Classics in Total Synthesis - I
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Lecture - 37
Lysergic acid

So, good morning everyone and welcome back to the NPTEL lecture series on Classics in Total Synthesis part 1. So, we have been discussing about total synthesis of few alkaloids. And today we will continue our discussion and also on total synthesis of one of the very important alkaloids called lysergic acid. So, the lysergic acid belongs to a family called ergot alkaloids.

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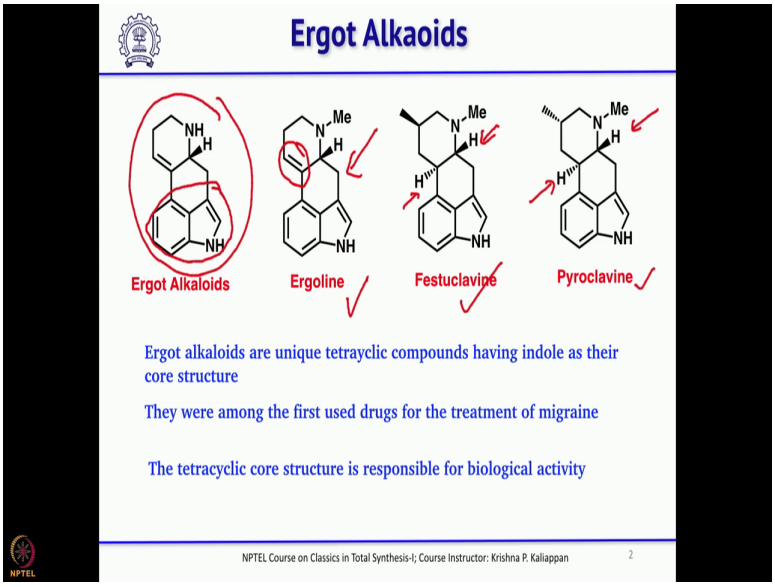

The lysergic acid belongs to a family called ergot alkaloids. So, the ergot alkaloids have this basic skeleton, thus this a tetracyclic skeleton. If you look at carefully so they have the indole as their core structure ok, they have indole and two more 6-membered ring fused with this indole ok.

In fact, they were the first drugs used or first among the they were among the first drugs used for the treatment of migraine, headache and all ok. And they believe that the tetracyclic core structure ok, the tetracyclic core structure is responsible for its biological activity. So, most of the derivatives further derived from this basic skeleton, they made

sure that tetracyclic skeleton was kept as such, only there was some functional group transformation around the tetracyclic ring.

So, these are three ergot alkaloids, you can see this is ergoline ok having a double bond here and festuclavine where the double bond is reduced and the ring junction is trans. And pyroclavine, so here also you can see the ring junction is trans. So, whenever the double bond is not there then the ring junction is trans in ergot alkaloids ok.

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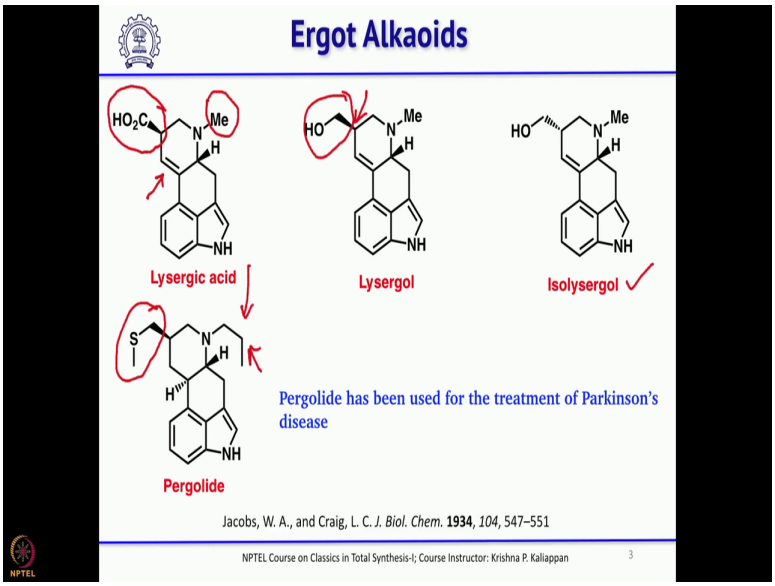

And if you look at lysergic acid so, double bond is there ok, you can see in the tetracyclic ring there is a double bond and here instead of methyl group you have carboxylic acid.

So, that is why it is called lysergic acid and if you reduce the carboxylic acid then it is called lysergol ok. And the stereo center if it is opposite then this is called isolysergol. There was one semi synthetic derivative which is called pergolide and the difference between pergolide and lysergic acid is instead of methyl group here.

So, what you have is a propyl group, n-propyl is attached to the nitrogen and in this case on the left hand side, instead of carboxylic acid what you have is -CH_2-SMe and this pergolide is used for the treatment of Parkinson's disease as of now, ok.

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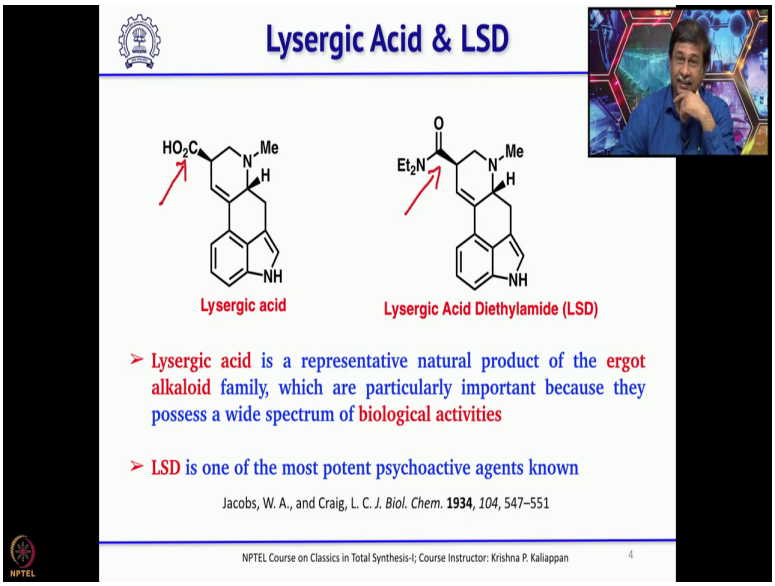

The more important analog of lysergic acid and infamous one is LSD. So, LSD is nothing but lysergic acid diethyl amide. So, that is this carboxylic acid is converted into the corresponding diethyl amide ok. So, the small change from carboxylic acid to the diethyl amide makes huge difference. In fact, LSD is one of the most potent psycho active agents known in the literature.

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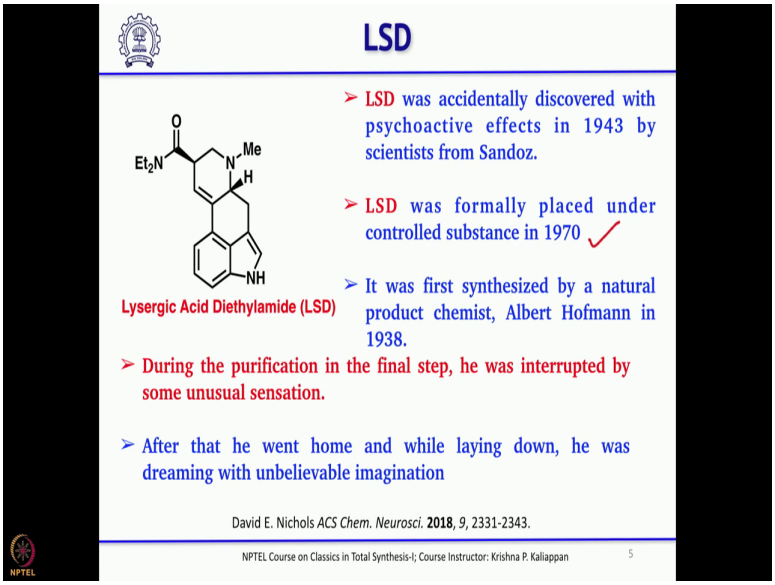

If you look at the history of LSD that is lysergic acid diethylamide. So, this was accidentally discovered, in 1938, when a scientist called Hofmann when he was

synthesizing this molecule that is a derivative of lysergic acid, during the purification and crystallization, during the purification and crystallization he felt something unusual.

So, he had different sensation. So, he immediately wanted to go home, so he went home and then he was just lying down on the sofa and then you could imagine so many things, you know many are know he had a very nice feeling of imagining so many things.

So, then immediately wrote to the other scientist and in Sandoz said this compound has some unique type of you know effects, ok. So, this molecule should be taken further. So, that is how this molecule was developed and in 1970, it was formally announced that LSD is a controlled substance ok. But today we are not going to talk about LSD, but what we are going to do is talk about two total syntheses of its precursor, that is lysergic acid.

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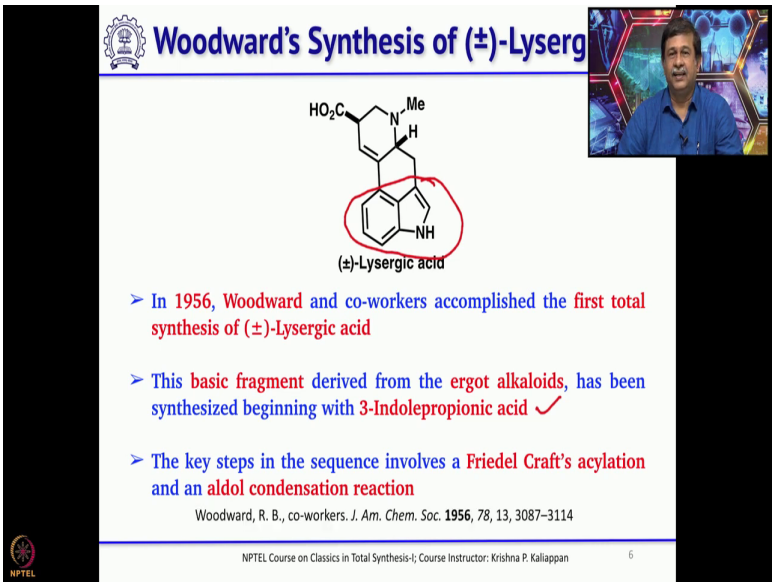

The first total synthesis was by as usual Woodward. So, Woodward thought this can be easily obtained, starting with the basic skeleton. So that means, you start with indole and try to append the two 6 membered rings over the indole. So, his starting material was indole 3 propionic acid and the key reactions which he used for the synthesis of lysergic acid are Friedel Craft's acylation that is intramolecular Friedel Craft's acylation to construct the first 6-membered ring and an aldol reaction to construct the second 6-membered ring ok.

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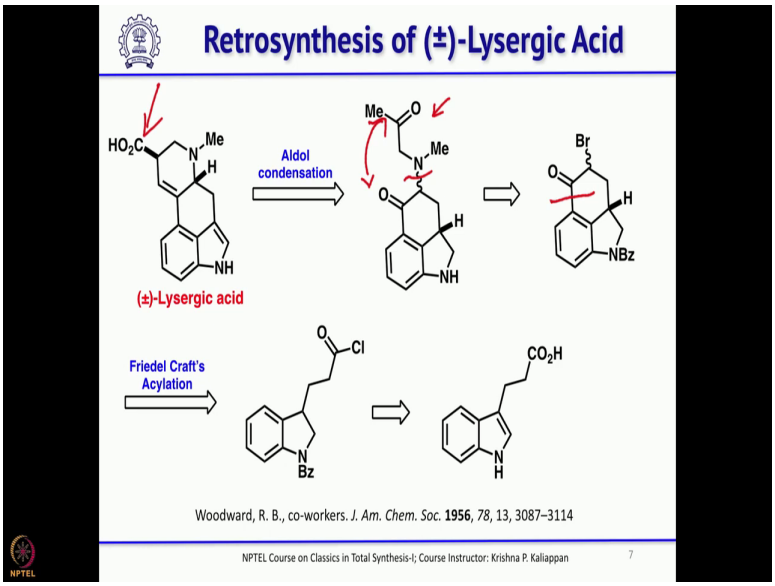

Let us see how we originally thought of making lysergic acid. So, his initial idea was as I said you can do an aldol here; is not it? You can do an aldol to form the second 6-membered ring ok, then the carboxylic acid can be easily added ok, that was the first major disconnection. Then the second disconnection was an S_N2 substitution reaction ok, you have bromide α-bromo ketone. So, you can do S_N2 reaction to introduce this methyl amino ketone which can be further used for intramolecular aldol condensation.

The third disconnection was; obviously, the CO bond because it is so clear that one can easily use Friedel Caft's acylation reaction to introduce the second 6-membered ring and this acid chloride of course, can be obtained from indole three indole propionic acid ok.

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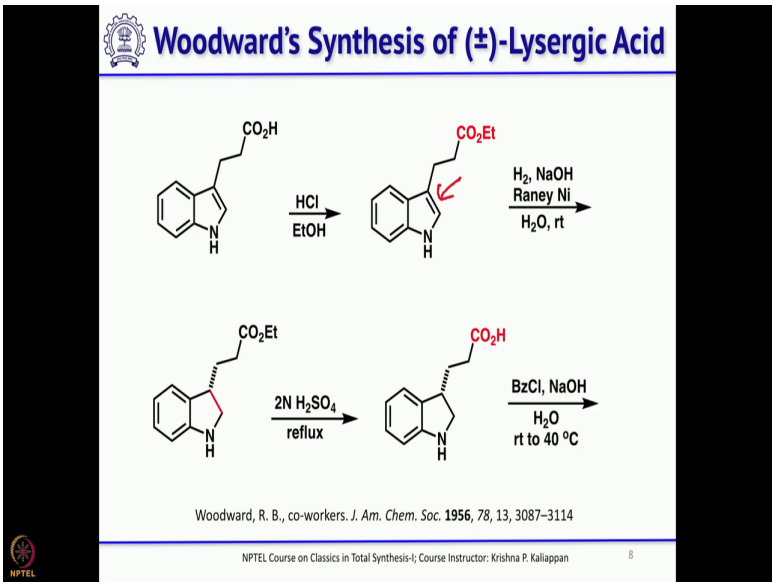

Let us see how he has done. The synthesis he started with indole 3 propionic acid and first step was esterification with the ethanol and HCl, gave the ethyl ester. So, then this double bond. So, this double bond was reduced under Raney nickel hydrogenation condition. Then the ester was hydrolyzed to get the corresponding carboxylic acid ok.

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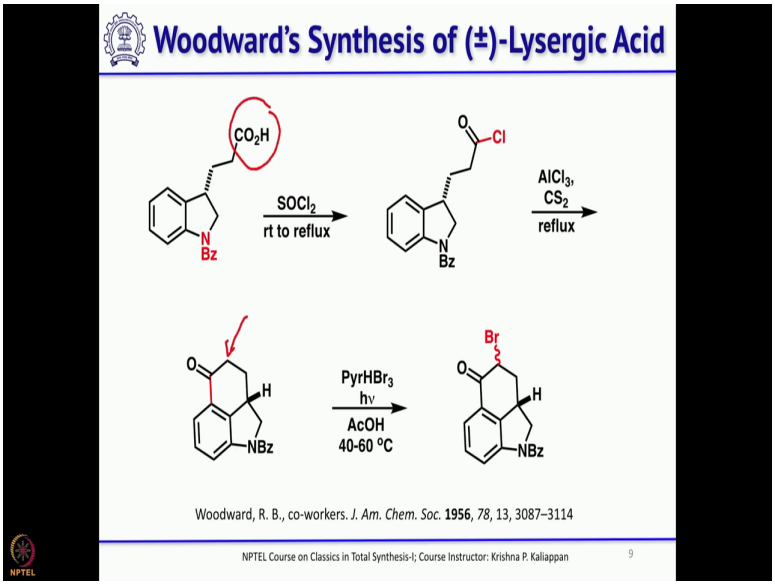

So, acid then the NH was protected as benzoate, then the thionyl chloride converted the carboxylic acid into acid chloride which is the intermediate for the Friedel Craft's acylation reaction, the Friedel Craft's acylation reaction worked well to get the first 6-

membered ring added over the dihydro indole. So, after that α bromination was done ok with a little bit complex reagent, but it is not really complex pyridine HBr and bromine ok.

So, under photochemical condition. So, he introduced bromine α to the carbonyl group.

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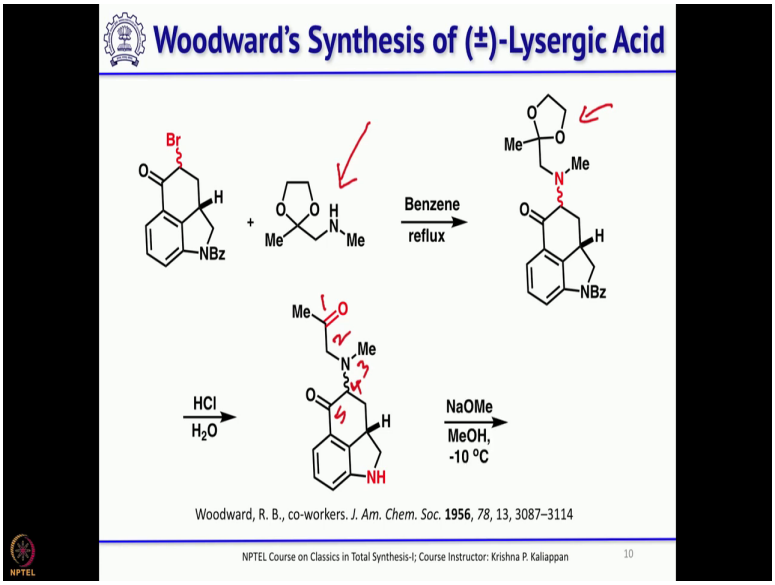

So, once the bromine was introduced, the next step was to carry out the intermolecular S_N2 reaction. So, he took the amine and then treated with this α bromo ketone, reflux in benzene. So, the S_N2 reaction took place. So, next step is to remove the ketone. So, that you will have the di-ketone ready for the intramolecular aldol reaction.

So, it was easily removed under acetic condition to get the 1,5 di-ketone; 1, 2, 3, 4, 5. So, the 1,5 di-ketone upon treatment with sodium ethoxide methanol under an intramolecular aldol reaction to give this 6-membered enol ok.

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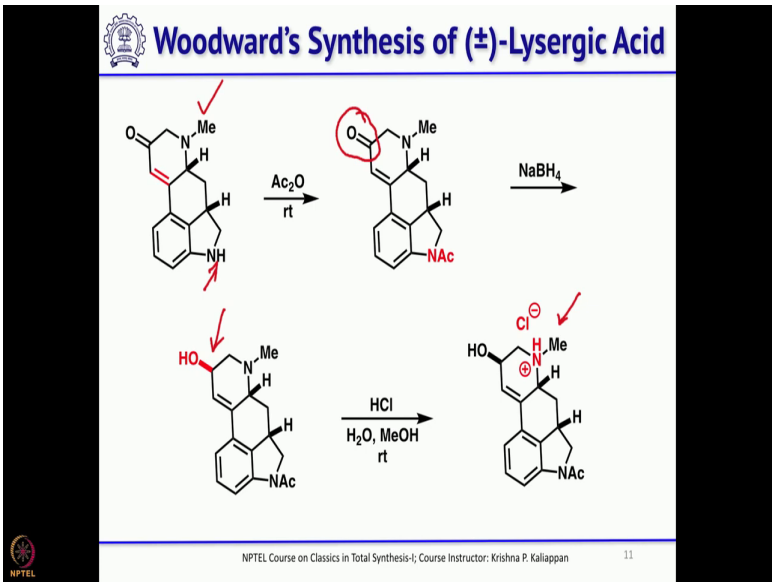

And the free NH was again acetylated using a acetic anhydride pyridine, then the α-β unsaturated ketone was selectively reduced to get the corresponding allylic alcohol. And once you have the allylic alcohol it requires two steps to introduce a carboxylic acid synthetic equivalent. The synthetic equivalent for carboxylic acid in this case is cyanide, if you can introduce cyanide then cyanide can be hydrolyzed to carboxylic acid ok.

So, the allylic alcohol was treated with first HCl. Why HCl? Because this free NH should be protonated ok.

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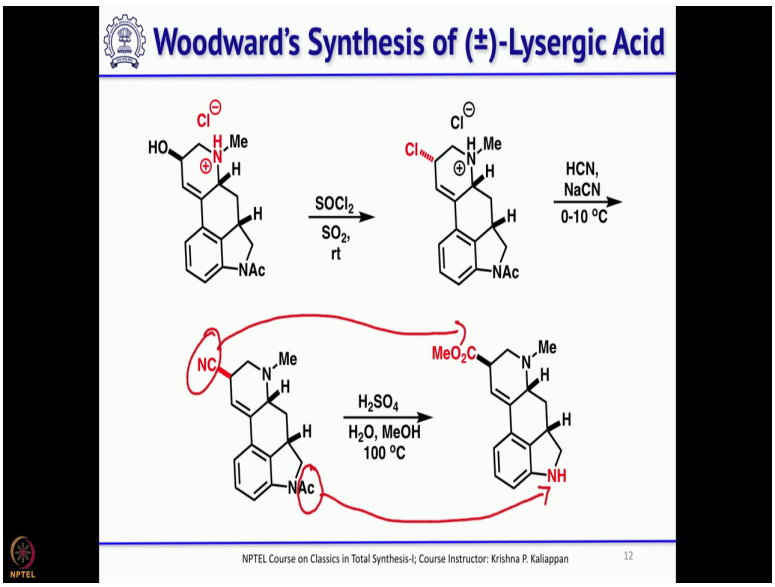

So, after protonation then thionyl chloride treatment, thionyl chloride treatment converted the allylic alcohol into the corresponding allylic chloride, in this specific case. Then treat with sodium cyanide. So, it underwent S_N2 reaction and this upon treatment with sulfuric acid and methanol. So; that means, the cyanide you are hydrolyzing to carboxylic acid and in that process, since you are using methanol the carboxylic acid which is formed also getting esterified because of the presence of acid and methanol ok.

So, the cyanide is directly hydrolyzed and esterified in one step to get the corresponding methyl ester ok. So, once you have this ester, then what is next is only to hydrolyze. During the formation of ester from cyanide, you one also should know that acetate also was removed ok, under acidic condition one can remove the acetate to get the corresponding free amine.

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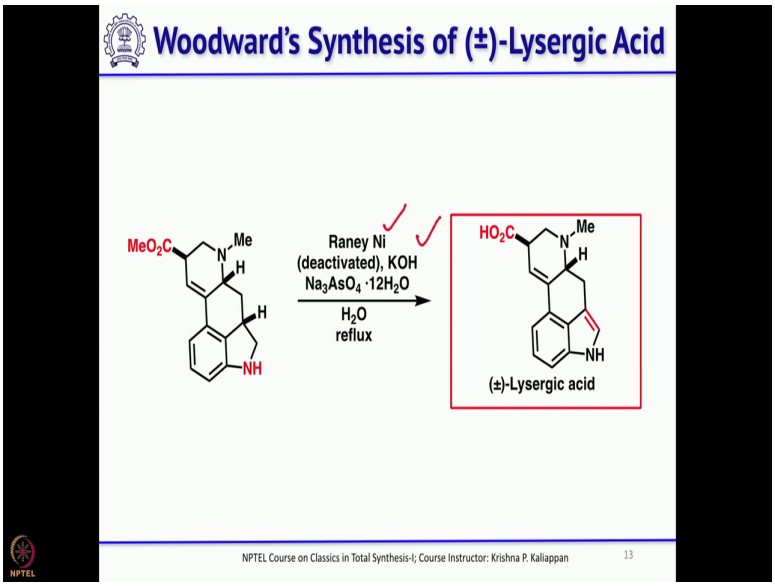

So, then simple hydrolysis was done here he has used potassium hydroxide, Raney nickel to get the corresponding carboxylic acid, which is the natural product ok.

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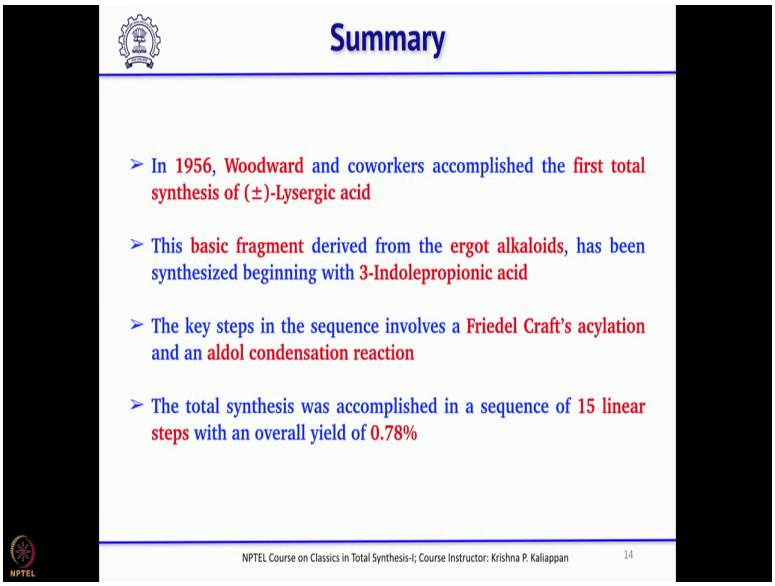

So, this lysergic acid reported by Woodward overall involved about 15 steps and yield was close to 1% ok, and as I already mentioned the key reactions involved in the synthesis of lysergic acid reported by Woodward or Friedel Craft's acylation that is intramolecular Friedel Craft's acylation to get the first 6-membered ring and again an intramolecular aldol condensation reaction to get the second 6-membered ring. Then we will move to the second total synthesis which was reported by Wolfgang Oppolzer, ok.

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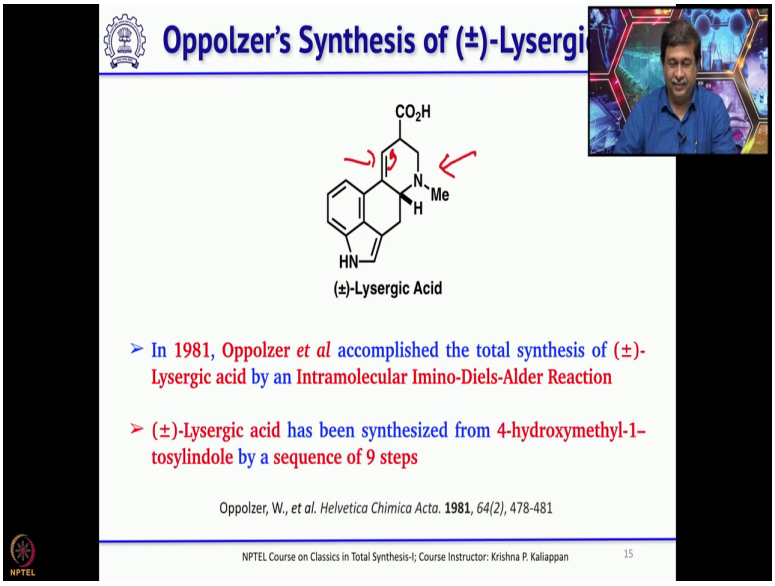

So, his idea was, when you look at this 6-membered ring you have a double bond ok. So, he thought if he can migrate this double bond here ok, if he can migrate this double bond here then it should be possible to use an intramolecular Diels-Alder reaction to form this 6-membered ring ok. Only thing is here the dienophile will be an imine ok. So, then one can call this as intramolecular Imino-Diels-Alder reaction ok, that was his original idea and let us see how he has done this.

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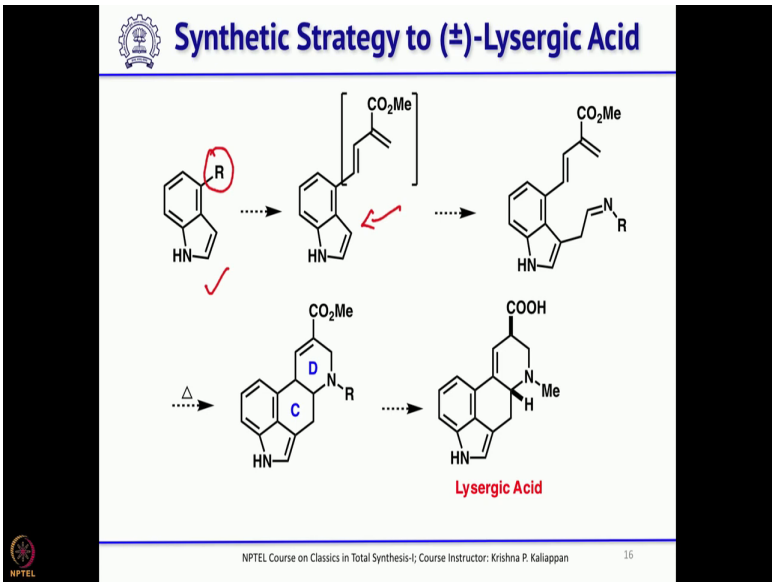

So, as you can see here again the starting material is indole and with a substituent here, so that you can introduce this diene which is required for the intramolecular Diels-Al reaction, then you attach the dienophile which is required that is hetero dienophile required for the Diels-Alder reaction, then you carry out this intra molecular Diels-Alder reaction followed by migration of the double bond and hydrolysis will give lysergic acid. So, this is the simple strategy planned by Oppalzer for the total synthesis of racemic lysergic acid ok.

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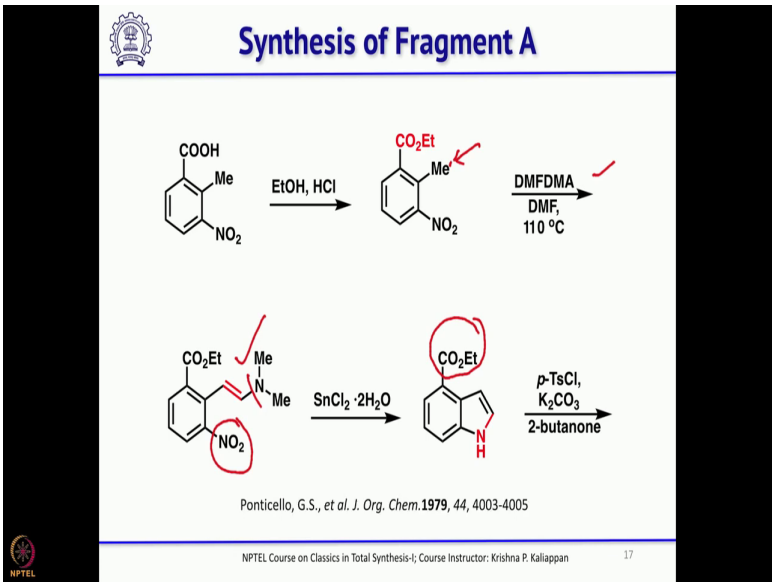

Let us see how he actually carried out the total synthesis, for the synthesis of fragment a he started with this nitro carboxylic acid ok. So, esterification of carboxylic acid with ethanol and HCl we got the corresponding ethyl ester, then this methyl group ok, this methyl group was converted into this enamine that is done with dimethylformamide dimethyl acetal in DMF ok. So, basically you know you generate an anion you generate an anion and then attack the DMF ok, to get the double.

Then you reduce with tin chloride. So, what happens, first the nitro group is reduced to get the corresponding amine then this enamine also gets hydrolyzed, once the enamine gets hydrolyzed you get the aldehyde ok. So, $-CH_2-CHO$ you get the $-CH_2-CHO$ and then $-NH_2$, they will form aminol followed by dehydration overall what he got was the corresponding indole with an ester here ok. So, what needs to be done for the next few steps? You have to attach the diene and also you have to attach the dienophile to this indole ok.

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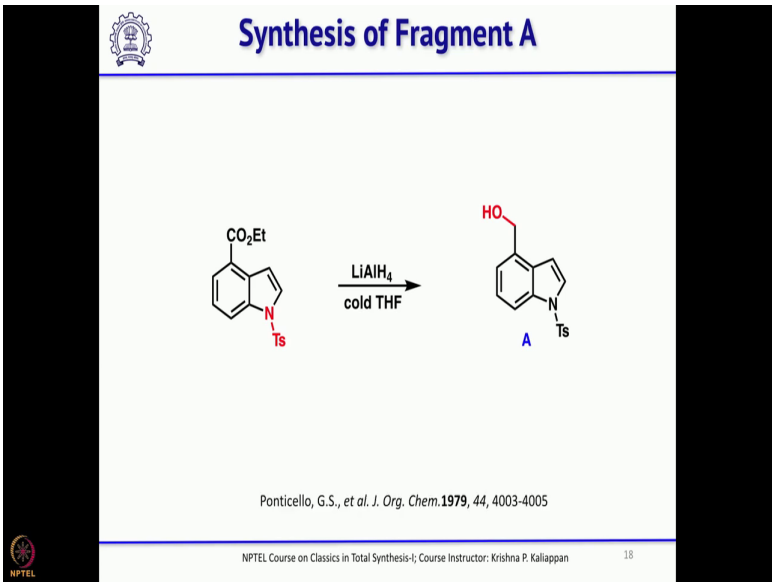

So, before that protect the indole nitrogen as N-Ts ok, then you reduce the ester with LAH to get the corresponding primary alcohol.

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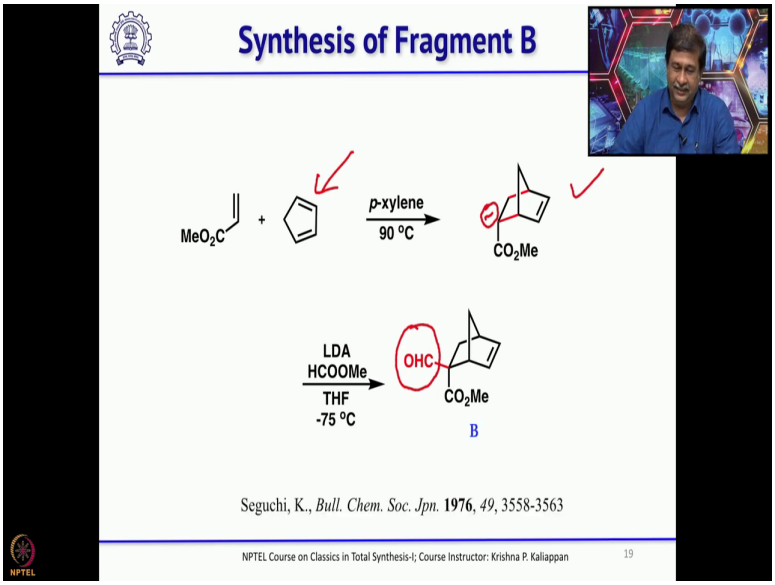

And this primary alcohol can be further homologated. So, here the introduction of diene, he followed a unique method what he did was first he took methyl acrylate and then treated with cyclopentadiene to get this bicyclic compound through Diels-Alder reaction. Then he deprotonated this carbon because, that is attached to ester.

Then quenched with methyl forming, basically what he had done is he has introduced an aldehyde here, ok. So, why he has introduced this aldehyde? I will tell you.

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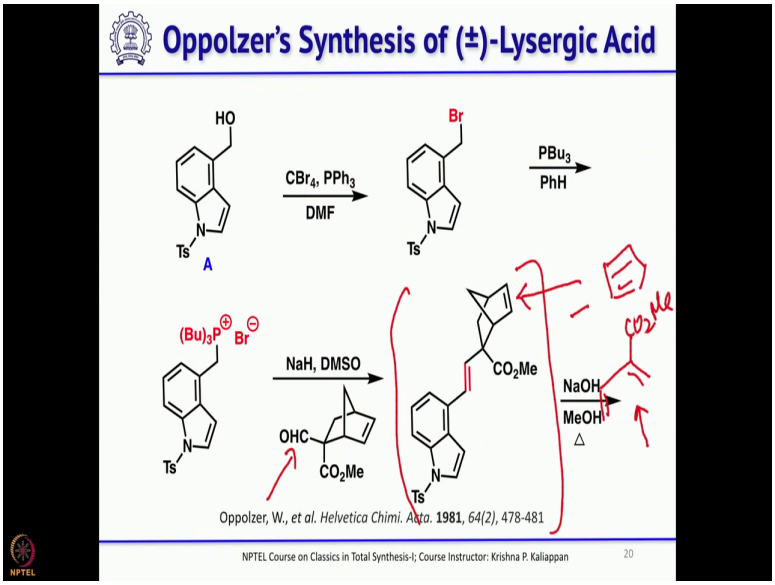

So, once he had this B, that is the aldehyde bicyclic adduct then this fragment A, that alcohol he converted into the bromide followed by treatment with tributyl phosphine. He made the Wittig salt. So, then the Wittig reaction with this aldehyde was done with dimsyl anion ok.

So, why this intermediate he wanted to make? So, if you look at this intermediate, this portion can undergo a retro Diels-Alder reaction ok. The retro Diels-Alder reaction will remove the cyclopentadiene ok, remove the cyclopentadiene and it will generate the other diene which is required for the Diels-Alder reaction.

So, basically one of the double bonds of the diene is protected by cyclopentadiene ok, that will be released when the retro Diels-Alder reaction takes place. This diene is not reactive, this diene is not reactive. So, that is why he has to follow this indirect method.

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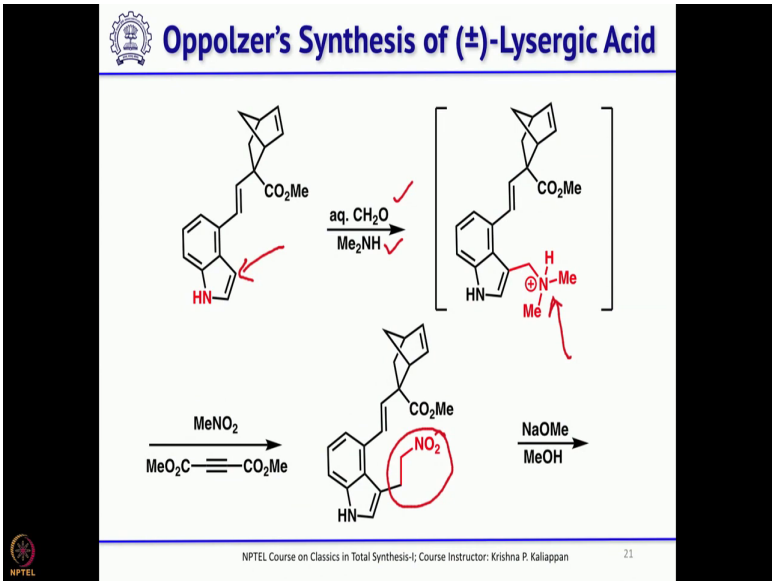

Next, so he took this compound and then treated with aqueous formaldehyde and dimethyl amine ok. So, that means, he is introducing a -CH_2-NMe_2 ok, this is nothing, but Mannich reaction; is not it? So, upon treatment with aqueous formaldehyde and dimethyl amine he carried out a Mannich reaction at carbon number 3 of indole to introduce this functional problem ok.

What he has to do is, he has to introduce one more carbon for that he took nitro methane and dimethyl acetylene dicarboxylate, it underwent a sort of SN_2 reaction to get this -CH_2-CH_2-NO_2, ok. From this -CH_2NO_2 he needs a double bond N and OR. So, he needs an imine ok, so the imine should be rare for an intra molecular amino Diels-Alder reaction ok.

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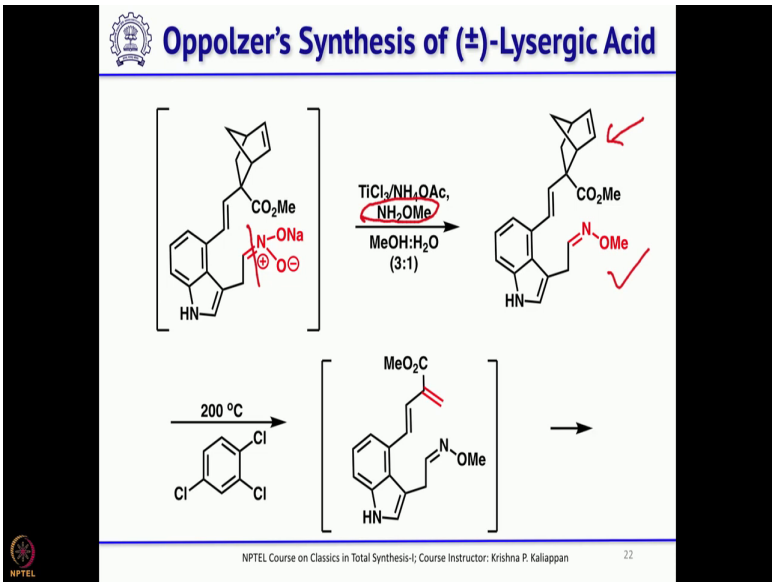

So, what he did? First, he treated with sodium ethoxide methanol so that forms this intermediate, this intermediate when it forms you can immediately recall. So, this is nothing but Nef reaction ok, if you have a $-CH_2-NO_2$ ok, Nef reaction first you have to treat with base then followed by treatment with titanium, titanium trichloride ok

So, what happens? This will be hydrolyzed to the aldehyde then that aldehyde will react with NH_2-OMe to give this corresponding imine ok. So, now, the diene dienophile is ready, what he needs is the diene should be released through the retro Diels-Alder reaction then it can undergo spontaneous intramolecular [4+2] cycloaddition reaction. So, that was done at high temperature, so 200 degrees so that retro Diels-Alder reaction took place and followed by intramolecular Diels-Alder reaction gave this tetracyclic compound ok.

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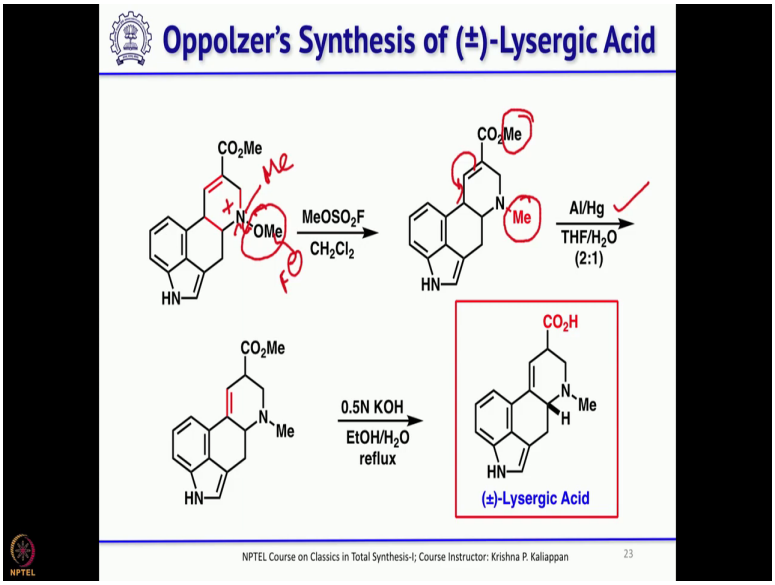

So, now you have OMe here, but in lysergic acid you have -Me group ok. So, just one oxygen you have to remove. So, that was done using fluoro methane sulfonate, it is a good methylating agent. So, what happens? So, first the nitrogen will be methylated ok. So, then the fluoride can attack and -OMe bond, -NO bond can break to give the corresponding n-methyl ok.

So, what needs to be done now? You have to push the double bond here and hydrolyze the ester to carboxylic acid, if these two are done synthesis of racemic lysergic acid is completed ok.

So, the isomerization of the double bond was done with aluminum amalgam to push the α-β unsaturated ester to β-γ unsaturated ester then simple hydrolysis that is alkaline hydrolysis hydrolyzed, the ester to carboxylic acid. Thus, he completed the total synthesis of racemic lysergic acid ok.

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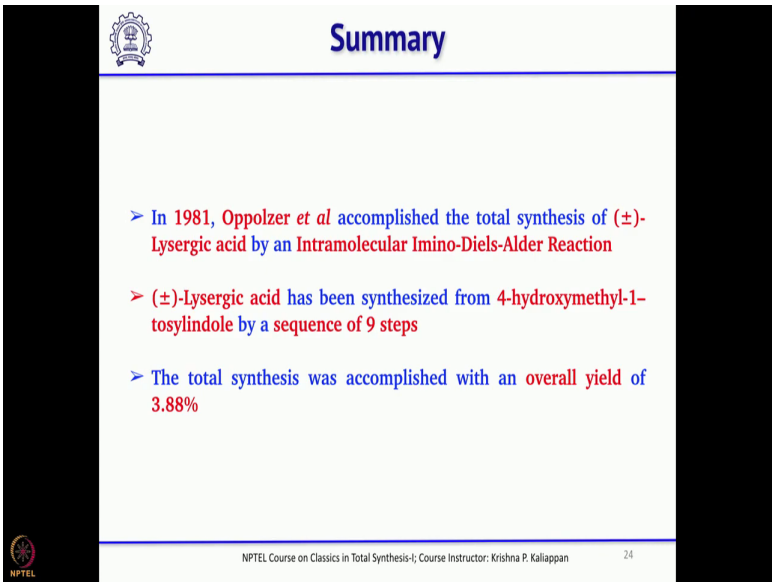

So, the key reaction as I mentioned was intramolecular imino Diels-Alder reaction and overall it took 6 steps less than what Woodward has taken, Woodward took about 15 steps. Whereas, Oppolzer took only 9 steps to complete the total synthesis. As a result the overall yield also went from 0.78% in the case of Woodward to 3.88%, that is 4 times he got better over yield than Woodwards, ok.

So, now, we have completed the total synthesis of lysergic acid now. Now, we will move to total synthesis of 3 or 4 more total synthesis of alkaloids, before we move to total synthesis of steroids ok.

Thank you.