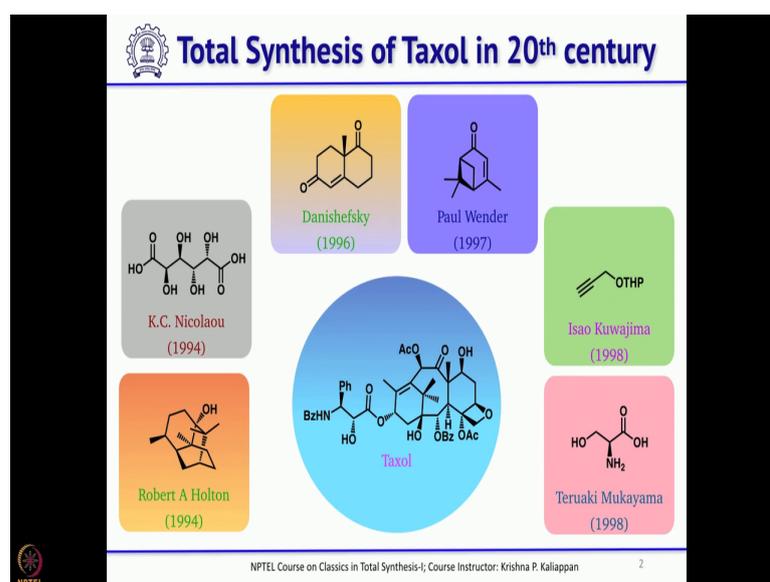


Classics in Total Synthesis-I
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Lecture – 48
Taxol (Danishefsky)

Good morning and welcome back to NPTEL course on Classics in Total Synthesis. So, we have been discussing Total Synthesis of several natural products. In the last class, we talked in details about K. C Nicolaou's total synthesis of taxol using Diels Alder reaction as the key reaction. So, today so, we will move ahead and then we will talk about one more total synthesis which was reported by Danishefsky's group.

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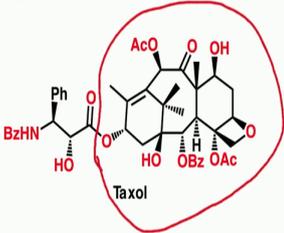


As you know in the 20th century there were six total synthesis and the first one was reported by Robert Holton and are almost at the same time Nicolaou also reported total synthesis of the Taxol, and two years later Danishefsky reported the total synthesis, and a year later Paul Wender reported the total synthesis from a chiral terpene called verbenone, ok.

And, in 1998 Kuwajima reported the total synthesis of taxol and Mukayama reported the total synthesis of taxol from an amino acids.

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 **Total Synthesis of Taxol by Danishefsky**



Taxol

- > The total synthesis of baccatin III has been achieved by Danishefsky *et al.* in 1996
- > The most rewarding aspect of the synthesis was the ability to start with Wieland-Miescher ketone

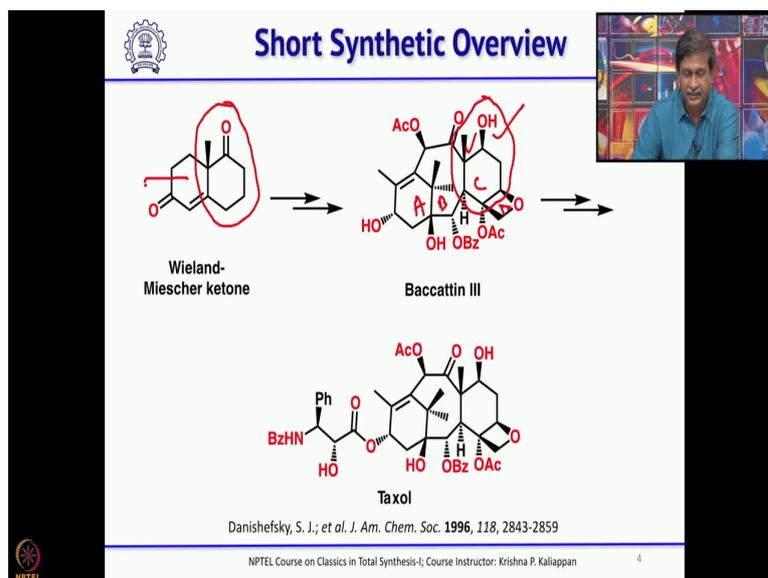
Danishefsky, S. J.; *et al.* *J. Am. Chem. Soc.* **1996**, *118*, 2843-2859

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So, today when we talk about total synthesis of taxol by Danishefsky, so, what he did was he made first the baccatin. So, the baccatin means. So, this is the baccatin structure ok. First he made the total synthesis of baccatin, then followed by attaching the side chain. Thus he completed the total synthesis of taxol. It was reported in 1996 and he started with a very well known starting material called Wieland-Miescher ketone.

So, Wieland-Miescher ketone is commercially available as well as one can prepare in optically active form from 2-methyl cyclohexane 1, 3-dione using L proline as the chiral promoter in the Robinson annulation sequence ok.

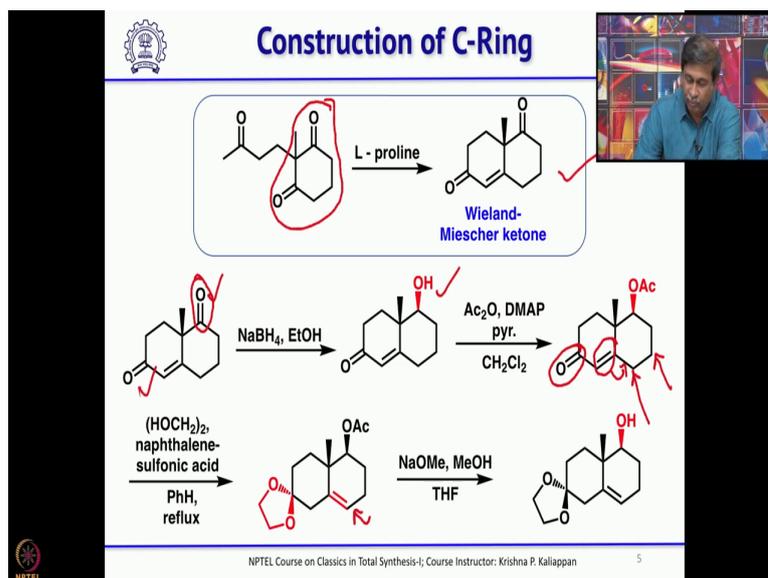
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So, his scheme was started with as I said Wieland-Miescher ketone and if you look at the Wieland-Miescher ketone and then taxol you can see here this x-membered ring has the carbonyl function which later will be converted into the hydroxyl group here and then you have the angular methyl group already fixed. So, this forms the C-ring of taxol, ok.

So, he thought of making the C-ring of taxol. This is A-ring, this is B-ring, this is C-ring and then you have D-ring also, ok. So, the C-ring of taxol came from this cyclohexanone and later he cleaved the other 6-membered ring which later became the 8-membered ring of taxol, ok.

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So, let us see how he worked on the total synthesis. So, first let us start with the construction or synthesis of C-ring because as I said he started with Wieland-Miescher ketone with the intention of making the C-ring from the cyclohexanone ring, ok. So, this was made from the cyclohexane 1, 3-dione 2-methyl cyclohexane 1, 3-dione using asymmetric Robinson annulation to get the Wieland-Miescher ketone ok in optically active form.

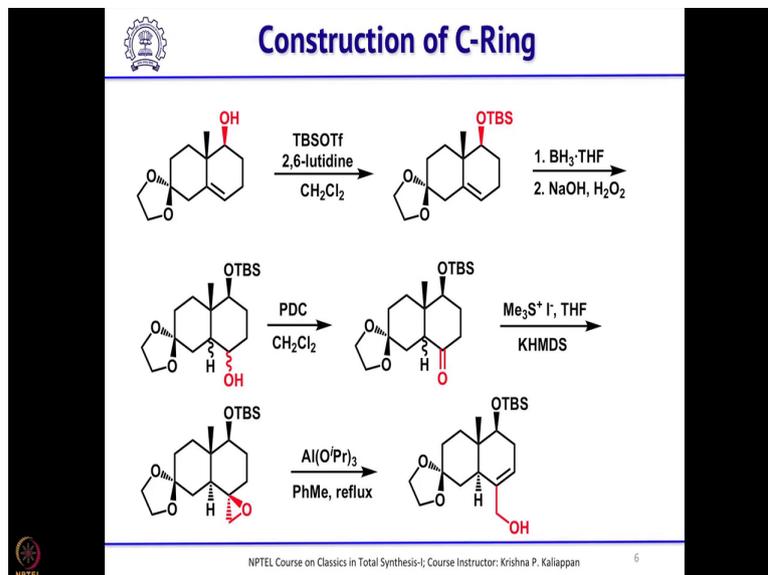
Then you have two carbonyl groups one is α - β unsaturated ketone, other one is a normal carbonyl group, ok. One can selectively reduce the carbonyl group of C-ring using sodium borohydride and ethanol. You can take 0.25 equivalents of sodium borohydride and do it at sub 0, you can get this alcohol. Once you have this alcohol you can protect the alcohol as acetate by treating with acetic anhydride and DMAP.

Now, when you protect the carbonyl group of the α - β unsaturated ketone under acidic condition what happens invariably their double bond migrates to the other ring, ok. So, this is well known in the literature when you protect the ketone of α - β unsaturated ketone the double bond migrates to the other ring, ok.

Now, as you know for the C-ring you need to functionalize these two carbon atoms because that is where you have the oxetane ring. So, the pushing of the double bond to the other ring actually helps. So, how it helps? Now, the double bond if you do hydroboration and oxidation you will get the hydroxyl group at this carbon ok.

So, before that you have to remove the acetate ok. So, that could be easily done by treatment with sodium ethoxide methanol.

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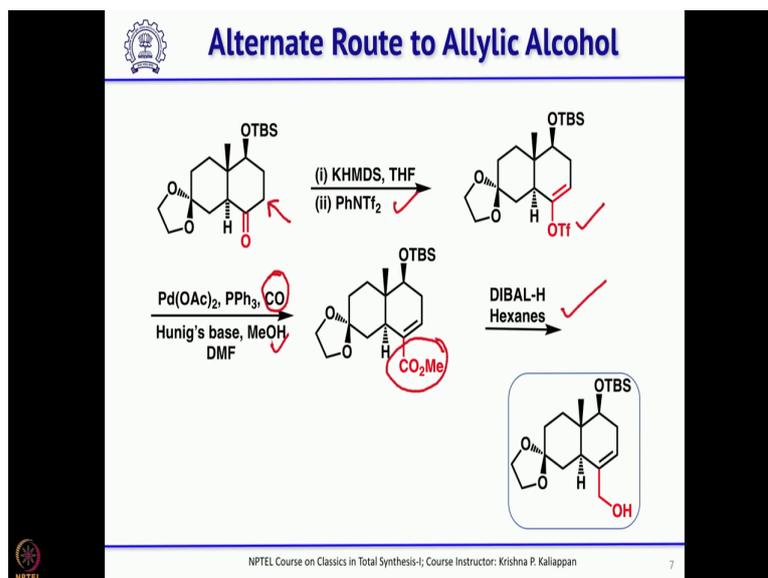


Then protect the alcohol ok, pre protect the alcohol as TBS ether ok. Protect this as TBS ether, then as I said you do the hydroboration oxidation and you introduce the hydroxyl group.

Now, using this hydroxyl group using this hydroxyl group you have to introduce the oxetane ok. The first step is obviously, the oxidation of the secondary alcohol to the ketone, ok. So, now, you have the ketone. From this ketone he got the oxetane by two different routes ok. The first route where he has used trimethyl sulfonium ylide ok, when you have this trimethyl sulfonium iodide treatment with potassium hexamethyldisilazide it forms trimethyl sulfonium ylide ok. That ylide attacks this carbonyl group and it forms the epoxide ok.

Now, if you treat with a Lewis acid aluminum tri isopropoxide that opens the epoxide and it generates a positive charge followed by loss of proton you get the allylic alcohol. So, now, what you have done? You have introduced another function group. So, using this double bond one can get the oxetane which is required in the CD-ring.

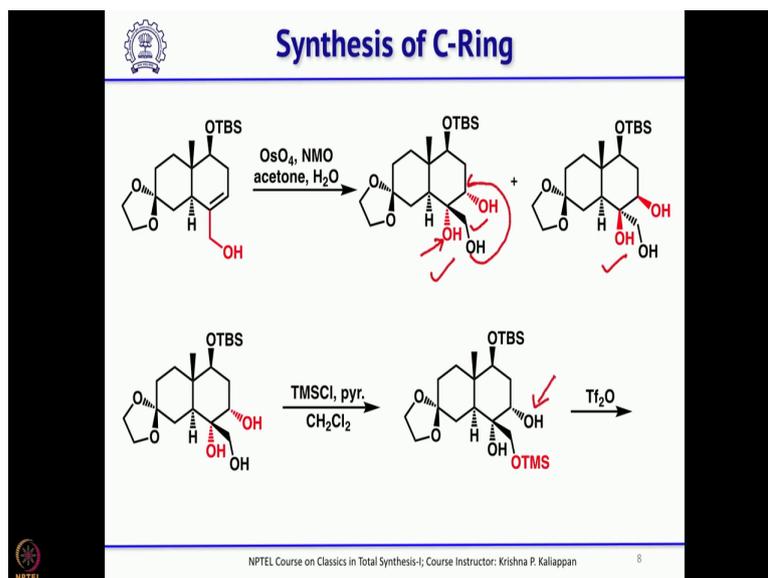
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Another method to get this allylic alcohol he started with the same ketone, but what he did was he treated with a base potassium hexamethyl disilazide generates an anion and you quench that enolate with PhNTf₂ to form the enol triflate, then palladium catalyzed carbonyl insertion ok palladium catalyzed carbonyl insertion followed by attack of the intermediate with methanol, one can convert the enol triflate to α - β unsaturated ester, ok.

Once you have α - β unsaturated ester simple reduction with **DIBAL** gives the same allylic alcohol, ok. So, the allylic alcohol was prepared by two different routes. This method actually involved four steps whereas, the earlier method involved only two steps.

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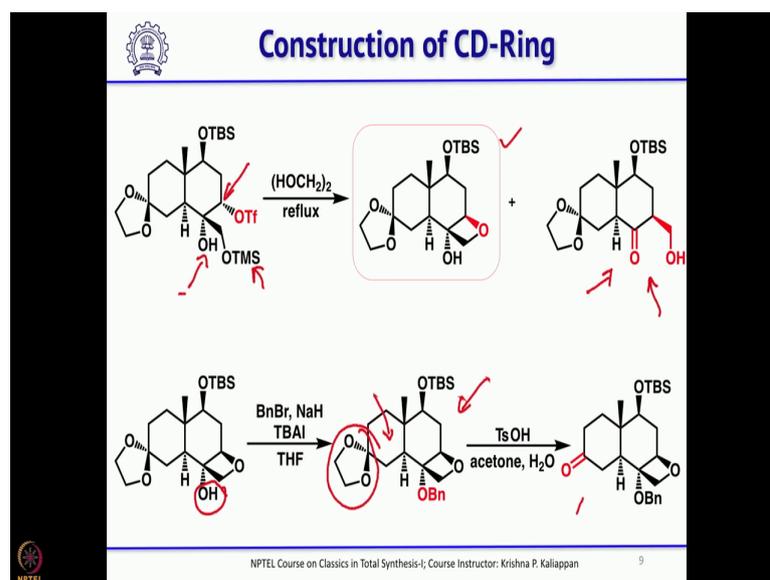


So, with this allylic alcohol in hand the next task for Danishefsky's group is to make the oxetane ring that a 4-membered oxetane ring. So, for that you need to do a dihydroxylation ok. So, simple osmium tetroxide di-hydroxylation gave a mixture of the required triol with some amount of the unwounded triol with some amount of the unwanted triol, ok.

Now, if you see so, the hydroxyl group here which is should be α in the taxol if you see that is OAc , then this $-CH_2OH$ also should be β and using this you can cyclize here, ok. So, what you need to do is the primary alcohol you have to protect it, then the secondary alcohol you have to make it as a good leaving group, then you make the oxetane ring followed by protection of the tertiary alcohol.

So, the primary alcohol was in situ in situ protected as a TMS ether; as you know TMS is a labile protecting group and that was protected. Then the secondary alcohol so, the secondary alcohol was protected as triplet, ok the secondary alcohol was protected as a triflet.

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So, now you can see the secondary alcohol is made as a good leaving group. Now, if you remove the TMS if you remove the TMS automatically the O^- can attack intramolecularly and form the oxetane ring. So, this was accidentally observed by treating with ethylene glycol. So, when they reflux with the ethylene glycol. So, it removed the TMS and then also formed the oxetane.

They also got a very interesting product. If you look at this product you can easily you know explain how this would have formed when you see a 1, 2 diol when you see a 1, 2 diol. One rearrangement which should come to your mind is pinacol – pinacolone rearrangement, is it not? So, here the secondary alcohol is made as a good leaving group and you have a tertiary alcohol.

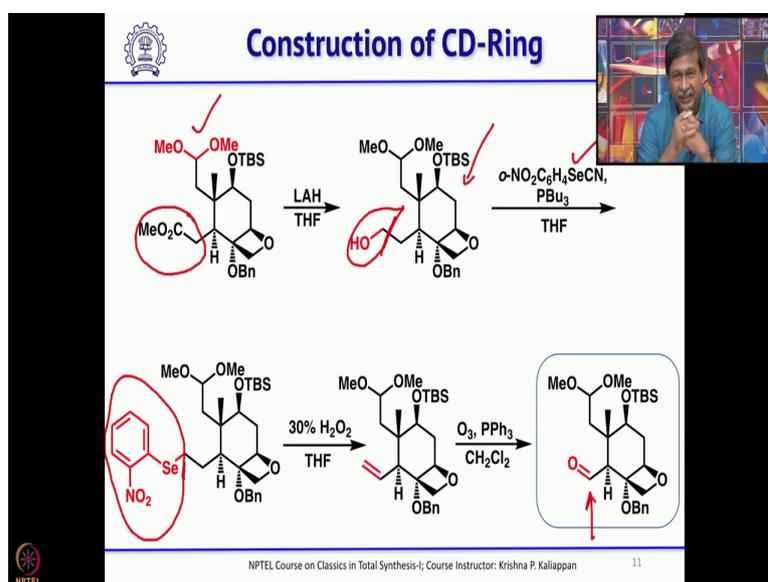
So, automatically the reaction which should come to your mind is pinacol pinacolone rearrangement. So, this product is obtained by pinacol – pinacolone rearrangement, ok. The expected product the required product was converted into the corresponding benzoate that is the tertiary alcohol. The tertiary alcohol was protected as benzyl ether though if you look at the natural product, the tertiary alcohol should be protected as acetate, but acetate is a level protecting group.

And, this has to undergo so many functional group transformation. This particular intermediate has to undergo so many functional group transformation. So, it is better to

earlier it was 6-membered ring, now that has been opened ok. So, it has to be converted into 8-membered ring and at the same time you also have to attach the A-ring, ok. A-ring and B-ring together it should be attached. So, how he did?

So, if you look at this you have a carbonyl group in the form of aldehyde and another carbonyl group in the form of ester one can easily differentiate these two, ok as you know carbonyl group of aldehyde is more reactive. So, that aldehyde is protected as acetal with methanol and mild acid. So, you have protected the aldehyde now.

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Now, what you need is you have to remove one carbon you have to remove one carbon and get aldehyde there, ok. I will tell you why we need that when I come to the attachment of A-ring to this ok.

So, this is done first you reduce the ester to alcohol with LAH, then what you need? As I said you need to remove one carbon basically you have to cleave this, ok. You have to cleave this to get this aldehyde. So, this is the intermediate you need because this upon treatment with A-ring. So, you have A-ring which is a 6-membered ring. The 6-membered ring can be easily attached to this aldehyde, ok.

This has one extra carbon; this has one extra carbon that extra carbon should be removed. How one can remove? If you carefully look at this, if you can convert this alcohol into a double bond ok if you can convert this alcohol into a double bond then

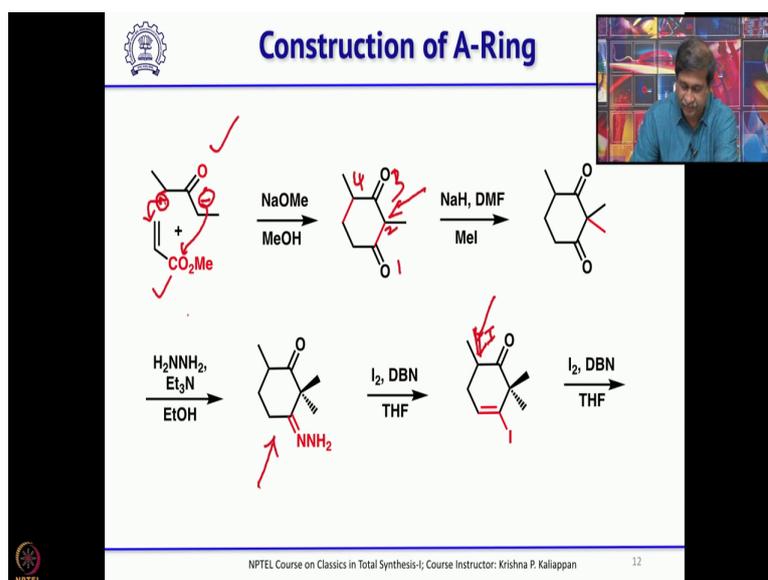
simple was ozonolysis you can get this aldehyde, is not it? You can remove one carbon. So, how do you introduce a double bond ok? So, that is a very interesting method where you can treat this with this corresponding selenocyanate ortho-nitrophenyl selenocyanate in the presence of tributylphosphine.

So, what happens? The OH is replaced with this corresponding selenium ok. When we introduce selenium you know in the literature it is well known. For example, if you have a ketone, if you want to introduce a double bond next to the ketone normally what do you do? You treat with the base and then treat with phenyl selenium chloride so that you can introduce a -SePh at the α carbon.

Now, mild treatment with you know per acids like mCPBA, hydrogen peroxide it will oxidize the selenium to selenoxide and then automatically selenoxide elimination will take place to introduce the double bond. So, once you have done this now you introduce the seleno group just to treat with hydrogen peroxide. So, as I said it will oxidize the selenium to corresponding selenoxide followed by elimination of a corresponding ortho-nitroselenic acid you get the double bond.

So, once you have the double bond it is very simple and straightforward you do the ozonolysis, ok. Ozonolysis will give the aldehyde. So, now, you have the real CD-ring with two substituents at C-ring which can be attached to A-ring to form the B-ring, ok.

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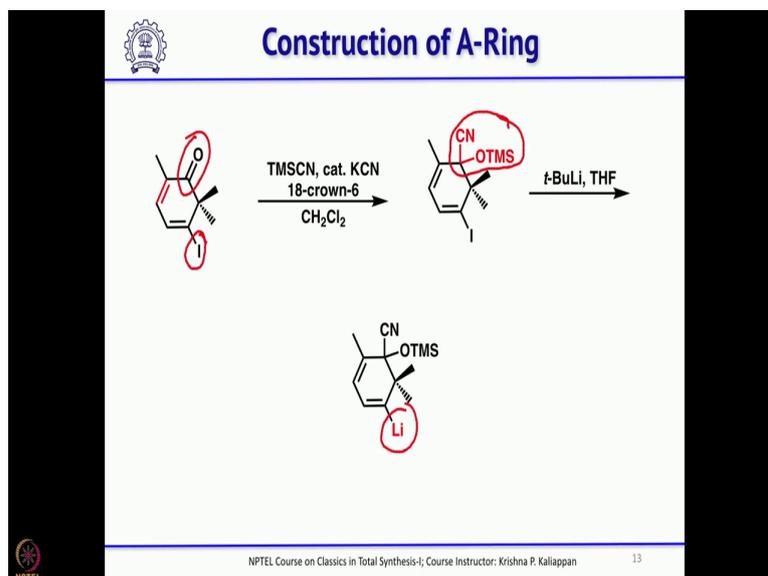
So, with this now, we will see how they made the A-ring, ok. They started with very very simple compound. So, one is methyl acrylate, other one is 3-pentanone, these two are commercially available, ok methyl acrylate and 3 pentanone.

Now, if you treat with sodium ethoxide methanol, ok very interesting. See you can see first the enolate that is carbanion is formed here and it undergoes 1, 4 addition and another enolate forming on the other carbon the carbanion can attack this and it gives a very good yield a decent yield of this cyclohexane ok cyclohexane 1, 3-dione ok 1, 3-dione ok.

And, then 2 position you have methyl group and 2 and 4 position you have methyl group 2, 4 dimethyl. Now, what you need is you need if you look at taxol at this carbon you need one more methyl group. So, that is very simple you treat with sodium hydride and then methyl iodide you get this component, ok. So, now, it has all the functional groups present in A-ring.

You treat with hydrazine, ok. Why hydrazine? Because later he wanted to introduce a vinyl iodine. He wanted to introduce a vinyl iodine. So, it is well known if you have hydrozone and then treat with bases like DBU or DBN and iodine it will form the corresponding vinyl iodine. So, that is what he did ok. But, what happened? When he treated with excess iodine and DBN excess iodine and DBN ok so, one more iodine was introduced at this carbon ok.

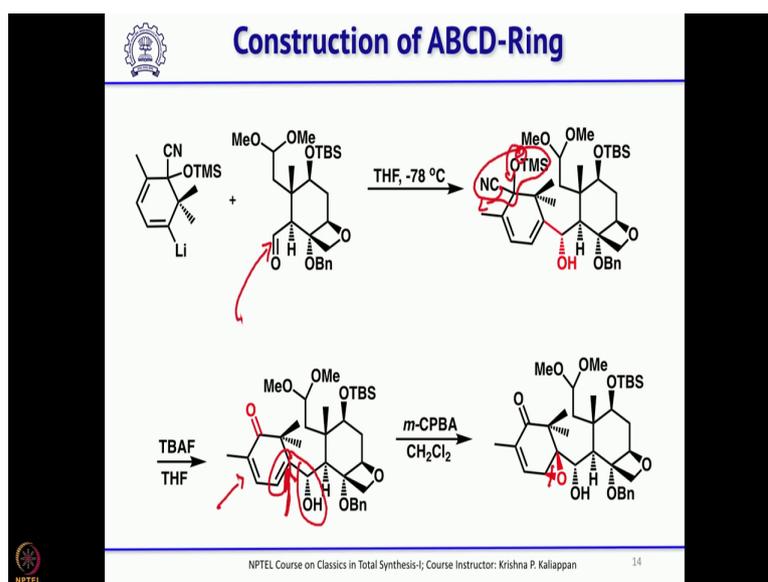
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And, followed by elimination, so, we got another double bond, ok. Two double bonds were formed, it is ok. Good. So, now, what we need is as I said this iodine should be exchanged with lithium and added to the aldehyde ok. So, before that this carbonyl group should be protected is not it if you have to treat with tertiary-butyllithium to exchange the carbonyl group should be protected, ok.

So, how to protect the carbonyl group? You can in situ protect with TMS-CN and catalytic amount of potassium cyanide. So, basically it is a cyanohydrin formation, ok. The cyanohydrin formation and the cyanohydrin hydroxyl group is protected as TMS ether, ok. Then if you treat with tertiary-butyl lithium, the iodine will be exchanged with lithium. So, this is the A-ring once you have this A-ring already we have made the C-ring with the aldehyde ok.

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Straight away you can add this final lithium which is prepared in situ and added to this aldehyde, ok. Now, you can see you have coupled the A-ring and CD-ring A-ring and CD-ring ok now what you should do you should get back you should get back the ketone here. So, if you take one equivalent of TBAF ok you have TBS as well as OTMS, but OTMS is very labile.

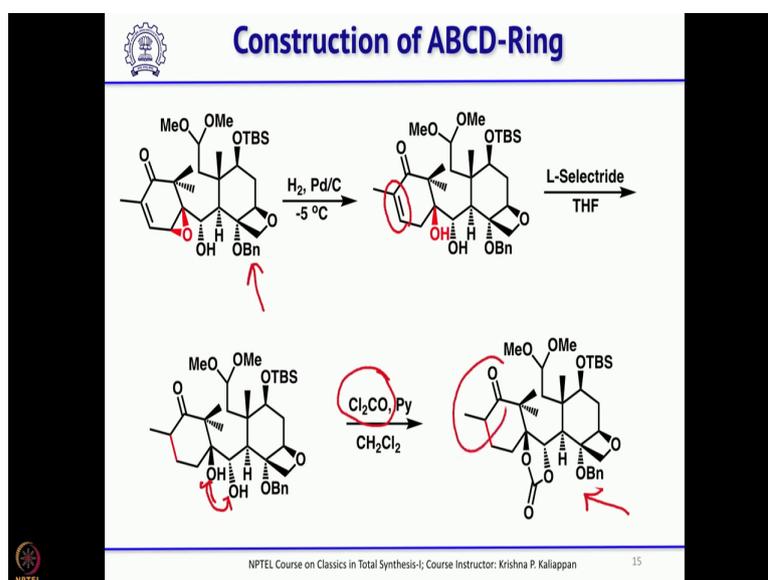
So, you can easily cleave the OTMS. So, that means, it becomes O⁻. As you know cyanohydrins are unstable that is because cyanohydrins if we have base then it will form O⁻. When O⁻ is there O⁻ will come back and then eliminate cyanide.

So, here that is the same principle once you treat with TBAF immediately TMS group goes and then you form O⁻. That O⁻ here comes and then cyanide comes out and you get the ketone ok. So, what is to be done? If you look at taxol at this position you have a hydroxyl group, is not it? At this position you have a hydroxyl group. So, now, you have a double bond. So, that double bond should be converted into a hydroxyl group.

So, if you treat with m-CPBA, if you treat this compound with m-CPBA there are two double bonds ok. One is electron rich, other one is electron deficient because this double bond you can say it is allylic alcohol, ok. So, now, if you treat with m-CPBA only this double bond will be epoxidized only this double bond will be epoxidized, ok. Then you have to open the epoxide you have to open the epoxide.

As you know if we have allylic ether, benzylic ether, allylic epoxide, then under hydrogenolysis condition one can cleave this type of C-O bond, ok. It is like hydrogenolysis of allylic ethers, benzyl ethers and this is also an allylic ether, is not it.

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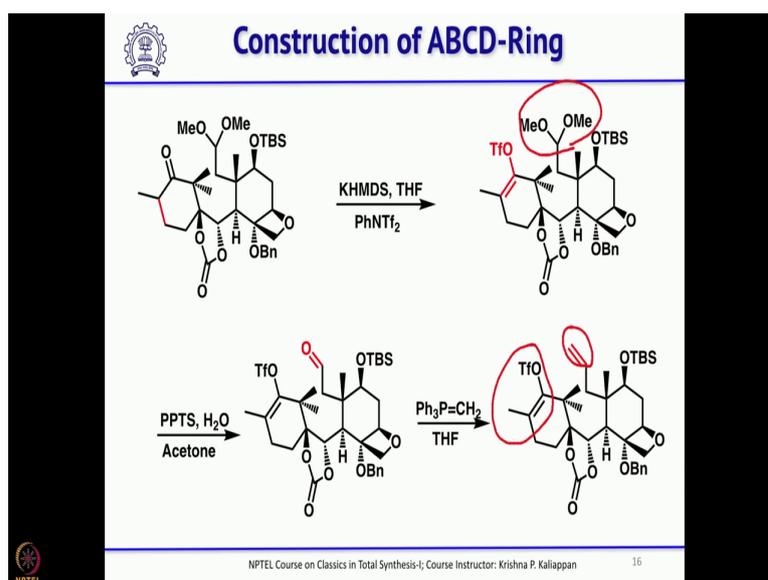
So, if you treat with hydrogenation condition at low temperature very important because otherwise you have benzyl group here O benzyl that also will be removed, ok. Under -5^o C one can selectively open the epoxide to get the hydroxyl group ok.

Now, once you have these two hydroxyl group just reduce the enone reduce the enone with L selectride, ok. Then you protect this diol protect this diol 1, 2 diol with posgene

ok with pos gene to get the corresponding cyclic carbonate. The southern hemisphere now it is fully functionalized southern hemisphere of taxol is fully functionalized, ok. Now, what we need to do is you have to connect the northern hemisphere ok.

So, original plan was to carry out an intramolecular heck reaction ok. So, for that what you need? You need this to be enol triflate ok.

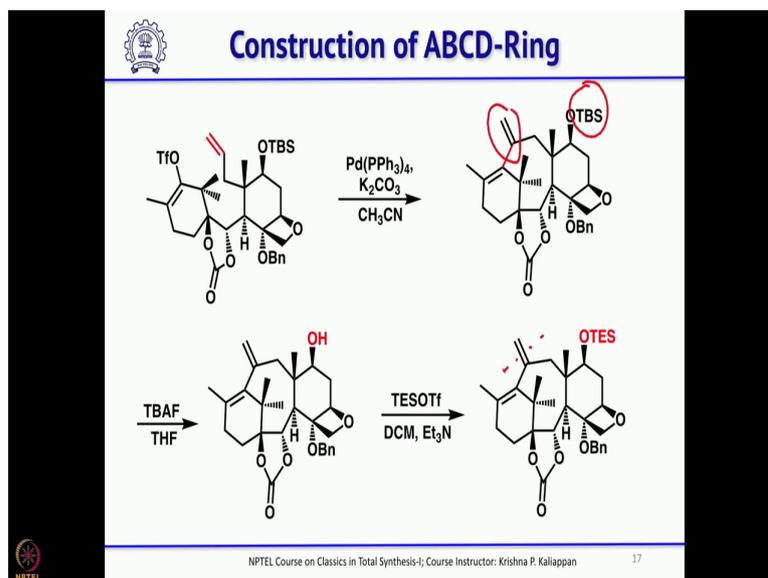
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So, that is very easy you treat with base and quench with the corresponding triflate agent. So, you get the enol triflate and for heck reaction other side you need double bond. So, you have to remove this acetal and convert it into double bond that is also simple. So, remove the acetal and then do a Wittig reaction you get the double bond.

So, now, you see the key intermediate is there and a successful intramolecular heck cyclization between this vinyl triflate and the double bond should give 8-membered ring with the exocyclic double bond ok.

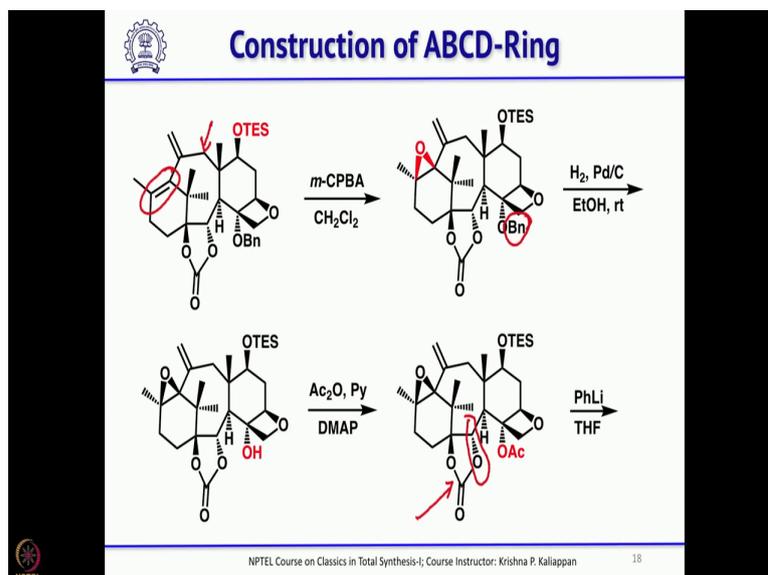
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So, that is what happened. So, you take the vinyl triflate and then treat with you know tetrakis palladium phosphorous. So, as you know this is a very interesting reaction and he got a decent yield of this 8-membered ring, ok. This intramolecular heck cyclization gave this 8-membered ring, ok.

So, now you remove the TBS with TBAF and re protect it as TES because TBS was creating trouble. So, they changed to TES ether. So, now, what you need to do is you need to remove the double bond, ok.

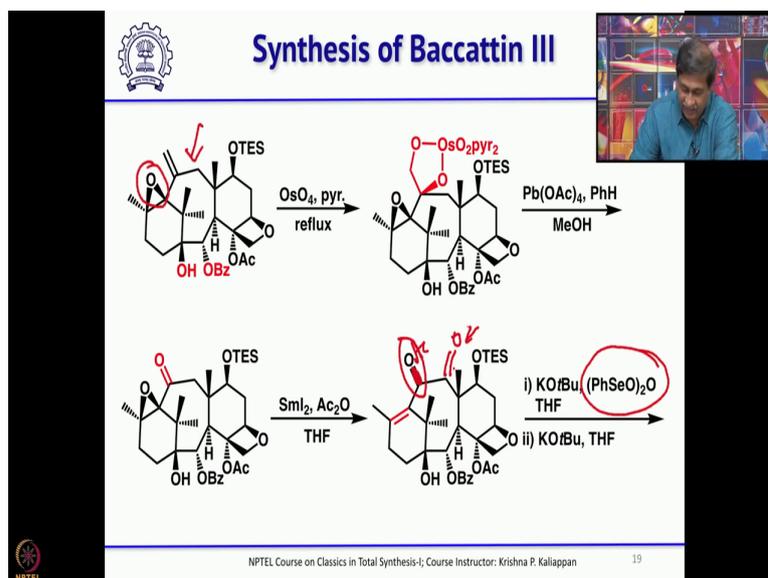
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So, the removing the double bond at the same time you have to introduce a hydroxyl group here, carbonyl group here ok. So, before removing the double bond first he has to protect this internal double bond ok. So, that was done with m-CPBA ok. Then you do the ozonolysis and before doing ozonolysis you can remove the benzyl group now.

Now, the benzyl group ok it has served its purpose, ok. You can remove the benzyl group and get the alcohol then acetate because in taxol you need the acetate, is'nt it? Yeah. So, do the acetate protecting group. Now, you treat with phenyl lithium as you know in the B-ring this is O benzoate, ok. To get O benzoate if you treat with phenyl lithium it opens regio-selectively and you get o benzoate here and at the bridge head you have hydroxyl group.

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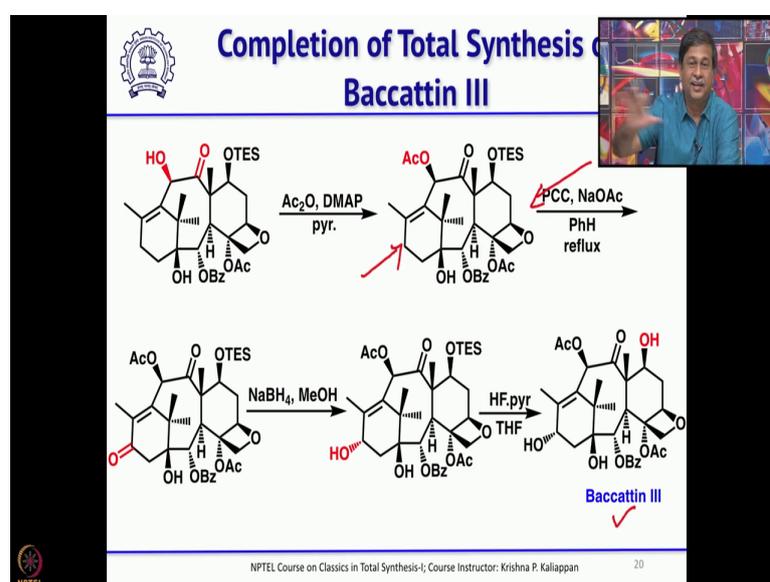
So, this is well established by others. So, straight away you get this compound. Now, if you look at this it has almost all the functional groups except in B-ring you need a ketone and acetate, and also this epoxide which was originally protected is not required ok. So, now, what you do? You treat with osmium tetroxide followed by cleavage with ditetra acetate. This is a standard method to get the ketone ok double bond to ketone.

Now, if you treat with samarium iodide samarium iodide a radical anion followed by opening up this epoxide to get aldol like product that upon treatment with acetic anhydride undergoes elimination and you re-introduce the double bond in A-ring at the same time what you got is the keto functional group.

But, in taxol you have ketone here and you have O acetate here, is not it? So, how will you do that? How you introduce ketone here and a acetate? So, how it is done? You generate enolate ok generate enolate and then treat with you know introduce an oxygen using this particular reagent.

So, basically what you have done is you enolate and then introduce a hydroxyl group and once again when you treat with potassium tertiary butoxide the it rearranges. It becomes this side it becomes ketone, this side it becomes hydroxyl group ok.

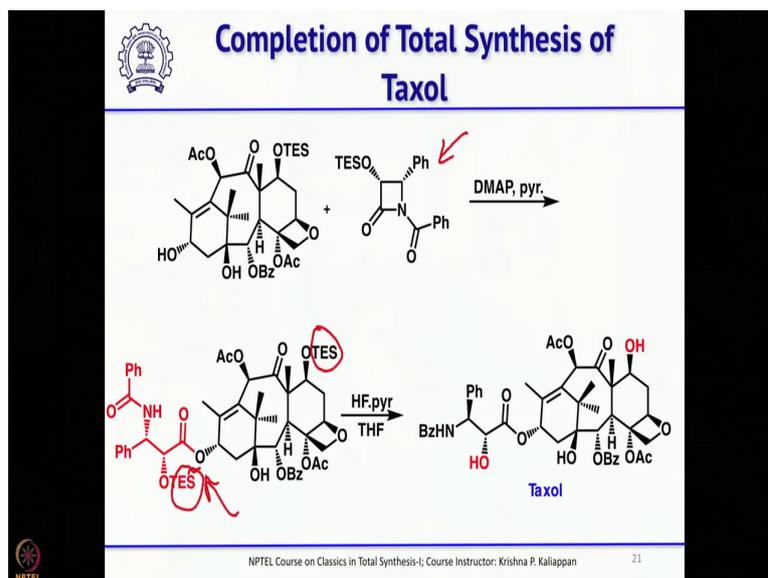
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Now, that compound if you acetylate and this is what you need this is what you need for taxol. Now, if you see you have everything what is required in the ring except the side chain here, ok. So, that is simple. So, you oxidize with PCC and you get the α - β unsaturated ketone. That α - β unsaturated ketone if you reduce the sodium borohydride you get the allylic alcohol ok.

So, now the allylic alcohol if you treat with HF pyridine, if you treat with HF pyridine then you get a natural compound called baccatin III ok. So, you synthesize baccatin III, but instead if he takes this compound if he takes this compound then treat with Ojima's lactam, ok.

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This we already discussed when we talked about total synthesis of taxol by K. C Nicolaou we discussed this ok. So, you take this alcohol and treat with Ojima's lactam, then you can get or you can easily introduce the side chain.

So, now what you need is you have to remove this TES group. If you remove the TES group that will be the taxol molecule ok HF pyridine, he could successfully remove the TES group that gave taxol. So, he could successfully synthesize taxol from commercially available Wieland-Miescher ketone and also the 2, 4-trimethyl cyclohexane 1, 3-dione which also can be easily prepared from methyl acrylate and 3 pentanone, ok.

So, that is how his synthesis was very simple and straightforward and it is though the number of steps is more, but it involved you know very simple and straightforward synthesis ok.

Thank you.