Classics in Total Synthesis - I
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Lecture - 39
Epibatidine

So, good morning everyone and welcome back to the NPTEL lecture on Classics in Total Synthesis Part I. So, let us continue our discussion on total synthesis of natural products and today we will talk about a very interesting, but small alkaloid called Epibatidine.

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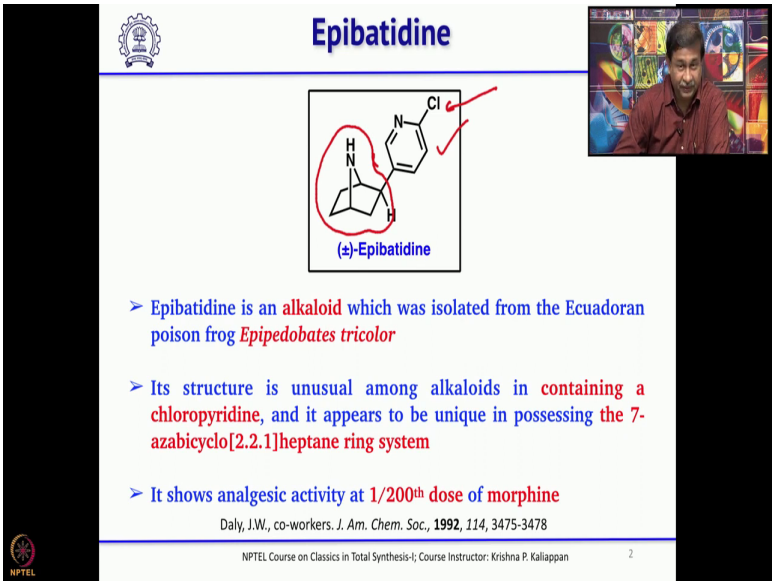

As you can see here it is a bicyclic compound having a substituted pyridine attached to the azabicyclo compound. This compound was isolated from a poisonous frog in Ecuadoran ok. And earlier we all know that strychnine was the most poisonous compound isolated in nature.

But Epibatidine is more poisonous than strychnine and also it shows analgesic activity at $1/200^{th}$ dose of morphine, as a morphine has been used as a analgesic for long time and this is much more active than morphine. And from synthetic point of view when you look at this molecule it has a 7-azabicyclo [2, 2, 1] heptane system ok. So, this is the 7-azabicyclo [2, 2, 1] heptane system with a chloro-pyridine ok with a chloro-pyridine attached at the side ok.

So obviously, when this molecule was isolated because of its biological activity people are interested in photosynthesis of this particular natural product.

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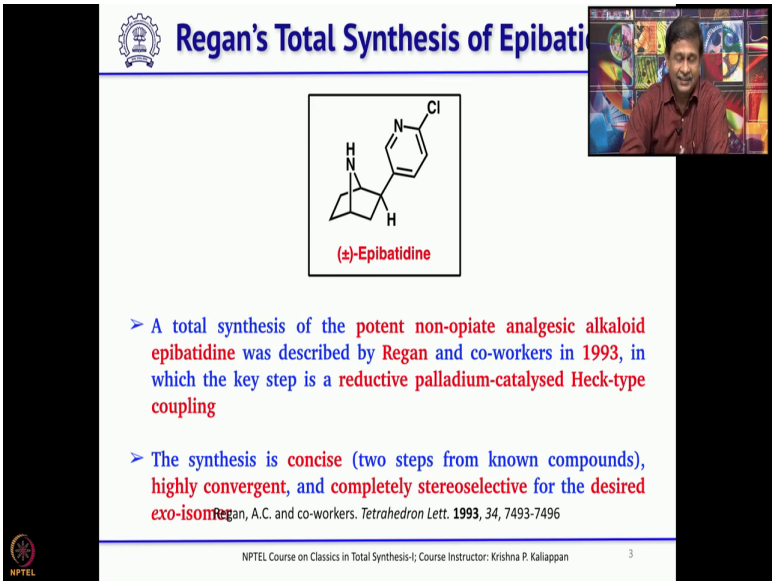

And in this lecture we will talk about 3 different strategies to synthesize this molecule. The first one which we will talk is about Regan's Total Synthesis and what he did was he used 2 key reactions one Diels Alder reaction second a reductive palladium catalyst Heck type coupling reaction to synthesize epibatidine ok. And this synthesis is highly stereo selective and they could get only the *exo* isomer in the end. Of course this is a racemic synthesis and not a chiral one.

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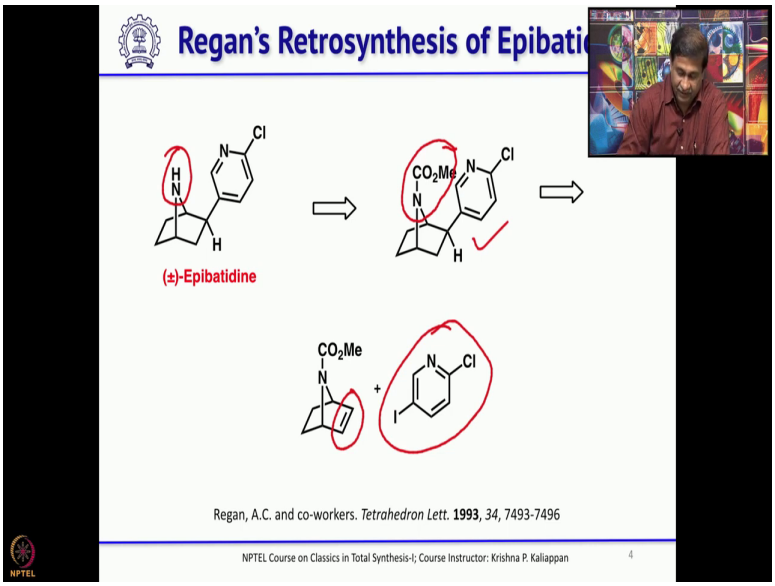

So, from the retrosynthetic point of view as you can see this -NH should be protected first, so the -NH was protected as a carbamate. So, that was the first retrosynthesis where you add a functional group in the form of a protecting group, then this can be obtained by a key reaction which I mentioned that reductive Heck coupling.

So that means, you have a double bond here and a palladium catalyzed reductive coupling on this should give your the key intermediate which can be converted into epibatidine in one step.

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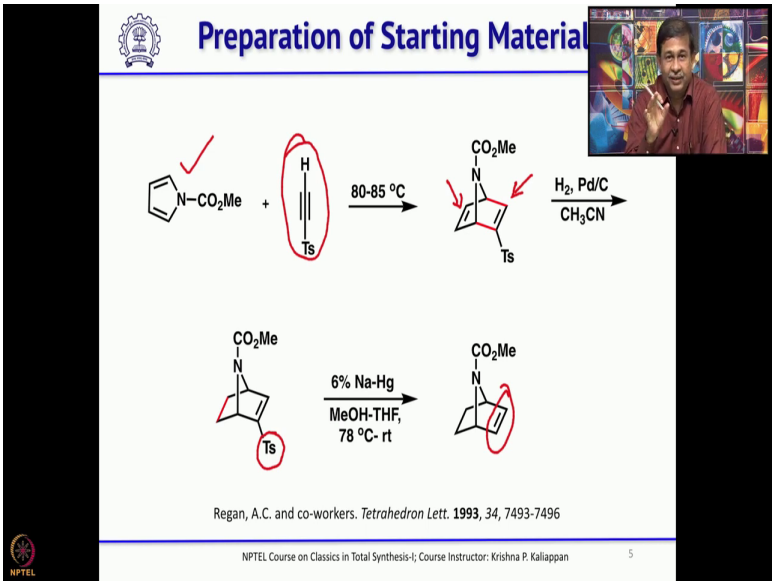

Now, the starting materials the azabicyclo [2, 2, 1] system is prepared from pyrrole. So, the pyrrole if you treat with chloro methyl format you get the diene which on treatment with tosyl acetylene, here the triple bond acts as the dienophile. You heat these 2 and it undergoes a Diels Alder reaction to form this azabicyclo [2, 2, 1] system ok. So now, it has two double bonds one is electron deficient that is on the right side and other one is electron rich.

So, selectively one can reduce the electron rich double bond under standard hydrogenation condition. Now you do not need this tosyl group. Is not it? You do not need this tosyl group. So, this tosyl group can be easily cleaved under sodium amalgam condition ok. Still you need the double bond intact because that is required for the reductive Heck coupling reaction.

So, without touching the double bond the tosyl group was reductively removed under sodium amalgam condition. So, that way the bicyclo [2, 2, 1] azabicyclo system was prepared in 3 steps from substituted pyrrole.

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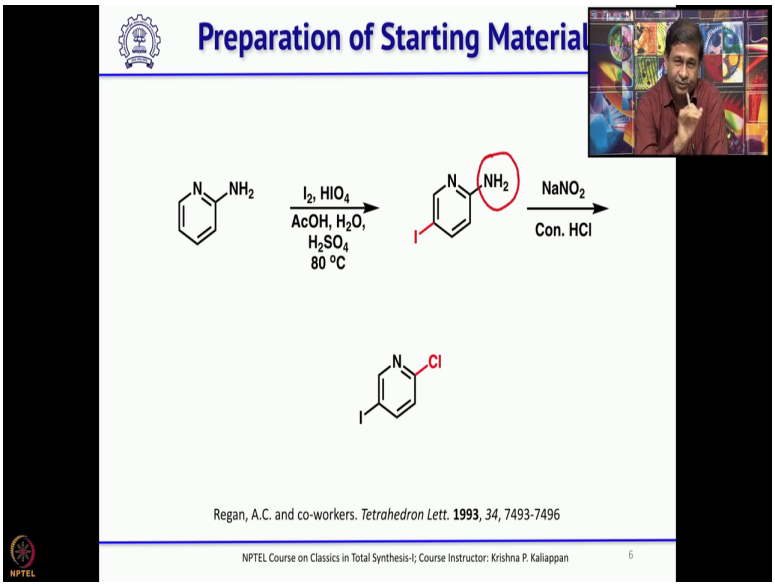

Next starting material is the pyridine that is 2 chloro 4 iodopyridine. So, for that we started with 2 amino pyridine as you know 2 amino pyridine is very easy to make if you have pyridine using Chichibabin reaction, you can easily get 2 amino pyridine in large quantity. So, this upon treatment with iodine and acetic acid you can introduce the iodine at 3 position with respect to the nitrogen in the pyridine.

Then you can do diazotization and sandmeyer reaction to convert this amino group convert the amino group at 2 position to chlorine. So now, this fragment is also ready. Already we have prepared the azabicyclo [2, 2, 1] system.

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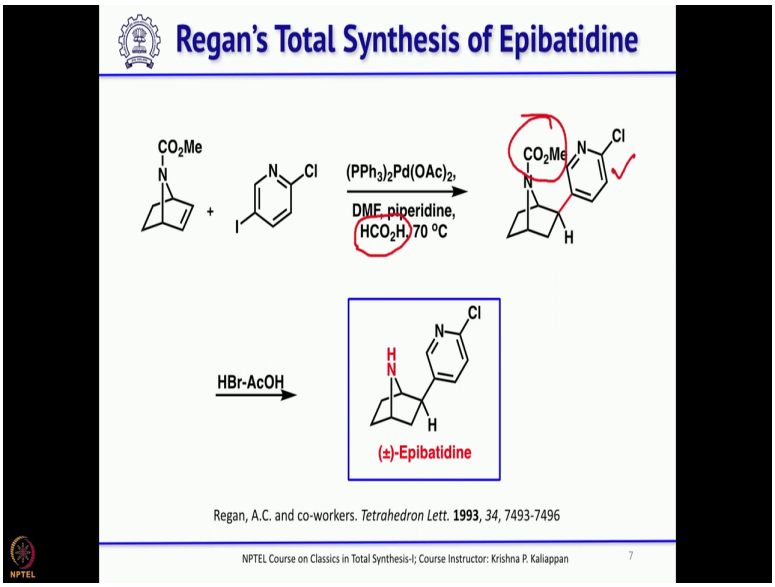

What we need to do is only the Heck coupling reaction. So, the Heck coupling that is reductive Heck coupling work very well. So, for reductive Heck coupling as you know you have to use the formic acid. So, that is a proton source and that reaction worked very well and it gave exclusively the *exo* isomer. As you know the natural product this 2 chloro pyridine is in *exo* position ok.

So, that is one key transformation which is very much required for making the *exo* isomer ok. Then what is left is just to remove the protecting group. The protecting group was easily removed by treating with HBr and acetic acid to get the natural product and this natural product epibatidine was synthesized in racemic form.

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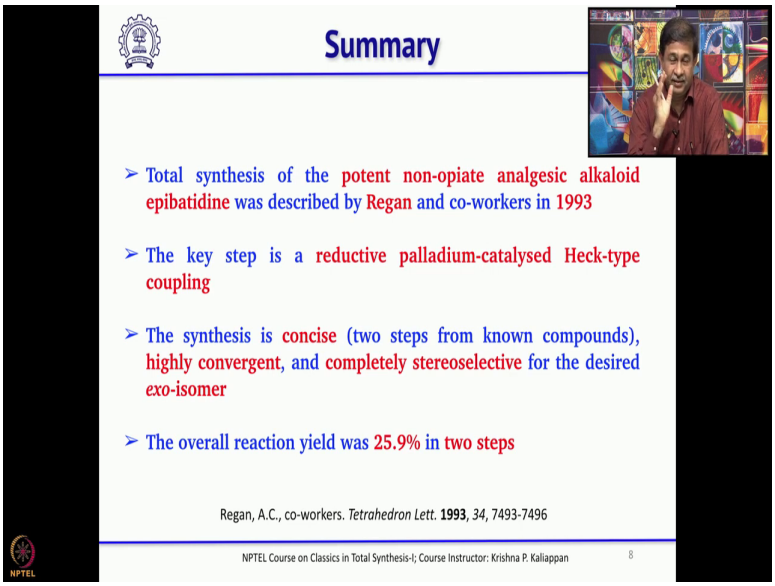

If you look at this synthesis, this synthesis was reported in 1993 and there are two key reactions one is intermolecular Diels Alder reaction and then second one is the palladium catalyst reductive Heck coupling reaction ok. And this reaction this whole synthesis is convergent because you prepare two different starting materials and then couple and highly stereo selective where you have seen the formation of only *exo* isomer during the Heck coupling.

And overall if you look at the yield it is 25.9% in two steps this is significantly very high, any total synthesis which gives 25.9 overall yield should be considered as you know excellent synthesis ok.

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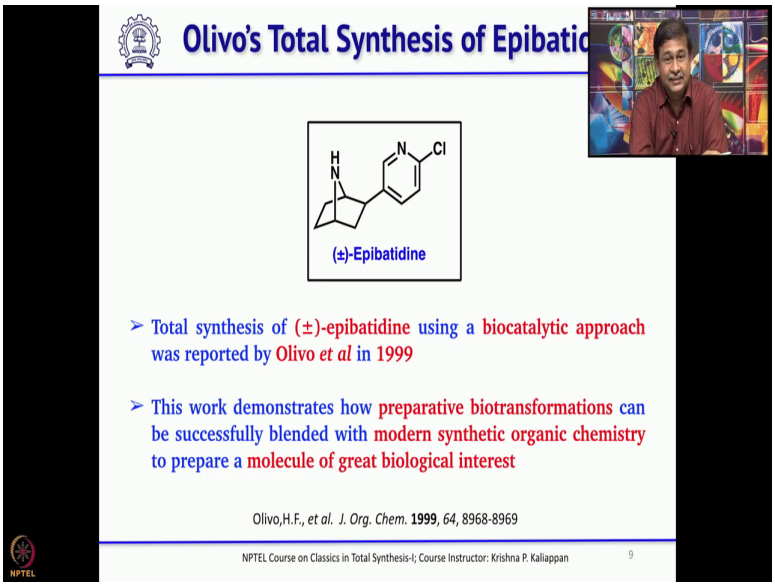

So, now we will move to the second total synthesis of epibatidine reported by Olivo. Here, what is important was a very clever use of bio catalyst to introduce a hydroxyl group ok. So, now a days there are many C-H activation method to introduce hydroxyl group, but those days a bio catalytic approach to introduce a hydroxyl group and followed by attack of 2 chloro pyridine was the key step ok.

So, that was one of the key reactions in the synthesis of epibatidine.

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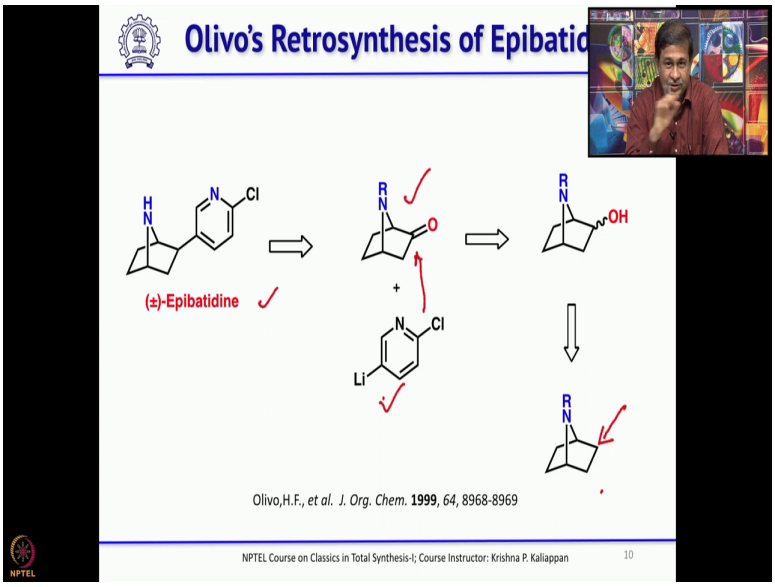

So, from retrosynthetic point of view it was divided into 2 fragments again it is a convergent strategy. So, this is the azabicyclo [2, 2, 1] heptanone system and this is the lithio species ok. So obviously, addition of this lithium to this azabicyclo [2, 2, 1] system will give the alcohol, then if you do dehydration followed by hydrogenation you will get epibatidine.

So now, this ketone was obtained from alcohol by simple oxidation and the key step as I said is the bio catalytic hydroxylation here. If you look at this system this is azabicyclo [2, 2, 1] heptane system ok. Introducing a hydroxyl group by simple chemical transformation is not that easy, whereas here Olivo cleverly used by a catalytic method to introduce the hydroxyl group.

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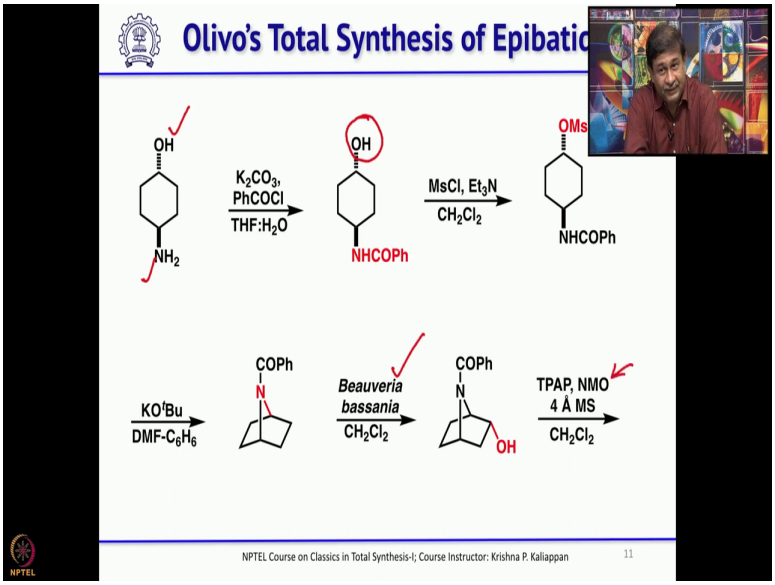

So, the starting material was you know well known hydroxy amino cyclohexane and they are one four related ok and a modified Schotten Baumann reaction. One can easily you know benzoylate the amino group ok. After benzoylation then you need to convert this hydroxyl group into your leaving group.

So, it was mesylated to get the corresponding mesylate, then intramolecular S_N2 displacement reaction was done with potassium tertiary butoxide to get the bicyclo [2, 2, 1] system ok. Here comes the key bio catalytic reaction and this was responsible for the introduction of hydroxyl group, here the hydroxyl group as you can see you got was endo alcohol ok.

Now once you introduce the hydroxyl group what you need to do is you have to add the lithio chloro pyridine. So, for that simple oxidation with the TPAP that is tetra n propyl ammonium perruthenate as a catalyst and the co oxidant is n methyl morpholine N oxide gave the ketone.

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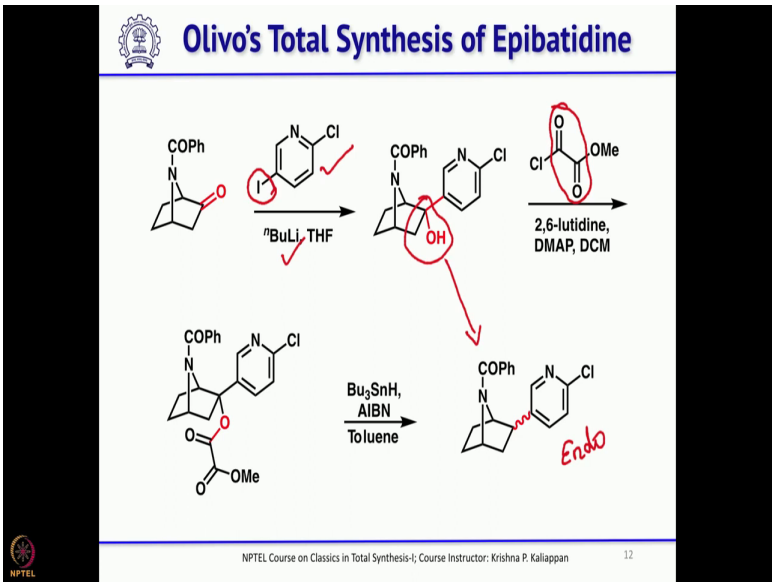

Then you take this iodo chloro pyridine and treat with butyl lithium to give the corresponding tertiary alcohol. So, once you have the tertiary alcohol there are two possibilities. One you can do the dehydration ok, you can do the dehydration and then hydrogenate or you can do the deoxygenation ok you can do the deoxygenation. So, Olivo opted for the second option that is the deoxygenation. So, this is derived from oxalic acid; oxalic acid of ester ok.

So, once he got this ester then tributyltin hydride mediated deoxygenation worked very well. So, overall from here you can see he could deoxygenate using these two step process. But unfortunately during this two step process he got maximum of endo isomer ok, but what you need is *exo* isomer is not it *exo* isomer is the natural point.

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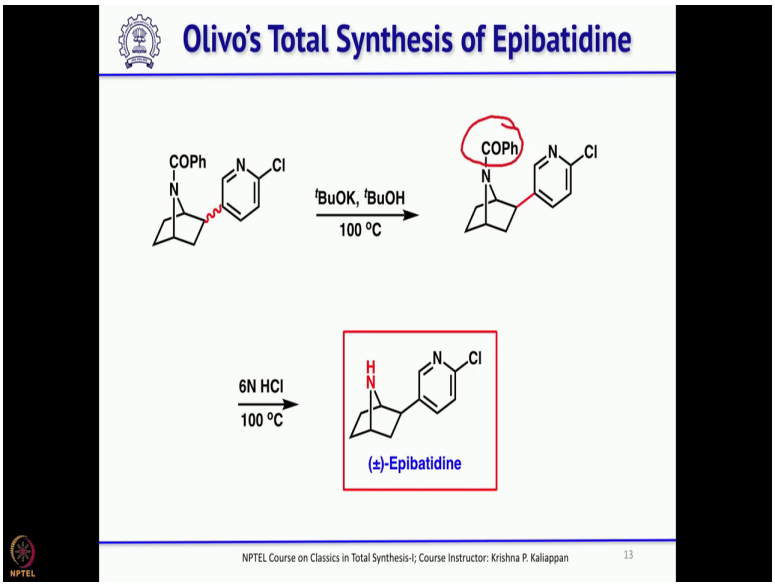

So, you took this mixture and then treated with potassium tertiary butoxide in tertiary butanol. So, he could get exclusively the *exo* isomer. Now, once you have this *exo* isomer what you need to do is to remove this benzyl group. So, that was very simple, straight forward you it is an amide. So, you have simply treat with six normal HCl and heat it at 100°. So, the benzyl group was cleaved and it gave the natural product again this natural product if the synthesis led to the recemic epibatidine.

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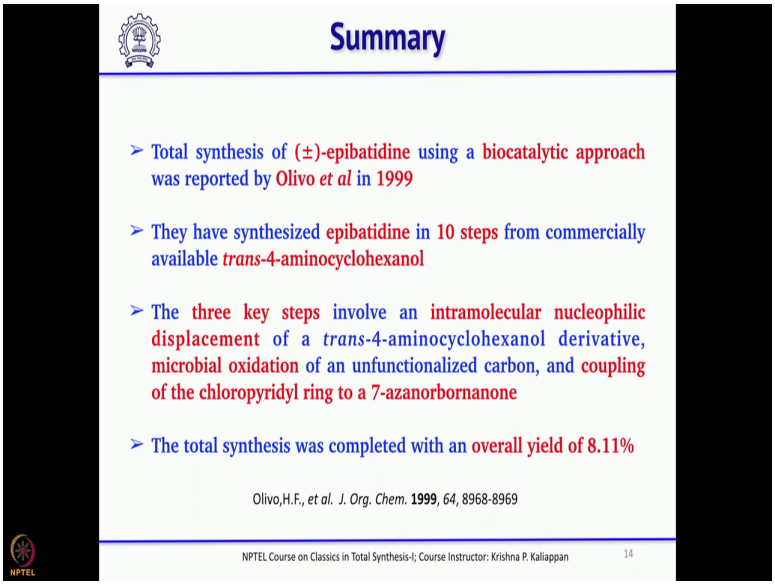

And here if you look at this synthesis, this synthesis was done in 10 steps and from commercially available trans four aminocyclohexanol and the overall yield of this total synthesis is about 8%, still 8% is quite good considering the starting materials are commercially available and they are not that expensive.

The third synthesis is about Steve Ley's. Steve Ley what he has used in this total synthesis was mostly polymer supported reagents in the whole synthetic scheme.

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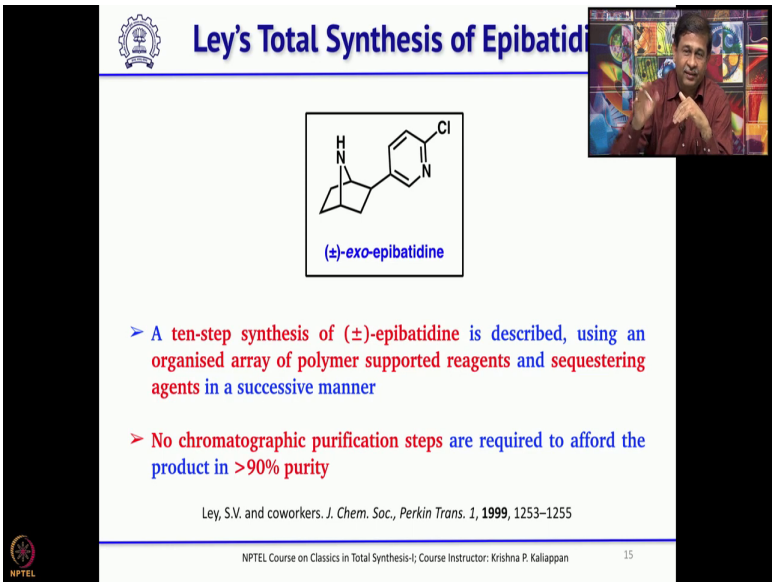

So, that is something which is unique except a few reactions most of the reactions you use polymer supported reagent, why polymer supported reagents? So, when you use polymer supported reagents the purification becomes very simple ok. So, then one polymer supported reagent to another polymer supported reagent, one can do it, now people talk about flow chemistry.

This was pre flow chemistry time where polymer supported reagents played a very important role in synthesis of natural products. And this is one classical example how polymer supported reagents were used in the synthesis epibatidine and the main advantage is you do not have to purify through chromatography ok. Just to do the reaction filter it, remove the solvent, go to the next step, just filter and then remove the solvent, go to the next step.

So, it is very easy if you use polymer supported reagent and because of this purification less synthetic route polymer supported reagents are well known.

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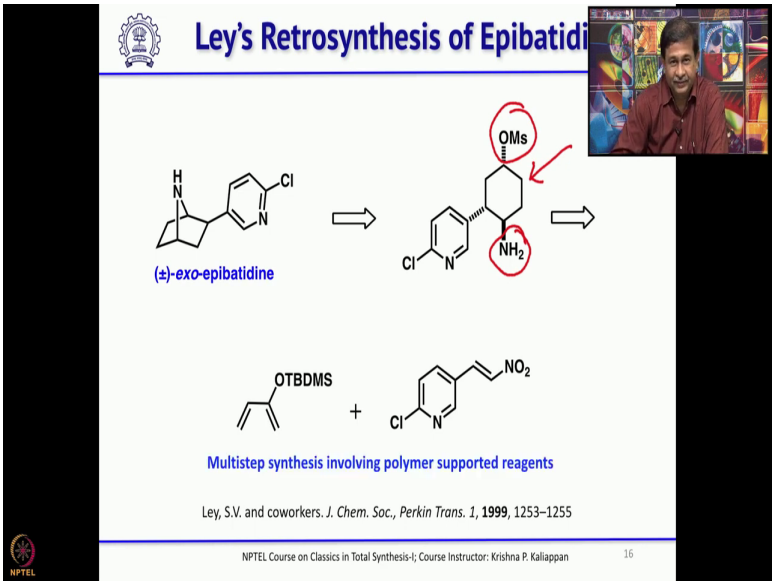

So, his total synthesis was based on again the intramolecular S_N2 reaction as the key step. So, you can see here. So, this is a nucleophile and this is the leaving group. So, intramolecular S_N2 reaction will give the bicyclo [2, 2, 1] system ok. Now the difference between this S_N2 reaction based total synthesis epibatidine and Olivo's total synthesis is here Steve Ley used a Diels Alder reaction between a diene and a dienophile that way he constructed this cyclohexane ring. Let us see how we did that ok.

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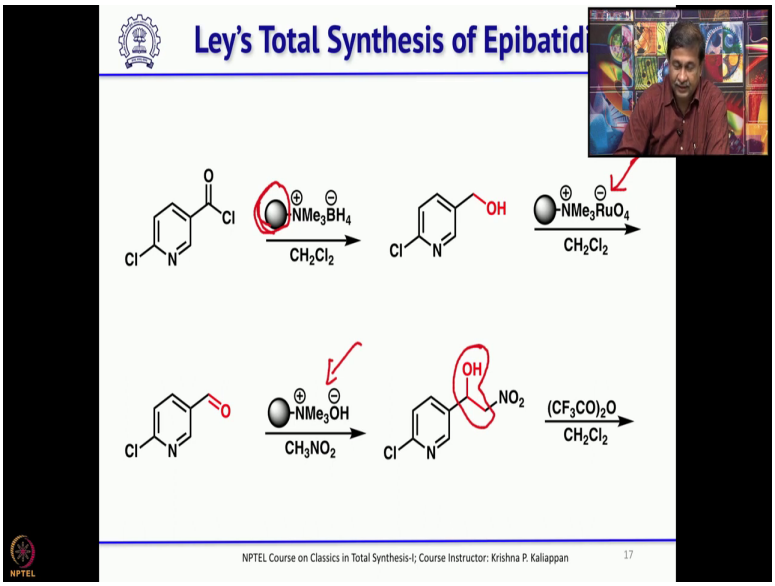

First we started with the 2 chloro-nicotinic acid chloride and as you can see here this is the polymer support. The acid chloride was reduced with this polymer supported tri methyl ammonium borohydride region ok. So, that reduced the acid chloride to primary alcohol ok.

So, once this reaction was done it is very easy to purify, then oxidize again here you use another polymer supported reagent. And if you look at this is polymer supported perruthenate reagent ok, we know what is TPAP Tetra n propyl ammonium perruthenate. So, here so another ruthenate reagent which is attached to polymer ok, so one can easily oxidize the primary alcohol to aldehyde using this reagent.

Now you carry out a Henry reaction with nitro methane. So, nitro you take nitro methane and use this base and you do the end reaction to get the nitro aldol products. Now you need a double bond; that means, you have to dehydrate this nitro aldol and for that first you treat with trifluoroacetic anhydride to make it as a tri fluoroacetate, because that is a good leaving group ok.

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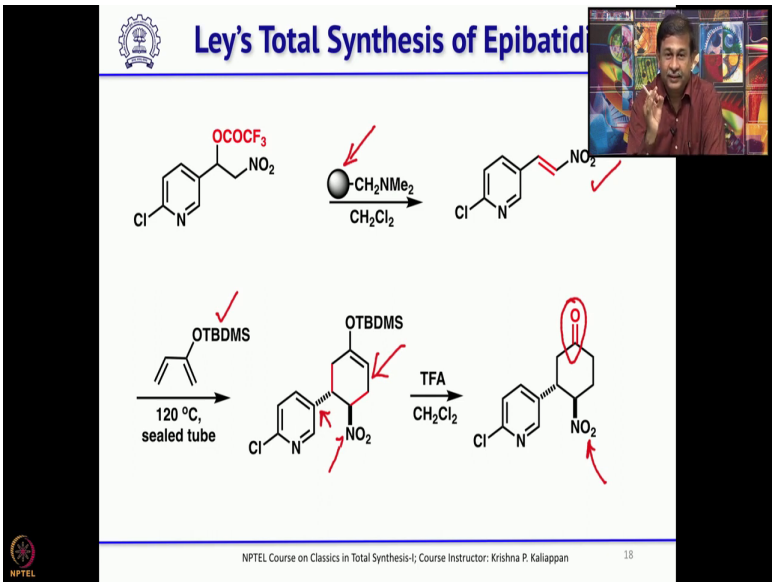

So, then you treat with base ok. Again you could have treated with normal tri methylamine, but here you use a polymer substituted tertiary amine. Polymer substituted tertiary amine which gives the required dienophile, that is α-β unsaturated system, here it is α-β unsaturated nitro compound ok.

You can call it as nitro alkene. Once you have this nitro alkene then you do a Diels Alder reaction with the diene having an electron donating group that is enol TBDMS and you do this Diels Alder reaction in a sealed tube you get this tri substituted cyclohexene ok. So, here the nitro group and this aryl are trans to each other and you have enol TBDMS that can be easily hydrolyzed to get the ketone.

To proceed further as you know this ketone should be reduced to get alcohol, then that alcohol should be made as good leaving group then followed by reduction of the nitro bond. So, these are 3 steps before you do the intramolecular S_N2 substitution to get 2 azabicyclo [2, 2, 1] heptane system ok.

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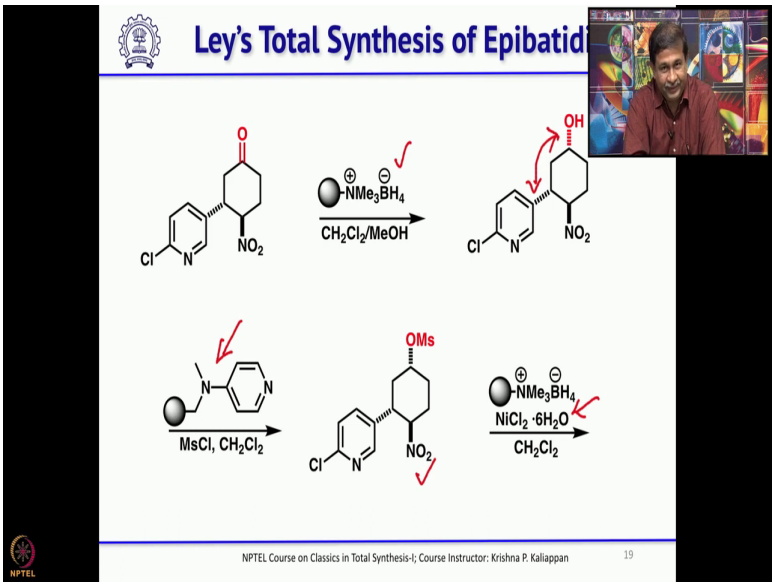

You take this ketone and again polymer substituted borohydride reagent. So, this is the same reagent which we have seen used for reduction of acid chloride to primary alcohol ok. In the first system the same reagent was used to reduce acid chloride to corresponding primary alcohol.

So, here again this reagent was used to reduce the ketone to corresponding alcohol and this is again very stereo selective and you get a maximum only this *syn* alcohol. Now the alcohol should be made as good leaving group; that means, you have to treat with either mesyl chloride or tosyl chloride or you have to convert into halide.

So, here mesyl chloride was used and instead of DMAP that is dimethyl amino pyridine you can see a polymer substituted, a polymer substituted dimethyl amino pyridine was used as a base and the hydroxyl was mesylated. Again the nitro group; nitro group was reduced with the borohydride reagent, here in addition they also used nickel chloride ok.

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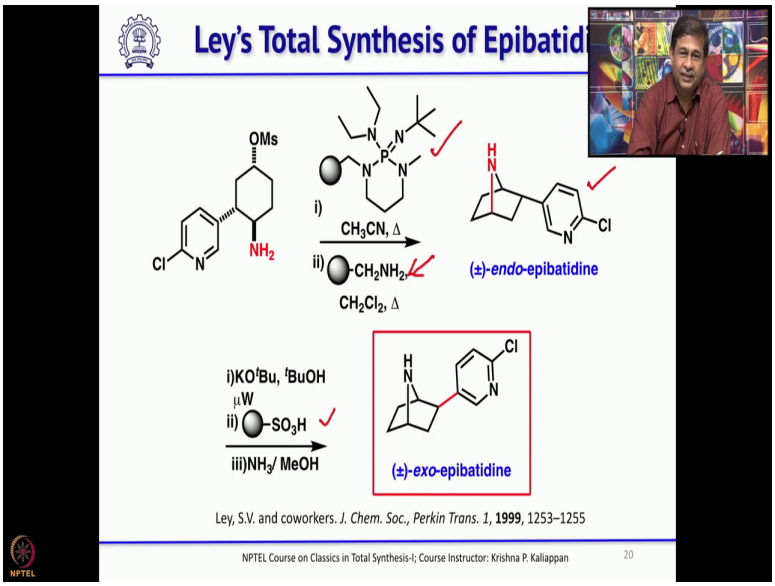

So, to selectively reduce the nitro group to get the corresponding amino compound. So, once you have this amino compound, the next step is to carry out an intramolecular SN_2 reaction this was done with this sterically crowded base and that worked very well. Then you have to use this polymer supported primary amine polymer supported primary amine to remove all acidic by products which are formed during this reaction ok.

So, that you do not need purification. Why the second polymer supported primary amine was used that take care of the acidic impurities formed in this reaction ok, so that you will get only the epibatidine. But unfortunately when they did this reaction they got *endo* epibatidine ok, but what we want was *exo* epibatidine.

So, it was easy. So, again it was treated with potassium tertiary butoxide under microwave condition. So, the epimerization took place to the *exo* and once it was formed again it should be treated with a polymer supported sulfonic acid to take care of some basic impurities and followed by treatment with ammonia methanol, it gave exclusively the natural product which is *exo* epibatidine.

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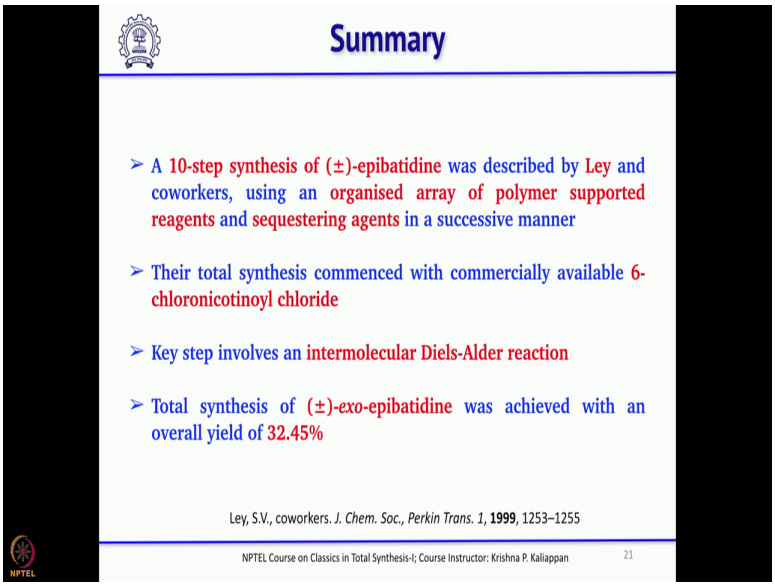

And if you look at this whole synthetic sequence it involved 10 steps and started with you know known pyridine nicotinic acid chloride and the key step in this whole synthesis was inter molecular Diels Alder reaction inter molecular Diels Alder reaction between nitro alkene and two substituted butadiene.

Overall the synthesis was achieved with a yield of 32.45% and this is really significant considering that 10 step synthesis with 32.45% yield is really commendable. And more importantly since this is the whole sequence involved many polymer supported reagent the number of chromatography purification was very very less.

So, with this I will stop here. So, about the racemic total synthesis of epibatidine and now we will move to two asymmetric total synthesis of epibatidine in the next few minutes.

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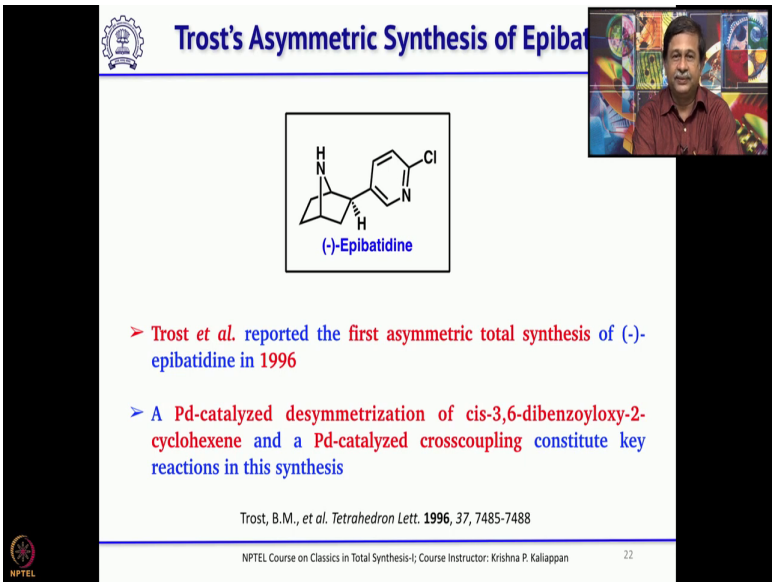

The first asymmetric total synthesis of epibatidine was reported by Barium Trost group in 1996. So, what he has used was he has used a palladium catalyst cross coupling as well as a desymmetrization as the key reactions to synthesize epibatidine.

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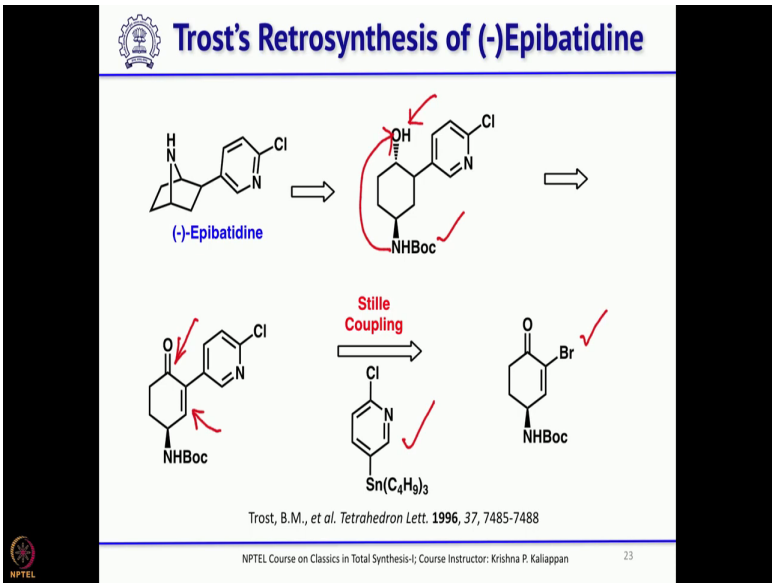

Let us see how he has done the retrosynthesis and how he finally accomplished the total synthesis of epibatidine. So, first retrosynthesis was it is a very simple one that is you know you do the intramolecular S_N2 reaction. So, you make this hydroxyl as a good

leaving group followed by intramolecular S_N2 reaction and remove the Boc group will give the corresponding epibatidine in optically pure form.

And this can be obtained from this enone by reducing the double bond first and followed by reducing the ketone to corresponding alcohol. And this is where the first key step comes where he has used stille coupling between this α bromo substituted cyclohexanone with the corresponding stanane from the pyridine unit and this α bromo substituted cyclohexanone was made from this azide.

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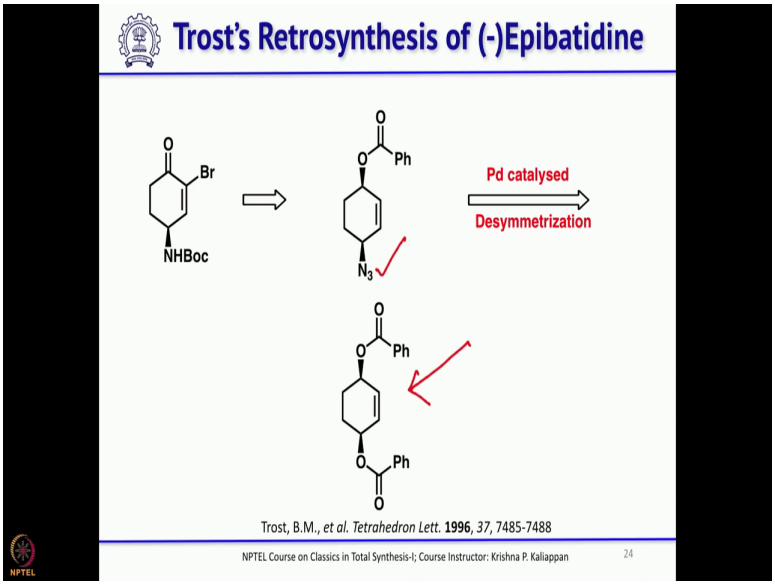

As you know azide can be easily reduced and then protected as NH-Boc and the next key reaction was the desymmetrization of this particular compound using a chiral palladium catalyst ok. So, this truss group has been using in the synthesis of many other natural products. So, they just extended that methodology to synthesize epibatidine in optically pure form.

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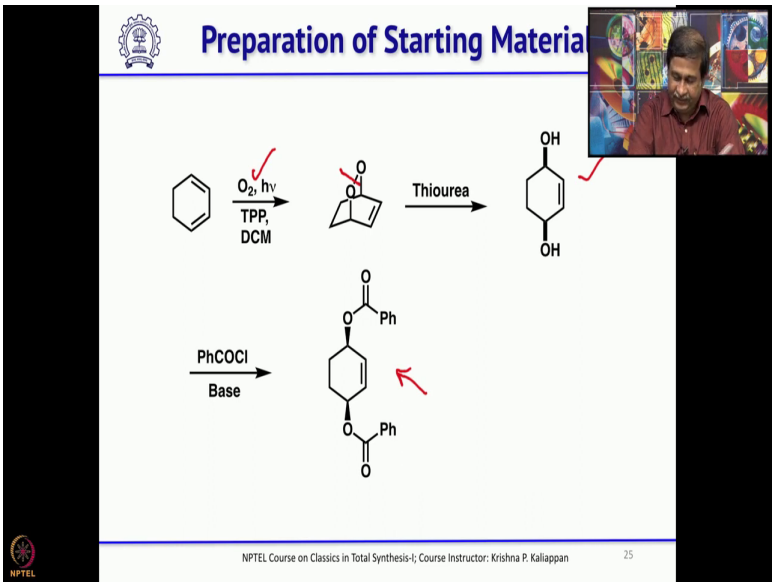

The starting material for this reaction that is this di benzoate was prepared from cyclohexadiene using a photochemical [4+2] cycloaddition reaction with oxygen followed by treatment with Thiourea cleaves the O-O bond to get this cis diol with a double bond and both hydroxyl groups were benzylated using benzyl chloride.

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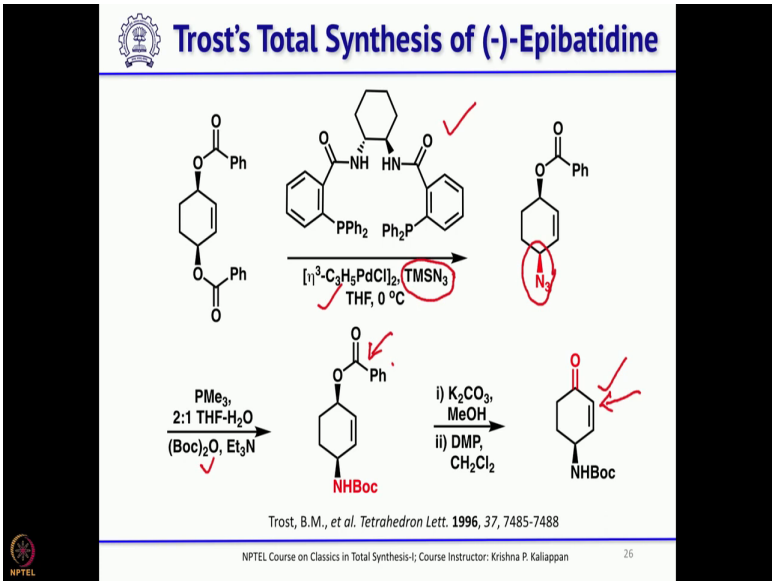

And base then he did this desymmetrization with this palladium catalysts and this ligand followed by attacking with nucleophile TMS azide to introduce the azide as well as the chirality ok. So, once we have the azide as you know azide can be easily hydrolyzed

using starting a reaction condition and followed by protection as Boc derivative by treating with Boc anhydride.

Then he has to hydrolyze the benzoate and followed by oxidation gave this 4 substituted cyclohexenone and what is required is to introduce a bromine at α position which is required for the stille coupling.

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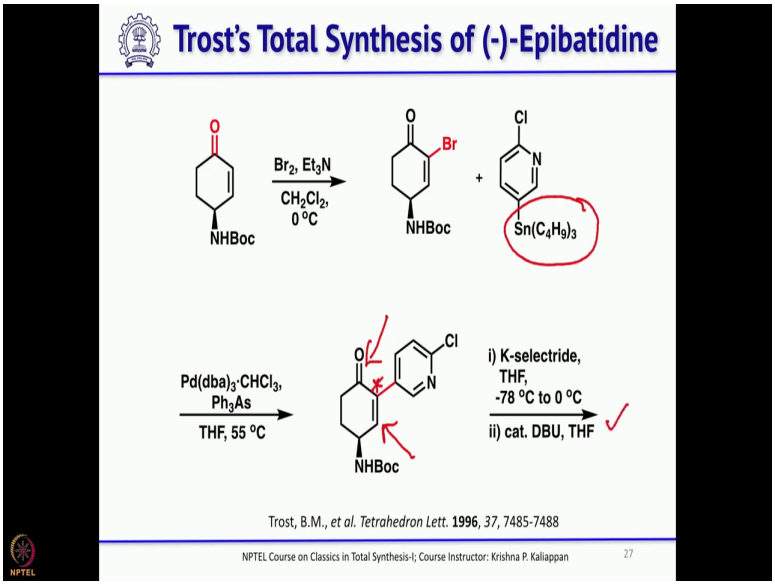

So, that was done using bromine and triethylamine and this was followed by Stille coupling with this stanane derivative gave the key precursor ok. So, what is left is to stereo selectively reduce this double bond as well as reduce the ketone. So, these 2 are very critical. The double bond which is in conjugation with the ketone. So, it can be easily reduced with k-Selectride and then he got a mixture at this carbon, so treatment with catalytic amount of DBU so epimerized to get only 1 isomer.

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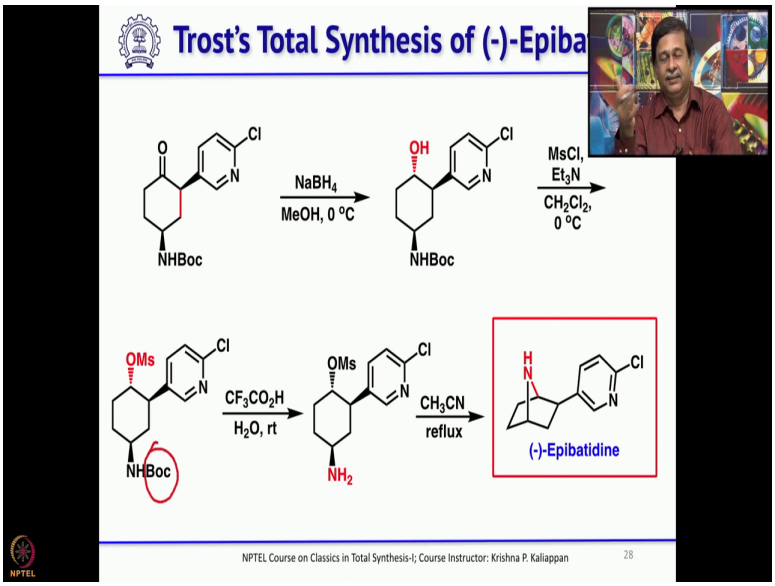

Now reduction of this ketone with sodium borohydride gave this alcohol ok. So, once you have this alcohol you convert this alcohol into a good leaving group by treating with mesyl chloride. This methylates upon treatment with trifluoroacetic acid. First the Boc was removed to get the amino alcohol. Once you have this amino alcohol then reflux with acetonitrile it undergoes spontaneous intramolecular S_N2 reaction providing minus epibatidine directly.

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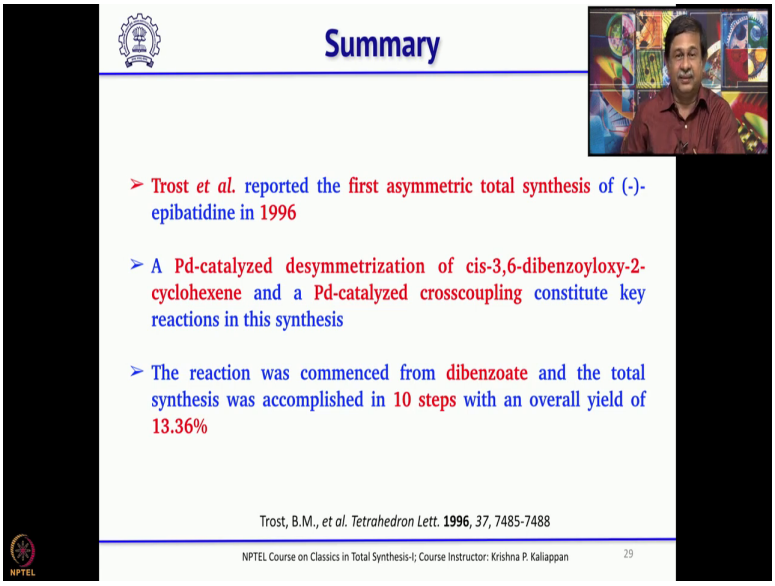

So, Trost could accomplish this first asymmetric total synthesis using 2 key reactions. One is palladium catalyst cross coupling reaction that is Stille coupling second is the palladium catalyst de symmetrisation. Overall it took about ten steps and the overall yield was about 13%. The second asymmetric total synthesis which we will discuss was reported by Kibayashis group in 1998.

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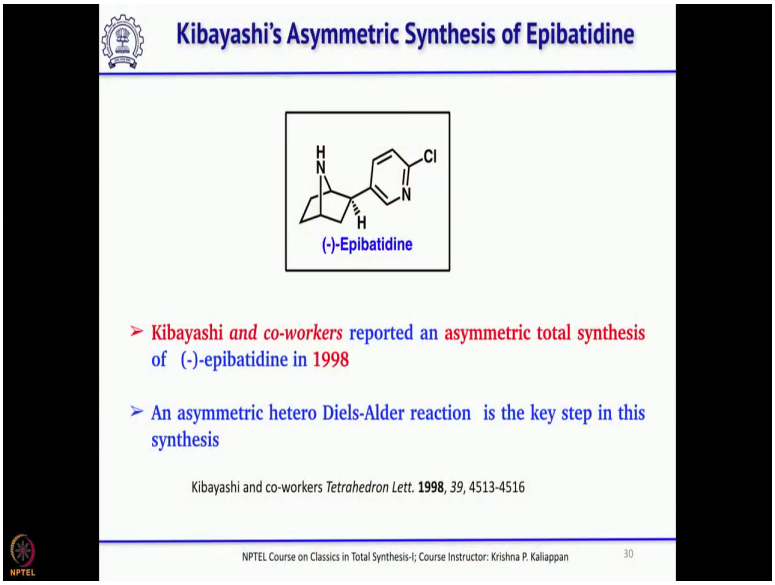

So, what he has used was an asymmetric hetero Diels Alder reaction as the key reaction to construct a bicyclo [2, 2, 2] system and from there you could go on to make minus epibatidine.

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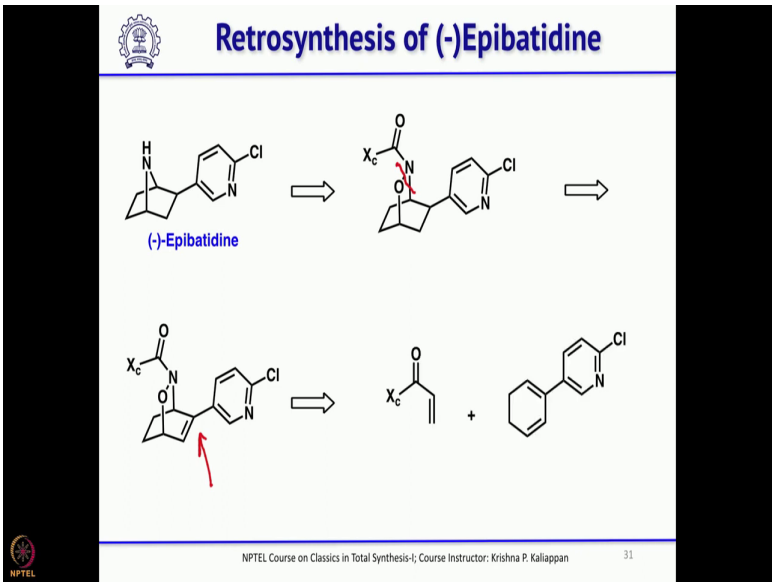

So, his retrosynthesis was if you have this bicyclo [2, 2, 2] system, then one can selectively cleave this -NO bond ok. Once you cleave this -NO bond then followed by converting that OH into a good leaving group then an intra molecular S_N2 reaction should give the epibatidine.

And this can be obtained by reduction of this double bond ok and obviously once you look at this compound it is a cyclohexene and that can be obtained from this dienophile as well as this diene ok. So, that is the idea.

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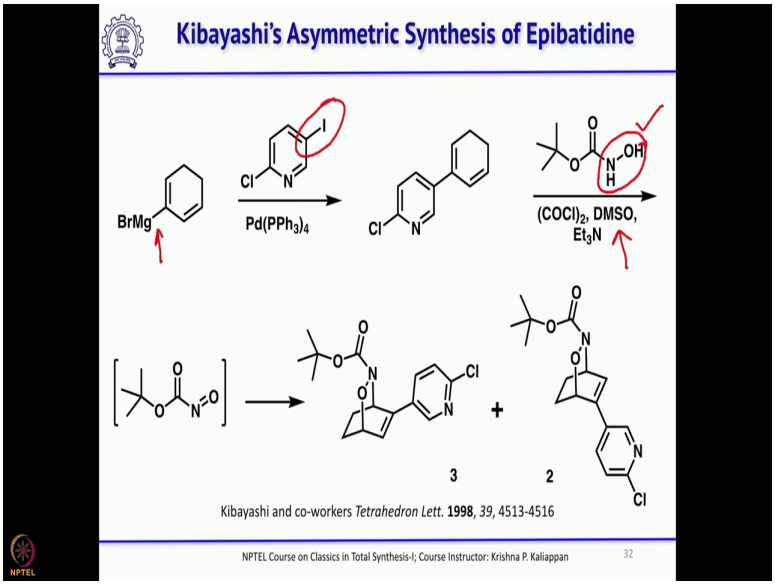

And let us see how he has done this total synthesis. So, he started with this diene and having a Grignard at this carbon. This Grignard was then coupled with this iodide ok. It is like Kumada coupling to get the substituted diene which is required for the intermolecular Diels Alder reaction. Then the dienophile the hetero dienophile was in situ generated from this hydroxylamine ok substituted hydroxylamine ok.

This upon oxidation with oxalate chloride DMSO that is nothing but swarn condition, you oxidize this NH-OH to N=O ok. So, once you have this N=O that can undergo intermolecular Diels Alder reaction to give these 2 regio isomers in 3:2 ratio ok. So, this is racemic one. So, once you are successful in getting this bicyclic adducts then he wanted to use a chiral auxiliary to see the asymmetric induction.

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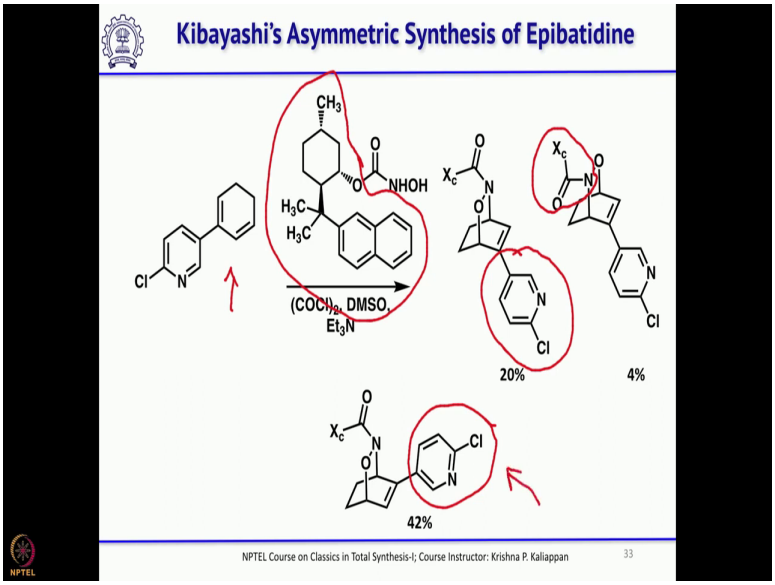

So, the chiral auxiliary which he used was derived from pullingo. So, 9,2 naphthyl menthol was used as a chiral auxiliary you can see that. So, this is the chiral axillary; 9,2 naphthyl menthol ok is the chiral auxiliary this upon treatment with phosgene followed by treatment with hydroxylamine you get this product.

And this upon treatment under swan conditions will generate N double bond O which in situ will undergo Diels Alder reaction with this dien to give 3 compounds ok. One, you can see the regio chemistry of this chloro pyridine is on the unwanted side, then the required one where your chloro pyridine is on the right side, but he got about 42% yield of the required one.

He also got 5% yield of the other side chiral auxiliary you can see where the chiral auxiliary is ok. So, these are the three compounds he got and the major one is the required one, so you took the major isomer proceeded further.

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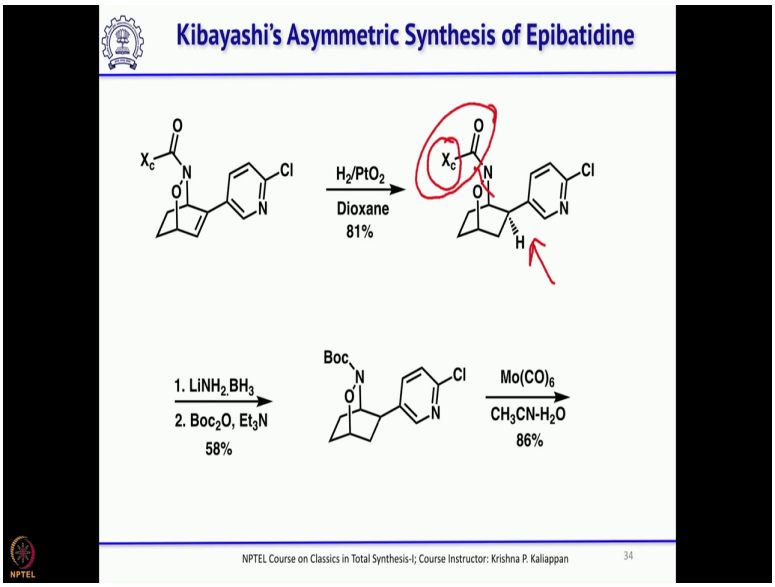

First he reduced the double bond under hydrogenation condition. So, he that is how he could establish the stereochemistry at this carbon next is to cleave the -NO bond. So, there are many methods to cleave the -NO bond, so he used molybdenum hexacarbonyl to cleave the -NO bond. But prior to that he has to cleave or remove the chiral auxiliary ok.

So, the chiral auxiliary was removed using lithium amine borane and when you remove the chiral auxiliary this carbonyl group also comes out and that free -NH was protected as N-Boc ok. So now the NO bond was cleaved using molybdenum hexacarbonyl to get the corresponding amino alcohol where the amine was protected as Boc derivative.

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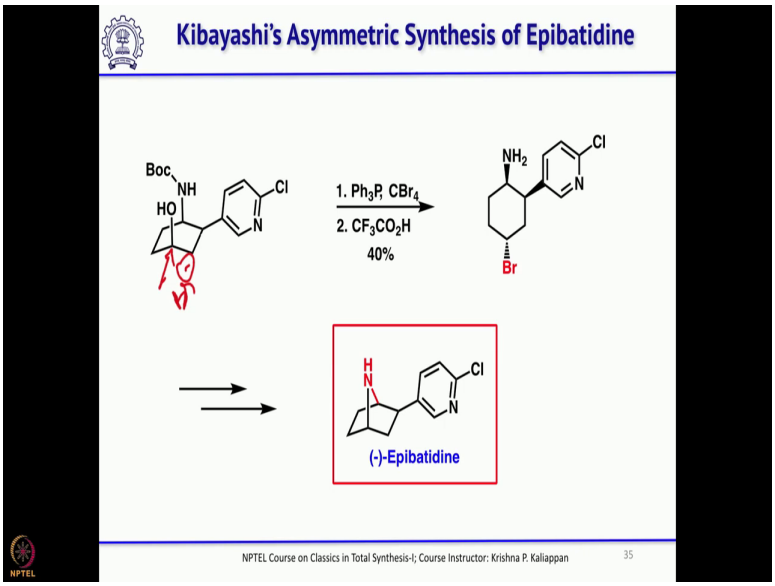

Now, for the intramolecular S_N2 reaction to take place first of all this stereocenter should get inverted ok, the chlorine should be α or bromine whatever the leaving group should be α then only intramolecular S_N2 reaction will take place. So, what he did he converted that alcohol into bromide by treating with tri phenyl phosphine and CBr_4, so, which underwent an S_N2 reaction to form bromide at this position ok.

Then trifluoroacetic acid removed the Boc to get the amino alcohol. As you know once you have this amine and then bromide you can reflex with acetonitrile or chloroform and which automatically undergoes intramolecular S_N2 reaction to give epibatidine.

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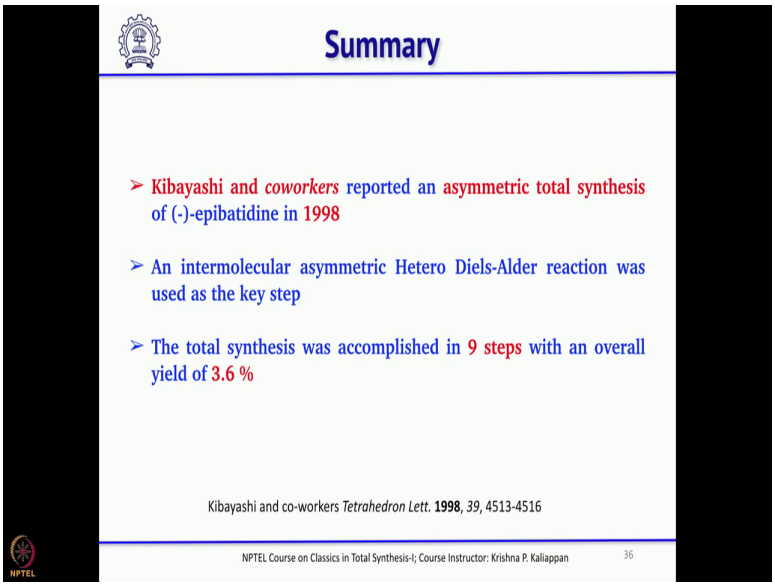

So, to summarize Kibayashi has reported an asymmetric total synthesis involving an intermolecular asymmetric hetero Diels Alder reaction as the key step. Then the number of steps involved in this total synthesis was 9 and the yield of this whole scheme was about 3.6% ok.

So, with this we completed the total synthesis of epibatidine and now we will move to total synthesis of two more alkaloids before we look into total synthesis of steroids ok.

Thank you.