Classics in Total Synthesis-I
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Lecture - 33
Dendrobine

Good morning and welcome back to the NPTEL course on Classics in Total Synthesis Part-1. So, we have been talking about total synthesis of alkalides we will continue our discussion on one more alkali today that is Dendrobine and this is a very interesting tetracyclic compound we can see that there are 3-5 membered rings 1, 2, 3, the third one is a lactone and second one is a substituted pyrroline ring and the fourth one is a 6-membered ring.

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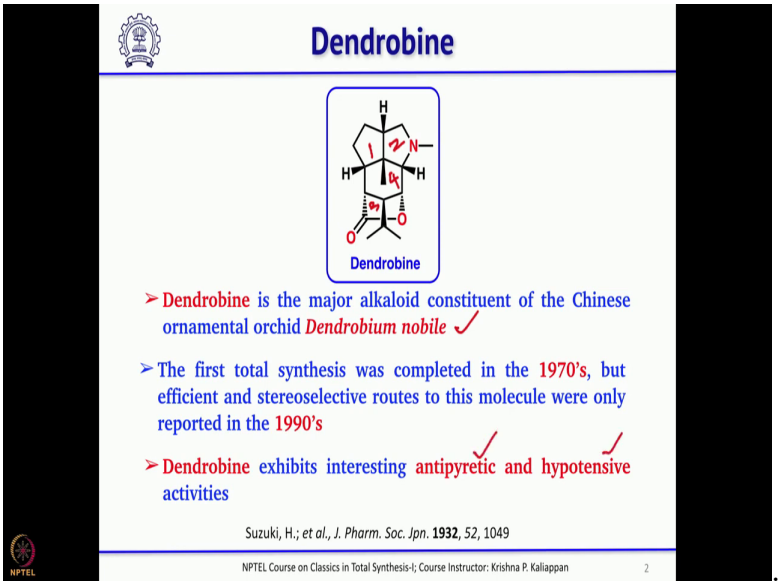

So, this molecule was isolated way back in 1932 almost 90 years ago as the major alkaloid constituent of Chinese ornament orchid called Dendrobium nobile ok. It is almost 90 years ago we if this molecule was isolated. Though the first total synthesis of dendrobine first reported in 1970's the better synthesis in terms of asymmetric as well as the shortest synthesis were reported after 90s.

So, what we will do today. So, we will talk about three total syntheses of dendrobine one suppose to be the shortest synthesis less than ten steps, the other two are asymmetric

synthesis ok. I should say they are chiral synthesis chiron approach they start with a chiral compound ok. So, they are called chiron synthesis and dendrobine exhibit some interesting biological activity so, they show antipyretic and hypotensive activities.

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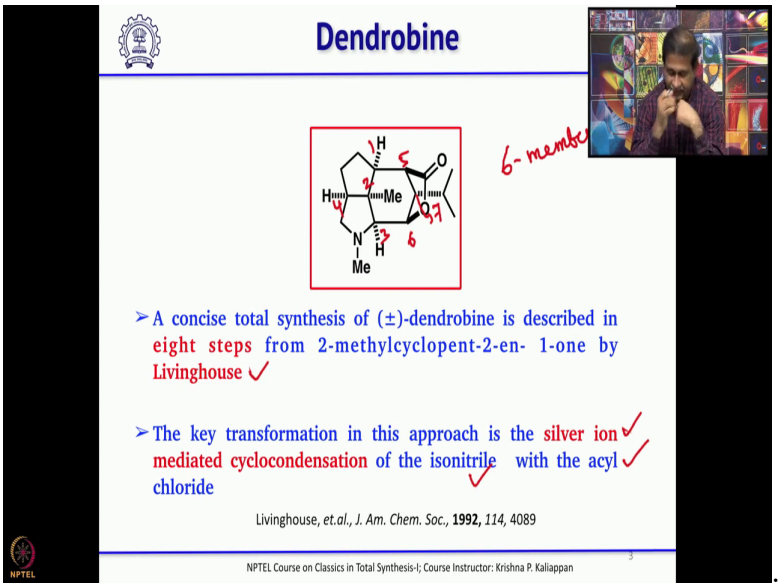

So, if you look at this molecule from synthetic point of view as I said. So, this is a tetracyclic compound that itself is a big challenge and yeah more importantly if you look at the number of chiral centers you can count 1, 2, 3, 4, 5, 6, 7 there are 7 chiral centers ok of which 1, 2, 3, 4, 5, 6, six contiguous chiral centers; that means, the 6 - membered ring the 6-membered ring has all the carbons chiral ok all the 6 carbon atoms of the 6 membered ring are chiral ok.

First let us start with simplest and then the best synthesis so far for dendrobine. So, this is synthesis reported by Thomas Livinghouse. So, he reported in eight steps starting from 2- methylcyclopentenone ok. And the key reaction there are couple of key reactions and the best one is the silver ion mediated cyclocondensation of an isocyanate with an acid chloride ok. Cyclocondensation of an isocyanate and acyl chloride to generate the dihydro pyrroline ring, you have the 5-membered pyrroline ring to generate that ring he has used this key reaction.

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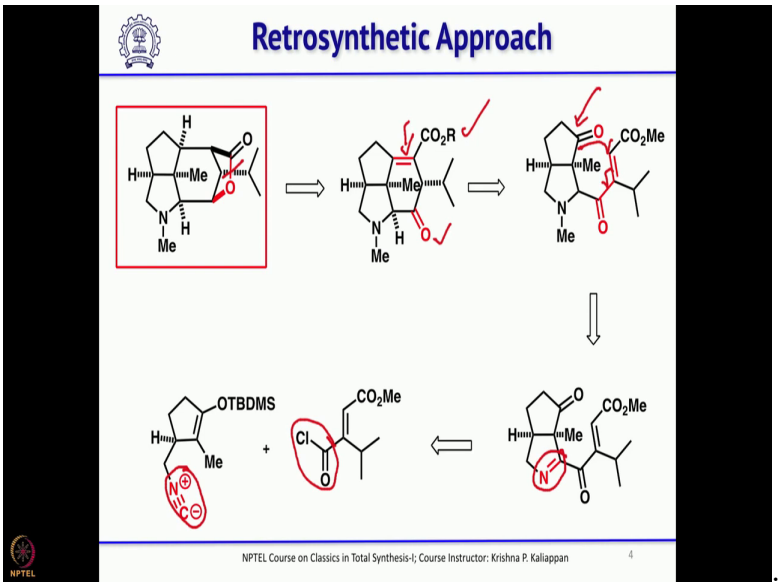

So, from a retrosynthetic point of view if you look at this compound his first retrosynthesis was this cleavage of this lactone ok. So, one side he has ester, the other side he has ketone, if you moment you reduce this double bond and reduce this ketone automatically the hydroxyl cyclizes and then you get the corresponding 5-membered lactone. So, that was the first major disconnection.

Then the second major disconnection was the double bond, the double bond which he has introduced. Here what he wanted to do was he wanted to use here ketyl radical cyclization. So, if you put a metal which can donate an electron then it will form ketyl radical that radical can undergo a 1,4 addition ok the radical can undergo 1,4 addition followed by dehydration one can generate not only the 6-membered ring, but also the hydroxyl group which can be dehydrated. So, that was his plan.

Then as you can see the imine ok, imine can be methylated and hydrogenated ok to get this 5- membered ring and this is the key transformation which he thought will be really very nice if it can be exploited in total synthesis, the cyclocondensation reaction where you have an isocyanate which on treatment with acid chloride forms this cyclic imine ok.

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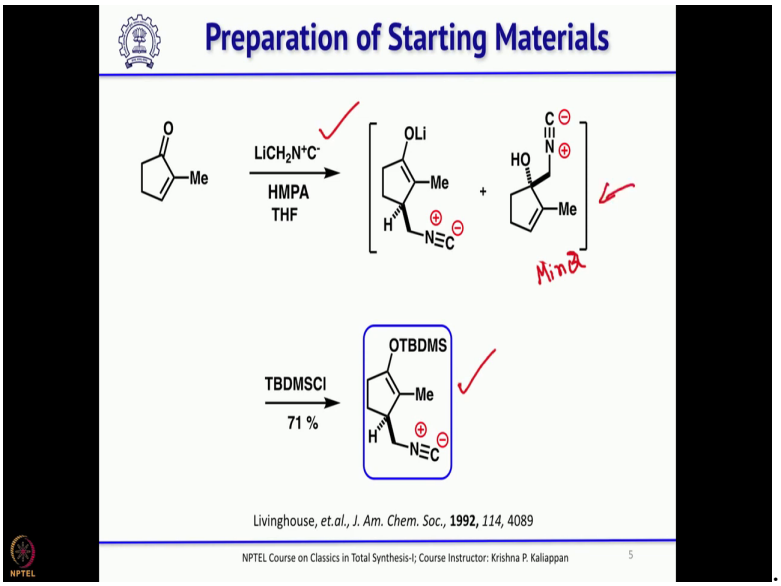

Let us see how we made it and then before we move further on the total synthesis of dendrobine from Livinghouse group first let us see how he prepared the two starting materials one based on the cyclopentenone, other one acid chloride ok. So, he started with 2 methyl cyclopentenone and then he did a 1,4 addition with lithium $LiCH_2$-NC ok.

So, he got a mixture of 1,4 addition and 1,2 addition product though this 1,2 addition product was minor he thought it is better to isolate. So, he quenched this with TBDMS chloride. So, when he quenched with TBDMS chloride he could get exclusively only one product.

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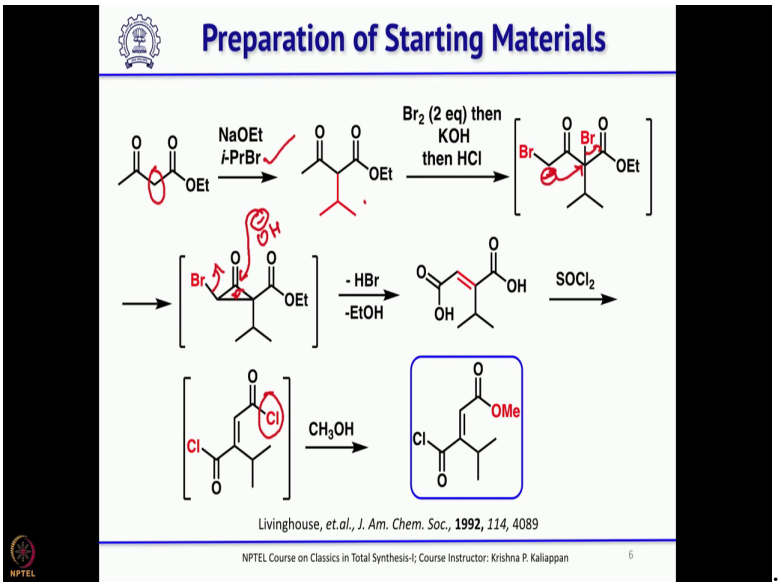

And the other starting material that is a acid chloride he started from ethyl acetoacetyl so, where first he did the alkylation with isopropyl bromide after treating with sodium ethoxide. So, you generate an anion and quench with isopropyl bromide to get this isopropyl, then he did a quasi Favorskii rearrangement. So, what he did, he first he did bromination. So, a dibromination gave this dibromo compound this upon treatment with base potassium hydroxide.

The first step is Favorskii rearrangement so, which gives the cyclopropanone ok. Now, the second step is the base which attacks the carbonyl and this bond migrates and the bromate goes out and in the process the ester also gets hydrolyzed to get this dicarboxylic acid ok. This dicarboxylic acid if you treat with thionyl chloride you get the corresponding acid diacid chloride.

Now, when you add 1 equivalent of methanol 1 equivalent of methanol the least hindered one least sterically hindered 1 is esterified leaving the other acid chloride as such which can undergo cyclocondensation with the isocyanate which we discussed in the last slide.

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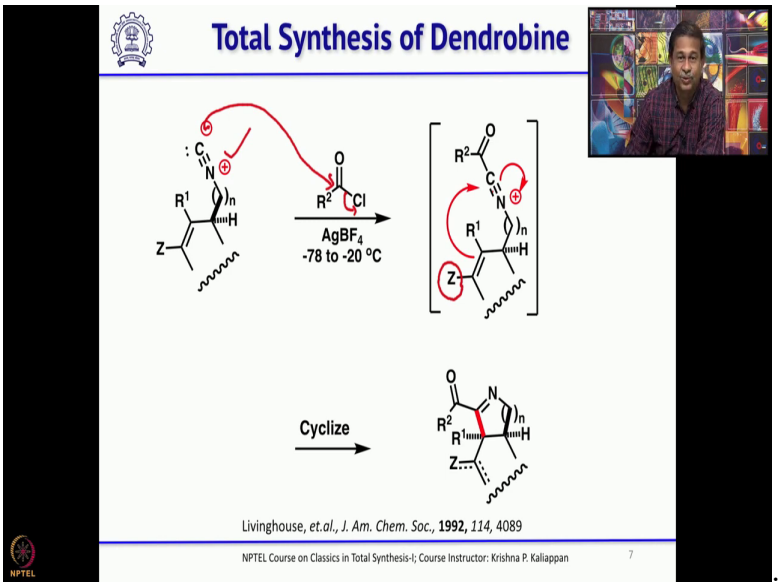

So, the key reaction as I said it is a cyclocondensation, how does it work? So, if you have an isocyanate like this ok, then this C^- can attack the carbonyl group of acid chloride and then you get this acylium ion, it is like you know iminium ion it is a iminium ion you have a triple bond. Now, if we have a double bond at appropriate place the double bond can neutralize the positive charge on the nitrogen ok.

Then if for example, if Z is oxygen if Z is oxygen then this is like the higher order of Mannich reaction, isn't it Mannich reaction is you have enol and then iminium ion. So, here you have a triple bond ok. So, it is like Mannich reaction. So, then it can cyclize to give the corresponding imine. So, that was the key reaction which Livinghouse used in the total synthesis of dendrobine.

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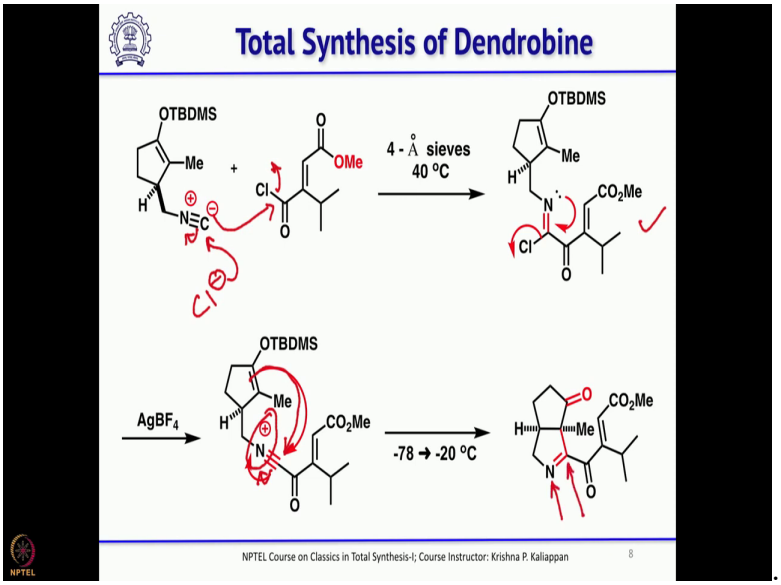

Let us see how this was successful. So, first when you mix these two in the presence of molecular sieves at slightly elevated temperature than room temperature the first step as usual was the addition of attack of the nitrile and the -Cl^- goes out. Now the -Cl^- which came out can attack this to neutralize the positive charge on the nitrogen. So, you get this compound ok.

Now, what it can do? The lone pair on the nitrogen lone pair on the nitrogen can push the chloride out. So, once that happens in the presence of silver tetrafluoroborate you generate this positive charge on the nitrogen and already you have enol TBDMS. So, that can come and neutralize the positive charge and in the process that will become ketone ok.

Now, you can see you started with cyclopentanone one ring, now the second ring is constructed ok, the second ring is constructed. So, what is left is you have to introduce a methyl group in nitrogen and also you have to reduce the imine.

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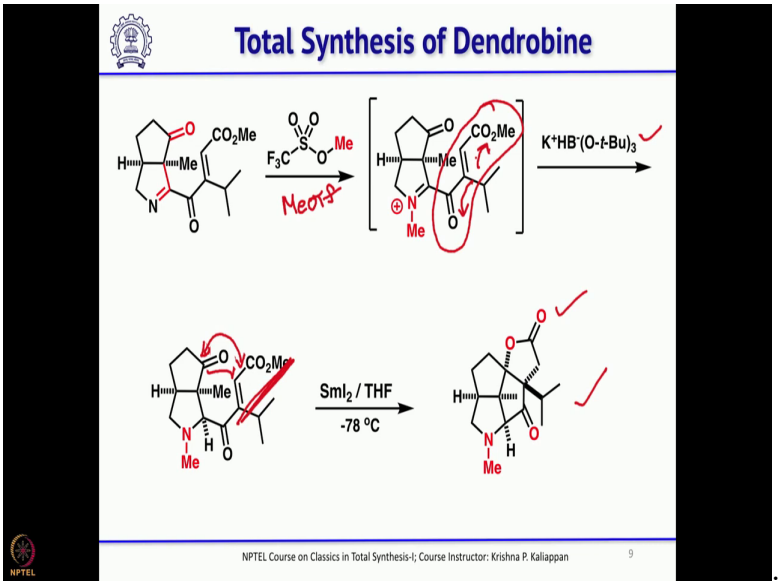

So, both are done in one step, actually I should say one part reaction first methylation of nitrogen was done with methyl triflate, you know methyl triflate is known to methylate and N methylation and followed by in situ reduction of this iminium ion was done with potassium tri tertiary butoxy borohydride ok potassium tri tertiary butoxy borohydride. So, bulky one which is you know known to reduce iminium ions in the presence of ketones and esters ok.

So, now two 5-membered rings are done. So, what he needs to do is to connect this ok connect this. So, he thought he can use samarium iodide is well known one electron donor. So, a ketyl radical can form that can attack that can attack this double bond in a Michael fashion. So, 6-membered ring can be formed that was his idea, but what he got was a very interesting tetracyclic compound ok. So, here it is very easy to visualize how he would have got this tetracyclic compound.

Now, if you look at this particular compound ok we can see this there are two Michael acceptors one you have α–β unsaturated ester ok α–β unsaturated ester, other one α–β unsaturated ketone ok. So, the Michael addition the expected one was to undergo the α–β unsaturated ketone ok. It was as per his plan the Michael addition was supposed to happen at α–β unsaturated ketone, but here if you look at this product the Michael addition took place at α–β unsaturated ester ok and once that happen the hydroxyl group

attack the ester and then it form the lactone ok. So, he thought maybe he has to work around and then increase the temperature change the conditions.

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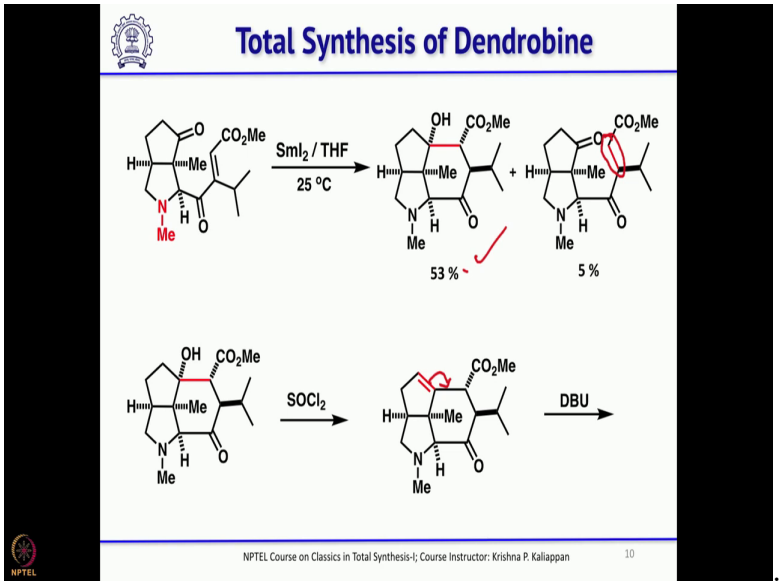

So, simply by rising the temperature ok simply by rising the temperature to ambient temperature he got the required product as the major product. So, you can see. So, this is the major product 53% and the simply reduced compound that α–β unsaturated ester was reduced. So, that he got 5%. So, both are easily separable.

So, he took the required compound and then treated with thionyl chloride. So, thionyl chloride is well known for dehydration. So, it introduced the double bond. So, now, you treat with bases like DBU so, that the double bond can be migrated here. So, you wanted to migrate the double bond here, but what happened the double bond migrated all the way to here the tetrasubstituted double bond, it is ok no problem.

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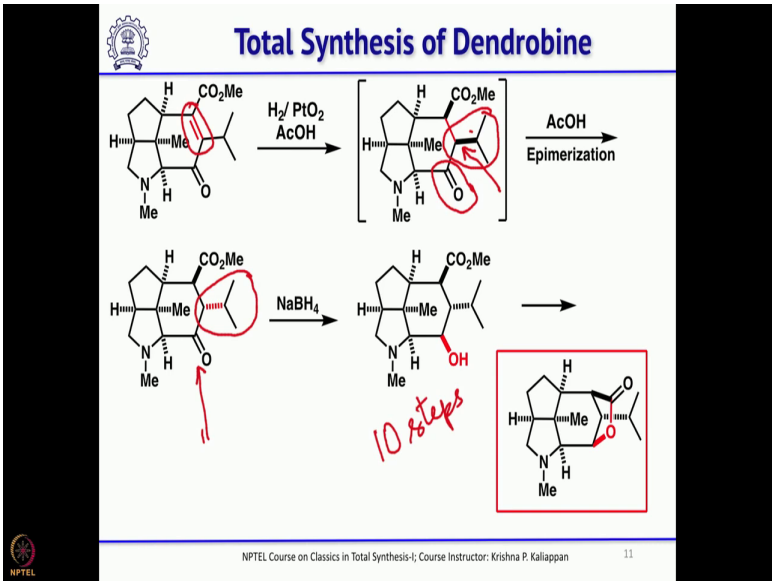

Next he reduced the Adams catalyst. So, the tetrasubstituted double bond was reduced to give the cis substituted compound and you need this isopropyl group in the natural product α ok, what you got is β. So, you need α and you have a ketone adjacent to that. So, one should be easily isomerize or epimerize this stereo center. So, treatment with acetic acid could epimerize that center to get the isopropyl at the required stereo position.

Now, reduction with sodium borohydride came from and the hydride came from α. So, you got the β alcohol and then the β alcohol spontaneously cyclized to give the natural product dendrobine. So, overall including the starting material preparation Thomas Livinghouse took about 10 longest linear steps to complete the total synthesis of dendrobine. Though this is a racemic synthesis, but the shortest synthesis involve a clever cyclocondensation reaction.

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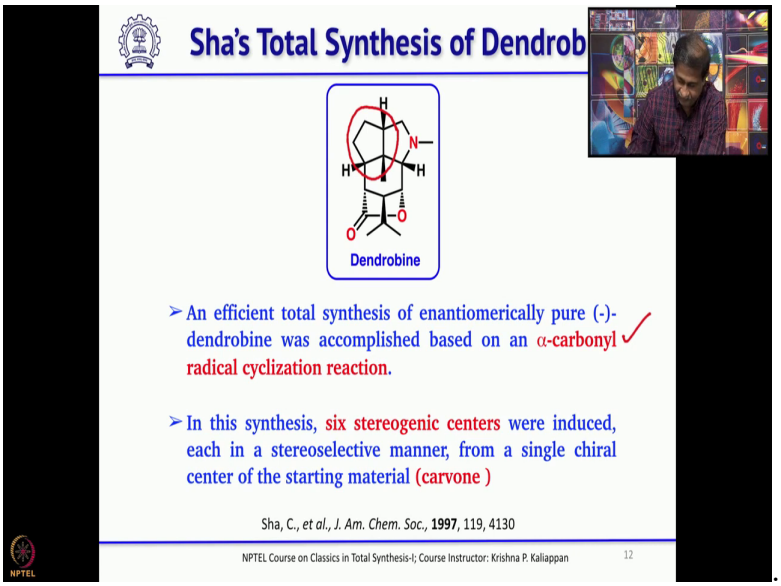

So, now we will move to the next synthesis it is a Chiron approach synthesis reported by Sha and here he started with chiral starting material called carvone ok. And the key reaction in this total synthesis was generating a radical generating a radical next to carbonyl group because usually when you generate a radical next to carbonyl group that is not very reactive ok.

So, he could successfully generate a radical next to the carbonyl group and then he carried out a 5-exo-dig cyclization to get this 5-membered ring ok. This 5 - membered ring he could achieve the synthesis of this 5- membered ring using 5- exo- dig- radical cyclization.

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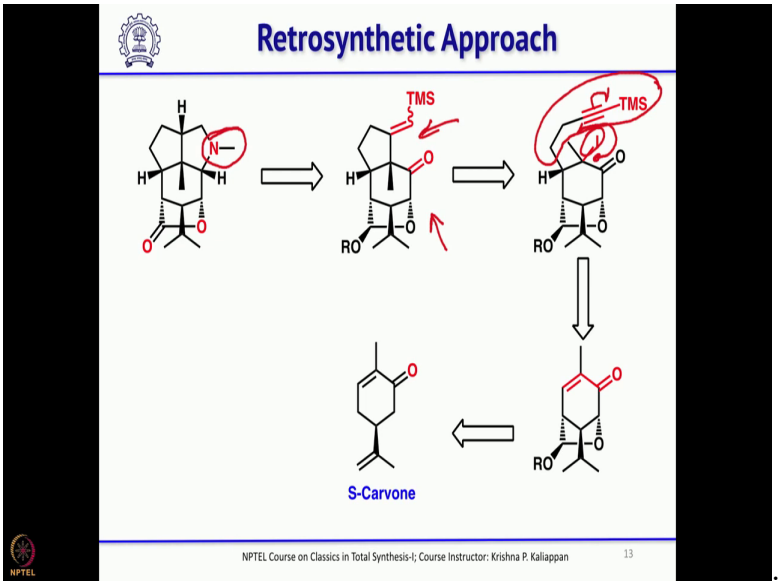

So, let us see how he has done. So, the first retrosynthesis was to cleave this ok he wanted to introduce the nitrogen at a later stage ok and he thought this will be the precursor for that and why this precursor, that is where his key reaction that is the radical cyclization. So, once you generate a radical here if you replace the iodide then this can undergo radical cyclization to generate the 5-memebered ring. So, that was the idea behind this precursor ok.

Now, now this can be easily obtained by a 1,4 addition. So, you can have the whole unit you can add in a 1,4 fashion followed by quenching the enolate to get the iodide at α–position α to carbonyl. And this can be made from carbon which is commercially available it is one of the monoterpenes available in plenty and not expensive.

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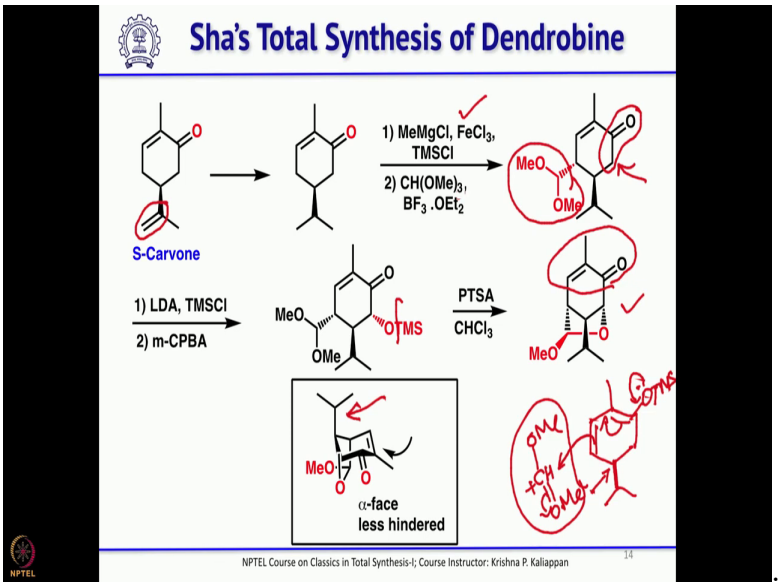

So, let us see how he did the total synthesis he started from as I said carbon now the selectively this disubstituted double bond and electron rich double bond can be reduced with either Wilkinson catalyst or with Adam catalyst to get the reduced carvone. So, now you have the enone and this enone it went through a very interesting reaction wherein in the first step when you treat with methyl magnesium chloride and catalytic amount of ferric chloride it undergoes it forms a dienolate ok the dienolate that is a thermodynamic dienolate and quench with TMS chloride he got this compound this is a known reaction ok.

So, this is the first step when you take methyl magnesium chloride and catalytic amount of ferric chloride and quench with TMS chloride you get this upon treatment with Lewis acid and trimethyl orthoformate ok to give this compound ok. So, when this happens the whole group comes opposite to this isopropyl group ok. So, this is how he introduce.

Now, if you look at this carefully this is the equivalent of the ester carbonyl group in dendrobine you need carbonyl group. So, this is the equivalent of ester carbonyl group ok, then you need to introduce a hydroxyl group to form lactone isn't it, you need to introduce a hydroxyl group to form lactone.

So, this upon treatment with LDA you can generate enolate here and then quench with TMS chloride followed by m-CPBA you can introduce a hydroxyl group only thing it is in the protected form, OTMS now if you treat with PTSA that is para toluene sulfonic

acid it forms this lactal methyl ether. So, this gets hydrolyzed and then it cyclizes to form this lactal methyl ether which is quite stable ok, this can be this molecule can be written like this ok, this molecule can be written like this.

Now, if you look at this compound particularly the enone ok particularly the enone you can see the top phase is blocked the top phase is blocked by the isopropyl group. So, any attack on this enone has to come from the α phase any attack on the enone should come from the α phase.

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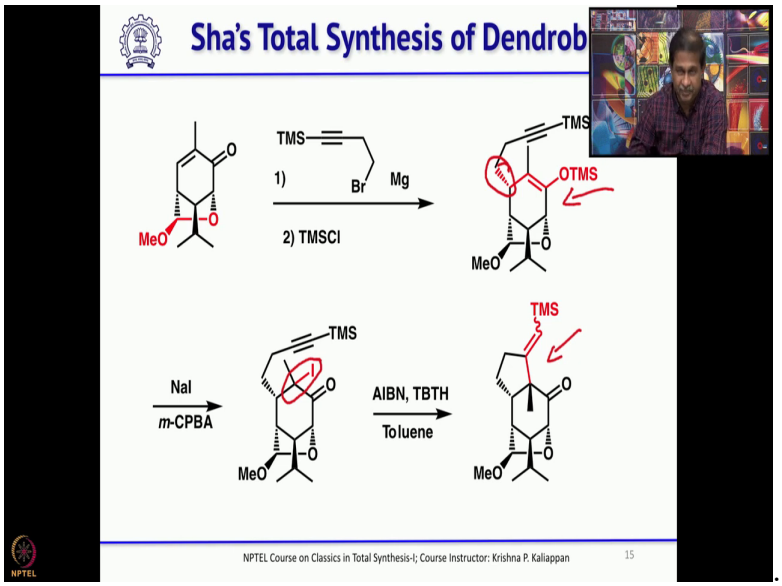

So, because of that when you add this the 4 carbon unit in a 1,4 fashion followed by quenching with TMS chloride you can see this 4 carbon unit comes from the less hindered α site ok. Now, once you have the enol TMS in one step you can convert that into iodide. So, that is a precursor required for the 5 – exo- radical- dig cyclization ok.

So, did it work yes when it was treated with tributyltin hydride with radical initiator AIBN this undergo the 5-exo-dig radical cyclization to get the key tricyclic compound. The key tricyclic compound required for the total synthesis of dendrobine. So, now, what he has to do is finally, combine these two to get the 5- membered ring.

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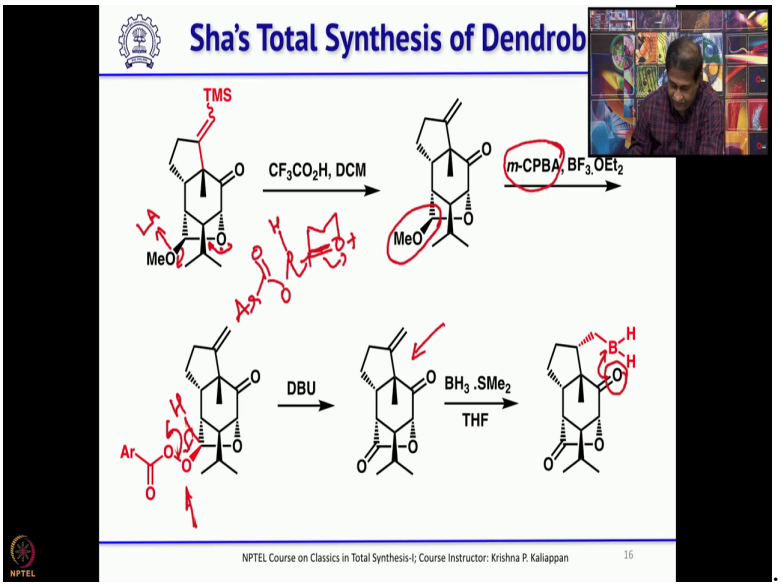

So, the vinyl TMS the TMS group was removed with acetic acid to get the exocyclic double bond, now hydroboration ok. So, before doing hydroboration before doing hydroboration this methoxy group that is lactal methyl ether should be converted into lactone ok.

So, what he did, he treated with m-CPBA in the presence of BF_3 etherate. So, BF_3 etherate you know what happens is the for example, if you take this compound treat with BF_3 etherate the lone pair come like this and then it will go. So, basically what you will get is like this oxonium ion ok like this oxonium ion you will get ok.

Now, when you are adding m-CPBA what will happen? The m-CPBA will attack m-CPBA will attack and neutralize the positive charge. So, that is what happens as you can see here the oxonium ion is formed which is formed in situ was attacked by m-CPBA and m-CPBA also comes from the same β site ok. Then if you treat with DBU what it will do it will pick up this hydrogen ok it will pick up this hydrogen and as you know meta chloroperbenzoic acid it is a good leaving group.

So, it will pick up this hydrogen and you get the corresponding lactone. So, in two steps the lactal methyl ether was converted into the lactone. So, then as I said the next step is to introduce the 5-membered ring here. So, first step was adding borane dimethyl sulfide complex. So, when you do that, the double bond will be hydroborate the double bond will be hydroborate.

Now, when the hydroboration takes place you can see the oxygen electron rich oxygen carbonyl oxygen can immediately attack the boron, isn't it.

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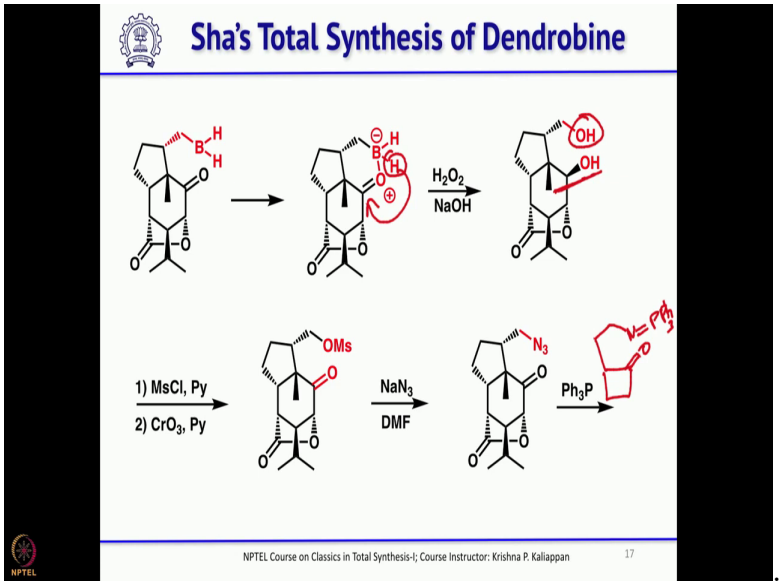

When it attacks the boron what you get is this corresponding negative charge on borane and positive charge on oxygen. Now, intramolecular transfer of hydride will take place from α intramolecular hydride transfer will take place from the α to the carbonyl. So, that you will get β alcohol ok, this will give the β alcohol after workup with H_2O_2 sodium hydroxide ok. You get a diol, now what you need is one of the hydroxyl group you should convert that into nitrogen ok. So, how this happens you treat with mesyl chloride.

So, when you have primary hydroxyl and secondary hydroxyl group; obviously, you can selectively mesylate the primary one. So, you do convert the primary alcohol to corresponding mesylate meanwhile oxidize the secondary alcohol with chromium trioxide to get the ketone ok in two steps you get this. Now, once you have the mesylate one can easily convert that into corresponding azide, see azide is the precursor for nitrogen ok NH. So, the sodium azide displaced mesyl group to get the corresponding azide.

Now, when you treat this with triphenylphosphine you know this will undergo intramolecular schrodinger reaction; that means, what will happen, it forms the

iminophosphorane and the with ketone what will happen it will undergo immuno Wittig lines ok.

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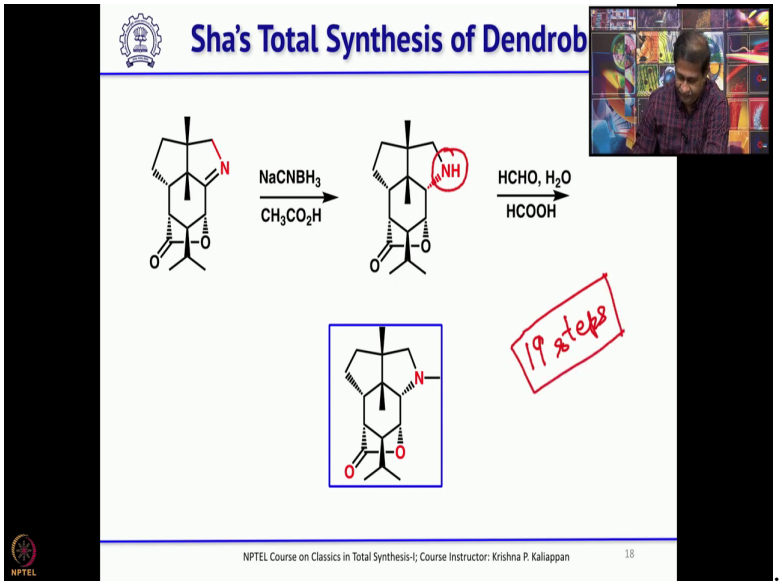

So, that will give you the corresponding cyclic imine ok that will give you corresponding cyclic imine. Then once you have that then sodium cyanoborohydride under acidic acid condition you can reduce the imine; that means, you protonate the nitrogen then you reduce with sodium cyanoborohydride, what is left now in the total synthesis of dendrobine is to methylate the NH.

So, that is simple if you treat with formaldehyde and formic acids you can easily methylate the NH to get the corresponding N methyl group. So, this is the second total synthesis which I discussed about dendrobine. So, which took about in 19 steps and it started with the commercially available monoterpene called carvone.

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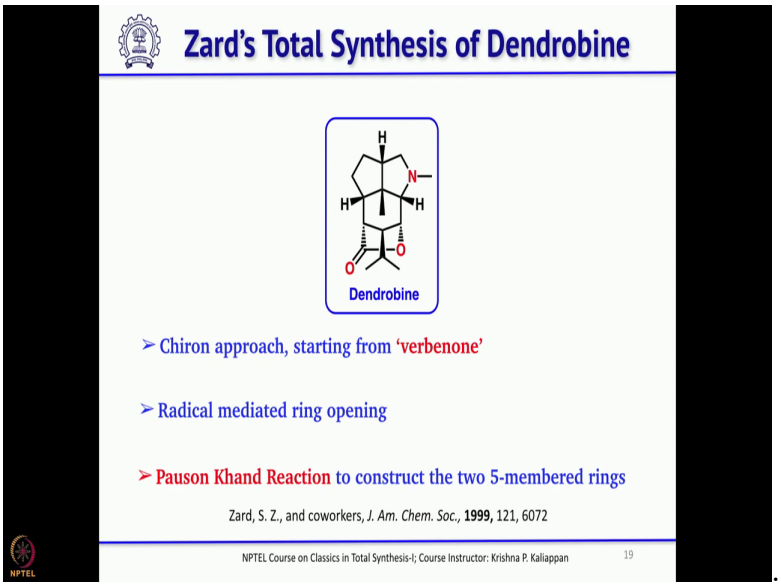

The third total synthesis very interesting total synthesis reported by Samir Zard involved two key reactions one Pauson- Khand reaction to construct two 5-membered rings the both the 5-membered rings were constructed using Pauson- Khand reaction. And second one is using a radical reaction to open the cyclobutane radical reaction to open the cyclobutane of another commercially available monoterpene called verbenone to get this isopropyl group ok.

So, he also took about 19 steps to complete the total synthesis, but these two key reactions were very very important in the total synthesis of dendrobine ok.

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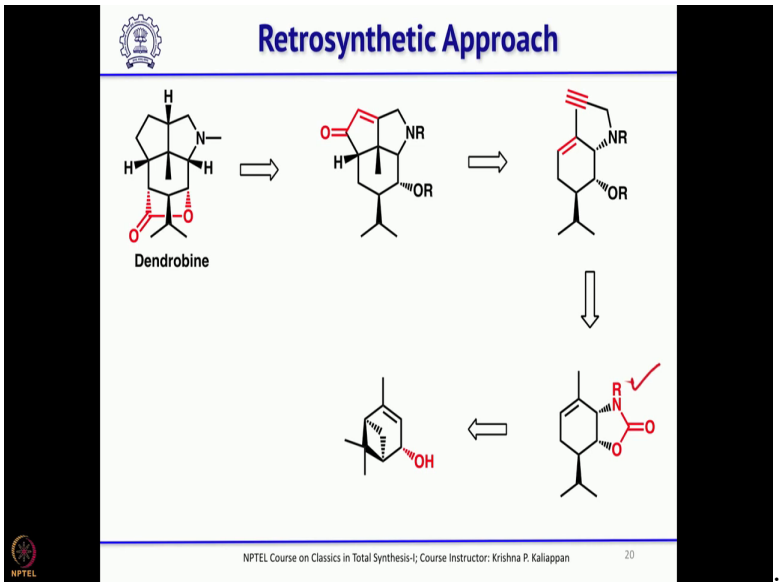

So, his idea is as I said this is the key reaction that where you use Pauson- Khand reaction to get the two 5-membered rings and this can be obtained from the corresponding you know cyclic carbamate ok and the cyclic carbamate he got it from this verbenone ok verbenone ok by a radical cyclization step ok.

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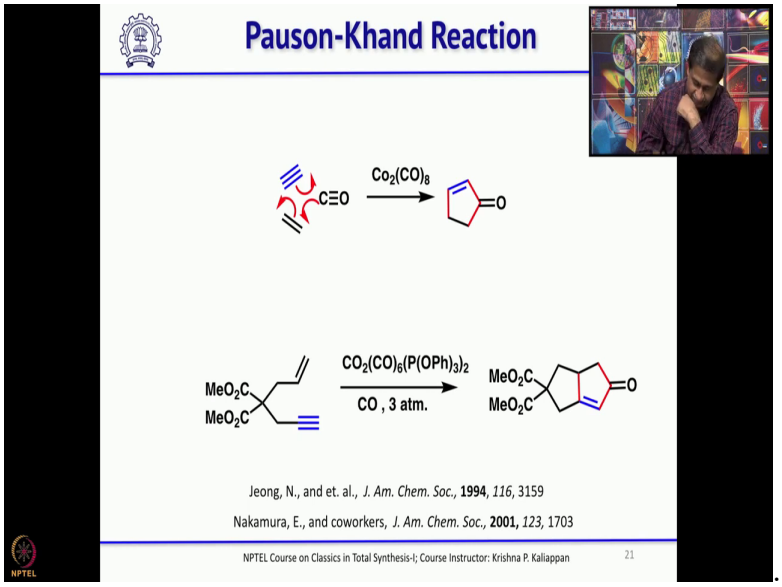

So, let us see how he has done and you know what is Pauson- Khand reaction, if you have a triple bond and double bond and if you treat with dicobalt octacarbonyl in the presence of carbon monoxide you can get cyclopentenone. So, it is a very well-known

reaction for making highly substituted cyclopentenones ok and not only cyclopentenone the depending on the nature of the substituent the cyclopentenone can be fused with other rings ok.

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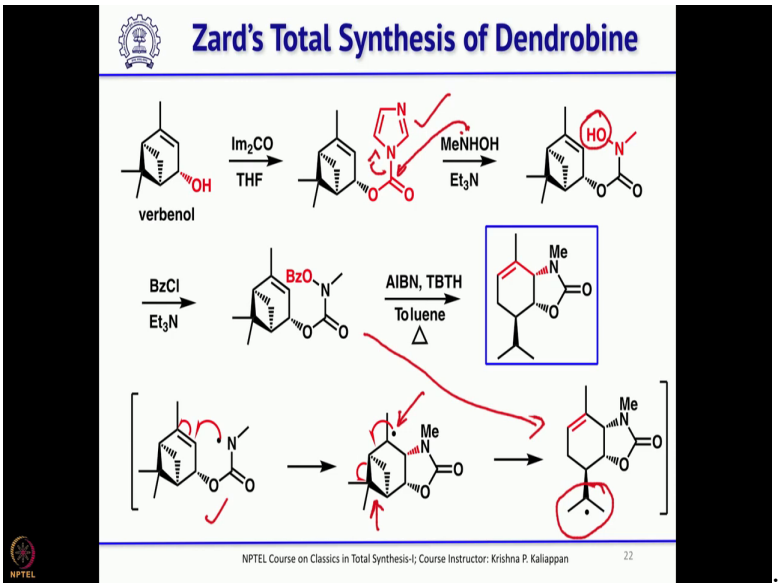

So, now he started with verbenol which was obtained from verbenone in one step once you have the verbenol or you can also get verbenol from directly from α-pinene in one step. So, then you protect this verbenol with carbonyldiimidazole ok. So, you get this intermediate now if you add methylhydroxylamine.

So, methylhydroxylamine is a good nucleophile it attacks and then imidazole is a good leaving group. So, you get this now the NOH the OH should be converted into a decent leaving group, so that you can generate N radical. So, what was done was convert the OH into O benzoate by treating with benzyl chloride and you get the radical precursor ok.

Once you have this radical precursor you treat with radical initiator that is AIBN azobisisobutyronitrile and tributyltin hydride you generate the radical and that radical is like this ok. First you generate the radical and this radical adds in a 5-exo-dig fashion 5 exo dig fashion to generate the tertiary radical.

Once the tertiary radical is generated now the tertiary radical can open up the strained 4-membered ring, you have strained 4- membered ring, the strained 4-membered ring can

be opened by the formation of this tertiary radical and when it does that what you get is a more stable tertiary radical. So, this again it will pick up hydrogen from tributyltin hydride and it will form isopropyl and that is how in one step cleverly ok Samir Zard converted this radical precursor to the bicyclic compound ok.

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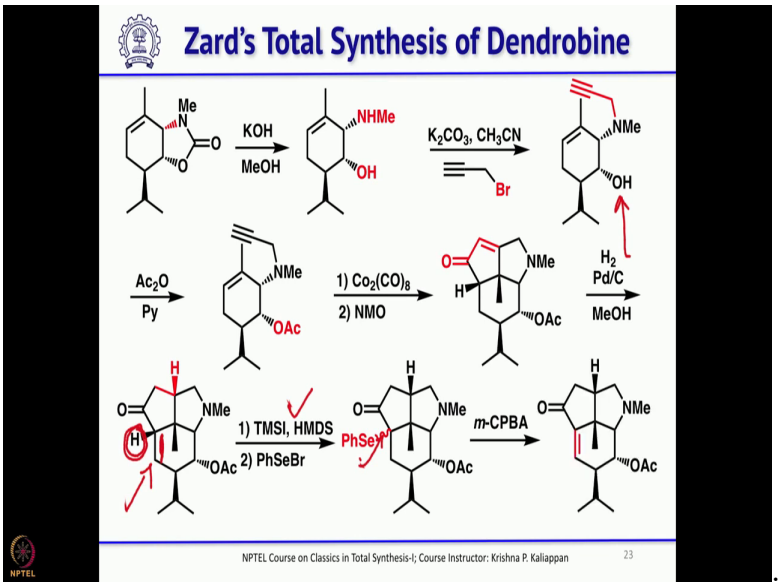

Then you can hydrolyze this ok. So, the cyclic carbamate you hydrolyze to get the corresponding amino alcohol and then NH can be propargylated by treatment with potassium carbonate and propargyl bromide and the free hydroxyl should be protected. So, that was protected as acetate then he carried out the key reaction that is the Pauson-Khand reaction.

So, the Pauson- Khand reaction worked very well and as you can see here it gave the key tricyclic compound very nicely and two 5 membered rings are formed using Pauson-Khand reaction ok. Then the double bond of α-β unsaturated ketone the 5-membered ring can be reduced under hydrogenation condition.

Then what you have to do if you look at is you need to introduce an ester group isn't it, you need to introduce an ester group now if you look at that carbon unless you introduce a functional group you cannot introduce a carbonyl group. So, if you have to introduce a functional group it is important you introduce a double bond here ok, then you can do a 1,4 addition or introducing the double bond you have to pick up this hydrogen ok this hydrogen; that means, you have to generate more substituted enolate isn't it.

The more substituted enolates are generally formed by treatment with trimethylsilyl iodide and hexamethyldisilazane ok. Once you make the enol TMS then treat with phenylselenyl chloride you can introduce the seleno group and that carbon then simple oxidation with m-CPBA first it will form phenyl selenoxide followed by elimination you introduce the double bond.

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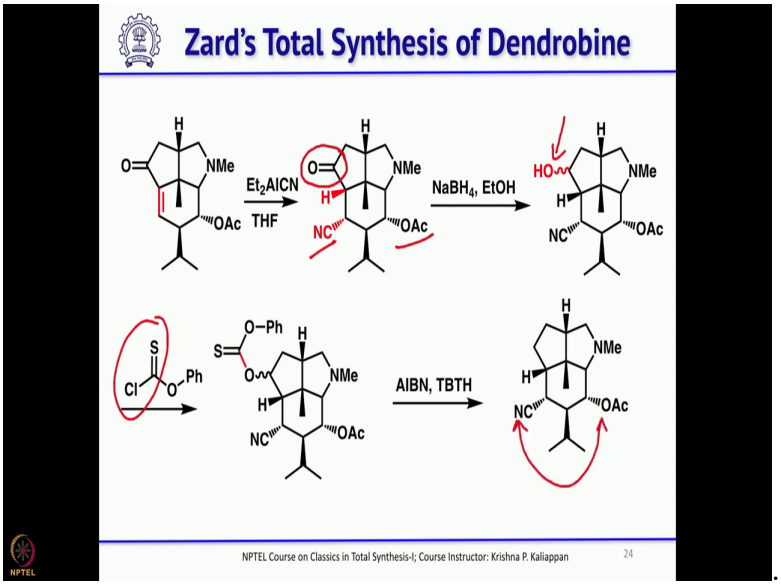

Once you have the double bond next is very simple you have to introduce a carbonyl group one carbon carbonyl group and the best reagent one can think of is cyanide. So, treatment with the diethylaluminium cyanide smoothly underwent 1 4 addition to introduce the cyanide. Now, you can see the cyanine and then acetate both are in α position both are in the same side. So, it should be possible to cyclize to get the corresponding lactone.

Nevertheless before you do it you should remove the unwanted keto group you have a keto group that you do not want. So, reduce with sodium borohydride to get the alcohol and once you have alcohol one can do deoxygenation using again radical reaction convert this hydroxyl into xanthate ok one can convert this into xanthate and or you know here you treat with this corresponding trioxide chloride then treat with tributyltin hydride and AIBN you remove the hydroxyl group ok.

The next step as I said you have to connect these two to form the lactone and that is done by treatment with sodium methoxide and methanol.

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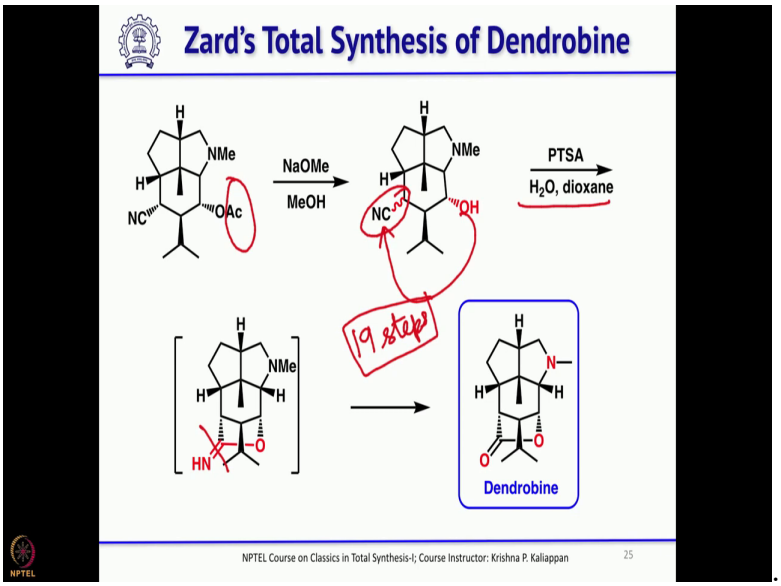

So, sodium methoxide methanol first it hydrolyzes the acetate, first it hydrolyzes the acetate to get the alcohol, but unfortunately it also he epimerizes the carbon bearing cyanide ok no problem.

Now, if you treat with para toluene sulfonic acid *p*-toluene sulfonic acid the OH will attack the cyanide to form the corresponding a weight. Now, since you are adding water and then doing the reaction dioxin this can get hydrolyzed to give the corresponding lactone ok that is nothing, but the natural product dendrobine.

Again Samir Zard took about 19 steps, but remember this involve chiral starting material and also involve two key reactions one is the Pauson - Khand reaction to get two 5 - membered rings and the second one is opening up the cyclobutane of verbenone by radical reaction to introduce the isopropyl group required in the with correct stereochemistry ok. So, with this we have completed total synthesis of two alkalides and we will discuss few more alkalis in the next few classes.

Thank you.