Classics in Total Synthesis - I
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Lecture - 20
Triquinanes by other reactions

So, welcome back to NPTEL lecture series on Total Synthesis of natural products. The last four lectures we talked about many total synthesis of triquinanes and there are many more methods for making five-membered rings. So, today I will just talk about few methods where five-membered rings can be made and also discuss one more total synthesis of triquinane. Pauson Khand reaction is one reaction where routinely people use to make five-membered rings.

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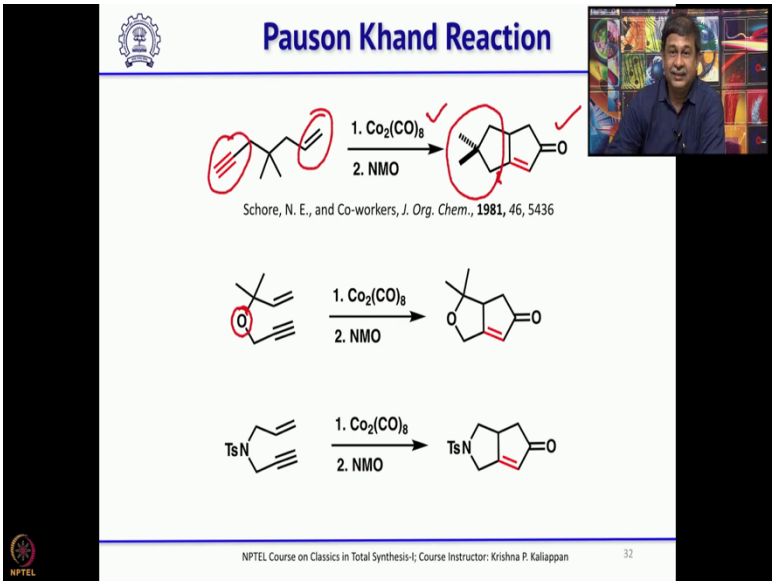

See for example, if you have a double bond and a triple bond at appropriately placed. Then if you treat with dicobalt octacarbonyl and followed by oxidation with N-methylmorpholine N-oxide or dimethyl sulfoxide one can get the corresponding cyclopentenone. So, depends on the ring size you get the other ring can be five membered, four-membered or any ring, but this Pauson Khand reaction will give five-membered ring.

Particularly this reaction works on the other side if it is six-membered and five-membered ok. So, here you have a diquinane structure and this is another example where

you can see you can put a heteroatom ok. It can be the heteroatom can be oxygen or heteroatom can be nitrogen still this reaction works well to give the corresponding cyclopentenone.

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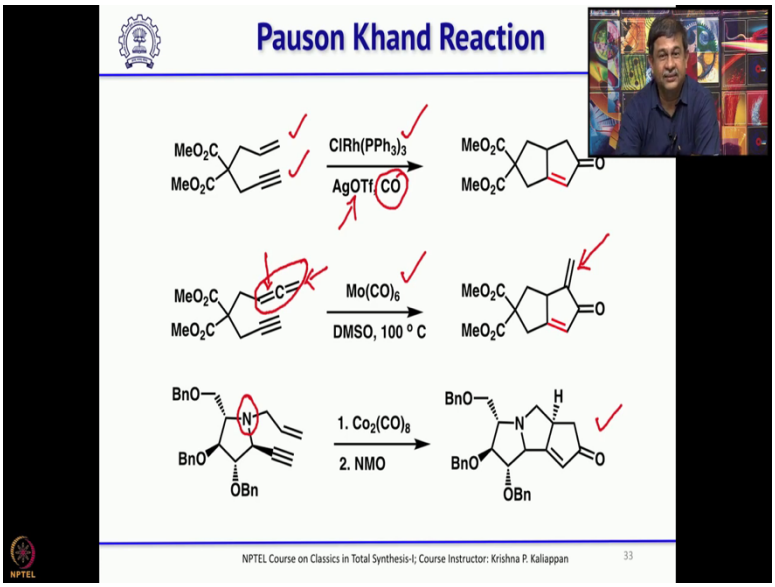

And one can also use other reagents for example, one can use Wilkinson catalysts. The same condition you have a double bond you have a triple bond, but here for the carbonyl source you do this reaction in under carbon monoxide atmosphere. And you also have to use silver triflate to get the corresponding bicyclic compound. One can also use molybdenum hexacarbonyl in DMSO and if you reflux at 100 degrees you can do the same thing and this is interesting combination where instead of double bond you have an allene ok.

So, allene that internal double bond undergoes Pauson Khand reaction. So, you see this double bond the terminal double bond becomes exocyclic double bond in this case. And one can also use this for hetero triquinanes in this particular case you have a nitrogen and with this nitrogen one could make the aza triquinanes using Pauson Khand reaction as the key reaction.

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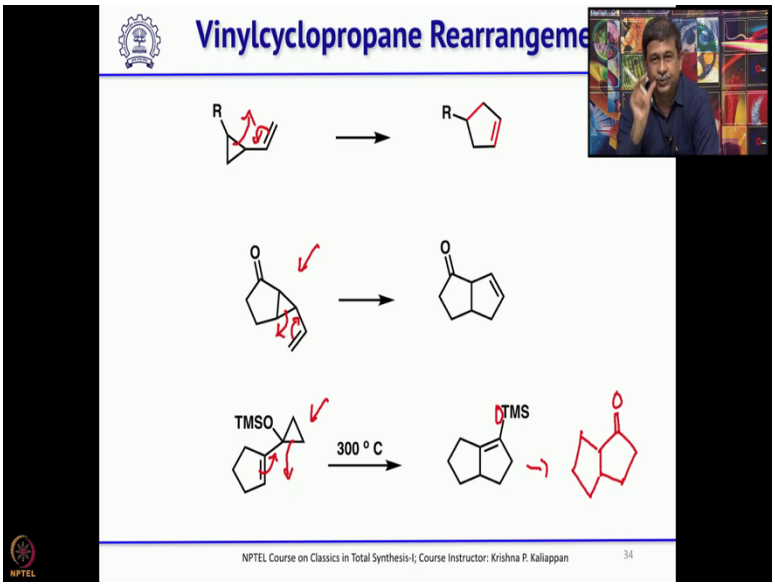

And there are other methods as I said for used for making five-membered ring. One of the methods which are which is quite frequently used is vinylcyclopropane as you know vinyl group attached to cyclopropane can undergo like this rearrangement. For example, you can write like this the cyclopropanes are like double bond and sometimes cyclopropane as you know because of this ring strain it tries to open. And if you heat it this can undergo this type of cyclopropane vinylcyclopropane rearrangement to give cyclopentene.

So, here is another example. So, this can undergo vinylcyclopropane rearrangement to give this di quinane. This is another interesting example where you have a cyclopropane attached to the double bond and the double bond is part of a five-membered ring. So, this will give you this enol TMS ether and one can hydrolyze this to give the corresponding ketone.

If you hydrolyze this with acid you will get the corresponding di quinane having a carbonyl group. So, this vinylcyclopropane rearrangement also has been used to make at least two five-membered rings if not for 3 or 4.

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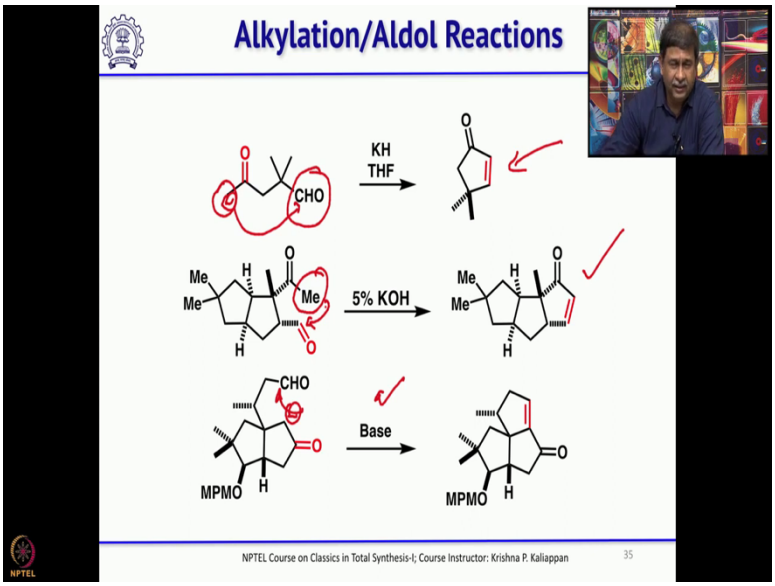

Then the standard reaction which is routinely used for making five-membered ring is aldol reaction. So, you have an aldehyde here and methyl group. So, you can generate anion here that anion can attack this aldehyde followed by elimination of water you can get the five-membered ring and same thing you can see you have methyl group you can generate anion add to this aldehyde.

So, that also will give a five-membered ring of course, this has been used in the total synthesis of one of the triquinanes that is a linear triquinane. And this has been used this particular example has been used in the total synthesis of an angular triquinanes. So, you can see you can generate anion attack this aldehyde followed by elimination of water you get angular triquinane.

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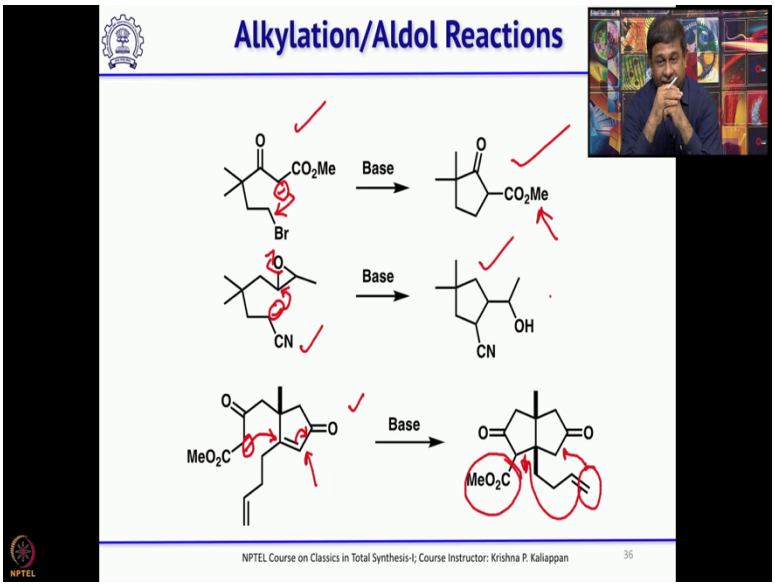

So, alkylation aldol reaction sometimes even Michael addition or opening of the epoxide have been used successfully for making five membered ring. So, if you look at this example it is a beta keto ester. So, one can easily generate anion here and intramolecular SN_2 substitution will give this five membered ketone ok.

So, if you decarboxylate then you get corresponding ketone otherwise you get the corresponding beta keto ester. The next example you have a cyanide of course, because of the cyanide you can remove this proton once you remove this proton using a base maybe you need strong non-nucleophilic bases like LDA that can immediately open this epoxide to give the corresponding five-membered ring.

And this particular example is very interesting you have a Michael acceptor and you have Michael donor. It is a keto ester beta keto ester the anion can be easily generated selectively this can undergo a 1, 4-addition intramolecular, 1, 4-addition to form two five-membered ring it is a diquinane. Now one can remove this ester because it is a beta keto ester. So, that will give symmetrical molecule then this double bond can either cyclize here or it can cyclize at this carbon.

So, that that is how one can make angular triquinanes. So, Michael addition followed by an aldol reaction one can construct a triquinane and in this case it is an angular triquinane.

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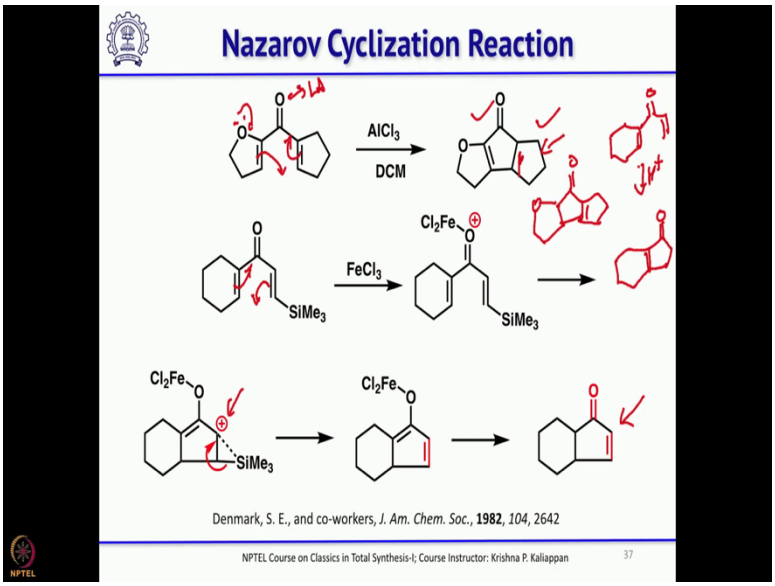

So, there is another reaction which is called Nazarov cyclization. See this Nazarov cyclization is nothing but if you have a dienone ok so like this you have. Then this on treatment with acid you get corresponding five-membered ring and more substituted double bond you get a cyclopentenone and the double bond is more substituted ok.

And you can also control the regioselectivity of the double bond formed say for example, if you take this example ok. So, there are two possibilities one what I have written here another one it can also form like this is not it. But between these two only this forms the reason is as soon as it coordinates with Lewis acid more than this double bond migrating this double bond will migrate. And because of the lone pair here next this double bond will migrate. So, that will give you this as the major product.

So, depending on what you want you can use a substituent in the dienone to get exactly where the double bond is required you can also use silicon, silicon also used to control the double bond which is required. So, for example, if you want the double bond to be here in this double bond here so then what you do you put a silicon at that carbon ok.

So, now what happens? Instead of this double bond migrating first this will migrate followed by migration of this. So, what will happen? Silicon is known to stabilize carbocation or beta-carbon. So, this is called beta silicon effect silicon carbon bond can be easily cleaved ok. And particularly if it has to neutralize the positive charge at the beta

carbon then this can be easily cleaved to get this diol ether this upon hydrolysis will give you this ketone.

So, basically under normal Nazarov cyclization you get more substituted double bond. Whereas, if you use a silicon then you can also get less substituted double bond as the major product ok.

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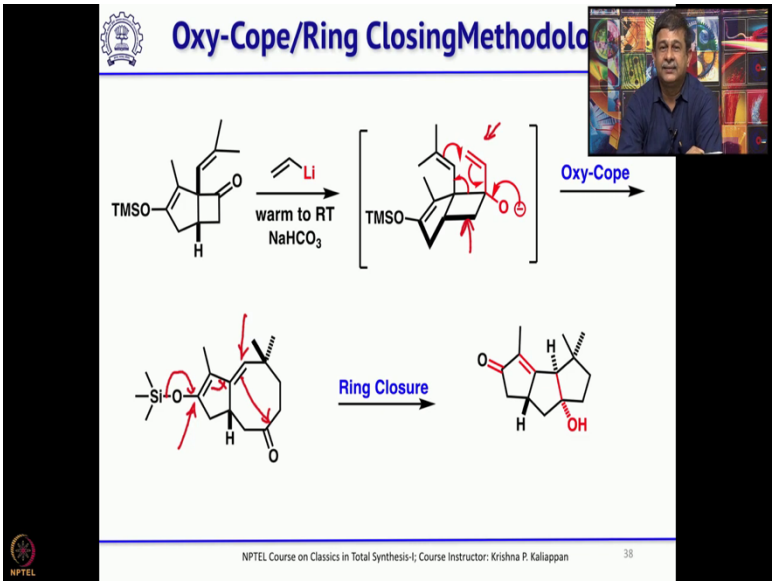

Then there is another very interesting methodology is a tandem reaction where oxy Cope rearrangement followed by ring-closing methodology. It is almost like oxy cope rearrangement followed by intramolecular Mukaiyama type aldol reaction ok. So that also could be successfully used or has been used for the synthesis of triquinanes.

So, for example, this bicyclic compound if you treat with vinyllithium if you treat with vinyllithium you get this intermediate. Now if you look at this intermediate this intermediate is a classical oxy Cope intermediate classical oxy Cope intermediate. So, this will give you the corresponding eight-membered ring. So, this will this four-membered ring also will break and here it will form six-membered ring. So, overall it will form an eight-membered ring.

And if you look at this particular product in that process you have generated an enol TMS ether and also another double bond which is in conjugation with enol TMS ether ok. So, you can call this as vinylogous enol ether. So, this what will happen? This lone

pair or the silicon bond come here this will come and this will attack the carbonyl so that will give you the corresponding triquinane. It is a linear triquinane isn't you have five membered eight membered. So, the eight-membered ring cyclizes intramolecularly to give this linear triquinane ok.

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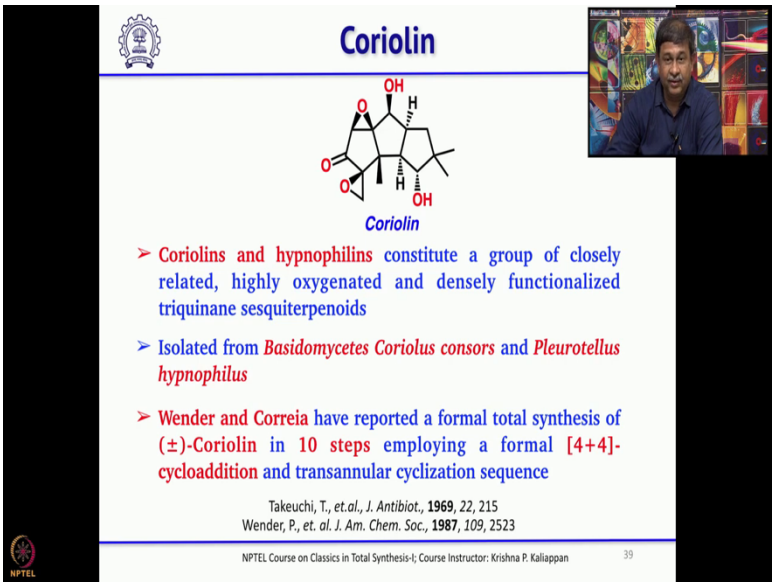

So, what I will do? I will talk about one more total synthesis I mentioned that is about synthesis of coriolin this is reported by Paul Wender's group. And interestingly what he has used is again little bit extension of the method which I discussed in the last slide where you convert the eight-membered ring into two five-membered rings.

And this eight membered ring he made using 4 plus 2; 4 plus 4 cycloaddition. See 4 plus 2 will give six-membered, 4 plus 4 will give eight membered ring and this 4 plus 4 can be done using photochemical condition ok. How he successfully accomplished the total synthesis of coriolin using this 4 plus 4 cycloaddition and also the transannular cyclization which I briefly discussed.

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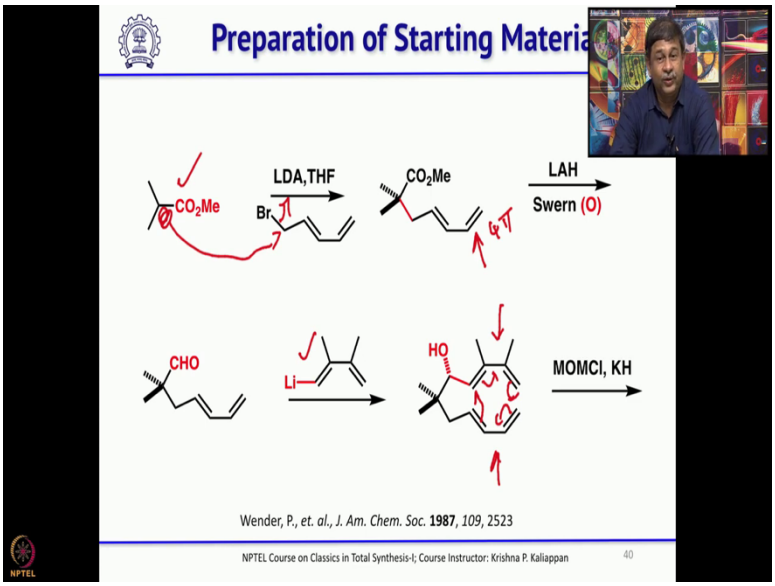

For that starting material is methyl isobutyrate. So, you take isobutyric acid and then methylate that upon treatment with LDA you generate anion here and that you quench with this allyl bromide substituted. So, you introduce a diene so you have already introduced 1 diene as I said the key reaction is 4 plus 4. So, now, you have already a 5 pi, 4 pi unit, you need another 4 pi unit.

So, you reduce the ester to corresponding primary alcohol and oxidize that under Swern condition to get aldehyde. So, now, use another four carbon unit that is the corresponding lithium add to this aldehyde you can see you got a tetraene ok a diene here diene here. So, a tetraene and this tetraene can undergo an intramolecular 4 plus 4 cycloaddition reaction ok. So, the intramolecular 4 plus 4 cycloaddition it can undergo.

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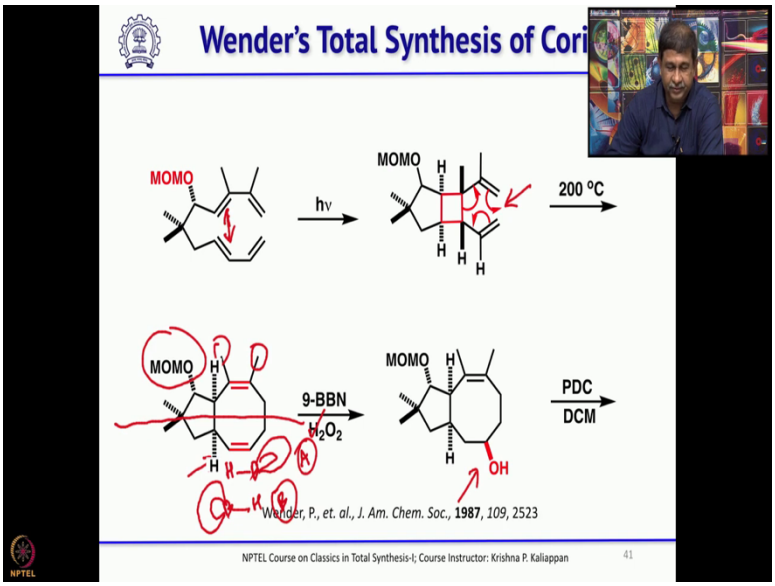

So, before that you have to protect the hydroxyl group you protect the hydroxyl group as MOM ether then you do this photochemical reaction. So, there are two ways to look at it one it undergoes 4 plus 4 cycloaddition or one can think about doing a 2 plus 2 between these two followed by Cope rearrangement 2 plus 2 followed by Cope rearrangement to give this cyclooctadiene ok.

It is a symmetrical compound cyclooctadiene symmetrical compound. Is it symmetrical? No because you have two methyl groups mom group it is not a symmetrical compound. Nevertheless you can selectively do hydroboration on one of these double bonds which double bond will undergoes hydroboration that too if you have to use 9-BBN. So, 9-BBN is a bulky hydroborating agent so; obviously, it will not go to tetra substituted.

And it will go to the disubstituted and then even disubstituted there are two possibilities one this way it will add other one. So, this is A this is B so; obviously, the addition of hydroboration will take place by A and not by B the reason is BBN is bulky ok. So, this side you have already methyl group. So, it will not go to left hand side. So, this upon hydroboration with 9-BBN and oxidation with hydrogen peroxide you will get the secondary alcohol. And this secondary alcohol you can oxidize using PDC to get the corresponding ketone ok.

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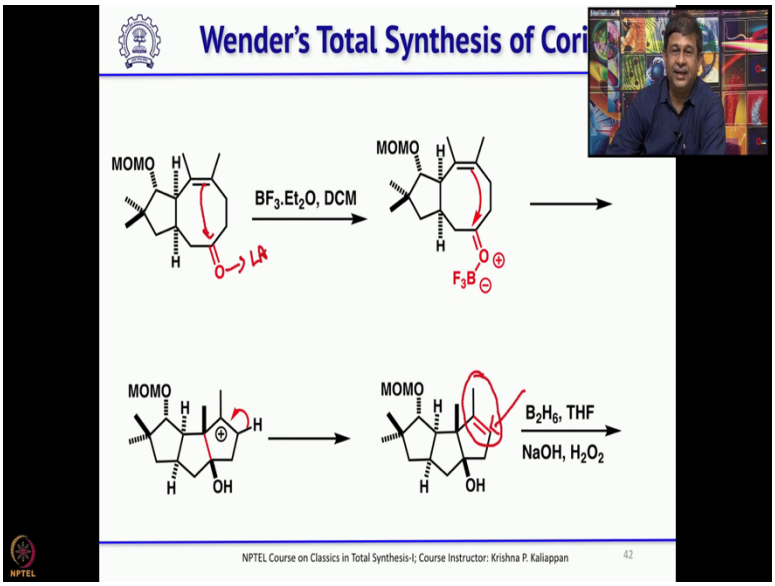

Then you treat with BF_3 etherate. So, BF_3 etherate what will happen? It will coordinate here and this double bond will come followed by elimination ok. So, when you have when the double bond comes here. So, you will have carbocation and that carbocation will lose a proton and you will get this ok.

So, now you have got the linear triquinane. So, few more functional group transformations should be done. So, what are the functional group transformation? Again you have to do hydroboration oxidation. So, you have a tri substituted double bond and if you do hydroboration oxidation this carbon you will get or you will introduce a hydroxyl group ok.

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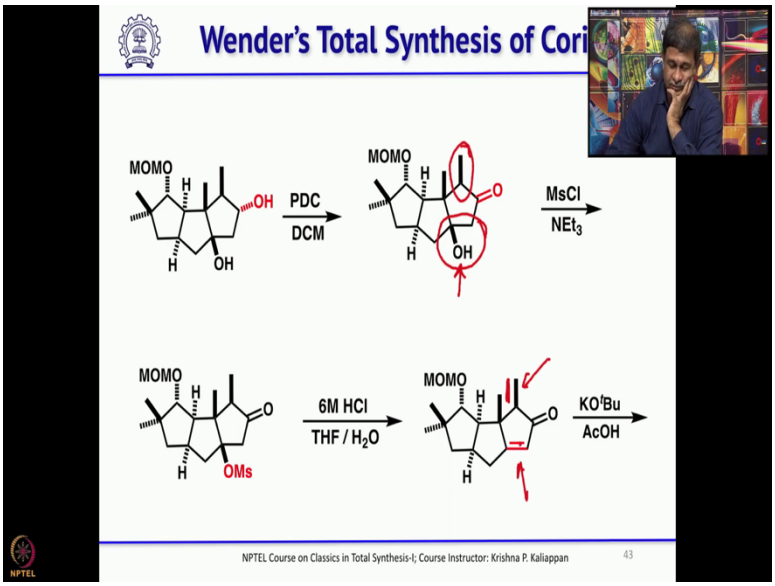

So, you introduce a hydroxyl group and once you have this hydroxyl group oxidize with PDC you get a ketone. And basically you need to introduce a double bond here and you have to introduce a double bond both sides you have to introduce double bonds. So, if you treat with mesyl chloride not only it will become mesylate, but also it will undergo elimination to get the corresponding enone ok. So, once you have this enone basically you need a epoxide epoxide here and you need epoxide here.

That means you also have to introduce a double bond here. So, what you do? Before that you migrate this double bond here.

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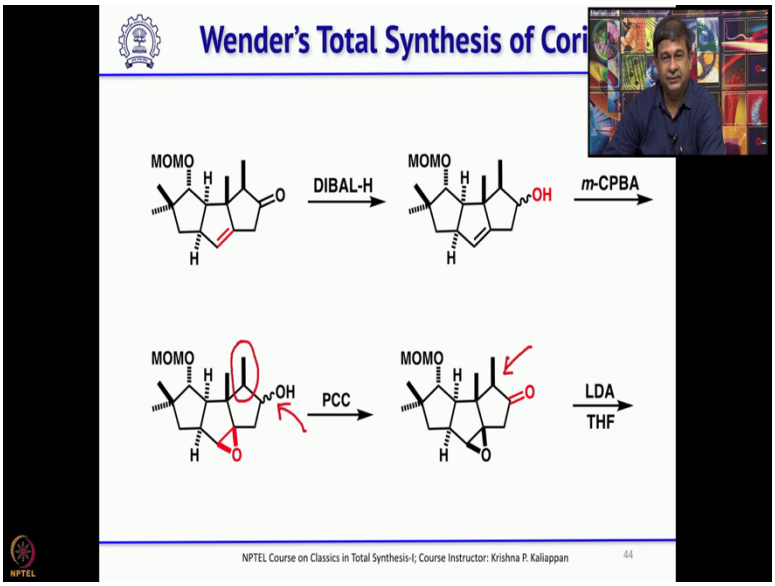

So, potassium tert butoxide you migrate the double bond then reduce the ketone to alcohol. Now if you treat with m-CPBA you get corresponding epoxide ok. Then as I said you need an epoxide here and also this should be ketone. So, you oxidize the alcohol using PCC to get the ketone. Later a double bond should be introduced.

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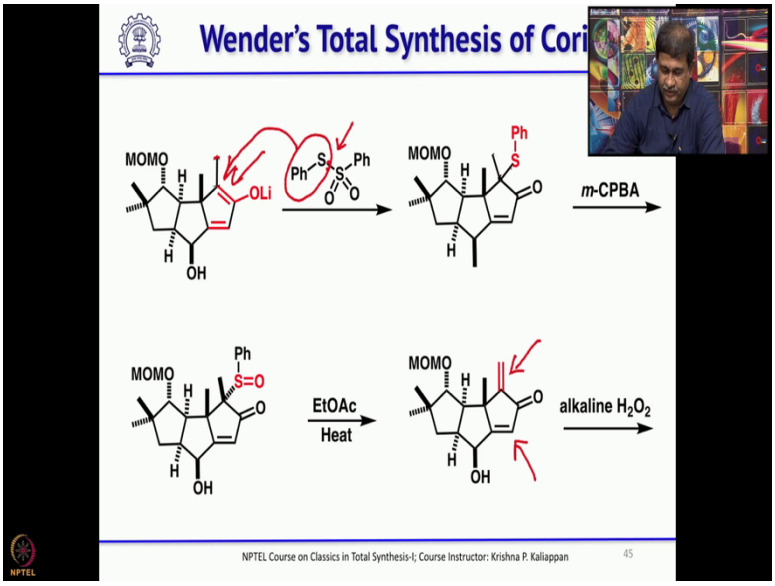

So, that can be done in two steps first you generate enolate using LDA and that time what happens when you generate enolate with LDA the epoxide also will be open the epoxide also will be open. So, you get corresponding alcohol. Now this side you have the

enolate that upon quenching with this reagent where this will go to the corresponding carbon ok.

So, this is nothing but oxidized version of diphenyl disulfide. One of the sulfur is oxidized other sulfide is remaining as such the sulfide upon further oxidation with mCPBA it gives phenyl sulfoxide. This upon heating it undergoes elimination of phenyl sulfonic acid to get the exocyclic double bond ok. To complete the total synthesis you need epoxide here and you need epoxide here. So, this was done by treating with alkaline hydrogen peroxide.

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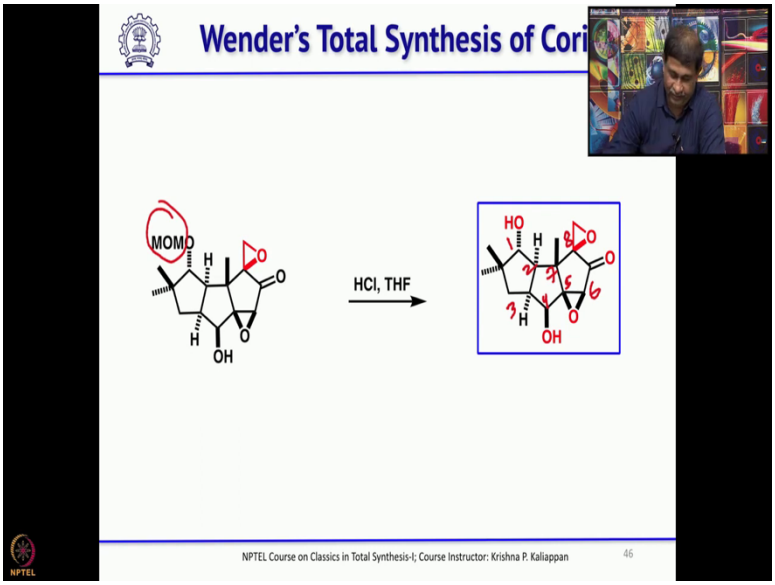

You get both the epoxides and finally, to complete the total synthesis what is required is removal of this MOM group. So, that was done using HCl, THF and that gave the final natural product that is coriolin. If you look at this molecule how many chiral centers are there? 1, 2, 3, 4, 5, 6, 7, 8 out of 11 core carbons. If you look at the triquinane there are 11 core carbons.

In that 8 are chiral centers 8 are chiral centers. See that is the beauty of this synthesis ok. So, highly selective total synthesis and here he has used the intramolecular cyclization as well as 4 plus 4 cycloaddition to get this triquinanes.

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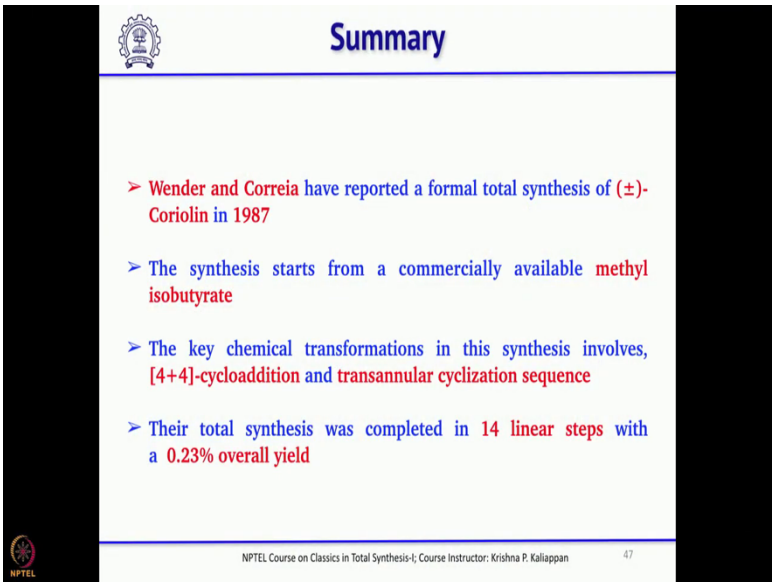

So, he reported this total synthesis way back in 1987 and he started with methyl isobutyrate and key step involved in this total synthesis are 4 plus 4 cycloaddition. One can also give explanation that it can be a combination of intramolecular 2 plus 2 followed by another electrocyclization that is you have a diene 1 pi diene that can undergo cycloaddition reaction.

And finally, a transannular cyclization takes place between the eight membered ring diene that octadiene was the one of the double bond you oxidize to ketone. Then you carry out this intramolecular cyclization using transannular cyclization protocol. Overall this total synthesis was accomplished in 4 longest linear steps, but the yield was not very high.

So, yield was about 0.23 nevertheless if you look at the total synthesis of this molecule reported by Coriolin it involved 3, 4 key reactions and these key reaction actually really worked well so that you could accomplish the total synthesis of Coriolin ok. So, with this we have completed the total synthesis of all the triquinanes whatever we planned to cover. And next week onwards we will start talking about six-membered rings and then slowly we move to alkaloids and terpenoids ok.

So Thank you.