Classics in Total Synthesis-I
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Lecture - 41
Staurosporine

So, good morning everyone. Today, we will talk about one very interesting alkaloid called Staurosporine as you can see.

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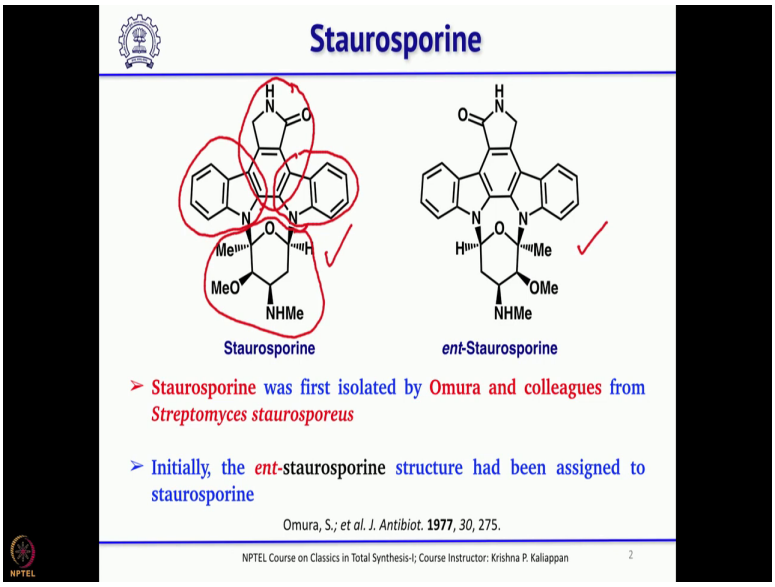

So, this is the structure of staurosporine. Actually originally, they assign the enantiomer of staurosporine as the structure of staurosporine. It was isolated from streptomyces staurosporeus by Omura and colleagues in 1977. And, if you look at this molecule, it is a very interesting combination of 3 important substructures.

One; obviously, you can see this is a sugar unit, ok. Then, you have 2 indoles, ok. One here one on the left-hand side. So, 2 indole moieties and then sugar in the bottom. Then, you have an iso indolinone, ok. So, this 2 indoles are connected to iso indolinone on the northern hemisphere and sugar portion in the southern hemisphere, ok. So, this is a very very interesting and challenging alkaloid.

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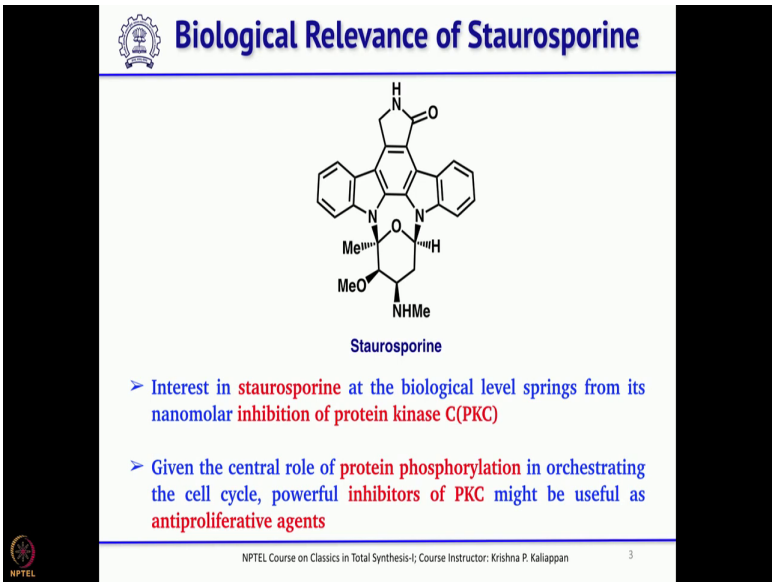

And, it also showed very interesting biological activities. For example, it showed protein kinase inhibition activity at very low concentration, a nanomolar concentration it showed activity. And, because of that, it was expected that it could be a potential anti-proliferative agent.

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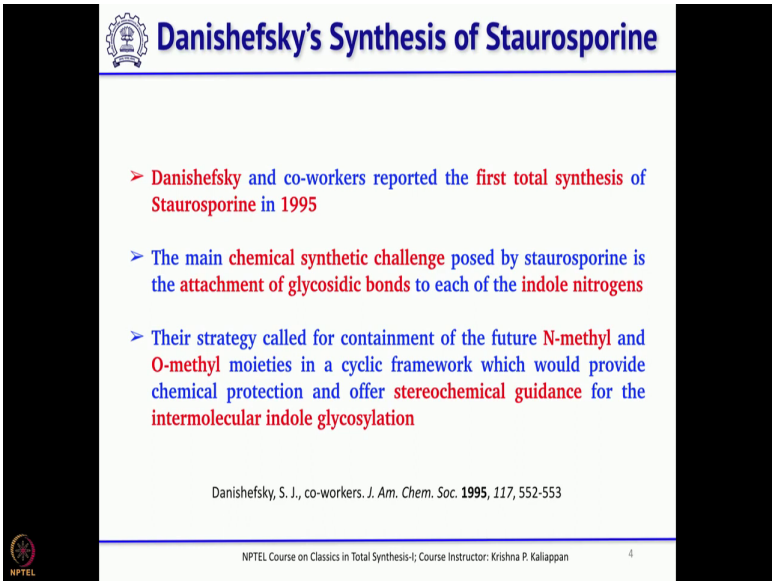

And, the first total synthesis of Staurosporine was reported by Danishefsky. And, here, the major synthetic challenge when you look at this molecule was the connecting these 2 indoles, ok the 2 indoles to that sugar portion, ok. So, you have to connect in such a way

that you have to get only the required enantiomer, that has been the major challenge. And, this all these challenges in addition to this were overcome by Danishefsky in his total synthesis.

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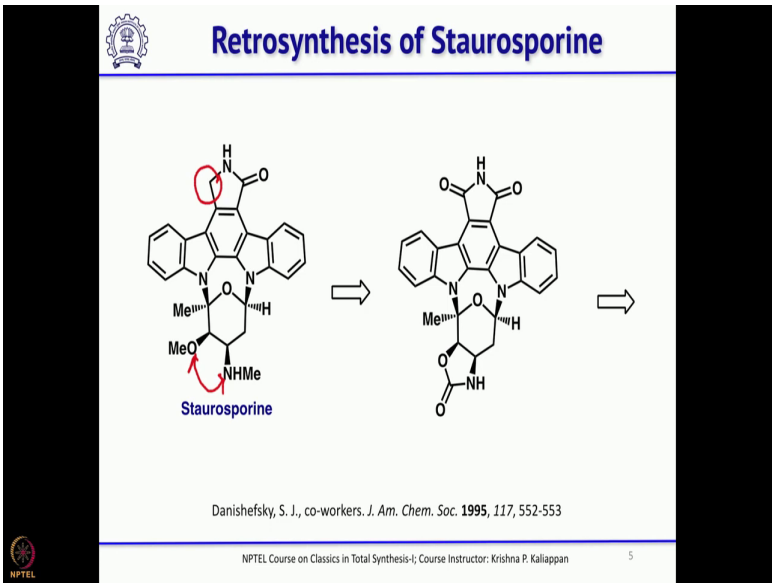

And, his retrosynthesis actually started by introducing a carbonyl group here, ok. So, later he thought it can be selectively reduced and when they reduce it may be possible to make both the staurosporine as well as the other epimer. And, he also connected this oxygen and nitrogen by a carbonyl group. So, it is a cyclic carbamate. So, this is a precursor while making staurosporine in the total synthesis of Danishefsky.

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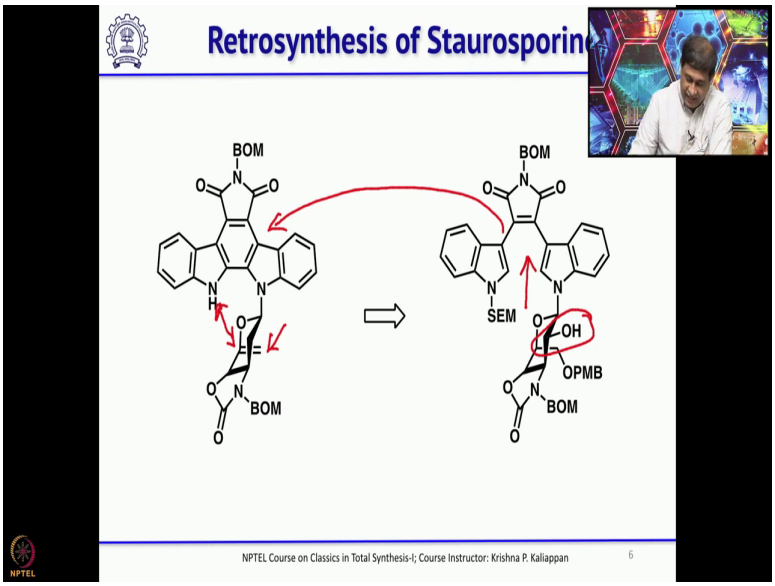

That was further disconnected, as you can see clearly, what he has done is he has removed this -CN bond, ok. So, this can be made using iodo. So, once you make iodonium ion here, ok, on the double bond then the nitrogen can open the iodonium ion to form a -CN bond as well as the -CH_2-I, that I can be easily removed with tributyltin hydride. And, this, as you can see you have a hydroxyl group, that is because, why that hydroxyl group is required?

You start with glucose, ok. So, that is why the hydroxyl group is there. And also, you can see here. Now, the 2 indole portions can be clearly seen. And this can be cyclized through a combination of electrocyclic reaction followed by aromatization, ok.

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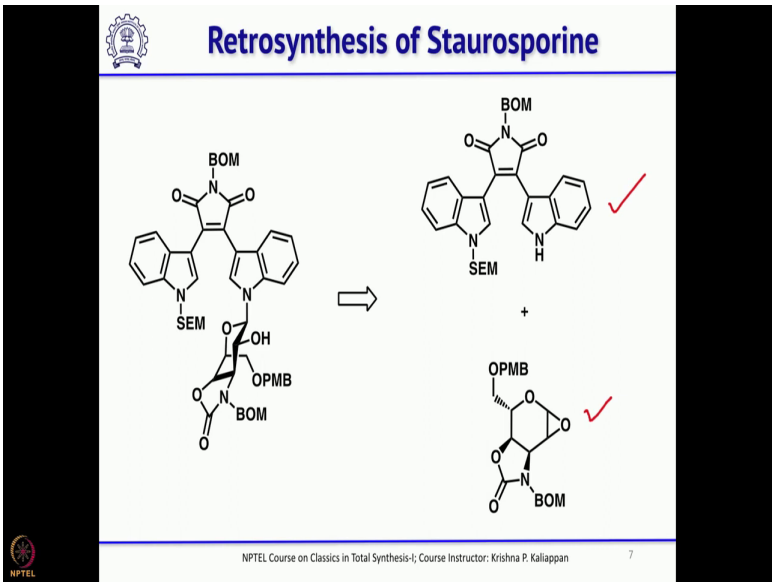

And this can be easily made from these 2 fragments. So, one is from bis indole moiety the other one is derived from the sugar moiety. So, basically it is derived from glucose, ok.

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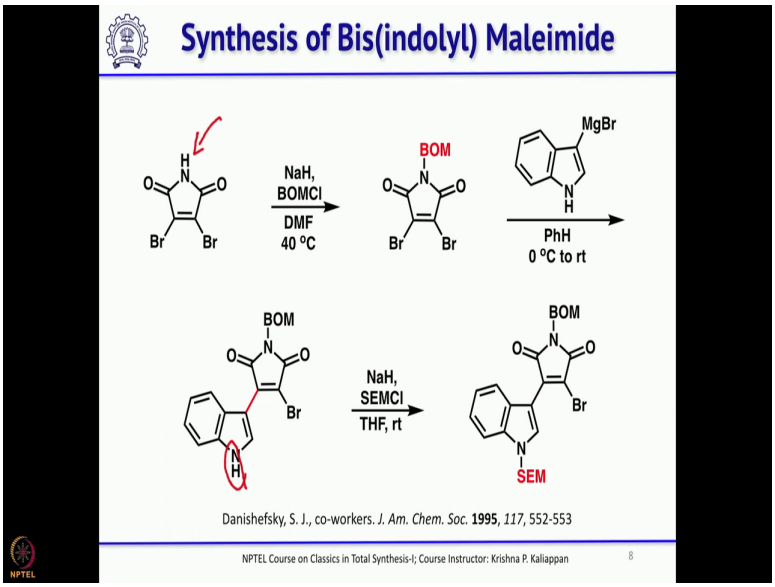

Now, let us see how he started his synthesis and how overall he accomplished the total synthesis of staurosporine. He started with this di bromo maleimide, ok and then you protected this nitrogen as N-BOM, ok, by treating with Benzyl-oxy methyl chloride and

base. Then, he did two successive 1, 4 addition followed by elimination, first with this 3-Indolyl magnesium bromide.

So, the addition of 3-Indolyl magnesium bromide took place in a 1, 4 fashion, while coming back the bromide will go. Then that -NH was protected as SEM, ok by treating with Sodium hydride and SEM chloride. Now, the second 1, 4 addition and elimination was done with another Indole-3-magnesium bromide.

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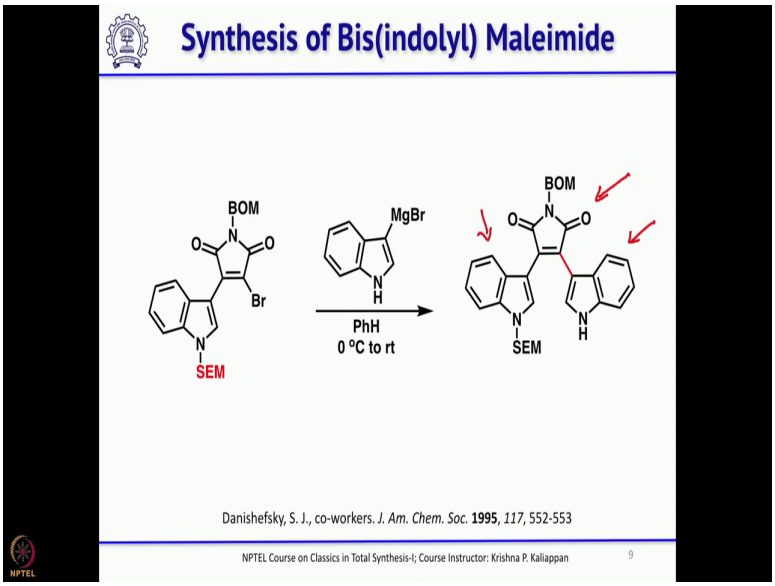

So, now, you can see the 2 indole moieties are attached to the maleimide, ok. So, what needs to be done? Now, you have to add the sugar unit in the southern side.

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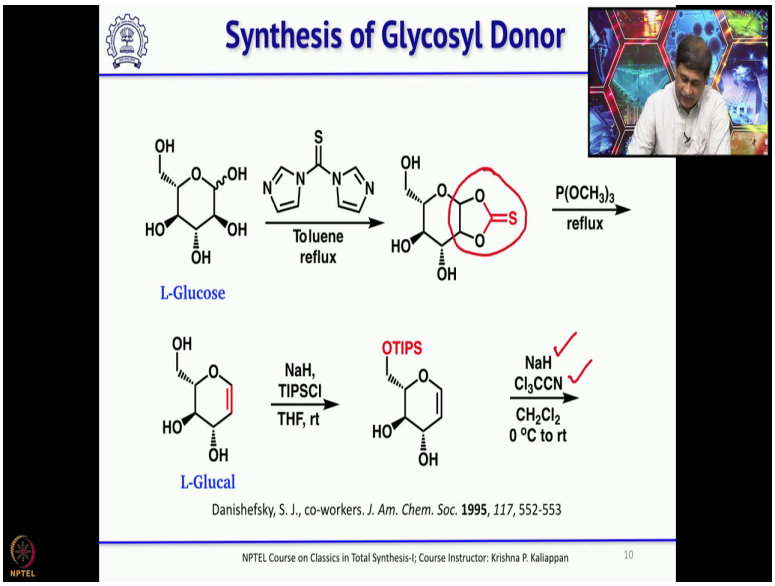

So, before that you have to prepare the sugar unit. So, he started with L-Glucose opposite to the one which is commercially available. So, the L-Glucose was treated with carbonyl di imidazole to form this cyclic thiocarbonate, ok. So, that is a 1, 2-diol. And, then when you treat with CDI that is Carbonyl di imidazole, it can form the cyclic thiocarbamate.

The reason for making the cyclic thiocarbamate is to remove these 2 hydroxyl groups to introduce a double bond. So, that was easily done when you treat with a trimethyl phosphite. So, the trimethyl phosphite or triethyl phosphate is known to do this job. So, you could easily introduce the double bond, ok. So, this is called L-Glucal, ok that was a starting material. In fact, ok.

The L-Glucal once you have, the primary alcohol can be easily selectively protected as TIPS ether by treating with Sodium hydride and TIPS chloride. Then, you have the 2 secondary hydroxyl groups. This upon deprotonation with Sodium hydride followed by addition of trichloro acetonitrile, it forms trichloro acetimidates, ok.

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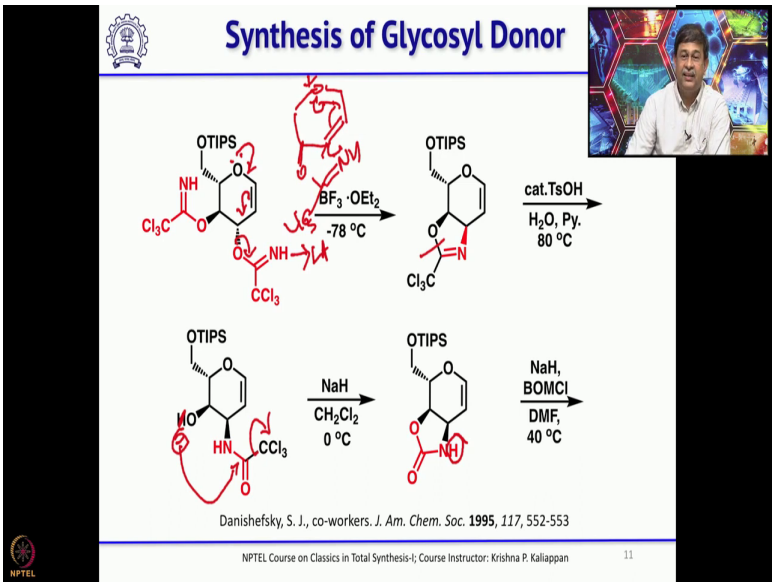

Then he treated with BF 3 etherates. So, when you treat this with BF_3 etherates, what happens? You can see, the Lewis acid can coordinate with this nitrogen; then the lone pair on the oxygen of L-glucal can come and then expel this Trichloro acetimidate. So, that will give you this intermediate, ok. Now, this nitrogen can neutralize the positive charge on the oxygen. So, you get a five-membered ring, ok.

And it also comes from the same β side. Now, if you hydrolyze this, just if you hydrolyze this you will get hydroxyl group and this side on the amide, ok. Then the next step is you simply treat with base, ok. If you treat with bases like sodium hydride, what will happen? It will form anion here. That will intramolecularly attack the carbonyl group and $-CCl_3$ minus which is a good leaving group.

So, that will lead to the formation of the carbamate, ok. Once a cyclic carbamate is there then this NH is protected as BOM. So, by treating with sodium hydride and benzyl oxy methyl chloride, ok.

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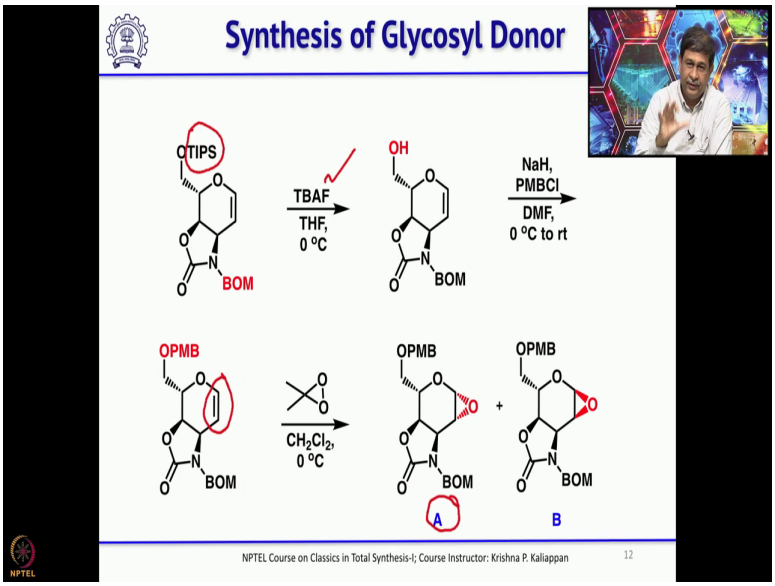

Now, the primary hydroxyl group which was protected as TIPS can be released. So, that was done easily by treating with a fluoride source like TBAF then, you protect the same primary alcohol with a sturdy protecting group like para methoxy benzyl group, ok. Then, you have to epoxidize this double bond, ok. This was done with dimethyl dioxirane so, when they did they got a mixture of these two epoxides, where the required one that is A was a major isomer. So, he took both the epoxide, ok.

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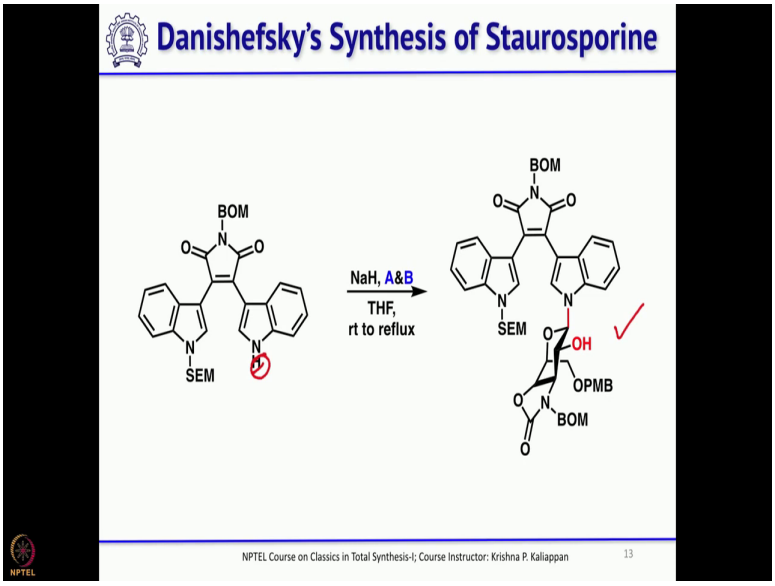

And then treated with the bis-indole which he has already synthesized. So, now, you take this compound and then treat with sodium hydride. So, it forms the N minus and that opens the epoxide. So, when it opens the epoxide, you get this as the major products.

I have written the sugar unit with the standard chair like conformation, ok. So, once you have this the next step is to remove the hydroxyl group, ok.

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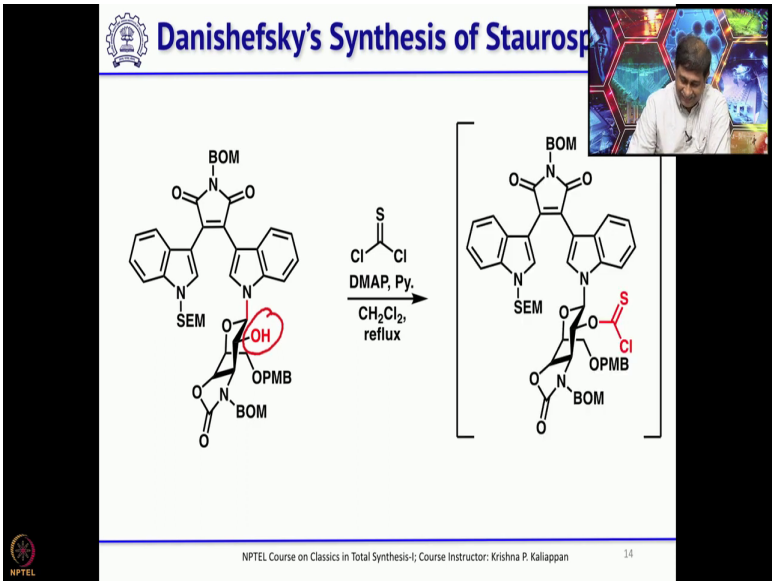

So, now once you formed the -CN bond using this epoxide opening, next the hydroxyl group is normally removed via Xanthate formation. So, it was treated with thiophosgene to get the half ester and this further addition of penta fluoro phenol gives this intermediate, ok.

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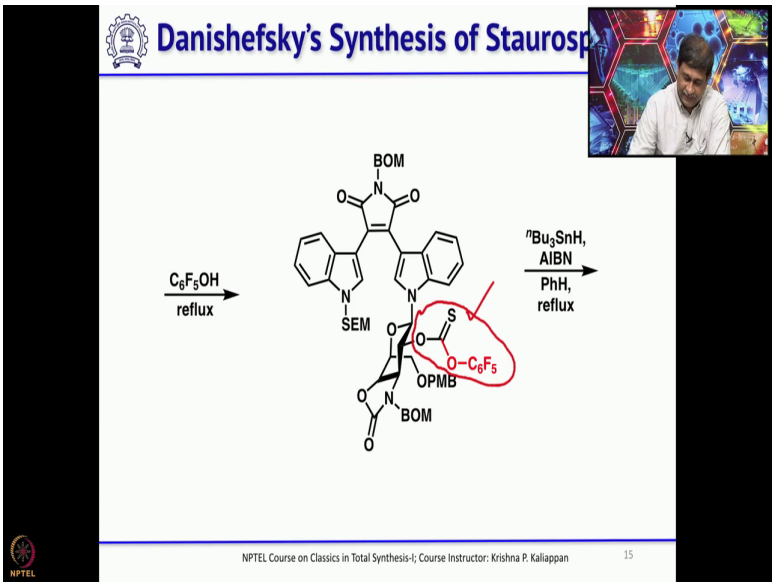

This upon treatment with tributyltin hydride and it undergoes elimination of the whole group to give a -CH_2 at that corner.

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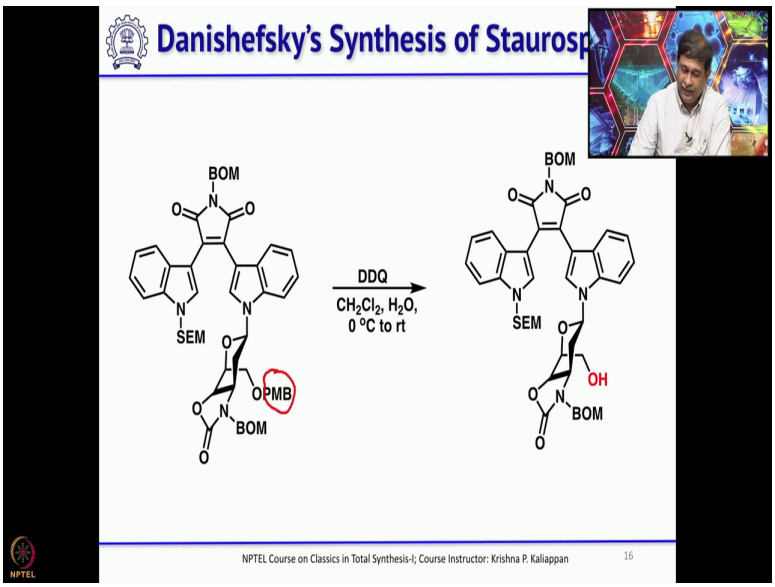

Basically, you have removed the hydroxyl group there, ok. Now, what is the next step? You have to connect the second indole ring with this sugar unit, ok. So, the first step is to remove the PMB, ok. So, because basically you want to convert that into -CH_2-I. So, first remove the PMB group with DDQ to get the primary alcohol.

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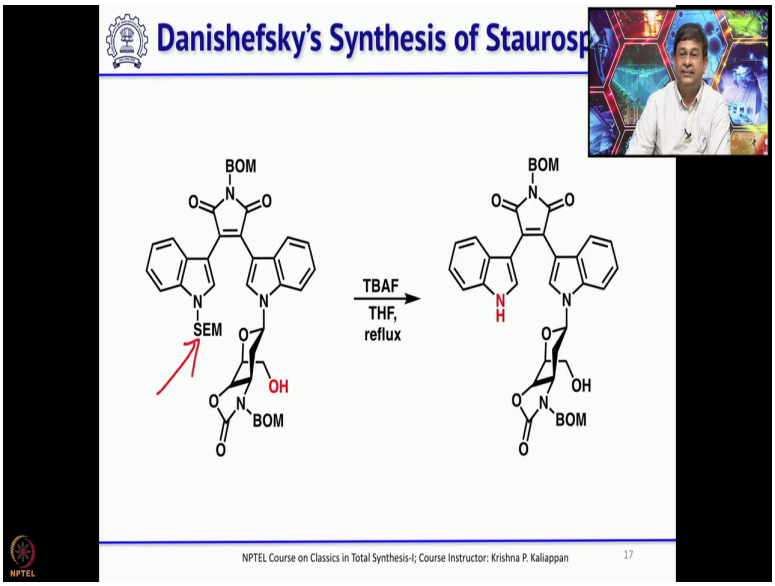

So, once you have the primary alcohol, then remove the SEM, using TBAF to get the NH.

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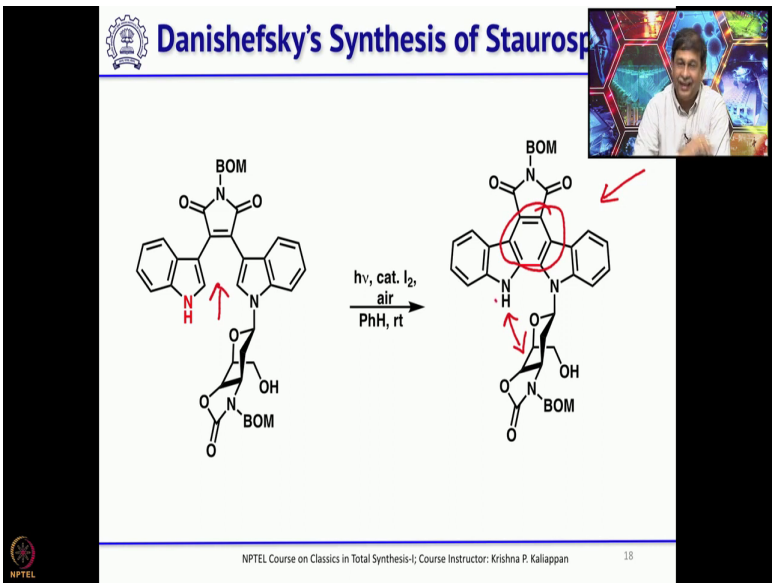

Then, you treat with photochemical condition, ok. Then, you subject this compound under photochemical condition in the presence of catalytic iodine. Why catalytic iodine and aerobic condition this reaction should be done because, once you do this electrocyclic ring closure of this hexatriene you get a cyclohexadiene, ok. This was

oxidized with catalytic amount of iodine, under aerobic condition to get this aromatic ring, ok.

So, now, you can see the top portion is done, ok; you attached this indole with maleimide. Now you have to connect these 2 carbons. So, these 2 atoms nitrogen and carbon.

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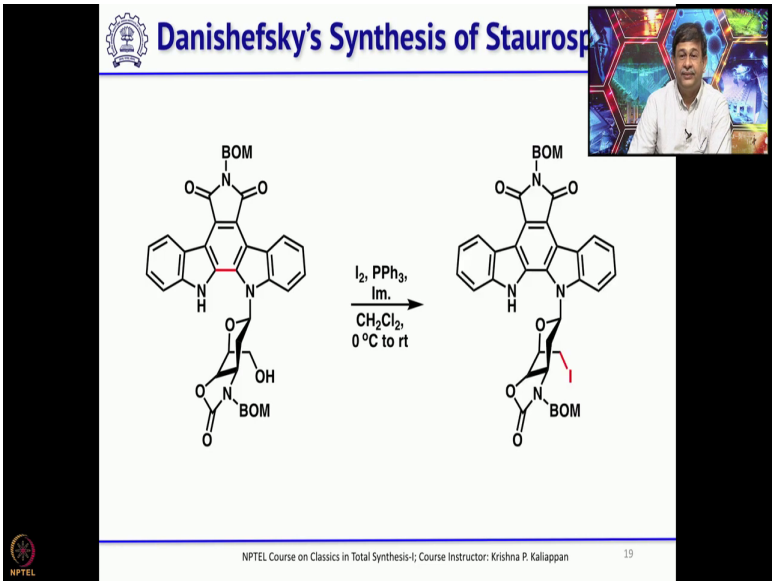

So, how we did? So, he converted the primary alcohol to -CH_2-I.

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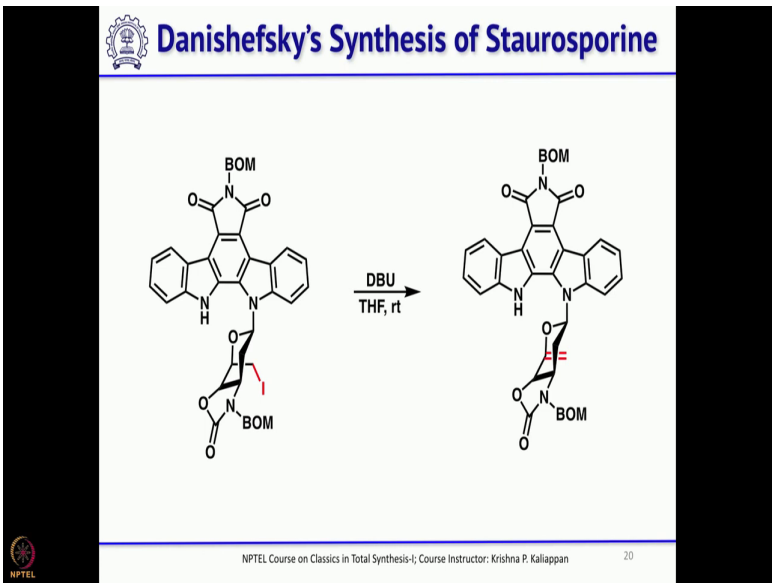

Then treated with base. So, the base underwent elimination of HI to form the corresponding enol ether, ok. So, once you have this enol ether.

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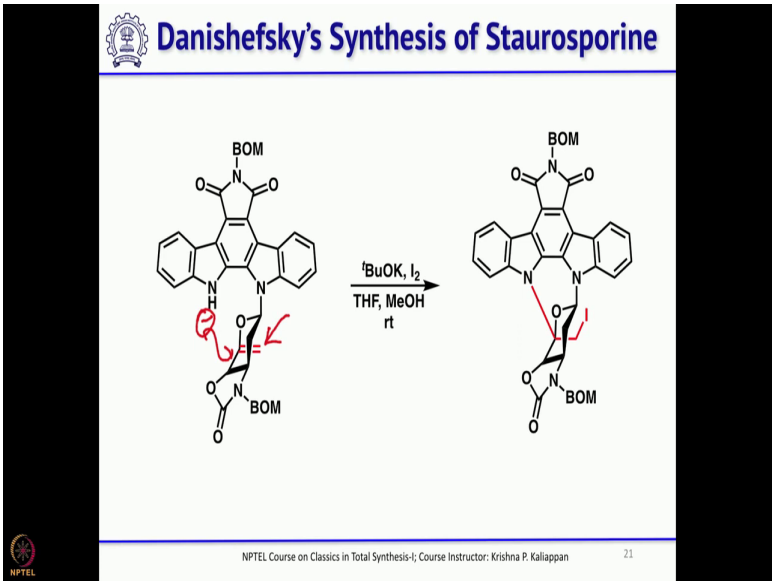

So, treatment with iodine and bases like Potassium tertiary butoxide, first iodonium ion will form then this N^- will attack and open the iodonium ion to give the $-CH_2-I$ at the same time, you can see the other endole also is attached to the sugar units. So, what is left? Now, the iodide should be removed to have the methyl group.

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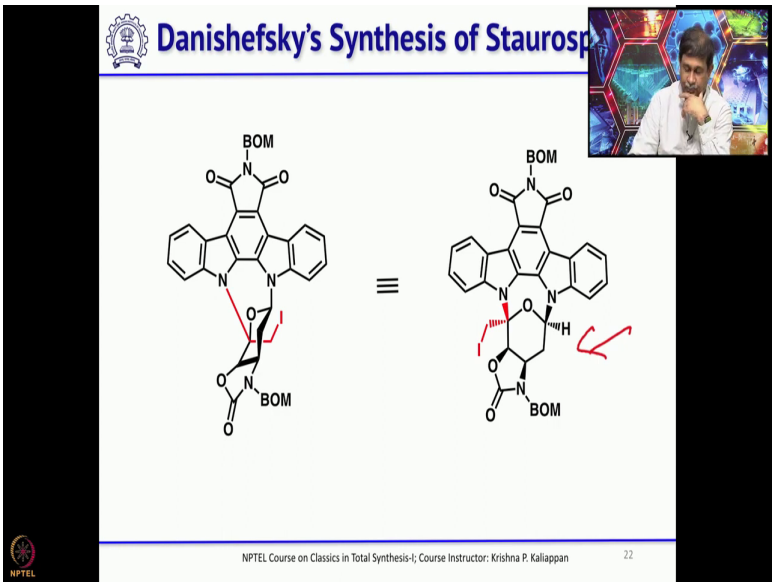

So, that was done with the tributyl tin hydride. So, you can see this is the structure which you would have seen in staurosporine.

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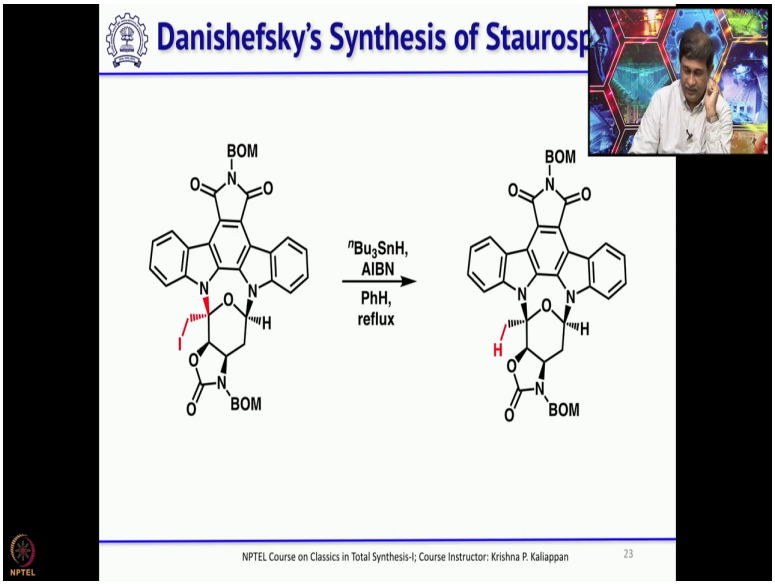

Now, remove the iodide, using tributyl tin hydride to get the methyl group, ok.

So, now what is to be done?

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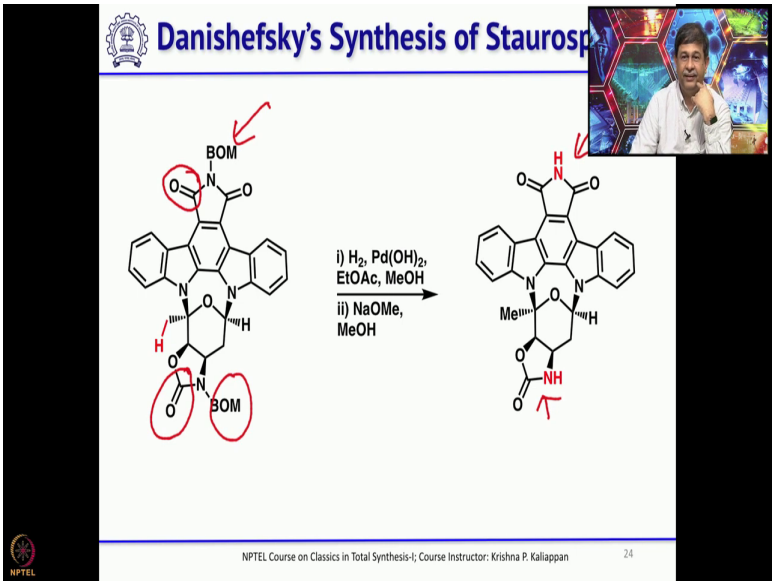

You have to remove this carbonyl and also remove one of this carbonyl and cleave the BOM group, ok. So, these are the things he has to do to complete the total synthesis of

staurosporine, ok. First, he has tried the hydrogenolysis. So, hydrogenolysis will remove both BOM group, ok. So, to get this carbamide as well as the maleimide.

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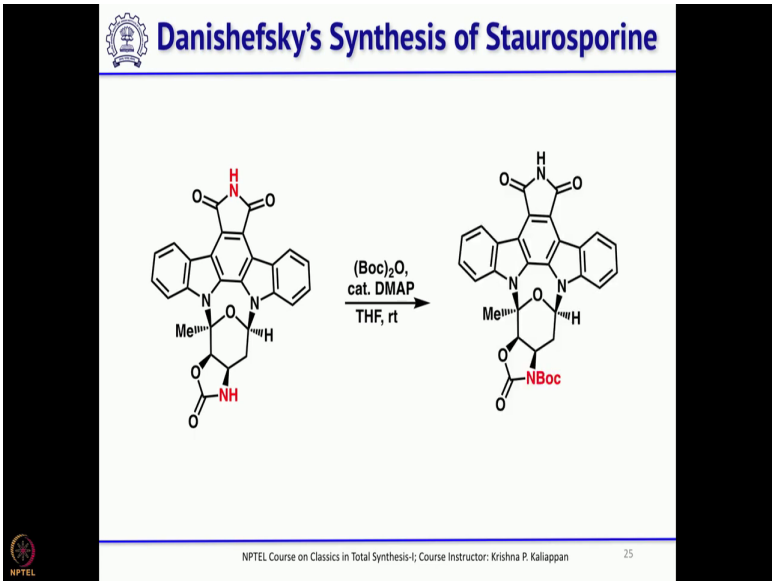

Then, you selectively protect the carbamide nitrogen as -N-Boc.

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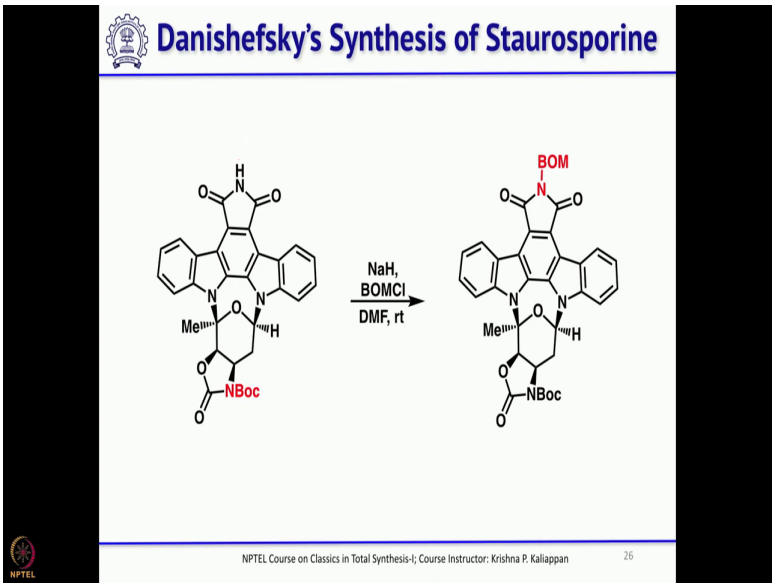

Then you do protect the melamine nitrogen as -N-Boc, by treating with sodium hydride and benzyl oxy methyl chloride.

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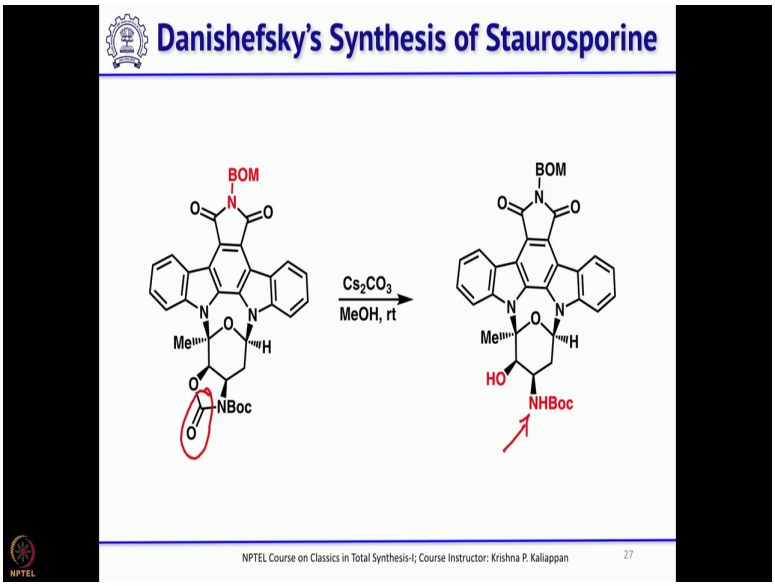

Now, you have to cleave or remove this carbonyl group. So, that can be done by treating with caesium carbonate and methanol. So, you get an amino alcohol and amine is protected as Boc. What is to be done? The -NH should be made as -NH-Me so; that means, the Boc should be removed and methylation should be done.

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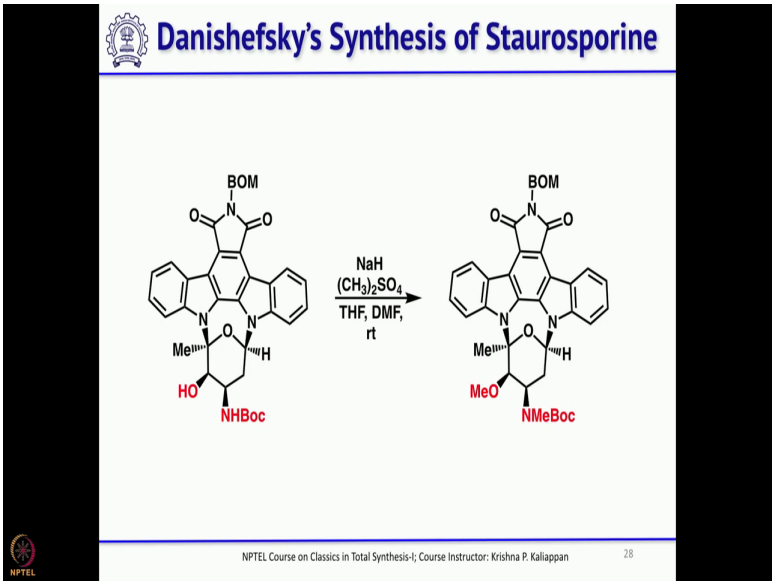

So, this was done by treating with sodium hydride and dimethyl sulfide to introduce the methyl group.

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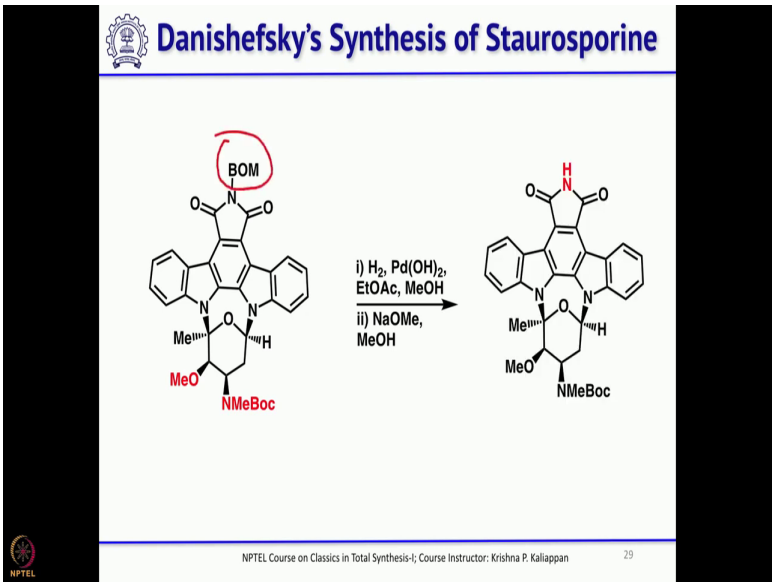

After introducing the methyl group then hydrogenolysis removed the BOM group.

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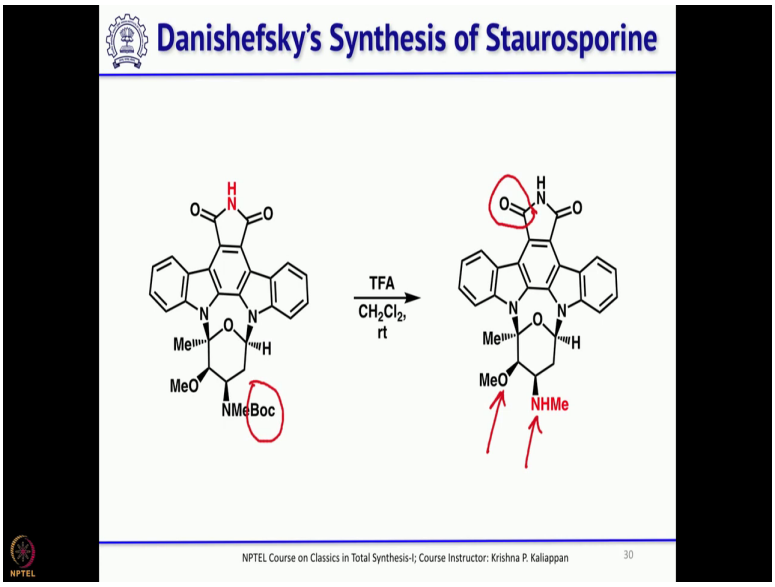

And if you treat with TFA, tri fluro acetic acid is known to remove the tertiary butyl oxy carbonyl group that is the Boc group. So, the Boc group was removed and you have the NHMe and OMe.

So, only one thing is left, that is selectively this carbonyl should be converted into CH_2 to complete the total synthesis.

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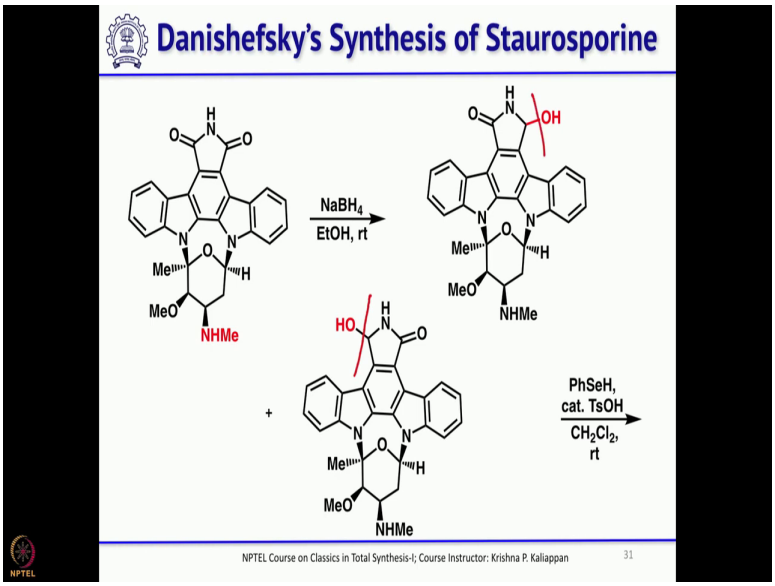

So, what he did? So, he reduced with sodium borohydride. So, it was known earlier similar compounds when you reduce sodium borohydride, one of the carbonyl groups can be reduced to corresponding alcohol, alcohol in the sense -CH-OH which we can call it as amidol, ok.

But what he got was, he got a mixture of both carbonyls getting reduced in 1:1 ratio there is no selectivity. Nevertheless, he moved ahead and further treatment with phenyl selenide in the presence of catalytic amount of toluene sulfonic acid, para toluenesulfonic acid you could cleave this C-OH bond and replaced with hydrogen.

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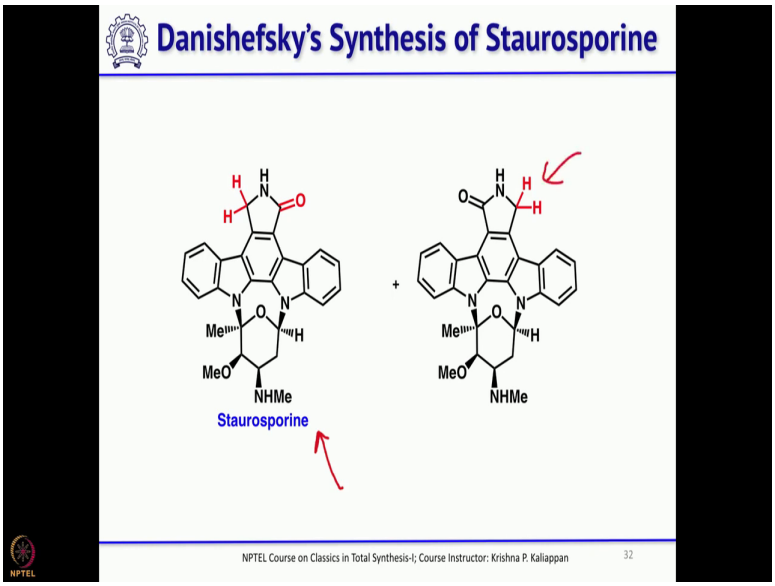

So; that means, he got a mixture of the naturally occurring staurosporine plus its other isomer in 1:1 ratio.

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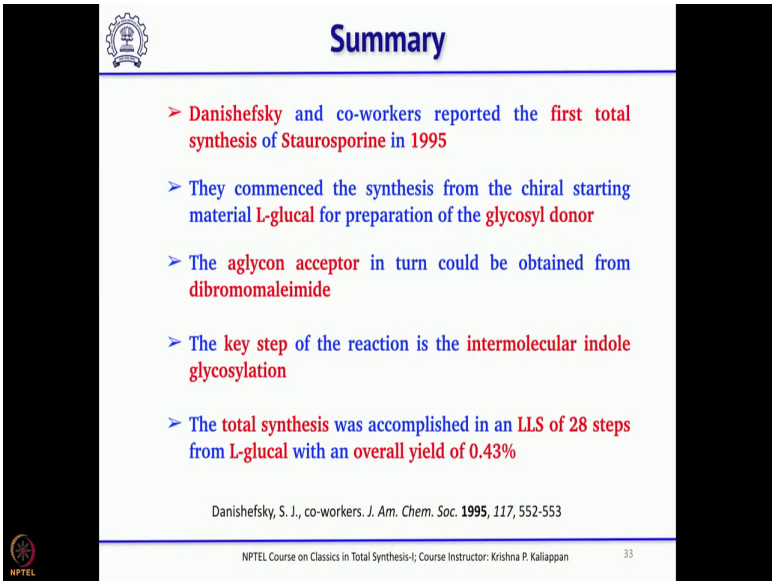

So, this is how he completed the total synthesis of staurosporine and as I said he started with L-glucal for the glucoside fragment. And, the tough fragment is started with di bromo N protected maleimide, then he attach the two indole units through 1, 4 addition followed by elimination.

Then the next key reaction which he used was the electrocyclic ring closure followed by aromatization to construct the central aromatic ring. Overall, he took about 28 steps starting from L-glucal and yield was close to 0.5%. Nevertheless, this was one of the very good total synthesis on an alkaloid which is quite complex; however, as the number of steps were more, there are many groups which were interested in the total synthesis of staurosporine to improve as well as reduce the number of steps.

So, one such report came from John Woods group that was reported a year after Danishefsky's report on the total synthesis of staurosporine.

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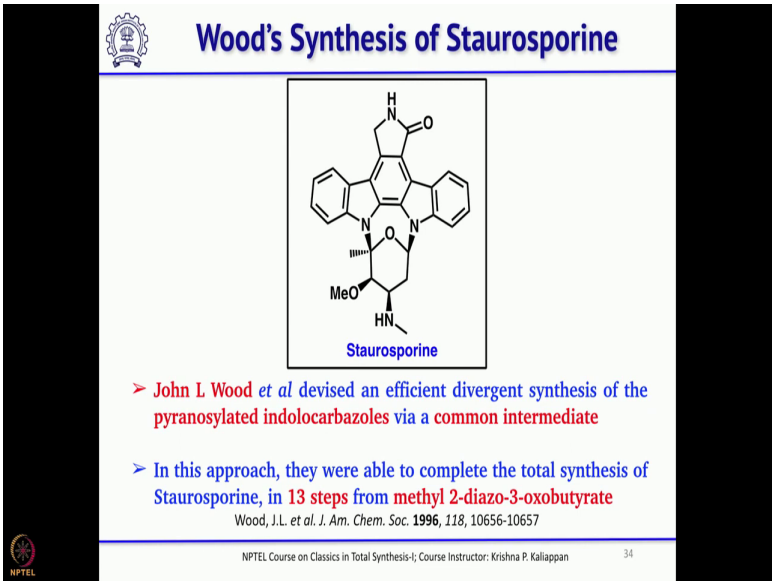

And here, he took only 13 steps and he used few interesting domino reactions, ok.

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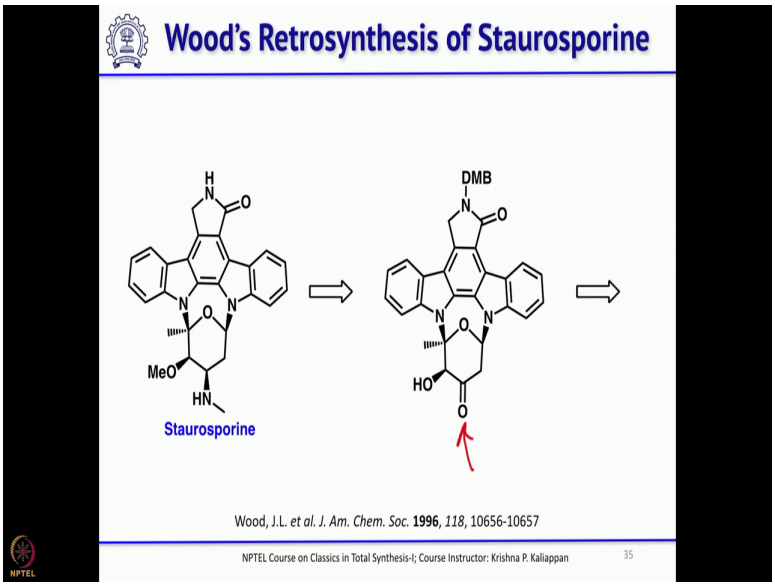

So, his retro synthesis was, basically the first retrosynthesis was to remove the -NH. So, that can be introduced by reductive amination.

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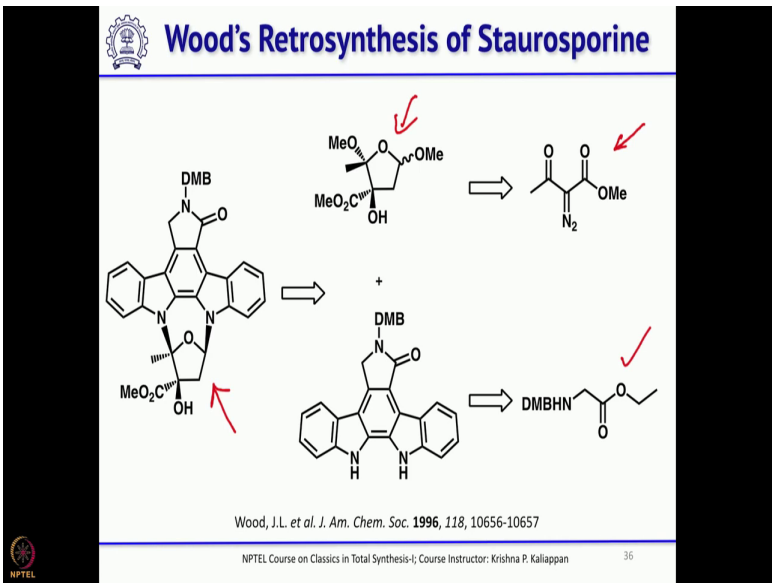

And, the second retrosynthesis was the ring expansion reaction, that is you start with the five-membered that is the sugar unit you start with the five-membered then you do a ring expansion to get the six-membered ring. And this can be obtained by an acid catalyzed cyclization of bis indole with this five-membered compound, ok. And, here this five-

membered compound, that five-membered highly substituted furanose was made from this diazo compound which is made from Methyl acetoacetate, ok.

So, commercially available methyl acetoacetate which upon diazo transfer you get this compound and that is the starting material for making this five-membered and this was made from this glycine ester, ok.

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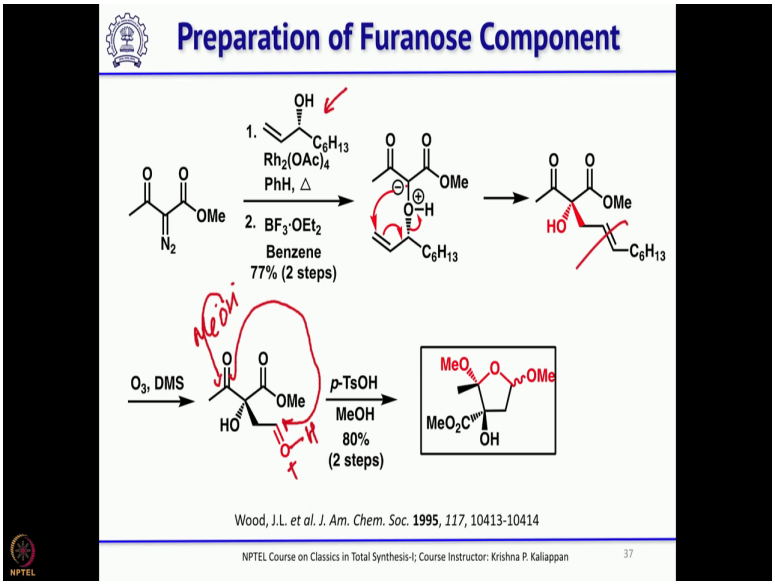

So, let us see how he has done the total synthesis. First, the substituted furanose portion was prepared from this diazo compound, on treatment with this chiral allylic alcohol and di-rhodium tetra acetate.

Followed by treatment with Lewis acid like BF_3 etherate. So, what happens? As you know, first it forms a rhodium carbonite and since you have allylic alcohol, chiral allylic alcohol. So, that immediately attacks the rhodium carbonite carbon. So, it forms a negative charge. So, that undergoes you know a rearrangement to give this, ok. So, I will leave it for few seconds to understand this mechanism.

So, he could get this in 2 steps and yield is quite high 77% for such interesting rearrangement. Next, he was analyzed the internal double bond to get aldehyde, followed by treatment with para toluenesulfonic acid and methanol, ok. So, what happens? This is protonated, ok. Then, methanol attacks this carbon and this attacks this carbon, ok. So, that is how he got this furanose compound. So, the furanose compound is easy.

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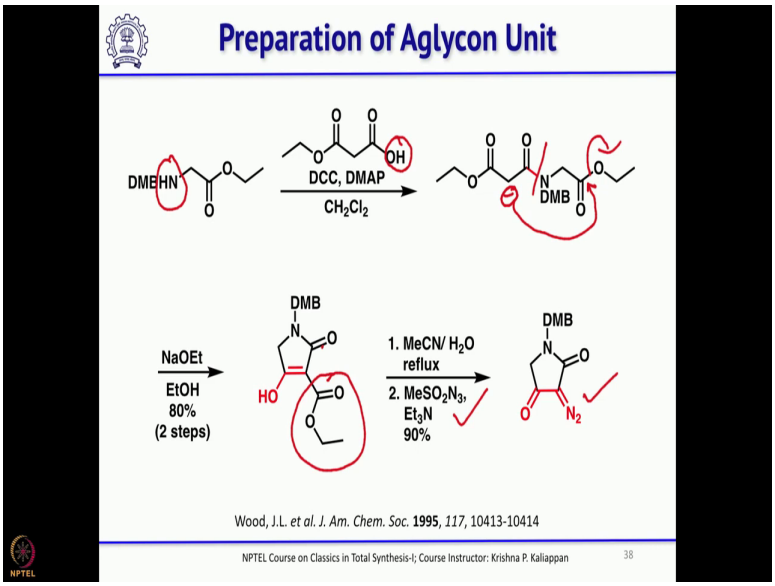

Then the, other component that is bis indole moiety, he started from the protected glycine and then treated with mono ester of malonic acid. So, he coupled this -NH with this carboxylic acid using dicyclohexane carbo diamide, ok. So, once this amide was formed, his next step was to treat with sodium ethoxide and ethanol.

So, sodium ethoxide methanol will generate an anion here that will add to intramolecularly to the ester and this -OEt will come out, ok. So, this is what you get after this sodium ethoxide ethanol treatment. Now, if you treat with acetonitrile and reflux it, if you look at this ester. So, this is nothing but, β-keto ester, ok. So, that undergoes decarboxylation.

So, that will give you a carbonyl group here and this enol. Then, treatment with Methyl azide and base one can introduce this diazo group. So, standard method, if you have a keto-ester or keto-amide or 1, 3-diketone you can introduce the diazo group by treating with tosyl or mesyl azide in the presence of base.

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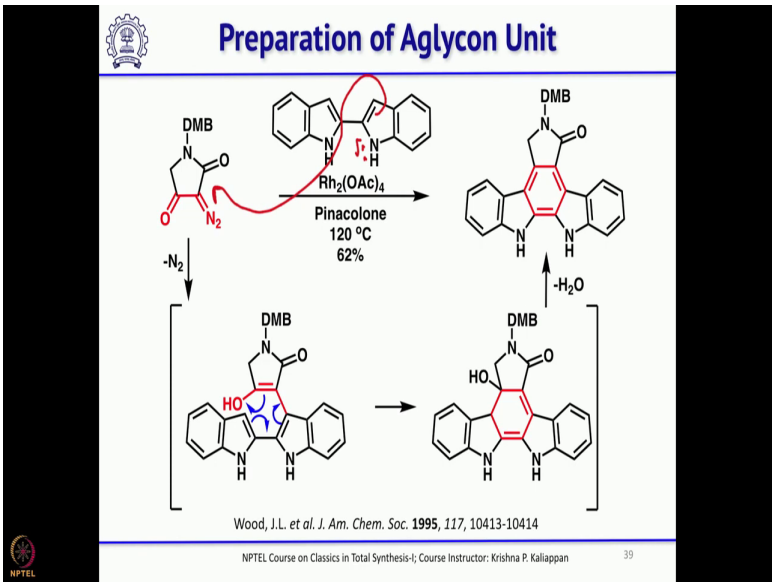

So, once you have this, take this compound and then treat with bis indole, ok, in the presence of di rhodium tetraacetate.

So, that gives first you know from here it goes and then attacks here and then it forms an enol, then that undergoes the electro cyclization reaction and followed by elimination gives the corresponding the northern hemisphere bis indole moiety, ok. So, this bis indole moiety is ready and the other side the glycoside, that is the furanose portion also is ready. Now, he has to connect this bis indole with this furanose moiety, ok.

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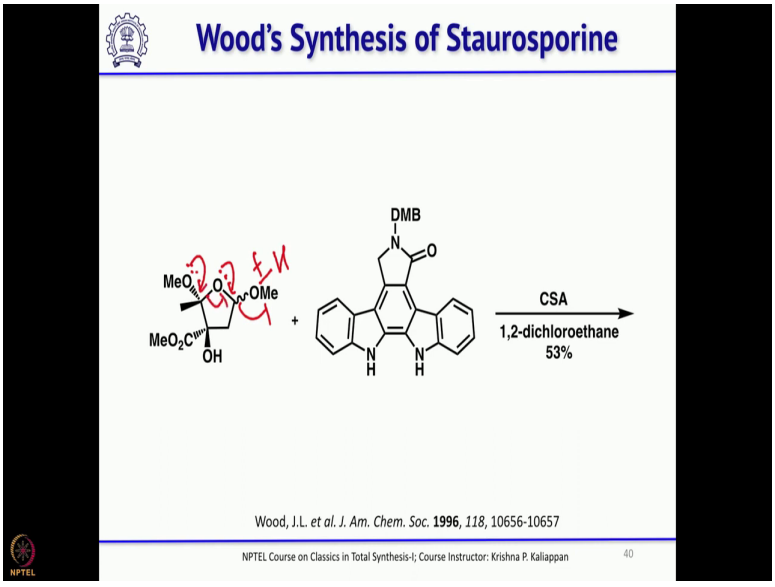

So, what he did he took both and then treated with camphor sulfonic acid. What he got was, the five-membered ring. Once you treat with camphor sulfonic acid, it protonates and then it comes out. So, that leads to the formation of oxonium ion, ok. Now, since you have another lone pair on the oxygen at adjacent carbon. So, this can open.

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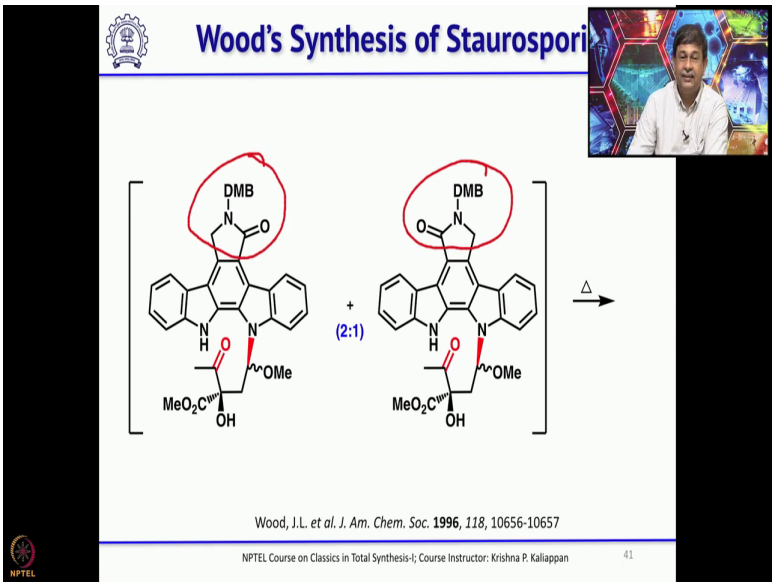

So, that will give you your methyl ketone and then aldehyde.

The nitrogen intermolecularly attacks to give this compound in the ratio 2:1. Why 2:1? You look at this carefully, ok, because both indoles can attack, ok, that is why you get this mixture. So, you take this compound and treat with again reflux it. So, then nitrogen can attack the carbonyl group, ok

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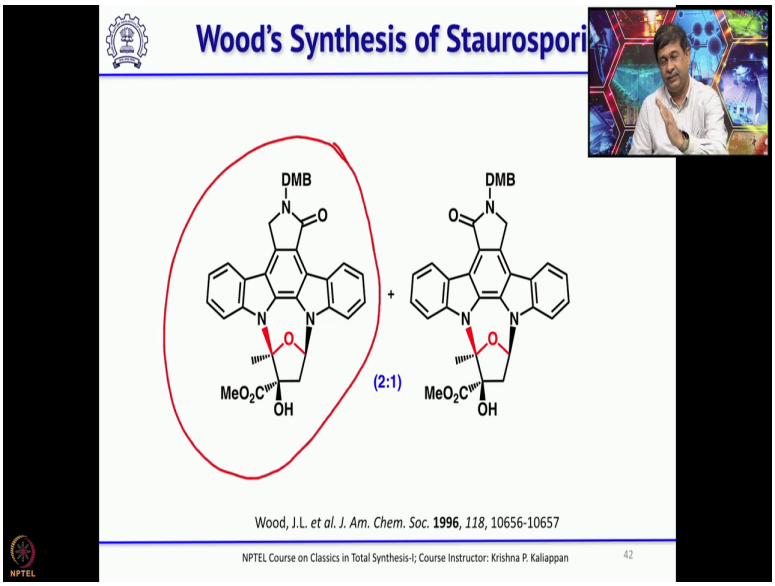

Nitrogen can attack the carbonyl group that -OH can attack. So, you get the five-membered, ok. So, again in the same ratio 2:1. So, this is what you need. If you look at this structure so, this is what you need for the total synthesis of staurosporine.

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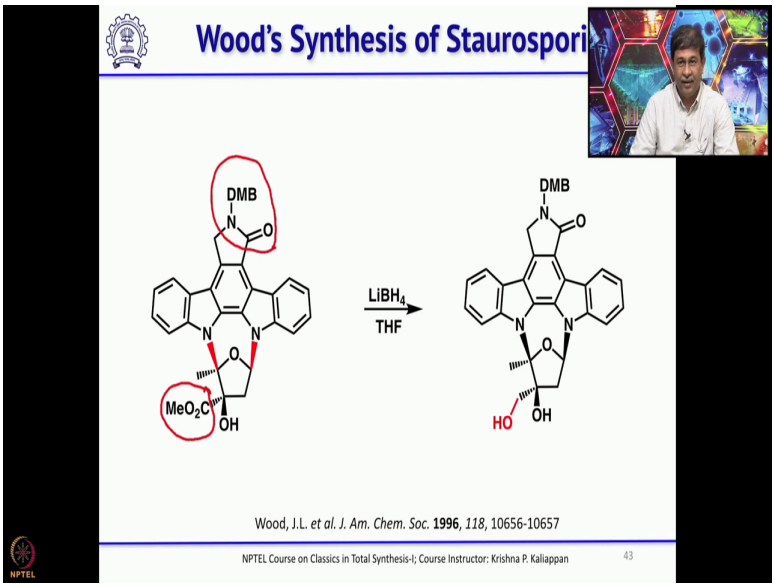

So, you take this compound, then treat with Lithium borohydride. So, Lithium borohydride selectively reduces ester in the presence of lactam. So, you get primary alcohol without touching the lactam.

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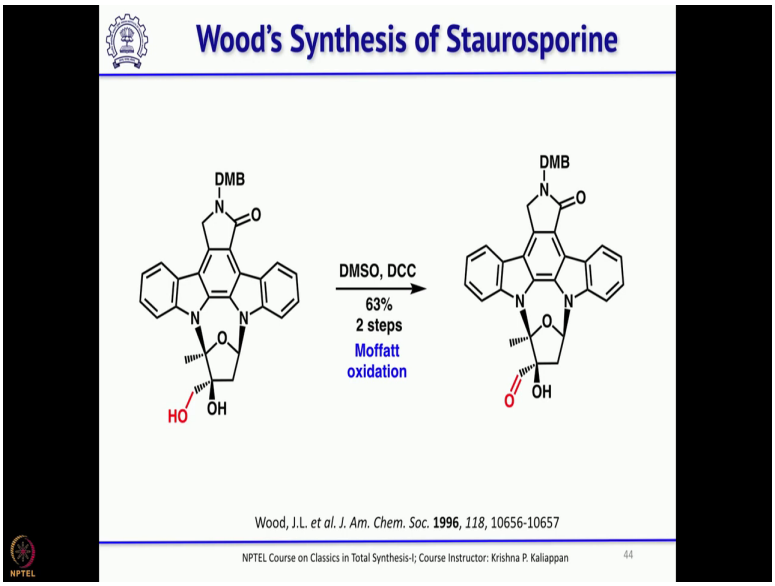

Then, you take this primary alcohol and carry out Moffatt oxidation. So, Moffatt oxidation is nothing but, you take an alcohol and treat with DMSO and DCC. So, you oxidize the primary alcohol to aldehyde.

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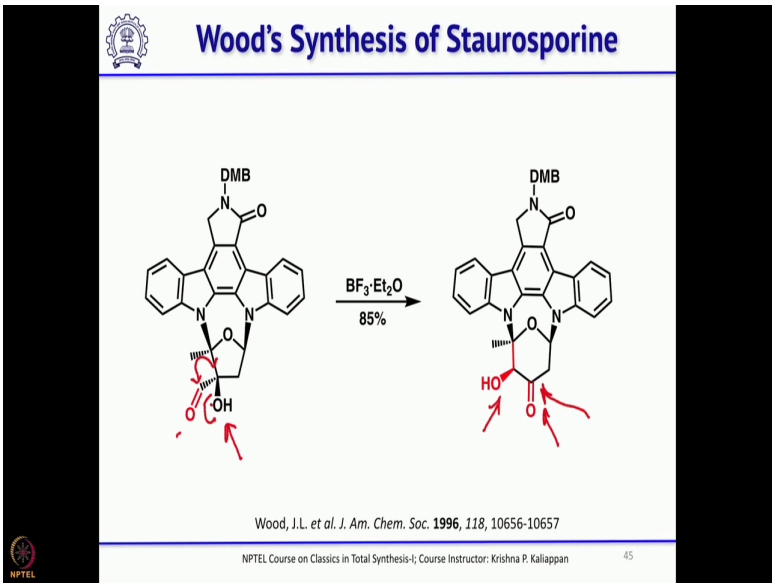

Then you treat with BF_3 etherate. So, BF_3 etherate it triggers a rearrangement. What happens? Now, the lone pair comes like this and this bond migrates, ok. So, that is more nucleophilic, is not it? That bond migrates, when that bond migrates you get this six-

membered and this hydroxyl originally here, it becomes ketone that aldehyde becomes lactal.

This highly stereo selective rearrangement gives the six-membered that is the pyranose ring, ok. So, what is to be done now? You have to reduce the ketone; not simply reduce the ketone, you have to treat with nitrogen and then reduce it; that means, you have to do a reductive amination, ok.

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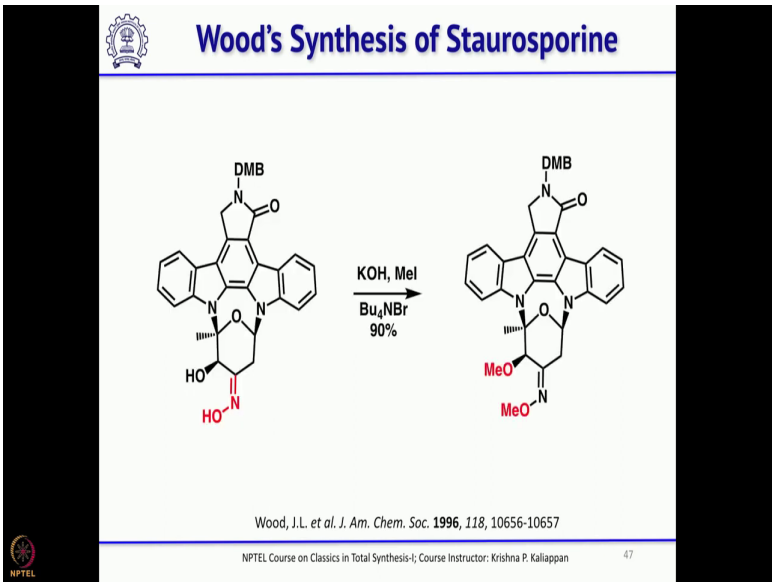

So, that was done by treating with hydroxyl amine, first you get oxime, then oxime must methylated.

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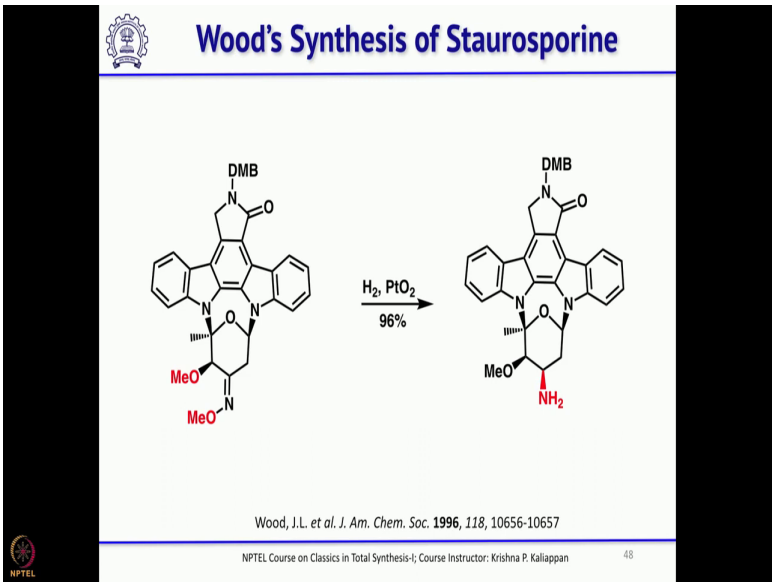

Then, he did hydrogenation with Adam's catalyst. So, you got correctly, you got directly the amine.

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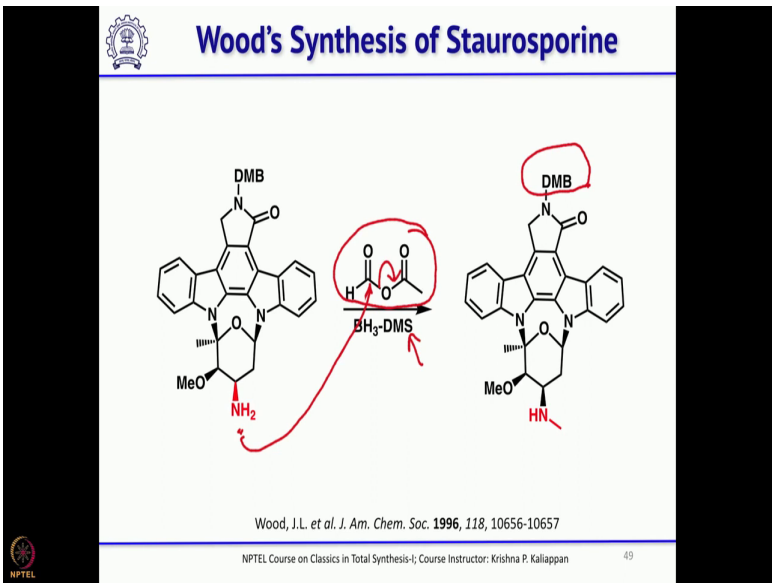

Then, that amine was treated with this particular reagent. Here, what happens, this -NH two attacks this carbonyl and acetate goes out. So, basically you get -NH-CHO. The NH-CHO can be in-situ reduced with borane dimethyl sulfide to form NH-CH_3, ok. So, that leaves only the removal of this dimethoxybenzyl group.

Once you remove the dimethoxybenzyl group that will give staurosporine.

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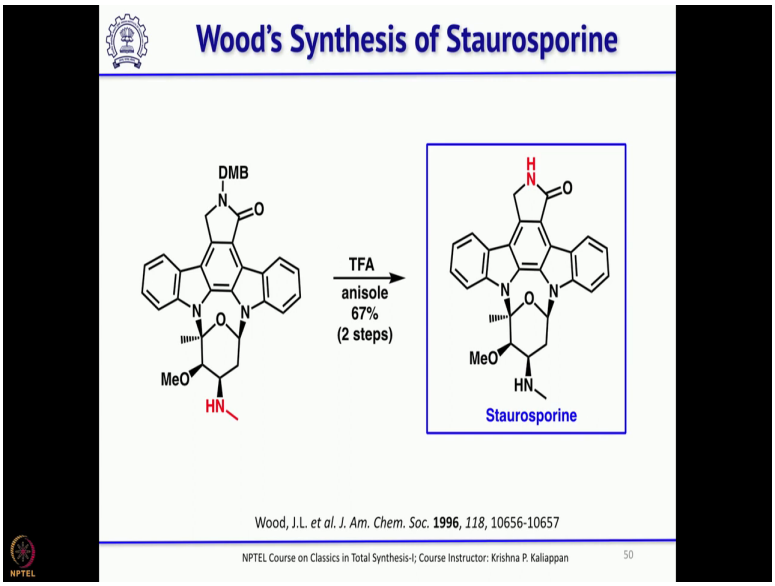

So, the dimethoxybenzyl group was removed by treating with trifluoro acetic acid. So, that gave the natural product staurosporine.

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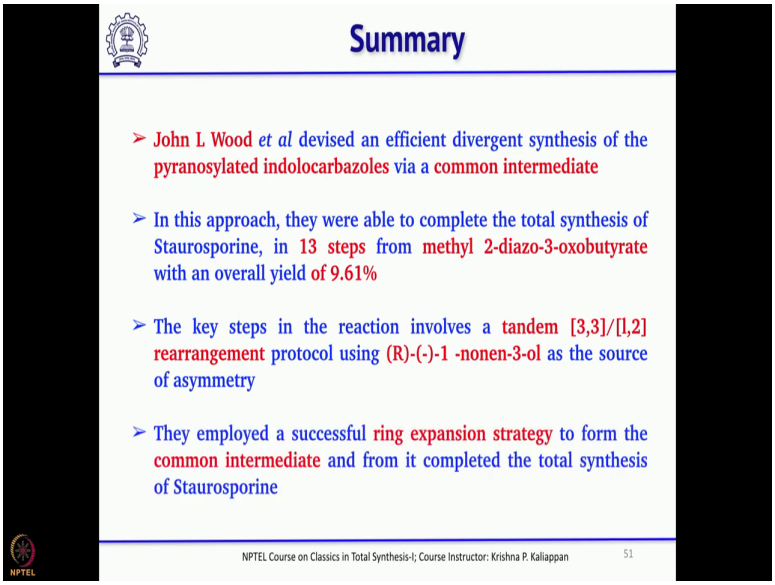

So, if you look at the total synthesis of staurosporine reported by John Wood. So, he accomplished it in 13 steps with an overall yield of close to 10%, which is significantly higher than the first total synthesis reported by Danishefsky.

And second thing is, if you look at this synthesis it involved 2 times rearrangement, first when you did the di rhodium tetra acetate catalyzed rearrangement, ok. The second

rearrangement was when you had hydroxy aldehyde this upon treatment with Lewis acid, the furanose ring was converted into the pyranose ring.

So, this synthesis involved these two rearrangements as key reaction to complete the total synthesis, ok. So, with this we completed the total synthesis of staurosporine using two different strategies one reported by Danishefsky the other one reported by John Wood, ok. So, we will see you in the next class, ok.

Thank you.