Classics in Total Synthesis-I
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Lecture - 46
Taxol (Nicolaou)

Good morning. And, welcome back to the NPTEL course on Classics in Total Synthesis part 1. And today so, we will talk about very important natural product called Taxol. And we discuss at least 4 total synthesis of taxol. And the first one we will talk about is total synthesis of taxol reported by Nicolaou.

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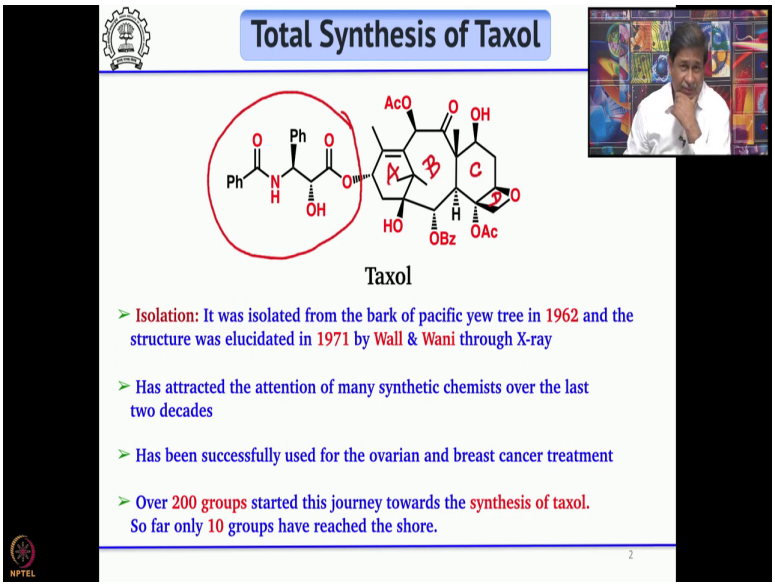

So, this is a complex structure of taxol. As you can see here, there are 4 rings. So, these 4 rings are, A, you can see A ring which has which is a 6 membered ring, and B ring which is supposed to be the more complex one which is a 8 membered ring, then we have C ring which is a 6 membered ring, and D ring which is a 4 membered ring with oxetane. In addition, we also have an ester substituent, ok.

This was isolated from the bark of pacific yew tree way back in 1962. But the elucidation of structure took quite some time. Almost it took 10 years to get the correct structure of taxol. So, this was isolated and elucidated by two natural product chemists called Wall and Wani, and they propose the structure through X-ray. Obviously, when you look at

this molecule it is quite complex, and more importantly this molecule showed a wonderful activity against the ovarian and breast cancer.

So, many groups across the globe, so wanted to work on the total synthesis of this molecule and about 200 groups worked on this molecule and so for about 10 people have successfully completed the total synthesis of taxol.

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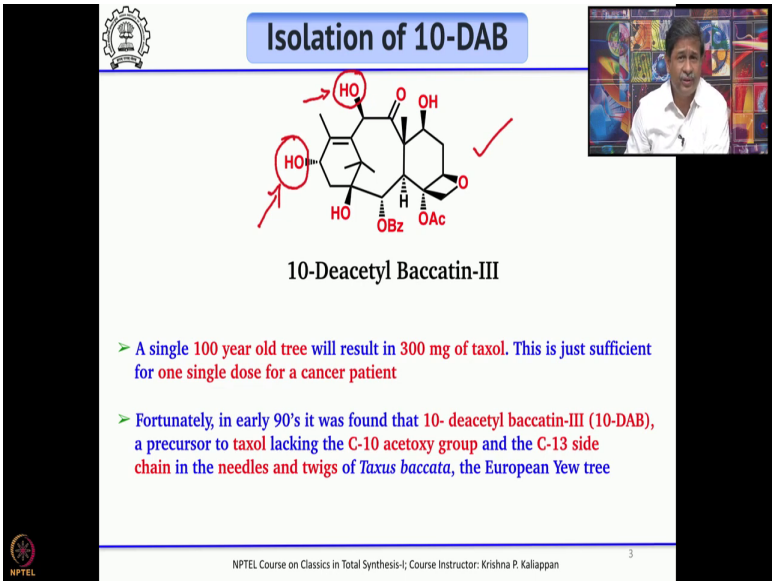

So, why this molecule is so important? Ok. And if you look at this molecule, first of all this molecule was isolated from the pacific yew tree, ok. The pacific yew tree is a very very slow growing tree, ok. And this was isolate from the bark of pacific yew tree. And if you need 300 milligram of taxol, ok you have to kill 1 pacific yew tree which is 100 year old, ok. You can imagine a single 100 year old pacific yew tree may maximum give 300 milligram of taxol and that may be about sufficient for 1 single dose of a cancer patient, ok.

Then, you can imagine if you want to produce more taxol, then there should be other ways. It cannot be from the natural source. Nature has shown a way, ok. Here it is a molecule, ok. You can identify, and then see this is this could be used for the treatment of ovarian and breast cancer. Now, you make your own, ok. So, that was the biggest challenge nature has given, ok.

And interestingly, the second major problem for taxol was the pacific yew tree is a very very slow growing tree. As it was isolated from the bark of pacific yew tree, if you have to isolate more of taxol, you have to kill this tree, ok and then it will take so many years to grow. But interestingly and surprisingly, the leaves of pacific yew tree has another natural product called 10-de-acetyl baccatin III, ok.

If you look at this structure 10-de-acetyl baccatin and compare it with taxol, you will see there are two things which are missing in this 10-de-acetyl baccatin. One is obviously, the acetate group is not there here, the acetyl group is not there, only 3 hydroxyl is there. And the second major change is the hydroxyl group. This hydroxyl group in the case of taxol it has a long side chain with two chiro centers, that is missing in 10-de-acetyl baccatin.

But the good thing about this 10-de-acetyl baccatin which is being isolated from pacific yew tree's leaves is that by simple functional group transformation one should be able to introduce the acetate here as well as the side chain here. That will constitute the semi synthesis of taxol, which already I discussed what is semi-synthesis in the first lecture. So, you have this isolated from the leaves of pacific yew tree, now through functional group transformation one should be able to make taxol.

Another most important thing about this is these leaves can grow faster, ok unlike the tree, the tree though the tree is a slow growing tree, but the leaves grow can grow faster. So, you can pluck the leaves and isolate the 10-de-acetyl baccatin from there you can you can make taxol, but after some time the leaves will grow again, ok. Again, you can pluck the trees and then isolate 10-de-acetyl baccatin and so on. So, that way, so the leaves played a very very important role initially in the synthesis of taxol.

However, considering the complexity of the natural product, now it was always you know big challenge for many synthetic chemistry across the globe to think about a good synthesis for this interesting molecule.

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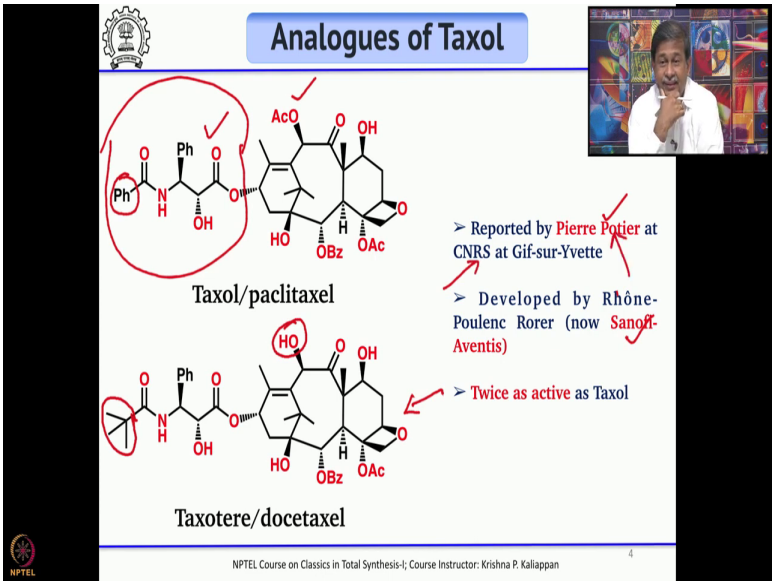

So, as I said already 200 groups were done this molecule. And there were people who were also interested in making several analogs of taxol. That is just because when you have 10-deacetyl baccatin, ok that is a core structure of taxol from there, not only one can attach the side chain, ok, not only you can attach the side chain as well as acetyl you can introduce different side chain, ok.

So, when you do that, who knows the analogs of taxol may be more active than taxol. Say that is how Potier he made a derivative of taxol. And if you look at these two, you can see there are two changes, ok. Closely if you observe in the in this molecule, there is no OAc, you have free hydroxyl group. And you have free hydroxyl group you know it is good for solubility, ok. It will have better solubility.

Another thing is in the side chain you have a tertiary butyl group whereas, in taxol you have phenyl group. These are the two major changes in this analog. And this is called taxotere or docetaxel, ok. This was reported by Pierre Potier from CNRS and later you know he licensed to now the company called Sanofi Aventis, earlier it was Synthelabo.

Then, as I said some of the analogs may be more potent than taxol, and this was two times more potent than taxol, ok. So, the docetaxel is currently being used for the treatment of ovarian and breast cancer and the CNRS and Pierre Potier got lot of royalty from Sanofi Aventis for this drug.

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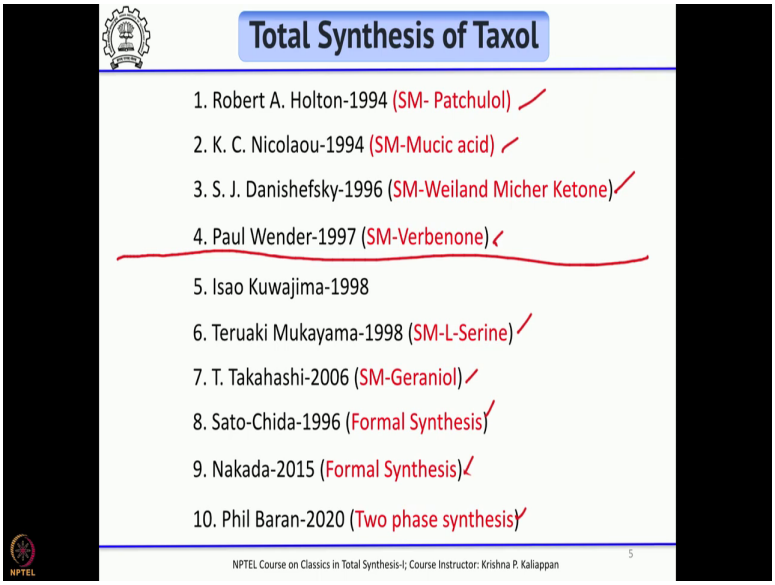

And these are the people who completed a total synthesis or formal synthesis, as starting from the different sources, different starting materials, ok. So, they could complete the total synthesis of taxol. But today what I will do, I will talk about the total synthesis of Nicolaou.

I in this lecture series, I will talk about 4 total synthesis from Robert Holton. In fact, he was the first one to report the total synthesis of taxol. And the second one from KC Nicolaou's group who actually their work published in nature and then third one by Samuel Danishefsky group and fourth one by Paul Wender's group, ok.

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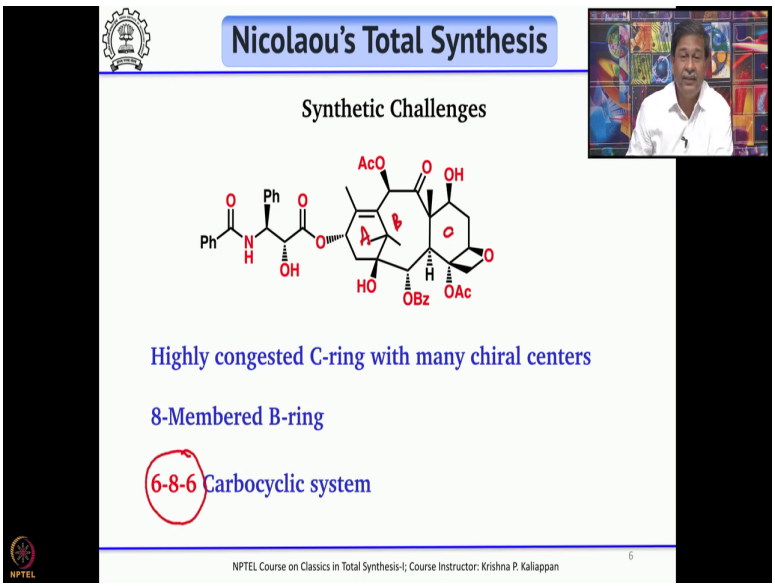

I will try to cover these 4 total synthesis. And today, let us start with Nicolaous total synthesis. As I said it is a very complex molecule, there are many challenges you know to make this molecule. And first of all if you look at this molecule there are so many chiral centers, and they are all congested, particularly in the C ring and B ring you can see they are all very very congested, ok. And the second problem which most of the synthetic chemists faced in the synthesis of taxol is the construction of 8 membered ring.

The construction of 8 membered ring is not that easy. So, we all know. So, that has created quite a bit of problem for many many synthetic chemists. And the third challenge is the tricyclic core that is 6-8-6. So, these two that is A and B if you look at, so they are bridge system. They are they connected by through a bridge, whereas, B and C are fused system, ok. The 6-8-6 carbocyclic system gave a different type of problems for synthetic chemists while attempting the total synthesis.

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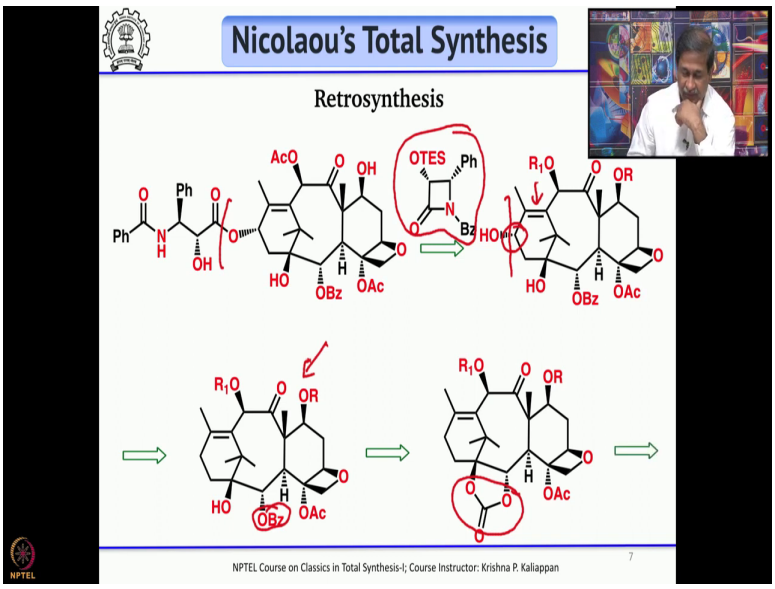

So, let us see how Nicolaou though about making this molecule. So, first and then foremost retrosynthesis was obviously, you know you can remove the side chain. That is the easiest one. Keep the side chain out and what you get is this compound, ok. So, one can always attach the side chain later, ok. So, that will give you this intermediate, ok. Now, next one is you remove or break the CO bond.

The reason for breaking the CO bond is, you know there is a double bond, once you have the double bond you can do the allylic oxidation to get the hydroxyl group. That reduces

the oxygen functionality in A ring and this became the target molecule, ok. Now, if you look at this, this could be obtained from this cyclic carbonate, ok. This cyclic carbonate if you treat with phenyl magnesium bromide or phenyl lithium, then they should open up to give this benzoate and a free hydroxyl group, ok. So, with that idea, the two hydroxyl groups were protected as cyclic carbonate.

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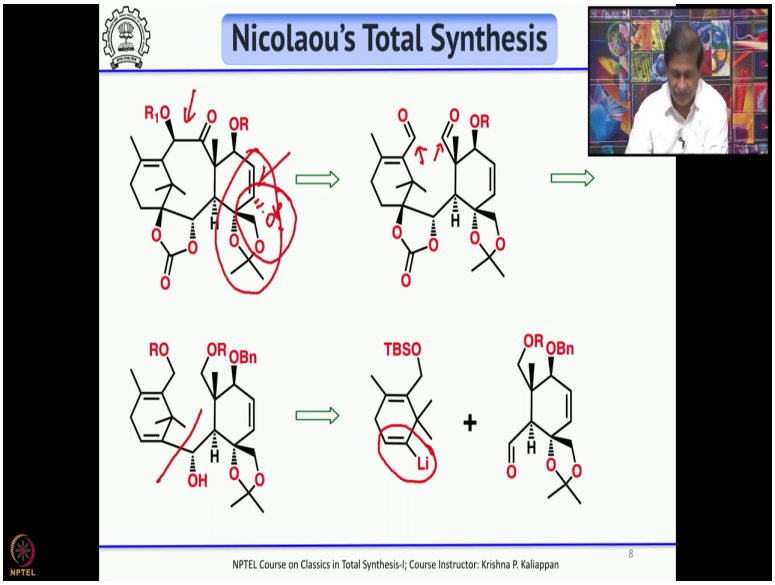

Now, this can be obtained from this double bond. If you look at this, from here if you do a hydroboration stereo and regioselective hydroboration, one should be able to get hydroxyl group here. Once you have that then one can get this oxetane ring, ok. So, that was the idea. And if you look at this particular molecule, then the 8 membered ring, 8 membered ring can be obtained by a well-known reaction called McMurray coupling.

So, if you have a dialdehyde, then under McMurray coupling it can give a diol, ok. Once you have diol, you should be able to differentiate the diol and then oxidize one of them, ok. So, the precursor for this keto alcohol is this dialdehyde. Now, if you look at this dialdehyde, the dialdehyde can be obtained from corresponding primary alcohol, is not it, protected primary alcohol. Normally you remove the protecting group and oxidize, you will get this compound.

Now, how do you get this? So, this is very interesting transformation. What he did was he broke this bond, ok and kept the vinyl lithium species on the left hand side. The other side you have aldehyde, ok. This spinal lithium species can be prepared by or through

eschenmoser reaction. If you have a tosylhydrazone and treat with butyl lithium, it will generate vinyl lithium. Once you have vinyl lithium and then you can quench with aldehyde to get the allylic alcohol, ok.

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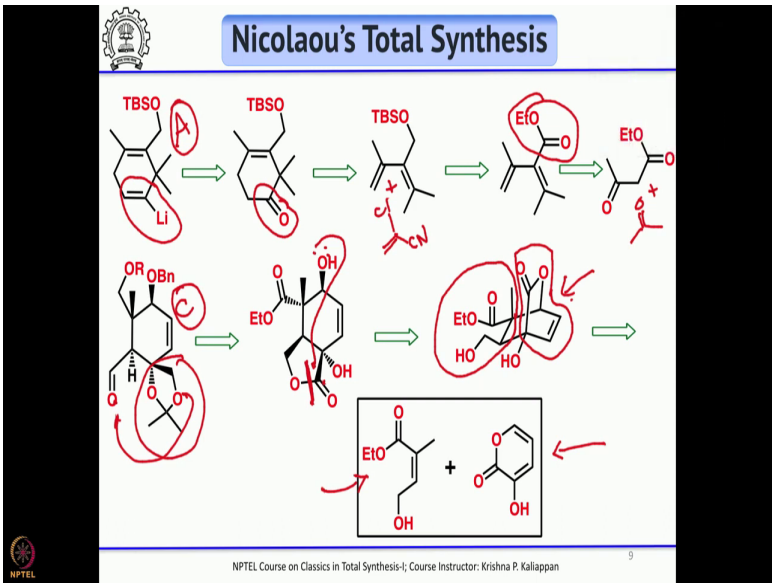

Now, these two can be obtained from a simple precursor. So, since you need a tosylhydrazone to generate this vinyl lithium species, the tosylhydrazone can be obtained from the corresponding ketone, is not it. Well, this ketone as you know can be obtained from this diene and that dienophile.

So, here the dienophile, this is a ketene equivalent, so you should have a diene equivalent like this α chloronitrile and this diene should undergo Diels-Alder reaction followed by hydrolysis, one should get the ketone. And this can be obtained from this ester upon reduction, and then protection, and that can be obtained from ethyl acetoacetate and acetone. So, Alder reaction look at that.

So, the simple starting material which was used for the total synthesis of taxol by Nicolaou is ethyl acetoacetate, ok. Ethyl, which is commercially available and very inexpensive. The other one again if you look at this, this diol if you remove and then connect it here, the primary alcohol if you connect it here, you get a lactone, ok. Now, this lactone if you carefully look at, it can be obtained by a Diels-Alder reaction.

How this one this bond is broken; now this alcohol is attacking here, ok. If that is the case then you will get this, understand. This one I just leave it for a minute. Just see, the alcohol attacks this lactone and then this CO bond breaks and then you get a -CH_2-OH. And then bridge head alcohol is there. So, this will become a 6 membered ring. And you can see the 6 membered ring is the diene. This 6 membered ring is the diene and this is the dienophile. So that means, this should be able to prepare or synthesize from this diene and this dienophile.

So, Nicolaou total synthesis had two key reactions, one that is the Diels-Alder reaction to make this A as well as C ring, ok, you can see this is A ring and this is C ring. So, both A and C rings are made by Diels-Alder reaction. And this B ring, the B ring was made by the famous McMurray coupling. So, these are the two key reactions Nicolaou has utilized in the total synthesis of taxol.

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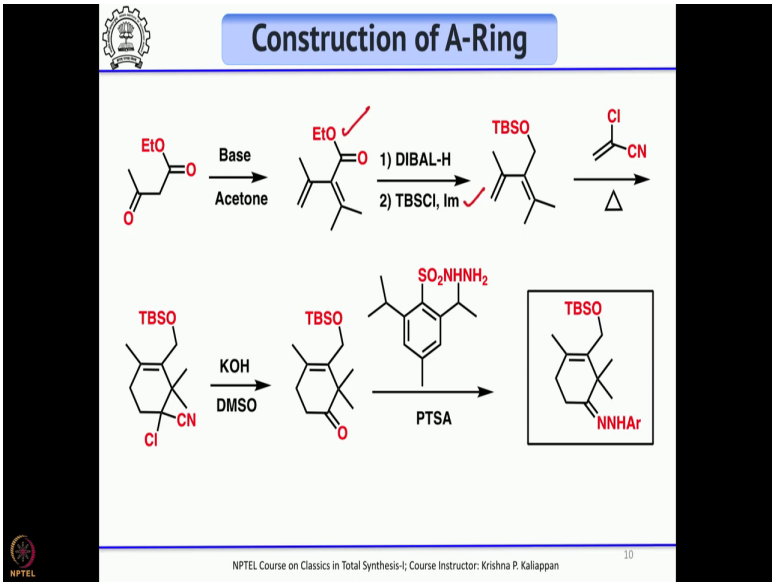

So, now let us see how he successfully made A ring, C ring, and then combine them to get A, B, C ring and so on. For the A ring, he started with ethyl ester state and then treated with the base in the presence of acetone. So, he could easily introduce the -C-CH_3 and reduce the ester with the DIBAL, you get alcohol that alcohol was protected as TBSCI ether, so you get the diene which is ready for the Diels-Alder reaction. So, heat it with α chloronnitrile and you get this as the major product followed by hydrolysis with potassium hydroxide DMSO, you get the ketone.

Now, as I said you need for the A ring, to interact with C ring you need to tosylhydrazone. So, the tosylhydrazone either simple tosylhydrazone or 2, 6 diisopropyl tosylhydrazone. So, he made that and then it is ready, ok. The A ring is ready. Now, let us see the C ring. How he made the C ring?

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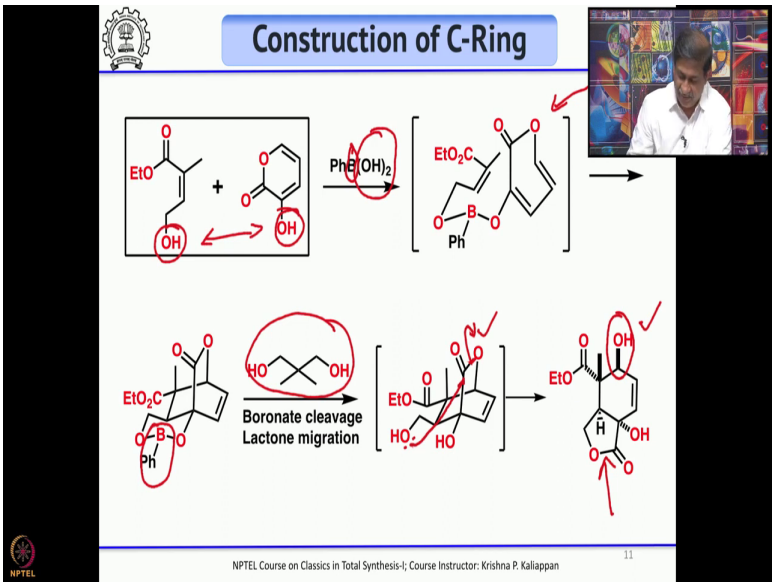

So, these are the two starting materials. Now, if you treat with phenyl boronic acid, phenyl boronic acid, see boronic acid what will happen? The boron, ok will have a lot of affinity towards the hydroxyl group. So, that way this is the first intermediate which will be formed, ok. This is the first intermediate which will be formed. The two -OH's attached to phenyl boronic acid will be replaced by these two.

I have drawn this structure in such a way that this will undergo an intramolecular Diels-Alder reaction facilitate by the boron bridge, intramolecular Diels-Alder reaction. And of course, when you know when you when you talk about Diels-Alder reaction, it will give endo-isomer as the major product, that is ester will be endo to the diene which is going to be formed. So, this is what you will get.

Is it easy to visualize? Just see the diene reacts with the dienophile, the dienophile is attached to the diene through boron bridge and it undergoes Diels-Alder reaction that is intramolecular Diels-Alder reaction where the ester is now in endo position, ok. Now, you have to replace the boron, ok. Very simple, you treat with a diol. It is very easy to

cleave boron by treating with a diol. So, now, what will happen? The boron will be cleave, ok.

Now, if you look at the structure you have a diol, ok. And when you isolate the product this is not the product you get. What happens? Can you visualize how this compound you get? How do you get this compound? Think. Some minor rearrangement is happening. What type of rearrangement is happening? You can see this 6 membered lactone is being broken and a 5 membered lactone is being formed.

So, what happens? This lone pair, this primary alcohol attacks the carbonyl and breaks the 6 membered lactone. So, that will give you directly your 5 membered lactone and free this secondary hydroxyl group, ok.

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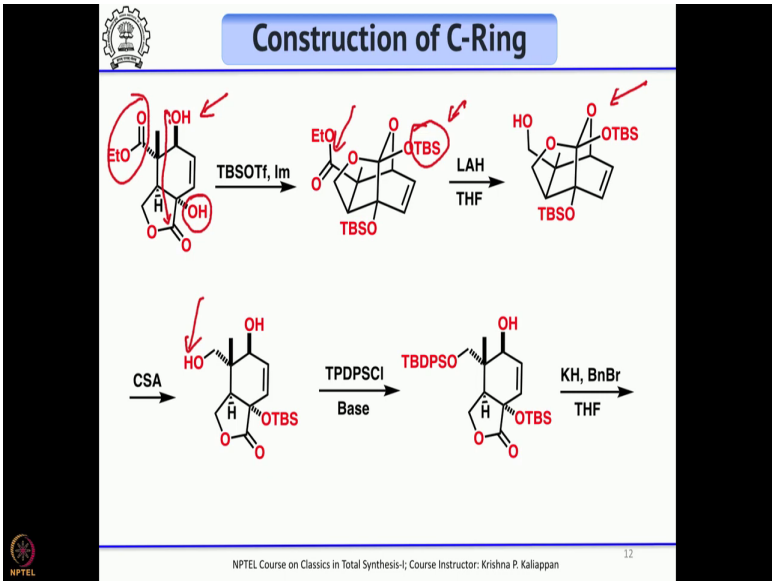

So, once you have that now you treat with TBS triflet. So, what do you expect this alcohol will be protected as TBS ether, is not it? No. What happens? This alcohol attacks the lactone and forms this hydroxyl group without TBS that hydroxyl group is protected as TBS ether plus this hydroxyl also protected as TBS ether, ok. It is not the protection of secondary hydroxyl group. The secondary hydroxyl group attacks the carbonyl of lactone and the final hydroxyl is protected as TBS ether along with the protection of tertiary alcohol.

Now, this helps in selectively reducing the ester to get the primary alcohol. Now, once you have the primary alcohol camphor sulfonic acid treatment. What will happen camphor sulfonic acid treatment? That will, this is a you know orthoesters, is not it. This is a orthoester. So, that will hydrolyze the orthoesters. So, when it hydrolyze the orthoester, you get back. Basically, you know if you look at this carefully the ester group was selectively cleaved, ester group was selectively cleaved. That is all. That is a process which originally planned, ok.

Now, the primary alcohol, primary alcohol can be easily protected, the presence of secondary alcohol by bulky protecting group. So, here you use TBDPS chloride which protected the primary alcohol as TBDPS ether, ok. Now, what is left? You have to protect the secondary alcohol.

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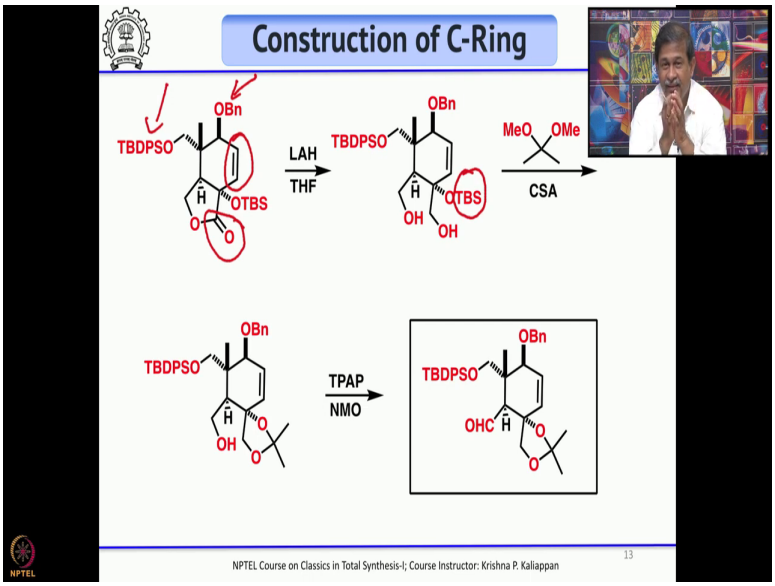

So, the secondary alcohol was protected as benzyl ether with potassium and you treat with potassium hydride and benzyl bromide. So, primary alcohol is protected, secondary alcohol is protected. Now, what is required? You have to reduce or open this 5 membered lactone and functionalize the double bond to hydroxyl group, ok. LAH will reduce the 5 membered lacton to diol, ok.

Then, when you treat this with dimethoxy propane and camper sulfonic acid, you get this compound. When you treat this with dimethoxy methane and camphor sulfonic acid, you get this compound. That means, under this condition this TBS also is getting removed.

And 1, 2 diol is protected in the presence of 1, 3 diol, 1, 2 diol always gets protected faster if we use acetone or ketone, ok. So, that is how that was protected leaving the primary alcohol as such.

Now, when you oxidize the primary alcohol, when you oxidize the primary alcohol you get the C ring fragment, ok. This is the C ring fragment Nicolaou wandered for the Shapiro reaction, ok.

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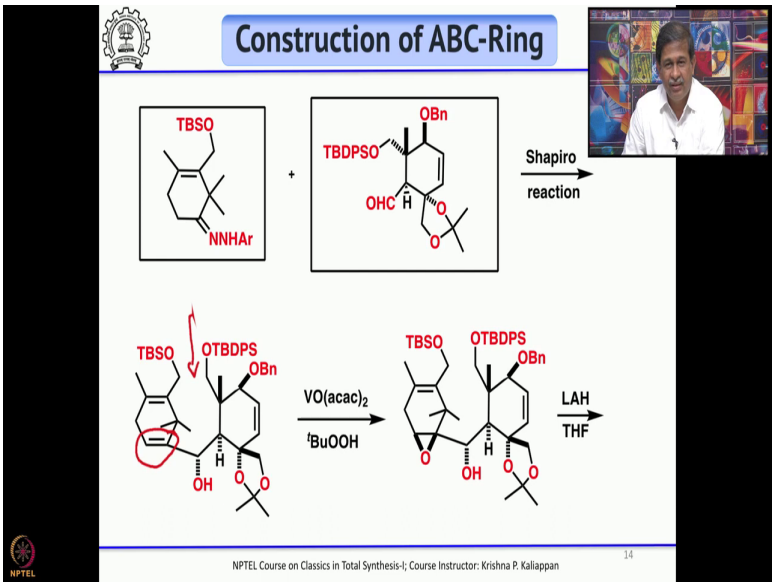

So, you take this tosylhydrazone and then treat with 3, 3.3 equivalent of butyl lithium that will generate the vinyl lithium species, then quench with this aldehyde. So, this reaction as I said it is a Shapiro reaction. So, you get this allylic alcohol, ok. Now, you see everything is there, A ring is there, C ring is there, and B ring all the carbon atoms are there. Only thing is you have to connect these two carbon atoms.

Before that, you have to convert this double bond into a hydroxyl group. So, you do epoxidize the double bond selectively that can be achieved by treatment with vanadium attack in the presence of tertiary butyl hydro peroxide. You get this epoxide, then if you treat with LAH or DIBAL will give you 1, 2 diol. So, LAH or DIBAL will give you 1, 2 diol. So, you get the 1, 2 diol.

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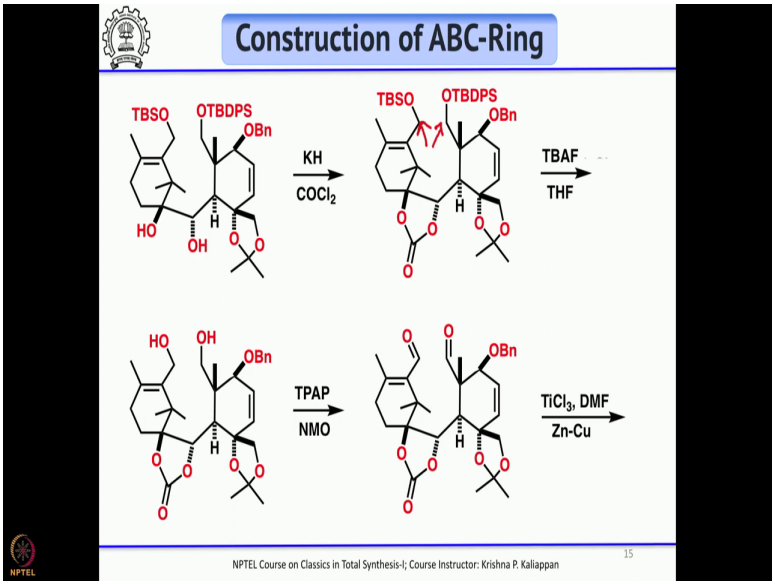

Once you have the 1, 2 diol, protect this 1, 2 diol a cyclic carbonyl. 1, 2 diol now is protected as a cyclic carbonate. So, A ring is ready, C ring is ready, B ring is almost ready except that they have to carry out McMurray coupling here. For carrying out McMurray coupling here what you need is aldehyde on both sides.

So, if you treat with TBAF, both TBS and TBDPS could be removed, then oxidation with the tip of tetrapropyl ammonium perruthenate gives you the dialdehyde, now the dialdehyde under McMurray coupling titanium (0), you could get the corresponding diol, ok.

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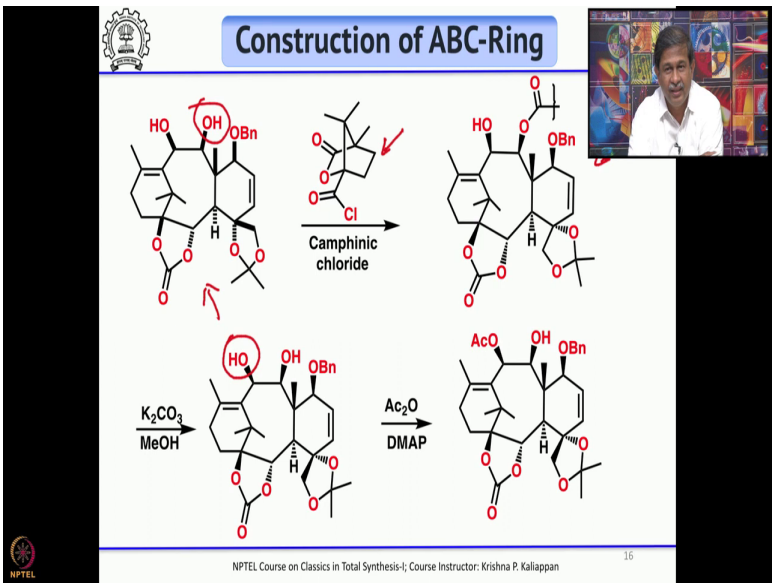

So, you have the diol now. So, now, if you look at this carefully, you have constructed A ring, you have constructed B ring and you have constructed C ring. Now, what you need to do? You need to do some functional group transformation and also attach the side chain. So, before that, whatever we have done they are all racemic, is not it. We have not started with any asymmetric chiral starting material.

So, we have started with all racemic starting material. So, this product is also racemic. If you want to convert this into a chiral one, obviously you have to resolve. So, the resolution was done with camphanic chloride. The camphanic chloride reacts with this alcohol and this is this can be both diol can be β, both diol can be α, ok. These are the two you know +/- diol, but present in 50-50, and using this you can separate this isomer.

And then hydrolysis of this will give you the dial. Now, this is chiral now this is chiral. So, once you have that acetic anhydride give up, so selectively one can acetylate the allylic alcohol. Then, you oxidize the secondary alcohol, oxidize the secondary alcohol with TPAP to get the ketone.

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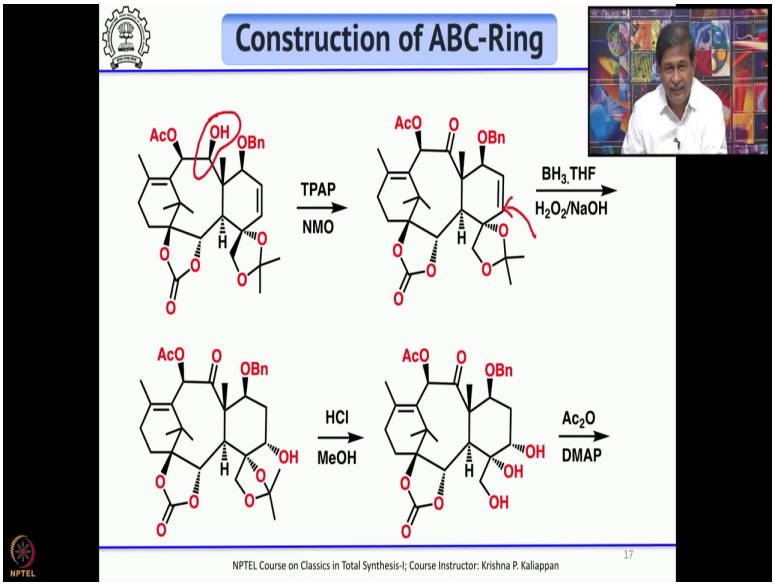

Now, if you look at this B ring is fully functionalized, B ring is fully functionalized. Now, what is required is fully functionalized C ring. So, for that you need a hydroxyl group here. So, that was successfully done with borane THF and then further oxidation to get that alcohol. Now, removal of this acetonide when you remove this acetonide, you get a triol.

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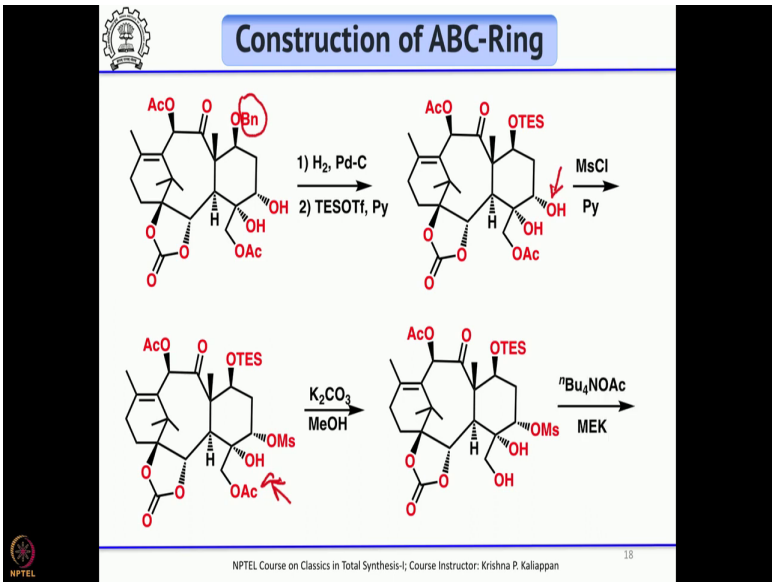

The triol, if you look at carefully, if you treat with acetic anhydride DMAP, only the primary alcohol will be acetylated. The secondary and tertiary will be as such, if you use only one equivalent. Then, we want to form an oxidant intermediate. For that the secondary alcohol should be made as a good leaving group, ok. So, before that, so the benzyl group was removed and then protected as TES ether, ok. Then, subsequently this was mesylated, the secondary alcohol was mesylated to get the corresponding mesyl group.

Now, potassium carbonate methanol hydrolyze selectively the primary acetate here. Then, you get the primary alcohol, this upon treatment with tetra butyl ammonium acetate in the presence of methyl ethyl ketone gives the oxetane ring. It is a SN_2 reaction, ok.

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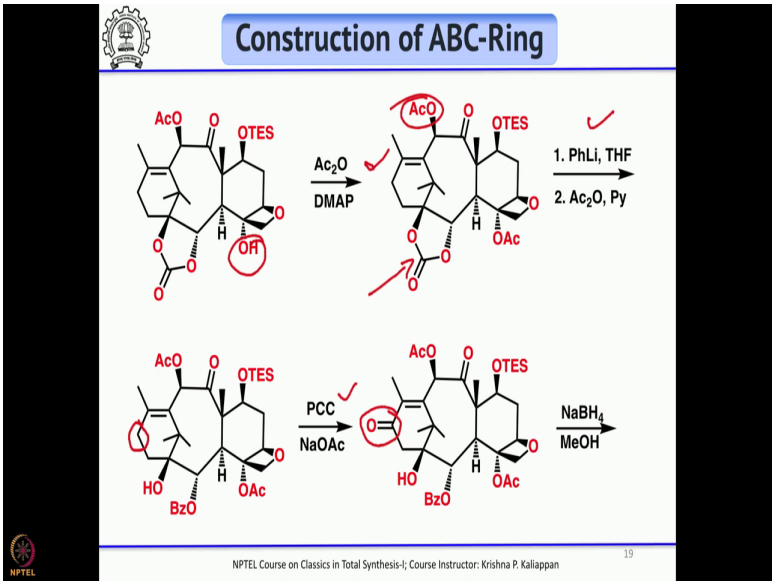

So, for the C ring, to complete the C ring you need acetylation, so that was done easily with acetic anhydride DAMP. Now, you have to open this cyclic carbonate, with phenyl lithium you can see a selectively open this cyclic carbonate to get the benzoate. If you look at this is CH_2, is not it. This is CH_2, you need CH-OH.

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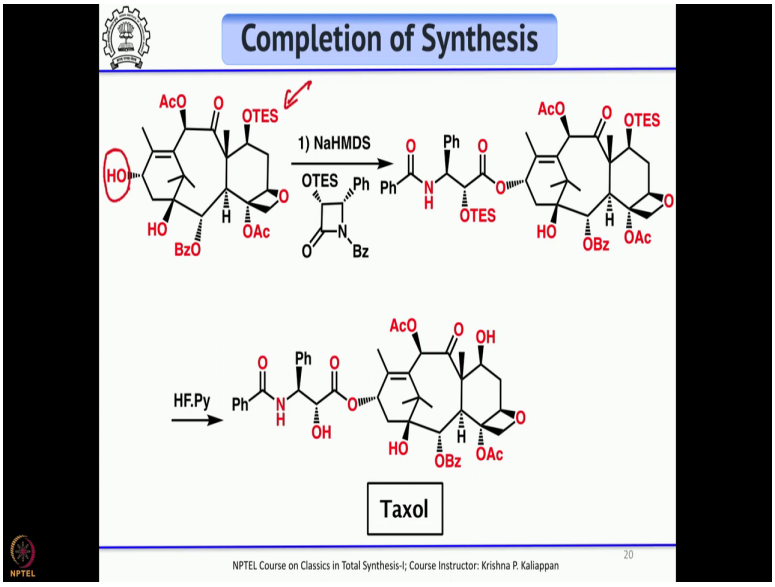

So, PCC and sodium acetate carries out that allylic oxidation to α-β unsaturated ketone. Then, if you reduce the sodium borohydride methanol, you get the corresponding alcohol. And this alcohol upon treatment the sodium hexamethyldisilazide, and this β lactam, I will tell you how this β lactam is made, ok. Commercially, one can make in large quantity. So, that will that free hydroxyl will open up and you get this intermediate.

Now, if you look at this intermediate, except these two all are present in taxol. So, basically you have to remove the TES group. So, removal of the TES group in this intermediate with HF pyridine gave taxol, ok. So, it is so simple, straightforward, but thinking wise you know very very you know complex molecule.

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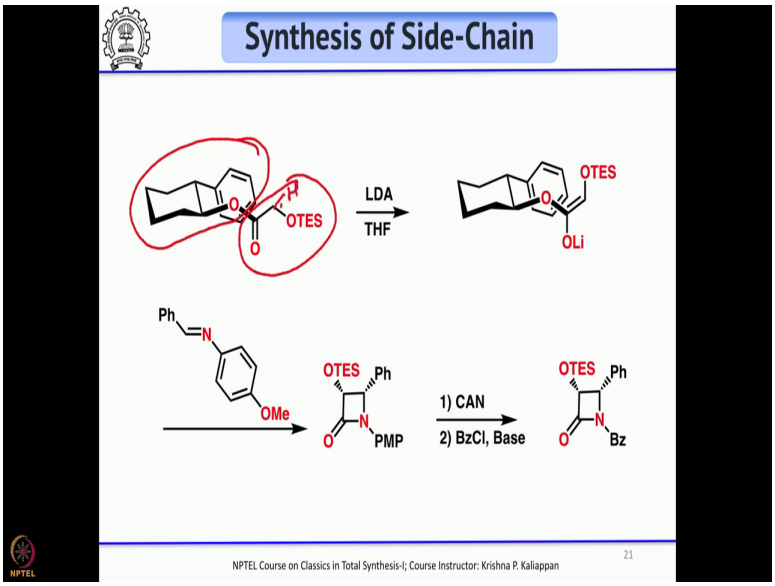

And the side chain was made from this chiral alcohol that is phenyl the cyclohexane alcohol and then this was attached to that. Now, if you treat with LDA, this hydrogen is subtracted by LDA and then it forms the enolate. That enolate upon quench enolate upon quenching with this imine, ok it forms this β lactam, ok. Now, PMP is para-methoxyphenyl group that can be cleaved with CAN, and then protect it as benzyl chloride, so n benzoate and that is the one which was used to attach the side chain, ok.

So, overall if you look at the total synthesis of Nicolaou, Nicolaou used cleverly two reactions, one the Diels-Alder reaction, intermolecular Diels-Alder reaction to construct the A ring and intramolecular Diels-Alder reaction to construct the C ring. Later, he used McMurray coupling to make the highly strained 8 membered ring. Now, all as you know the standard functional group transformation, so you could successfully complete the total synthesis of taxol. So, tomorrow what we will do, we will talk about the total synthesis of Taxol by Robert Holton, ok.

Thank you.