Classics in Total Synthesis-I
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Lecture - 30
Reserpine (Woodward)

So, good morning and welcome back to NPTEL course on Classics in Total Synthesis part I and we have been talking about total synthesis of various alkaloids and we will continue our discussion on total synthesis of one more alkaloid well known alkaloid called Reserpine.

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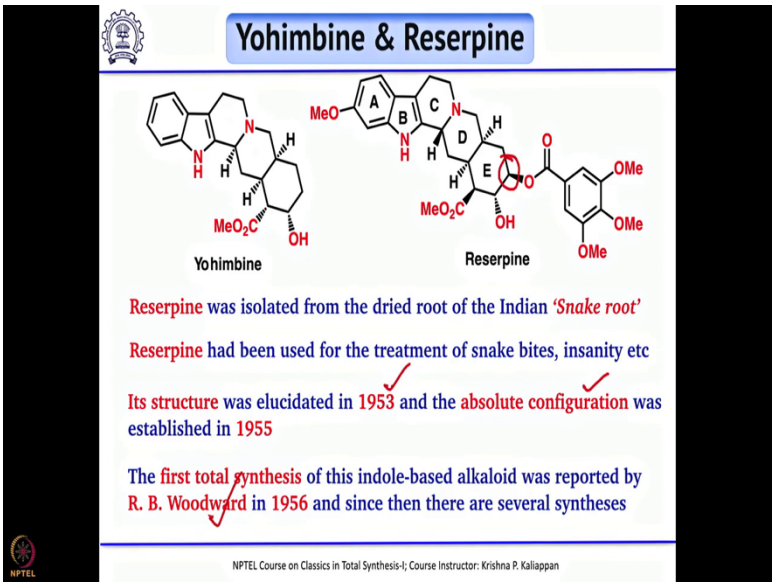

So, the reserpine and yohimbine another alkaloid if you look at these 2 alkaloids you can find some commonalities between these two they are pentacyclic compound and only reserpine has more substituents. Basically it has one more substituent here you can see that is the substituted benzoic acid attached to the hydroxyl group. And this was isolated from the dried root of Indian snake root actually earlier this reserpine was used for the treatment of snake bites insanity etc. and you can look at this molecule how complex this molecule is.

So, the structural illustration took quite some time after it was isolated took almost 2 decades to arrive at the correct structure of reserpine. And finally it was the correct structure was proposed in 1953 and it took 2 more years to propose the correct absolute

configuration. A year later the first total synthesis of this complex alkaloid was reported by none other than the father of modern organic synthesis R.B. Woodward ok.

And of course, there are many synthesis of reserpine afterwards, but in this lecture we will talk about how Woodward thought about and successfully completed the total synthesis of reserpine ok.

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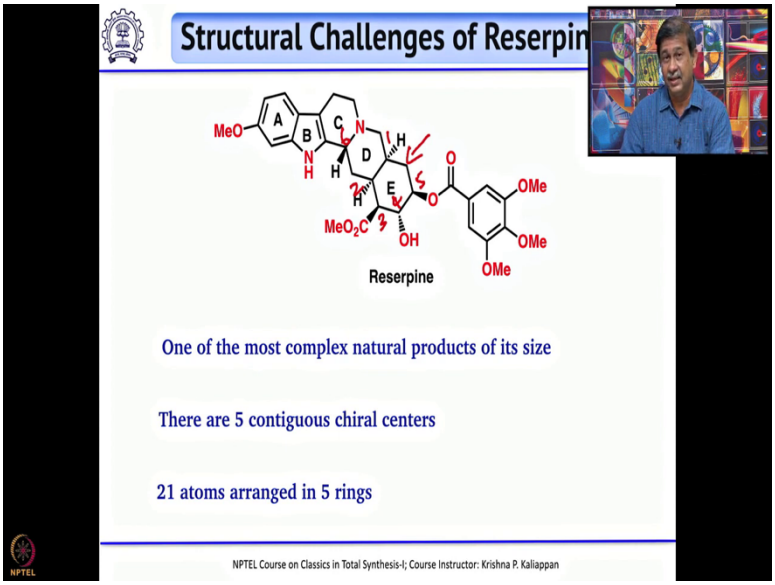

So, when you look at the molecule; obviously, it is quite complex and what are the challenges one can see when you look at this reserpine? And that time I am talking about 70 years ago when this molecule was isolated and then structure was proposed it was the most complex natural product isolated. And then obviously when you have more challenging structure available many synthetic chemists were interested in developing new strategies for the synthesis of reserpine and of course Woodward was the first one to complete the synthesis.

If you have a closer look at this natural product you can see there are 5 contiguous chiral centers 1 2 3 4 5 there is one more here there are 6 chiral centers and in that 5 are in one ring this E ring has 5 chiral centers that makes this molecule quite complex. And more closer look at this natural product will suggest that there are 21 atoms ok 21 atoms put up in 5 rings ok.

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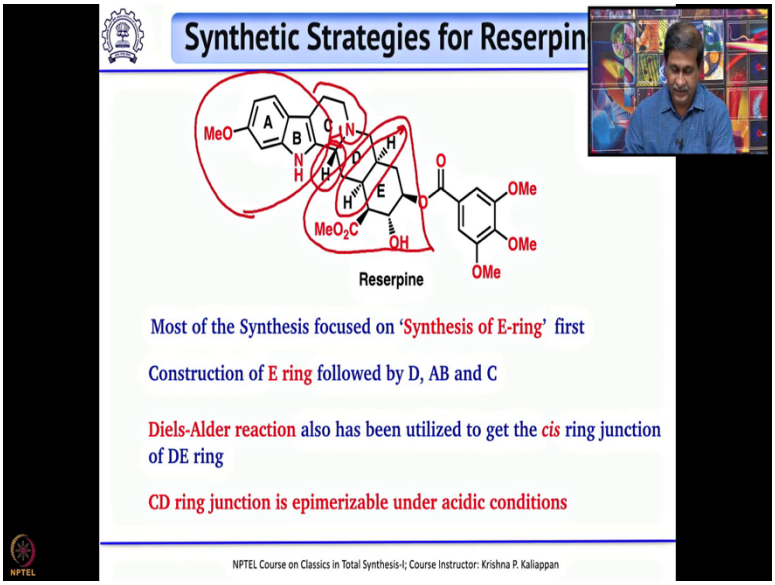

So, these are the real challenges when you talk about total synthesis of reserpine, from synthetic point of view what Woodward thought was see this is indole ring is not it this is indole ring substituted indole and if you take this nitrogen also it is like tryptamine ok. So, he thought if we have to succeed in total synthesis of reserpine first thing is he has to focus on E ring ok, E ring has 5 chiral centers ok.

So, that was the idea of Woodward as well as many people who followed after Woodward's total synthesis. So, they wanted to make the E ring first then add D and then you add AB and C. So, this is how most of the synthesis of reserpine were reported and when you look at E and D ring ok D and E ring when you see the ring junction is cis, the ring junction is cis and the E ring is 6 membered, E ring is 6 membered, D ring is 6 membered.

So, when you have a 6-membered ring which is attached to another 6-membered ring and the ring junction is cis. So, one reaction one can think of is Diels Alder reaction, as you know Diels Alder reaction will normally give cyclohexenes and one can also properly plan and then think about having a cis ring junction ok. So, that is what many people did and if you look at CD ring junction; CD ring junction can be epimerized can be epimerized at under acidic condition.

Here if you look at CD ring junction the hydrogen is beta ok. So, how these are all fixed in the total synthesis of reserpine let us have a look at it.

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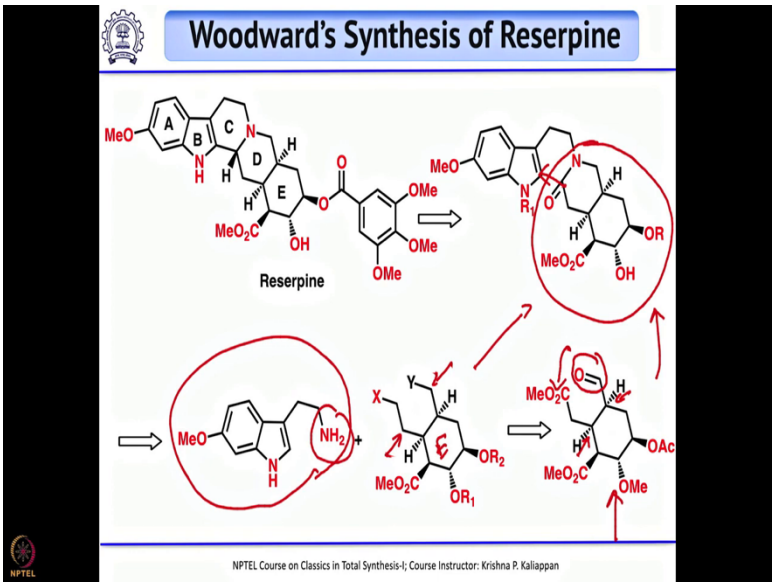

So, let us start with Woodward's total synthesis. So though that time the retro synthesis was not known. So, in his thought process what Woodward thought was he wanted to use Bischler Napieralski synthesis ok. So, if you have this DE ring then you can easily connect with the indole using Bischler Napieralski synthesis ok and once we have this. So, this is the commercially available compound.

So, 7-methoxy tryptophan and if you have E ring with 2 substituents then it should be possible to make this ok, that was the idea. And this can be obtained from this aldehyde. So, when you have this aldehyde and this amine it can form an imine ok that imine if you reduce it with sodium borohydride it will form secondary amine, that secondary amine will attack this ester directly to give this compound.

So, he simplified the target molecule that is reserpine to this highly substituted E ring of reserpine. Now if you look at this it is a penta substituted E ring with cis ring junction ok penta substituted E ring with cis ring junction ok.

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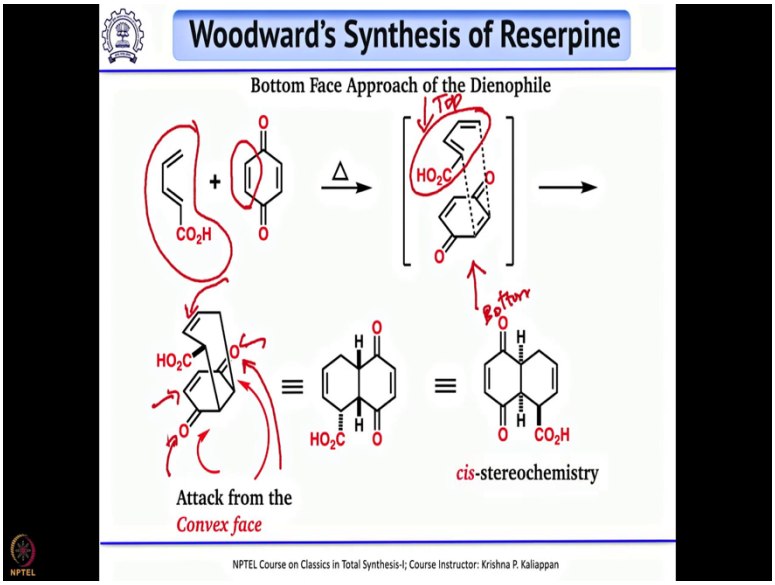

So, now as I said he wanted to use Diels Alder reaction as the key reaction. See when we talk about Diels Alder reaction ok. Now you have to keep either diene or dienophile static ok. So, then what you do if you are keeping diene static then the dienophile can approach the diene either from the top face or from the bottom face. So, he started with the Diels Alder reaction between this diene having a carboxylic acid and benzoquinone where this double bond will act as dienophile.

So, from the stereochemical outcome what you do you keep the diene static ok diene you keep the diene static. Now the dienophile approaches the diene from the bottom face there are 2 faces is not, it can approach either from the top face or bottom face ok of the diene this is the top face this is the bottom face. So, first let us see when the dienophile that is quinone approaches the diene from the bottom face.

So, this is the transition state that will give you this product ok, I will leave it for few seconds just see whether this is the correct structure ok. This is what you get if the dienophile approaches the diene from the bottom face of the diene ok and this can be written ok this can be written like this. Now, another interesting thing is if you want to carry out any reaction on this double bond or this carbonyl or this carbonyl or this double bond, the reagents will attack only from the convex face ok this is the convex face ok.

This is the convex face from this place only the reagents will attack because that is the least hindered ok. So now, what I have done if you look at I have drawn this in the 2 dimensional form ok, is it clear. Now, what I have done is what I have done is I have

rotated this compound I have rotated this compound and written like this ok. Are they same? Are they same? Yes ok they are same. So, this is one way to look at the Diels Alder reaction where the dienophile approaches the diene from the bottom face.

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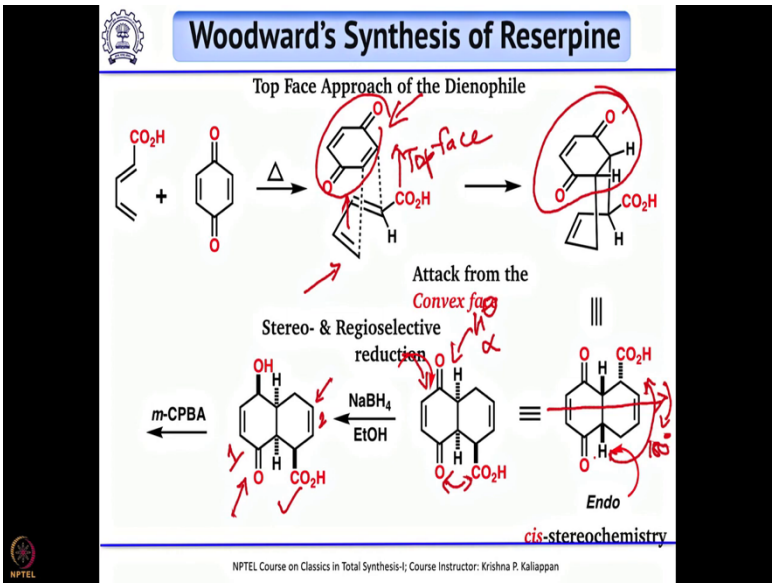

Now, what we will do same thing we will do where the dienophile approaches from the top face. So, now you see your diene is static, but the dienophile approaches from the top face ok, this is the top face ok. That will give you this product that will give you this product ok. Again can it be drawn like this can it be drawn like this look at this. So, you have this cyclohexenedione ok that is here, then the other ring with carboxylic acid is here ok. Of course, as you know the Diels Alder reaction the major product is the endo product also that is why you see the whole dienophile is just above the diene.

Now, can you rotate this can you rotate this, how do you rotate? You go through this plane; go through this plane and rotate it by 180 degree ok, if you go through this plane and rotate it by 180 degree you will get this. So, this is the first step of the total synthesis of reserpine reported by Woodward. Now he treated with sodium borohydride ethanol. So, there are 2 carbonyl groups ok and this carbonyl group will have; this carbonyl group will have hydrogen bonding with carboxylic acid.

So obviously, one can selectively reduce this carbonyl group and I already told you here only the convex face is more open, so the reagent will come from the convex face. That means, the hydride will be delivered from alpha. When the hydride is delivered from

alpha the alcohol will be beta ok. So, what you get is the beta alcohol ok what you get is the beta alcohol.

Now, if you take this compound and then treat with m-CPBA; if you take this compound and treat with m-CPBA, what will you get? There are 2 double bonds double bond 1 double bond 2 which double bond it will epoxidize question number 1. Question number 2 whether the epoxide will be alpha or beta ok, to answer our questions 1 is alpha beta unsaturated ketone.

So, that needs alkaline hydrogen peroxide the other one that is second alkene is electron rich alkene. So, you need normal peracids. So, between these 2 only 2 will be epoxidized when you treat with m-CPBA that is the answer for question number 1, answer for question number 2 whether the epoxide will be alpha or beta as I told you the convex face is the free face. So that means, the epoxide will come from the alpha side.

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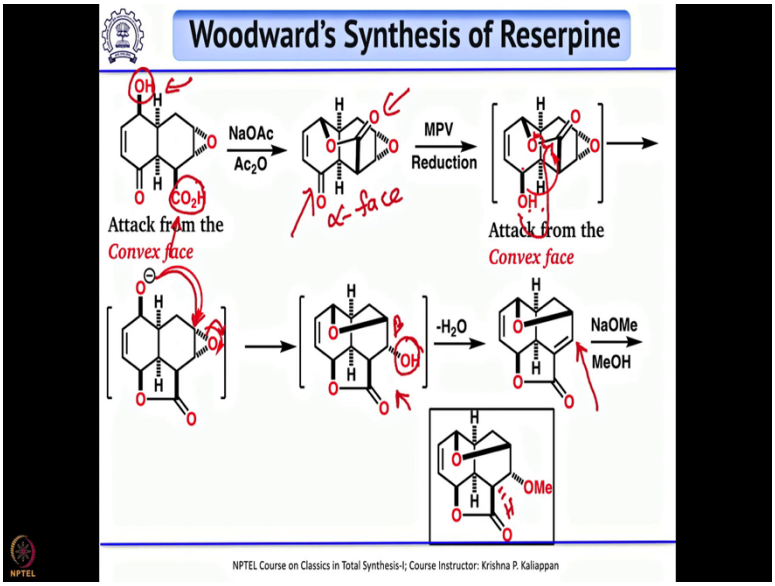

So, when you do that this is what you will get ok. Now, you have a hydroxyl group and you have a carboxylic acid group, if you treat with acetic anhydride sodium acetate what will happen? This will form an ester cyclic ester that is called lactone ok, this carboxylic acid and this alcohol will couple to form a lactone ok. Next you have few more functional groups and the enone if you reduce under MPV reduction condition that is mere Meerwein Ponndorf Verley reduction condition this carbonyl group will be reduced again alpha face is more free the hydride will come from the alpha face.

So, you get beta alcohol, but what you get is this compound ok. So, that is the beta alcohol and does not stop there, the beta alcohol now it attacks this carbonyl of the lactone and opens this. The reason is this will give you a 5 membered lactone this will give you a 5 membered lactone; whereas, if you look at this this is a 6 membered lactone. So, 5 membered lactone is preferred over 6 membered lactone and does not stop there ok after opening the lactone the intermediate does not stop there.

What happens this O minus attacks the epoxide this O minus attacks the epoxide and you get the corresponding ether cyclic ether and alcohol corresponding cyclic ether. So, that is the 5 membered cyclic ether and alcohol ok. This is what you get when you do when you take the lactone this lactone and then treat it under MPV reduction condition and of course, if you see this hydroxyl group it is beta beta to this carbonyl. So, it is a good leaving group under this condition.

Otherwise hydroxyl is not a good leaving group it undergoes elimination to give the correct corresponding alpha, beta unsaturated lactone ok understood. So, in one reaction it is MPV reduction condition how many reactions are taking place and what is more important is those days NMR was not there crystal structure was not there ok. With just UV, IR, melting point they could assign correct structure for many such interesting transformations ok, products arising out of many such interesting transformation.

So, now when you treat this with sodium ethoxide and methanol, so sodium ethoxide will add in a 1, 4 fashion again the alpha face is the free one so because of convex face. So, the methoxy will come from the alpha side and while quenching the enolate also this hydrogen also will come from the alpha side ok. So, in few steps you could get this complex tetracyclic structure, starting from benzoquinone using Diels Alder reaction as the key reaction ok.

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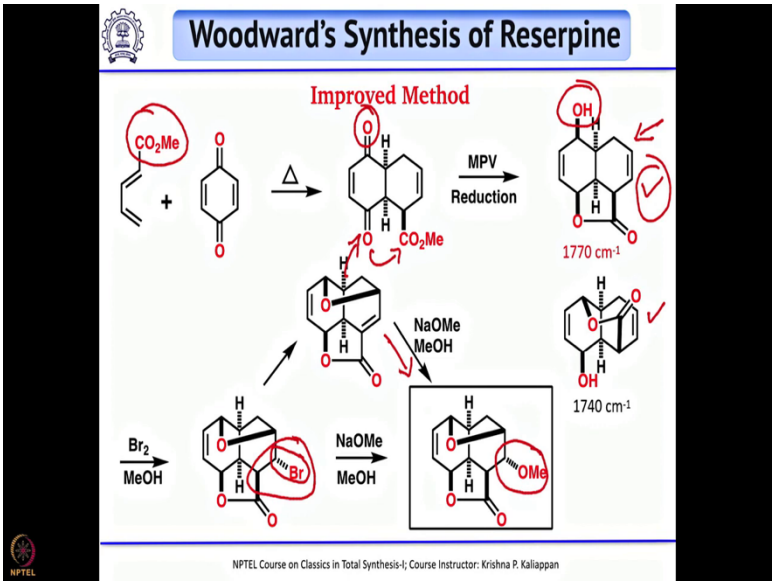

Later he also used a very simple method ok, he improved the method which he earlier used and got the same intermediate in few steps. How? Instead of carboxylic acid what he did was he used ester, his idea is when you do the Diels Alder reaction when you do the Diels Alder reaction. Now instead of selectively reducing only this carbonyl why do not we reduce both carbonyls why do not we reduce both carbonyls. So, when we do that directly this ketone when it is reduced it will form the 5 membered lactone ok.

Now, you have the allylic alcohol ok this allylic alcohol can be functionalized, but the problem is how do you know you got only the 5 membered lactone and not the 6 membered lactone, how do you know that you got only the 5 membered lactone and not the 6 membered lactone ok? Those days you know you can use IR and 5 membered lactone where it will come and 6 membered lactone where it will come. So, 5 membered lactone you get around a very strong peak around 1770.

Whereas for 6-membered it is between 1730 and 1740 he got only this because the IR peak was around 1770, so that confirmed that he got only the 5 membered lactone. So, once you have this lactone now if you treat with bromine and methanol. If you treat with bromine and methanol again the bromine will attack only from the alpha side, once the bromine attacks from the alpha side that is bromonium ion the free hydroxyl will attack and it forms the cyclic ether ok.

Now, if you treat with sodium ethoxide methanol if you treat with sodium ethoxide and methanol you get the carbon which we discussed in the previous slide. So, if you look at

the stereochemistry if you look at the stereochemistry you see the bromine is alpha and methoxy also is alpha bromine is alpha methoxy is alpha. So, what does it mean? So, do you think we are talking about not SN_2 reaction SN_2 means it should be beta the methoxy should be beta. But what is happening is here the sodium methoxide acts as a base as well as nucleophile.

As a base it eliminates HBr; it eliminates HBr and then it gives this intermediate once you get this intermediate sodium methoxide. Now acts as a nucleophile ok then it undergoes 1, 4 addition and you get this product. So, this is the same intermediate you saw in the earlier slide, but that took more steps. Here it took only you can see 1 2 3 4; 4 steps you could make this compound starting from benzoquinone ok.

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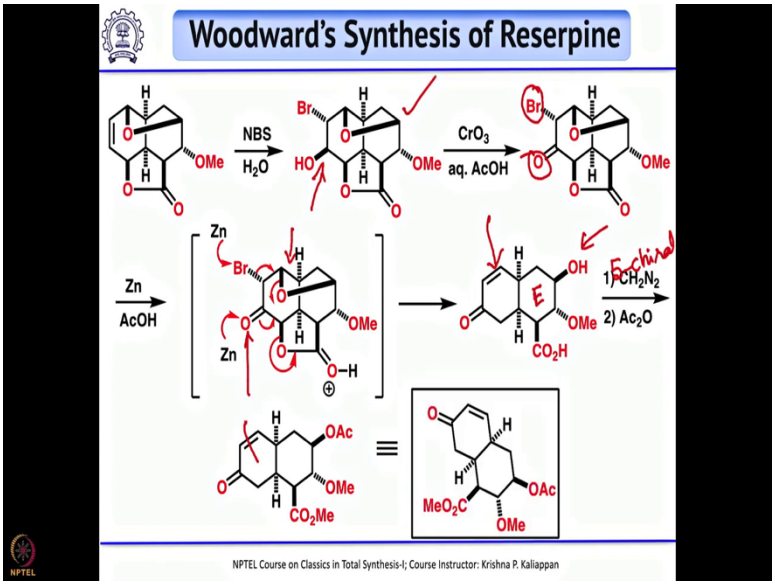

Once you have this next you have one more double bond and treat with NBS water, if you have a double bond and then treat with NBS water it will give bromo hydrate it will give bromo hydrate where will the bromine go where will the hydroxyl come. Obviously the bromine will be alpha that is the first step is it, the bromonium ion formation. The bromonium ion will come from the alpha side, then the hydroxyl group which opens the bromonium ion will come from the beta side. So, this is what you get ok.

Now if you oxidize the secondary alcohol if you oxidize the secondary alcohol using chromium trioxide acetic acid you get the ketone ok. Here he did another very interesting reaction to get the precursor for the total synthesis of reserpine. So, the key reaction is

see you have a bromine and you have a carbonyl group. What he did? He treated with zinc acetic acid zinc acetic acid is known to give one electron is not it.

So, first it open the cyclic ether at the same time it also open the lactone starting with donating electron to carbonyl group, when this happens carefully you see the arrow which I have written ok. Then what you get is this compound I will leave it for a few seconds, so that you can understand how does it happen ok. So, you get essentially you get a cyclohexenone and if you look at this E ring if you look at the E ring all the 5 chiral centers though it is a relative stereochemistry it is not a symmetric synthesis it is a relative stereochemistry.

All the 5 chiral centers are fixed all the 5 chiral centers are fixed ok. Now what he did the carboxylic acid was esterified with the diazomethane and the free hydroxyl was acetylated in 2 steps he get this compound ok. And for the intermediate which you want what you need is you need to cleave the double bond and you should get a aldehyde here and you should get an ester.

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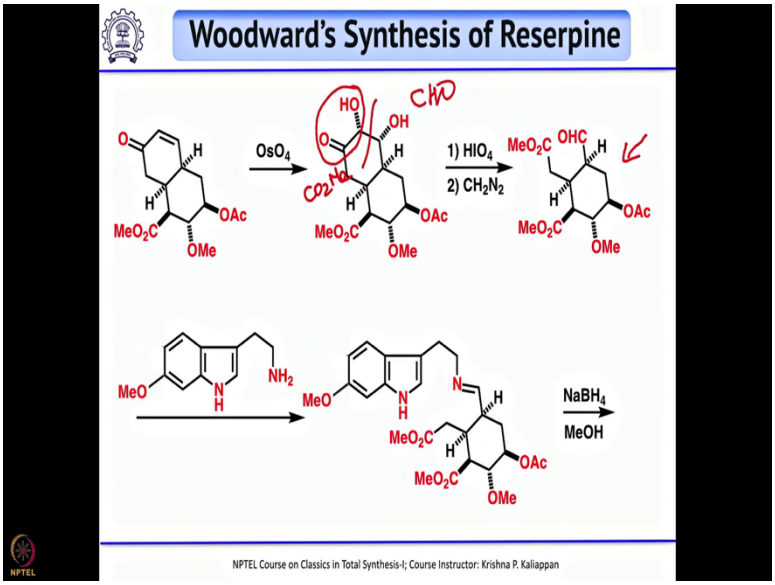

So, that is very simple you take this compound and then treat with osmium tetroxide when you treat with osmium tetroxide you get the diol. The diol now if you treat with periodic acid followed by treatment with the diazomethane. So, this side it will become aldehyde and this whole thing will become carboxylic acid followed by treatment with so

diazomethane it will become CO_2Me. If you look at the retrosynthesis or whatever synthesis Woodward has planned he planned using this, is not it.

So, he wanted to treat that aldehyde with methoxy tryptophan and then reduce it with sodium borohydride to get the lactone. So, you took this and then treated with the corresponding amine it form the imine, then reduction with sodium borohydride methanol reduce the imine and that also spontaneously cyclized with the ester to form the cyclic lactone ok.

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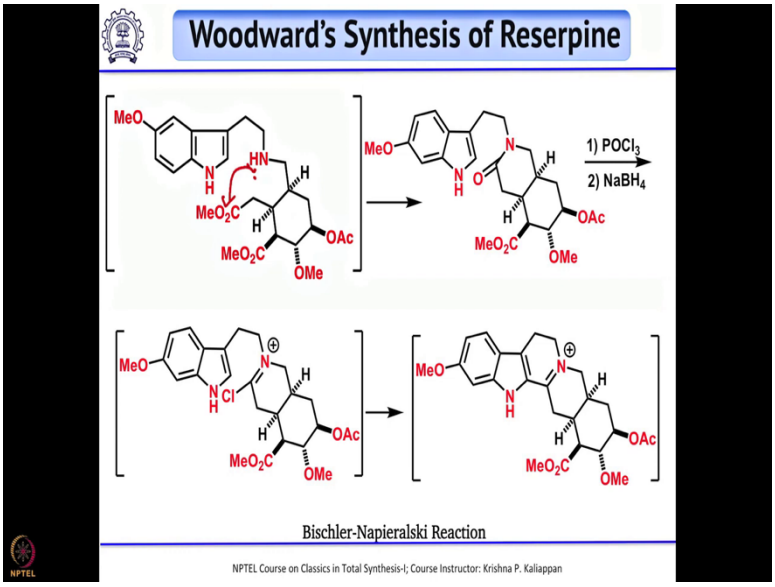

So, C ring is ready D ring is ready already AB ring you started with the corresponding with methoxy tryptophan ok. Now we have to make the C ring, C ring is the last ring to be made and then C ring has one chiral center and based on the earlier reports the chiral center is when you when you want to generate normally you get the other one ok. So, $POCl_3$ sodium borohydride that these are the standard conditions used for Bischler Napieralski reaction.

So, it forms this iminium intermediate then addition elimination takes place to give the corresponding iminium. So, C ring is formed in situ you reduce with sodium borohydride you get

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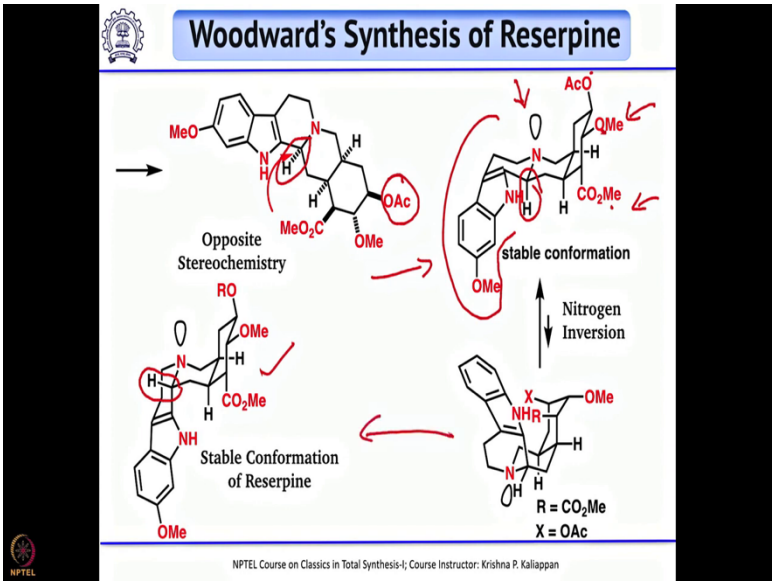

the complete penta cyclic structure of reserpine there are 2 things missing in this one the acetate should be replaced by OCO and then aryl group and the second thing is in reserpine this particular chiral center has beta carbon this particular chiral center has a beta carbon. But this is the most stable conformation this is the most stable conformation.

So, how you can change the Stereochemistry ok, if you draw a 6 membered chair like conformation you can see this is how you can draw the 6 membered chair conformation for what you got in this reaction. But as I said for reserpine this is the stable conformation where you can see this hydrogen is beta; whereas, here this hydrogen is alpha. So, you have to change that how do you change? One you can think about nitrogen inversion.

So, if you do nitrogen inversion ok if you do nitrogen inversion everything will change every conformation. So, this you know if it is equatorial methoxy equatorial ester is equatorial acetate is equatorial, when you flip it will become axial and same thing here. So, the whole indole unit it will come axial. So, this is nitrogen inversion which can be done by treating with the acid ok. Now, afterwards if you reduce it then that can come here ok that can go to this one.

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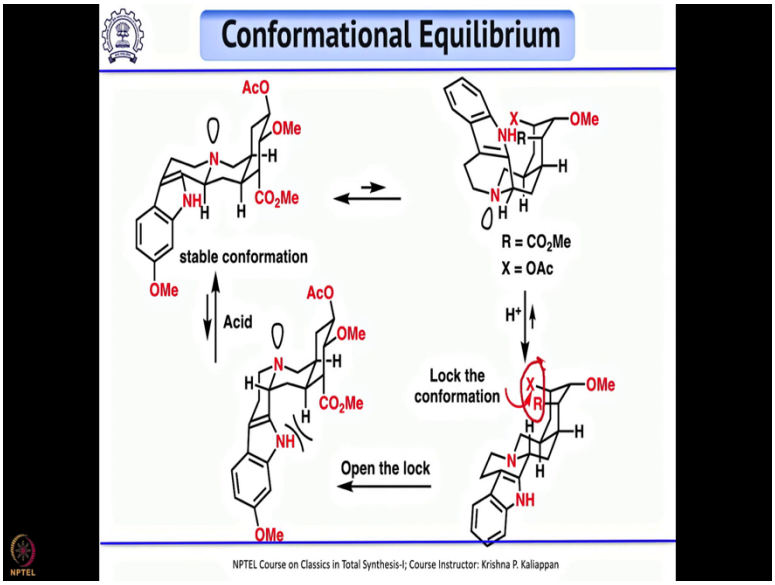

So, this conformational equilibrium can be utilized ok. So, first you treat with acid so it flips, then during this process you are locking the conformation you should lock the conformation then only it will not go back. So, these 2 so one is ester another one is acetate. So, if we can lock this conformation through a lactone formation through a lactone formation then this is what you will get then followed by just open it you get the most stable conformation of reserpine ok.

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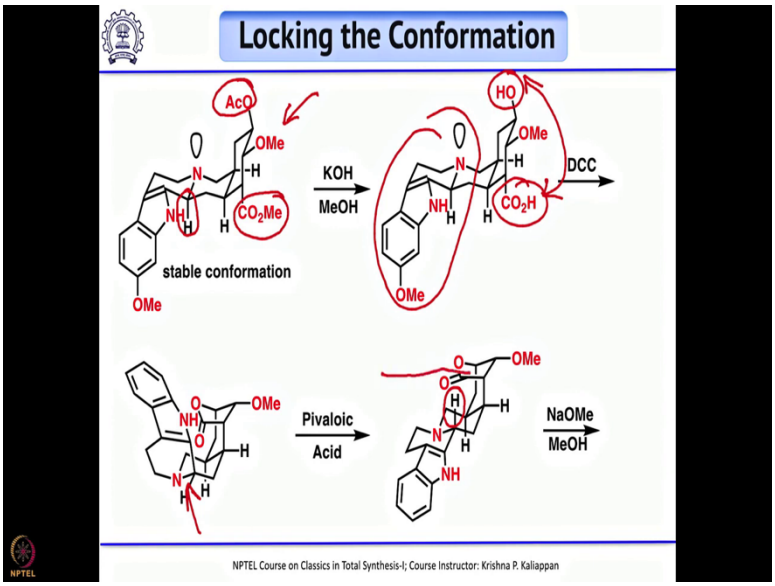

So, what you did you whatever you got this is what you got when you did the total synthesis this is what you got, where you have alpha hydrogen here, but what you want is beta. You took this compound and then treated with potassium hydroxide methanol

potassium hydroxide methanol acetate will get hydrolyzed and ester also will get hydrolyzed you get a carboxylic acid and hydroxyl group.

Now, to freeze the conformation what you have to do you have to make a 5 membered lactone between these 2, you have to make a 5 membered lactone between these 2. So, if you treat this with DCC as I said it undergoes ring flipping and you get the lactone and you can see this one also this side also whole thing underwent ring flipping. Now if you treat with acid; now if you treat with acid the whole thing whole thing will undergo epimerization and you will get this conformation.

Now, if you look at this hydrogen is beta ok, from alpha you brought it to beta. Next is just cleave this lactone cleave this lactone with sodium ethoxide methanol.

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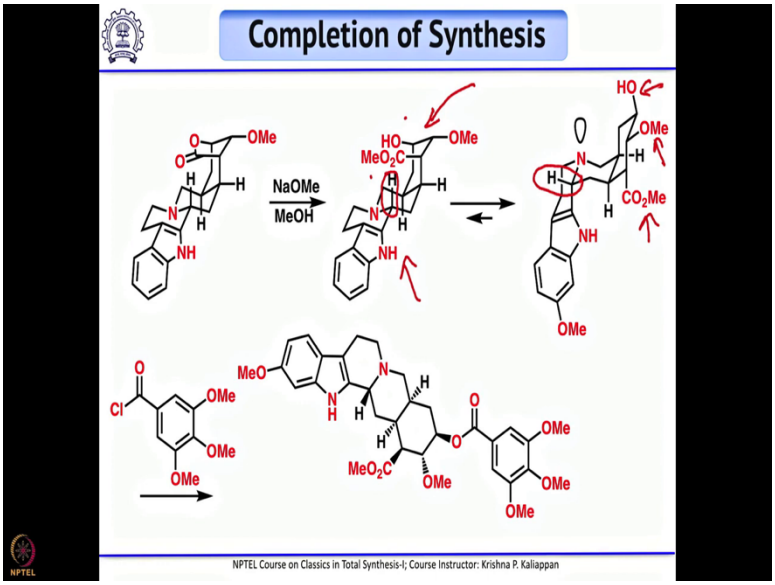

So, when you do that you get this compound ok. Now if you look at these 3 substituents methoxy, hydroxyl and ester they are all in axial position. So, that is not stable; that is not stable. So, what it will do? It will undergo ring flipping. When it undergoes ring flipping this is what you get because everything will be in equatorial position. Now, ok and same way this also will undergo exactly opposite ring flipping. Now still you see this hydrogen is beta, earlier it was beta axial here now beta equatorial ok.

So, that is how he cleverly used acidic condition and the locking the conformation followed by acidification to get that. Then what you do you have the free hydroxyl group

attach the tri methoxy benzyl chloride that is the side chain present in reserpine. So, that is how the total synthesis of reserpine was completed successfully by Robert Woodward ok. This is really very very important total synthesis reported in 1960's, one of the classical synthesis and it is taught in almost all textbooks ok.

Thank you