thing about this particular molecule is since this was isolated from marine soft corals as you know marine soft corals particularly if it is in very sensitive region then you cannot go back and then isolate more of them.

So, from that angle also if this molecule has to be made or to be made available for further medicinal and biological studies and this could be done only through synthesis. So, from these two angles it was very important to develop a good strategy and using this strategy one should be able to make not only eleutherobin, but also several analogues.

So, as I said many groups were involved in the total synthesis of eleutherobin, but I will talk about two total synthesis today, I will talk about one total synthesis reported by K C Nicolaou.

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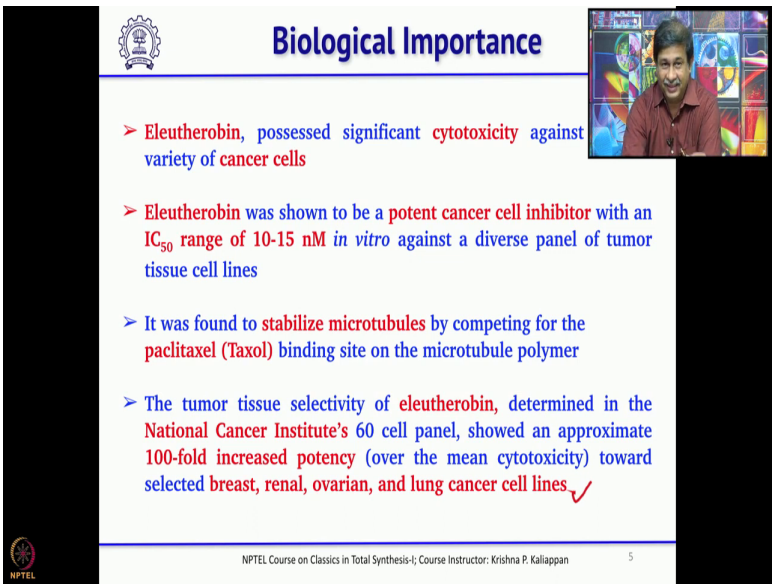

And as I said, this was as active as taxol ok and it showed a high activity against various cancer cells and it worked with the IC 50 range of 10 to 15 nM ok that is quite

significant.And the mechanism of action of eleutherobin was almost like paclitaxel ok. So, this is another reason why many groups were interested in making this molecule ok. And also it worked against various types of cancer like breast renal ovarian and lung cancer.

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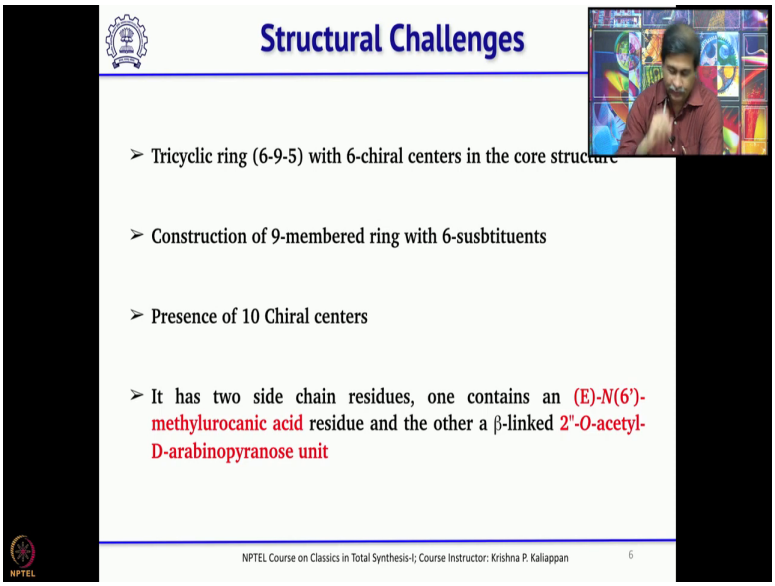

From the structural point of view when a synthetic chemist wants to synthesize, it has three rings tricyclic core structure having a six membered ring and the middle ring is nine membered and the right hand side ring is five membered. So, all these three rings have six chiral centers and the middle ring nine membered ring that is a medium size ring has six substituents. So, construction of six membered rings with six substituents is quite challenging. And overall in this molecule there were ten chiral centers and out of that four are coming from the sugar unit.

And in addition to the core structure that is the tricyclic ring six membered, nine membered and five membered ring, it also has two side chains one at the northern hemisphere. So, that is an α- β unsaturated system and down it has a arabinose system ok. These are the two side chains.

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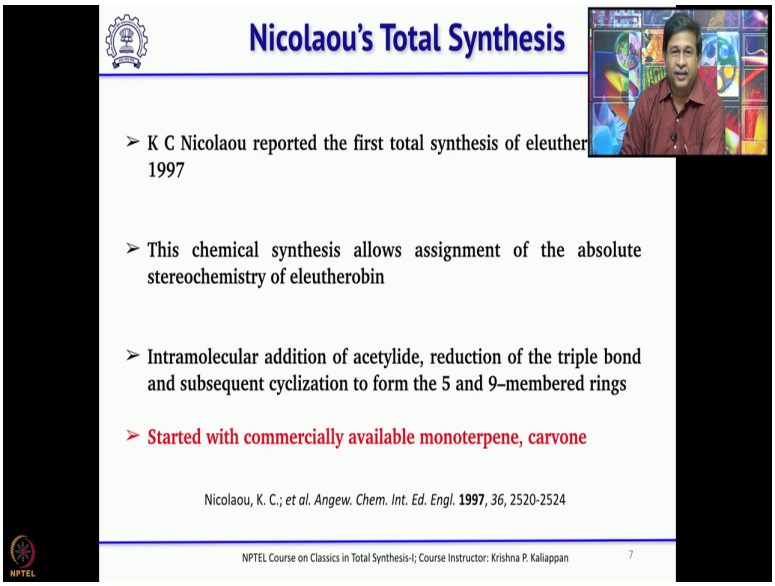

So, a successful synthesis of eleutherobin not only should address the synthesis of core structure, but also an efficient synthetic route to the two side chains. And Nicolaou he was the first one to report the total synthesis in 1997 and of course, as I mentioned one of the major issue was to assign the absolute configuration of eleutherobin.

So, he could successfully assign the absolute configuration based on the starting material which he used and then further stereochemical elaboration. And the key reaction in the synthesis of epothilone was an intramolecular addition of lithium acetylide; intramolecular addition of lithium acetylide to an α- β unsaturated aldehyde ok. That was the key reaction to make the 10 membered and afterwards the 10 membered ring was converted into 9-5 bridged system ok.

And of course, it was made easy since he started with a commercially available monoterpene called a carvone.

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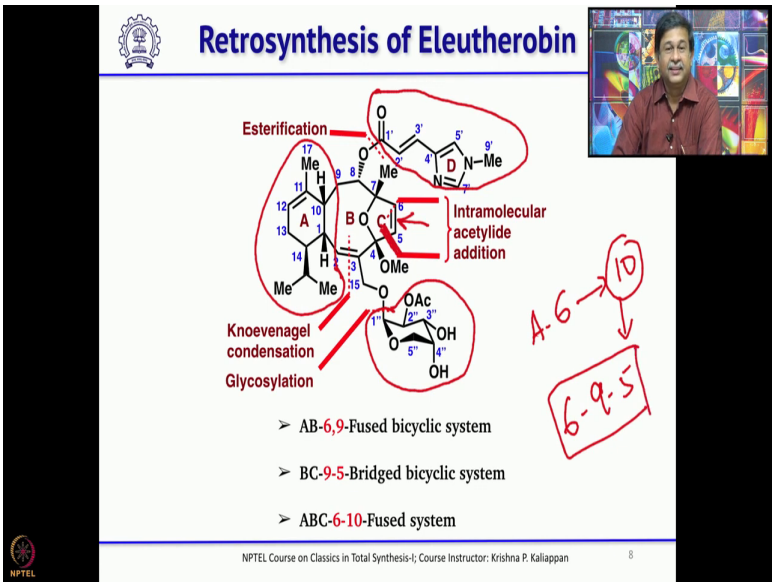

And look at this structure. So, it is quite complex and is retrosynthesis started with you know removal of this side chain first that can be attached by simple esterification, likewise the other side chain this arabinopyranose can also be easily attached. So, the first disconnection of eleutherobin was removal of these two side chains. Removal of these two side chains. And the third important connection as I said first, the starting material is from carbon which has the same six membered ring with double bond methyl group and an isopropyl group.

So, it was very easy to identify the starting material and construction of B, C ring is quite challenging. Because A ring is commercially available you have to attach the B and C ring. So, he used two three key reactions, one as I said the intramolecular addition intramolecular addition of the triple bond. The triple bond later became double bond here. Overall, how he planned was he first may started with A ring that is A ring at six membered ring then he attached a 10 membered ring ok.

So, the 10 membered ring is the combination of B and C ring. Then the 10 membered ring he converted into 9 and 5 B and C ring he formed from the 10 membered ring that is how he made essentially 6- 9-5 tricyclic ring ok.

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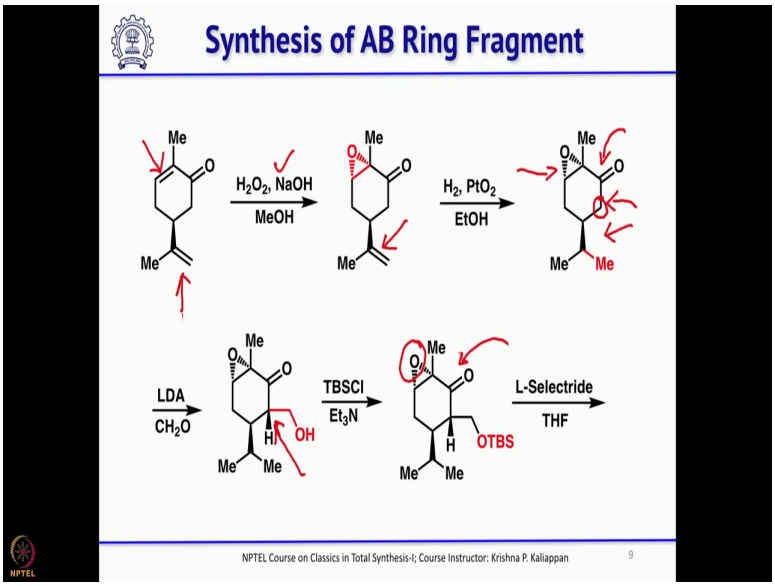

Let us see how he did this. First he started with carvone and as you know the carvone has two double bonds, one is electron rich the other one is electron deficient. So, what can selectively epoxidize the electron deficient double bond in the presence of electron rich double bond by alkaline hydrogen peroxide. So, alkaline hydrogen peroxide epoxidize the electron deficient double bond. So, now, what one has to do is to reduce the electron rich double bond.

So, that was easily done under standard hydrogenation condition. So, now, you have introduced the isopropyl group which is required for eleutherobin A ring ok. What is required now? Now, you need to attach two substituents at these two carbons ok; two substituents at these two carbons. At the same time, you do not want this epoxy what you want is a double bond is not it.

Now, we have basically we have to we have protected the double bond as epoxide, but in the long run before we go for total synthesis you need that as a double bond. So, what you can do one can think about a *trans* position ok. So, what he did before that you need to introduce a functional group here ok.

So, if you treat with LDA, one can generate enolate and followed by quenching with formaldehyde now you could introduce a functional group at this carbon ok. So, that is done. Now, you have to protect the primary hydroxyl group that can be easily done; since it is primary hydroxyl group protection was done with TBS chloride.

And after protection, now the next job is to as I said you have to introduce a functional group here and you have to remove the epoxide ok. So, what he did? He reduced the ketone he reduced the ketone with L-Selectride stereo selectively to get α alcohol ok then this α alcohol was converted into a mesylate ok.

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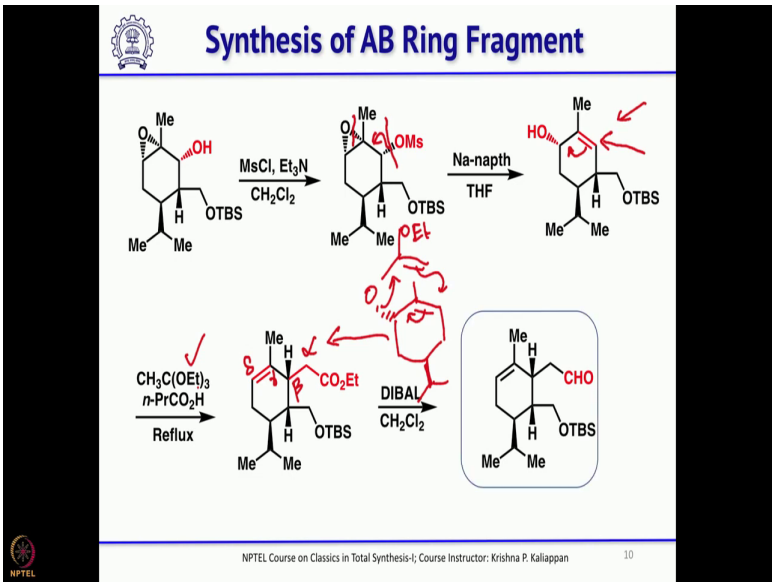

So, you got the mesylate. His idea was to cleave the epoxide ok to cleave the epoxide and bring this as an allylic alcohol ok that can be done with sodium naphthalene and sodium naphthalene will cleave this C-OMs bond then it will open up the epoxide to get allylic alcohol ok. So, now, if you look at this structure, if you look at this structure what one needs is you need a functional group here and the double bond should shift here.

And what you have is an allylic alcohol ok. This allylic alcohol if you recall, some of the rearrangements you have studied allylic alcohols if you attach appropriate substituents on the alcohol, then it can undergo a [3,3] sigmatropic rearrangement that is Claisen rearrangement it can undergo that way the double bond will migrate and in the process you can also introduce a functional group ok.

So, with that idea the Claisen rearrangement was done. The Claisen rearrangement you treat with triethyl ortho acetate ok. Triethyl ortho acetate in the presence of propionic acid catalytic propionic catalytic amount of propionic acid followed by heating ok. So, that will give you this intermediate.

And this goes through this intermediate on treatment with triethyl ortho acetate it undergoes intramolecular Claisen rearrangement and that will give you this γ, δ unsaturated ester α, β, γ, δ unsaturated ester. Whenever you see a gamma delta unsaturated ester the reaction which should come to your mind is Claisen rearrangement.

So, now you have an ester and what you need is an aldehyde. So, that can be easily done by reducing with DIBAL-H ok DIBAL will reduce the ester to get the aldehyde ok. So, that is A B ring fragment ok. A B ring fragment that means, so now, you have to attach the C ring and then make the B C ring. So, this fragment is made now. So, what is required now? You have to make the two side chains.

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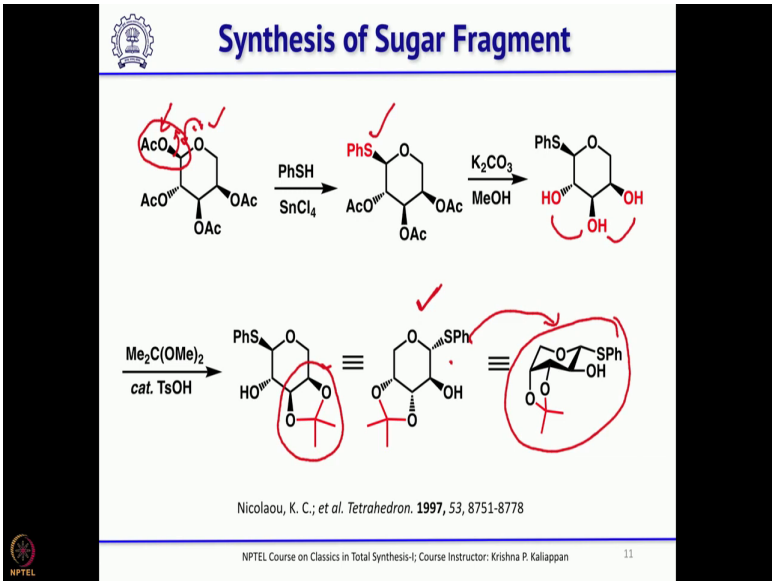

First you have to make the sugar fragment. So, for that you start with arabinose. So, arabinose when you convert that into acetate that per acetylation will give you this tetraacetate ok. Now, if you treat with phenyl thiol in the presence of lewis acid this anomeric acetate, anomeric acetate can be easily replaced by SPh right, it is a standard reaction.

So, lewis acid will coordinate here and then this will expel the -OAc. So, you will get an oxonium ion then phenyl thiol will attack and you will get the SPh replacing the -OAc ok. Then you can remove all the acetate in one part by treating with potassium carbonate methanol. So, you get the corresponding triol. If you look at this triol these two diols are *cis* whereas, these two are *trans*.

So, *cis* 1, 2 diol can be easily protected as acetonoid. So, that is what is being done. So, you protect the cis 1, 2 diol here and this can be written like this you know it is just 180° just rotate if you rotate and this is what you get why I have drawn this way was this will be useful while you convert this into chair like transition state chair like product ok.

The chair conformation when you want to convert this into chair conformation then this will be more useful than this. So, that is why I ask you to rotate it by 180° ok. Now, you see this is a chair conformation and the diol is protected cis diol is protected and the equatorial alcohol, now you can protect it as PMB ether ok sodium hydride PMB chloride will give you the protected PMB ether.

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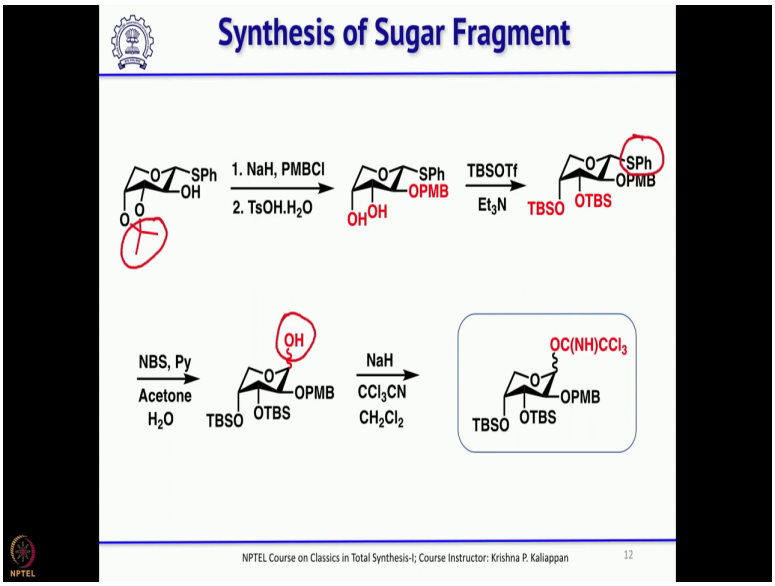

Then you can also remove the acetonoid. You can remove the acetonoid by treating with *p*-toluene sulfonic acid and water ok. Now, both hydroxyl groups are protected as TBS ether and this -SPh, -SPh can be removed by treating with NBS acetone and water ok. So, this should be converted into a good leaving group now. This should be converted into a good leaving group.

So, that when you make the core structure when you make the core structure of eleutherobin then you should be able to couple ok. So, for that you treat with tricholoroacetonitrile ok sodium hydride and tricholoroacetonitrile and this OH becomes OC-NH-CCl_3 that is trichloroacetimidate ok. So, this is the sugar fragment which we need to couple with their allylic alcohol. In the B ring you will have an allylic alcohol

that allylic alcohol you have to couple ok. So, we have made now the sugar fragment and then A, B ring fragment.

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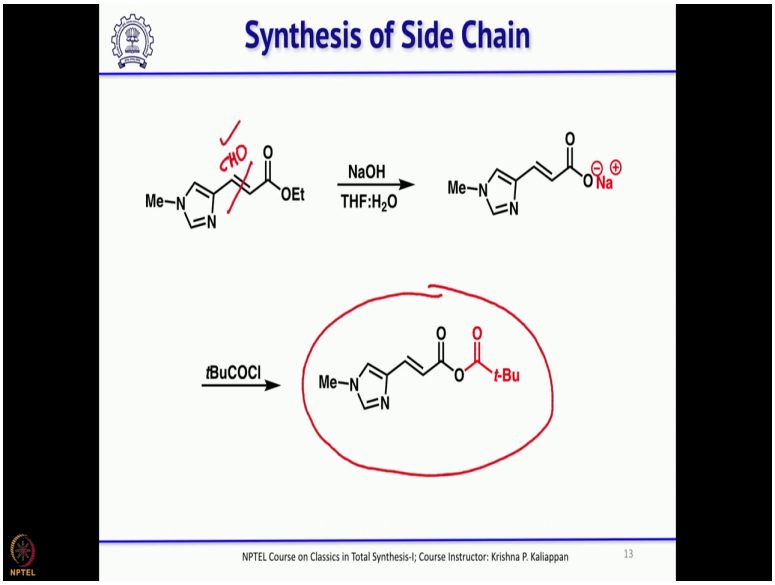

And the third fragment which we need is the α- β unsaturated carboxylic acid. So, this is a commercially available carbon and it can be also easily prepared from the corresponding aldehyde. If you have an aldehyde here ok then one can do Wittig reaction to get this α-β unsaturated ester.

Then hydrolyze the ester to get the corresponding acid or in situ one can also add pivaloyl chloride, so to get this mixed anhydride ok. So, now, you have the side chain of the northern hemisphere and you also have the sugar fragment and you have the A, B fragment what you need is you have to attach the C fragment.

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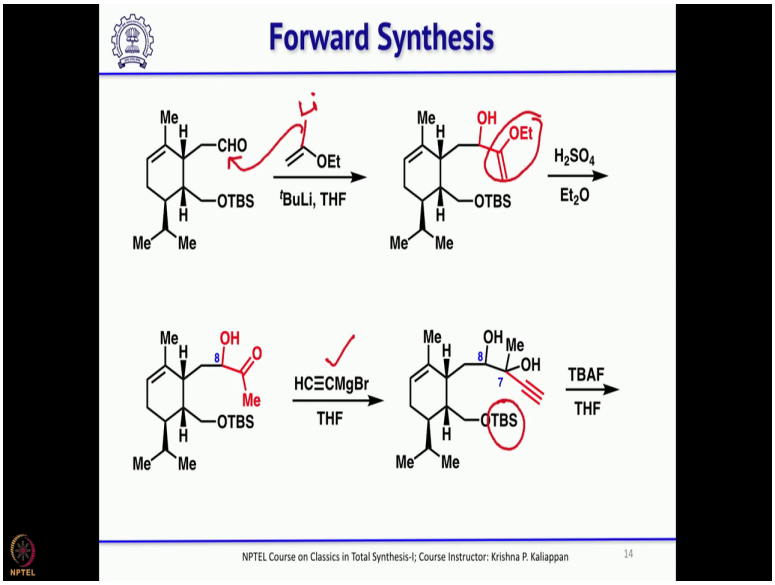

So, how one can do that is you have this aldehyde ok. So, this upon treatment with ethyl vinyl ether and tertiary butyllithium. So, what does it do? When you have ethyl vinyl ether on treatment with tertiary butyllithium it will pick up this proton and it will generate this lithium species ok. This lithium will add to this aldehyde and you will get the corresponding allylic alcohol ok. And this is enol ether is not it this is still enol ether. So, the enol ether upon hydrolysis with acid you will get the corresponding ketone ok.

Now, as I said you have to make C ring also and the key reaction in the total synthesis of eleutherobin by Nicolaou is a intramolecular addition of lithium acetylene. So that means, you need to add a triple bond. So, the triple bond was added in the form of acetylene magnesium bromide ok, you take acetylene and then treat with you know you convert it into the corresponding Grignard; this gives you the corresponding tertiary allylic alcohol.

So, once you have this tertiary allylic alcohol, now what one can do see the TBS which is protected the primary alcohol can be cleaved with TBAF to get the corresponding primary alcohol ok.

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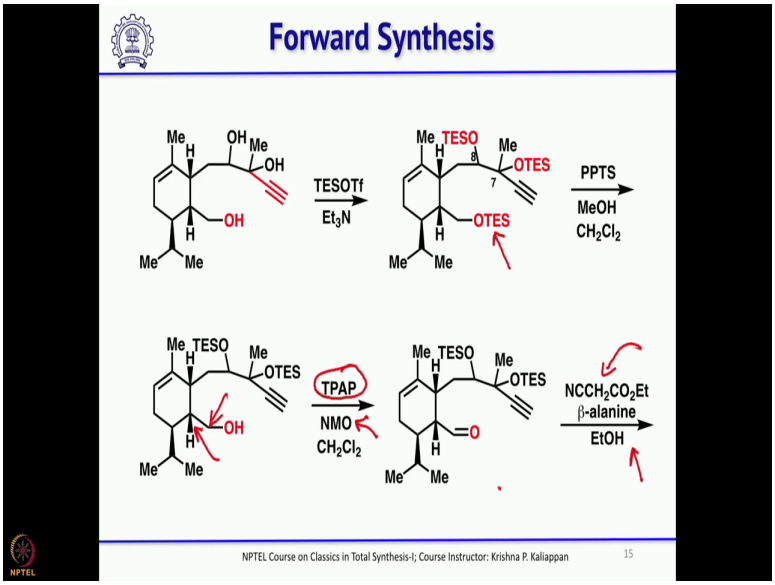

Once you have this primary alcohol you already have a secondary alcohol and tertiary alcohol ok. All the hydroxyl groups can be now protected as TES ether ok. So, now, you see you have 3 hydroxyl groups being protected as TES ether. Now, once you have this selectively one can remove the primary TES ether primary TES ether is level compared to secondary and tertiary. So, this is easily cleaved with PPTS and methanol ok. Once you have the primary alcohol, now you need to homolog it ok.

If you see the eleutherobin structure you need an allylic alcohol here; you need an allylic alcohol here; that means, this primary alcohol should be oxidized and then homologate ok. The primary alcohol should be oxidized and homologated. So, what you should do you should oxidize this primary alcohol and that can be done under very mild condition. So, that you do not see the epimerization at the adjacent carbon.

So, this is done by several oxidizing agents what Nicolaou has used is tetra n propyl ammonium perruthenate, tetra n propyl ammonium perruthenate its a ruthenium based reagent in short it is called as TPAP in catalytic amount and the co oxidant is NMO. So, that oxidizes the primary alcohol to corresponding aldehyde. So, once you have this aldehyde then you carry out a Knoevenagel condensation with this ester cyano ethyl cyano acetate. In the presence of β alanine ethanol you carry out a Knoevenagel condensation.

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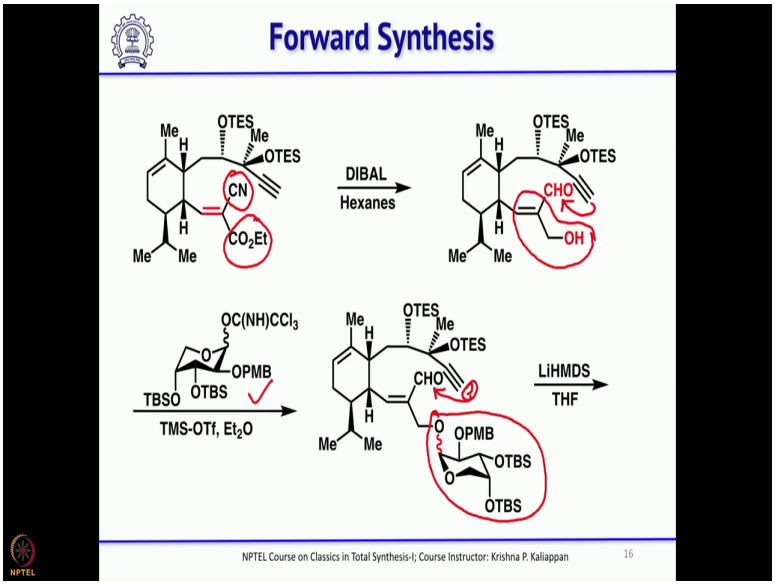

To get this α- β unsaturated ester which also has a cyanide which also has a cyanide. So, now, if you reduce this with the DIBAL. So, you have two groups which can be reduced one is cyanide and the other one is ester. So, cyanide if you reduce with DIBAL we know that it can be reduced to aldehyde. And if you take ester if you take ester and then treat with DIBAL and ester can be reduced to corresponding primary alcohol. So, in one part he converted the cyanide into aldehyde and ester into $-CH_2-OH$.

And if you look at again the structure of eleutherobin this is what you need in B ring and what you need is you have to somehow connect this the triple bond and aldehyde if you connect it, you will get a ten membered ring ok. So, here he wanted to connect this with that aldehyde, before that he thought it is better to connect the side chain ok; it is better to connect the side chain to the primary alcohol.

So, already made the sugar unit. So, this on treatment with TMS triflate then you can see the sugar unit was attached to the primary alcohol ok. So, now, all free hydroxyl groups are protected. If you look at this structure all the free hydroxyl groups are protected that paves way for generating anion here and then adding to the aldehyde.

So, that paves way for generating anion here and adding to the aldehyde. So, this is easily done by treating with LiHMDS. So, when you take LiHMDS, it generates a acetylate and under dilute condition the acetylate intramolecularly adds to the aldehyde to form the corresponding allylic alcohol ok.

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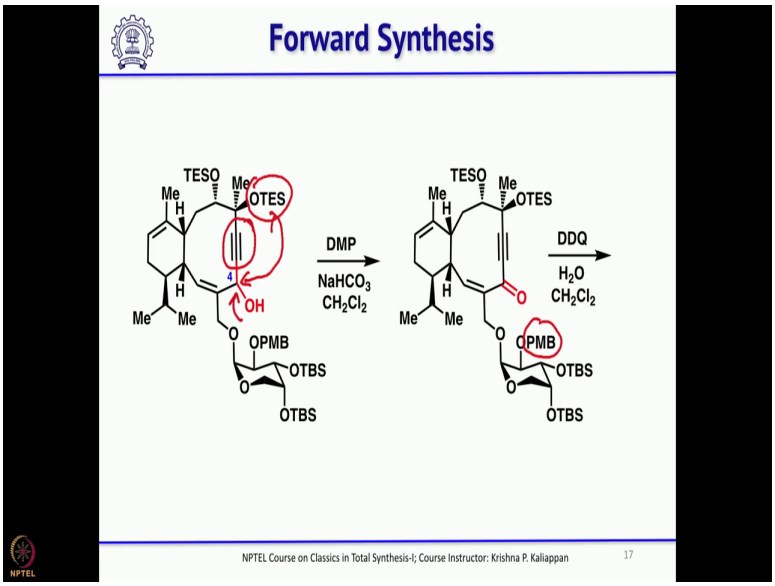

So, now what we have done we have started with A ring, we have attached the sugar unit and we also made a joint B C ring ok. So, now, from the B C ring, we have to really make B and C ring ok. So, B C ring is 10 membered ring. Now, we have to make a nine membered B ring and five membered C ring and for that what one has to do?

You have to reduce this triple bond and this hydroxyl group this OTES should be made as hydroxyl group and that has to attack here ok. So, to do this first we need to oxidize the alcohol here. To do this we should oxidize the alcohol here. So, when you treat with Dess-Martin periodinane ok; Dess-Martin periodinane is a very good reagent for oxidation of allylic alcohols you know like manganese dioxide, PDC Dess-Martin periodinane is a very good reagent for oxidation of allylic alcohol.

So, that gives the α- β unsaturated ketone ok. Now, when you remove the PMB group because the PMB group is little bulky.

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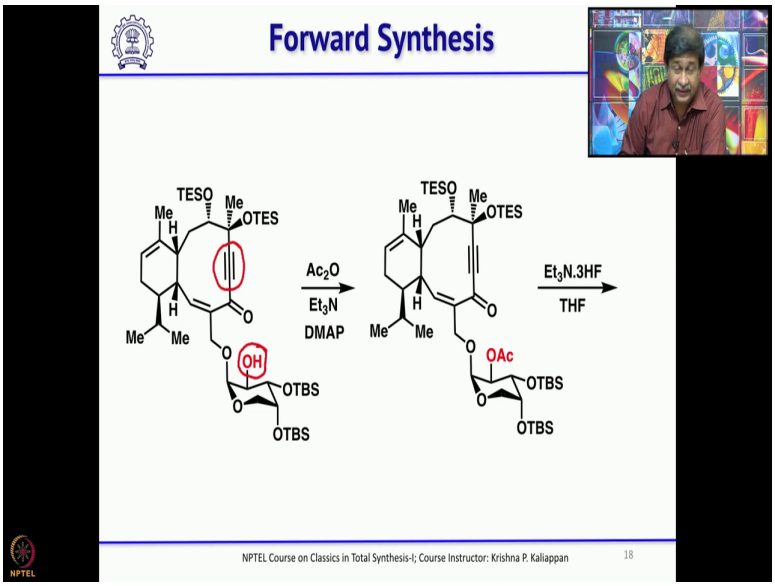

So, it is better to remove the PMB group by treating with DDQ you get the free hydroxyl group then you reduce the triple bond to the double bond; at the same time, it is better to re-protect the hydroxyl as acetate ok.

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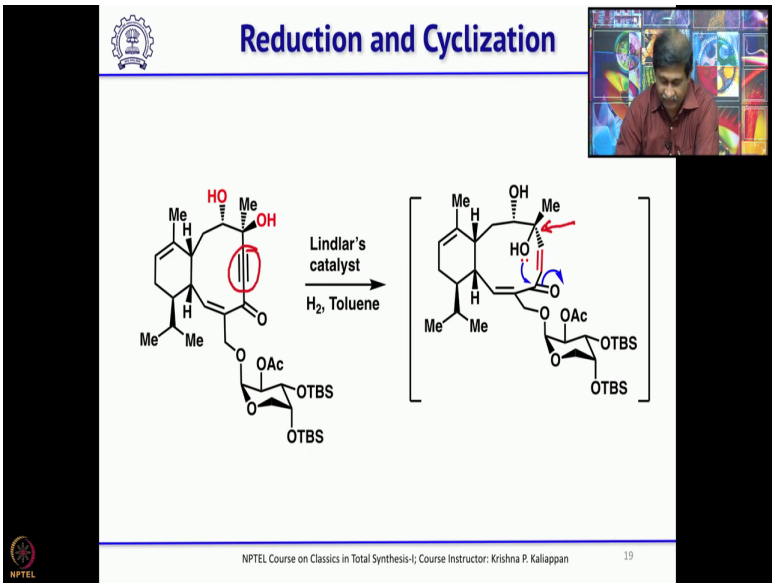

So, first the secondary alcohol was protected as acetate and secondary Ts group and then tertiary Ts group were removed and followed by the key reaction the that is the reduction of the triple bond followed by the key reaction that is the reduction of the triple bond and

when you do that with lindlar catalyst, the triple bond is reduced to *cis* double bond ok. Triple bond is reduced to *cis* double bond.

At the same time, the tertiary alcohol ok it can attack the ketone intramolecularly to form the lactol ok.

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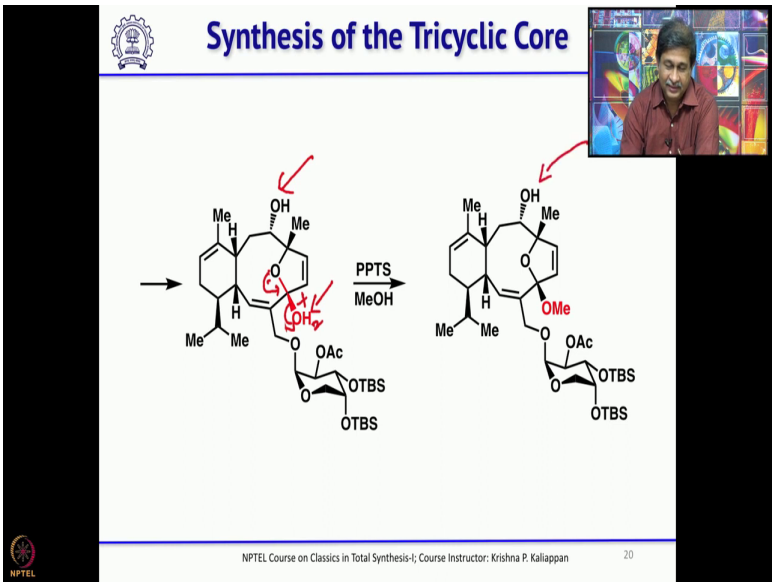

So, now, you can see the real core structure of eleutherobin A B C ring everything is there what needs to be done is you need to convert this hydroxyl into methoxy and also attach the side chain ok. So, these two can be done subsequently, first you treat this with PPTS methanol.

So, PPTS methanol what happens, if this makes this hydroxyl as a leaving group and then the lone pair comes and then this breaks the oxonium ion was attacked by methanol to form the methoxy ok; oxonium ion was attacked by methoxy group that is methanol to get the methoxy group ok.

So, now the methoxy group is introduced, the sugar unit is introduced only thing left is the attachment of side chain in the northern hemisphere ok.

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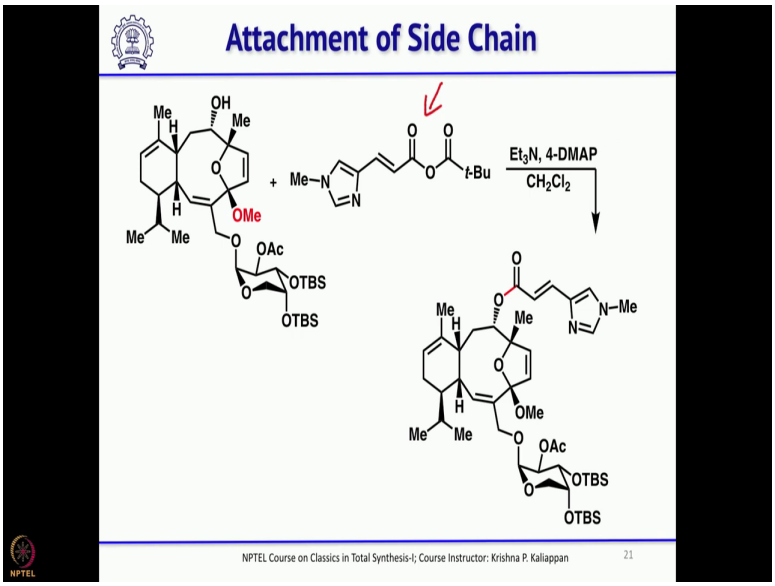

So, already we prepared this side chain mix these two in the presence of base that gives the α-β unsaturated ester ok. So, you have this.

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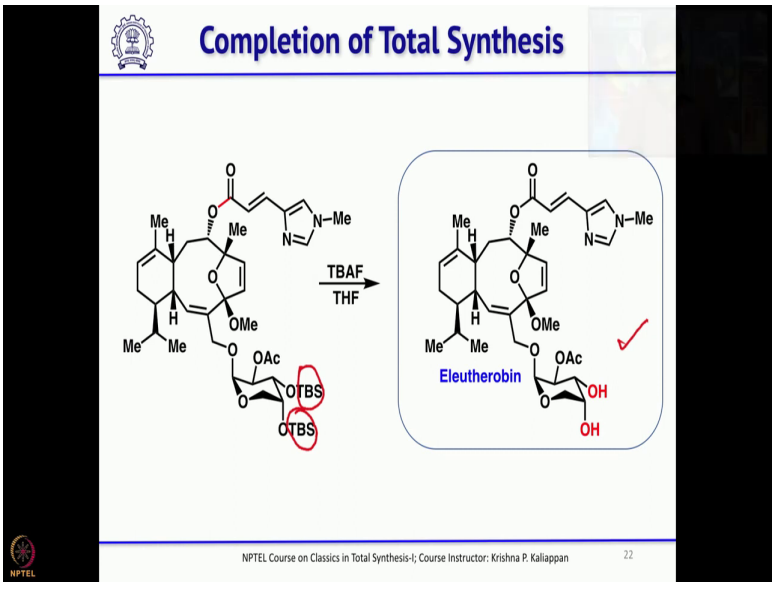

Next only one step that is to remove that TBS group. There are two TBS group in the sugar unit and that can be easily removed by fluoride reagent. So, TBAF treatment will remove the TBS group leading to the formation of the natural product eleutherobin ok. It is a very important total synthesis and it was the first total synthesis of eleutherobin reported in the literature and if you look at the key reaction, the key reaction is the

intramolecular addition of lithium acetylate to the aldehyde to get the 10 membered ring ok.

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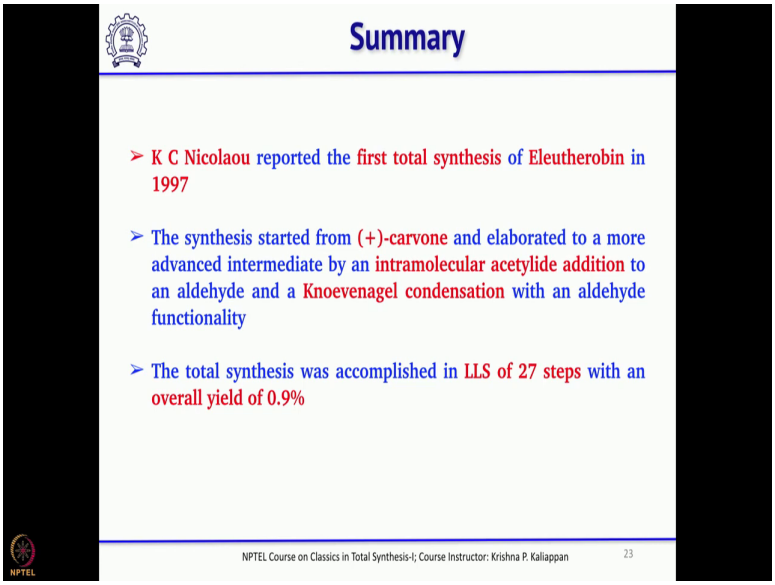

And then the hydrogenation of the triple bond to double bond followed by cyclization to form the five membered ring. These are the two key steps in the total synthesis of eleutherobin reported by K C Nicolaou and overall this total synthesis was done in 27 longest linear steps, 27 longest linear steps it is a linear synthesis.

If you look at this linear synthesis carefully it is a linear synthesis and with an overall yield close to 1%. So, considering the complexity of this natural product and overall yield of 1% and starting with the commercially available monoterpene carbon is really a significant and then a classical one ok. So, with this we will stop here and then tomorrow, we will talk more about another synthesis of eleutherobin and this time the synthesis was accomplished by Samuel Danishefsky ok.

Thank you.