Classics in Total Synthesis-I

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Lecture - 56

Epothilones (1.Schinzer, 2.Danishefsky)

So, good morning and welcome back to NPTEL lecture series on Classics in Total Synthesis. So, yesterday we talked about total synthesis of epothilone by Nicolaous group. In fact, we discussed two synthesis of Nicolaous group. So, today we will discuss two more total synthesis of Epothilone, a one by Schinzer's group, the other by Danishefsky group.

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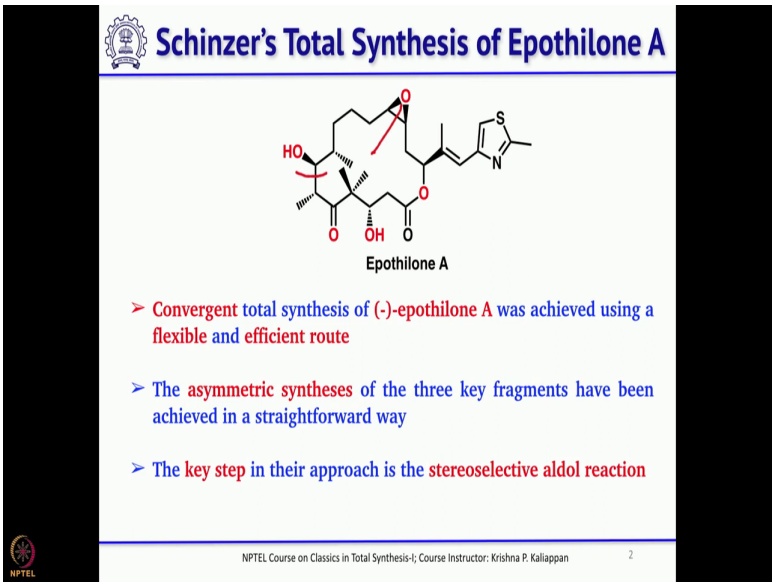

The Schinzer's group what they wanted to do was again they wanted to use the aldol reaction; the highly serious selective aldol reaction was the key reaction and, then also the ring closing metathesis as the key reaction to get the double bond followed by epoxidation.

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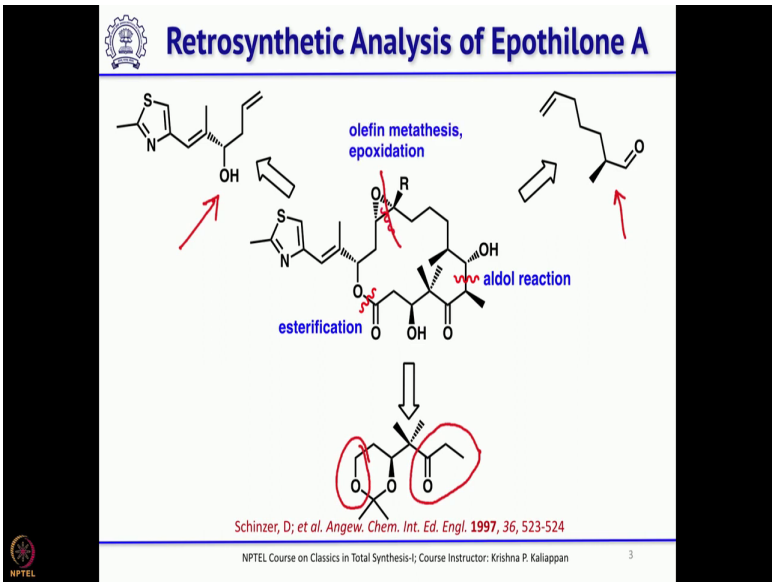

So, if you look at the retro synthesis, on the right hand side the aldol the cleavage of aldol followed by you know the ring closing metathesis. You can see the left hand side you have this homoallylic alcohol, right hand side the aldehyde. This is almost similar to what Professor Nicolaous has done and, the southern hemisphere is this a ethyl ketone. The case of Nicolaous group, this used to be carboxylic acid. Here, the 1 3 diol as a ketone ok.

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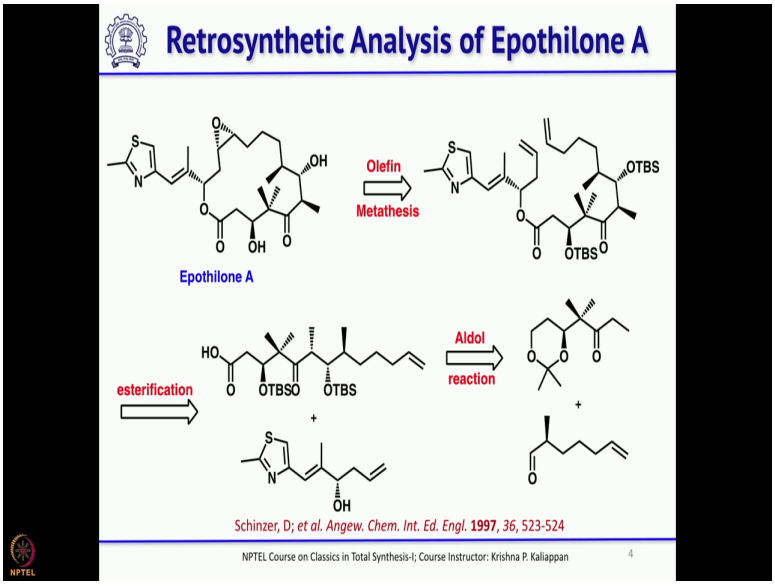

Now, these three fragments were synthesized using the standard asymmetric root. Now, let us see one by one how his group synthesize all the three fragments ok.

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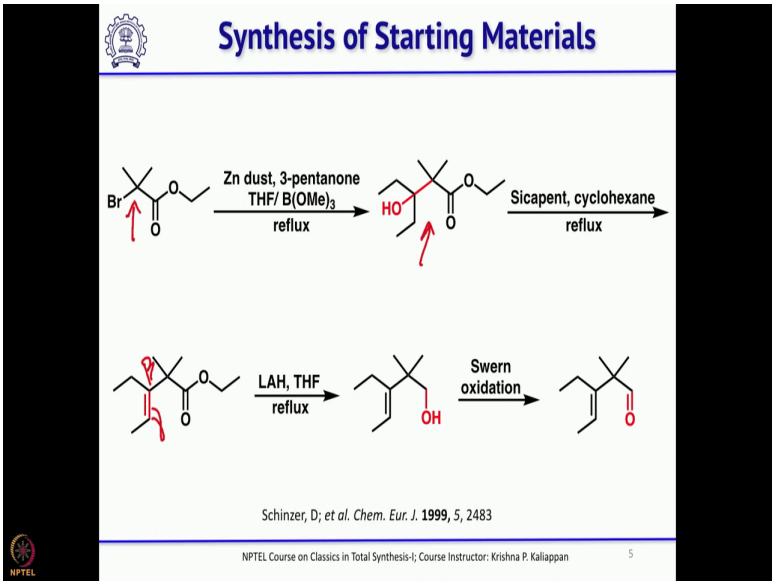

First, he carried out a Reformatsky reaction on this ester with 3 pentanone. So, the α bromo ester upon Reformatsky reaction with 3 pentanone to get this β hydroxy ester ok. This beta hydroxy ester then upon treatment with acid, it underwent dehydration to give β–γ unsaturated ester ok.

This β–γ unsaturated ester was reduced to get the corresponding alcohol, then it was oxidized under Swern condition to get the aldehyde. Now, this aldehyde is ready for asymmetric aldol reaction, for asymmetric aldol he used a very interesting chiral auxiliary.

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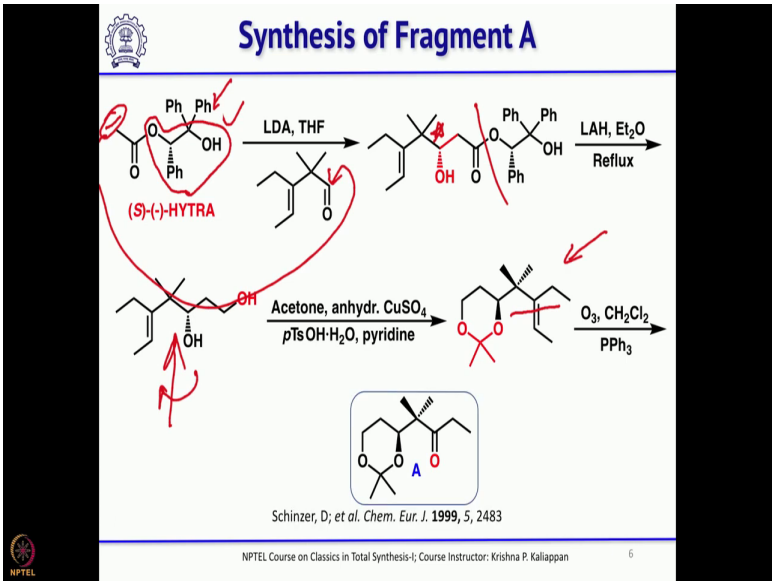

So, what is used was this ester, this ester is obtained from mandelic acid if you see so, this is mandelic acid ok. The mandelic acid ester upon treatment with excess phenyl Grignard, you will get the corresponding tertiary alcohol and the secondary alcohol was acetylated. Now, this upon treatment with LDA, you generate anion here and that enolate attacks this aldehyde you introduce a chiral center here now ok.

So, once that is served, you have to remove the ester. So, reductive removal of the ester gives your chiral auxiliary as well as the 1-3 diol. Now, 1-3 diol, if you rotate it by 180 degree ok, if you rotate this by 180 degree followed by protection of this 1-3 diol with acetone, you get this ketal ok.

Then, you need ethyl ketone here, you need ethyl ketone. So, that is easily done by cleavage of this double bond to have the fragment A. So, the fragment A was easily synthesized in few steps using Reformatsky reaction and asymmetric aldol reaction with a chiral auxiliary derived from mandelic acid.

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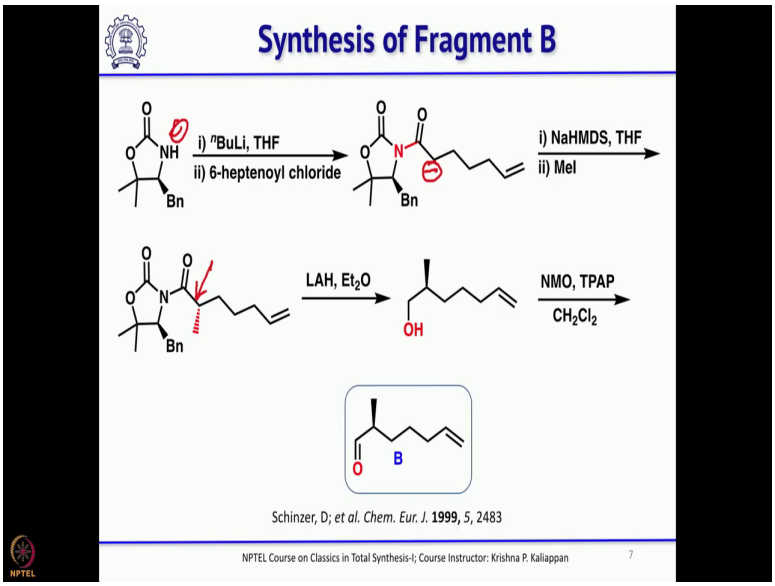

Then, the fragment B was synthesized using Evans chiral auxiliary. First, this was deprotonated and quenched with heptenoyl chloride ok. Then, deprotonation followed by quenching with methyl iodide, you could introduce the chiral center here with a methyl group and then removal of the chiral auxiliary with LAH gave the primary alcohol and oxidation with TPAP, that is tetra n propyl ammonium perruthenate with co-oxidant methyl morphine oxide gave the fragment B which is aldehyde ok.

So, aldehyde is ready and then that side ethyl ketone is ready.

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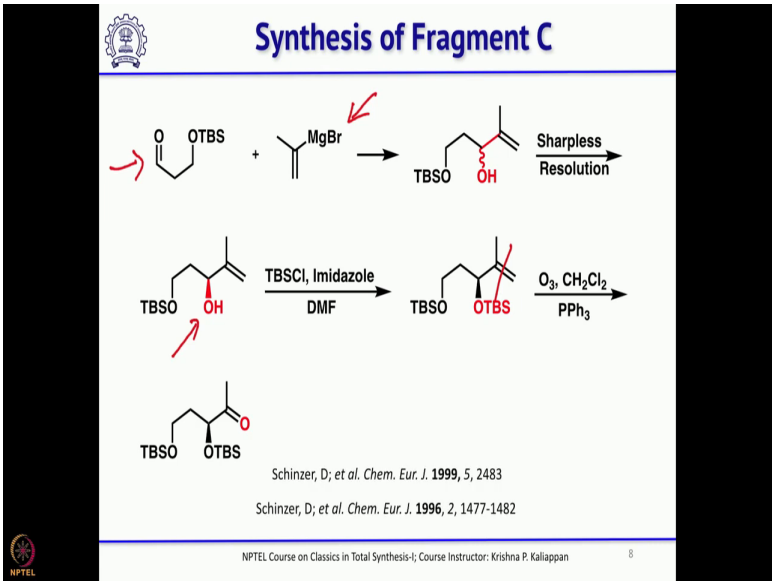

So, now the fragment C so, which is made from 1-3 propane diol. So, you take 1-3 propane diol and protect one of the alcohol as TBS ether and then oxidize the other primary alcohol to aldehyde. This upon Grignard reaction, this upon treatment with Grignard reagent derived from 2 bromo propene gives this allylic alcohol. As you know when you have allylic alcohol, one can think about sharpless asymmetric epoxidation.

But, when you have a racemic allylic alcohol, one can think about sharpless kinetic resolution. So, sharpless kinetic resolution you could get exclusively this alcohol of course, the yield will be less than 50%, that alcohol was protected as TBS ether and followed by ozonolysis, you get the ketone. Now, the thiazole unit should be attached to this ketone.

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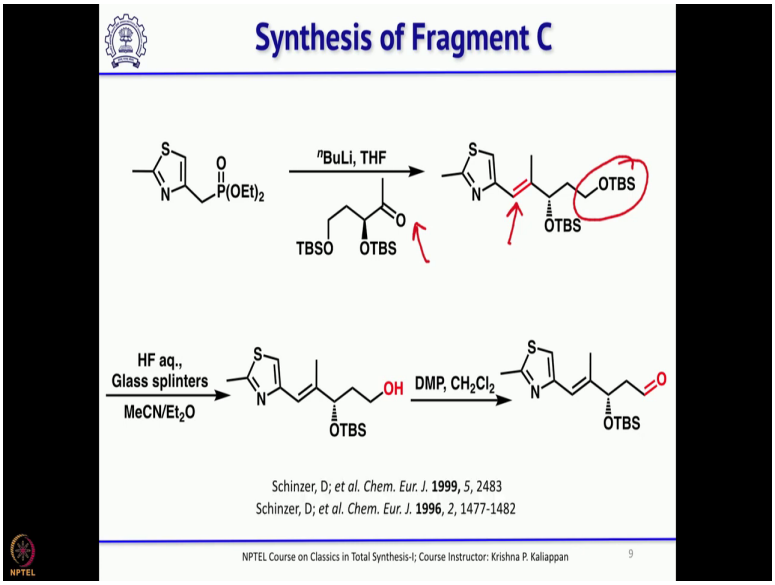

So, that was done using stabilized Wittig reaction. Now, this phosphonate ester derived from the corresponding bromide was treated with butyl lithium as well as quenched with this ketone to get this double bond ok. So, now, you need to remove the TBS group selectively oxidize and then convert it into double bond for the ring closing metathesis ok. So, selectively the primary TBS was removed, Dess-Martin periodine oxidation gave the aldehyde, that aldehyde upon Wittig reaction gave the double bond ok.

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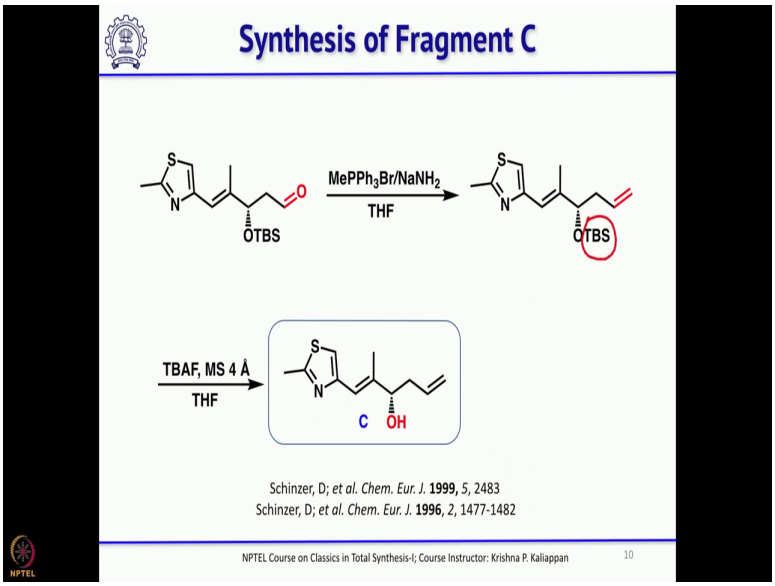

So, then you do not need the protecting group here, that is that alcohol is required for the esterification. So, removal of the TBS gave fragment C. So, you could make fragment A, fragment B, fragment C. Now, let us see how we combined all the three fragments and then completed the total synthesis of epothilone.

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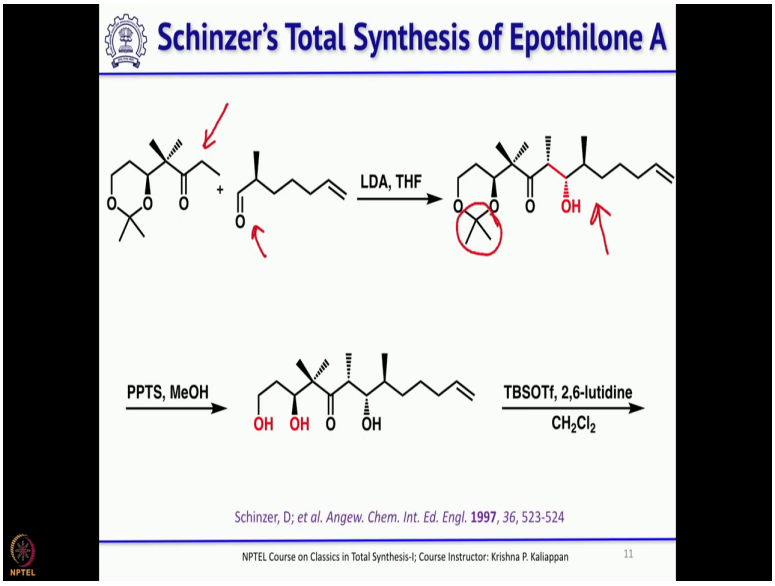

So, first we started with the ketone that is the ethyl ketone, generate anion and then quench with this aldehyde ok. So, 1.1 equivalent of LDA generates the enolate quench

with aldehyde. So, you get the aldol product, remove the astronite so, you get now the trial ok, take the trial and then treat with TBS triplet ok.

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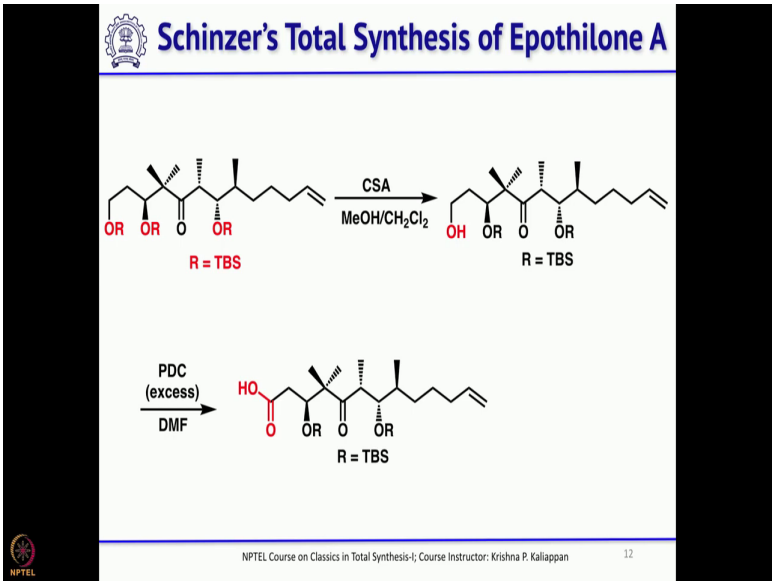

Now, all the hydroxyl groups, one primary, two secondary hydroxyl groups were protected as tri TBS ether ok. Then, the primary one can be selectively removed by treating with camphor sulfonic acid. So, now, the primary TBS is removed, you have the primary alcohol; as you know the primary alcohol should be converted into carboxylic acid to make the ester. So, that was done with excess PDC in DMF.

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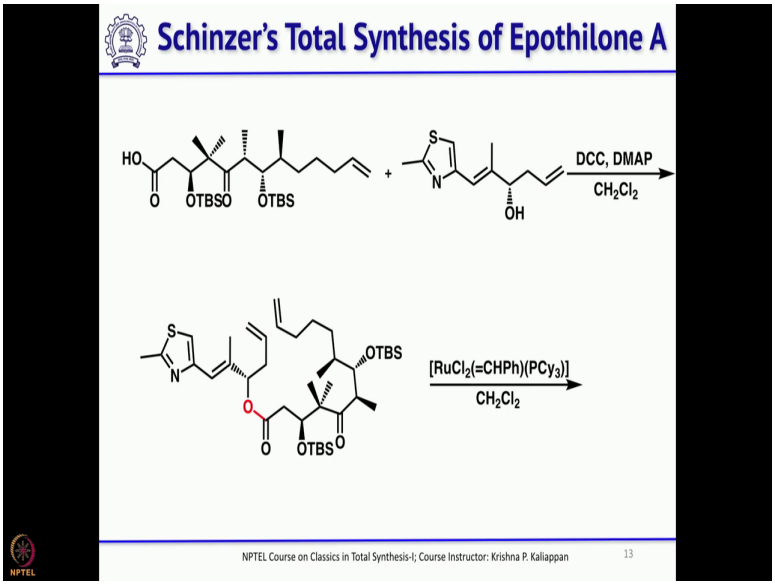

So, once you have the carboxylic acid, already the homo allylic alcohol was already prepared. So, couple this with DCC, you get the precursor for ring closing metathesis. So, then the ring closing metathesis with Grubb's first generation catalyst gave a mixture of *cis* and *trans* alkene ok.

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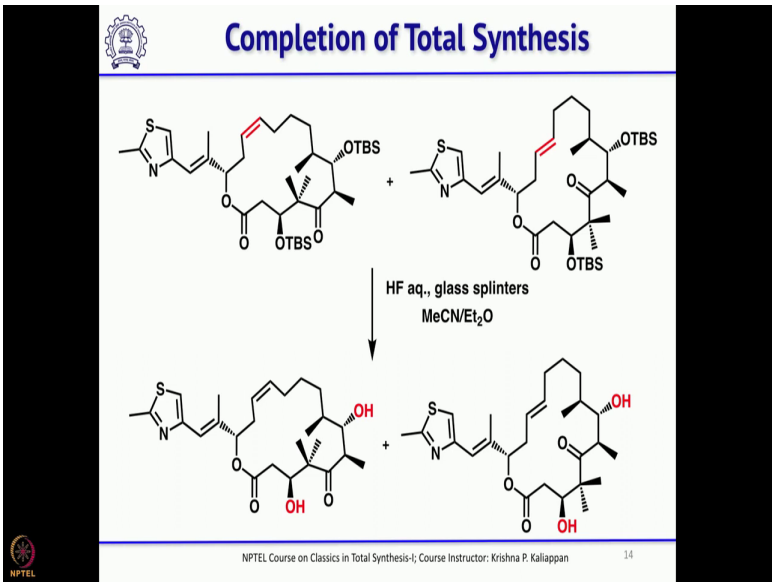

He took the mixture and then went ahead removed the TBS groups ok to get the precursor for epothilone A.

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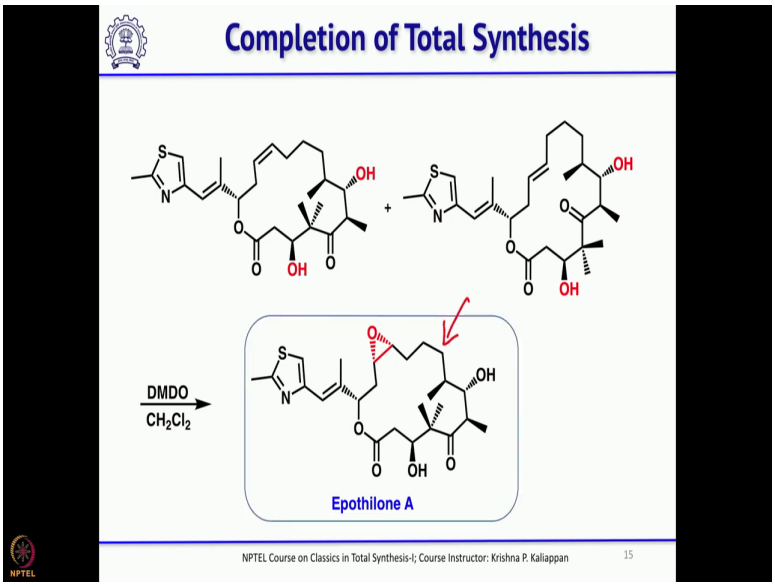

Treatment of these two alkenes cis and trans gave a mixture of epothilone A and the other isomer. And the epothilone A is the major isomer that is how he completed the total synthesis of epothilone A.

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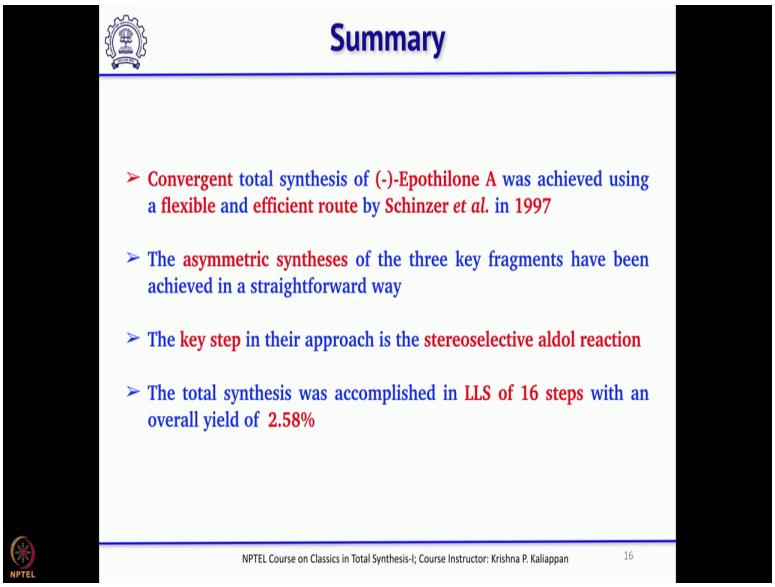

And, as you know the key reactions involved in this synthesis or aldol reaction esterification and ring closing metathesis. Overall, he took about 16 longest linear steps and yield was close to 3%.

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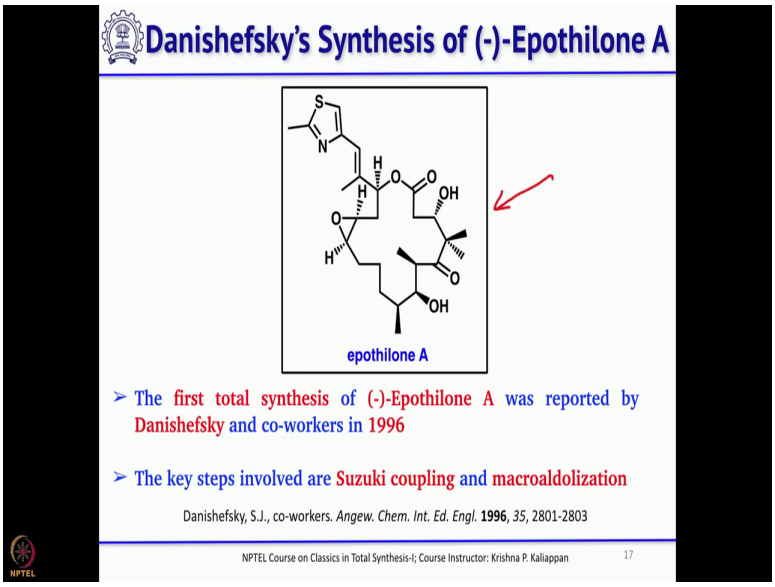

The fourth synthesis of epothilone which we discussed today was reported by Danishefsky's group ok. So, here I have written the molecule in a different way. So, do not get confused, sometimes any complex molecule can be written in so many ways, but people write the structure according to their convenience and then according to their retro synthetic analysis ok.

Now, let us see how he has synthesized epothilone A and what are the key reactions he has used. Danishefsky group used two key reactions which is completely different than the three synthesis which we already discussed. He used a Suzuki coupling ok and macroaldolization. So, that is the last step. He used aldol reaction that is a macro aldol reaction as the last step to form the macro actones. Let us see how he has done.

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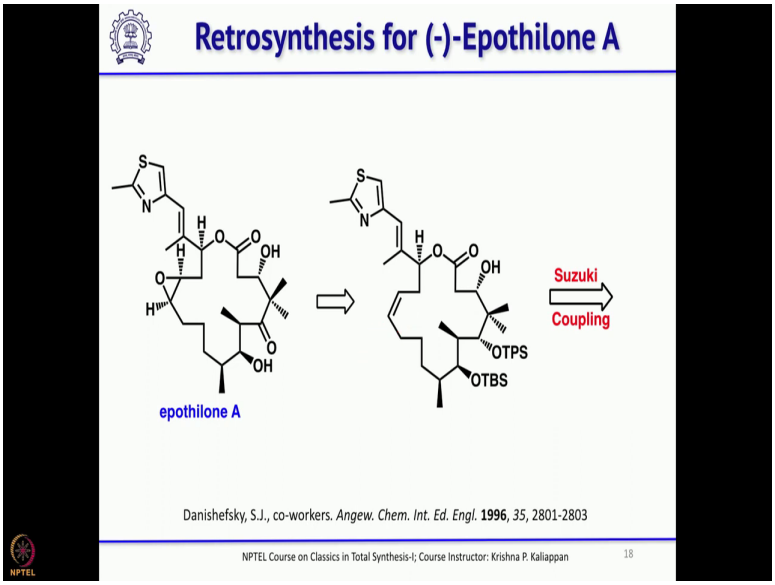

The first retro synthesis is; obviously, the epochs information; that means, the double bond is the precursor for epothilone A. Then, what he thought was he can use a Suzuki coupling. So that means, this side you have boron and this side you have iodine, then you can carry out a Suzuki coupling.

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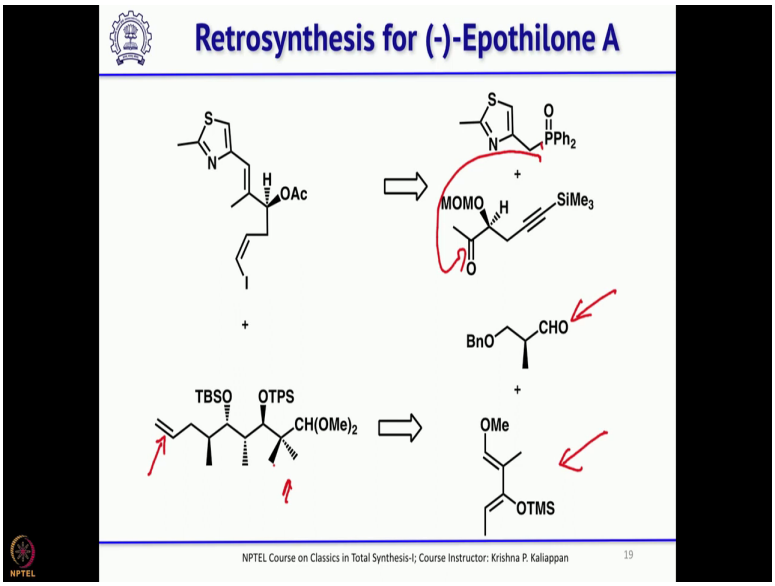

So; that means, he divided that molecule into three or four fragments. So, now if you look at these two fragments, now if you look at these two fragments; this double bond upon hydroboration will give the precursor for Suzuki coupling ok that can undergo Suzuki coupling with cis iodide final iodide. On the other side, you can see these two can undergo Wittig reaction to get the double bond ok.

And, this molecule, this particular molecule in principle can be obtained between this substituted Danishefsky's dying and this aldehyde using hetero Diels-Alder reaction. So, overall if you look at the synthesis of epothilone A reported by Danishefsky, hetero Diels-Alder reaction, Suzuki coupling and aldol reaction; these are the key reactions he has used to complete the total synthesis of epothilone. Now, let us see how he made fragment A.

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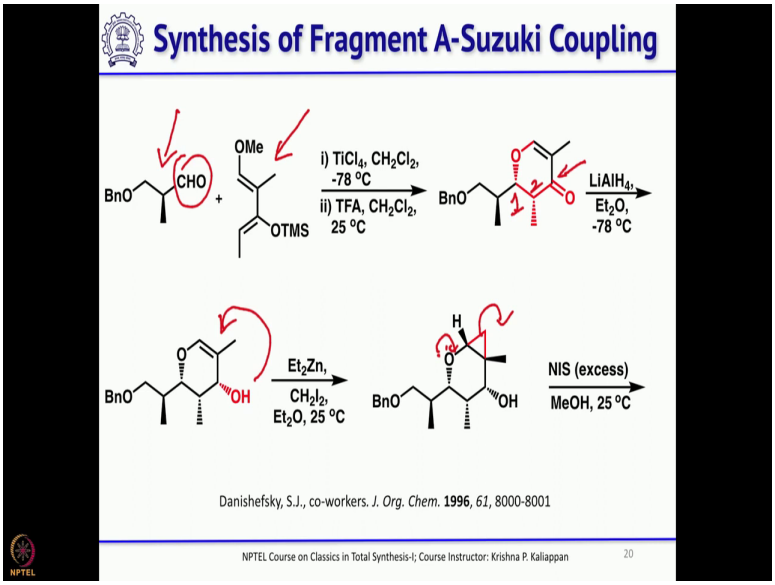

The fragment A, this molecule was prepared from Rochester, we already discussed about Rochester when we talked about total synthesis of disco dermolide by Schreiber's group ok. Now, he did a hetero Diels-Alder reaction between his dien and this aldehyde. So, that upon hydrolysis gave this six membered enone ok.

So, in this process what he has achieved is two new chiral centers, two new chiral centers are established using this intramolecular hetero Diels-Alder reaction ok. Now, the third chiral center, he could introduce by reduction of this enone with lithium aluminum hydride ok. Now, using this chiral center, he carried out a cyclopropanation.

The hydroxyl group played as a handle to deliver the $-CH_2$ group from the same side ok. The alpha cyclopropanation was carried out using charts protocol. Now, the cyclopropanes can be opened. How? If you use N-iodosuccinimide then this can break and that will lead to oxonium ion and $-CH_2I$. The 6 membered ring will become oxonium ion and at third position you will get $-CH_2I$ ok.

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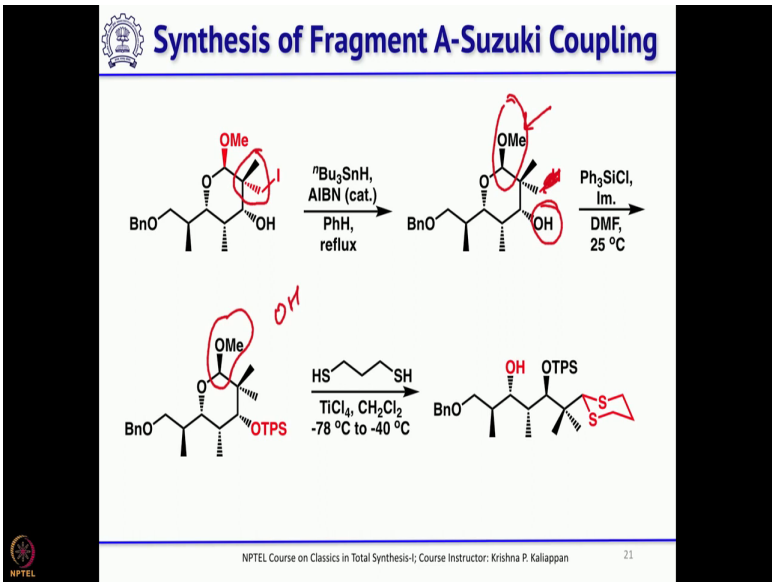

So, that is what he get, that oxonium ion if you use methanol or any other alcohol that alcohol will attack and neutralize a positive charge on the oxygen. So, now you need dimethyl group so; that means, the iodide should be removed. So, that was easily removed using tributyltin hydride. So, you got the methyl group ok. Now, the OMe is a lactal protected lactal ok.

So, before you do something, you have to protect this hydroxyl group. So, that was protected as triphenyl silyl ether ok, that hydroxyl was protected as triphenyl silyl ether then the lactal should be opened. So, the lactal methyl ether, first it has to be hydrolyzed then it has to be protected. But, these two can be done in one step, if you use propane 1-3 diol in the presence of Lewis acid. So, what happened? You form a lactal and the lactal is protected ok.

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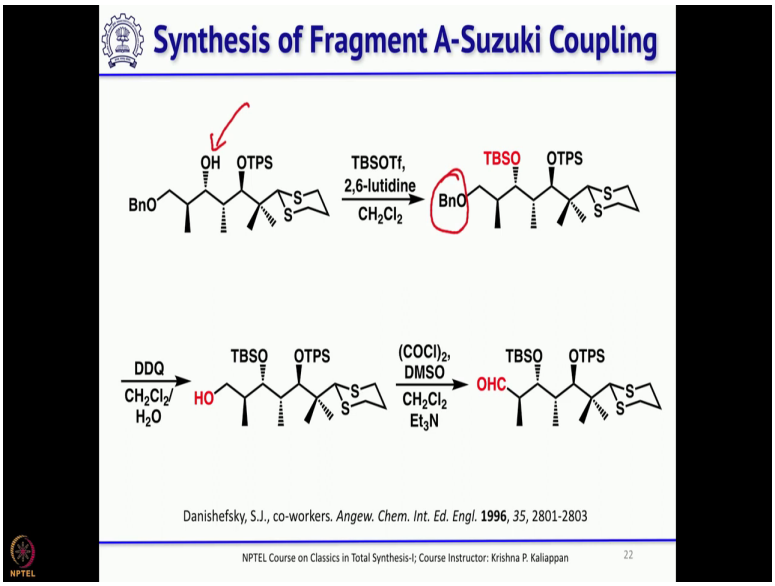

So, once you have that the free hydroxyl group should be protected again and this is protected as TBS ether by treating with TBS triflate. Then, DDQ the selectively the primary benzyl ether can be cleaved using DDQ to get the primary alcohol which upon oxidation under Swern condition gave the aldehyde.

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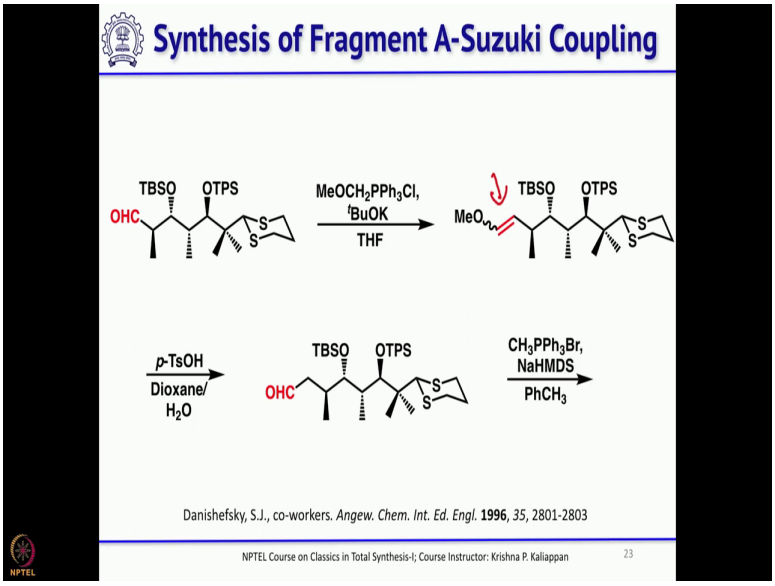

Now, Wittig reaction because you needed to homolog it. So, for homologation he carried out enol ether Wittig reaction to get the corresponding enol ether which upon hydrolysis

gave the corresponding homologated product. This upon Wittig reaction, simple methyl witting you get the double bond ok.

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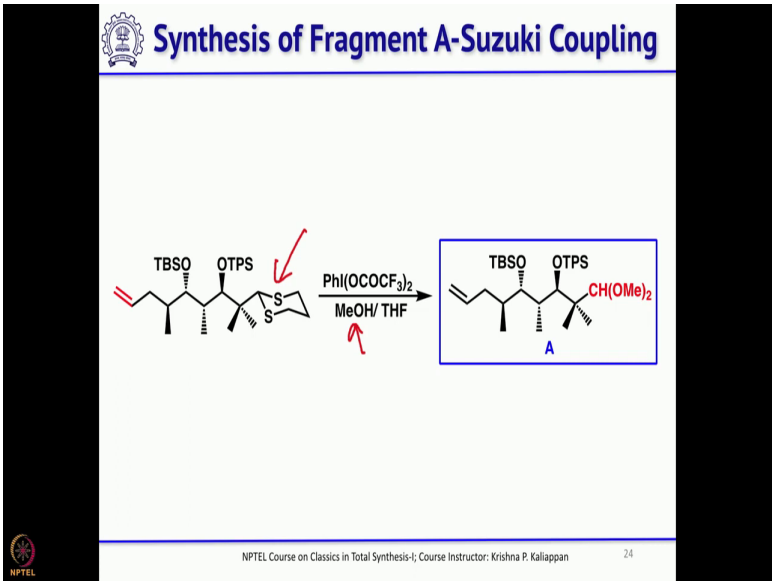

Now, the dithiane could be cleaved using BIAB , that derivative of BIAB and since you use methanol as a solvent, the aldehyde which is formed is in situ protected as acetal ok. So, now the fragment A is ready.

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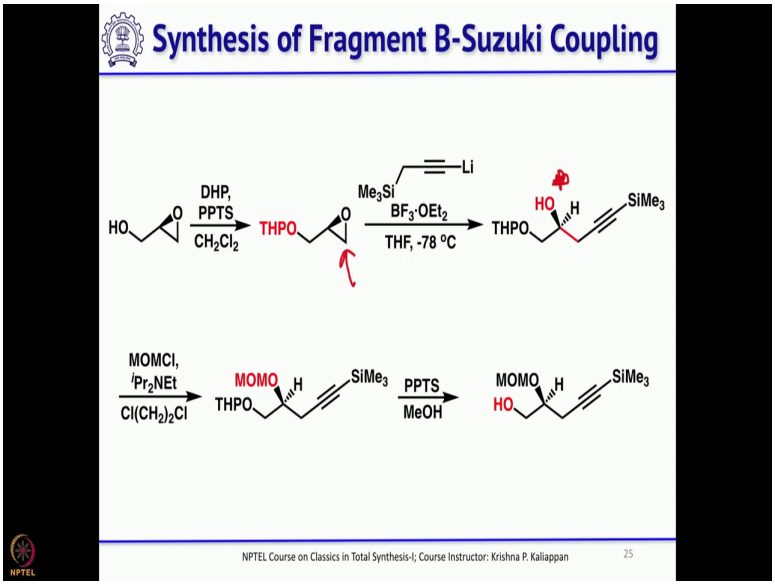

For fragment B, he started with the glycerol ok which is commercially available and protect the primary alcohol as tetrahydropyranyl ether ok. Then, open the epoxide, open

the epoxide with lithiotrimethylsilyl propane ok. So, that opens and then you can see this chiral center is formed ok, that is already you started with the chiral center. And, next you protect the hydroxyl as MOM ether and remove the tetrahydropyranyl group using PPTS methanol ok.

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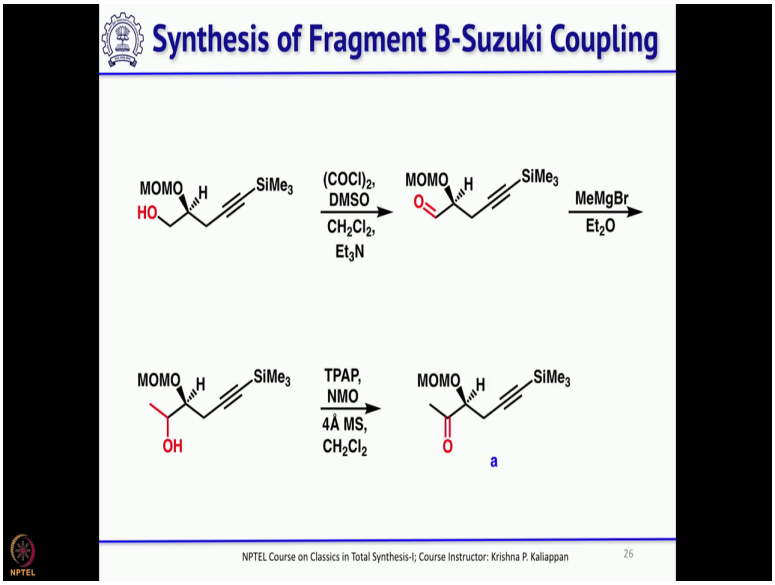

So, once you have that Swern oxidation will oxidize the primary alcohol to aldehyde and treatment with methyl magnesium bromide followed by oxidation with tetra-n-propyl ammonium perruthenate gave the methyl ketone ok.

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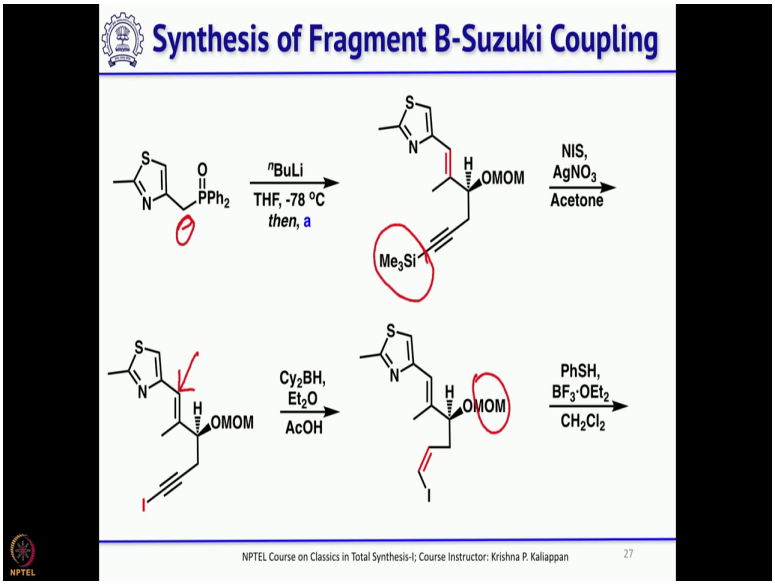

Now, this Wittig reagent upon treatment with butyl lithium you can generate anion and quench with that ketone you get this double bond ok. Now, the TMS group can be removed and iodine can be introduced in one step by treatment with N-iodosuccinimide and silver nitrate ok. And, this upon reduction with we can call it as hydroboration and reduction ok.

So, normally if you have a triple bond and then do hydroboration oxidation, we will get enol. But, if you treat with acetic acid, it will just to reduce the triple bond that is *syn* addition. So, you get the corresponding cis vinyl iodine. Then, the MOM group was cleaved using benzene thiol and $BF_3.Et_2O$ to get the corresponding alcohol.

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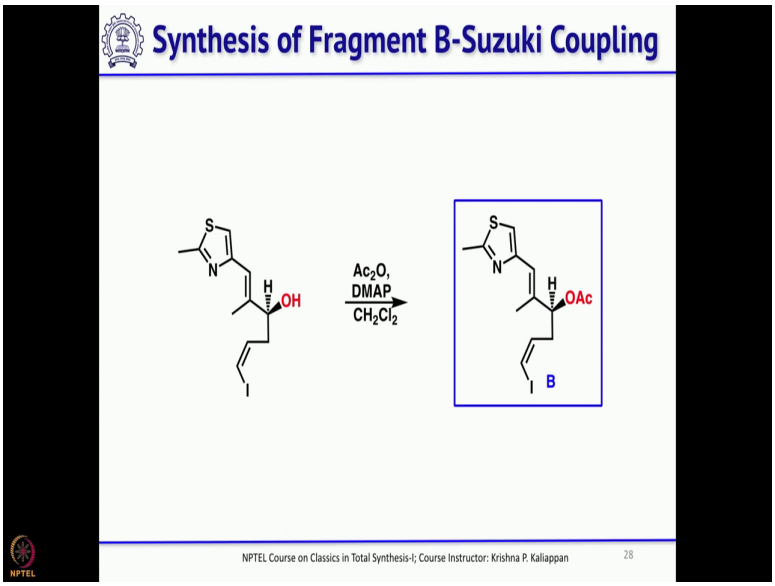

This was protected as acetate by treating with acetic anhydride and DMAP. So, now, the fragment B is ready.

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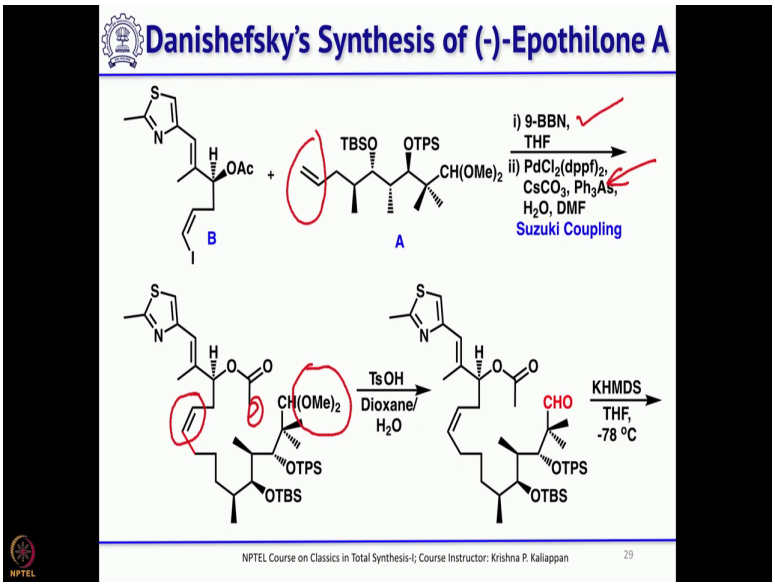

Already, we saw the synthesis of fragment A and now let us see how B and A can be combined. As I said this double bond should be converted into corresponding borane derivative so, that he could carry out Suzuki coupling reaction. So, we took this A and treated with 9 BBN ok. So, then the terminal position you have 9 BBN, then Suzuki coupling with this vinyl iodide. Now, you could see the *cis* double bond is methyl ok.

So, for the last step that is a formation of macro lactone; so, what is required? The protecting group of the aldehyde that is now acetal that should be hydrolyzed to the aldehyde and the intramolecular aldol reaction of the acetate with the aldehyde will give the corresponding aldol. So, *p*-tuluene sulfonic acid removed the acetal to aldehyde, then the key reaction that intramolecular macro aldol reaction was done with potassium hexa methyldisilazide.

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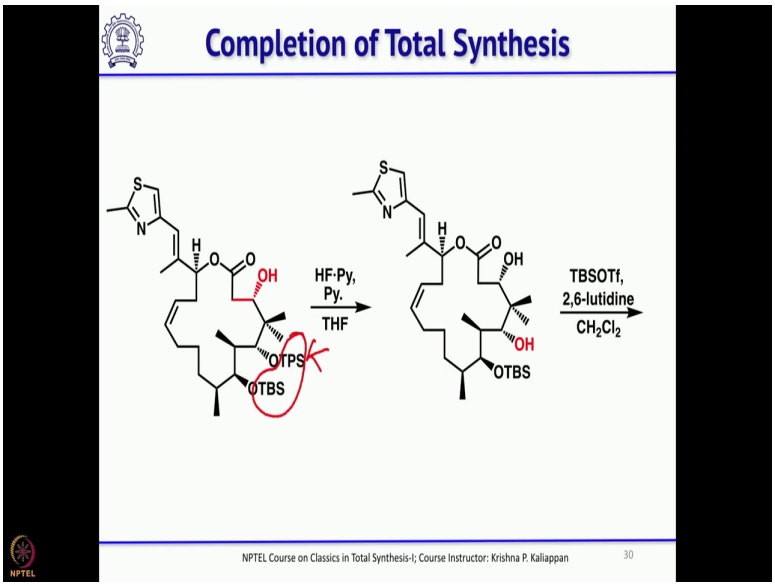

After the aldol, now you have to remove the TBS and TPS group ok. But, if you look at this carefully, this TBS,TPS can be selectively removed ok. So, with HF pyridine in the presence of TBS, TPS that is triphenyl silyl group can be cleaved.

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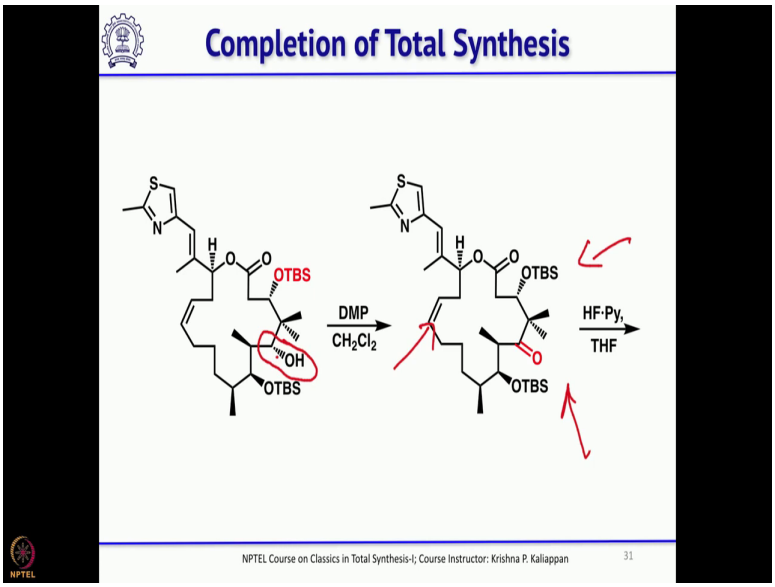

Then protect the other hydroxyl as TBS ether ok, then you oxidize this hydroxyl group. If you look at epothilone, this hydroxyl should be ketone ok. But, if you look at the precursors, all three are hydroxyl groups or protected hydroxyl group. So, now, you need this as ketone.

So, that is why selectively one has to remove the triphenyl silyl group in the presence of TBS and protect the aldol, other side aldol as TBS ether, then oxidize this secondary alcohol to ketone. Now, you have to epoxidize and then remove both TBS group ok. So, that was done first by treating with HF pyridine for a little longer time.

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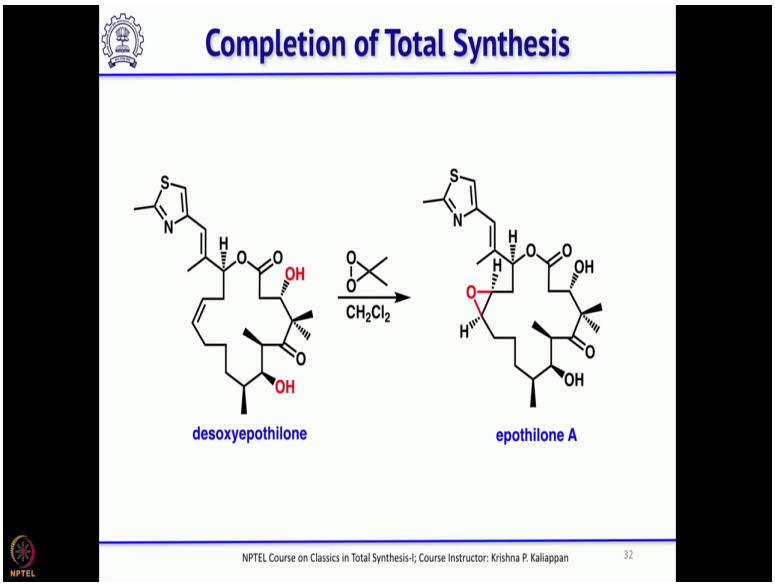

So, both hydroxyl groups are removed, then followed by treatment with dimethyl dioxidane you could get epothilone in good yield

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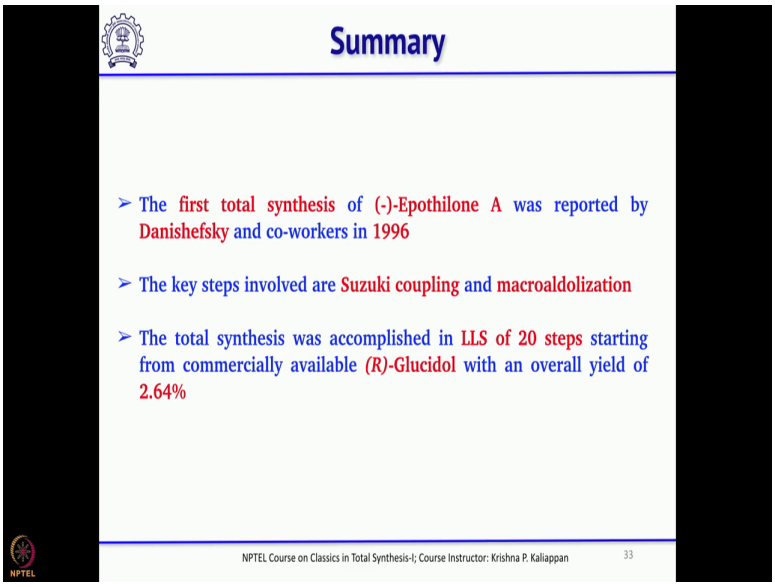

So, overall if you look at this synthesis, the key reactions are Suzuki coupling ok. First is Suzuki coupling, then the macroaldolization so, that is not easy. Actually, macroaldolization is a risk taking reaction for doing such a complex total synthesis. But somehow, he succeeded the macroaldolization to complete the total synthesis of epothilone A. Overall, it took about 20 steps starting from *R*-glucidol and yield was close to 2.6% ok.

So, now, we will move to two more natural products and then complete the syllabus tomorrow or day after tomorrow ok.