Classics in Total Synthesis-I
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Lecture - 55
Epothilones by Nicolaou

Yeah. Good morning and welcome back to NPTEL lecture series on Classics in Total Synthesis part I. So, we have been talking about total synthesis of various terpenoids in the last couple of weeks. And today, we will move to total synthesis of another very interesting natural product called Epothilones.

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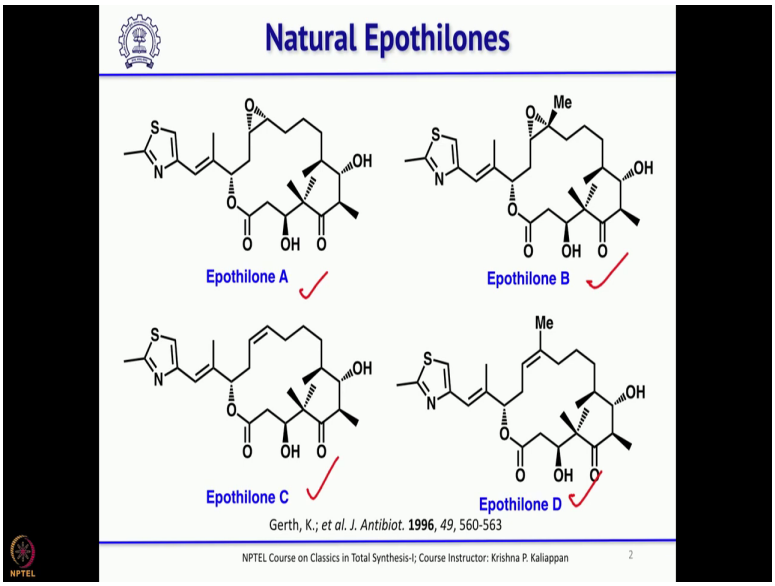

So, there are quite a few epothilones for example, Epothilone A, Epothilone B, and Epothilone C and of course, Epothilone D. So, there are four epothilones Epothilone A, Epothilone B, Epothilone C and Epothilones D.

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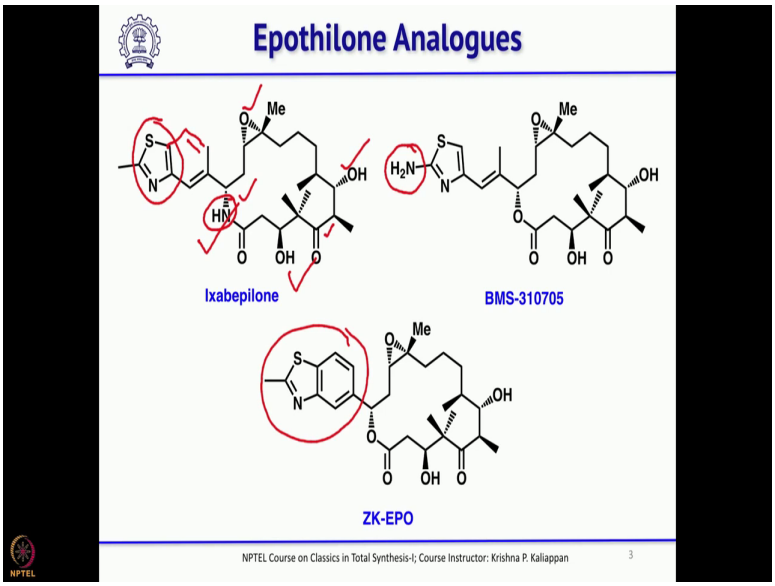

So, they were isolated from sand, it is a unusual source. And they were found to be showing exceptional anti cancer activities ok. And some analogs also were made while synthetic chemists were trying to make this natural products. One of the analogues which is now introduced as a drug is Ixabepilon.

You can see the major difference between the natural product that is epothilone B and this analog is instead of a lactone it is a lactum ok. So, epothilone if you look at carefully it is a macro lactone having an epoxide, an aldol, a ketone you can call it as another aldol ok. Both sides you have aldol and a lactone. So, here in this analog it is a lactum ok. And the side chain you can see you have thiazole ok.

And two methyl thiazole; and that has been replaced in this analog with two amino thiazole ok. And here a benzo thiazole also people used instead of the whole side chain that is if you connect these two and then put a double bond that is benzo thiazole. So, several analogs were made as epothilone showed exceptional anti cancer activity ok.

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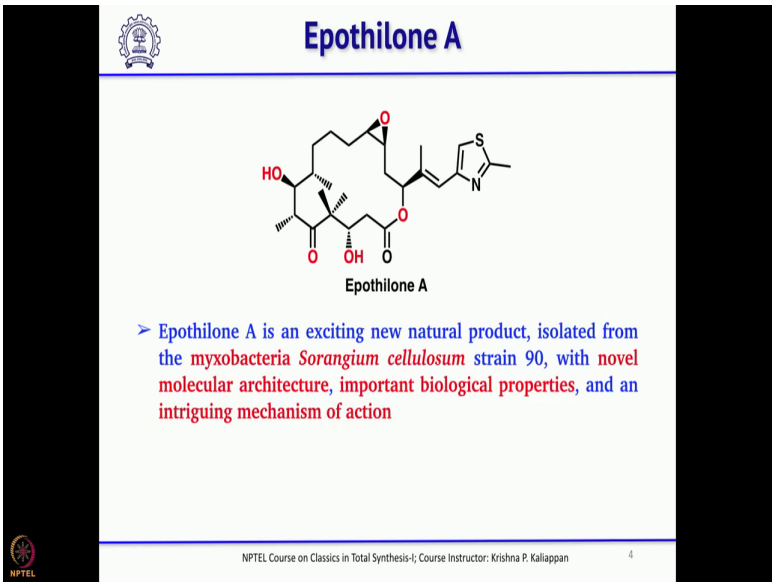

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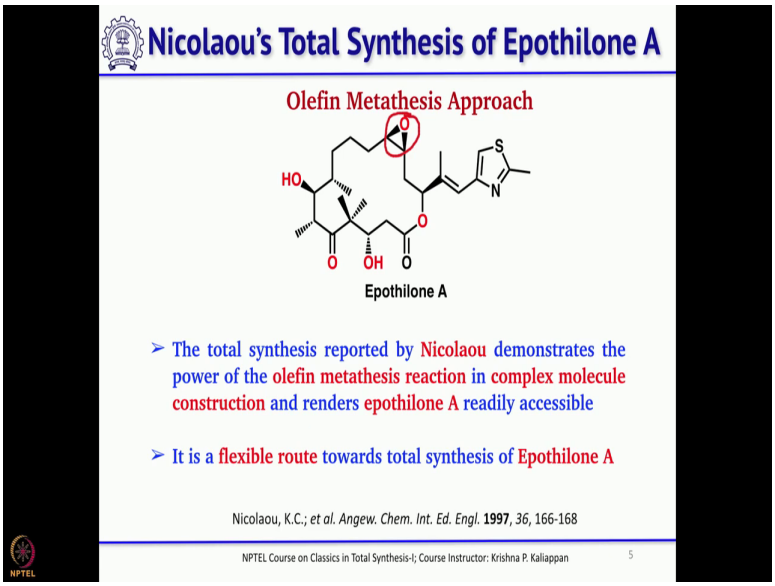

So, now let us see two total synthesis today both reported by K. C Nicolaou. So, K. C Nicolaou what he thought was if you look at the epoxide ok, in the case of epothilone you have an epoxide ok. So, he thought that epoxide can be made from a double bond and that double bond can be made through ring closing metathesis. So, directly this molecule can be open to a linear chain through metathesis.

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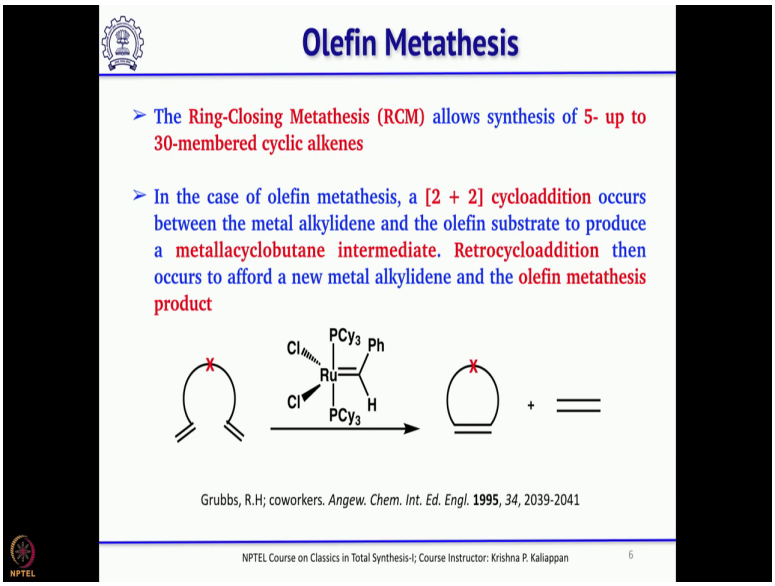

So, a metathesis is a well known reaction for the last three decades. So, one can make 5 membered to 30 membered cyclic compounds and simple mechanism you take either Grubbs I or Grubbs II. Now, there are many catalysts which are come to convert a diene into an alkene ok.

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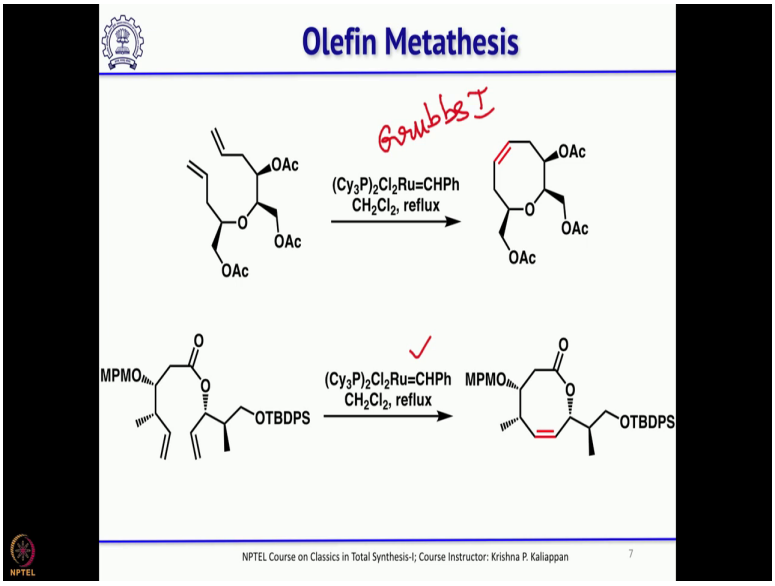

So, here are some examples where you can see an 8 membered ring has been formed with the help of Grubbs I. This is Grubbs I catalyst and this is another reaction again a

difficult 8 membered ring is formed through the Grubbs I st generation catalyst. So, there are as I said there are many other catalyst Grubbs, Grubbs Hoveyda and so on ok.

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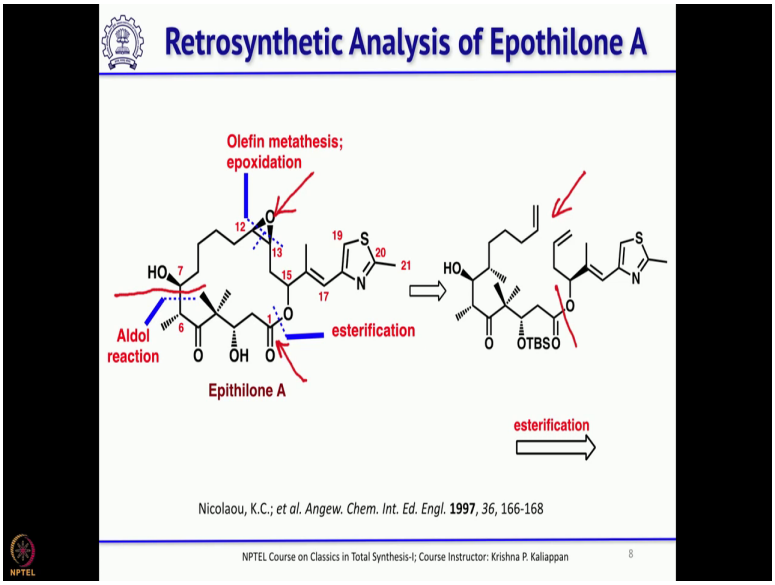

Coming to the total synthesis of epothilone, as I mentioned this epoxide was formed from olefin and that olefin was formed through ring closing metathesis. So, that was the first key retrosynthesis of epothilone by K. C Nicolaou. Then you can see this ester if you can cleave that you will get alcohol on one side and caroxylic acid on another side; and the next cleavage is here.

So, you have an ethyl ketone on the southern hemisphere and aldehyde on the northern hemisphere and intramolecular or intermolecular aldol reaction can generate these two stereocentres. So, the first disconnection as I said is the ring closing metathesis, and this can be obtained from the corresponding carboxylic acid and alcohol through esterification.

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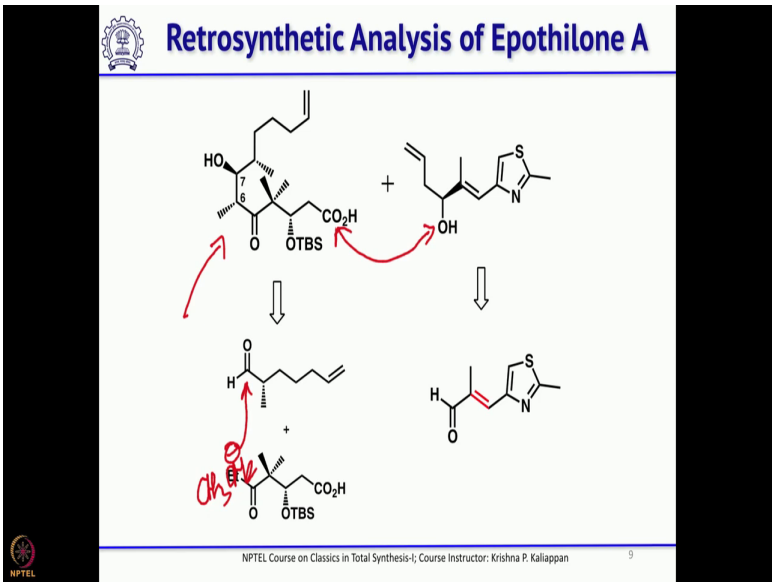

So; that means, these are the two precursors. So, you have a carboxylic acid and coupled with alcohol you get the ester ok. Now, this carboxylic acid can be obtained from this ethyl ketone and aldehyde. So, ethyl ketone you can see this is CH_2-CH_3. One can generate anion here that anion if it attacks aldehyde, you will get this aldol. And this allylic alcohol can be obtained from this α–β and saturated aldehyde through chiral allylation ok.

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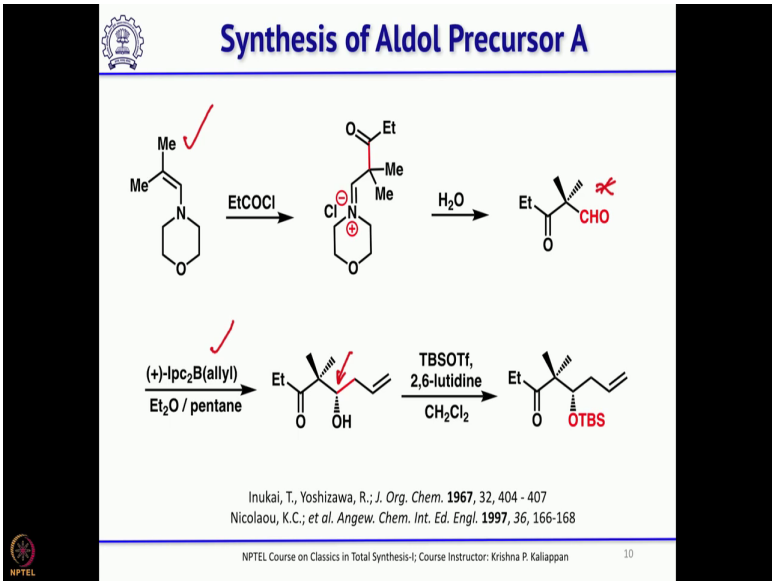

Now, let us see how Nicolaous group made all these precursors. First, they started with isobutyraldehyde, isobutyraldehyde the isobutyraldehyde and treatment with morpholine it form this enamine ok. This enamine upon acceleration with propanol chloride which gave this intermediate which upon hydrolysis gave this aldehyde ok. It is a beta keto aldehyde. Now, you do chiral allylation using browns allyl boron ok.

So, this is chiral reagent derived from alpha pinene. It is a well known reagent for introducing a chiral center upon addition to aldehyde. This align source depending on the nature of the pinene whether it is R- α or s-α you will get the corresponding chiral center here ok. So, now, one chiral center is introduced and that alcohol is protected as TBS ether.

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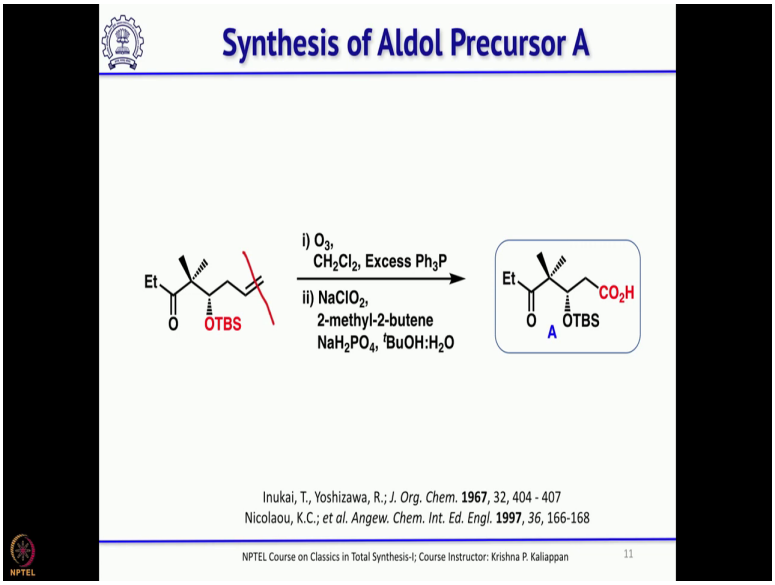

Then, you do the was analysis followed by oxidation of the resultant aldehyde to carboxylic acid. So, this is how you made the fragment A.

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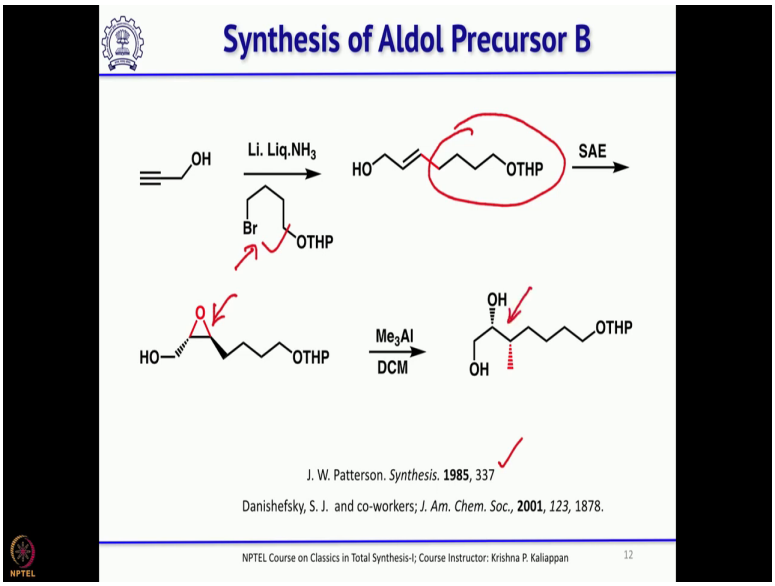

Now, for the synthesis of fragment B, he started with propargyl alcohol following Patterson's protocol. First, upon treatment with lithium in liquid ammonia followed by quenching with this bromide you could get this trans allylic alcohol where you can see the whole four carbon unit of the electrophile is attached. Now, Sharpless asymmetric epoxidation of this allylic alcohol gave this epoxide. This upon opening with trimethyl aluminium, it can give a *syn* hydroxy compound ok.

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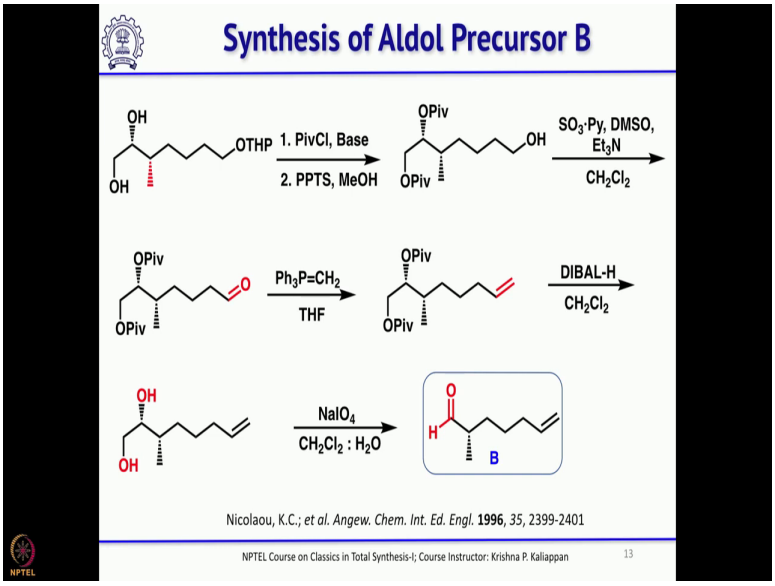

Then this was protected as pyrolite ester both hydroxyls were protected as pivalate ester and the THP was removed THP is tetrahydropyran ether that was removed using pyridinium p-toluene sulfonate and oxidation of the primary alcohol with sulfur trioxide pyridine and DMSO gave aldehyde this upon Wittig reaction gave the double bond. Now, reductive removal of the pivalate tester with DIBAL gave the diol and sodium periodate cleavage gave the aldehyde which is a precursor B.

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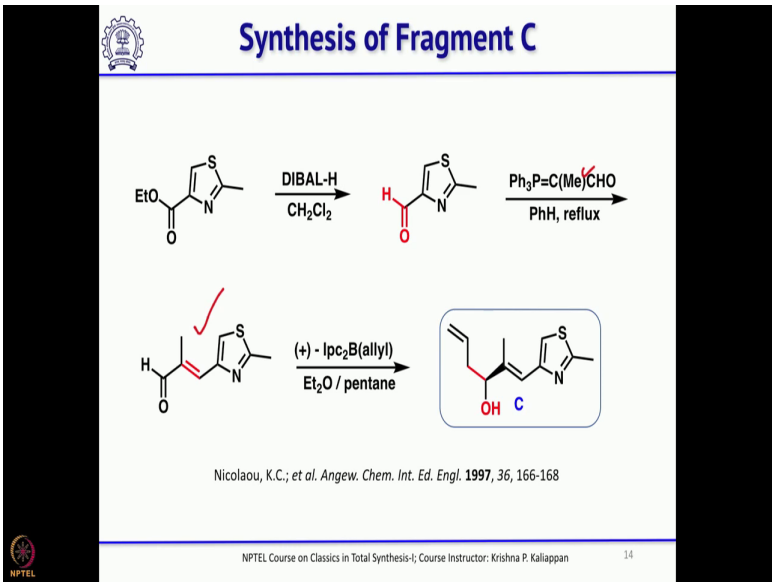

So, you have made A and B for the fragment C. He started with the thioazole ester reduction of the thioazole ester with DIBAL gave the aldehyde and the homologation with this Wittig reagent gave this α–β and saturate aldehyde then the brown allylation gave fragment C.

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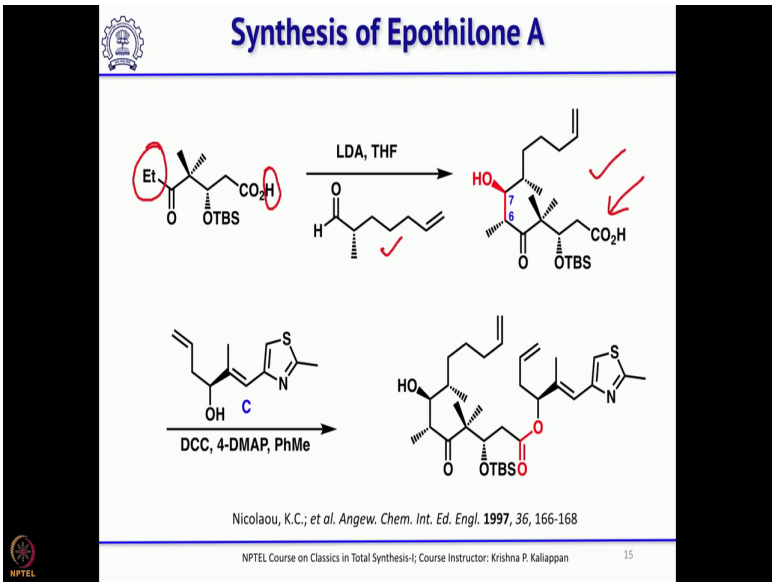

So, having the fragments A, B, C in place then he attempted the totals in this epothilone A. So, you took the carboxylic acid ok on the left hand side you see it is an ethyl ketone. So, two equivalents of LDA or more, first it will generate anion here as well as it will generate the enolate on the ethyl ketone side.

Then you quench with this aldehyde and you get the corresponding aldol products after acidification. Then you have to attach the alcohol to the carboxylic acid. So, that was done with DCC. So, quickly he could assemble the precursor required for the ring closing metathesis.

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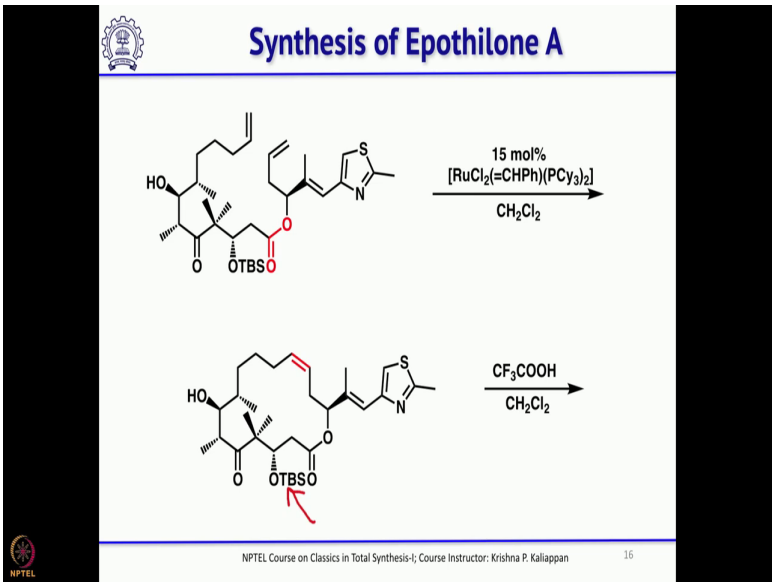

So, once you have that then Grubbs I[st] generation catalyst gave the ring closing metathesis product *cis* double bond. And now, if you want to remove you can remove the protecting group here because you do not need OTBS what needs to be done at this stage is removal of the TBS group followed by epoxidation.

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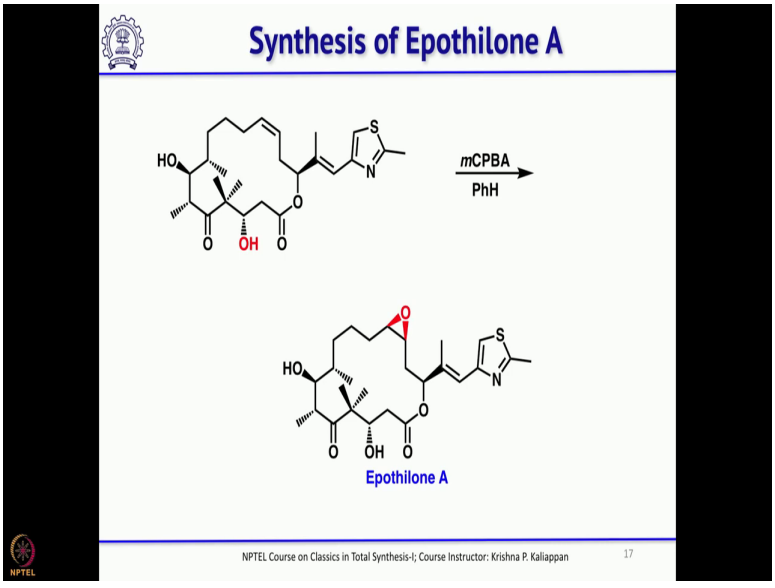

So, the TBS group was removed using trifluoroacetic acid, then epoxidation with *m*CPBA you could get epothilone A. So, these are first generation synthesis of epothilone A reported by Nicolaou's group.

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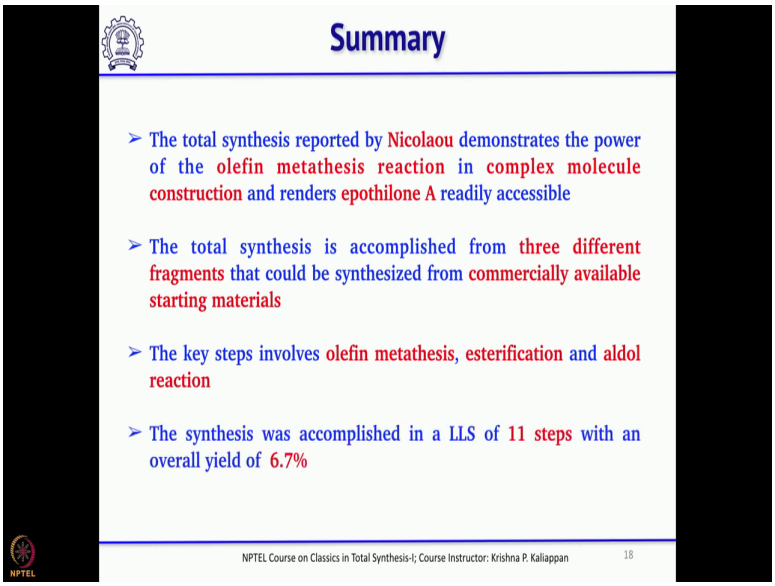

He also another root in this root as you know the key steps involved in this total synthesis or olefin metathesis, aldol reaction and esterification reaction. Overall, it took about 11 steps and yield close to 7%.

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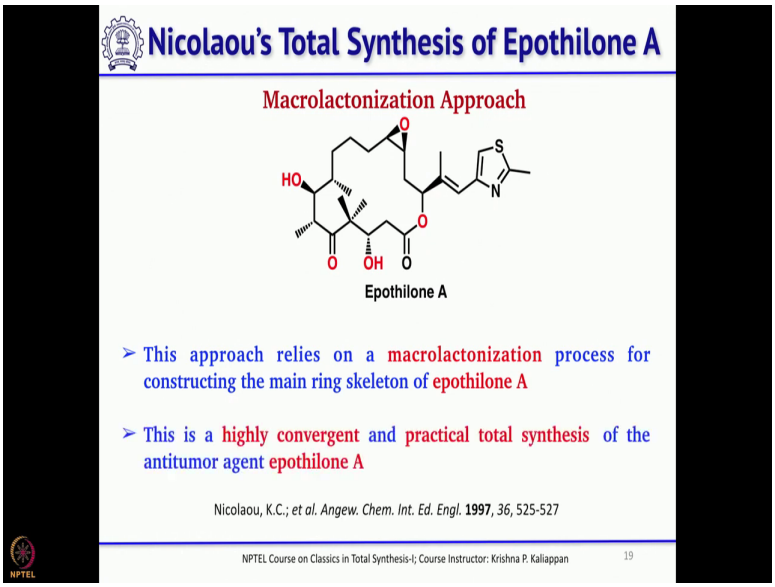

In the second generation synthesis, the major difference was instead of ring closing metathesis he wanted to use a macro lactonization ok, because you can see in epothilone if there is lactone ok; it is a macrolactone. So, he wanted to use Yamaguchi's macro lactonization approach to form the macrolactone ok.

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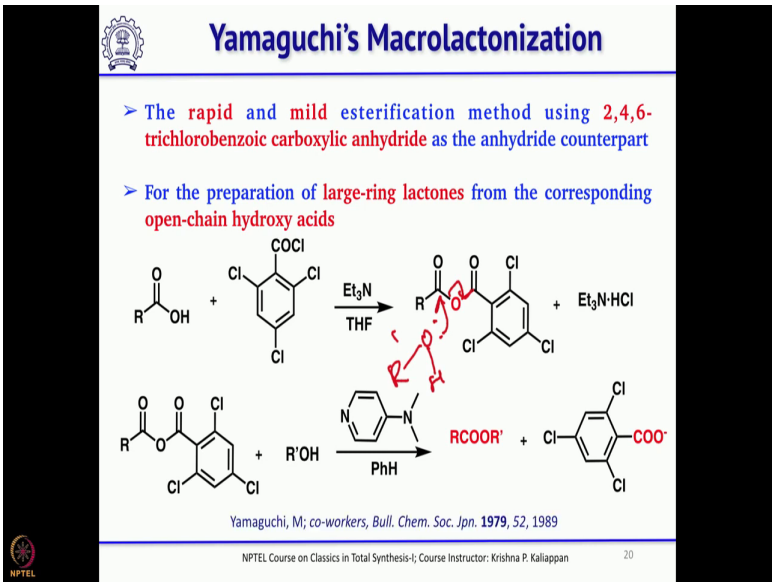

And for that first as you all know what is you know which is micro lactonization. If you have a carboxylic acid and if you treat with 2, 4, 6 trichloro benzoyl chloride so that will form a mixed anhydride this upon treatment with any alcohol that alcohol will attack the less hindered carbonyl group here and then this will come out. So, that is how esters are formed using this Yamaguchi's method. This is particularly very important for making macrolactones ok.

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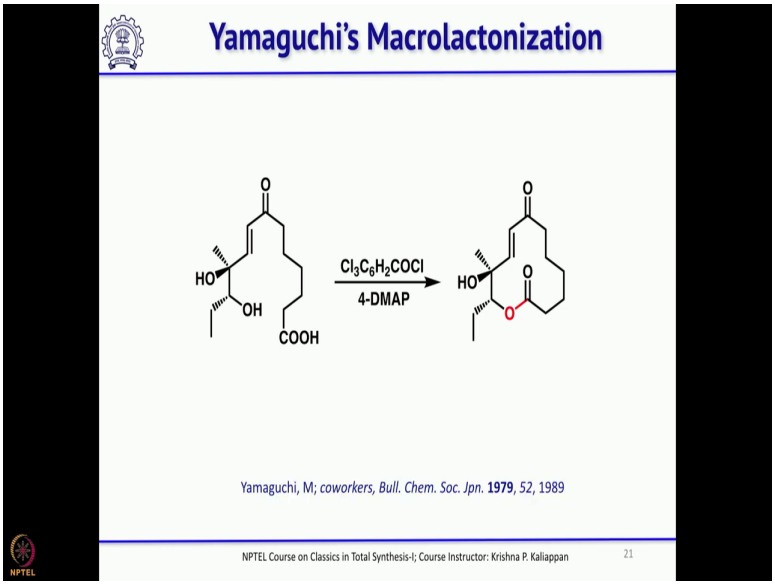

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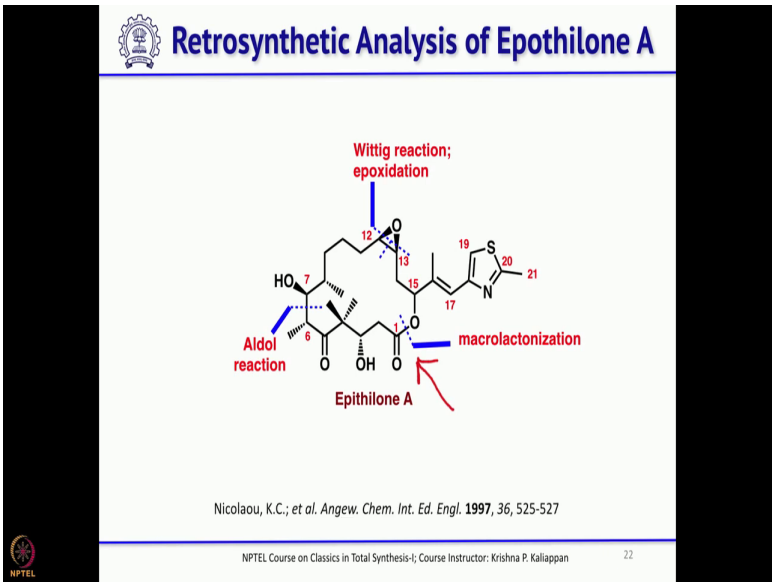

For example here, this macrolactone formed by Yamaguchi's method. And from the retrosynthetic point of view as I said this particular synthesis used macroelectronization as the key step in the last but one step ok.

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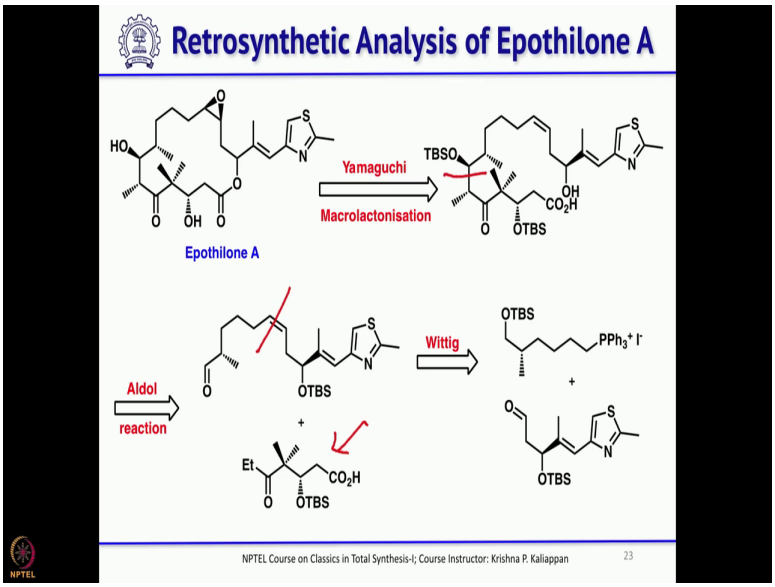

So, that should give you the corresponding hydroxy carboxylic acid hydroxy carboxylic hydroxy on the right side and carboxylic acid on the southern hemisphere. Then on the left hand side breaking up this bond will give an aldehyde and ethyl ketone. So, this already we discussed how this carboxylic acid could be formed ok. And now this can be

made from two fragment one side it should be aldehyde other side it should be Wittig salt ok.

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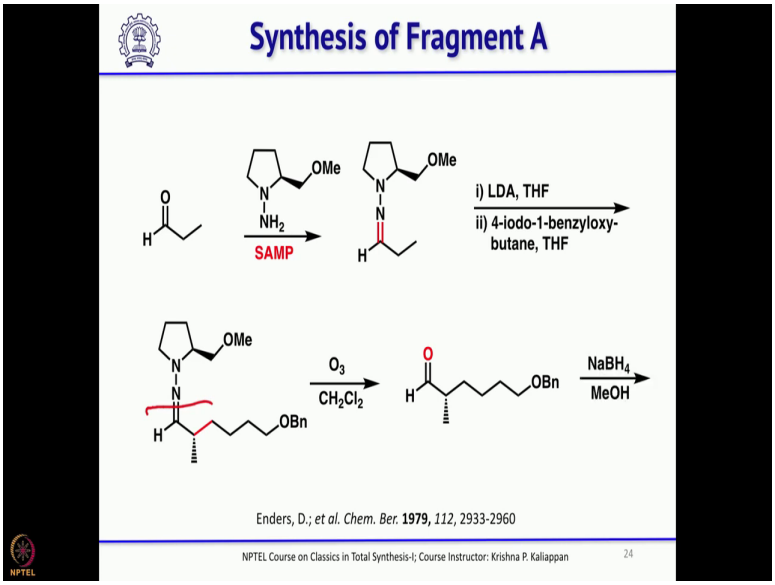

So, these are the two fragments already you know in the first synthesis he has made all these fragments, but he also followed some modification while making these fragments. For the fragment A, he started with propanaldehyde and then he used Hiders hydrazine. So, SAMP hydrazine to form the corresponding hydrazone. Now, if you alkylate with four iodo one benzyl oxybutane. So, you can introduce the four carbon chain.

Now, simply hydrolyze you get aldehyde. So, normally hydrazones like enders are hydrolyzed using ozonalysis; just to cleave this you will get aldehyde and on the other side you will get the hydrogen.

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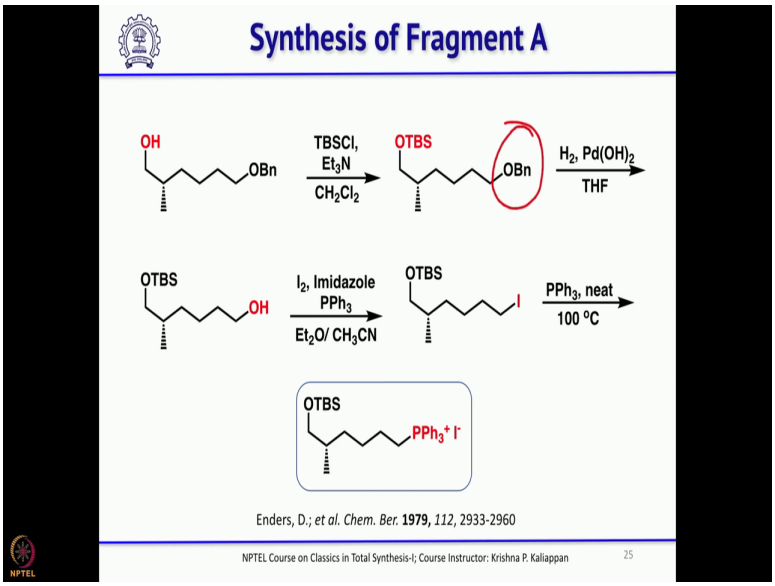

Reduce the aldehyde and protect it as TBS ether. So, you get the fragment A, and of course, you also have to remove the benzyl group and convert into living group here the OH was converted into iodide by treating with iodine imidazole and triphenylphosphine.

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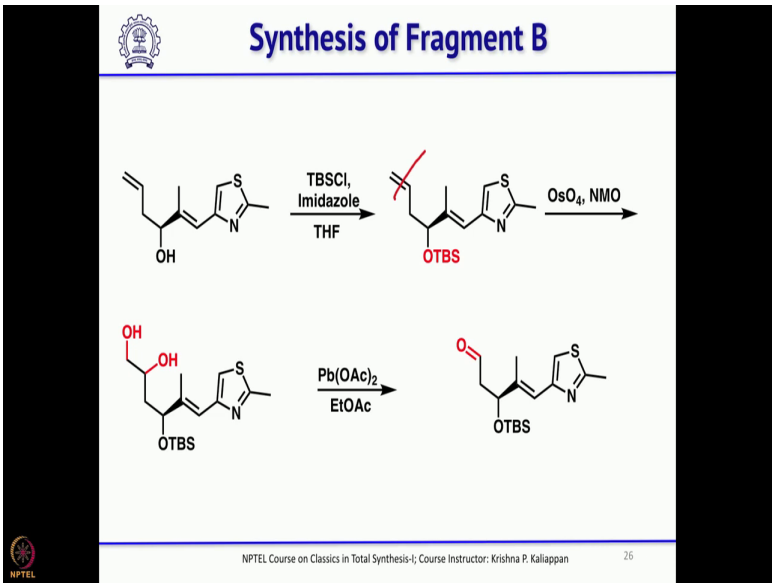

So, now the Wittig salt is made; for the fragment B already the synthesis of this homological was discussed during the first generation synthesis of epothilone by Nicolaou. Just protect the secondary alcohol and then do a two step protocol to cleave

the double bond to aldehyde ok osmium tetra oxide followed by sodium periodate or led tetra acetate cleavage gave the aldehyde.

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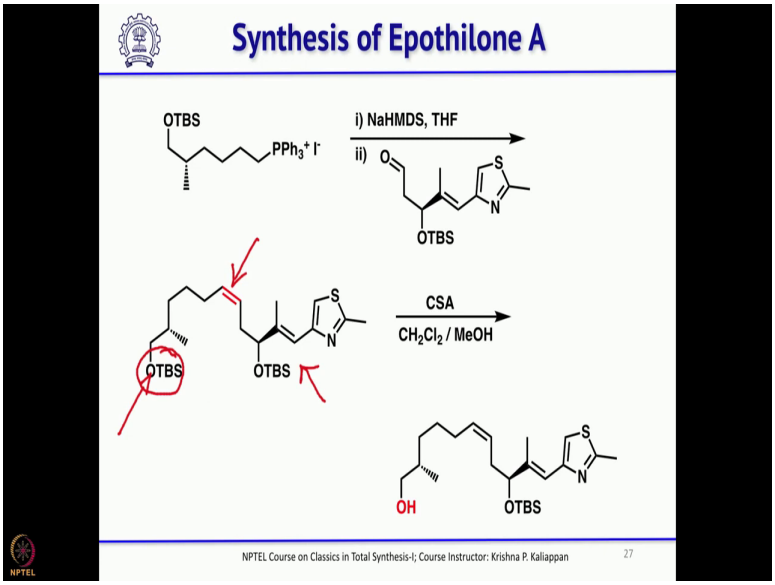

Now, fragment A and fragment B can be combined using Wittig reaction ok. So, this wittig reaction gives you know the *cis* double bond ok. Next you have the southern hemisphere keto carboxylic acid you have to remove this make it as aldehyde and then add the methyl ketone through aldol aldol reaction ok. So, for that what is required is removal of this TBS group selectively.

So, the left hand side TBS is primary alcohol protected TBS whereas, the right hand side one is secondary alcohol protected TBS. Normally, the primary ones can be easily selectively cleaved by treating with camphor sulfonic acid.

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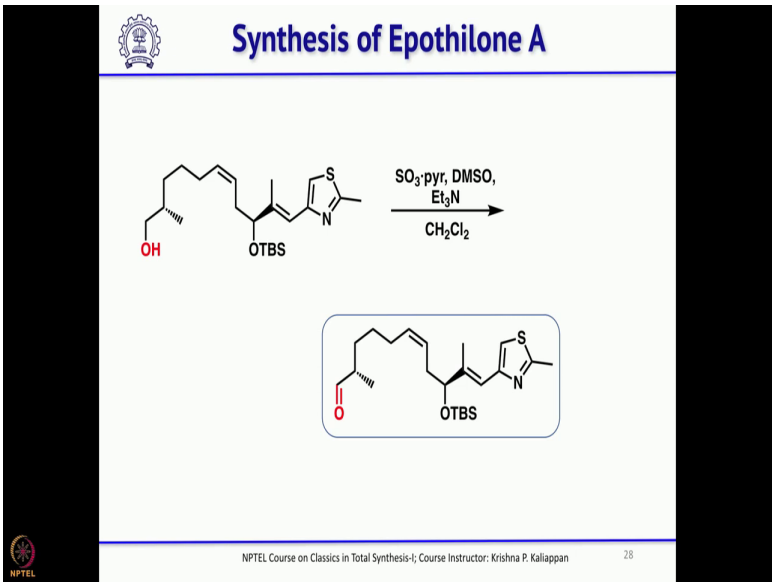

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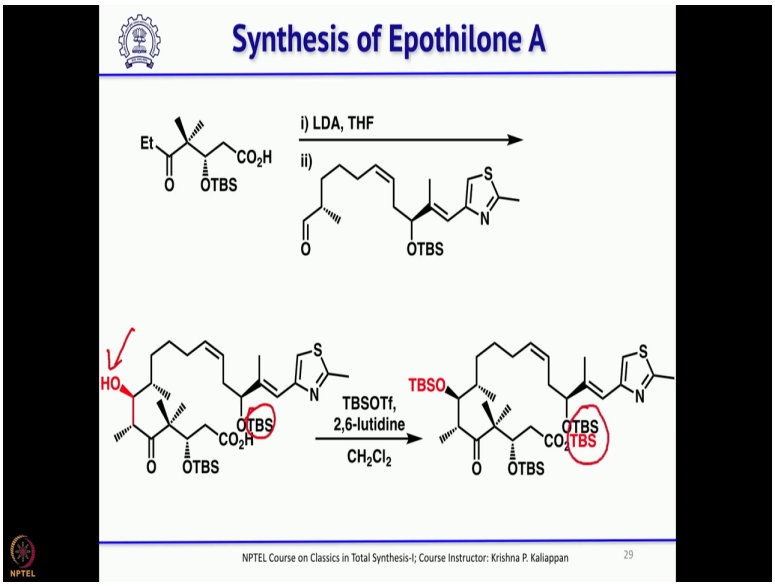

So, that is what he did then oxidation with SO_3 pyridine and DMSO gave the aldehyde ok. The other side that is the southern hemisphere ethyl ketone, it took the ethyl ketone treated with excess LDA and quench with the aldehyde. Now you can see almost all the carbons of epothilone A is ready.

So, what needs to be done? Now, you have to remove this and then do the macro lactonization, but you have free hydroxyl group here. So, that should be protected otherwise that lactone will be formed. So, that was protected, but when you want to

protect that hydroxyl group carboxylic acid also will be protected. So, both carboxylic acid and the hydroxyl group were protected as TBS ether and ester respectively. Now you have to remove these two TBS, ok.

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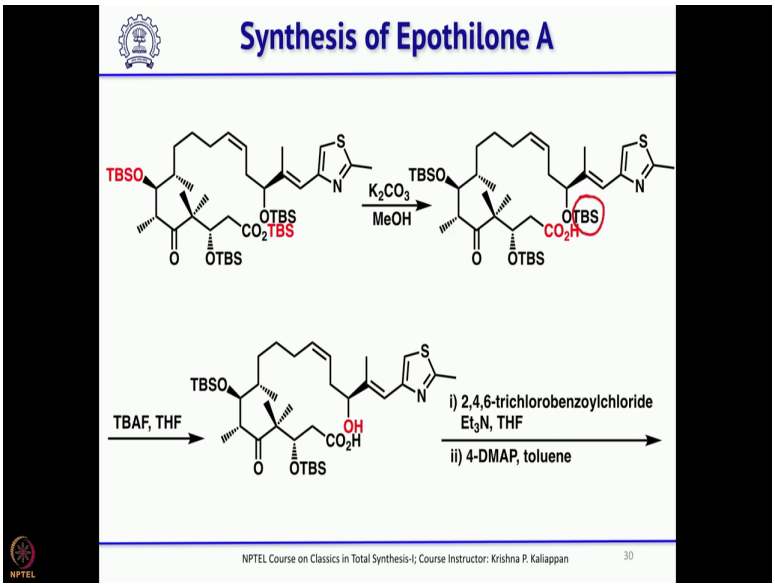

So, that was done by potassium carbonate methanol. First ester TBS was removed subsequently one equivalent of TBAF, one equivalent of TBAF to move this TBS in the selectivity followed by a Yamaguchi's macrolactonization gave the macro lactone.

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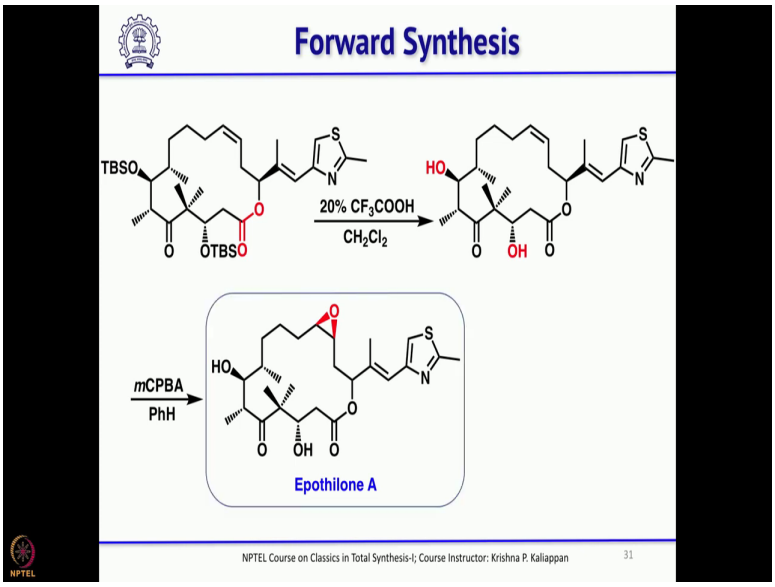

And now both TBS can be easily cleaved by treating with trifluoroacetic acid. And finally, epoxidation of the double bond with mCPBA gave epothilone A.

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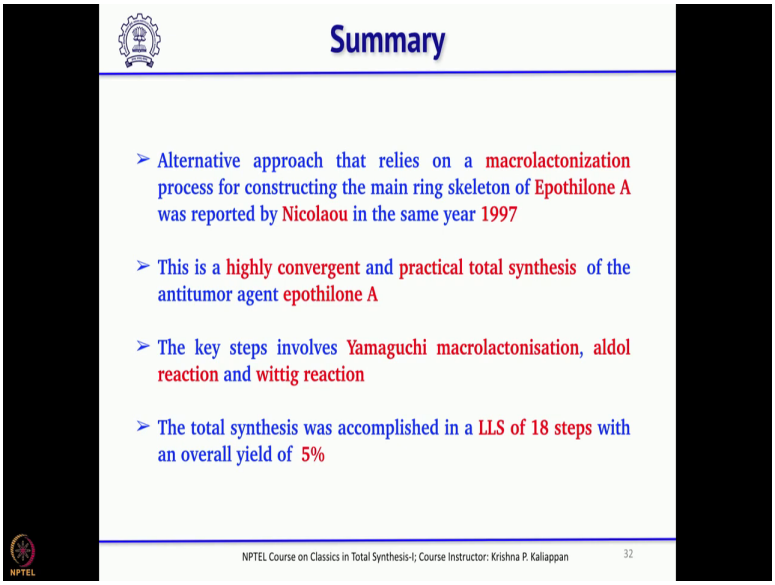

So, in summary Nicolaous group synthesize epothilone A in the same year after they reported the first generation total synthesis. Here the key reactions or Yamaguchi's micro lactonization and of course, on the left hand side highly stereo selective aldol reaction as the key step and the top the double bond was made using Wittig reaction. Overall the number of steps involved are 18 and yield was 5%.

Though the yield looks little bit lesser than the first synthesis the first synthesis he had he overall yield of about 7%. So, this is completely a new approach to make epothilone A ok. So, I will stop here, and then I will continue the discussion on total synthesis epothilone A by two more groups one by Dieter Schinzer and the second one by Samuel Danishefsky ok.

Thank you.