Classics in Total Synthesis-I
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Lecture - 49
Taxol (Wender)

Yeah, good morning and welcome back to NPTEL lecture series on Classics in Total Synthesis part 1. So, we have been discussing a few complex natural products total synthesis and today we will continue to discuss the total synthesis of Taxol. We already discussed total synthesis of Taxol by Nicolaou, Holton and Danishefsky. Today we will talk about the total synthesis of Taxol reported by Paul Wender, which was the shortest synthesis that time, he did it in 37 steps and let us see how he did it.

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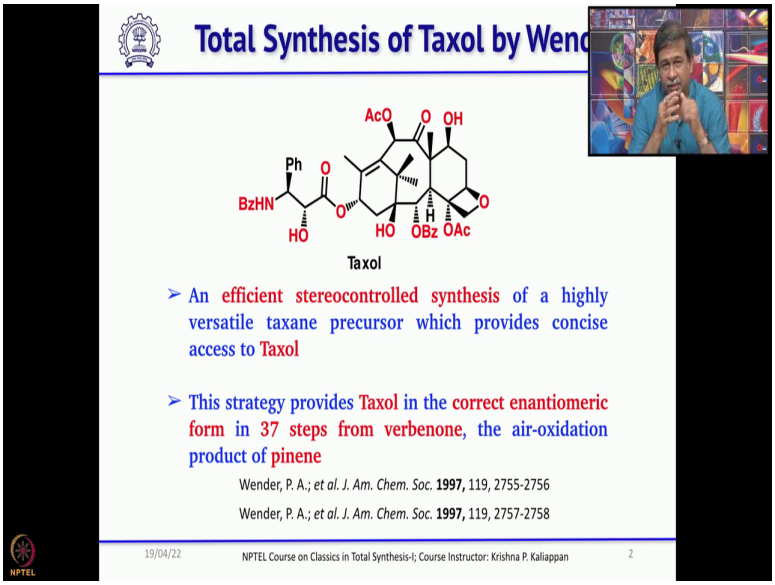

And his starting material was the air oxidized product of a monoterpene called verbenone. So, verbenone was oxidized from α pinene and that was the key starting material and his total synthesis actually involved two key reactions, one photochemical 1, 3 alkyl shift and second one is fragmentation reaction of an epoxy alcohol.

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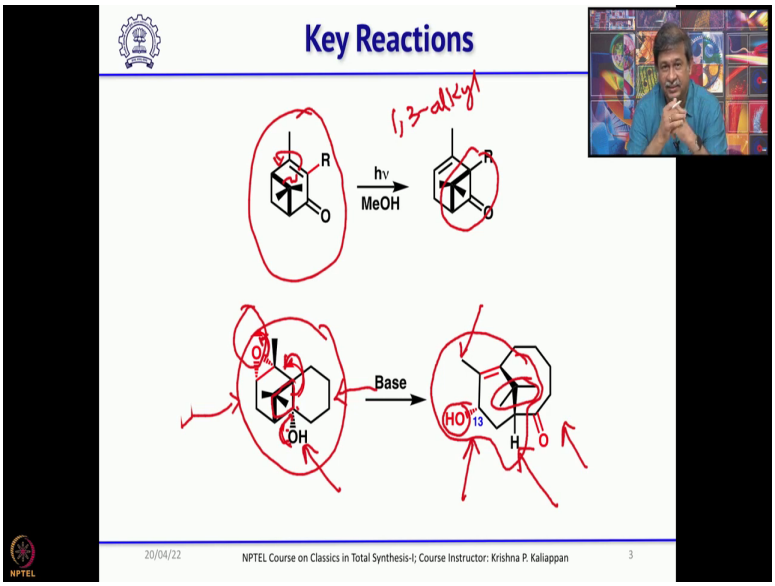

The first one as I said. So, this is the 1, 3 alkyl shift, you can see here in the left-hand side where the cyclo-butyl group is and after photochemical reaction, where the cyclopropyl is ok. This is the 1, 3 alkyl shift. So, this is a key step and it moves like this ok. So, when we talk about the total synthesis we know how important and this 1, 3 alkyl shift in the whole synthetic program.

The second key reaction is the fragmentation of an epoxy alcohol. The core structure only I have written there are substituents which I will discuss when I talk about the real total synthesis. Here if you look at the hydroxyl group ok, this hydroxyl group upon treatment with base it can come like this and open the epoxide. If you look at carefully you have already a six-membered ring, you have already a six-membered ring.

So, now this four-membered ring, this four-membered ring if it opens up then that will become eight-membered ring ok. So, the left-hand side will be six-membered ring and the right-hand side will be eight-membered ring. So, that was the key thing, it is almost like you know Holton's synthesis of Taxol. So, the lone pair on the oxygen pushes the breaking of the middle C-C bond and opens the epoxide to get this compound.

Just I will leave it for a minute, just to check whether everything is alright. This hydroxyl group now becomes ketone ok and the epoxide now it became alcohol, as you know in Taxol you need a hydroxyl group ok. And carefully you see the whole A ring, whole A ring that is cyclohexene with a methyl group here which is attached to the double bond

and then two methyl group gem dimethyl groups and you have a hydroxyl group α that is what you need in Taxol a ring.

What is missing in this is the bridge head hydroxyl ok; in Taxol you have a hydroxyl group at bridge head position. So, these are the two key reactions which Wenders group thought about and they wanted to use these two key reactions in the total synthesis of Taxol ok. Let us see their retro synthesis.

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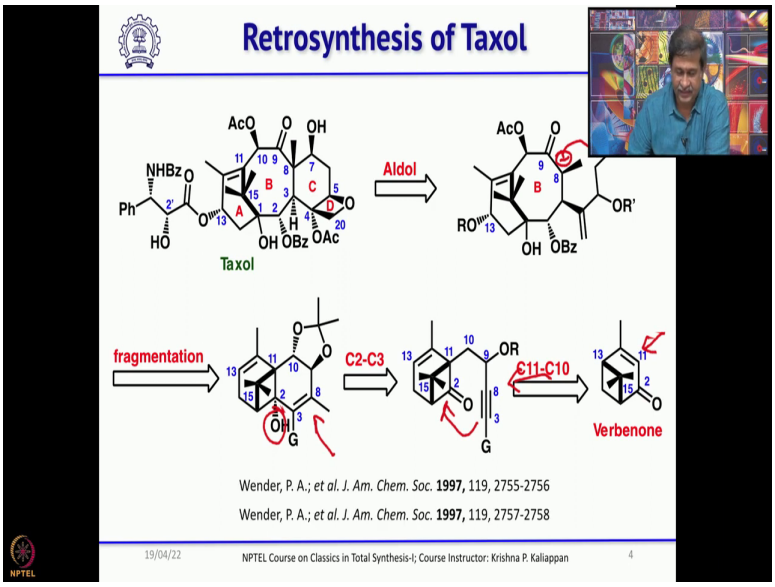

The third key reaction which is different from others is the aldol reaction ok. So, they wanted to use an intramolecular aldol reaction, intramolecular aldol reaction to construct the C-ring, you can see here you generate an anion and then add to this aldehyde and that will form the six-membered ring, which is the C-ring ok. So, intramolecular aldol reaction is another key reaction in their approach.

And this compound ok, so this is the one which I said after the rearrangement ok, after the fragmentation or rearrangement, then if you alkylate here ok you get this compound ok. So, when you alkylate you get this compound, we will come to that little later and this can be obtained from this monocyclic compound. So, here what you wanted to do is, if you do a 1, 4 addition with lithium dimethyl cuprate Gilman reagent then that anion can intramolecularly attack the carbonyl group ok.

That is how you generate this hydroxyl group, which is required for the fragmentation. Now, this can be obtained from verbenone, first you should do the alkylation here, you should do the alkylation here then you do the key reaction that is the 1, 3 alkyl shift. So, 1, 3 alkyl shift is very important ok. So, the then only you will get the eight-membered ring ok.

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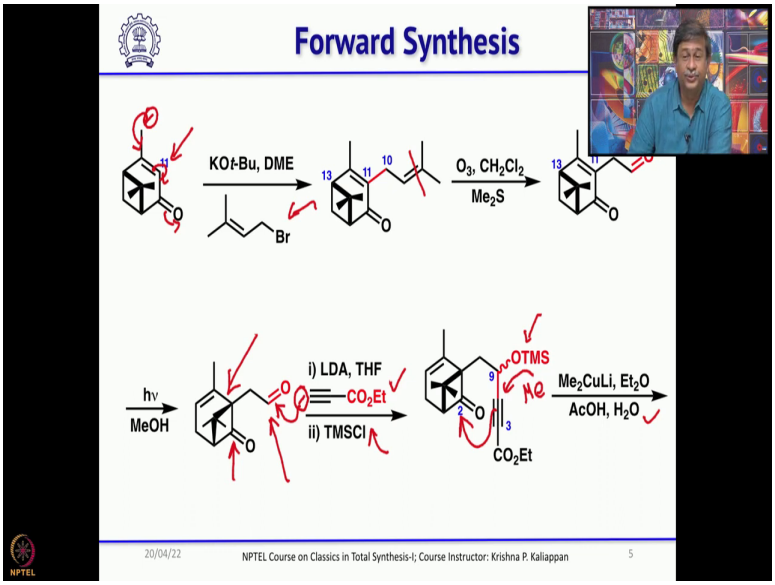

Let us see, how he did the total synthesis. First he started with verbenone, which is a commercially available and not very expensive. So, first job is to alkylate here and if you look at this enone, you can generate anion only here is not it? It is a γ position ok. So, when you generate anion and now it will be in the form of dienolate ok, it will be in the form of dienolate.

It will come all the way here and then you will get dienolate; however, when you quench that with any electrophile, the electrophile will go to α carbon. Electrophile will go to α carbon and followed by the migration of the β-γ double bond to α-β double bond. So, when you treat this with potassium tertiary butoxide ok, as I said dienolate will be formed.

Now, when you quench this with prenyl bromide so, this is called prenyl bromide, then what you get is the α alkylated product, here α prenylated product ok. Is it clear? Ok α prenylated products. Next, you can cleave this double bond selectively because the

internal double bond is electron deficient whereas, the side chain the prenyl group double bond is electron rich.

Electron rich double bond can be easily cleaved in preference to the internal electron deficient double bond. So, ozonolysis of this gives the corresponding aldehyde ok. Then comes the key reaction where when you do the photochemical treatment the 1, 3 alkyl shift takes place and when 1, 3 alkyl shift takes, place the double bond also migrates to the other side. So, this is one of the key reaction.

Then you have to add a nucleophile to this aldehyde. So, you have two carbonyl groups, one is ketone other one is aldehyde as you know ketone is less reactive compared to aldehyde. Moreover here in this particular case it is little bit sterically crowded as well. So, you take ethyl propiolate ok, this is called ethyl propiolate and when you treat with LDA, you can generate anion here.

The triple bond as acetylenic hydrogen you can generate anion, that anion can add to this aldehyde to give the corresponding alcohol that alcohol was in situ protected as TMS ether by treating with TMS chloride ok. Now, you have to form the six-membered ring ok, and as I mentioned during the retro synthesis, the formation of six-membered ring starts with addition of lithium dimethyl cuprate, ok.

So, now methyl group will add here ok, then followed by intramolecular aldol type reaction ok. And when you use acetic acid workup, the TMS group also goes. So, TMS is a labile protecting group, ok.

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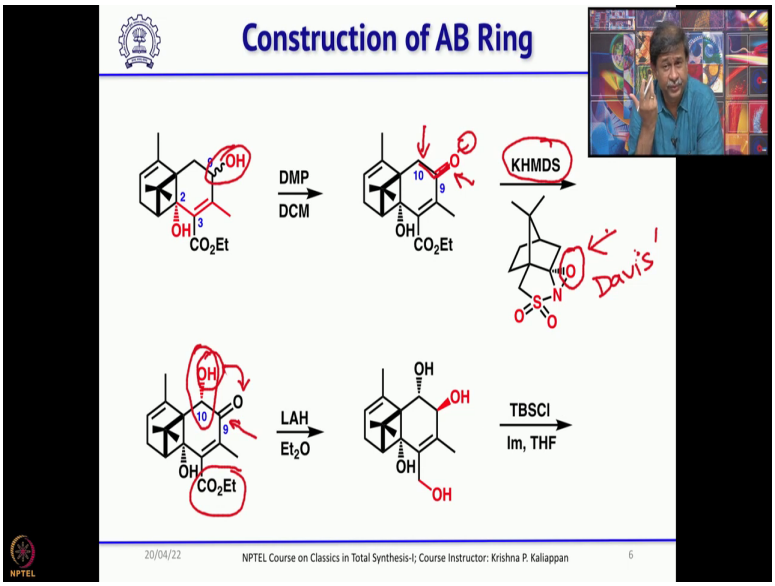

So, what you should get is a six-membered ring, with a double bond and an alcohol ok. Next, having got that you do not need alcohol here later I will come back how you can stereo selectively introduce hydroxyl group.

So, for time being you oxidize this alcohol to ketone using Dess-Martin periodinane reagent, you get the ketone ok. Next, you have to hydroxylate. If you look at Taxol, this is carbon number 9 and this is carbon number 10 ok. In carbon number 10 you have acetate ok, carbon number 10 you have acetate; that means, you should have a good method to introduce acetate or you should have good method to introduce at least hydroxyl group ok.

So, when you generate enolate with potassium hexamethyl disilazide ok, then enolate will be formed here ok, enolate will form here ok. Then this can be quenched with this oxaziridine, this is called Davis oxaziridine ok, this is called Davis oxaziridine. And this is derived from camphor sulfonic acid ok, derived from camphor sulfonic acid in 3 steps ok. Now, this oxaziridine can give the extra oxygen, ok.

This oxygen can be given here so that means, once you generate enolate and then add this oxaziridine, that will stereo selectively give the hydroxyl group. So, you could see a selectively introduced α hydroxyl at this carbon, but we will come to the stereochemistry later because we need β ok that can be done at the later stage ok. The idea is to introduce a hydroxyl group there first ok, that is done.

So, now you have α-β unsaturated ketone and you also have ester, if you reduce with LAH, both ester and carbonyl group that is the keto group will be reduced to corresponding secondary alcohol and then primary alcohol when you treat with LAH, this hydroxyl group which is α. So; that means, hydride will be delivered using this handle from the same side; that means, the resultant alcohol here will be β.

Because this hydride will come from α, so you will get β alcohol and the ester also will be reduced to corresponding primary alcohol ok. LAH reduces the ketone as well as the ester to get this compound. Next, you have to protect the primary alcohol selectivity, because you have two secondary alcohols, one tertiary alcohol and a primary alcohol as you know it is easy to protect selectively the primary alcohol in the presence of secondary and tertiary alcohol.

And for that what you should do is you should use a bulky protecting group ok. The bulky protecting group if you are thinking of you can use TBS chloride, TBDPS chloride triethyl chloride and so on.

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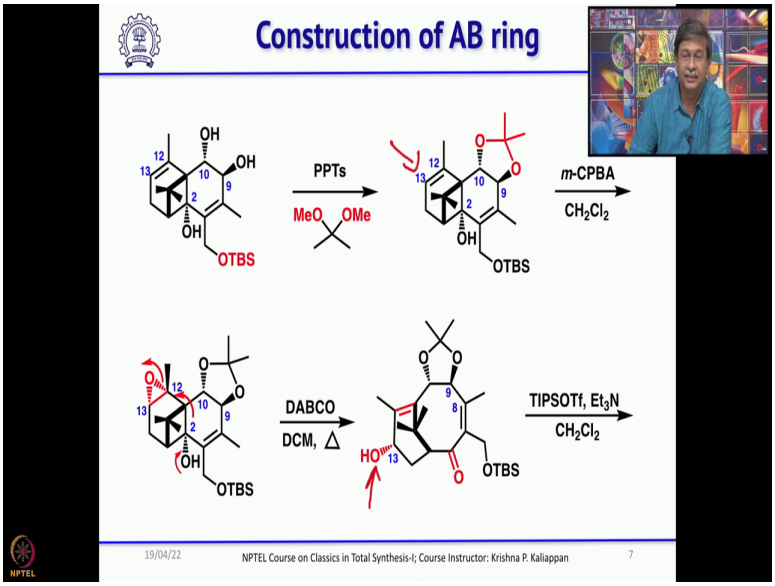

So, here they chose TBS chloride as a protecting group. So, the primary alcohol was protected. Now, you have two secondary alcohols ok, that can be protected as acetonide by treating with PPTs and dimethoxy propane ok.

This is a very simple reaction at room temperature one can do. So, this secondary alcohols were protected now. So, that sets the stage for the key rearrangement or key fragmentation. So, already we have discussed one key reaction that is a photochemical reaction where 1, 3 alkyl shift took place along with the migration of the double bond.

Now, for the second key reaction, we have come to the key precursor. What you need to do is you need to make the epoxide, you need to make the epoxide here followed by the fragmentations. So, treatment with one equivalent of *m*CPBA, one could get epoxide there are two double bonds, but still stereo selectively one can do the epoxidation at carbon 12 and 13 and this is the stage where he tried the fragmentation reaction.

So, for that he used a base DABCO non nucleophilic base and heat it and as expected the rearrangement or fragmentation took place smoothly to give the AB ring of Taxol ok. If you look at this is the AB ring of Taxol and it has almost all the functionalities ok, almost all the functionalities present in A and B ring, ok.

So, now what one has to do? You have to construct the C ring followed by construction of the D ring that is oxetane then you should attach the side chain. Before attaching the side chain some minor functional group modifications should be done, ok. So, next the secondary alcohol which is formed with allylic alcohol this that should be protected. So, that was protected as TIPS ether by treating with TIPS triflate and dichloromethane.

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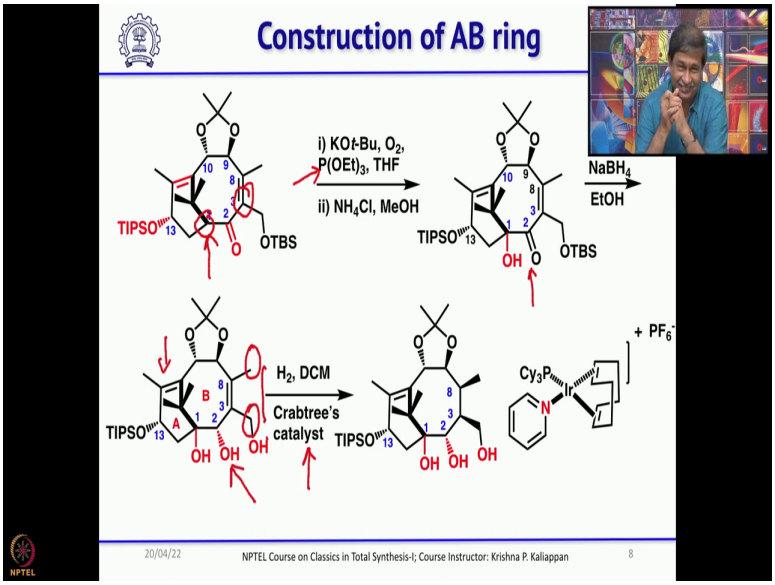

Once you have that, now you need to introduce a hydroxyl group at bridge head position; you need to introduce a hydroxyl group at bridge head position and this is the best time. Why? Because you can generate enolate here and not here ok, once you reduce the double bond then enolate can be generated at that position. So, it is better to do it at this position ok.

So, it was easy and it can be done by treating with potassium tertiary butoxide and oxygen and that the resulting hydro peroxide was converted into hydroxyl group by treatment with triethyl phosphate, ok. So, very easy and the hydroxyl group at bridge head position also being introduced. Now, if you look at this particular intermediate as all the functional groups, required for Taxol in A and B rings, ok.

What is next? You should reduce the ketone to hydroxyl group ok. So, this molecule if you look at it will be like this ok, this molecule it will be like this. So, the hydride will come from the β side ok. So, when you reduce this, you get α alcohol. In Taxol also if you look at carefully the structure of Taxol this hydroxyl is α, it is in Taxol as benzoate ok. So, now, the hydroxyl should be benzoated that can be done little later.

The next major task is to introduce the C ring ok. For that first you have to reduce the double bond ok and when you reduce the double bond it is very important you should do it stereo selectively. And when you do hydrogenation ok, it is a tetra substituted double bond and you also have another tetra substitute double bond and A ring. You need to selectively reduce this ok.

And when you are doing hydrogenation and hydrogenation; obviously, as you know it is a *cis* addition. So, both this methyl group and the CH_2-OH after reduction will come in the same side. Now, what he did he used cleverly Crabtree's catalysts. Crabtree's catalyst is well known for directed hydrogenation, if you have a polar functional group.

So, if you have a hydroxyl group here. So, you can see the α hydroxyl group. So, now, Crabtree's catalyst will coordinate with this α hydroxyl and deliver the hydrogen from the α side, when the hydrogen is delivered from the α side then automatically this methyl and hydroxyl methyl these two will become β. So, this is what you get ok, hydrogen comes from the same side as that of secondary alcohol so that the methyl and CH_2-OH comes from the β side.

So, this is a structure of Crabtree's catalyst, which is widely used for directed hydrogenation ok. So, now, you have methyl group, you have -CH_2-OH, but if you remember you have primary alcohol your secondary alcohol your tertiary alcohol ok, you need to protect some of them.

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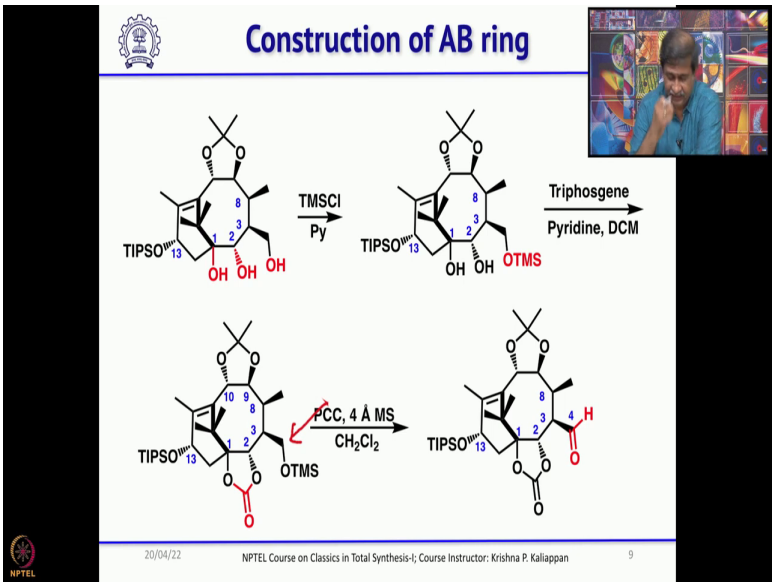

So, you can protect the primary alcohol in the presence of secondary and tertiary. So, in situ and temporary protection with TMS chloride you protect the primary alcohol. Then the secondary and tertiary alcohol can be protected as cyclic carbonate, if you treat with triphosgene and pyridine, you can protect that as cyclic carbonate ok. So, now, that is protected.

Now, what you need is you need to homologate, this you need to homologate the -CH_2 in TMS, then only you can carry out the intramolecular aldol reaction. So, for that you can straight away oxidize you know -CH_2-OTMS ok with PCC to get the corresponding aldehyde, ok. You when you want to homologate the best way is you have to do Wittig reaction or enol ether Wittig.

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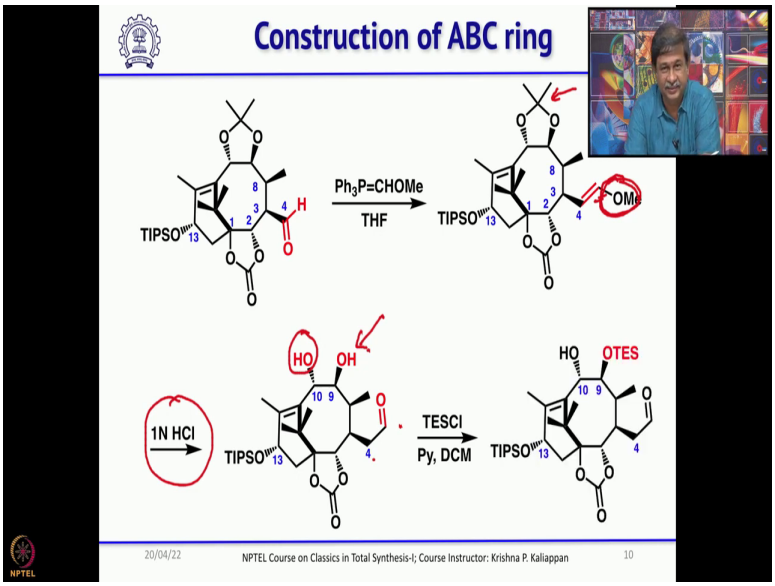

So, what he did was, he did so enol ether Wittig reaction. So, when you do enol ether Wittig reaction, you get the corresponding enol ether one carbon extra. So, normally you get a mixture of *cis* and *trans* isomer, but does not matter because once you hydrolyze this you are going to get aldehyde.

So, one normal HCL treatment and dilute one it hydrolyzes the enol ether you get the corresponding aldehyde. So, what you have done is now you can see you have introduced one extra carbon, the hydrolysis of enol ether as well as the removal of acetonide took place when you treat with one normal HCL, ok. So, you got -CH_2-CHO and the diol ok.

Now, if you look at this diol, this particular hydroxyl group is more exposed, this particular hydroxyl group is more exposed than this. So, selectively one can protect this hydroxyl group with TES chloride and then you get corresponding OTES, ok.

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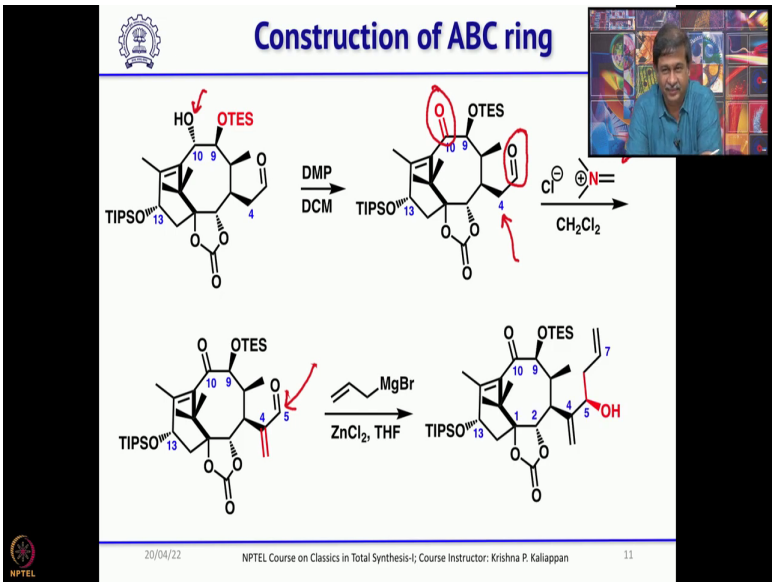

Then what you need to do is you have to oxidize the other hydroxyl group, other hydroxyl group. So, that is easily done with this Dess-Martin periodinane. So, you get the ketone. And if you look at this particular structure you have two carbonyl groups, one ketone and one aldehyde ok. Then as you know between aldehyde and ketone aldehyde is more reactive and you want to introduce a double bond here -$CH=CH_2$.

So, that can be easily achieved by treating with Eschenmoser's salt ok this is Eschenmoser's salt and that will give directly the exocyclic double bond, ok. Now, if you treat with allyl magnesium bromide with zinc ok, then the allyl group adds here to get the corresponding homo allylic alcohol, ok.

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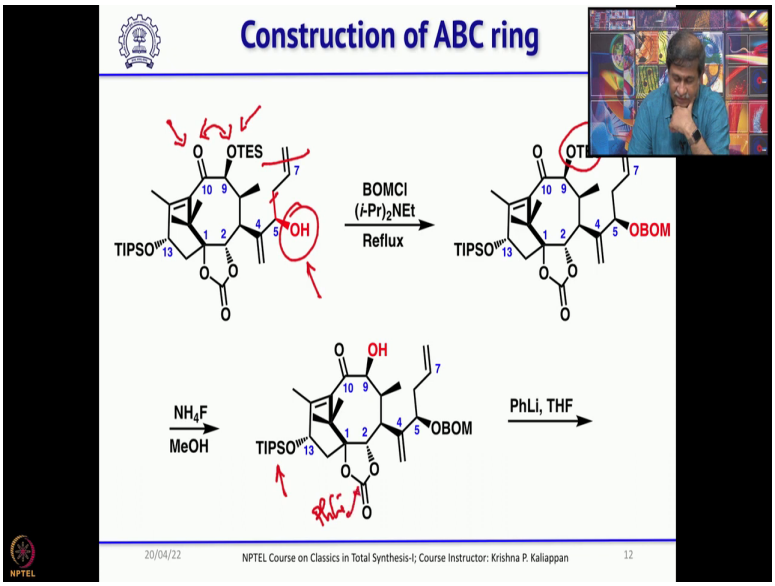

What is left now? You have to protect the secondary alcohol then you have to cleave this then you have to do the aldol reaction. But for doing aldol reaction these two functional groups should be exchanged, ketone should come here and then OTES should come here, ok.

One the double bond should be cleaved to get aldehyde and these two functional groups should be exchanged followed by intramolecular aldol reaction. So, before that the secondary alcohol that allylic alcohol should be protected. So, that was protected as BOM chloride that is benzyloxy methyl chloride. So, you get the protected compound.

Now, if you treat with ammonium fluoride ok, say ammonium fluoride removes the TES group which is more exposed as I said it is more exposed it is on the β side. So, it is easy to remove TES in the presence of TIPS, then you treat with phenyl lithium. So, the phenyl lithium you know cyclic carbonites are very labile protecting group, that phenyl lithium as we have already discussed it adds to this and opens and you get the corresponding benzoate ok, corresponding benzoate.

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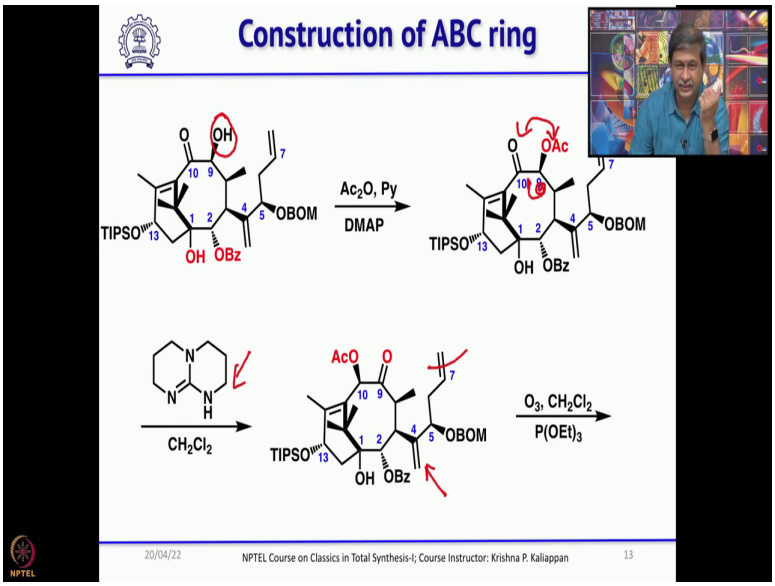

Now, if you treat with acetic anhydride pyridine, you protect the secondary alcohol at C9 as acetate ok, but again as I said acetate should be here and ketone should be here. So, how do you do that? So, you take this highly substituted guanidine ok and treat in the presence of dichloromethane. So, that generate it goes through enol form enolate then intramolecular acyl transfer takes place that gives the completely rearranged product, ok.

So, the ketone and acetate are exchanged and that sets the stage for the intramolecular aldol reaction ok. So now, what is required you need to cleave this double bond selectively in the presence of disubstituted double bond ok. And that can be easily done ozonolysis followed by treatment with triethyl phosphate. So, one can use dimethyl sulfide, now you can use zinc.

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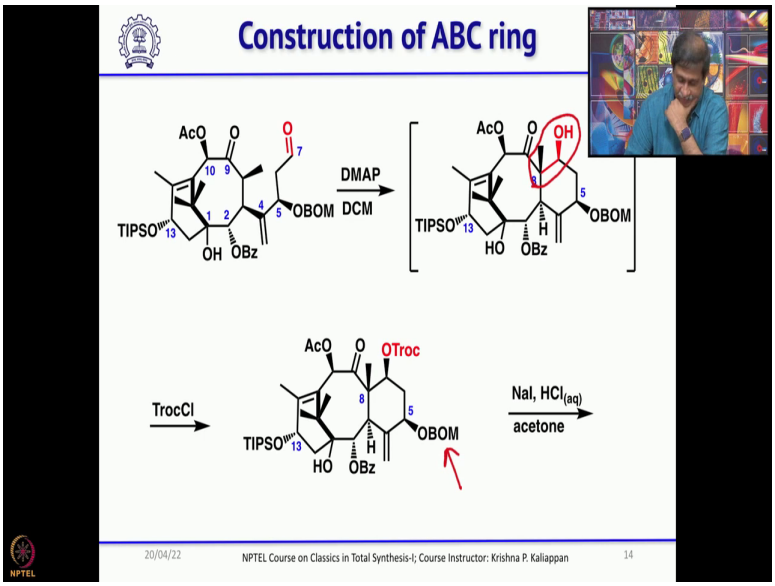

So, you get corresponding aldehyde ok. So, it is easy once you have ketone and aldehyde and treat with dimethyl amino pyridine, it undergoes intramolecular aldol reaction to construct the C ring, ok. One you can see the C ring is constructed and these two chiral centers also fixed ok.

Then the secondary alcohol was protected as rock ether ok, that is quite easy to prepare the protecting group, then you treat with sodium iodide and aqueous HCL, sodium iodide and aqueous HCL that is to remove the BOM group. If you have to remove the BOM group selectively you can use this ok.

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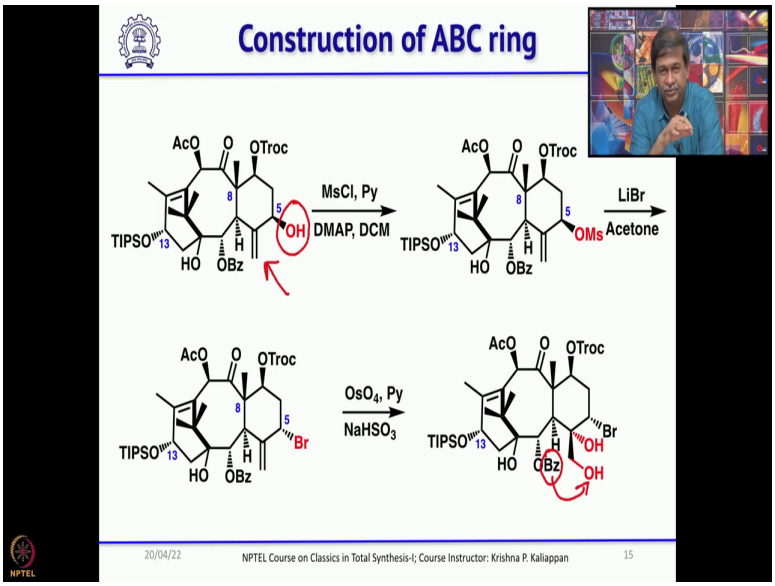

Now, you got allylic alcohol. So, what we have done so far? We have made the A ring, we have made the B ring; we have made the C ring. Now, we have to go for making the D ring. So, for the D ring you have to functionalize this exocyclic double bond, what will you do you can use dihydroxylation.

And before that you should make sure the β alcohol as a good leaving group, but the leaving group should be in α position, in case if you look at the oxetane is β. That means, the leaving group here should be α. So, mesyl chloride, first it converted into mesylate, then the mesylate was converted into corresponding bromide via SN_2 reaction to get the corresponding α bromide, ok.

Now, you have the α bromide. Next, we should do the dihydroxylation. So, the dihydroxylation comes from the β, so you get the diol. So, now, you have the primary alcohol and secondary alcohol ok. While doing this reaction there was some migration of this benzoate to this primary alcohol so; that means, the primary alcohol here intramolecularly attacked benzoate here. So, some migration took place so you got a mixture of both. So, they thought it is better to do complete migration.

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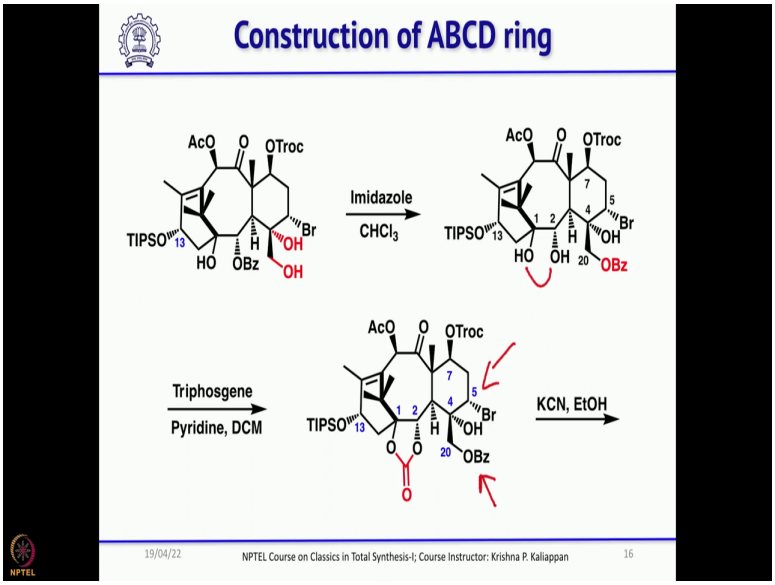

So, it was treated with imidazole, when you treated with imidazole the complete migration took place to the primary alcohol, complete migration took place to the primary alcohol. Now, you can again you have to reprotect this diol so that was done with triphosgene to get the cyclic carbonate ok.

Now, cyclic carbonate is protected. Now, what you need is to convert these functional groups into corresponding oxetane. So, potassium cyanide methanol selectively potassium cyanide methanol will selectively hydrolyze the benzoate ok and does not stop there.

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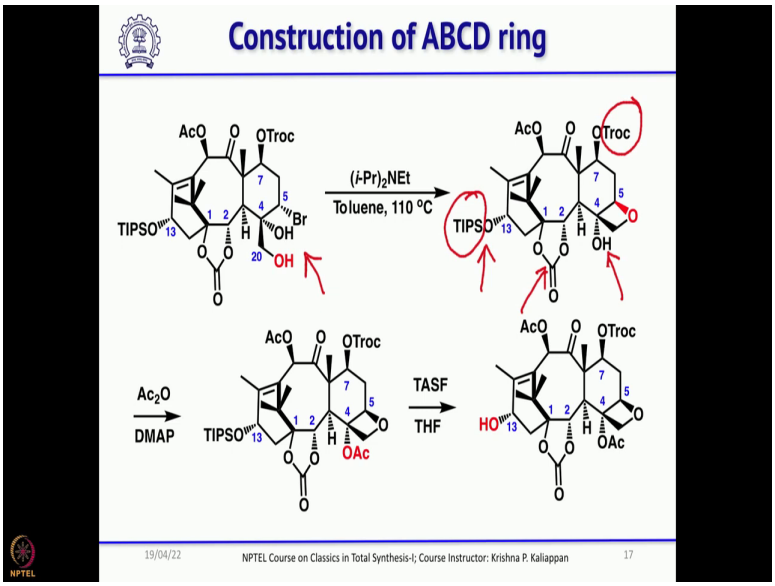

Immediately you can take this compound and treat with Hunig's base and reflex that will give the corresponding oxet ok. You take this compound and treat with Hunig's base ok, Hunig's base when you reflux it automatically intramolecular SN_2 reaction takes place to give the corresponding oxetane which is required.

So, now, if you look at this, all are present ok A, B, C everything is there with functional groups, you have to acetylate the tertiary hydroxyl group and you have to open this with phenyl lithium and you have to remove this protecting group as well as this protecting group and attach the side chain. So, these are the job left. So, first you acetylate the tertiary hydroxyl group. So, you get the acetate, then you can treat with TASF. So, the TASF will remove the TIPS group that is a fluoride source.

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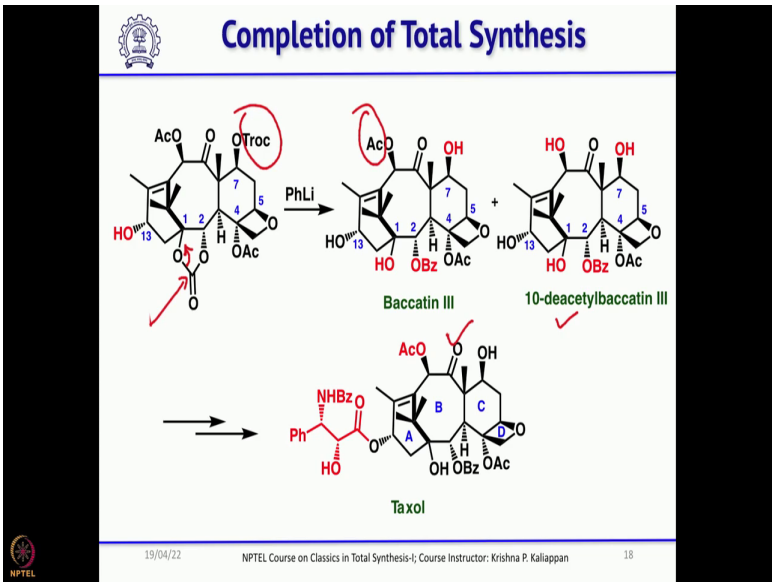

So, once you have that, then treat with phenyl lithium ok when phenyl lithium will add here and one opens up. So, you get Baccatin III and if you use excess there is a chance of acetate also getting hydrolyzed. So, he gets a mixture of Baccatin III and 10 deacetyl Baccatin III, as you know already we have discussed how Baccatin III has been converted into Taxol in few steps.

And addition of phenyl lithium also cleaves Troc ok; addition of phenyl lithium also cleaves Troc ok. So, once you have Baccatin III it is already converted into Taxol ok. So, that is how he completed the total synthesis of Taxol and this was the shortest total synthesis that time only 37 steps starting from where we know and it was one consider as one of the classical total synthesis of Taxol, ok so.

Thank you.