Classics in Total Synthesis-I
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Lecture - 40
Swainsonine

Yeah, good morning welcome back to the lecture series on Classics in Total Synthesis part I. So, we have been discussing about total synthesis of various alkaloids and today we will talk about one very interesting pyrrolizidine alkaloid called Swainsonine ok.

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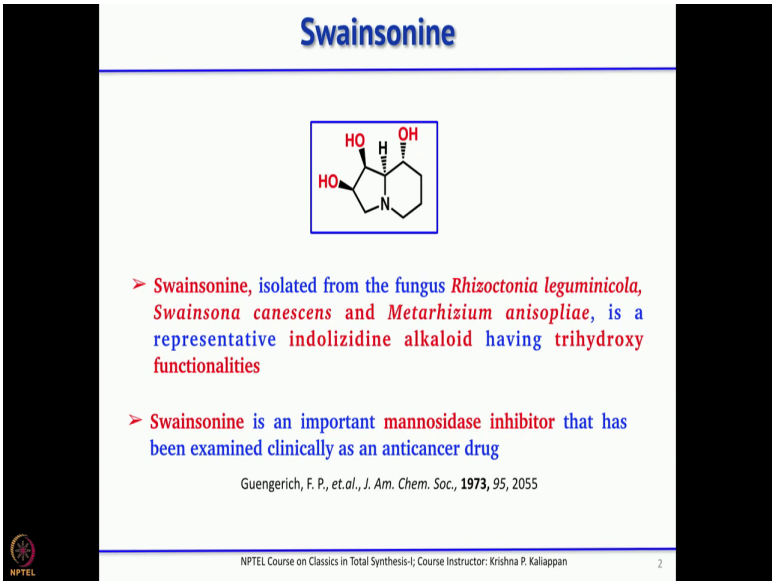

So, swainsonine is a very simple bicyclic compound and have 3 hydroxyl groups, you can see 1, 2, 3. So, these are very important mannosidase inhibitor and also has been examined closely as a potential anticancer drug. So, this molecule has attracted attention of synthetic chemists, because if you look at this molecule one can easily think of making from carbohydrates as starting material.

So, several synthetic approaches were known. What we will do today, we will talk about 4 short total synthesis and incidentally 3 of them are coming from carbohydrate starting material ok.

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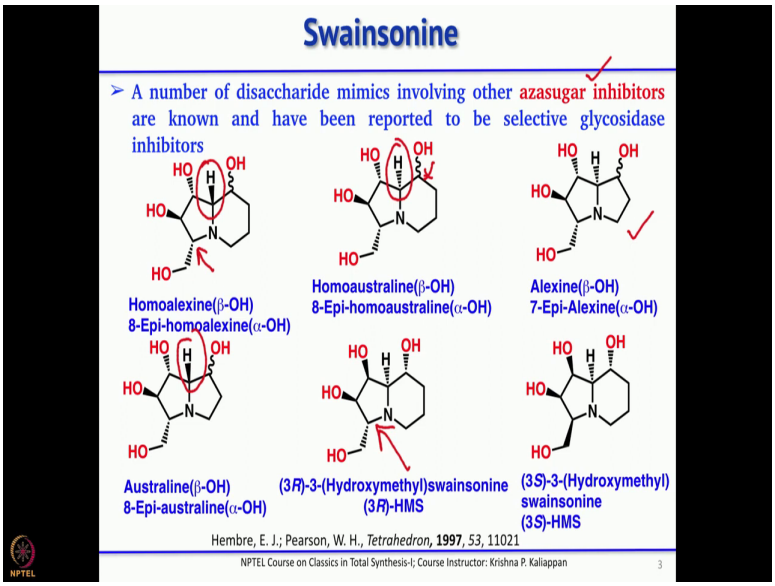

And, this as I mentioned this is a interesting indolizidine alkaloid. There are many alkaloids belonging to this family and some of them are shown here, this is homo alexine. And, that differs if you look at swainsonine and this one, you can see there is additional -CH_2-OH group and also stereo chemistry of this hydroxyl group you know varies.

And, in this case alexine you have a 5 membered coupled with another 5 membered whereas, in these two cases you have a pyrrolidine ring coupling with a 6 membered ring ok. And, this is australine, again it differs only with the you know ring junction here ok, here also the ring junction differs. And, this one it is a 6 membered ring and you can call it as hydroxymethyl swainsonine ok, swainsonine is without this -CH_2-OH. So, it is hydroxyl methyl swainsonine ok.

So, there are many related alkaloids and they are potential azasugar inhibitors ok. So, many of them have been used as glycosidase inhibitors and there are several synthetic groups who work on synthesis of such molecules.

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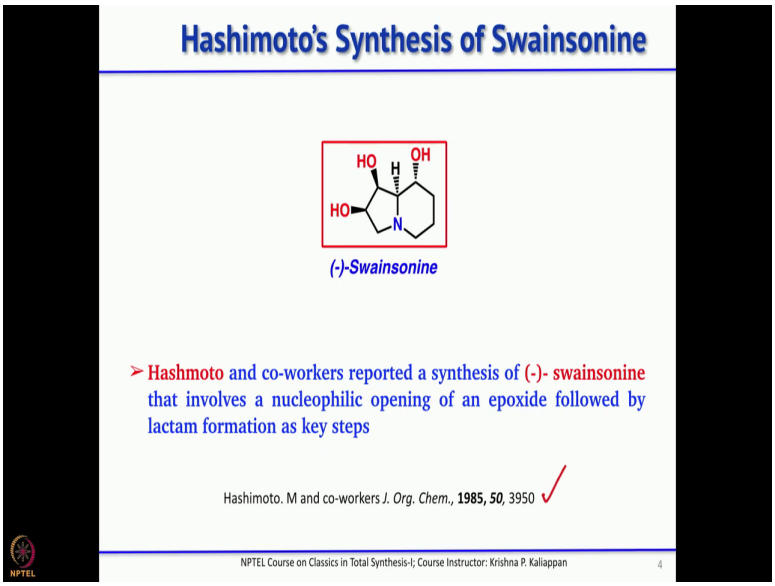

So, as I said we will talk about 3 total synthesis, starting from carbohydrates and let us start with Hashimoto's total synthesis of swainsonine, this was published in JOC in 1985. And, here the key reaction is you have one part nucleophilic opening of epoxide by an amine followed by formation of 6 membered lactam. So, both are happening in one part.

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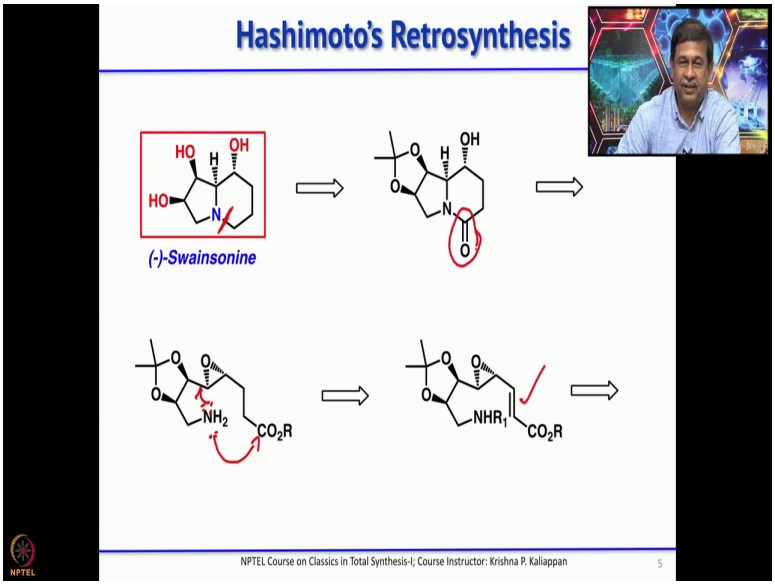

So, that is the key step. So, for the retro synthetic analysis so, the first disconnection was you just remove this bond before that can be easily made from the corresponding lactam

ok. So, once you have lactam and simply you reduce LAH or borane, you get the corresponding reduced to one.

And, the second disconnection is the key disconnection which I said already it is a one part reaction, where the amine opens the epoxide and at the same time this also attacks the ester where the -OR group comes out. So, in one part both the rings are formed ok and this can be obtained from the corresponding α- β unsaturated ester. And, as you know once you have α- β unsaturated ester, that can be obtained from the corresponding aldehyde by stabilized Wittig.

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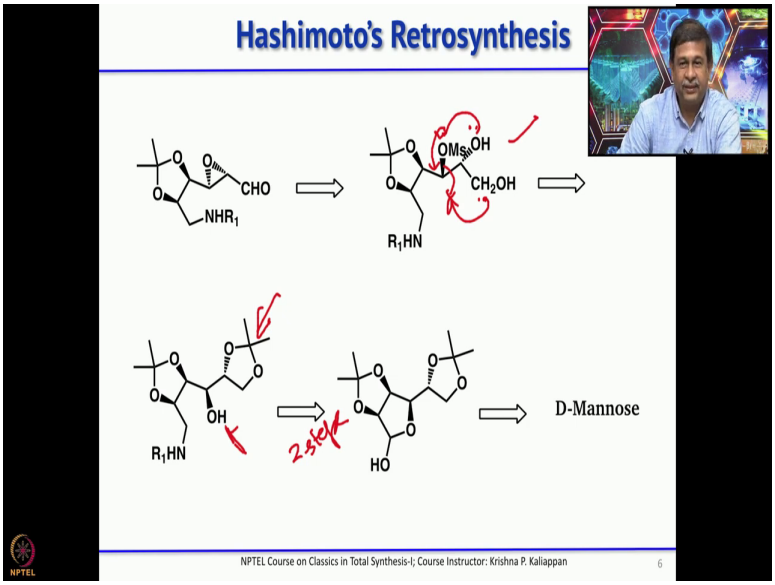

This aldehyde can be obtained from this diol ok. So, now if you look at this diol, if you treat with the base ok; so, this can attack this carbon and mesylate can go out forming the α epoxide ok. One can also see that the primary alcohol can attack, but that will lead to the formation of 4 membered ring. So, it is a highly selective epoxide formation where only 3 membered ring is formed and this in principle can be obtained from this hydroxy amine compound.

So, you can remove this acetonide ok, before that you have to mesylate the secondary alcohol. And, this in principle can be obtained from mannose diacetonide, this is called D-mannose diacetonide and this can be obtained from D-mannose acetonide in 2 steps. Of course, the starting material is D-mannose which upon treatment with acetone and

Lewis acid you will get D-mannose diacetonide. Now, let us see how Hashimoto's group successfully completed the total synthesis of swainsonine using this key reaction.

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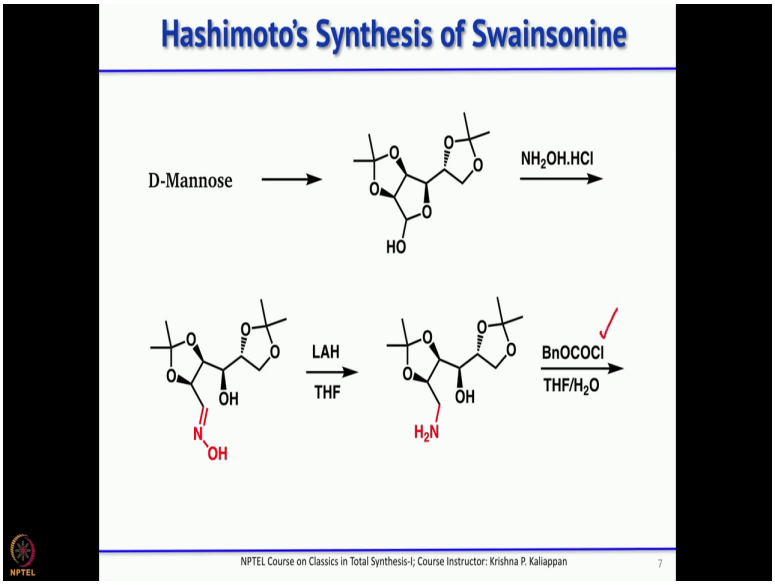

So, first the D mannose was protected as diacetonide and this on treatment with hydroxylamine hydrochloride form the oxime as once you form the oxime you treat with LAH, as you know oxime can be completely reduced to corresponding primary amine. So, that is what happened then that -NH was protected as as -CBz so, you treat with chloro benzyl oxychloride.

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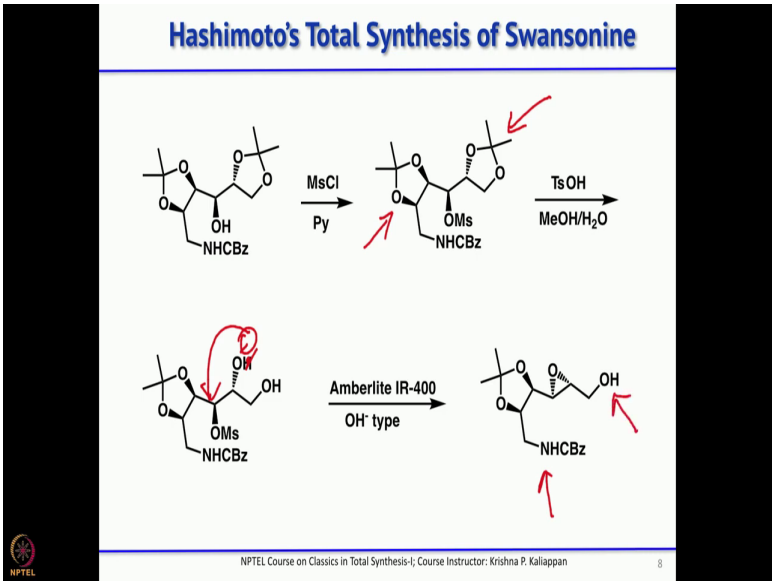

Then, now -OH is converted to the mesylate, then selectively you can remove this acetonide in the presence of the other one ok. This is a terminal acetonide so, more exposed and that can be selectively removed by treating with para toluene sulfonic acid with methanol to get the diol.

Then, this on treatment with amberlite having both minus type so, that generates anion here and attacks carbon bearing mesylate in SN_2 fashion so, you get the epoxide. So, now, you have got the epoxide in place and already the nitrogen is also in place; what you should do? You have to homolog it with the primary alcohol.

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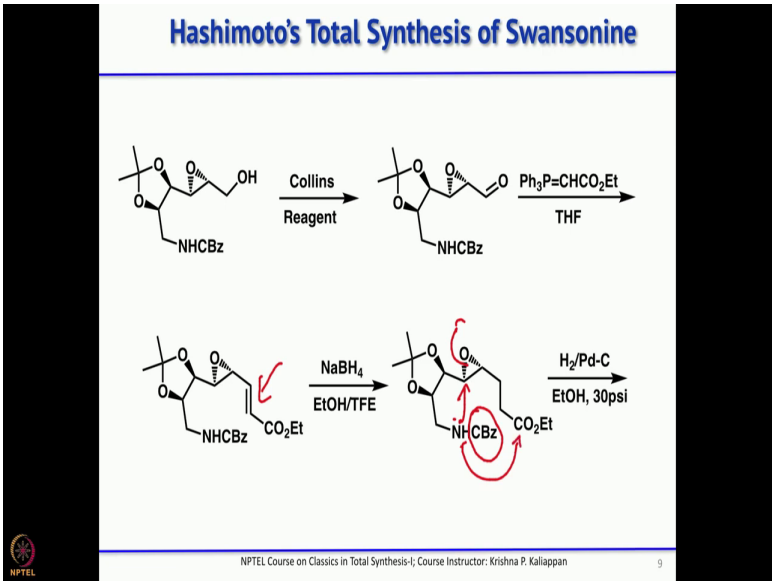

So, that is done by oxidation of the primary alcohol using Collins reagent to get the aldehyde. Then, you do the stabilized Wittig and homolog it to get the α- β unsaturated ester and this α- β unsaturated ester, you treat with sodium borohydride to reduce the double bond to completely saturated ester.

Then, the -CBz group ok, that is easily removed under hydrogenolysis condition. So, benzyl group gets cleaved, CO_2 goes and then what you get is the $-NH_2$. But, as soon as the $-NH_2$ is formed then this will open the epoxide and also the $-NH_2$ attacks the ester and in one part ok, in one part you get the bicyclic compound.

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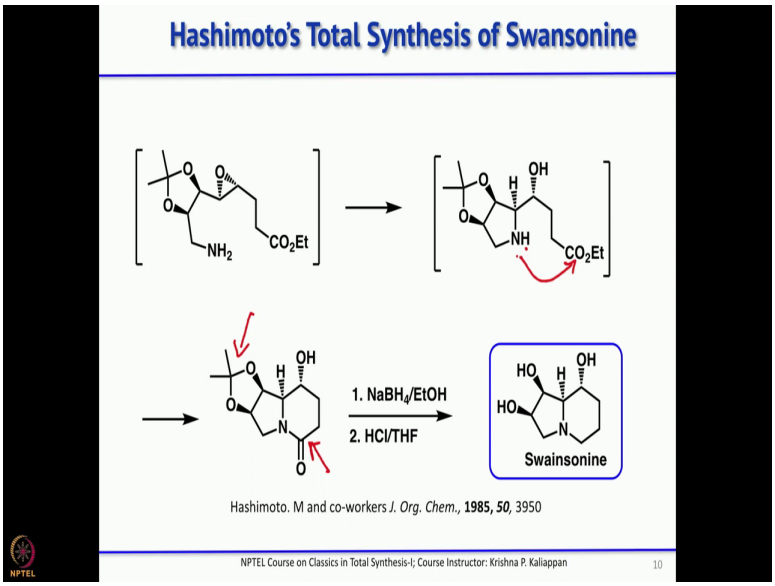

So, this is the first step, the -NH_2 attacking the epoxide to get the alcohol. Then, the -NH that is a pyrrolidine substitute of pyrrolidine attacking the ester to form the 6 membered lactam. So, now, what is left is to remove the carbonyl group of the lactam and remove the acetonide. So, with sodium borohydride ethanol you convert the lactam into corresponding amine and HCl THF. So, you remove the acetonide so, you get swainsonine.

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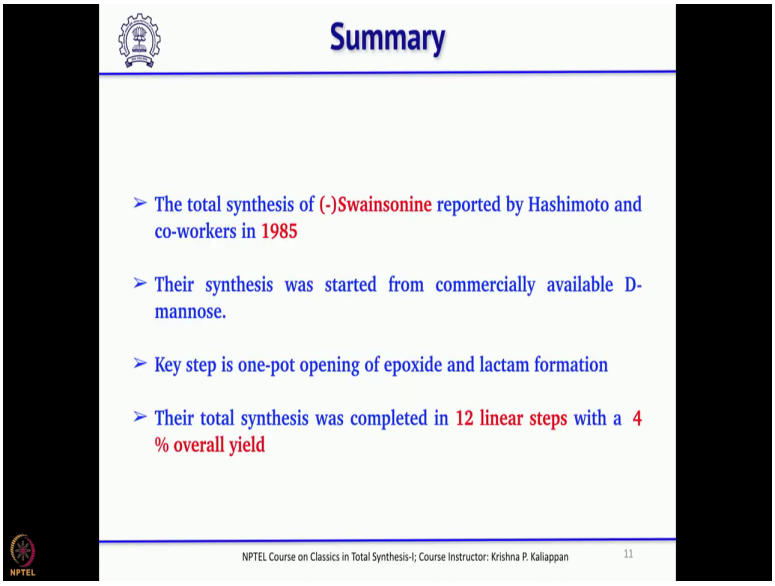

So, this was reported 37 years ago by Hashimoto's group and starting from D-mannose and overall he took about 12 linear steps and yield was about 4% ok. The key step was a one pot opening of the epoxide with a primary amine followed by lactam formation. So, in one part you basically they form 2 rings which are present in swainsonine.

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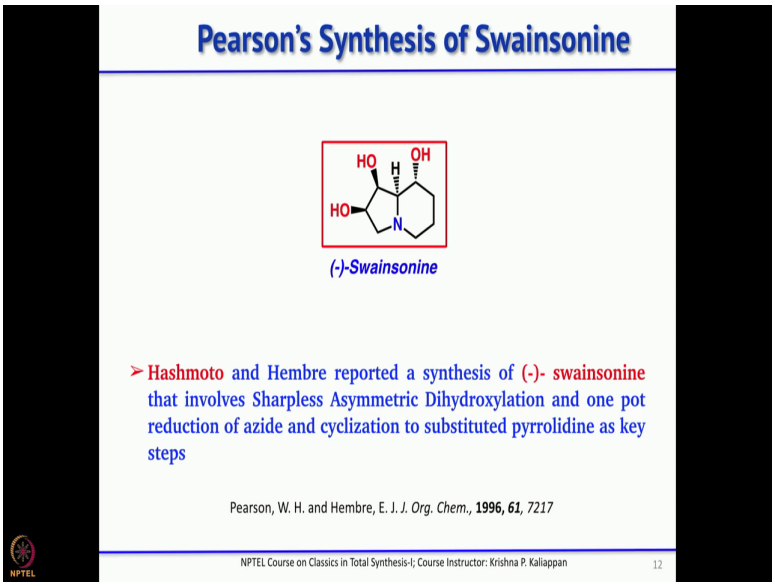

The second synthesis was reported by Pearson and Hembre and, this was the reported in 1996 and his synthesis started from again another simple carbohydrate called D-erythrose. And, the key reaction involved was sharpless asymmetric dihydroxylation and the second key reaction was reduction of azide and followed by cyclization to form the pyrolidine ring in one pot.

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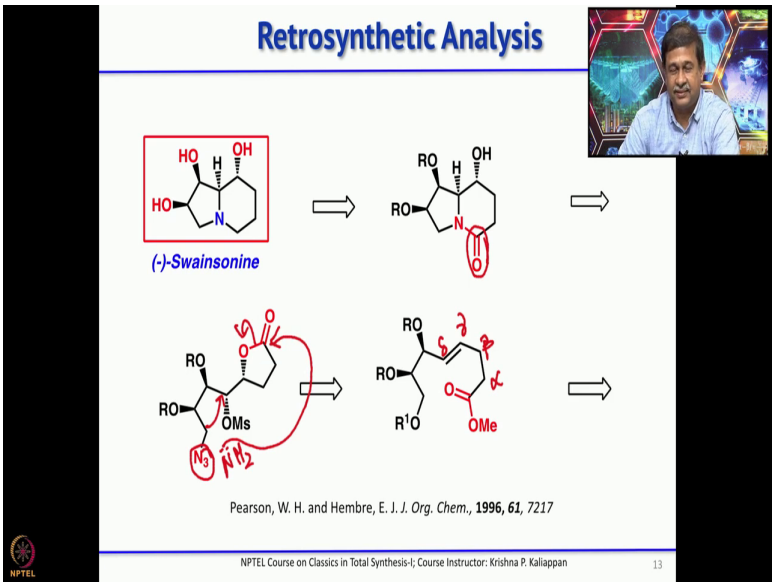

From a retro synthetic point of view, again the first disconnection was you know introduce a carbonyl group to form the lactam. Because, it is easy you know reducing the lactam to corresponding amine is very easy and straightforward and this type of lactam can be easily obtained by having a pyrrolidine as well as carboxylic acid. So, this can be obtained from this azide. So, this is the key reaction which I said.

So, what happens if you reduce this $-N_3$ to $-NH_2$ ok, this $-NH_2$ what will happen? It will straight away attack as soon as it is formed, it will attack the 5 member lactam and open this ok. So, what will happen? So, $-NH_2$ first it will attack the mesylate so, it forms the 5 membered ring, then that -NH attacks the lactone and open the lactone. So, you get the corresponding 6 membered ring.

This in fact, can be obtained from this γ, δ unsaturated ester ok, α, β, γ, δ unsaturated ester. If we have a γ, δ unsaturated ester and if you do a di hydroxylation, particularly if you do a Sharpless asymmetric di hydroxylation; so, what will happen? So, one of them immediately will cyclize to form a 5 member lactone and the other will be free alcohol. And, this γ, δ unsaturated ester or aldehyde can be easily obtained from the corresponding allylic alcohol through Claisen rearrangement.

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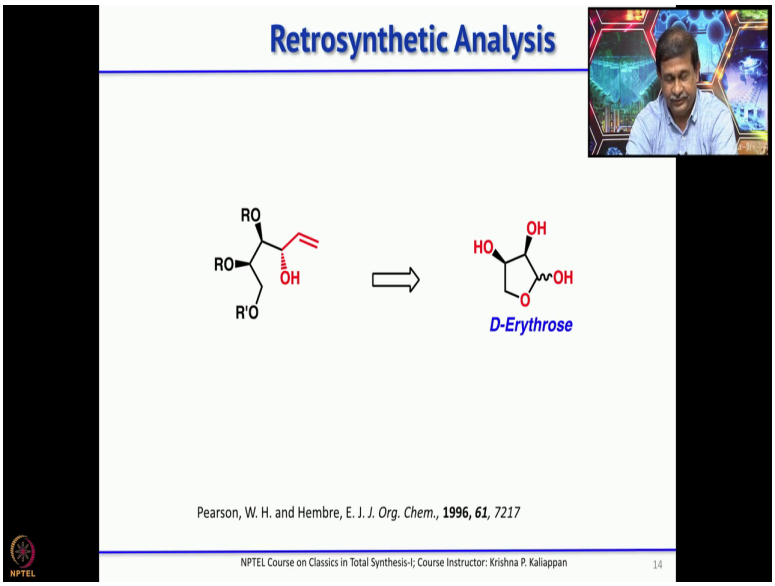

So, the precursor for this is this allylic alcohol. So, once you have this allylic alcohol, this can undergo intramolecular Claisen rearrangement to give the γ, δ unsaturated ester. And, this can be easily obtained from erythrose which is commercially available.

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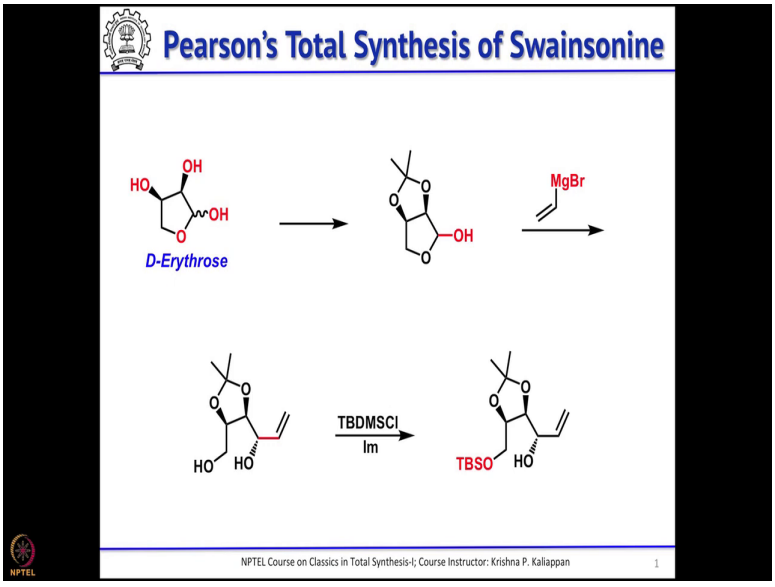

Now, let us see how this molecule was synthesized by Pearson's group. So, they started with D-erythrose. So, you take D-erythrose and then directly protect it with acetone, you will get this acetonide. Then, you treat with vinyl magnesium bromide so, that will give

you the corresponding diol ok. So, once you have this diol, then you can selectively protect the primary alcohol as TBS ether ok.

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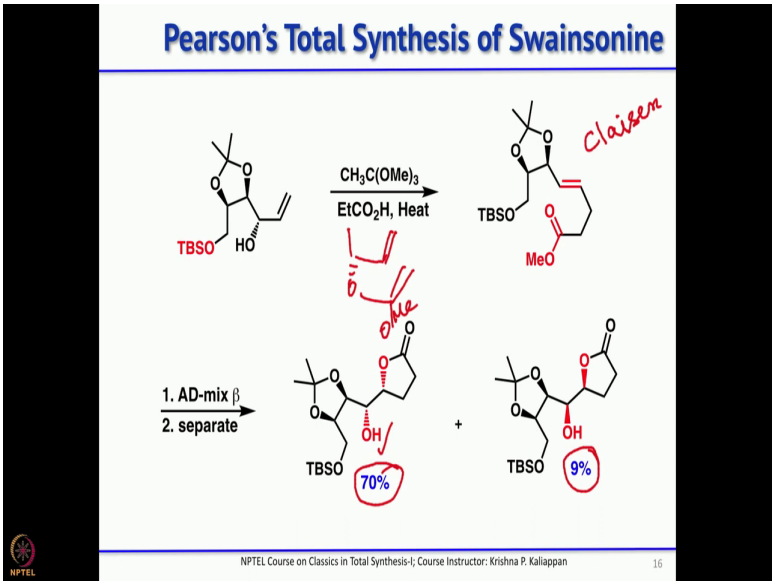

You can take this diol and treat with TBDMS chloride and imidazole, you protect the primary alcohol as TBS ether. Now, the allylic alcohol on treatment with tri methyl ortho acetate, the presence of catalytic amount of propionic acid undergoes a Claisen rearrangement to give the γ, δ unsaturated ester. So, this is the result of Claisen rearrangement ok and that goes through this intermediate.

So, once you have this γ, δ and saturated ester, then Sharpless asymmetric di hydroxylation gives a diol. And, one of the alcohol immediately attacks the ester and forming a 5 member lactone and the secondary alcohol which is formed can be easily mesylated ok. So, here as you can see there are 2 isomers, the α diol was obtained in 70% and β diol which was obtained in 9%. The α diol is the one which is required.

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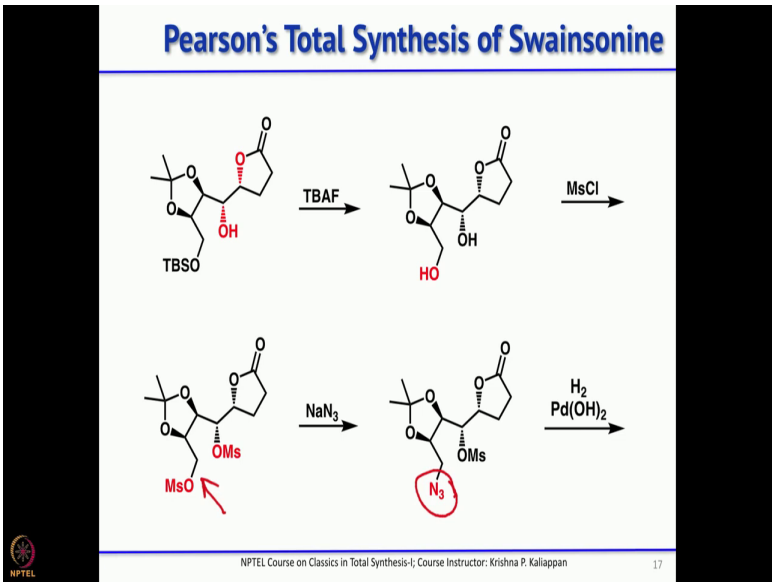

So, he took the TBS ether and removed the TBS group with TBAF to get a diol and the diol upon treatment with mesyl chloride, he got the di mesylate. Once you have the di mesylate, the primary alcohol can undergo SN_2 reaction with sodium azide. So, the mesylate was removed and you replace it with N_3. Now, the key reaction where the $-N_3$ was hydrogenated to get $-NH_2$ and that $-NH_2$ intramolecularly attack the carbon bearing mesylate to form the 5 membered pyrrolidine ring, followed by opening of the 5 member lactone to get the corresponding 6 membered one.

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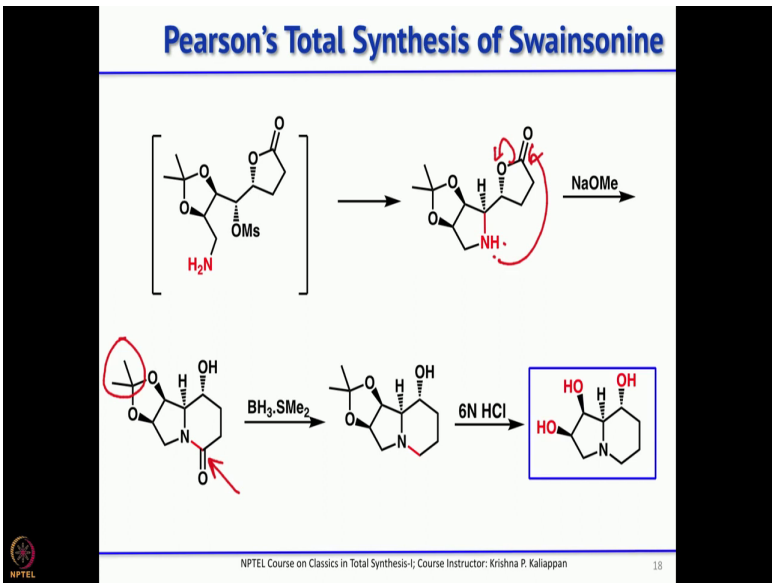

So, this is the first step and followed by intramolecular attack of this -NH to open this to give a 6 membered hydroxy lactam. So, now what needs to be done is you have to remove the carbonyl and also remove the acetonide. So, that is straightforward, if you treat with borane dimethyl sulfide the lactam becomes corresponding amine and then treat with dilute HCl so, you get swainsonine.

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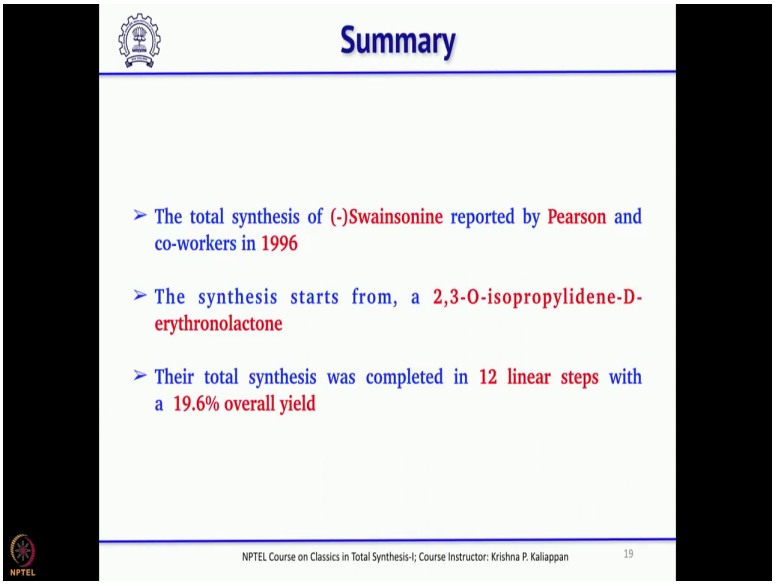

So, overall this particular synthesis reported by Pearson in 1996 started from erythrose and involve about 12 longest linear steps. However, the yield is quite good and they could get about 20% overall yield.

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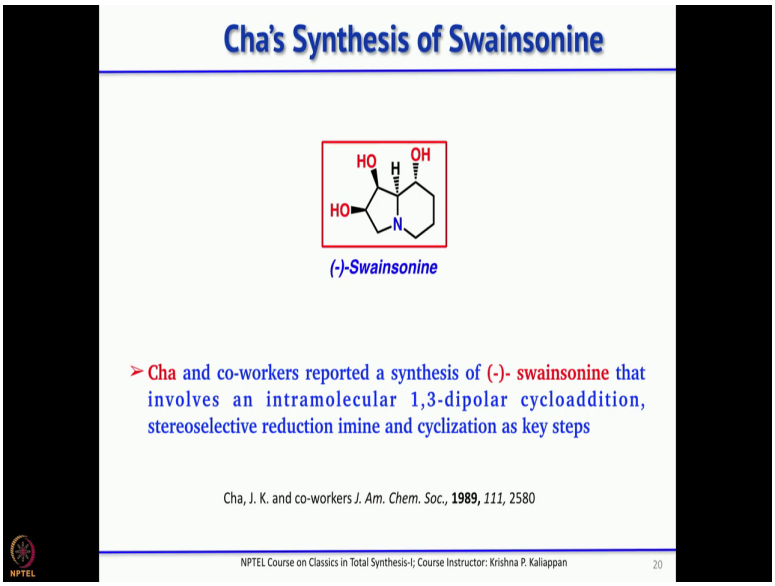

The third synthesis again as I said was started from commercially available D-erythrose and this was reported by J K Cha. But, the key reactions are 1, 3 dipolar cycloaddition between an azide and a double bond. So, this is an intramolecular 1, 3 dipolar cycloaddition. Then, the second key reaction was highly stereo selective, reduction of imine and as soon as the imine is formed, imine is reduced its cyclises to form the lactam.

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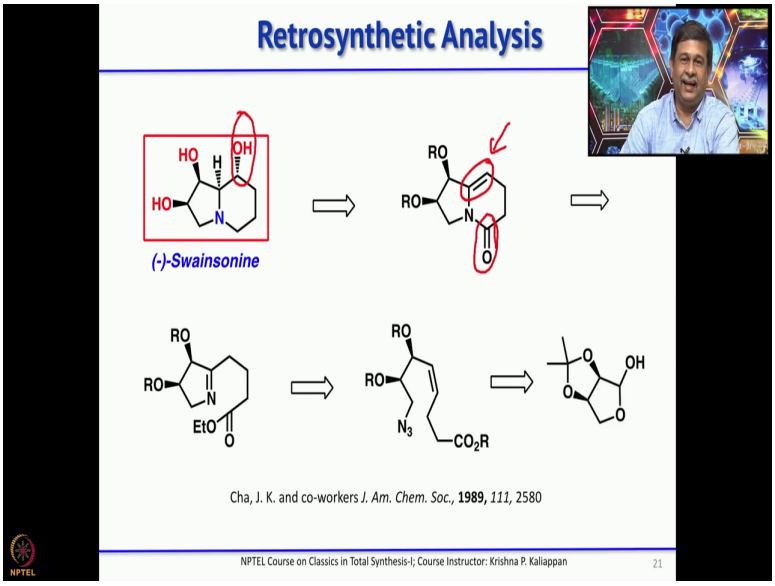

So, the retro synthesis again starts with the similar you know formation of the lactam, as you know the lactam can be easily reduced, but at the same time he also has a double bond. So, this double bond one can do a hydroboration to introduce the hydroxyl group, that this particular retro synthesis involves two key reactions. One removal of the lactam to the corresponding 6 membered piperidine ring and hydroboration of the double bond to give the corresponding hydroxyl group.

And, this can be easily obtained from this imine, just you know you just it forms inamine and then cyclises and that can be obtained from the corresponding azido alkene ok. This azido alkene undergoes an intramolecular 1, 3 dipolar cycloaddition followed by extrusion of nitrogen will give this imino compound and this can be obtained from the corresponding lactam.

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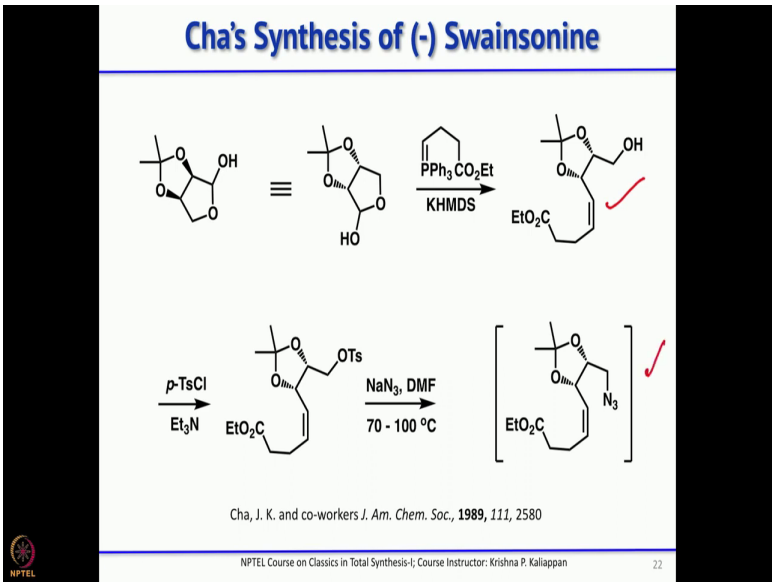

So, the synthesis reported by Cha started with D-erythrose and this one can write like this and if you do a Wittig reaction and you get this cis double bond. And, convert the primary alcohol into tosylate or mesylate because you have to convert that into a good leaving group.

Then, treat with sodium azide you get the corresponding azide. So, when you do this SN_2 reaction so, normally you have to heat it around 70 to 100°. So, that time not only SN_2 displacement took place, but also it underwent an intramolecular 1, 3 dipolar cycloaddition.

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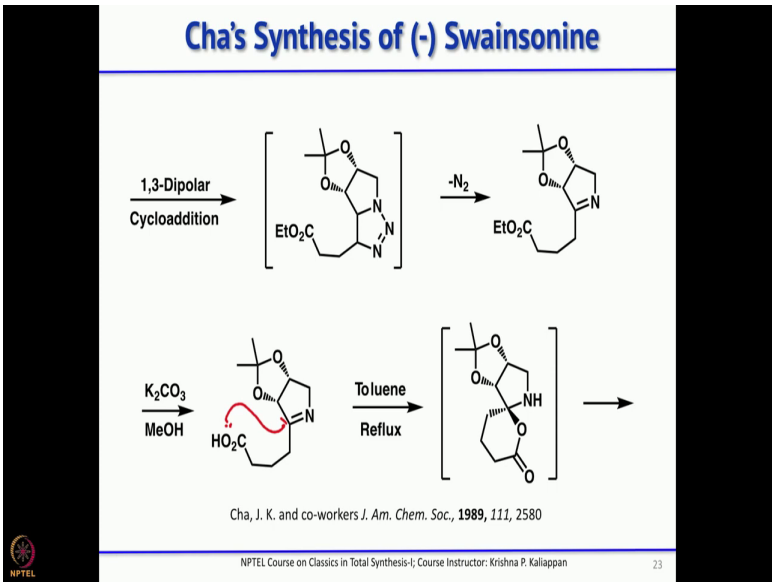

And, it did not stop there, once the intramolecular dipolar cycloaddition went, it underwent extrusion of nitrogen to form this imine ok. So, once you have this imine, if you treat with potassium carbonate methanol, you hydrolize the ester to corresponding carboxylic acid. This carboxylic acid when you reflex what happened the carboxylic acid adds to this imine to form a spiro lactone ok.

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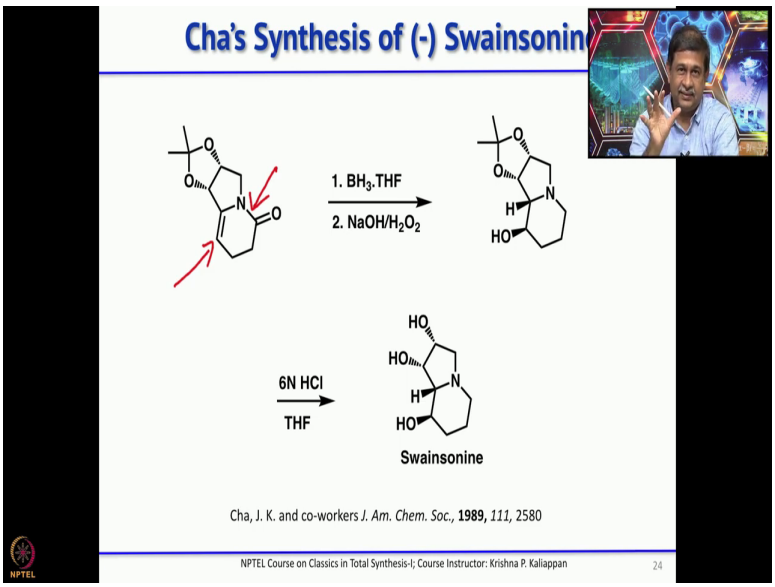

This spiro lactone upon further heating it undergoes a rearrangement to give this imine ok. So, it is very easy, it undergoes cleavage and followed by elimination and then

cyclization ok; 3 steps involved in this particular reaction to form this bicyclic compound.

Now, as you know what you need to do, you have to remove the carbonyl group and do a hydroboration. So, both are done in one pot ok, one when you treat with borane THF; you know borane THF is known to convert lactam to corresponding amine ok. And, also if you have a double bond, that will undergo hydroboration. So, both reactions are done in one pot to get this, now just removal of the acetonide gives swainsonine ok.

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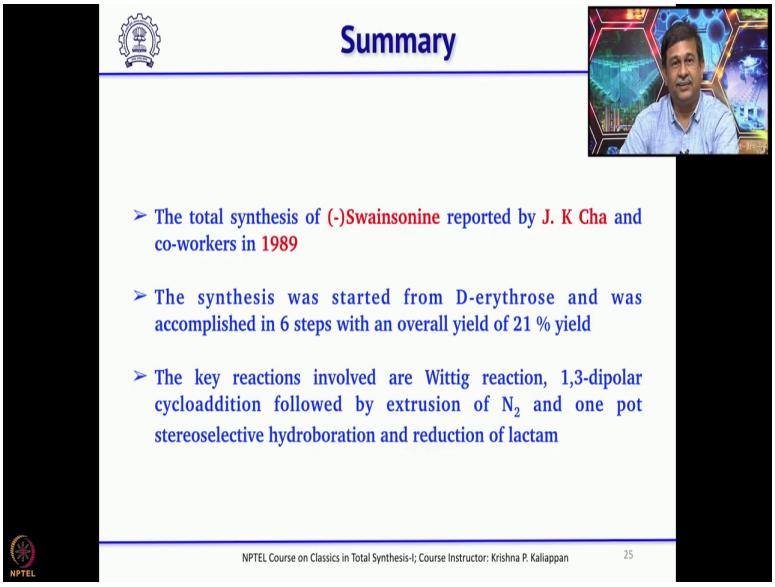

So, these three synthesis if you look at, all the three synthesis started with chiral starting material ok, 2 started with erythrose, the third one started with erythrose, the second one started with erythro lactone and the first one started with D-mannose. Here, Cha reported the total synthesis of swainsonine in 6 steps and with an overall yield of 21% ok.

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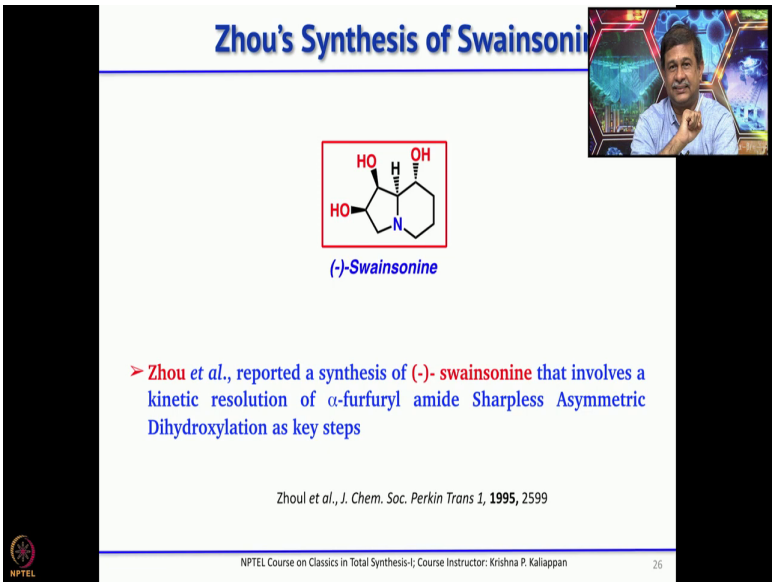

The fourth synthesis was reported by Zhoul and here the key reactions are Sharpless asymmetric dihydroxylation and also a kinetic resolution ok. So, a kinetic resolution of furfuryl imine ok. So, we know if we have a furfuryl alcohol then one can do Sharpless kinetic resolution. So, here instead of alcohol, it was done on NH-Ts ok, let us see how they have done.

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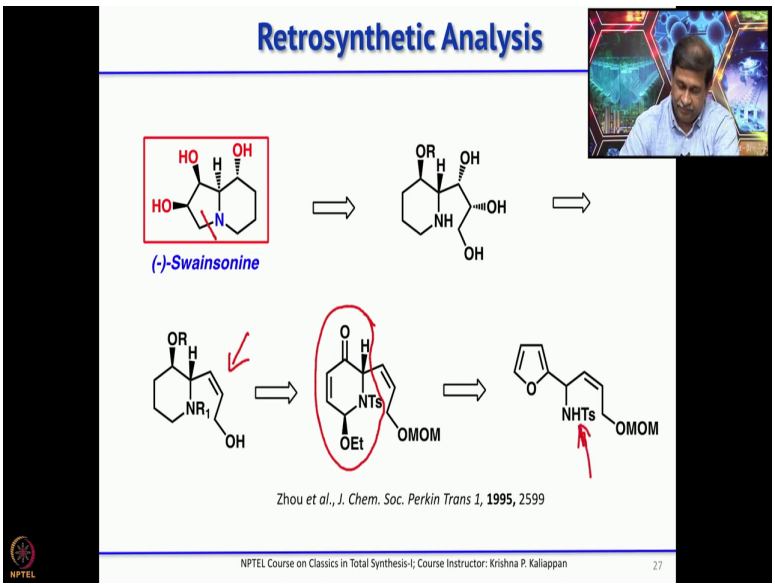

So, from retro synthetic point of view, this is the first disconnection ok. This is the first disconnection to get the corresponding triol and the triol can be obtained from this allylic

alcohol by sharpless asymmetric di hydroxylation. And, this in principle can be obtained from the 6 membered lactam and this 6 member lactam is obtained from the corresponding furfuryl amine ok, the tosylated amine and this is obtained from simple furfuryl.

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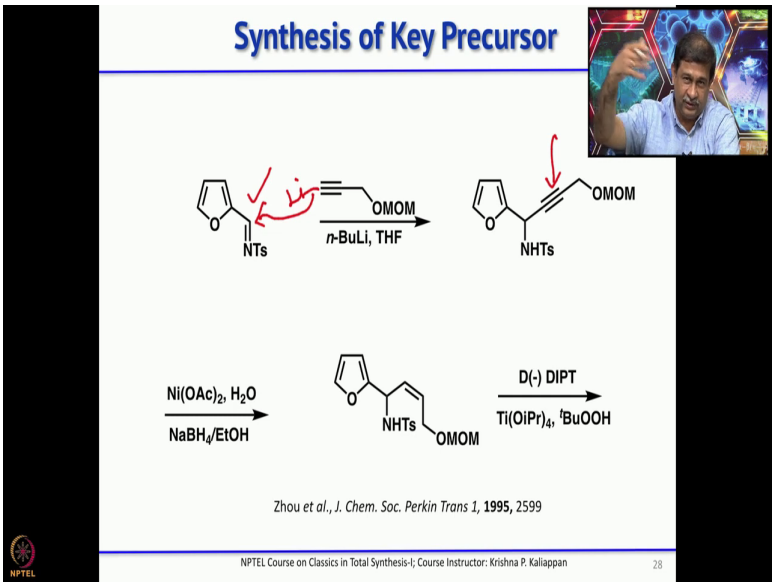

So, his total synthesis started from furfuryl and then you convert that into corresponding imine by treating with para toluene sulfonamide ok, it is a Schiff base. Then, you add the lithium derivative derived from propargyl alcohol protected propargyl alcohol. The MOM protected propargyl alcohol, if you treat with butyl lithium you get this lithium species; that adds to the imine and you get this compound.

Now, you have a you have a triple bond, the triple bond can be reduced to get a cis double bond and this was done with mixture of nickel acetate and sodium borohydride to get the cis double bond and here comes the key reaction that is kinetic resolution. So, if you use di isopropyl tartrate, titanium isopropoxide, tertiary butyl hydroperoxide; so, which is normally used for Sharpless asymmetric epoxidation and kinetic resolution ok, of course, you have to use molecular sieves and calcium hydride.

So, all these were used for the kinetic resolution. So, it not only resolves, but also it undergoes Achmatowicz rearrangement ok. The Achmatowicz rearrangement product is the one which he further carried out for the synthesis of swainsonine.

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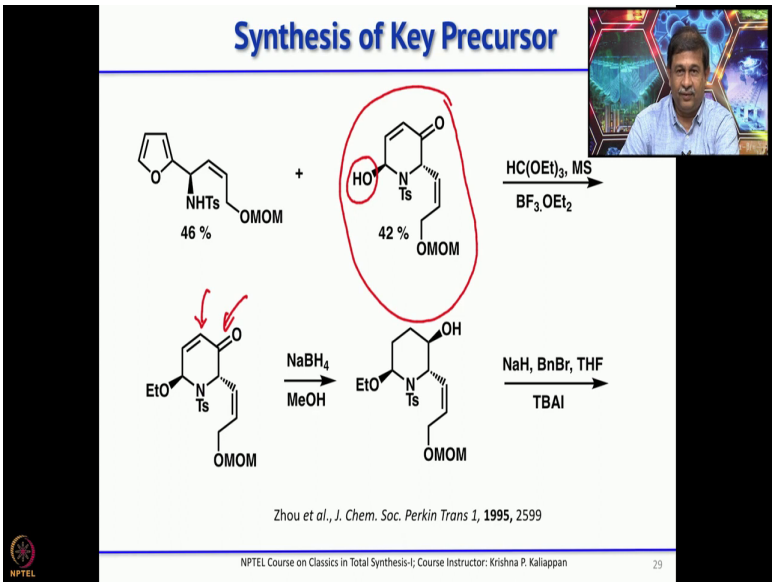

So, this is the simple kinetic resolution and this rearranged product is the one which he proceeded further for the total synthesis of swainsonine. So, now, once you have this compound, the next step is convert this -OH into -OEt ok. You treat with triethyl orthoformate and Lewis acid like -BF_3 etherate in the presence of molecular sieves. So, the -OH that is aminol is converted into corresponding ether ok.

Once you have this ether, then sodium borohydride methanol. So, sodium borohydride methanol not only can reduce the ketone, but also can reduce the double bond. If you take excess sodium borate methanol, it can do both. So, that is what happened. So, you get the alcohol. Now, the alcohol was protected as benzyl ether by treating with sodium hydride and benzyl bromide.

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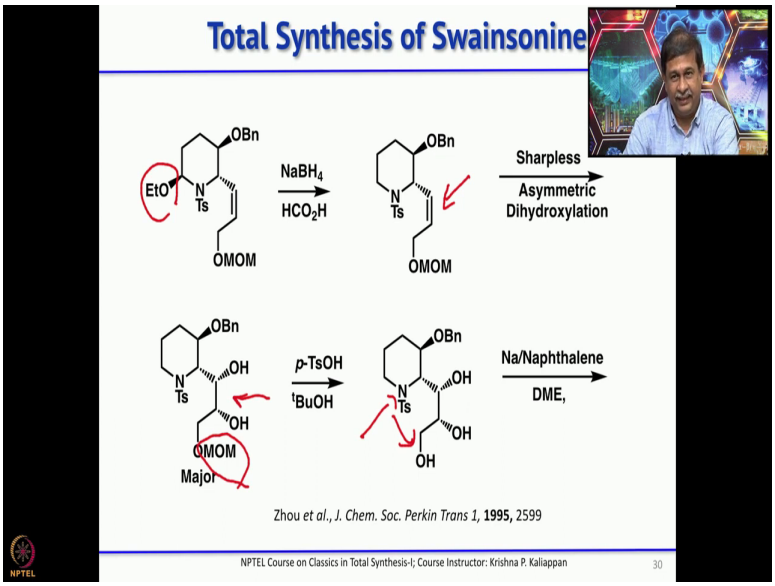

The next step is the removal of the -OEt group ok. So, if you treat with formic acid so, it forms the corresponding iminium and that iminium is reduced with sodium borohydride to form the 6 membered N-Ts piperidine ring ok. You have the cis double bond so, Sharpless asymmetric dihydroxylation will give the *syn* diol and that is a major product; of course, he also got little bit of β diol.

And, he took this β diol and then treated with para toluene sulfonic acid in solvents like tertiary butanol to remove the MOM group. So, basically he got the 3 hydroxyl groups now. So, now, what needs to be done? You have to remove this tosyl group and cyclise at this carbon to introduce the 5 membered ring. So, the tosyl group ok, how do you remove N-Ts? There are many methods. He use sodium naphthalenide so, that cleave the N-Ts to corresponding -NH.

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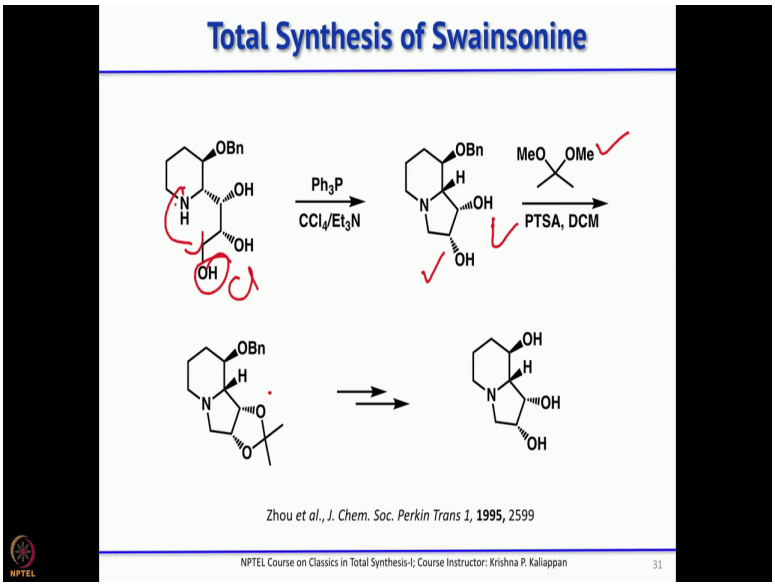

Now, this on treatment with tri phenyl phosphine and CCl_4. So, the tri phenyl phosphine and CCl_4 is a good reagent for converting OH to corresponding chloride ok. So, and it also is a good reagent for sometimes doing Mitsunobu like reaction ok. So, here what happens, this is converted into Cl and the lone pair on nitrogen immediately attacks and it forms a corresponding 5 membered ring. So, now, only one thing is left, that is removal of the benzyl group.

So, removal of the benzyl group can be easily done, but; however, what he did, he protected this diol as the corresponding acetonide. So, why he did that, was this compound was already converted into swainsonine in 2 steps. So, he wanted to compare the spectral data of this compound with already reported, that is why the compound which he made which is a diol and he converted that into acetonide by treating it di methoxy acetone. So, thus he completed a formal total synthesis of swainsonine and not starting from chiral starting material.

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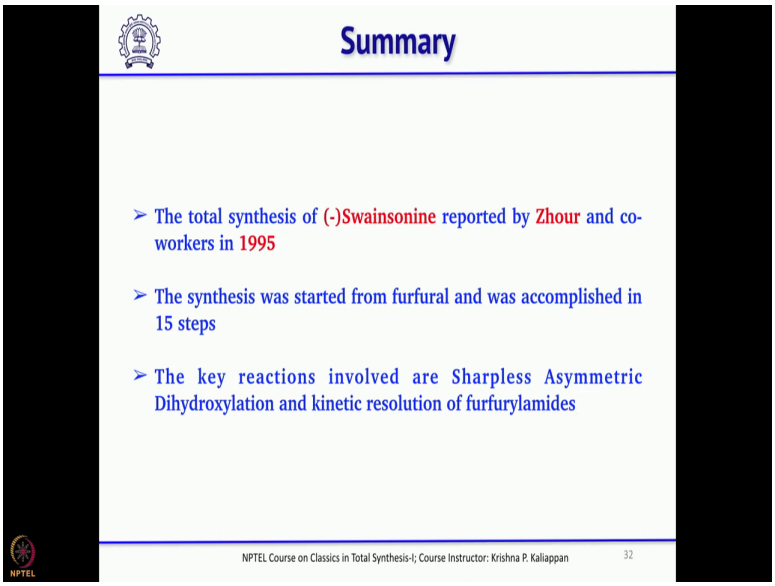

So, what he has done is he has used a kinetic dynamic resolution of furfuryl amine ok, followed by Sharpless asymmetric dihydroxylation as key reaction. The whole synthetic sequence took about 15 steps nevertheless. So, it was an interesting total synthesis where kinetic resolution was used as the key star ok. So, with this I will stop here and then we will continue our discussion on total synthesis of some more alkaloids in the next lecture.

Thank you.