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

Lecture - 47
Taxol (Holton)

Yeah, good morning and welcome to NPTEL lecture series on Classics in Total Synthesis- Part 1.

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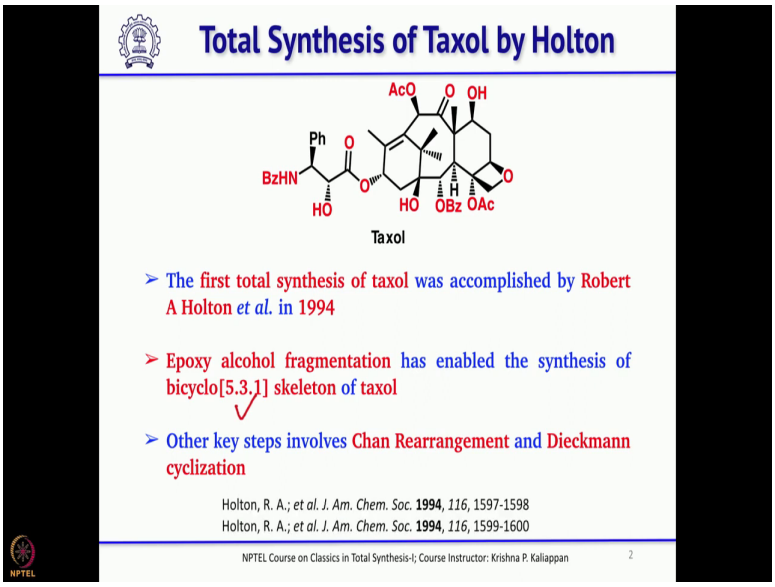

And today we will continue our discussion on Total Synthesis of taxol, in the last lecture we talked about totals synthesis of taxol by K C Nicolaus group and today we will talk about the taxol by Holton. In fact, Holton claims that he was the first one to report the total synthesis and let us see how he and his group achieved the total synthesis of taxol.

And it was reported in 1994 and the key reaction according to Holton is the fragmentation of an epoxy alcohol derived from another natural product to get the key 5-3-1 skeleton the key 5-3-1 skeleton he got it through a fragmentation of an epoxide which I will discuss in the next slide ok. And of course, there are other key reaction one more key reaction is a Chan rearrangement which also I will discuss briefly and then Dieckmann cyclization which you all know what is Dieckmann cyclization ok.

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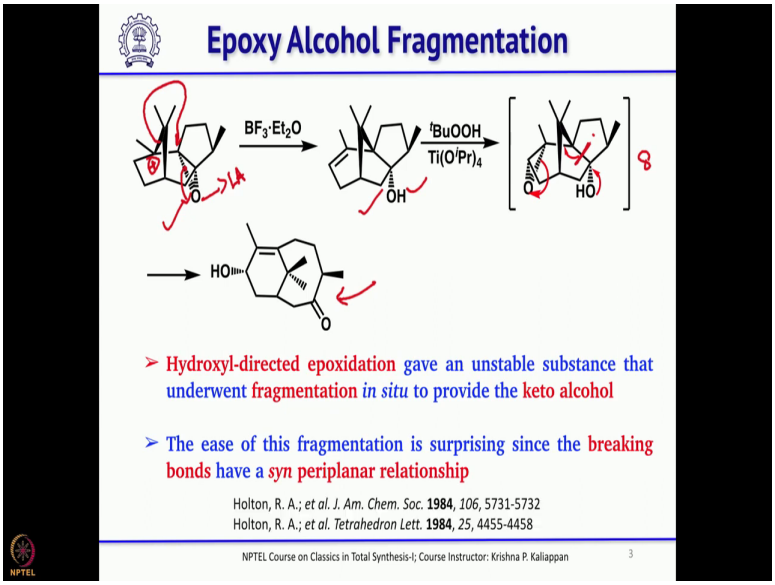

The epoxy alcohol fragmentation, which was really a very very clever reaction to be utilized by Holton in the total synthesis of taxol. So, he started with an epoxide which is commercially available called patchouno or patchoulene epoxide this his idea is when you treat this epoxide with BF_3 etherate. So, BF_3 etherate you know it can coordinate this oxygen coordinate with Lewis acid.

Then that epoxide will break then this bond will migrate this bond will migrate which is anti to that anti to the leaving group that epoxide, now you will get a positive charge here you will get a positive charge here then a loss of proton will give you this compound ok. So, this is the very very important fragmentation reaction, because is total synthesis involved two epoxy alcohol fragmentation, one is this subsequently what he does using this hydroxyl group he epoxidizes the double bond from the same side ok.

So, now, when he makes the epoxide automatically the epoxide this epoxy alcohol undergoes fragmentation to give this bicyclo [5,3,1] system. So, this is the A and B ring of taxol this is the A and B ring of taxol I will leave it for a few seconds, so that you will be able to understand after this hydroxyl group breaks this bond is broken ok, that is how it becomes 8- membered ring 5 and 5 5 and 5 becomes 8-membered ring ok that leads to the B ring of taxol ok.

Now, let us see the retro synthesis, how overall for the total synthesis of taxol using this particular rearrangement as a key reaction how Holton has cleverly made a retro synthesis ok.

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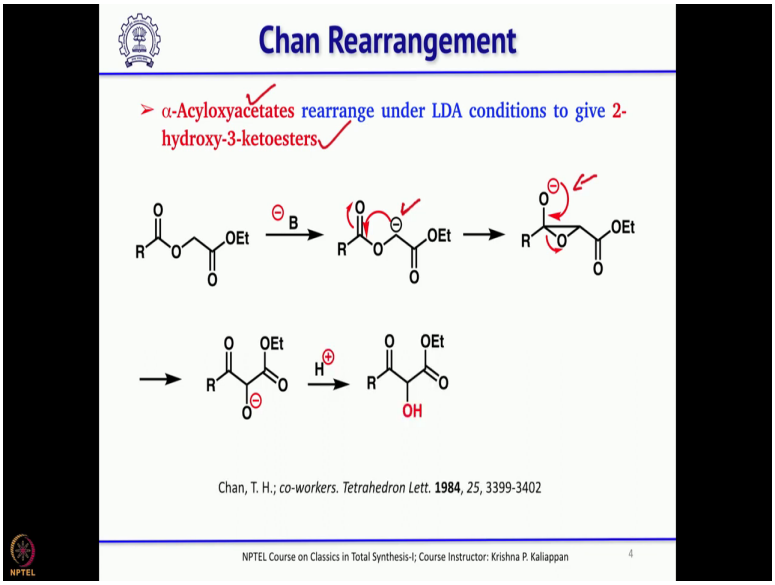

And as I said he also used another rearrangement called Chan rearrangement to obtain 2 keto 2 hydroxy 3 ketoester to obtain 2 hydroxy 3 ketoesters from α-acyloxyacetates. See, what happens when you have α-acyloxyacetates ok α-acyloxyacetates these are treatment with base ok, it can generate an anion and immediately it will attack the carbonyl group.

So, it forms an epoxide now the O^- will come the O^- when it comes the 3 membered epoxide will open ok. So, that will give you α hydroxy ketoesters ok. So, this is another key reaction which is used cleverly in the synthesis of taxol.

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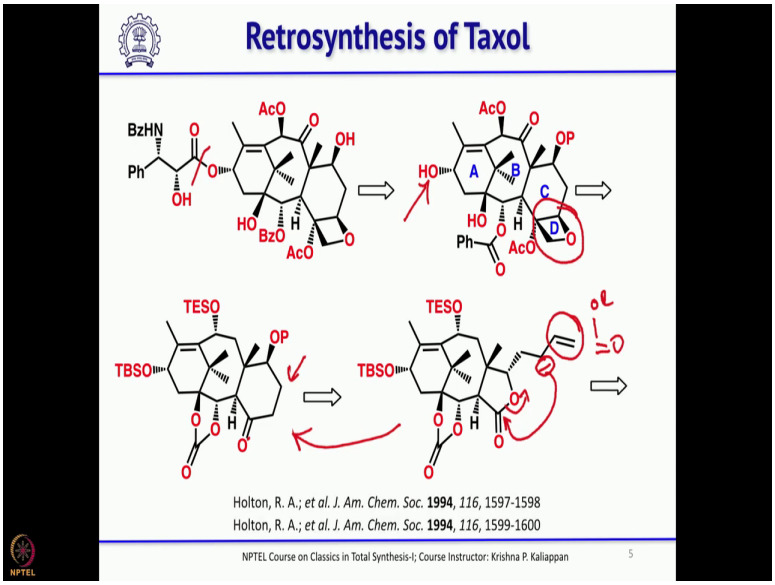

So, from retro synthetic point of view the first and easiest way to disconnect is to remove the ester ok. So, if you have the hydroxyl group always one can attach the side chain ester ok. That is a normal and easiest retro synthetic disconnection. The next disconnection which he has done was if you have a ketone here if you have a ketone here then this 4 - membered ring can be easily attached ok. So, the first step should be to make this 6-membered ring, once you have the 6-membered ring the oxygen ring can be easily attached. Now, how this 6-membered ring can be used.

So, this is where we used a Dieckmann condensation. So, Dieckmann condensation if you look at this double bond if the double bond is for example, cleaved and then converted into ester cleaved and converted into ester. Then one can generate anion here one can generate anion here and attack intra molecularly and if you open this what you will get is this compound, isn't it. The double bond should be converted into ester followed by treatment with base it will intra molecularly undergo Dieckmann cyclization to give cyclohexene. So, that was his plan.

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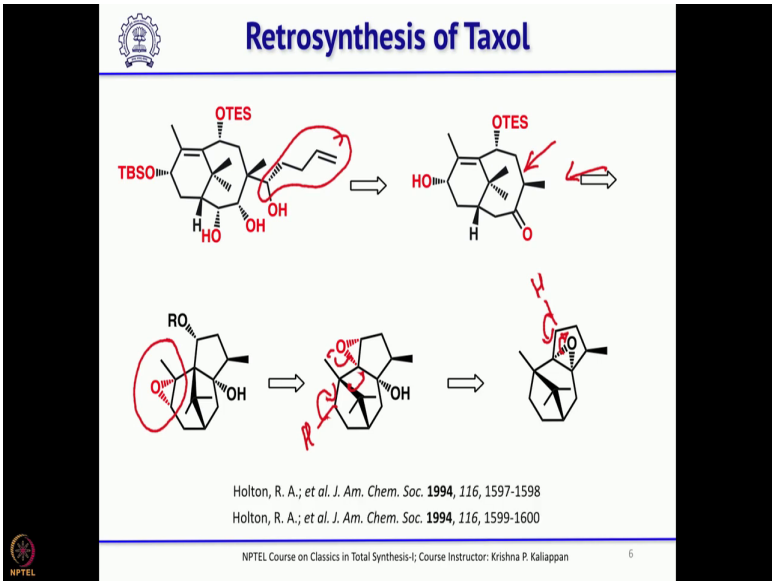

And this compound can be obtained by aldol reaction ok. If you have a ketone then you can generate anion the that enolate can add to; can add to the whole aldehyde ok. Now, if you look at this, this remains you of the rearranged product that is epoxy alcohol fragmented product. So; that means, this could be obtained from this epoxide this substituted epoxide ok.

Now, if you look at this, this can be obtained from the rearranged product again another rearrangement ok. So, now, this epoxide opens this bond migrates and this hydrogen is eliminated you get a double bond and that double bond is epoxidized ok. So, this epoxide can be obtained from another epoxide ok. Again what will happen when you treat with the strong base, this will open up and you will get an allylic alcohol, then the allylic alcohol the double bond can be epoxidize ok. So, this was a simple retro synthesis which he thought based on the epoxy alcohol fragmentation.

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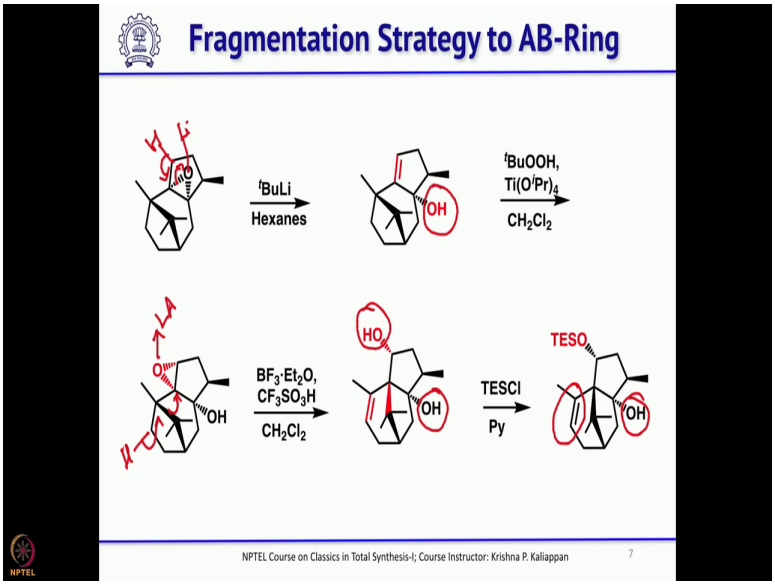

So, he started with the commercially available natural product, it was a natural product available in large quantity called patchoulene oxide and this patchoulene oxide on treatment with butyllithium. As I said when you have an oxygen particularly epoxide and then treat with LDA or strong base you know then it can open the epoxide to give the corresponding allylic ok. The epoxides can be open with LDA to give corresponding allylic alcohol ok.

This has been successfully used in many synthesis the epoxides are converted into allylic alcohol sometimes desymmetrization also has been done to give corresponding chiral allylic alcohols. So, once you have this then when you epoxidize the α hydroxyl group will direct the epoxide from the same side ok. So, you we get α epoxide. So, first you open the epoxide, now the epoxide will open at the same time rearrangement also will take place. So, if you treat with BF_3 etherate with along with trifluoro methane sulfonic acid as I said first it will coordinate with Lewis acid.

Then this bond will migrate and followed by loss of proton you will get the corresponding alkene at the same time the epoxide is open ok. Is it easy to visualize? Ok. So, once you have this alcohol now you have a secondary alcohol and tertiary alcohol. So, the secondary alcohol can be easily protected. So, this was protected as TES ether by treating with TES chloride and pyridine and the next step as we have seen in the retrosynthesis is to epoxidize this double bond ok.

And since you have a hydroxyl group which is in α position automatically that will direct the epoxidation so, you will get the corresponding α epoxide.

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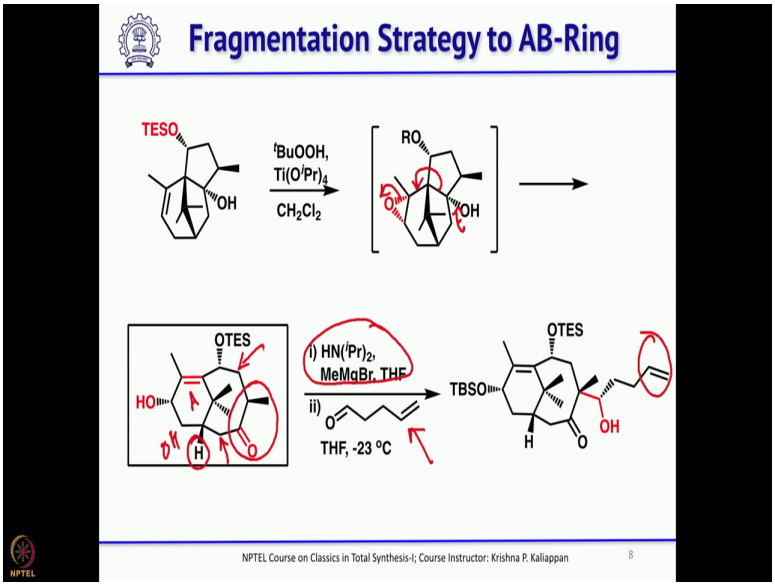

But this reaction is so clean it does not stop there ok, as expected this undergoes the rearrangement ok and opens the epoxide to get the bicyclo [5,3,1] system ok. The same part that is as soon as the epoxide is formed it undergoes opening of the epoxide to give bicyclo [5,3,1] system. So, that is a AB-Ring, now if you look at this carefully the A ring, A ring has all the functional group except at the bridge head position you should have -OH.

Now what you have is, H and B ring you need another oxygen functional group and here also you need another oxygen functional group ok. Let us see how he moves forward and then completes the total synthesis. So, instead of LDA ok he took a MDA that is magnesium diisopropylamide that is to generate enolate here ok and then quench with this pentinol ok.

So, that will give you the precursor that will give you the precursor which is required for making the C ring, C ring as you know it is a cyclohexane ring and later you plan for intramolecular Dieckmann cyclisation to get the 6- membered ring.

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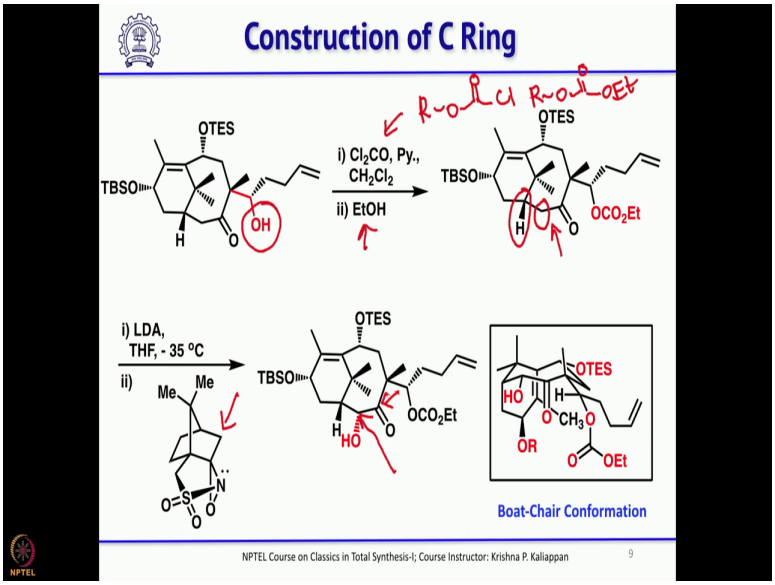

So, now the double bond is introduced, next step is to protect the hydroxyl group, first it was treated the hydroxyl group was treated with phosgene ok. So, phosgene what will happen that R group will become R-O-C=OCl ok. Then when you treat with ethanol what will what will happen it will become R-O-C=O then -OEt ok. So, that is what you get it is called ofester ok first you get ofester, then the chloride is replaced by ethanol to get O-CO_2Et. Once you protected the hydroxyl group now as I said you needed to have a hydroxyl group here and also you need to have a hydroxyl group.

So, if you treat with LDA the enolate will be generated here then quench with this oxaziridine ok. This is a chiral oxaziridine derived from camphor sulfonic acid ok, this is called Davis oxaziridine ok it is used to introduce a hydroxyl group stereo selectively and introduce chirality. So, selectively one can introduce a hydroxyl group which is required at this carbon. Now, if you look at this confirmation again I leave the structure for a minute, you will see that this has a boat chair conformation that 8- membered ring has a boat chair conformation ok.

I leave it like this because it takes some time to understand how this was drawn and when you look at this compound carefully now any attack on this carbonyl group any attack on the carbonyl group should take place from the front side; that means, that should give α hydroxyl group ok. So, this boat chair conformation was cleverly used for further steps.

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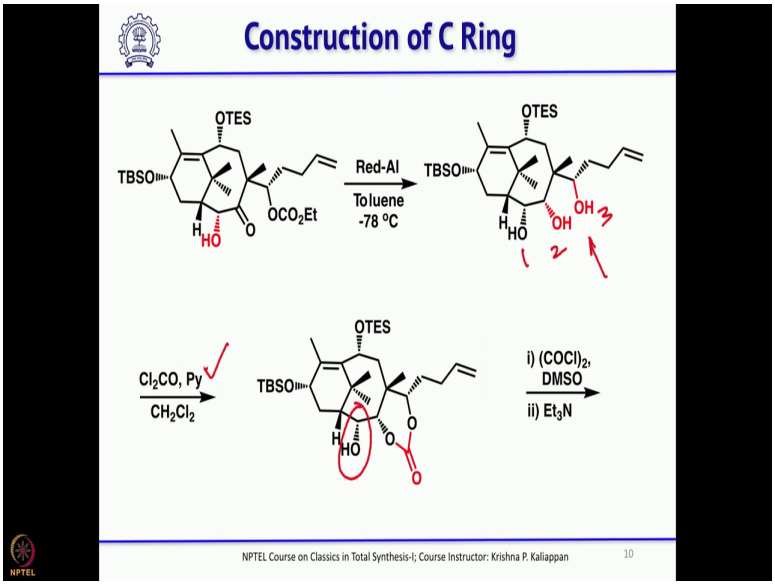

So, now you treat with the Red- Al as I said the hydride will come from the front side. So, you will get α alcohol you have 3 secondary alcohol 1,2,3 and when you treat with phosgene. So, when you treat with phosgene it can form cyclic carbonate. So, it can form with 1,2 diol or it can form between 2 and 3 ok there are two possibilities, but what he got was 6-membered cyclic carbonate. It formed a 6-membered cyclic carbonate then you can easily oxidize the other secondary alcohol under Swern condition ok.

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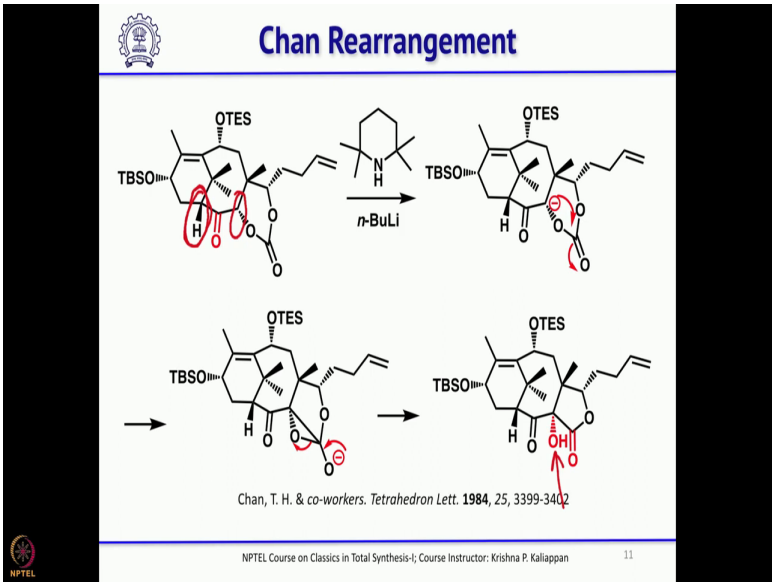

Once you have the ketone now you treat with tetramethylpiperidine ok tetramethylpiperidine and butyl lithium, there are two possibilities one it can generate anion here or it can generate anion here ok. So, it generates anion here then it undergoes

Chan rearrangement then it undergoes Chan rearrangement which I already explained what is Chan rearrangement.

So, after the Chan rearrangement what you have got is a hydroxyl group ok, hydroxy ester is the one which you get is a hydroxy keto ester is the one which you get and that is what you got here. So, now, the hydroxyl group, is it required? No, you do not require. So, how do you remove the hydroxyl group? You can easily remove the hydroxyl group with samarium iodide ok.

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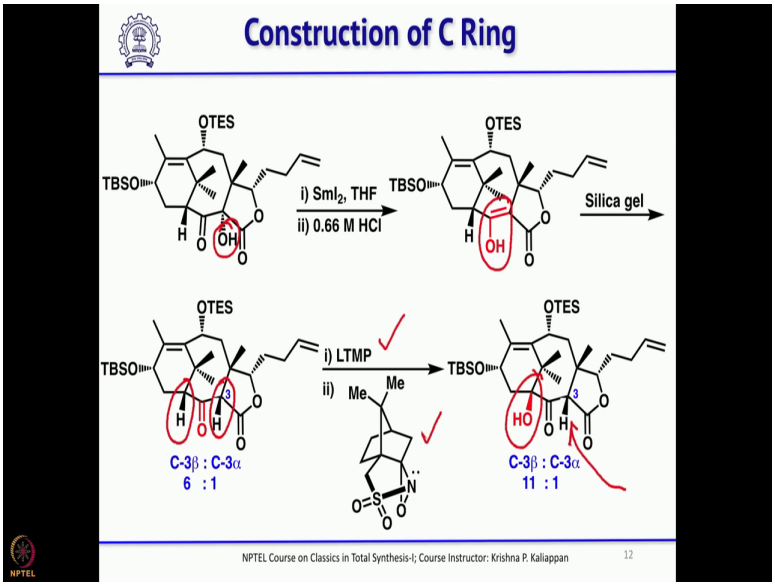

Samarium iodide one electron donor so that way you can easily remove halo or hydroxyl group which is next to carbonyl group and then you can ask why it is enol, once the hydroxyl group is removed then it will be in keto enol form which seems to be more stable ok. Now, you treat with silica gel, so that now you can get back your ketone and when you do that this particular carbon the hydrogen can be β or α.

But you get a mixture you get β which is the unwanted one for taxol you needed α hydrogen, but what you get is β as the major product, nevertheless with that again he treated that β ketoester with lithium tetramethylpiperidide and followed by treatment with Davis oxaziridine. So, the idea is to introduce a hydroxyl group. So, it was easy you can introduce the hydroxyl group still what happened during the process the 3 β is becoming more ok.

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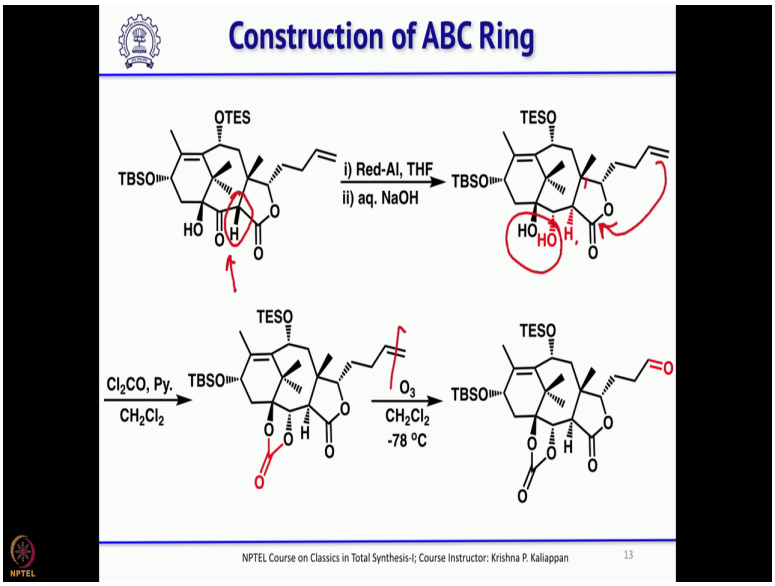

So, no problem so, one can easily solve that. So, now, if you reduce the ketone ok, if you reduce the ketone as I mentioned it is in boat chair conformation so; that means, when you add any reagent to this ketone it will come from the front side ok; that means, you will get α alcohol. So, the Red- Al you get α alcohol then what you do? You do a base treatment basic work up. So, the basic work up actually is used for epimerization.

So, this way now they could get that *trans* stereo centers ok. Now, what you have to do? Somehow, you have to connect this to get a 6- membered ring. So, before that you needed to protect this diol. So, that is easily done by treating with phosgene to get the cyclic carbonate then followed by ozonolysis of the double bond you get the aldehyde as I said that double bonds should be converted into ester.

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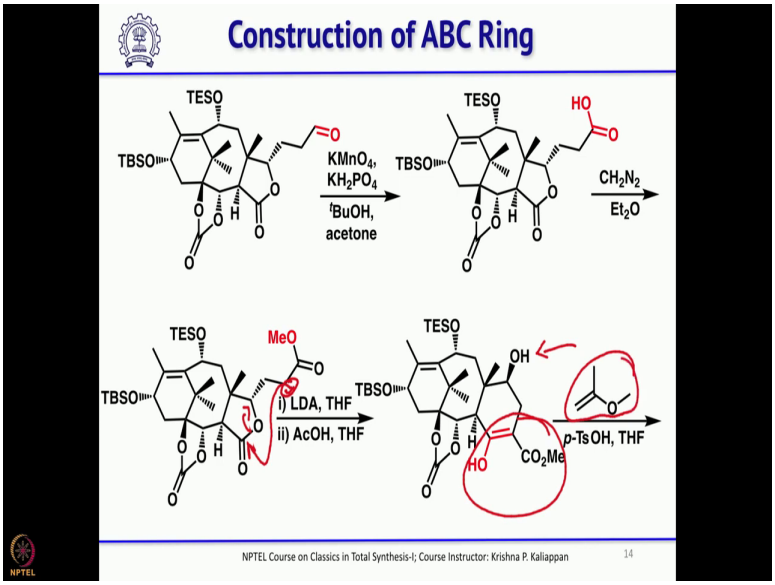

So, that was done in two steps first oxidize the aldehyde to carboxylic acid then treat with diazomethane you get the corresponding ester. Then the intramolecular Dieckmann cyclisation takes place by treating with LDA, LDA generates anion that attacks this lactone and opens up and that is what you get ok. So, what you have to do, you have to protect this hydroxyl group and the whole thing should be converted into oxetane ring. So, what he did next, he protected the hydroxyl group as with this is not ethyl vinyl ether, but a vinyl ether substituted vinyl ether.

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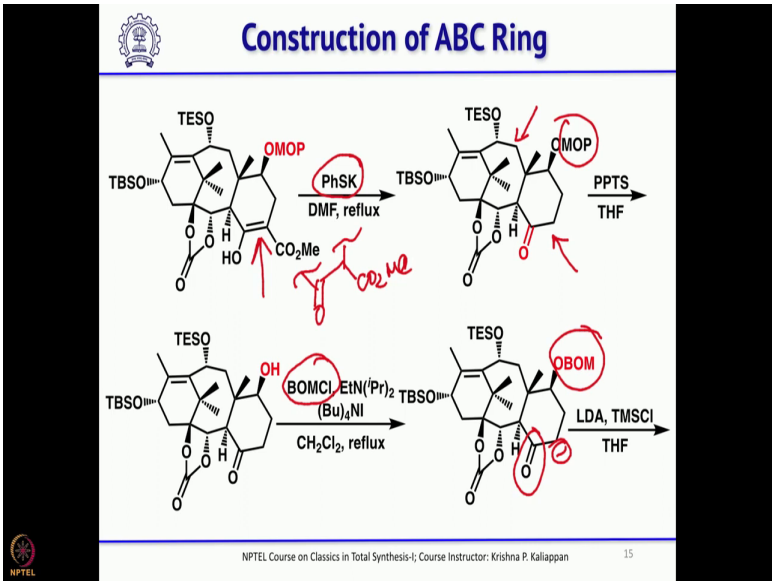

So, when you do that you can protect that alcohol as OMOP ok methoxy propyl ether. Then this is a β keto ester this is a β keto ester you can you can write like this, it is a β

ketoester as you know β keto esters can be easily cleaved under various conditions the tosyl group can be easily removed. And one of them is potassium thiophenolate the potassium thiophenolate is known to remove the ester. So, you get a keto ok.

Now, if you carefully look at this particular intermediate what you need is a functional group here and then what you need is oxetane ring ok. Then you treat with PPTS because the MOP group should be converted into some other protecting group to make it a better protecting group. So, that was done with BOM chloride benzyloxymethyl chloride and that was protected as BOM then you convert this ketone into oxetane, for that first treat to the LDA.

So, when you treat with the LDA you can generate anion it will form the enolate and quench with TMS chloride you get corresponding in enol TMS ether ok.

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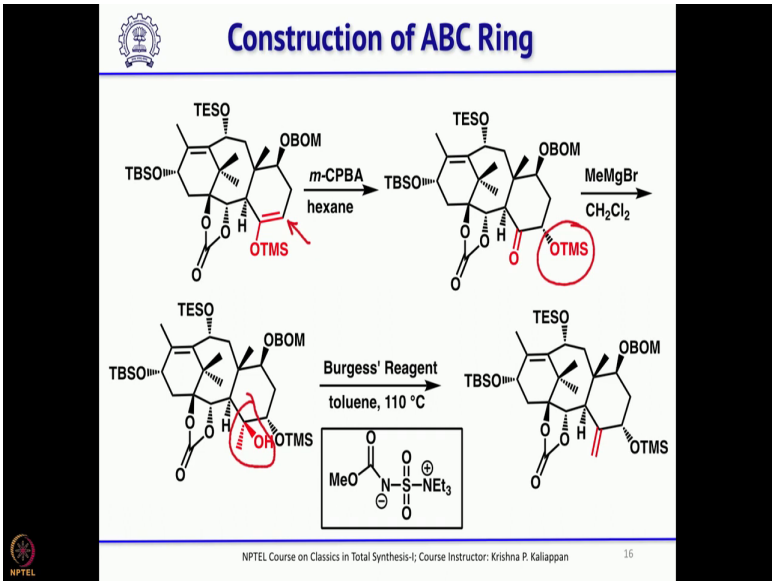

Once you generate enol TMS ether. So, you can functionalize here. So, treat with m-CPBA. So, it opens up and then it form OTMS ok, you have the ketone and if you do Wittig reaction you can get double bond and Wittig reaction was not that facile. So, he treated with methyl magnesium bromide to get corresponding tertiary alcohol. So, once we have the tertiary alcohol then he needs a double bond, the double bond was easily achieved by dehydration using Burgess reagent.

So, the Burgess reagent is nothing but this reagent. So, this is used for making or dehydrating and alcohol to get corresponding double bond. And usually it goes to less substituted double bond.

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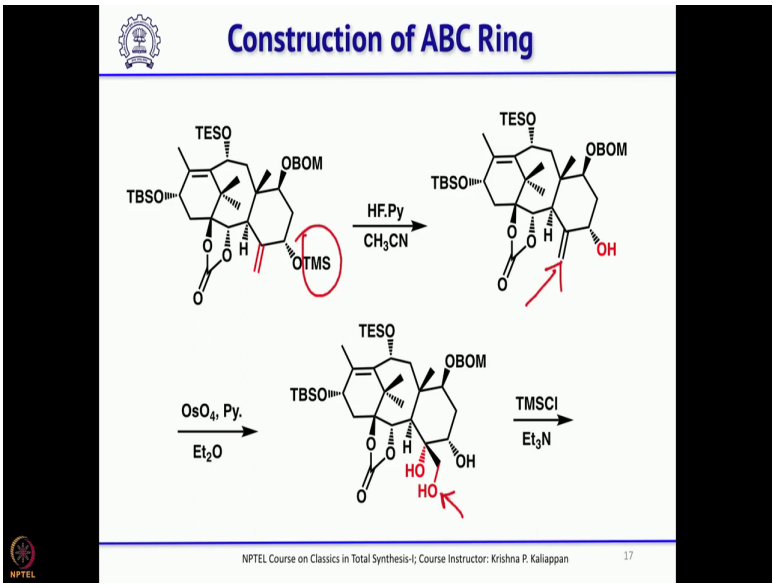

Once you have the double bond what is left? You have to do the oxetane formation and before that you remove the TMS group with HF protein to get the allylic alcohol then osmium tetroxide will give you the trial by dihydroxylation, dihydroxylation on the double bond will give you trial ok. So, now, almost everything is set for the oxide formation and selectively protect the primary alcohol, in situ you protect the primary alcohol as TMS ether.

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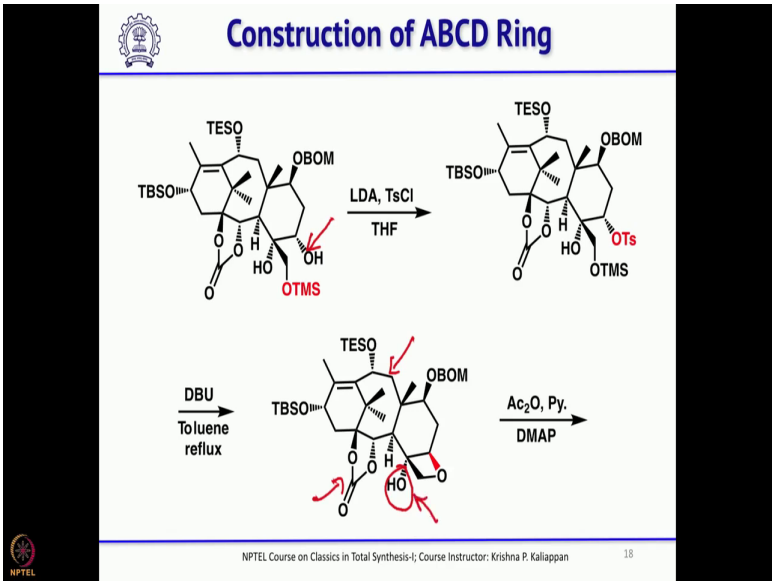

Then make the secondary alcohol as a good leaving room. So, you make it as tosyl group then treat with DBU. So, DBU will give corresponding oxidative. So, now, what needs to be done? You have to protect this hydroxyl group and open this cyclic carbonate and introduce another oxygen functionality here.

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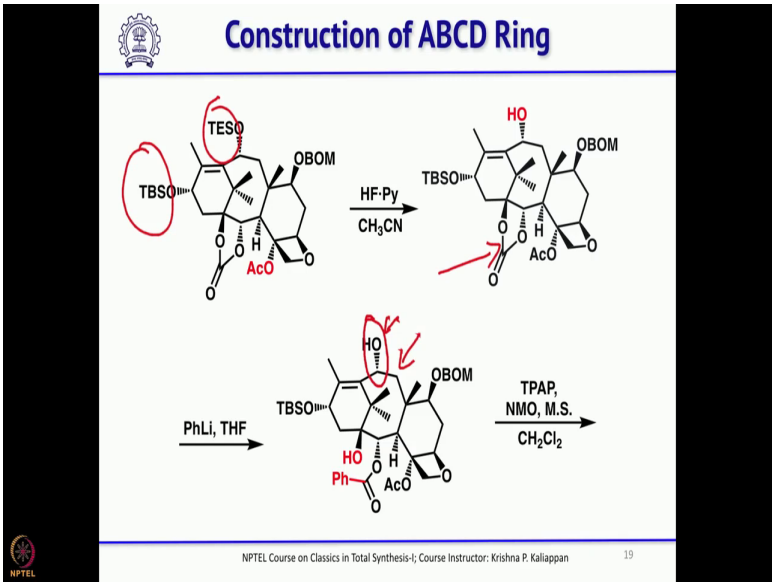

So, acetic aldehyde pyridine first it will a oscillate this hydroxyl group. So, that is taken care then HF pyridine. So, you have bulky TBS and then TES group. So, TES group can be selectively cleaved in the presence of TBS. So, once you have the OH then you also can open this the cyclic carbonate to get the corresponding benzoate and bridgette

hydroxyl group ok. Now, to introduce a functional group here this hydroxyl group should be oxidized.

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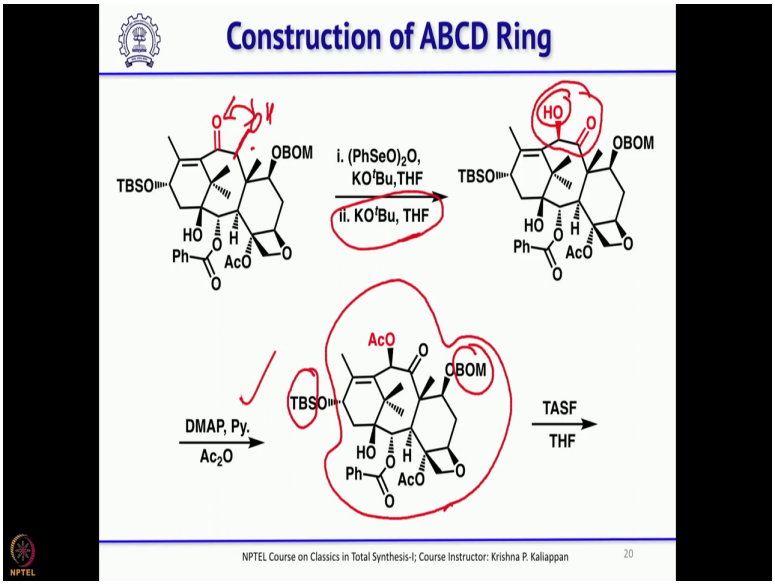

So, that was done easily with TPAP in the presence of co oxide NMO and so, you get the ketone. Once you have the ketone this is a standard method, where a hydroxyl group can be introduced next to the ketone here and followed by isomerization with potassium tert butoxide these two gets exchanged. So, ketone comes here and the hydroxyl group goes there ok that is what you need in taxol isn't it, that is what you need in taxol keto hydroxy ketone.

What is left, now in taxol this is O-Ac is not it, the taxol this is O-Ac. So, you have to treat with DMAP, pyridine acetic anhydride to get the acetoxy group. Later if you look at carefully this structure has all the functional groups present in taxol except the BOM group should be hydrogen and also the TBS group should be cleaved. And then attached to the side chain, the TBS group should be cleaved and attached with the side chain.

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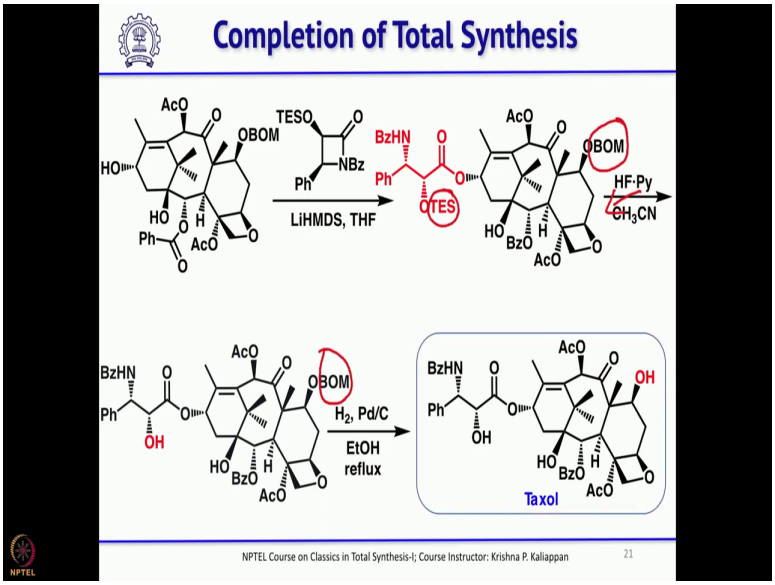

So, fluoride source removes the TBS group then you attach the side chain with Ojima lactam ok, now what needs to be done if you look at this particular products you have to remove the BOM group you have to remove the TES group ok. The TES group can be easily removed with this removed with HF pyridine ok, it is a silyl protecting group. So, HF is known to remove the silyl protecting group, you get the hydroxyl group.

And now hydrogenation ok benzyl oxy methyl chloride hydrogenation can be easily used to cleave the benzyl oxy methyl group benzyl group ok, all that can be done and once you remove that you get directly that taxol ok.

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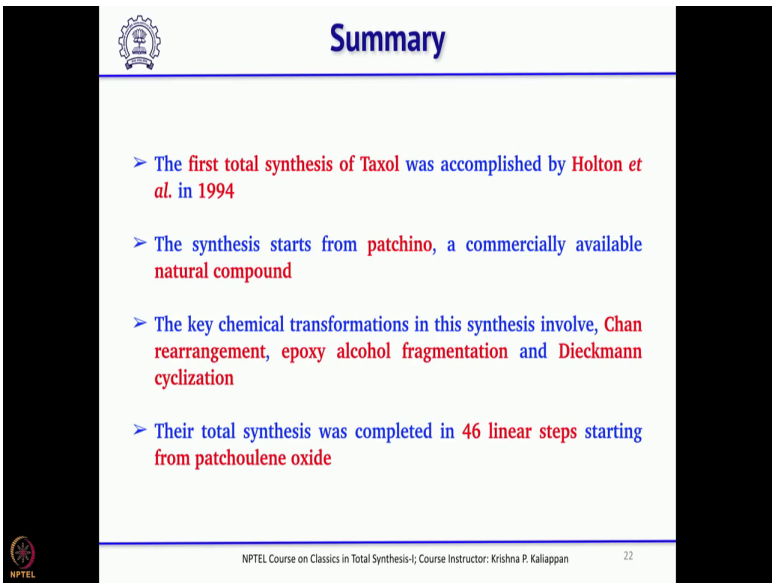

So, the overall if you look at the total synthesis of taxol reported by Holton it involved two epoxide rearrangements ok. He started with patchoulene epoxide and then under several acidic condition the epoxide were rearranged to give the bicyclic intermediate bicyclic [5,3,1] system ok. So, once you have the bicyclo [5,3,1] system then it was a matter of functional group transformation to achieve the total synthesis of taxol ok.

So, overall if you look at this synthesis the key features are one he started with a chiral naturally occurring compound called patchino or patchoulene oxide one. Second he used 2 epoxy alcohol fragmentation; 2 epoxy alcohol fragmentation to get the key bicyclo [5,3,1] system ok. Then like others of course, since he was the first one to report he used the Ojima protocol to introduce the side chain attached to a ring ok.

Overall he took about 46 linear steps nevertheless as you know this was the first total synthesis so, of first total synthesis of a complex natural product having so many functional groups. And it was very well thought about you know starting from a natural product to natural product, one can easily call this as a nature to natural product you start with a natural product and end with the natural product which is really of very significance ok.

As you know taxol has been used as anticancer agent for the treatment of ovarian and breast cancer the methodology developed by Robert Holton is a very interesting and clever methodology though this may not be the method to make taxol in good quantities, but it gave excellent scientific training for many co-workers worked on this project ok.

Thank you.