Classics in Total Synthesis-I
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Lecture - 31
Yohimbine

So, good morning and welcome back to NPTEL lecture series on Classics in Total Synthesis and we have been discussing about total synthesis of various alkaloids.

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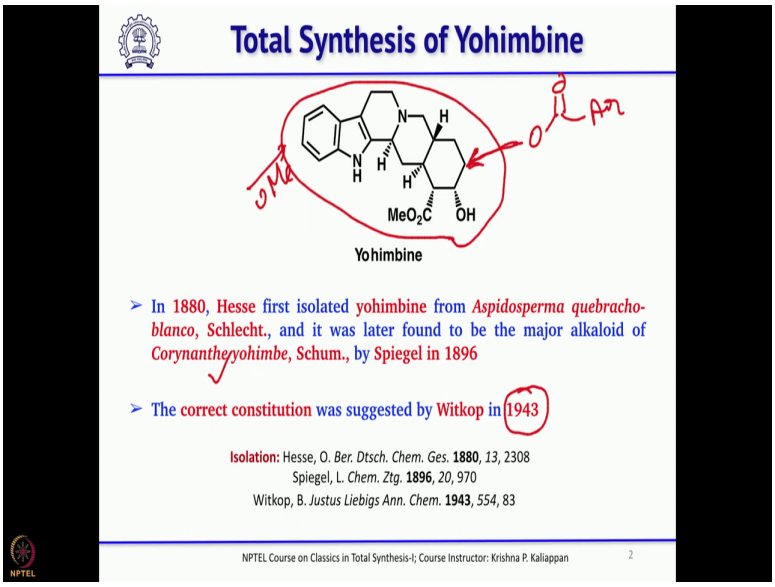

So, we have been talking about total synthesis of alkaloids and in the last lecture we talked about the total synthesis of reserpine and today we will talk about synthesis of Yohimbine and it has the same core structure of reserpine, but it has acyl group here. So, with tri methoxy aryl group attached to the carbonyl and you also have a OMe group in reserpine.

So, this natural product was isolated way back in 1880 and it was a major alkaloid isolated from Corynanthe yohimbe ok. And this correct structure was reported by Witkop in 1943 you can see it took about 63 years to assign the correct structure of your yohimbine.

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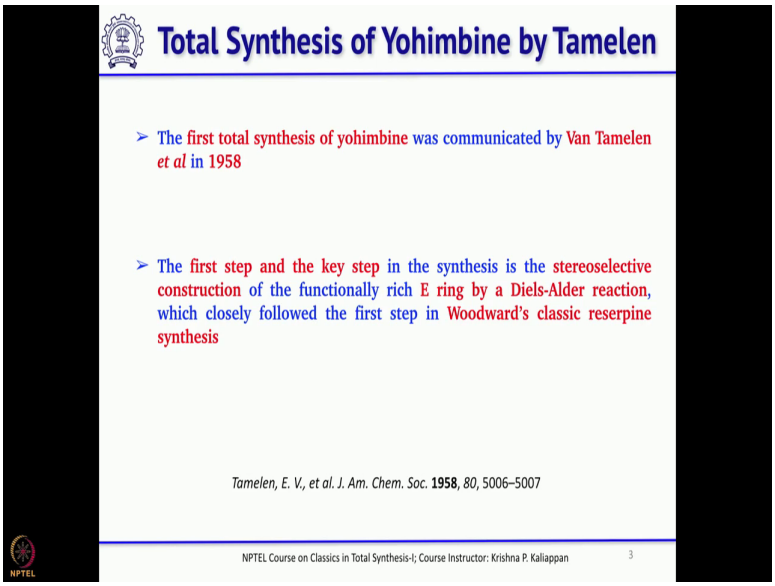

And it took another few years to complete the first total synthesis which was report reported by Van Tamelen in 1958 and the key reactions involved in the total synthesis of yohimbine was Diels Alder reaction. So, that Diels Alder reaction was used to construct the E ring and followed by the hydroxylation cleavage and cyclization which is almost like Woodward's total synthesis of reserpine ok.

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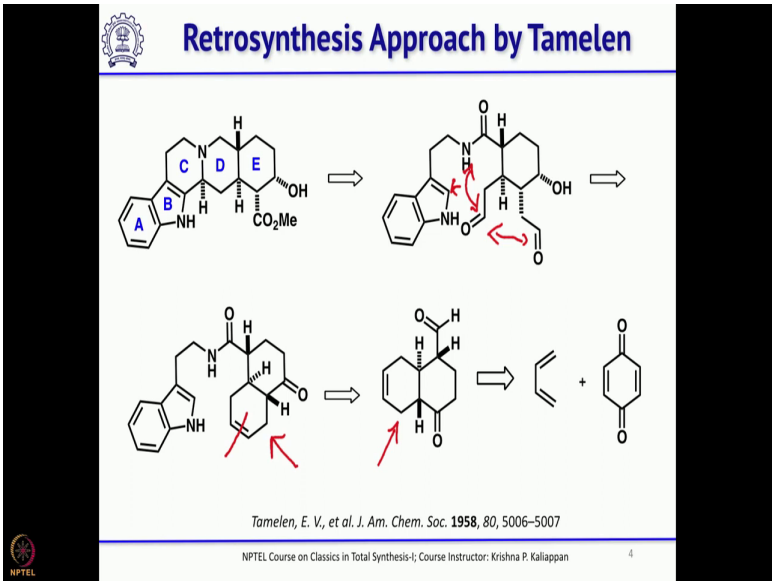

So, now let us see how Van Tamelen approached the total synthesis of Tamelen and let us see his retrosynthetic approach. So, he thought first he can cyclize this amide and this

carbonyl group followed by cyclization at this carbon ok, he tries to form the CD ring using these 3 functional groups. Then if you look at this di aldehyde ok this di aldehyde; the di aldehyde can be obtained by cleaving this cyclohexane if you do ozonolysis if you do a dihydroxylation followed by cleavage you can get this di aldehyde.

And once you see this cyclohexane ok wherever you see a cyclohexane one reaction which should come to your mind immediately is Diels Alder reaction. So, that is what he proposed here intermolecular Diels Alder reaction between butadiene and benzoquinone para benzoquinone as the key step and that is the first step in the total synthesis reported by Van Tamelen. Now, let us see how he did or how he accomplished the total synthesis of alder yohimbine starting from butadiene ok.

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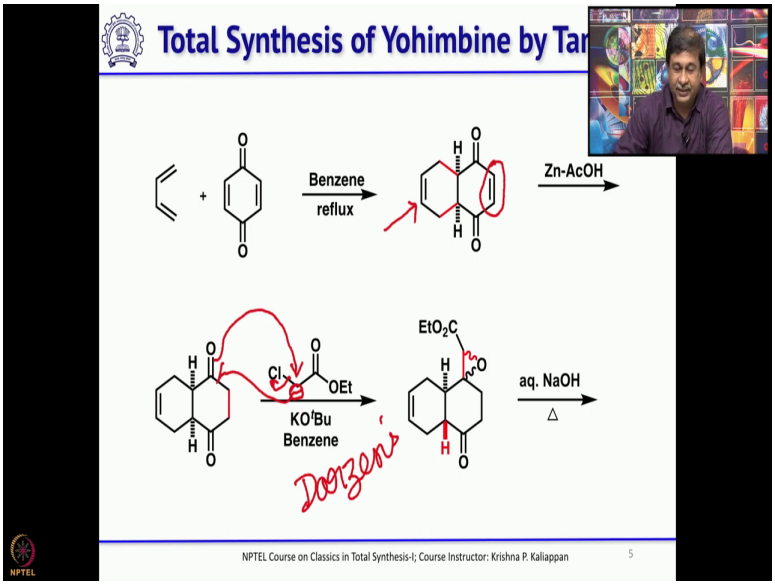

So, first step as he proposed in the retrosynthesis was the Diels Alder reaction between butadiene and para benzoquinone ok, in benzene when you reflux you get this bicyclic compound. Now, one can selectively reduce the ene dione the double bond of the ene dione by treating with zinc and acetic acid without touching the isolated double bond. So, this double bond is in conjugation with two carbonyl group, which can be easily reduced selectively by treating with zinc and acetic acid.

Now, this symmetrical di ketone ok, so next is carrying out Darzen's reaction, you know Darzen's reaction is to homolog it. So, here the homologation was done with α chloro ethyl acetate you generate an anion here that attacks the carbonyl group and this O^-

comes and expels the chloride to form the epoxide ok, that is the first step in Darzen's reaction. So, now, simple hydrolysis will give the carboxylic acid because it has to undergo decarboxylation followed by opening of the epoxide to get the corresponding aldehyde ok.

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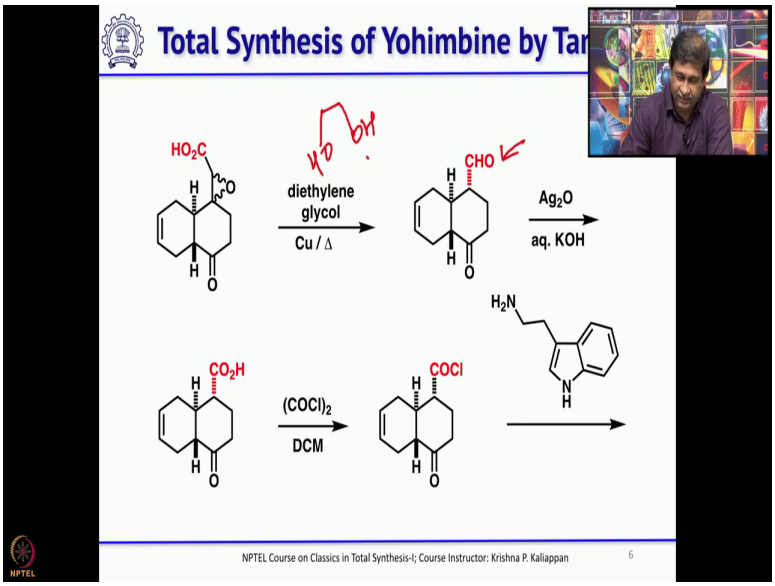

So, the hydrolysis saponification was done with a sodium hydroxide and followed by opening and protection of the resultant aldehyde ok, it is a homologation to get the aldehyde and the protection with diethylene glycol ok. So, this was done in the presence of the diethylene glycol to get the corresponding aldehyde.

So, homologation was done from carbonyl group to -CH_2-CHO. Now the aldehyde was easily oxidized at room temperature with silver oxide to get the corresponding carboxylic acid and that carboxylic acid was converted into corresponding acid chloride followed by treatment with tryptamine ok.

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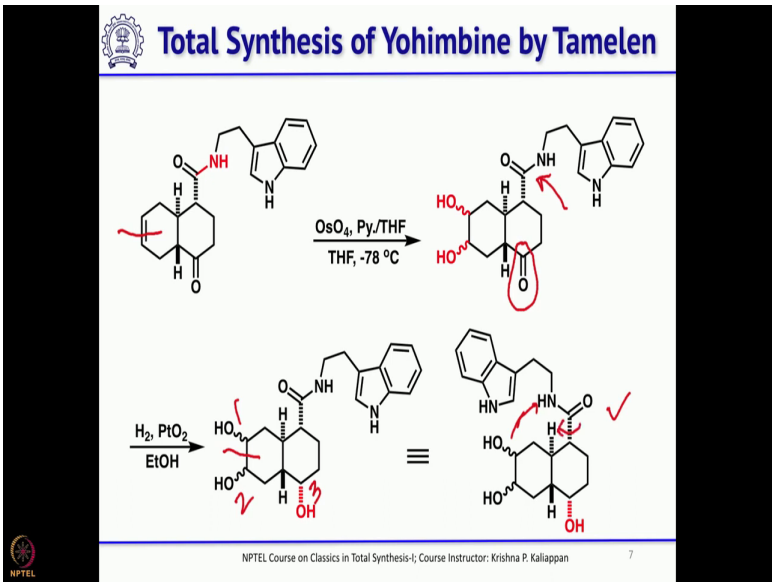

So, it forms basically the corresponding amide ok. Once you see this now the next step is to cleave this double bond ok, once you cleave this double bond you get a di aldehyde. So, this was done in two step protocol first you carry out the di hydroxylation to get the diol and then you reduce this ketone ok, you reduce this ketone under hydrogenation condition ok that is little bit tricky. So, you can see that normally one would use sodium borohydride or lithium aluminum hydride, but you also have the amide if you say LAH that can reduce the amide.

But they have used simple hydrogenation condition to reduce the ketone to get the corresponding triol ok. So, you have 1, 2, 3 alcohols in the products ok, but one can selectively cleave 1,2 diol with sodium periodate can cleave this 1,2 diol ok and this structure also one can redraw this way ok, this is for the sake of cyclization ok. Once you cleave this aldehyde has to cyclic with this amide ok. So, you rotate this bond ok you rotate this bond ok.

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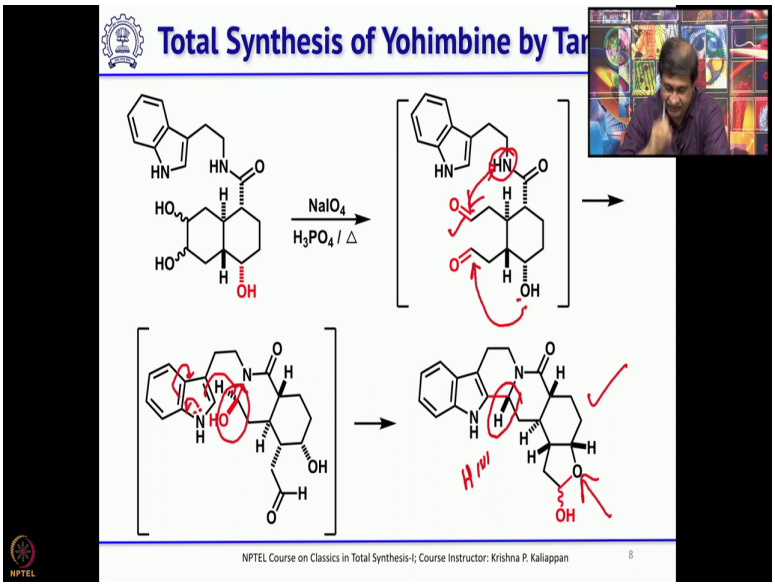

Now, this diol upon cleavage with sodium periodate you get this aldehyde and that aldehyde immediately you can see it forms an aminol ok immediately it forms an aminol with this particular aldehyde ok. And this on treatment under the same condition ok it undergoes cyclization ok it undergoes cyclization to get this products, here during sodium periodate reaction.

So, many reactions are happening one it forms the di aldehyde then this amide amine adds to this aldehyde to form this aminol, then you can see the indole moiety coming and attacking here ok; that leads to the formation of the 3rd ringing C ring ok. But the problem is the stereochemistry at this ring junction ok, here the hydrogen in yohimbine should be α, but what he got is β. Meanwhile you can also see this hydroxyl group attacks this aldehyde to form a 5 membered lactol ok, in one step as I said many reactions are taking place.

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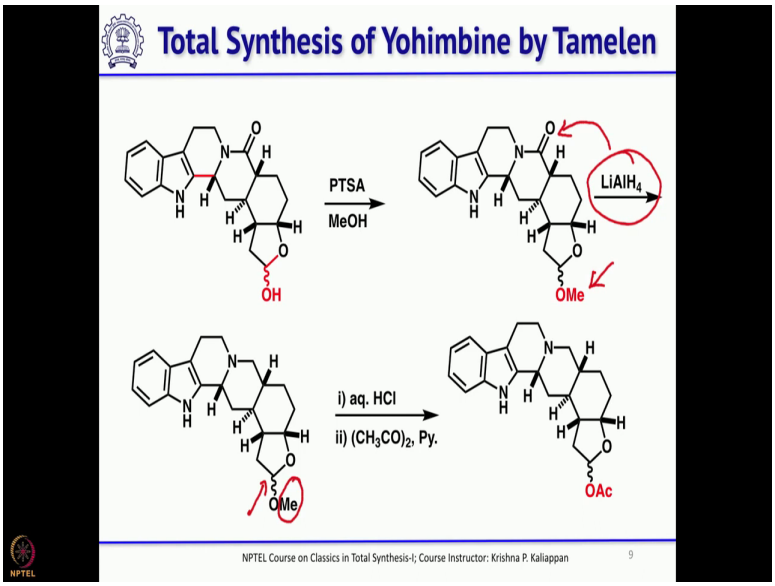

Now this lactol you treat with *p*-toluene sulfonic acid and methanol. So, it forms the corresponding lactol methyl ether, lactol methyl ether the lactol methyl ether, if you reduce with LAH the LAH is known to reduce the lactol ok. LAH can reduce the lactol to corresponding tertiary amine, so you got the tertiary amine.

Now you do the demethylation by treating with aqueous HCl to get the corresponding lactol, then acetylate you get the corresponding acetate ok. So, basically one why they have to do more steps because, if you have a lactol ok if you have a lactol LAH will reduce the lactol also ok, that is why the lactol should be protected ok, then your lactam should be reduced.

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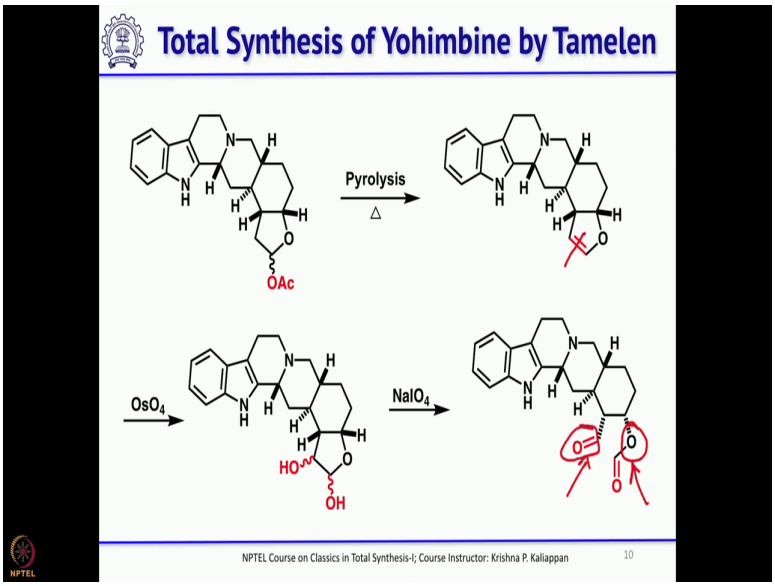

Now, the acetate you treat with or you carry out a pyrolysis; that means, you heat it at very high temperature and this can undergo elimination as you know acetates. When you heat at very high temperature it can undergo cis elimination to introduce the double bond ok. The pyrolysis gives the double bond now again you can cleave this double bond this is a enol ether.

So, if you do if you treat with osmium tetroxide again you get the diol and the diol if you treat with sodium periodate it gives one side aldehyde and other side -O-CHO ok. What you need here you need OH, is it not and here you need ester ok. So, this can be easily done by treating with chromium trioxide methanol.

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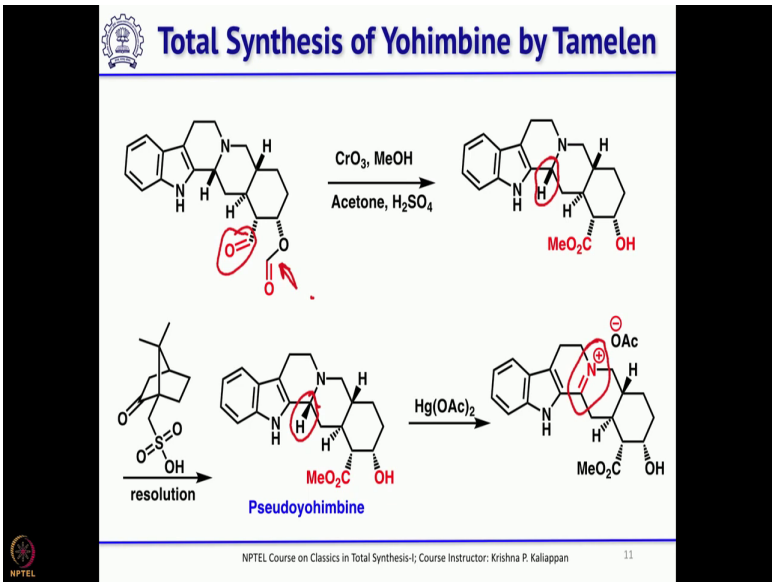

So, chromium trioxide methanol what happens it oxidizes the aldehyde to corresponding carboxylic acid and since you are using methanol that gets esterified and also during the process this -O-CHO also gets hydrolyzed to get OH. So now, if you look at this structure it has almost everything in place except this stereo center ok, this stereo center should be opposite.

So, that is one thing second if you want optically pure yohimbine ok then you have to resolve ok. So, the resolution was done by treating with camphor sulfonic acid. So, with camphor sulfonic acid first he got pseudoyohimbine. Why it is called pseudoyohimbine? As I said the stereo center is opposite at this carbon ok and it is known in the literature earlier when they did isolation of yohimbine, this stereo center can be inverted by treating with mercuric acetate ok.

So, when you treat with mercuric acetate it forms this iminium ion ok, when you treat this with mercuric acetate it forms this iminium acetate that iminium acetate if you reduce it now then the hydrogen comes from α ok.

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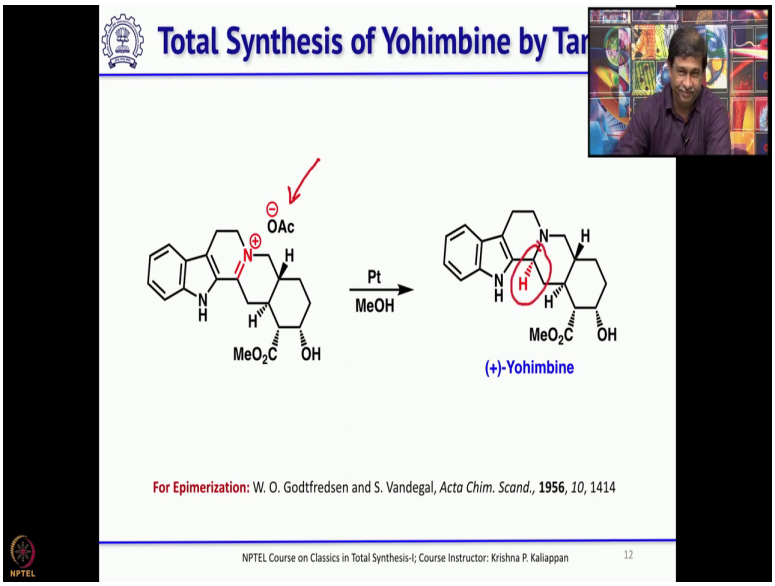

So, that is what he did? So, the from pseudoyohimbine first you treat with mercuric acetate to get this iminium ion and which is in situ reduced with platinum and methanol to get the corresponding isomerization at this carbon to get the natural product yohimbine ok.

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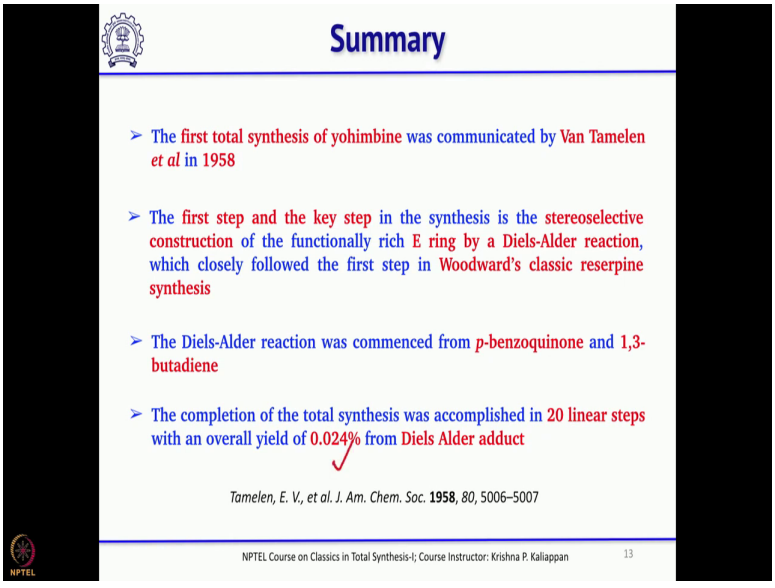

So, that is how Van Tamelen completed the total synthesis of yohimbine and the key steps as I discussed was Diels Alder reaction followed by one pot cleavage of diol to di aldehyde and then cyclization on the top portion to get ABC ring and the southern

hemisphere to form the lactol. There are 2 key reactions one is Diels Alder reaction other one is Sodium Periodate cleavage to form 2 rings ok. The synthesis involves 20 longest linear steps and overall yield of 0.024% from Diels Alder reaction adduct ok.

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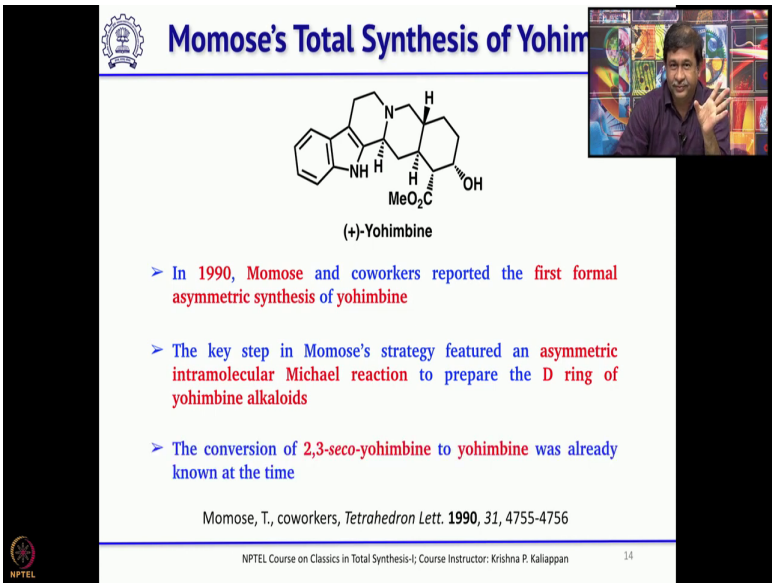

Now, we will move to the second synthesis here the synthesis is asymmetric one earlier one which you when we talked about total synthesis of Van Tamelen it was racemic synthesis, but they resolved at pseudo yohimbine stage and then converted into the naturally occurring yohimbine.

Here what we will do we will discuss about Momose total synthesis yohimbine it is an asymmetric synthesis and he used an intramolecular Michael reaction an intramolecular Michael reaction as the key reaction to form the D ring and that is where he introduced the chirality ok.

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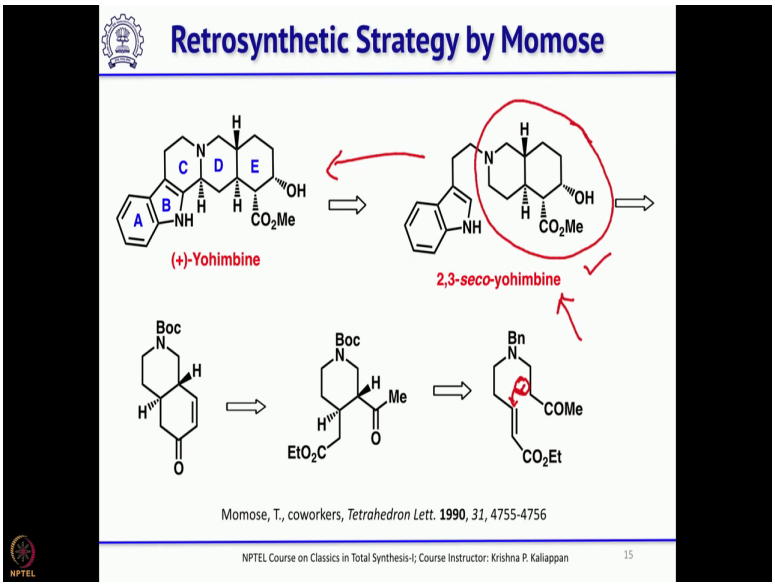

So, let us see how he is synthesized yohimbine was known to we made from this 2,3 -seco-yohimbine; that means, this has been already converted into yohimbine by 2, 3 groups Gilbert Stork and others they have completed 2, 3-seco-yohimbine to yohimbine. So, his idea was to make the 2,3 -seco-yohimbine, if you could do that that completes the formal asymmetric synthesis of yohimbine ok. So, his idea is basically to make this bicyclic compound ok in optically active form; for that he proposed this can be made from this bicyclic ketone ok.

This bicyclic enone and this bicyclic enone can be made from this keto ester by intramolecular cyclization. And this keto ester if you look at this carefully he wants to use an asymmetric Michael reaction. That means, you generate an anion here and add to this α-β unsaturated ester asymmetric Michael reaction that is the keto ester ok. Let us see how Momose completed the asymmetric total synthesis of yohimbine.

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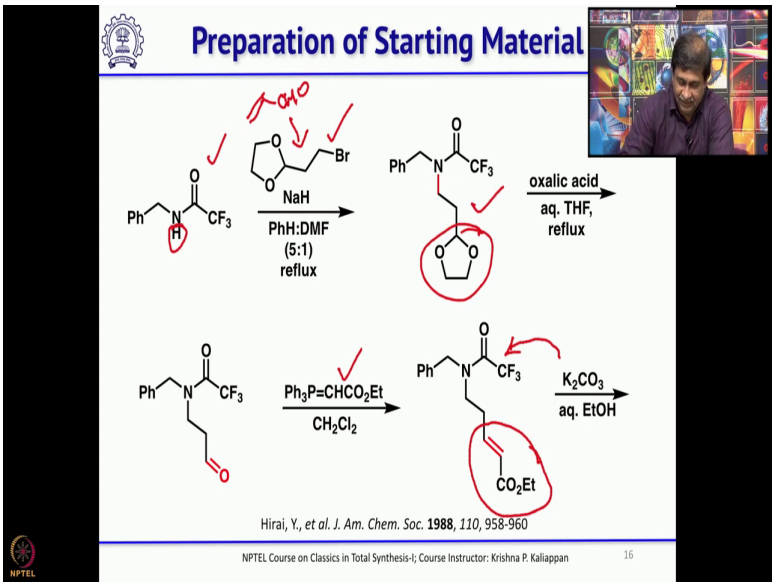

He started with protected benzyl amine trifluoro acetyl benzyl amine then treated with sodium hydride and quenched with this bromide. So, this bromide can be obtained in one step from acrolein. So, this is acrolein ok in one step one can make this bromide ok it is a protected compound. So, basically you remove this hydrogen and quench with this bromide. So, you get the corresponding alkaline alkylated compound ok.

Now, you can deprotect or remove the acetal using oxalic acid to generate the aldehyde, once you have the aldehyde then you do a stabilized Wittig reaction to get the corresponding trans α-β unsaturated ester. So, you have introduced the Michael acceptor now you can see that Michael acceptor has been introduced now what we need is you have to introduce the Michael donor. So, for that you hydrolyze the trifluoro acetyl group with potassium carbonate ethanol you get the secondary amine.

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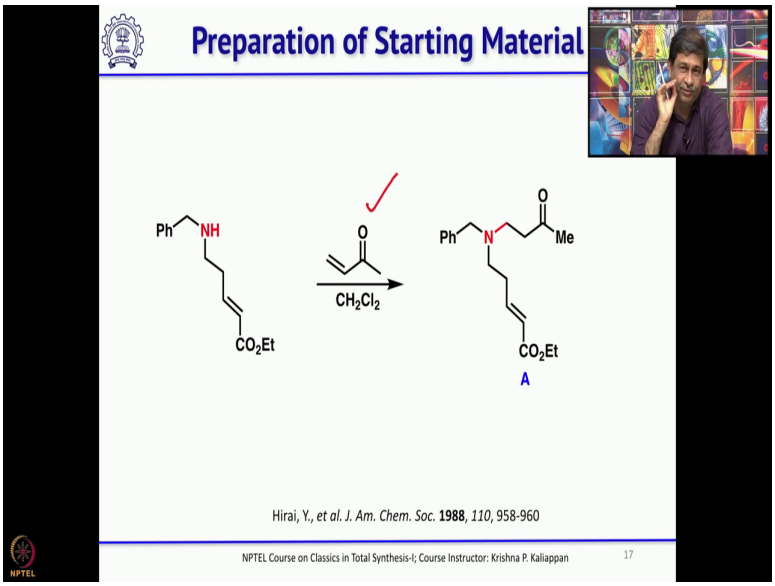

Now you do a Michael addition another Michael addition ok this Michael addition with methyl vinyl ketone you get the corresponding methyl ketone. So, now the stage is set for the key intramolecular asymmetric Michael reaction. So now, let us see which chiral reagent he has used for the key intramolecular Michael reaction

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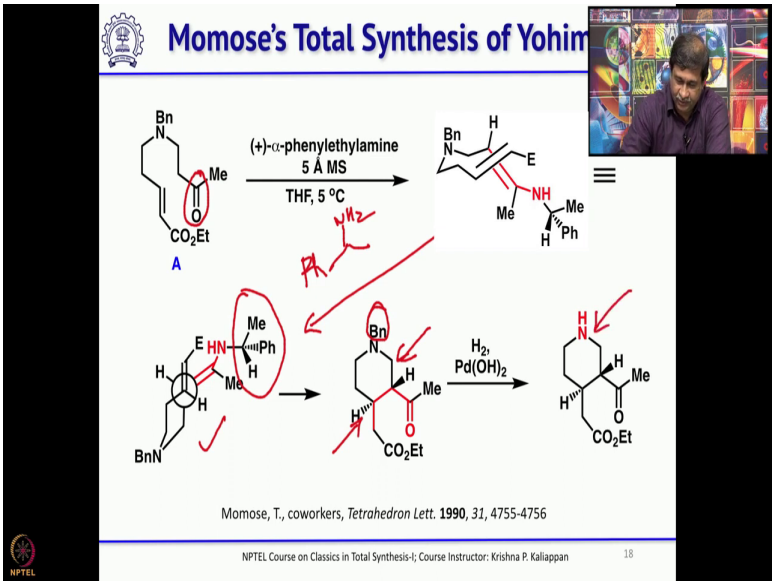

So, he took this compound and then treated with α phenylethylamine α phenyl ethyl amine. So, that is the chiral amine. So, α phenylethylamine is if you see this is this is the one ok. So, he took one isomer that is the (+) isomer of α phenylethylamine and then

made the corresponding enamine it took α phenyl methylamine and then treated with this ketone.

So, you have a ketone and then treat with primary amine it can form imine that imine can undergo you know isomerization to form enamine. So, this is the enamine now this enamine can undergo an intramolecular Michael reaction ok. So, you can see this can be redrawn in this confirmation.

So, I will leave it for 30 seconds, so that you can see how this can be redrawn like this ok. So, once you know how to redraw this and it is pretty easy how the chirality is transferred chirality that is this, it is like a chiral auxiliary ok α phenyl ethyl ammine it is a chiral auxiliary that is used successfully for the asymmetric Michael reaction ok.

So, that is how the 2 chiral centers ok you can see the 2 chiral centers are fixed using this asymmetric Michael reaction ok. Next you do not want the benzyl group because you have to remove the benzyl group, so that the NH can be attached to the indole ok. So, hydrogenolysis will remove the benzyl group to get the piperidine ring substituted piperidine ring.

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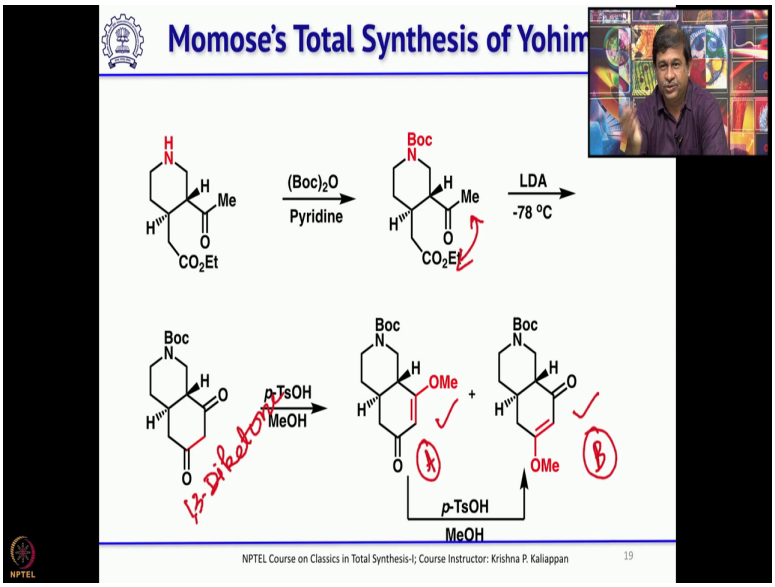

Now you protect the piperidine with Boc anhydride to get corresponding N-Boc then you try to cyclize these 2, you need the six membered ring ok. So, Claisen reaction you do this on this keto ester to form the corresponding 1,3 Di ketone corresponding 1,3 di

ketone. Once you have this 1, 3 di ketone, now if you treat with *p*-toluene sulfonic acid and methanol it can form enol ether this we have already discussed when you have 1, 3 di ketone and treat with para toluene sulfonic acid and alcohol a methanol ethanol isopropanol butanol. So, it will form the corresponding enol ether ok.

Since this is unsymmetrical you can get both isomers; however, what he found out was keeping this reaction for long time keeping this reaction for long time converts isomer A to B. So, basically if you run this for long time initially you get a mixture of A and B, but if you keep it for long time the A is converted into B which is what he wants.

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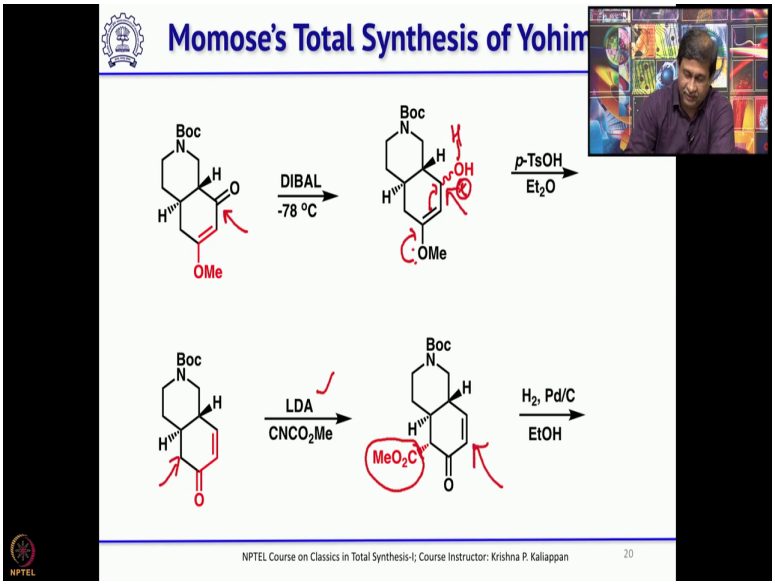

So, he took the enol ether now you can reduce the ketone ok you reduce the ketone with DIBAL to get the corresponding allylic alcohol ok. Now if you treat with acid ok *p*-toluene sulfonic acid. So, protonation will take place here ok then this lone pair will push the double bond and, in the process, you will get corresponding enone ok. That enone now you have acidic proton here ok you have acidic proton here.

So, that can be removed using LDA and quenched with Mander's reagent, Mander's reagent is cyano methyl formats ok. So, you can easily introduce a -CO_2Me group at α position ok, then you reduce the double bond with under standard hydrogenolysis condition so you get the corresponding bicyclic compound ok.

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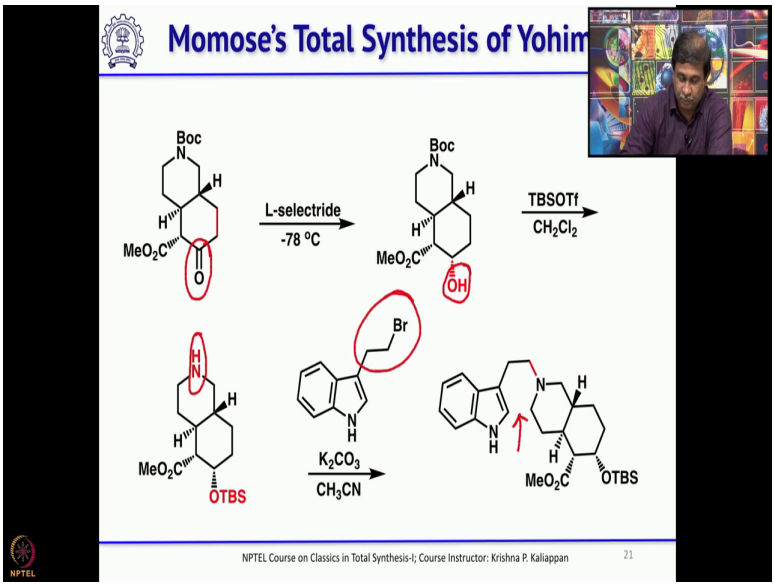

Now, what you need you need to selectively reduce the ketone to alcohol, then you have to remove the Boc group. So, before removing the Boc group you have to protect the hydroxyl group you protect the hydroxyl group as TBS and while protecting the alcohol as TBS group the Boc also got removed then you alkylate the piperidine with this indole ethyl bromide ok indole ethyl bromide. And now you can see you have the complete structure of yohimbine except that this bond is not formed ok except that this bond is not formed ok.

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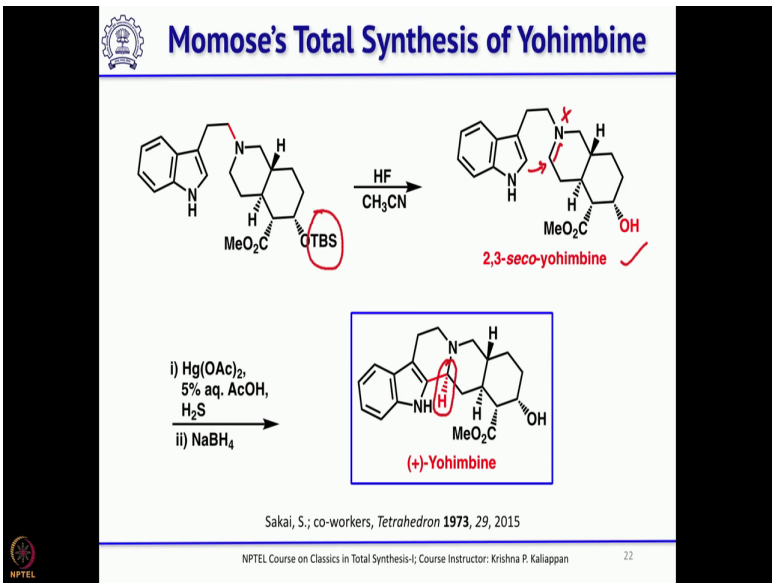

But as I said 2,3 seco-yohimbine has been already converted into yohimbine ok. There are at least couple of reports where 2,3 seco-yohimbine has been converted into yohimbine. So, if we can remove the TBS group ok, so that will give you 2,3 seco-yohimbine. So, from here the known steps are treatment with mercuric acetate in the presence of 5% acetic acid and followed by sodium borohydride reduction.

So, basically as you know it forms an iminium ion ok, then the cyclization takes place again followed by iminium ion and then reduction with sodium borohydride. The hydride is delivered from the α site to get yohimbine ok. So, that is how he could accomplish the asymmetric formal total synthesis of yohimbine ok.

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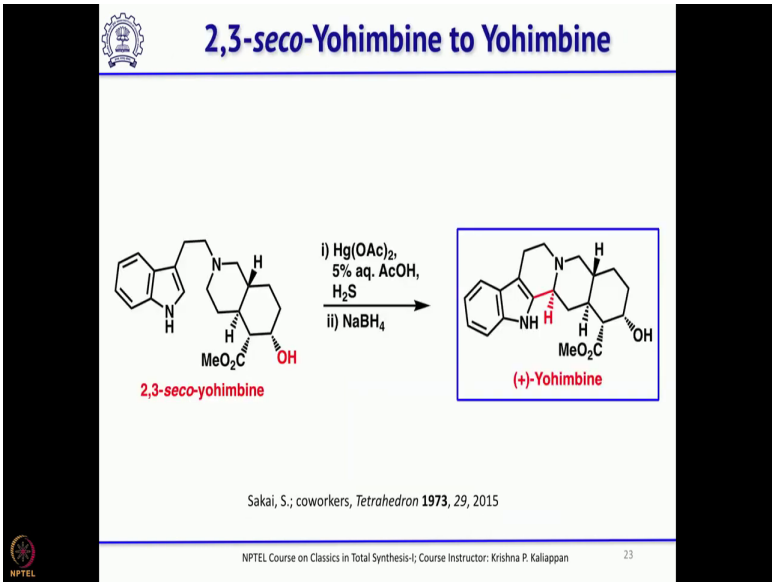

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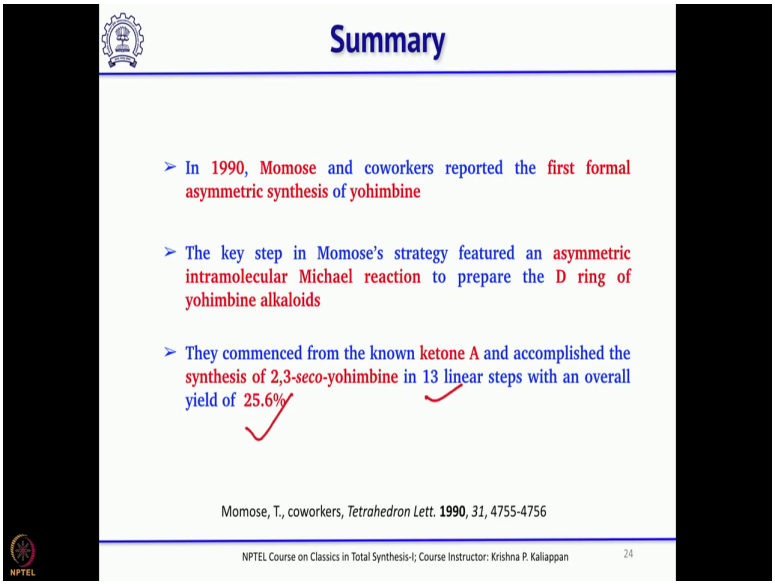

The key reaction in the asymmetric total synthesis of Momose is the asymmetric intra molecular Michael reaction. So, if you look at the structure of yohimbine only the D ring has 2 chiral centers ok. So, the chiral centers were introduced by asymmetric Michael intramolecular Michael reaction.

Overall, the synthesis was done in 13 longest linear steps and with impressive overall yield that is 25.6% yield. If you compare this yield with Van Tamelens this is significantly high, I would say it is 100 times higher than what Van Tamelen has reported ok, both are interesting synthesis and both had its unique key reactions to synthesize yohimbine ok.

So, thank you.