Classics in Total Synthesis - I
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Lecture - 38
Galanthamine

So, good morning everyone welcome back to the course on Classics in Total Synthesis, as you know we have been discussing about total synthesis of many alkaloids and today we will talk about total synthesis of one more alkaloid.

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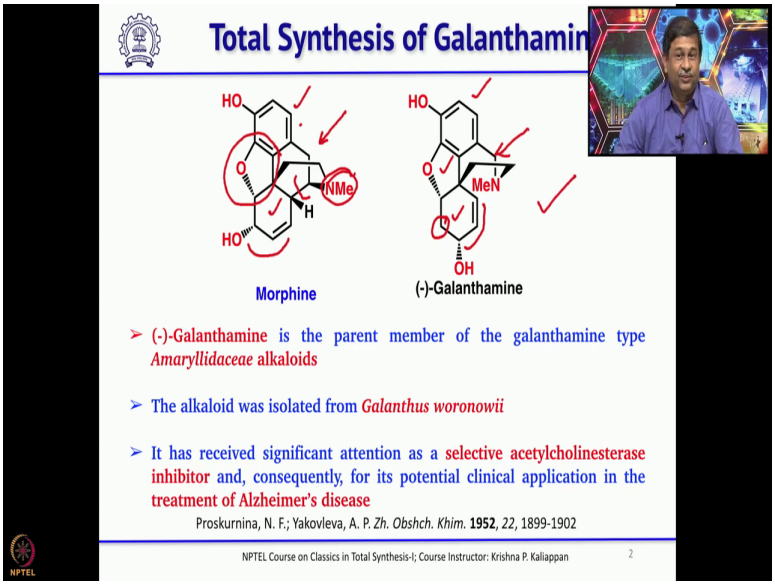

In fact, we will talk about three total synthesis of this alkaloid by name Galanthamine. So, this is the structure of galanthamine and if you look at this structure you can see some similarity with another famous alkaloid called morphine, already we discussed total synthesis of morphine earlier.

So, it is easy to compare and then see how this new natural product that is galanthamine differs from the earlier natural product morphine which we discussed ok. So, both have the same aromatic ring with a hydroxyl group and you can also see the 5- membered ring that is also there in galanthamine.

And next the cyclohexanol is also there in galanthamine only difference is here instead of first three carbon atoms the same allylic alcohol is there in the next three carbon

atoms. So, there is a -CH_2 here in galanthamine ok and the next major difference is this particular bond is not there ok this particular bond is not there and also if you look at the two bonds which are connecting the aromatic ring with nitrogen.

So, there are two -CH_2-CH_2 ok there are two -CH_2-CH_2 between the aromatic carbon and -NMe in morphine whereas, in the case of galanthamine there is only one -CH_2. So, these are the major differences between morphine and galanthamine structure wise. So, this galanthamine was isolated from Amaryllidaceae alkaloids, you know it showed potential clinical application in the treatment of Alzheimer disease due to it is selective acetyl cholinesterase inhibitor activity.

So, that is why many groups were interested in the total synthesis of galanthamine and also as I said it is closely related to the structure of morphine. So, morphine you know there are many totals synthesis of morphine and because of that you know you can see a similar number of people who are interested in the total number total synthesis of galanthamine.

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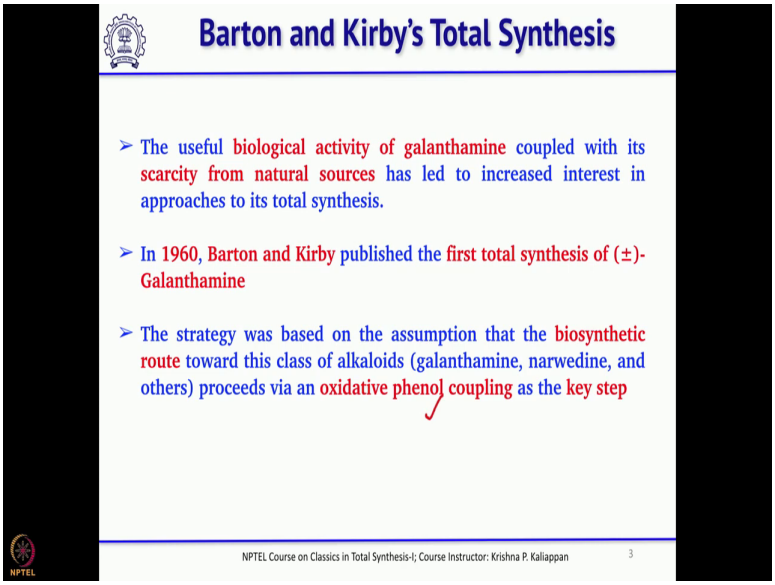

The first total synthesis was reported by Barton's group and he used a very interesting biomimetic oxidative phenyl coupling as the key reaction to form a bond between the two aromatic rings ok.

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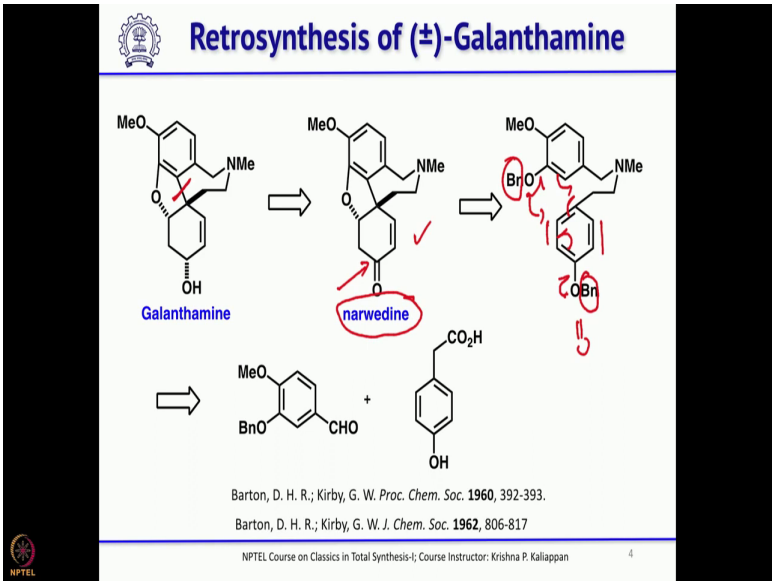

And how he has done is very interesting way and for that you can see this is the bond I am just talking about this is the bond he was trying to make using a bio mimetic approach involving phenolic oxidative phenolic coupling reaction. The first retro synthesis is the reduction of ketone so once you have this enone one can reduce it selectively to get the galanthamine. So, that also leads to another alkaloid called narwedine ok.

Then comes the key step. So, the key step involves actually first you remove this benzyl protecting group selectively. So, you get the phenolic hydroxyl then under you know conditions where you can generate radical. So, you generate radical here you generate radical here. So, they come all the way ok and then cyclise. So, once it cyclises you get a enone ok double bond here and double bond here like this enone.

So, then this phenolic hydroxyl group will undergo intramolecular Oxa-Michael addition to give narwedine. So, that was the idea that was that idea was based on bio mimetic strategy. And this can be obtained from, so these two you know for simple starting materials aldehyde and corresponding *p*-hydroxy phenyl acetic acid. Now, let us see how Barton's group synthesize galanthamine starting from commercially available isovanillin.

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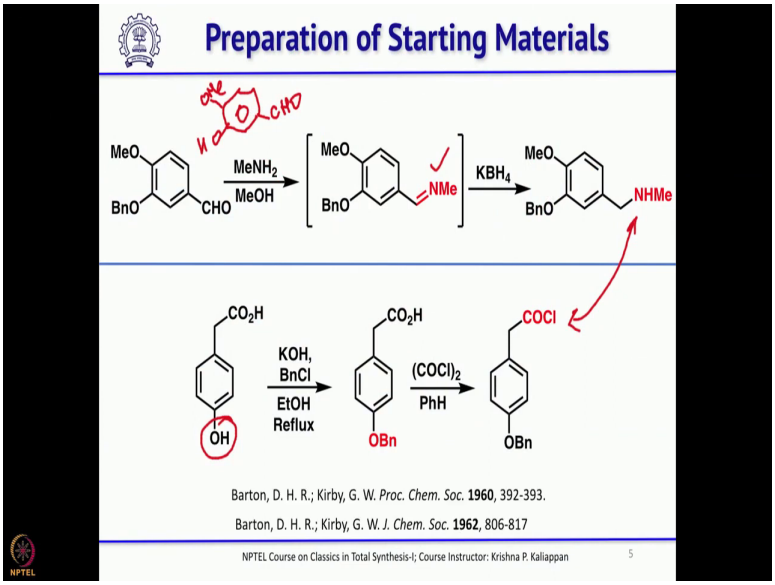

So, isovanillin is nothing but we have already discussed when we talked about morphine synthesis. So, this is isovanillin ok, you can benzylate the free hydroxyl group the phenolic hydroxyl group was benzylated under basic condition, then in *situ* you form an imine by treating with methylamine ok. So, this imine can be immediately reduced with potassium borohydride to get the corresponding -CH_2-NHMe ok, the for the other fragment you start from the para hydroxy phenyl acetic acid para hydroxy phenyl acetic acid.

So, then you protect the phenolic hydroxyl group as benzyl ether then convert the acid into acid chloride ok. So, these two fragments are you know very easily made from commercially available starting materials, once you have acid chloride and then amine just combine these two you know under mild base you get the corresponding amide ok.

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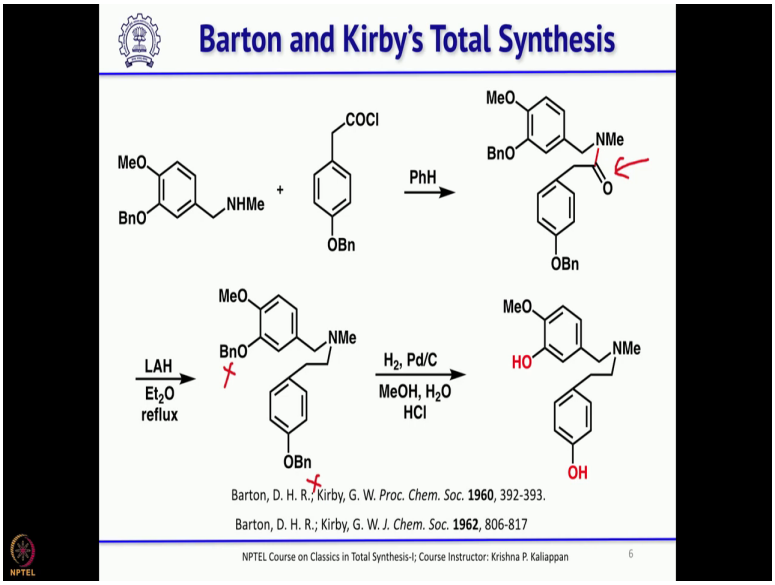

This amide now it can be reduced with LAH to get the corresponding amine, here comes the key step. Now, the first step is you have to remove the protecting group. So, that was done under hydrogenolysis condition to get the two phenolic hydroxyl groups ok.

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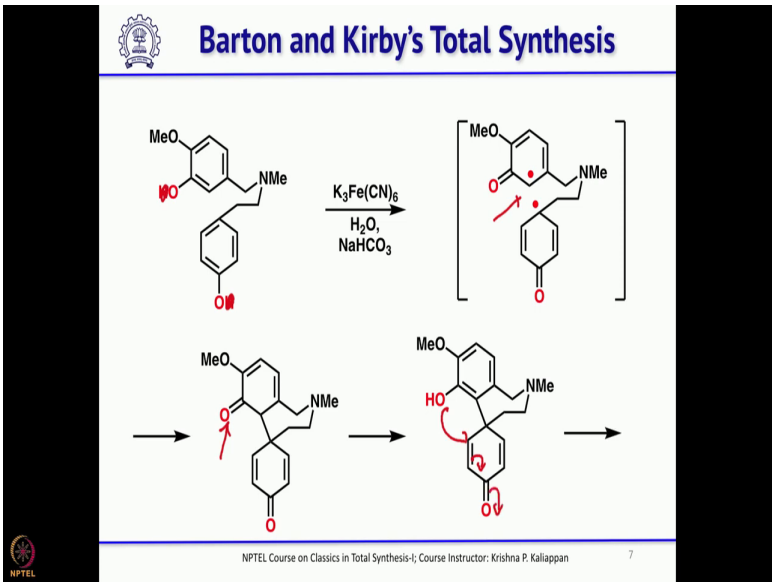

Once you have this phenolic hydroxyl groups then you treat with potassium ferricyanide ok. So, the potassium ferricyanide as I said first it forms the free radical. So, O radical and that goes all the way to here ok. So, then it couples that way this is the first C-C bond formation ok as a result of oxidative phenolic coupling. Once this is formed, now you can see this ketone can enolise, once it enolizes it becomes phenol, that phenol can immediately undergo an Oxa- Michael addition ok.

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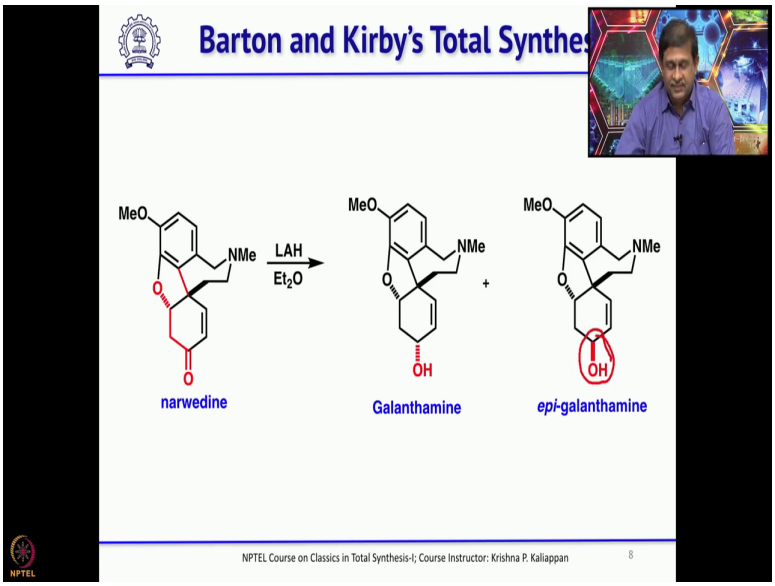

If that happens this is what you get that is a natural product narwedine, is not it? Now this narwedine if you reduce it with LAH you get a mixture of galanthamine and as well as a epi- galanthamine where this particular stereo centre is opposite.

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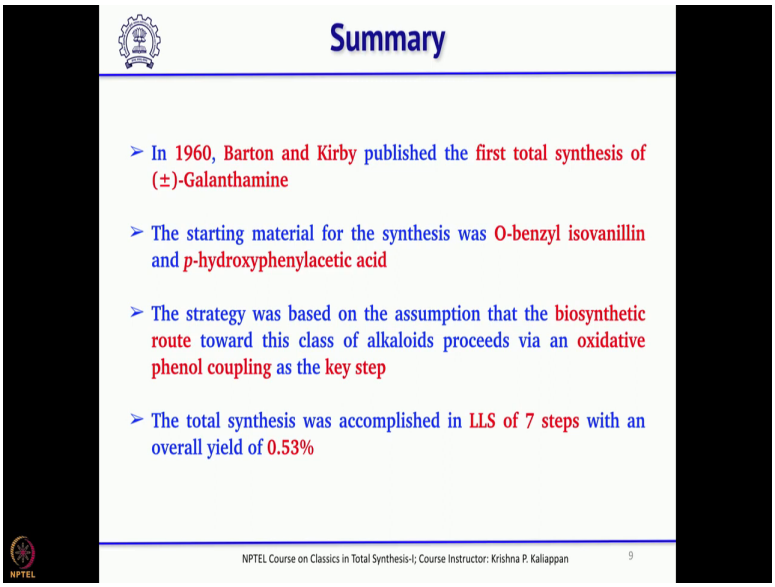

So, this is how he completed, he and his Barton and his group completed the total synthesis of racemic galanthamine and this was the first total synthesis and the starting materials are isovanillin and para hydroxyphenylacetic acid and the key reaction I already mentioned the key reaction was the oxidative phenolic coupling. Overall the

whole sequence took about 7 steps, but yield was not that high the overall yield was only 0.53%.

Nevertheless, this involved a very very important oxidative phenolic coupling as the key reaction, that actually way for many people to synthesize galanthamine via this method as well as improve the whole process. So, the next method which I am going to talk about was reported from industry.

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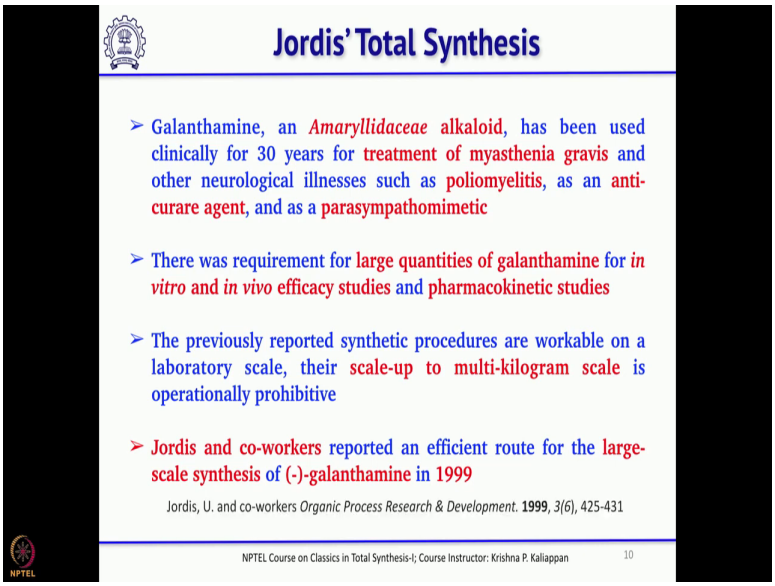

And how they synthesize this compound in multi gram quantity multi kilogram quantity using one of the key reaction is again the phenol oxidative phenolic coupling action ok. This was reported by Jordis and co-workers in 1999 and let us see how they have used oxidative phenolic coupling as well as other reactions as key reaction to make this.

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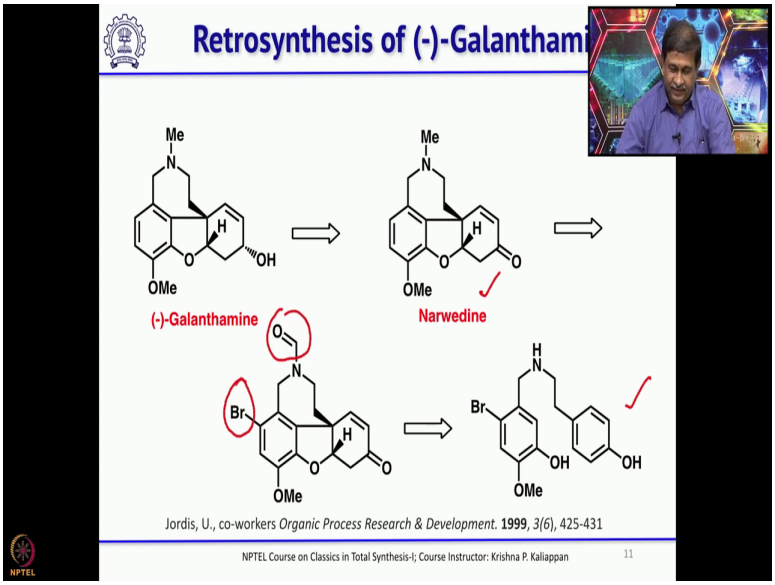

So, their retrosynthetic analysis of galanthamine again goes through the same intermediate that is narwedine. Then this was made from this aldehyde this N formyl piperidine ok that can be easily reduced to give methyl group at the same time this bromine also can be reductively cleaved this as I said can be obtained from this diol through oxidative phenolic coupling reaction which was already established by Barton's group.

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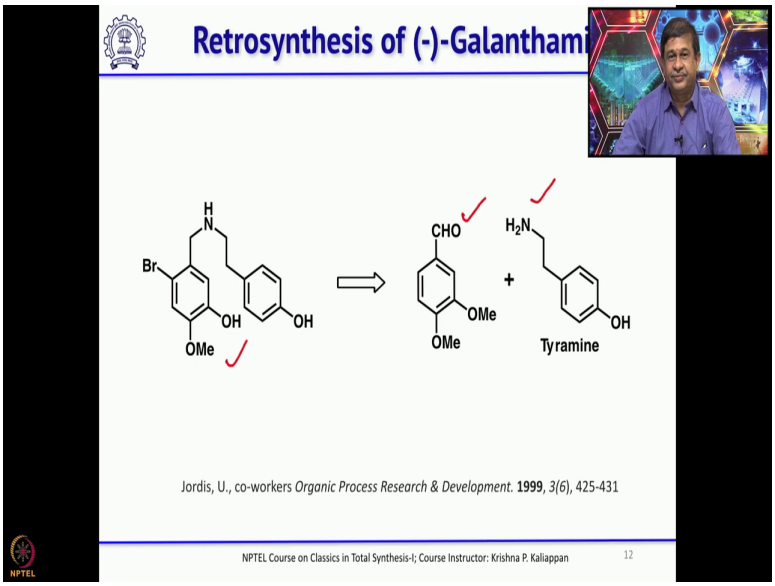

Then as you know this is very easy this intermediate is very easy to make that in the case of Barton's synthesis they started with acid chloride, here they started with aldehyde and

amine so you make skip base and then reduce it. So, reductive emination will give this key intermediate which can undergo oxidative phenolic coupling ok.

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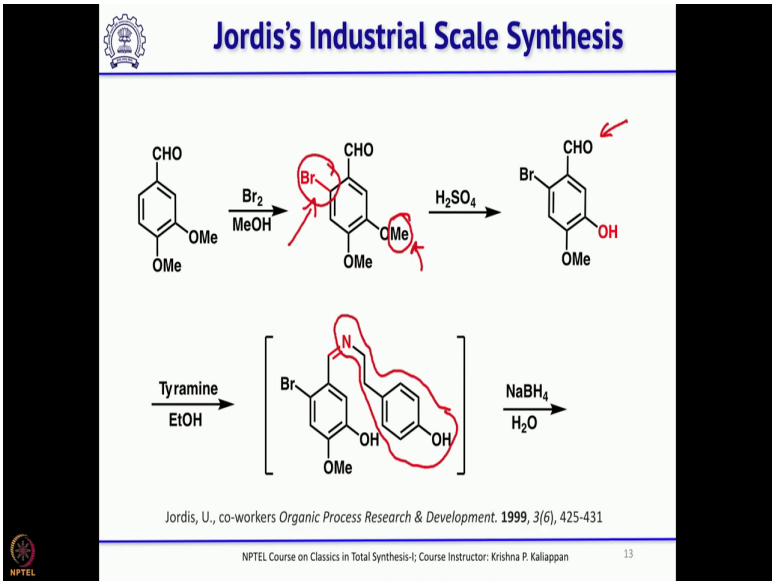

Now, let us see how this synthesis was done. So, this synthesis was done starting from commercially available dimethoxy benzaldehyde. So, this is available in large quantity one can start with 100 grams, 200 grams on here they started with the kilogram several kilogram scale then do the bromine and methanol ok. Later they also found better method was bromine and acetic acid to introduce a bromine at this carbon.

Then selectively this methoxy group the methyl of that methoxy group was cleaved by treating with sulfuric acid, actually this was required the introduction of bromine was required for the selective removal of this methyl group ok. So, when you treat with sulfuric acid the demethylation takes place and you get the corresponding phenol. So, now, you treat with tyramine. So, tyramine is nothing but this particular amine is called tyramine.

So, which is also commercially available, you take the tyramine and treat with this aldehyde you form this imine. And this imine can be in-situ reduced with sodium borohydride to form the corresponding amine.

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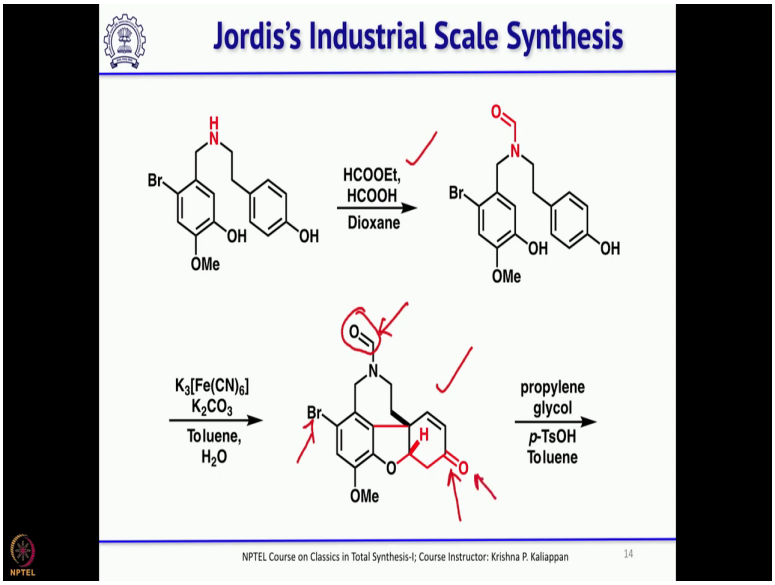

So, once you have this amine you have to protect that amine. So, the amine can be protected as N formyl derivative. So, that is normally done by treating with ethyl format and formic acid. Here comes the key reaction so, that is the oxidative coupling of phenols. So, that reaction worked very well and you can see the oxidative coupling followed by Oxa- Michael addition gives this very advanced intermediate.

Now, what is required from here? You should remove this bromine which is not required now, then this N formyl group should be converted into the methyl group then finally, the α–β and saturated ketone should be reduced to corresponding allylic alcohol. So, how it was done? So, to first to convert this N-CHO into N-Me group you have to protect the ketone here. So, it was done by treating with propylene glycol and that gave this ketal.

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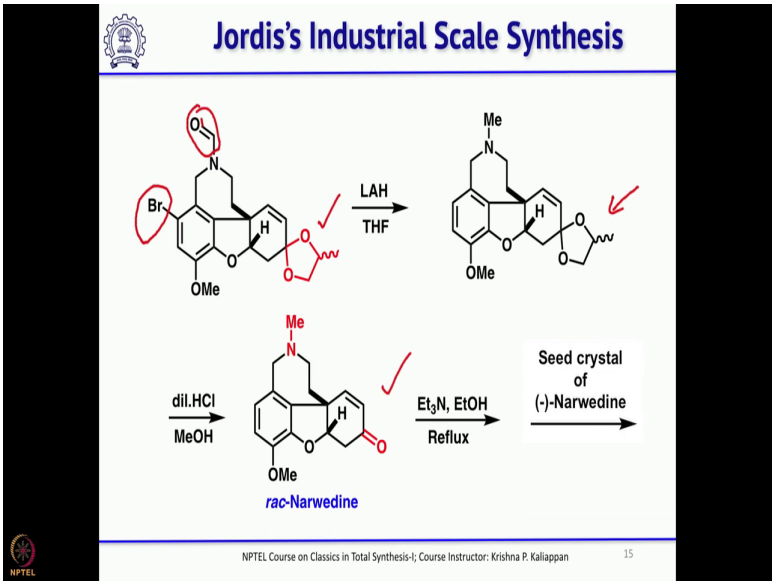

Next, if you reduce with LAH, LAH will convert this N-CHO into N-Me group at the same time that also will remove the bromine which is attached to the aromatic ok. Reductive removal of bromine as well as conversion of the N formyl to N methyl group takes place when you treat this compound with LAH ok. So, once that purpose is solved then the ketal no you do not want the ketl, so you can be removed using diluted Cl and THF to get the α–β unsaturated ketone so, that is nothing but the narwedine which is a natural product.

Here comes a very important reaction which normally it is done in industry in large scale that is called seeding of crystals ok. What they do? They took this racemic compound they took this racemic compound added ethanol and triethylamine and reflexed ok. So, that it dissolved it is a crystal so, they dissolve it in ethanol and triethylamine while reflexing.

Then they slowly added seeds of (-) narwedine ok they added the chiral one the (-) isomer which they have already. So, that they added it is a seeding. So, normally when you want to crystallize you do the seeding.

So, they use this seeding technique with the naturally occurring isomer with the naturally occurring isomer. So, once you do that the racemic one you know it can be it is possible to convert the racemic one into the same isomer ok. So, this is a very interesting process and they have done this on 70 kg scale to get the naturally occurring galanthamine ok.

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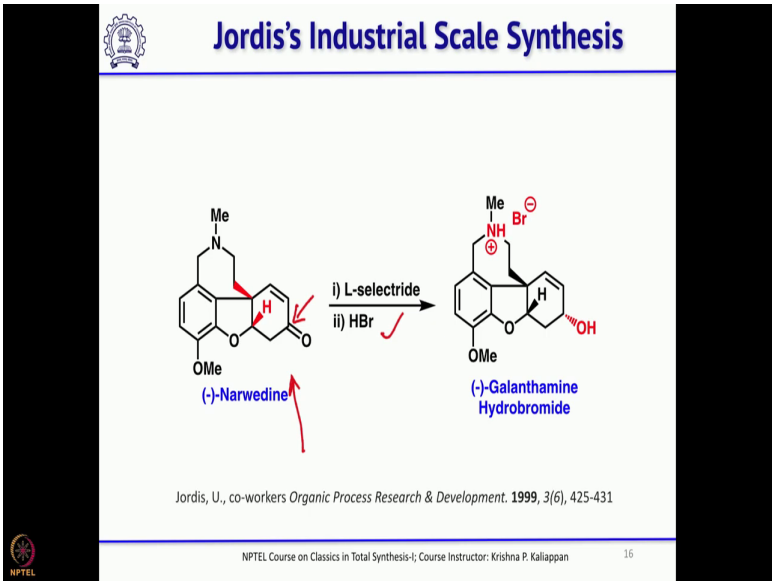

Once they form this narwedine in 70 kg scale they have to reduce only the α–β transistor ketone. So, that was done with L-Selectride to get galanthamine hydro bromide ok. So, after reduction they use HBr so, that it is good to isolate the galanthamine as it is HBr salt ok.

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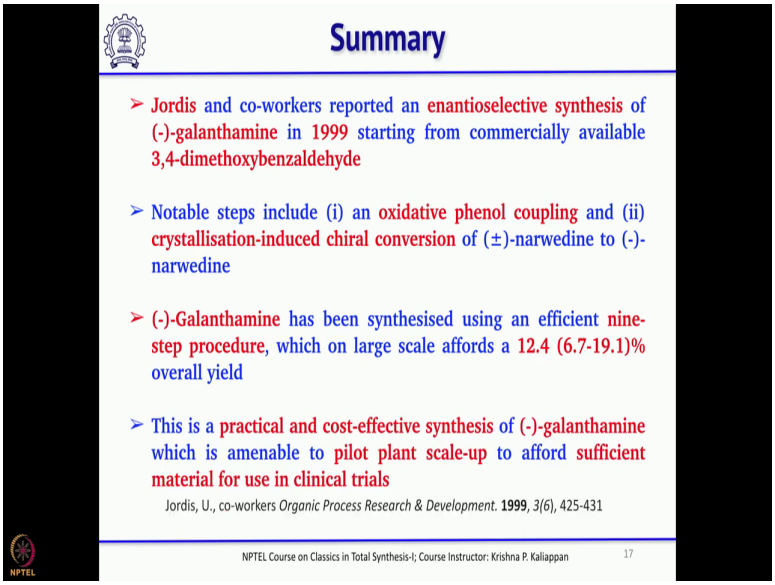

So, overall if you look at this they started with simple commercially available starting material called 3, 4- dimethoxy benzaldehyde and like Barton's group they also use the oxidative phenol coupling as the key reaction. And the most important one was they have used the seeding technique started with you know a chiral narwedine. So, they added to the racemic narwedine they prepared using their method and using this seeding

technique. So, they could convert the racemic into the expected naturally occurring minus narwedine.

So, overall this process was done in large quantity and it took about 9 steps and you can see the yield is 12.4% why I have written 6.7 to 19.1 because when they did on several batches the lowest one was 6.7 and then you know went up to 19.1. So, then I will move to the third total synthesis which was reported in 2000 reported by Barry Trost here he has used asymmetric allylic alkylation as well as Heck reaction as the key reaction to synthesize galanthamine.

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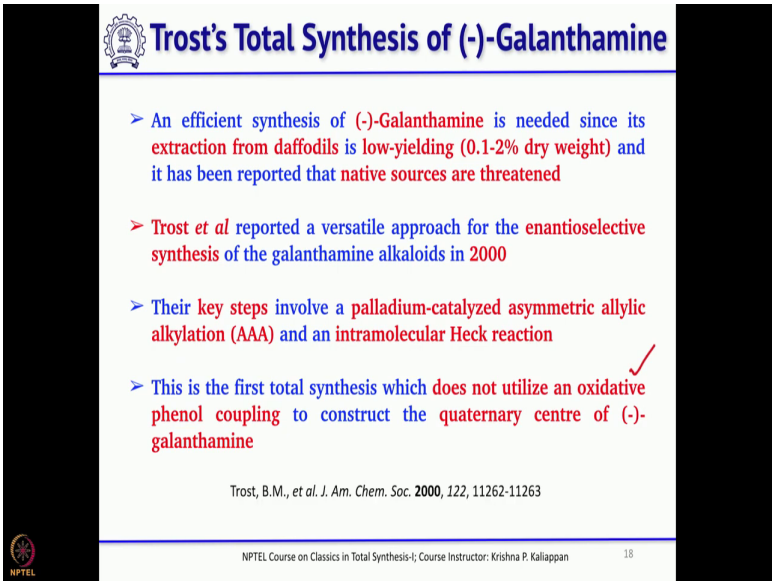

His total synthesis was the first total synthesis where the oxidative phenyl coupling was not used. Before that most of the synthesis you know involved oxidative phenolic coupling to get galanthamine and is synthesis came out of that and then started with a Heck reaction to construct that bond ok.

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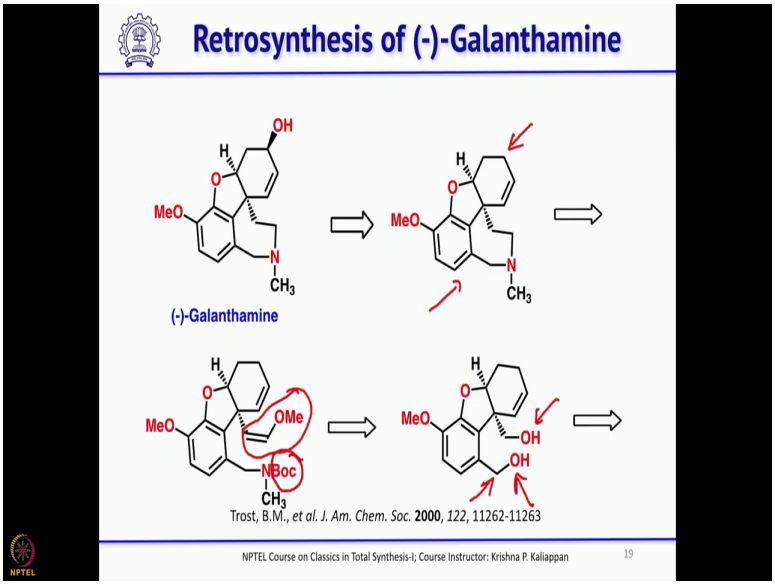

So, galanthamine here their first retro synthesis is you know you oxidize this allylic carbon to introduce the hydroxyl group and this can be obtained by you know from this enol ether if you have enol ether and N-Boc both can be hydrolysed. So, enol ether hydrolysis will give aldehyde. So, if you remove N-Boc you will get -NH. So, then this can undergo reductive amination to give this products and this enol ether as well as N-Boc can be obtained from this diol ok.

See, this though it looks you know almost same these two primary alcohols, but one is benzylic alcohol so, that can be selectively you know oxidized. So, that way you can easily differentiate these two primary alcohols.

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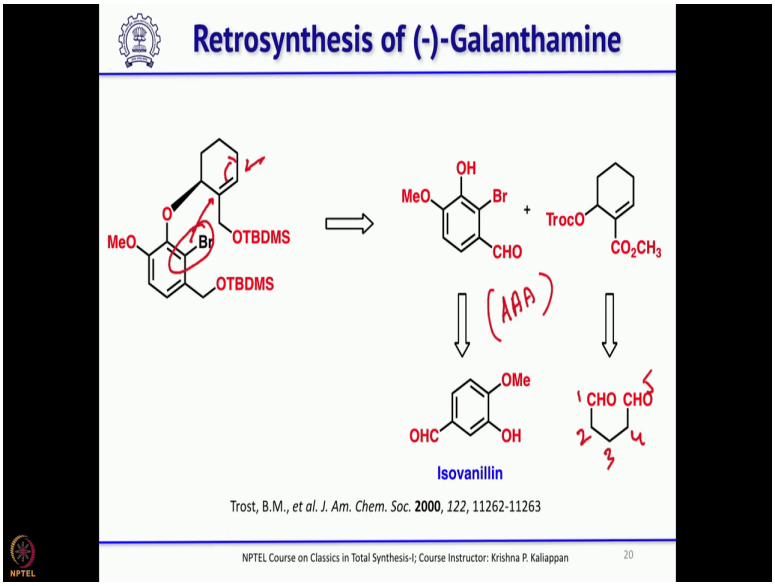

And this diol was obtained using Heck reaction. So, you can see you have a double bond and you have bromo aryl compound this can undergo Heck reaction and while doing that this double bond will migrate then followed by allylic oxidation you will get the galanthamine.

And this can be easily obtained from these two using asymmetric allylic alkylation ok. So, that is the key step in Barry Trost total synthesis of galanthamine, the of course, if you look at this can be easily made from isovanillin and that can be made from the corresponding 1, 2, 3, 4, 5 pentane diol ok.

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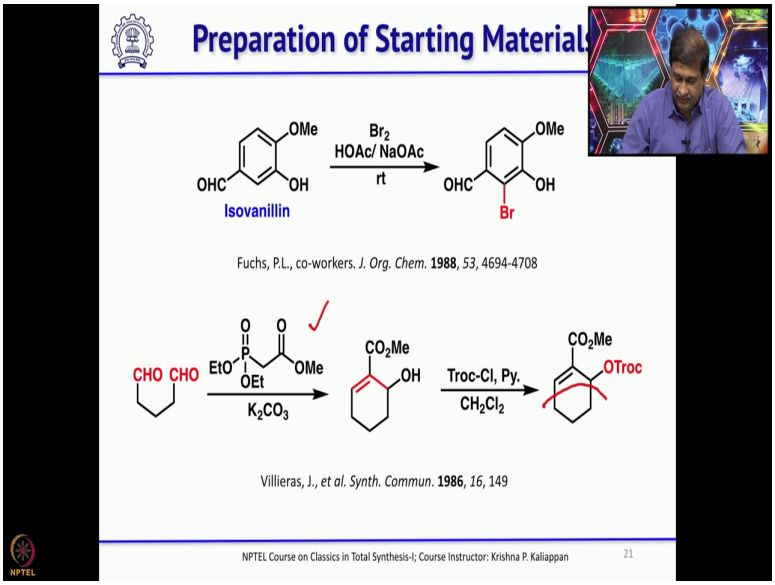

Let us see how it was done, started with isovanillin. So, isovanillin is one of the commercially available starting materials used in many synthesis of alkaloids. So, the bromine and acetic acid so, you introduce a bromine here. So, now, you the other fragment you start from this the dialdehyde and in one pot you treat with this phosphonate ok one pot you treat with phosphonate you get this allylic alcohol and also ester.

So, this is a very interesting mechanism try to write a mechanism for this and you will get an idea about how such allylic alcohol with an ester can be made in one step. So, once you have that so, you have to make you know you have to form the allylic carbonate. So, that was done with trichloride. So, now, so this is ready for the palladium catalysed reaction ok. So, what you should do? You have to combine these two.

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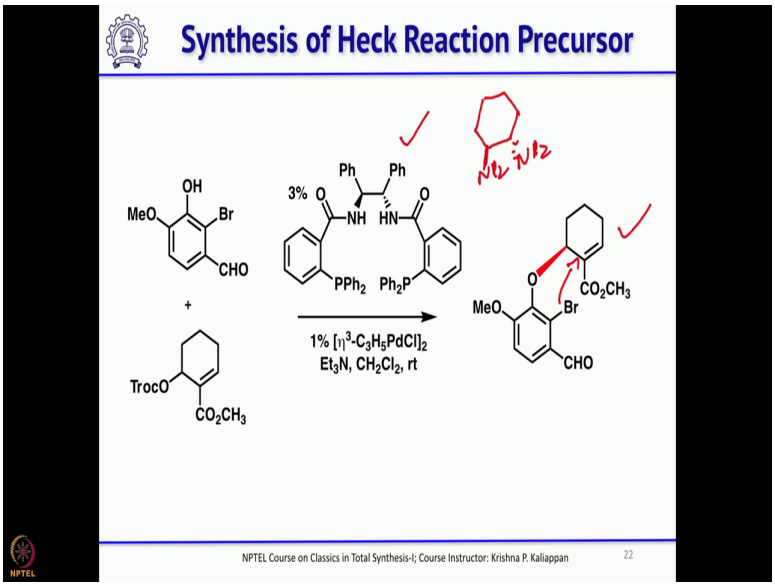

And so, once you have these two fragments the next step is the asymmetric allylic alkylation. So, for the asymmetric allylic alkylation Trost group used their well-established procedure. So, they use normally the P and ligands derived from the diamines the chiral diamines either they use this chiral di amine or they use the di amine derived from cyclo 1,2 di amino cyclohexane ok.

So, this is what they use and this reaction was well exploited by Trost group to get such allylic ethers. And once you have this ether and you can see so, you are set for the key Heck reaction ok. So, now, let us see how this was converted into the key Heck precursor.

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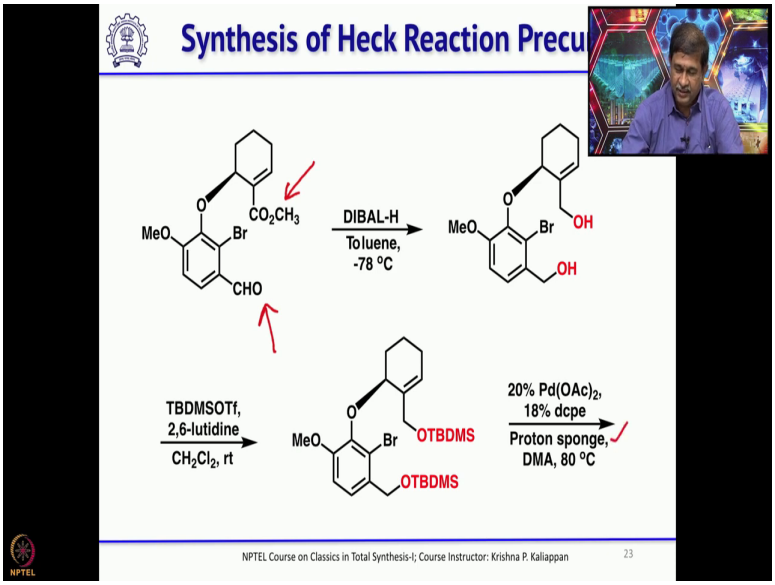

So, once you have this then you reduce the ester as well as this aldehyde in one pot to get the corresponding diol. The diol was then protected as TBS ether by treating with TBS triflate and 2, 6 lutidine then comes the next key reaction. So, that is the Heck coupling. Now, this asymmetric reaction was done with palladium acetate phosphine ligand like di cyclohexane phosphene ethane.

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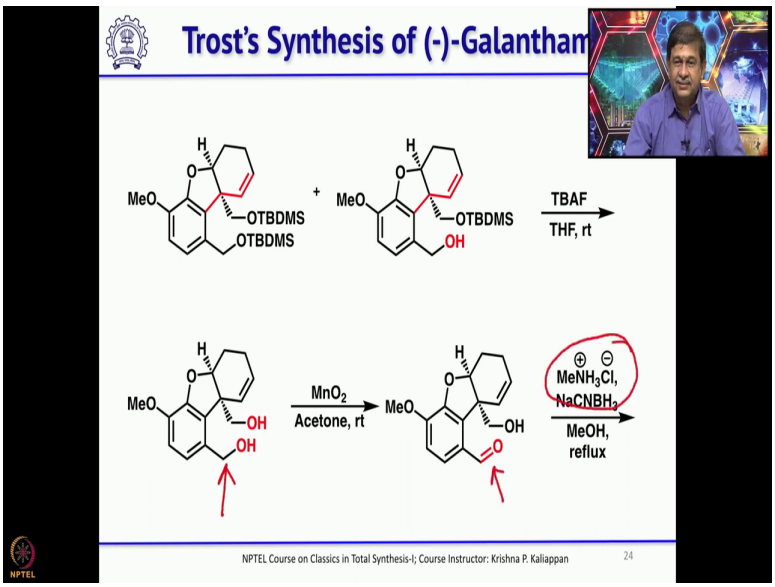

And in the presence of proton sponge, so this Heck reaction took place and here you know during the Heck reaction one of the TBDMS also got cleaved, does not matter remove both with TBAF you get the diode ok. As I said this benzylic alcohol can be selectively oxidized so, that was done with manganese dioxide to get the aldehyde. Now,

you treat with methylamine hydrochloride and sodium cyano borohydride. So, that undergoes a reductive amination with methylamine to get -CH_2 -NH-CH_3. So, you have an aldehyde and then treat with this.

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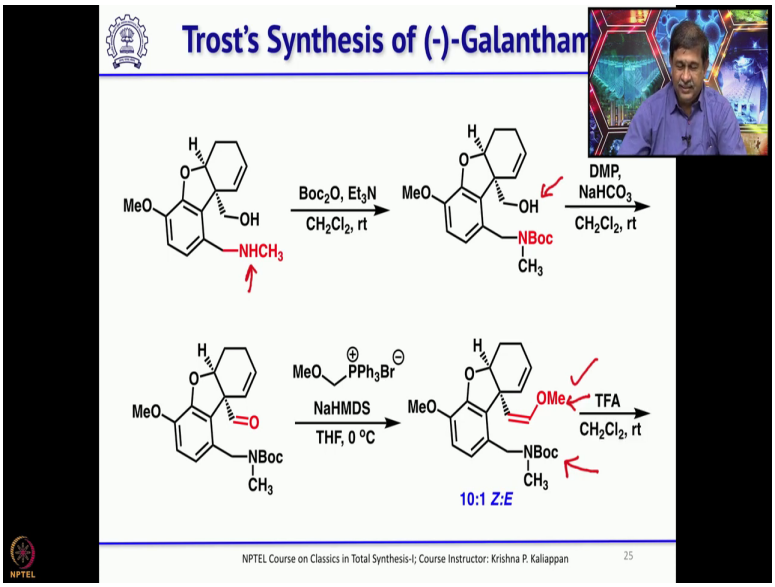

So, that will give directly the corresponding -CH_2 -NH-CH_3. Then you can protect this NH as Boc amine and Dess- Martin periodinane reagent oxidizes this primary alcohol to corresponding aldehyde. Now, you do this enol ether witting enol ether witting to generate the corresponding enol ether. The next step as I said you have to remove the Boc group as well as hydrolyse the enol ether to get aldehyde ok.

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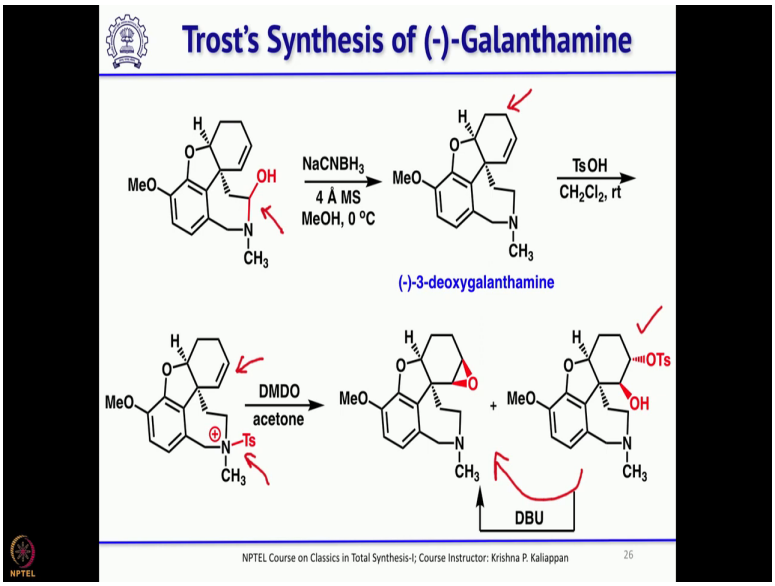

That was done using trifluoro acetic acid and that aldehyde as soon as the aldehyde is formed the -NH which is formed in *situ* will attack the aldehyde and then you will get the aminol ok. So, that aminol again you can use sodium cyano borohydride to reductively cleave that. So, that will give you 3- deoxy galanthamine ok, this is how Trost group prepared the 3- deoxy galanthamine. If you look at this structure and compare it with galanthamine.

So, what is missing is the extra oxygen here what is missing is the extra oxygen here. So, that can be easily done by epoxidation of this double bond and migration ok. So, before that the tertiary amine was protected by treating with toluene sulfonic acid ok. Then dimethyl dioxirane treatment with dimethyl dioxirane gives a mixture of the epoxide plus opening of the epoxide by the tosyl group ok, that the tosyl group is coming from here ok. Then this can be easily converted back to the epoxide if you treat with DBU ok.

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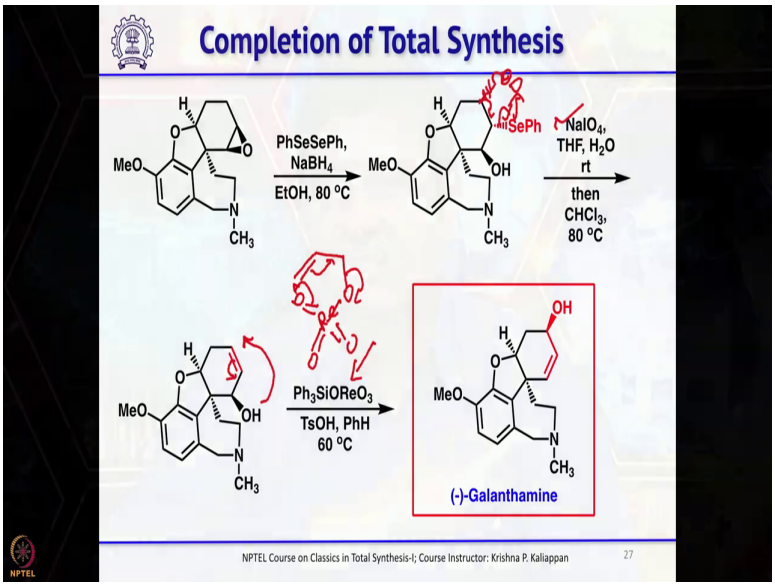

Once you have this epoxide you have to open the epoxide ok. So, that was done by treating with di phenyl diselenide in the presence of sodium borohydride. So, sodium borohydride cleaves the selenium-selenium bond ok. So, that you get PhSeSePh that opens up the epoxide to get the transisomer ok. So, normally once you introduce phenyl cylinder compound what you can do? You can easily oxidize and then eliminate. So, that was done using sodium periodate.

So, sodium periodate oxidizes this to selenoxide and the selenoxide picks up this hydrogen and removes phenyl selenic acid ok. So, if you look at this he got allylic alcohol, but that was not the one which you wanted. Basically, the alcohol should be here and then double bond should be here so, that is galanthamine, is not it. So, that transposition should take place, how the transposition takes place?

So, there is a reagent where you can use this type of rhenium trioxide substituted compound that is known to rearrange such things. How does it do? See for example, if you have like this system then it forms like this then this attacks followed by hydrolysis you will get the trans position ok. So, that is how galanthamine synthesis was successfully accomplished by Trost group.

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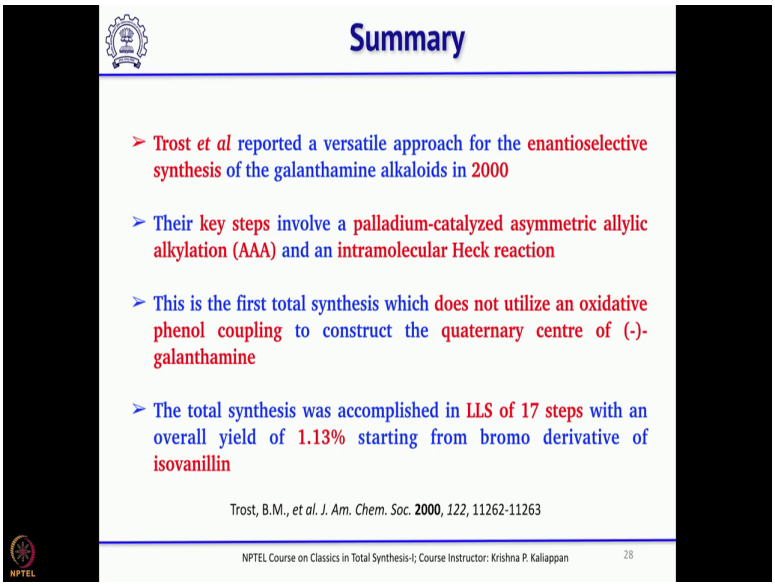

Though it took a little bit longer steps the key steps involved are their own laboratories palladium-catalyzed asymmetric allyl alkylation and also intramolecular Heck coupling ok. And as I already mentioned so, this is the first total synthesis where they have not used the oxidative phenolic coupling reaction.

So, the number of steps is reasonably high it is about 17 steps and overall yield is close to 1%. With this we will complete total synthesis of galanthamine and now we will move to few more natural products belonging to alkaloids before we move to total synthesis of steroids.