Classics in Total Synthesis - I
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Lecture - 26
Perhydrohistrionicotoxin

Good morning everyone. And welcome back to the course on Classics in Total Synthesis Part 1; so, we have been discussing about you know three membered ring, four membered ring, five membered ring, six membered ring based natural products. And today we will talk about very interesting alkaloid ok. This, alkaloids are very very interesting natural products. So, we will be discussing many synthesis of alkaloids.

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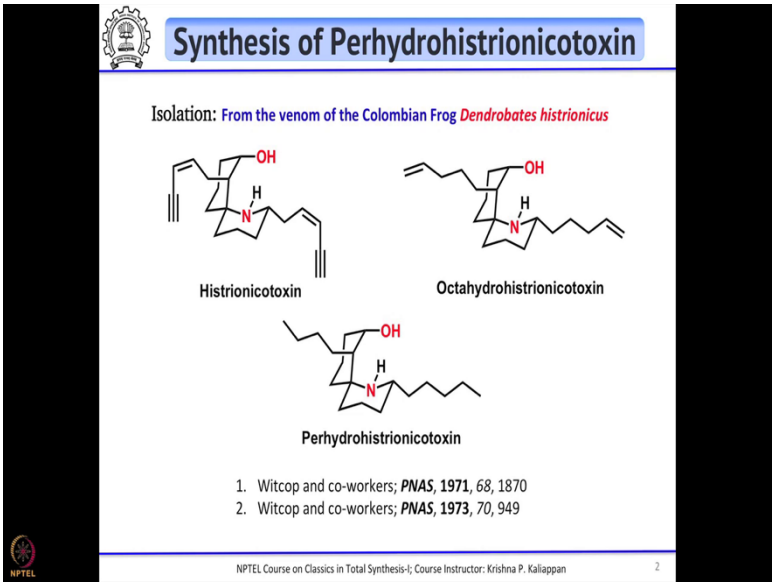

And the first synthesis of alkaloid today we are going to discuss about Perhydrohistrionicotoxin. The name it name itself looks little longer, but you can break it like this per hydro histrio nico toxin, per hydro histrio nico toxin ok. So, there are three natural products isolated from the same source. The first one is called histrionicotoxin ok.

So, here you can see there are two side chains, there are two side chains ok having an enyne moiety ok. There are two side chains having an enyne moiety, but the core structure is a spiro fused system ok. One six membered ring fused with a piperidine ring

ok. A six membered ring fused with a piperidine ring with two side chains having an enyne moiety ok.

The second natural product is the one where the triple bond is reduced to a double bond ok. The triple bond is reduced to the double bond while the double bond is fully reduced. So, this is called octahydrohistrionicotoxin ok. The third natural product is fully reduced natural product called perhydrohistrionicotoxin. It is completely reduced; the side chain is completely reduced.

So, this was isolated from the venom of a Colombian frog called dendrobates histrionicas. This was isolated and reported way back in 1971 and 73 by Witcop and coworkers ok and in fact, they asked Professor E J Corey to see whether this can be synthesized by his laboratory ok.

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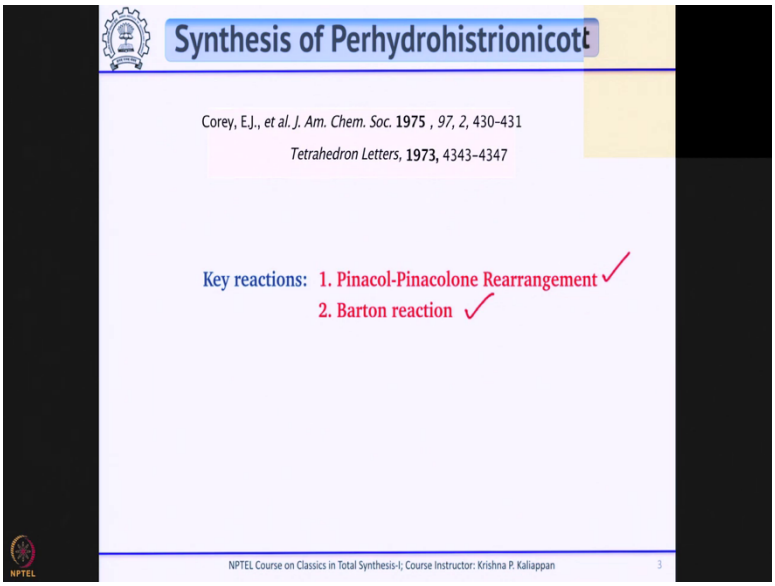

And immediately E J Corey's group took upon the total synthesis of this molecule and then they reported the first total synthesis of perhydrohistrionicotoxin and his synthesis involve 2 important reactions: One is pinacol-pinacolone rearrangement other one is a Barton reaction.

So, before we actually go into the details of the total synthesis of perhydrohistrionicotoxin by E J Corey we will briefly discuss about or briefly recall the pinacol pinacolone rearrangement and Barton reaction. I am sure all of you would have

gone through these two reactions, but it is a brief recall it is very important to know before we actually proceed to look at the total synthesis of perhydrohistrionicotoxin reported by E J Corey, which involves these two key reactions.

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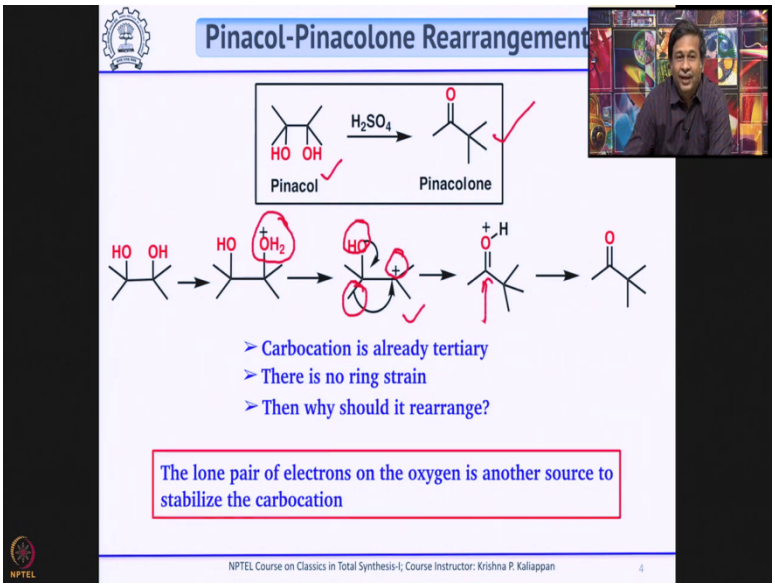

So, what is pinacol pinacolone rearrangement? So, if you have a 1, 2 diol ok if you have a 1, 2 diol and upon treatment with acid, this undergoes a facile rearrangement to a ketone called pinacolone. So, the whole process is called pinacol to pinacolone because it goes from pinacol to pinacolone. How does it happen?

So, when you have a diol one of the alcohol is protonated. So, once it is protonated automatically it becomes a good leaving group. So, once it goes then it generates a carbocation though this carbocation is stable because it is a tertiary carbocation it is stable, but the presence of a hydroxyl group presence of a hydroxyl group adjacent to that makes it less stable because the lone pair on the oxygen now can push one of the alkyl groups or aryl groups to migrate.

So, that you will get this intermediate, where now the positive charge which is formed here is stabilized by the oxygen ok; so, this is more stable than the tertiary carbocation. So, this is the driving force for the migration of an alkyne or aryl group from the adjacent carbon with respect to the carbocation form ok.

So, one can ask why this migration should take place when already the carbocation is tertiary and there is no ring strain, but still the migration takes place because the stability of the carbocation by the lone pair on the oxygen ok, that actually helps the migration of an alkyl or aryl group to facilitate this pinacol and pinacolone rearrangement ok.

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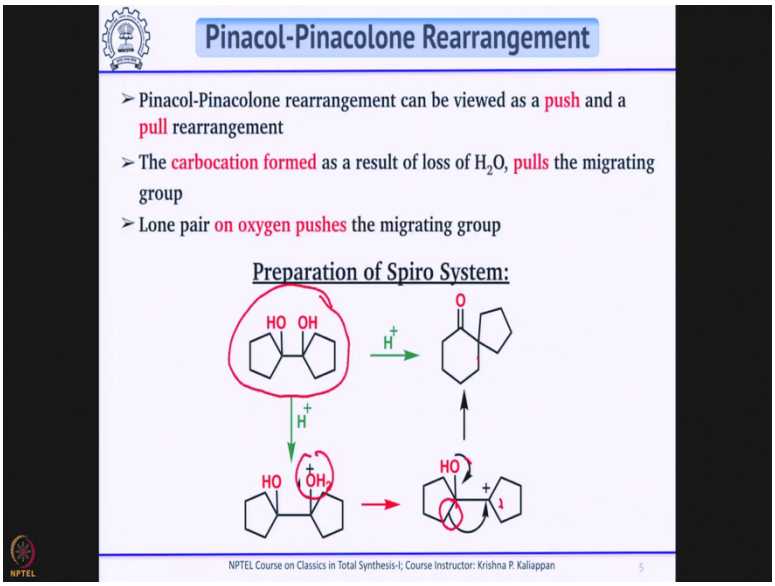

So, there are many examples I will just give few examples at least 2 or 3. So, when you have a diol like this. This upon pinacol pinacolone rearrangement first protonation takes place and followed by the leaving of water to generate the carbocation. Now the lone pair pushes this C-C bond ok. So, it is a symmetrical does not matter this C-C bond to migrate or in other words ring enlargement takes place because of the migration of the C-C bond ring enlargement takes place. So, what you get is a spiro system ok, the spiro 4, 5 system you get ok.

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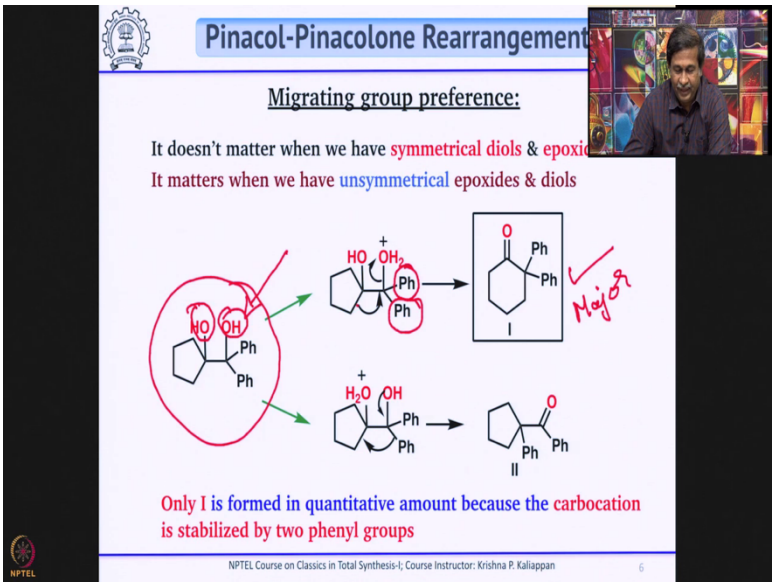

Then one can also see if we have unsymmetrical diols, which alcohol will be protonated first. So, if we have an unsymmetrical alcohol; obviously, it will protonate the alcohol which will give more stable carbocation. So, now if you look at this example there are two alcohols. So, between these two alcohol this alcohol will be protonated because that will give a carbocation, which is more stable than the other carbocation.

This carbocation will be stabilized by two phenyl groups ok. So, that is why that will be more stable and then this bond will migrate. So, leading to the formation of one and this is the predominant or major products and not the other one ok. So, the migrating group preference is important, but at the same time first the formation of most stable carbocation is the real driving force for the migration of the next one ok.

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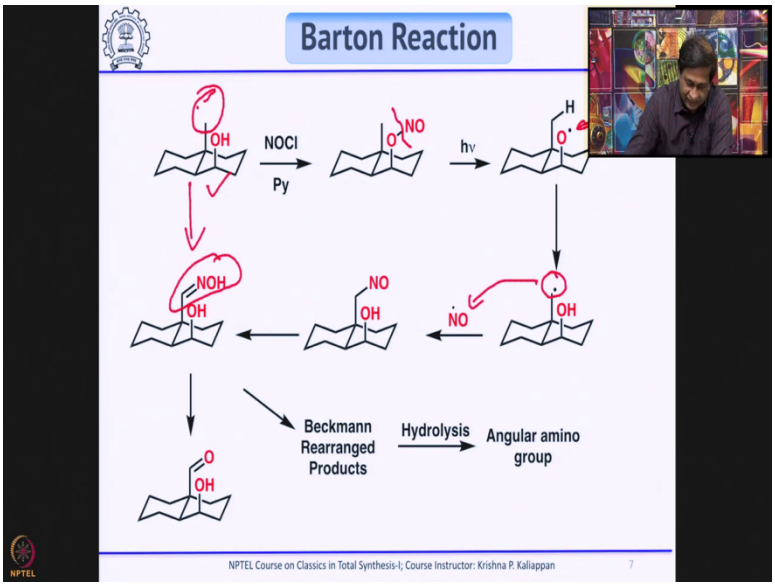

The second reaction which is used by EJ Corey in the synthesis of perhydrohistrionicotoxin is Barton reaction. In the last two decades or more, one has witnessed you know large number of publications on CH activation and functionalization. But Barton has reported this reaction long time ago where angular methyl group angular methyl group in steroids can be easily functionalized by this reaction. What is this reaction?

So, if you have an alcohol like this. It is very important that alcohol should be axial ok axial. Now if you treat with NOCl and pyridine ok. So, that OH will become ONO ok. OH will become ONO. Now this I am shining with light, it forms oxygen radical ok and my NO also comes out. Now, if you look at this carefully through a six membered transient state this oxygen radical can pick up this hydrogen.

If that happens then you will get OH and the CH_3 now will become CH_2 radical ok. The CH_2 radical immediately will combine with the NO radical which came out, when this O NO bond got cleaved you got oxygen radical and NO radical. So, now, what will happen? The CH_2 radical combined with the NO radical to form CH_2NO and the CH_2NO immediately tautomerize the CH_2NO immediately tautomerize to give the corresponding oxime ok.

So, what you have seen now in the whole process the angular methyl group which is really very difficult to functionalize has been functionalized by this reaction. So, this

reaction was reported by Barton. So, normally this is called Barton's reaction. Once you have this oxime one can hydrolyze the oxime to get the aldehyde or if you have an oxime you know another famous rearrangement can be considered. So, Beckmann rearrangement can happen.

So, that way the CH_3 will be converted into amine ok amide and followed by amine. So, many things can be done having the oxime moiety at angular methyl group. So, these are the two reactions, which you should remember when we talk about total synthesis of perhydrohistrionicotoxin reported by EJ Corey.

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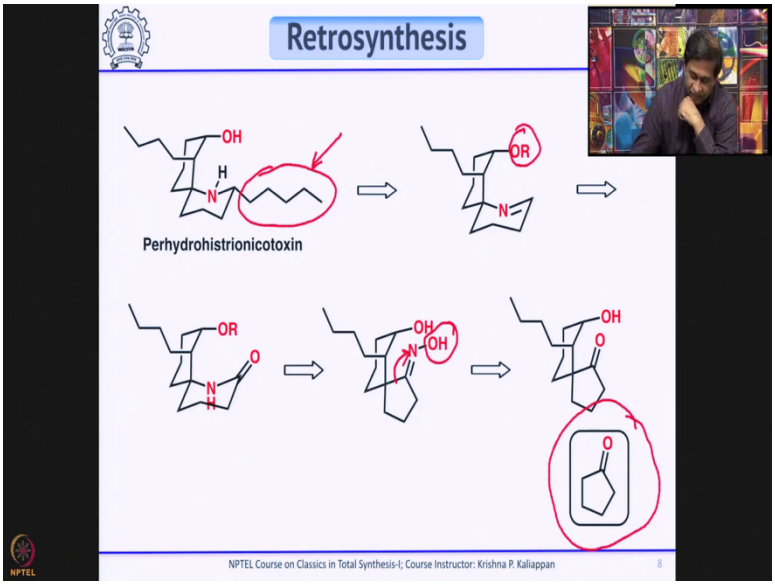

So, this is the structure of perhydrohistrionicotoxin, then the first step the first retro synthetic step was to remove the five carbon units ok, but before I actually talk about retro synthesis if I tell that this compound this natural product was made from cyclopentanone. Can you believe this compound was synthesized from cyclopentanone, cyclopentanone is the commercially available starting material and that was the starting material for the synthesis of perhydrohistrionicotoxin.

It may be difficult to believe for the simple reason that if you look at the natural product there is no five membered ring, is not it? Is there any five membered ring? No. You have two six membered rings. One is normal cyclohexane, other one is piperidine derivative ok. They are fused in a spiro fashion and I am claiming that the starting material is cyclopentanone.

So, that is the power of retrosynthesis. If you logically think and logically write a proper retro synthesis that can lead to a very very simple commercially available inexpensive starting material and also the whole reaction sequence will be very simple and straightforward ok.

So, now the first retrosynthesis was the addition of this five carbon unit addition of this five carbon unit to this imine ok. If you have an imine ok if you have an imine the equatorial addition equatorial addition of this five carbon Grignard or lithium that will give you the natural product and afterwards you have to protect the remove the protecting group. Of course, when you do this the hydroxyl should be protected. So, that is the first two retro synthetic steps.

Now once you have this imine this imine can be obtained from the lactam ok. This imine can be obtained from the lactam in two steps ok. So, whenever you have a lactam whenever you have a lactam or whenever you have an amide there are many reactions you can think of. One you can have a carboxylic acid and amine and intramolecular coupling reaction will give you the corresponding amide here it is cyclic. So, it is a lactam.

Then one can also think about Beckmann rearrangement, is not it? One can also think about Beckmann rearrangement, where you have an oxime that oxime can undergo Beckmann rearrangement. Again the position of the nitrogen depends on the regiochemistry of the oxime. So, for example, if we have this oxime ok, if we have this oxime then this can possibly this can possibly give you this lactam.

How? Because if this is the leaving group, then the bond which is opposite to that leaving group only migrates that will give you exactly the same lactam ok. So, the key reaction so far if you look at is the Beckmann rearrangement to get the six membered ring ok five membered to six membered ring ok.

Now normally how do you get oxime? Normally how do you get oxime? All of us will immediately think ok oxime it is very easy you can start from the corresponding ketone, is not it? You can start from the corresponding ketone. If you have the ketone then treat with hydroxyl amine you will get the corresponding oxime that is how normal people will think. But as I said this synthesis was reported by the Nobel Laureate E J Corey. So, he has some special disconnection for this particular step.

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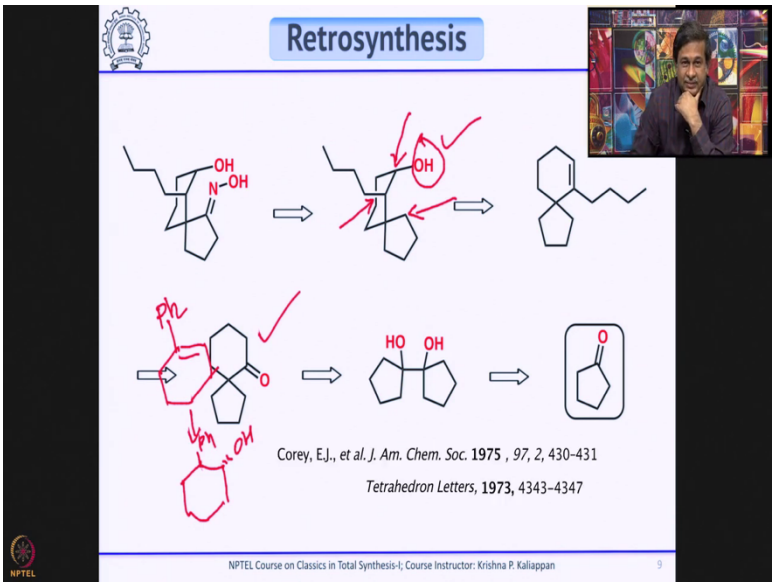

So, instead what he thought was this oxime should be prepared or can be prepared from this alcohol and there is no ketone ok. This is where you should recall the reaction which I mentioned that is Barton reaction. So, if we have this alcohol and then treat with NOCl pyridine and under photochemical condition the NO group will be transferred to the CH_2 through the six membered transient state.

Then that NO will become oxime and that oxime you can treat with acid to get the corresponding Beckmann rearranged product. So, this is a very very important reaction and people normally would not have thought about using Barton reaction to get the oxime ok. That is a very clever thinking and because of that because of that the whole synthesis become much much simpler ok.

Because you do not have to introduce a ketone just CH_2 is there just you do this Barton reaction. Now the next step if you look at you need to introduce a hydroxyl group ok. This is the five membered ring no problem, but here you need to introduce a hydroxyl group and as well as this 4 carbon unit. So, what is the relationship between these two? They are 1, 2 and they are trans to each other 1, 2 and trans to each other.

How you can introduce this ok how you can introduce this? See if you are thinking about alcohol you can start from the ketone reduce it. We do not know whether it will be selective. In that case your butyl group is in axial position; the hydroxyl is in axial position. Both normally you do not expect, is not it? The normally all the groups will try

to go to equatorial position here both butyl as well as hydroxyl groups are sterically hindered axial position.

So, another very interesting reaction E J Coley used to fix these two stereo centers. When you do a hydroboration when you do a hydroboration so what you do? See for example, if you take here phenyl cyclohexene ok. Now if you do hydroboration and oxidation if you do hydroboration oxidation hydrogen and boron hydrogen and boron will come from the same side because it is a cis addition ok.

Hydrogen and boron will come from the same side. That means, the boron which will essentially be converted into hydroxyl will be opposite to that of phenyl group correct, will be opposite to that of phenyl group. Basically what you get is the alkyl or aryl group and the hydroxyl group trans to each other and when the hydroboration takes place the hydrogen and boron will come from the least hindered side. So, that means, if you look at this the hydrogen and boron will come from the least hindered equatorial side pseudo equatorial side so that your alkyl group will go to axial.

So, the precursor is nothing but this alkene. If you take this alkene do hydroboration oxidation you will get this compound ok. Then how do you get this compound very simple? If you have this ketone then add butyl lithium followed by dehydration you will get this, is not it? Butyl lithium and dehydration and this compound when I talked about pinacol pinacolone rearrangement I told you this is a spiro ketone can be obtained from this pinacol ok, can be obtained from this pinacol.

Now, this pinacol is obtained from cyclopentanone. So, this is what I said when you can think about proper retrosynthesis and use some clever disconnection and use some nice reactions one can get a very simple starting material and the whole strategy will be a classical one. This is one of the classical total synthesis reported in the literature by E J Corey ok. Now, let us see whether the retrosynthesis what he had proposed he could easily follow it in the lab to complete the total synthesis ok. Those who are interested they can go through these two references.

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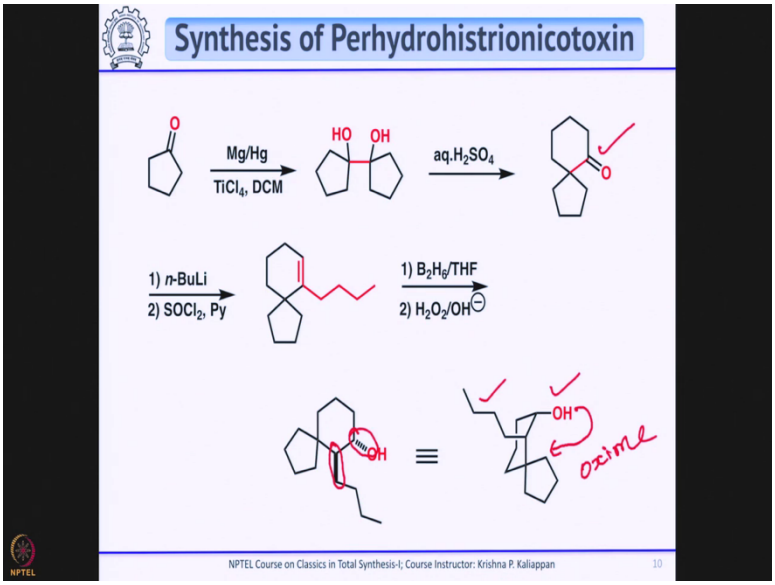

First he started with cyclopentanone, then pinacol coupling got the pinacol. This upon treatment with the aqueous sulfuric acid you get the corresponding the pinacol pinacolone rearrangement. So, this is quite easy and straight forward and once you have that add n-butyllithium.

So, n-butyllithium adds to the ketone and then followed by dehydration done by thionyl chloride pyridine to get the corresponding alkene ok. So, now that you have the alkene next step is the hydroboration oxidation. Yes hydroboration oxidation with hydrogen peroxide and sodium hydroxide gave the corresponding secondary alcohol and the secondary alcohol as well as the butyl group they are anti to each other ok.

Now, this can be written like this. This can be written like this. It is a relative stereochemistry it is not a asymmetric synthesis. This is relative stereochemistry and that is why I have written this solid bond ok. Now once we have this you can clearly see you have introduced the spiro system and the butyl group and the hydroxyl group with correct stereochemistry, Spiro system, butyl group, hydroxyl group with correct stereochemistry.

Now, you have to use this handle the hydroxyl handle to introduce the oxime ok. You have to introduce the oxime as planned. So, for that what one has to do? Barton reaction.

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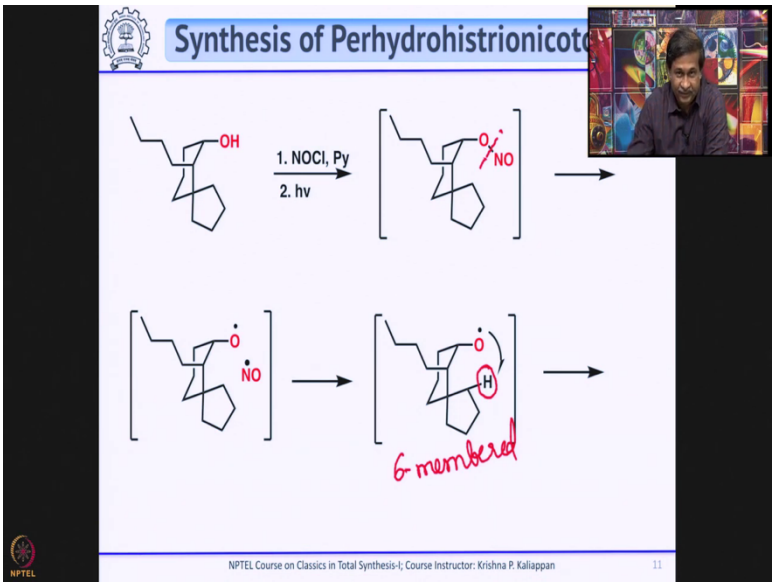

So, he took this alcohol and then treated with NOCl pyridine then shine light. So, first it forms the ONO. So, under photochemical condition the ONO bond breaks and then it gives oxygen radical and NO radical. Now, the oxygen radical picks up the hydrogen radical from here through a six membered transition state ok through a six membered cyclic transition state ok. It picks up the hydrogen and that gives you the corresponding radical at the five membered ring ok.

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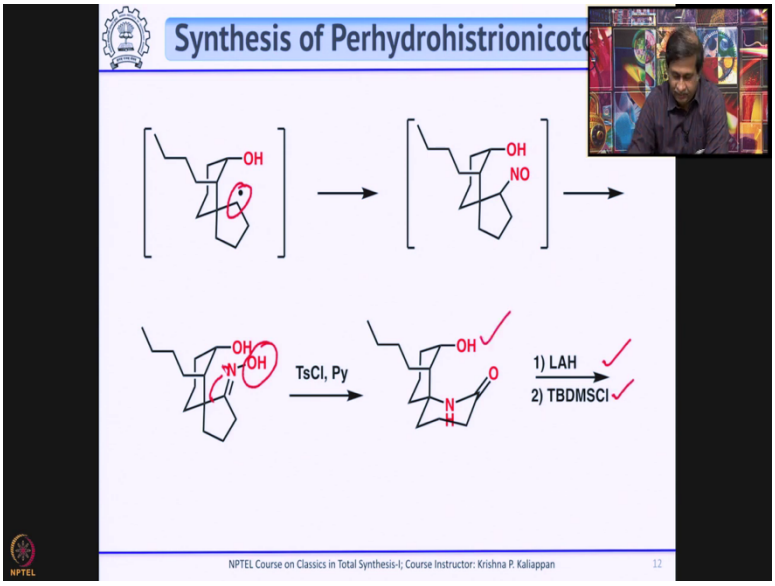

Once the hydrogen is picked up you get the corresponding radical here. Then the NO radical which went out will combine with this cyclopentyl radical to form the corresponding NO ok. It is like cut and paste. If you look at this chemistry it is very nice interesting chemistry you attach NO cut it, then attach to other side cut and paste chemistry.

Then once you have NO, this NO immediately tautomerizes to corresponding oxime. Immediately tautomerizes to the corresponding oxime. So, you have the oxime the next step is carry out the Beckmann rearrangement ok. The Beckmann rearrangement is very simple. So, one can use acid. So, what they have done is they have treated with para toluenesulfonyl chloride ok.

So, selectively they can tosylate the oxime OH then followed by migration of this bond gives you the lactam. You have the lactam the next two steps first treatment with LAH what will happen? If you treat with LAH what will happen when you treat a lactam with LAH? It will become the corresponding amine, is not it? The carbonyl group will be completely removed. The lactam will become the amine ok. Then you have the free hydroxyl the free hydroxyl will be protected by the TBDMS chloride.

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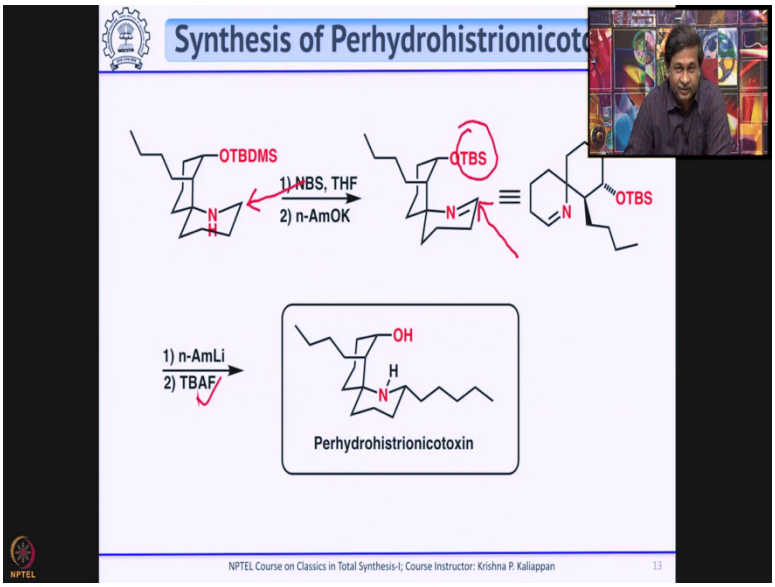

So, what you get is the corresponding OTBDMS or one can write OTBS also a TBDMS can be written as TBS as well. So, now what is left? So, you need to introduce the five

carbon unit at this carbon. You need to introduce a five carbon unit at this carbon and that five carbon unit also five carbon unit also has to come from the equatorial side ok.

So, for that as per the original plan as per the original plan you need to introduce a double bond ok, you need to introduce a double bond. You have NH and you need to introduce a double bond. How will you do? Yes you can brominate. Now if you treat with base potassium amylate n-amylate potassium n-amylate it undergoes elimination of HBr ok. It undergoes elimination of HBr to introduce the double bond ok.

Now, once you have the imine next you have to add the five carbon unit, you have to add the five carbon unit. What you have to do? The five carbon unit is corresponding n-amyl lithium, amyl is five carbon ok. So, you add the five carbon unit. So, once you do that then that five carbon unit also you can see it will add from the less hindered equatorial side ok. The five carbon unit we will add from the less hindered equatorial side.

After that of the TBAF it is a fluoride source is used to remove the TBS group. Addition of n-amyl lithium followed by removal of TBS group you get the natural product that is perhydrohistrionicotoxin ok. So, as I said this is one of the classical synthesis of an alkaloid where two very simple reactions, but cleverly utilized. One is pinacol-pinacolone rearrangement, the other one is Barton reaction.

The Barton reaction the use of Barton reaction is really ultimate, ultimate thinking otherwise normally people think that the oxime can be made from keto group. But, here he cleverly use the Barton reaction from CH_2 to introduce the oxime that once you have the oxime that paved the way for the ring expansion to get the lactam and that is how he could make the other six membered ring ok. So, overall in few steps E J Corey could and his group could synthesize this perhydrohistrionicotoxin starting from commercially available cyclopentanone ok.

So, thank you. I will stop here.