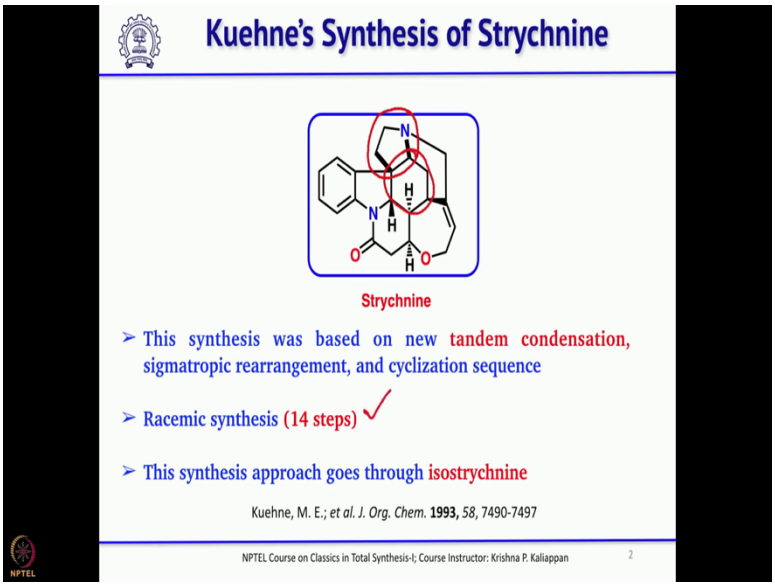
Classics in Total Synthesis - I
Prof. Krishna P Kaliappan
Department of Chemistry
Indian Institute of Technology, Bombay

Lecture - 29
Strychnine (Kuehne)

So, good morning and welcome back to NPTEL course on Classics in Total Synthesis part I. In the last lecture, we talked about the Total Synthesis of Strychnine by Viresh Rawal and Larry Overman's group. So, today, we will talk about another Total Synthesis of Strychnine reported by Martin Kuehne's group ok.

So, here in this total synthesis, again they used isostrychnine route; that means, they synthesize via isostrychnine and the key reactions which they used was a tandem Mannich cope rearrangement and Mannich reaction ok.

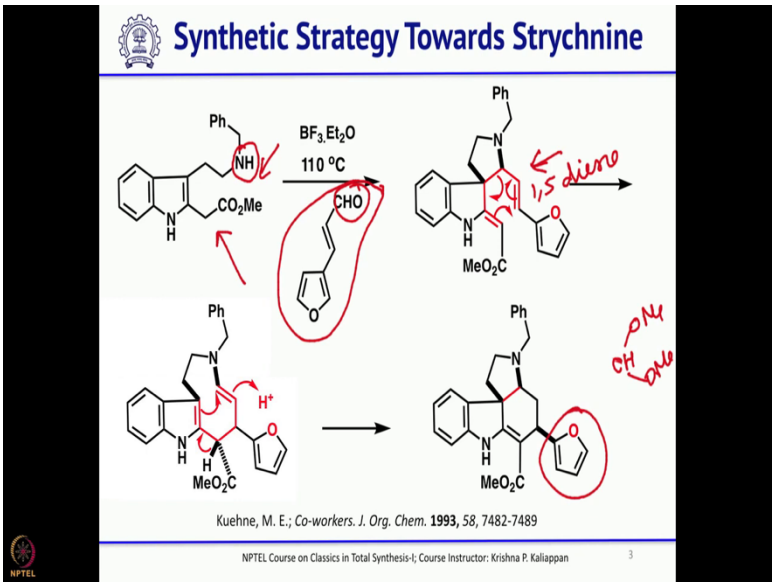
(Refer Slide Time: 01:01)



So, that is a key reaction used to construct the five-membered ring. So, this is this five-membered ring, they constructed using this key reaction; five-membered as well as this six-membered ring ok, together they constructed using this three reactions in one step.

First, they reported racemic synthesis; then, they used chiral version starting with corresponding chiral amino acid. So, overall, it took about 14 steps to complete this synthesis of strychnine.

(Refer Slide Time: 01:32)



So, their synthetic strategy as I said dependent on three reactions in one pot. They are Mannich reaction, followed by Cope rearrangement, followed by another Mannich reaction. So, they did a model study, where they started with this alpha beta unsaturated aldehyde derived from furan 3 carbaldehyde. So, they treated this with this corresponding amino ester in the presence of Lewis acid at high temperature. The first the aldehyde forms iminium ion with this amine; aldehyde forms iminium ion and the Mannich reaction takes place.

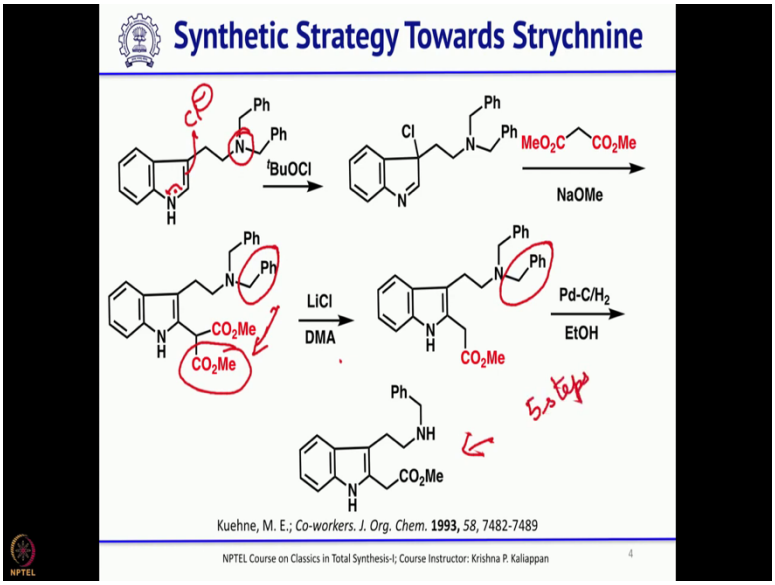
Once the Mannich reaction takes place, this is the intermediate you get. That is the first intermediate. Now, you can see this can undergo a Cope rearrangement. So, 1, 5 diene ok. This 1, 5 diene can undergo Cope rearrangement. So, once it undergoes Cope rearrangement, you get this intermediate. So, now, you have a nine-membered ring ok. So, what you have is a nine-membered ring because of the Cope rearrangement.

Then, as I said, it undergoes the second Mannich reaction. So, the second Mannich reaction cyclizes again back to the 6, 5 system ok. So, that is how in one pot, he could successfully make this tetracyclic compound. Basically he made two rings in one pot. So, that is the key reaction which he later used for the synthesis of strychnine.

So, for the synthesis of strychnine, he does not need this furan ok. He wants an aldehyde ok; he wants an aldehyde. So, what he did? He started with the corresponding protected

aldehyde, it is a furan he got this compound and the next slide, we also will see how this starting material was made from commercially available starting material.

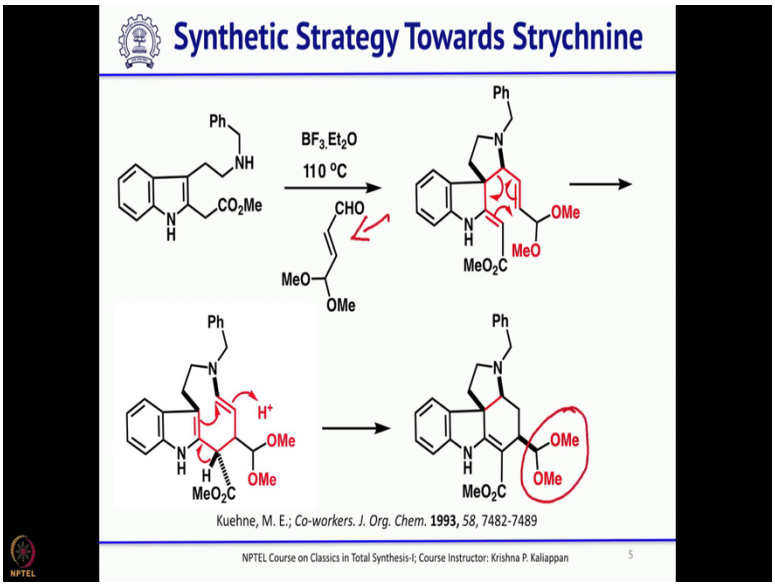
(Refer Slide Time: 03:34)



So, he started with this tryptophan; tryptophan is NH_2, then he treated with tertiary butyl oxychloride. So, tertiary butyl oxychloride is known to introduce chlorine here ok. So, that way, you get the chlorine here. Now, you treat with dimethyl malonate and sodium ethoxide ok. So, that will give you the $CHCO_2MeCO_2Me$. What you do not need here is 1 CO_2Me you do not need ok and one benzyl group you do not need. So, it is easy one of the esters can be easily removed by Krapcho condition, you heat it at high temperature lithium chloride and dimethyl acetone; then dimethyl acetamide.

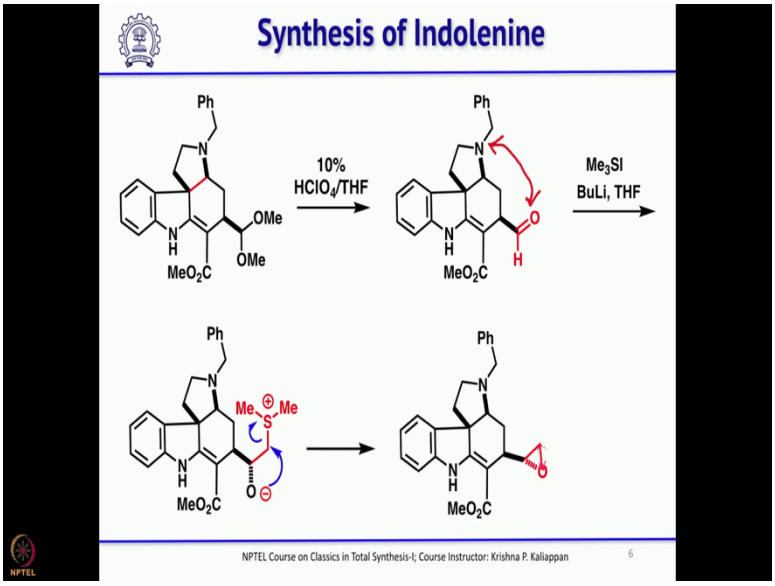
So, you treat this with lithium chloride and dimethyl acetamide, it undergoes decarboxylation. So, you get only one ester. Now, as I said you do not need one more benzyl group, so you can easily selectively remove by doing hydrogenolysis. So, that is how this starting material was prepared in 4 steps ok. Starting material was prepared in 4 steps, but I should say 5 steps from tryptophan ok.

(Refer Slide Time: 04:57)



So, once this was prepared, then this was treated with this alpha beta unsaturated aldehyde. So, as I said in one pot, three reactions taking place a Mannich reaction, 3, 3-sigmatropic rearrangement that is Cope rearrangement, followed by another Mannich reaction ok. So, then a Cope rearrangement followed by another Mannich, you get the corresponding tetracyclic compound. So, earlier, we had furan, now you have the dimethoxy carbon ok.

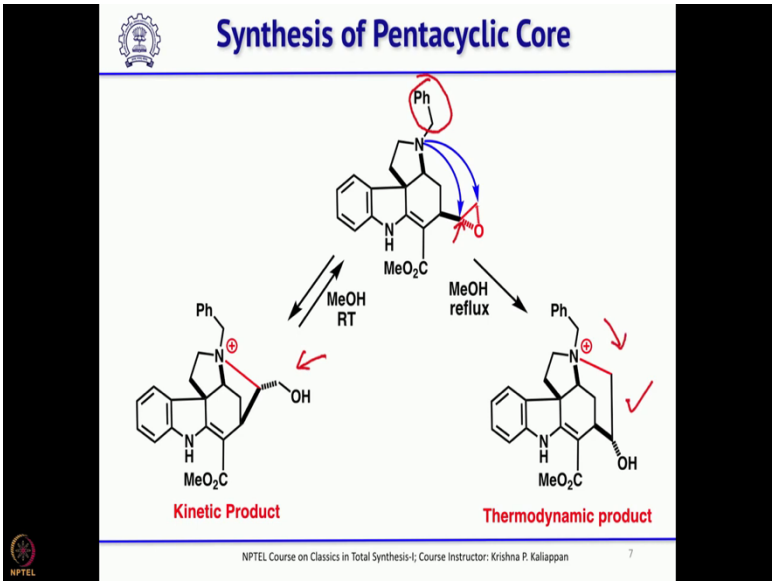
(Refer Slide Time: 05:33)



Once you have this, next what you should do is you have to hydrolyze the acetal to aldehyde; hydrolyze the acetal to aldehyde. So, you do that. Now, the aldehyde can be homologated. So, how do you connect this? Now, you have to connect these two; is not it? Now, you have to connect these two and you need one more carbon atom; basically you need one more carbon atom and connect this. So, that can be done.

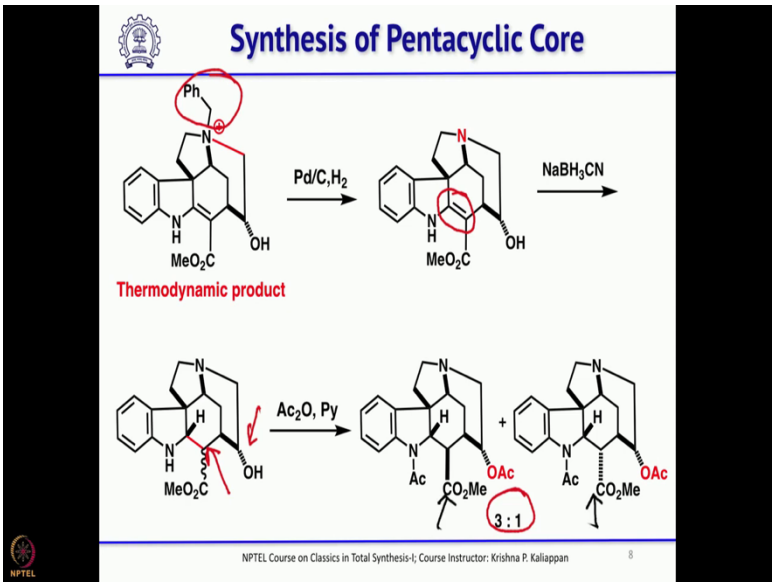
Now, if you take this and then, treat with tri methyl sulfonium ylide. The tri methyl sulfonium ylide as you know when it treats with aldehyde, it will form an epoxide; is not it? So, that is what you get you get an epoxide.

(Refer Slide Time: 06:17)



Now, this epoxide ok, if you remove the benzyl group, if you remove the benzyl group hydrogenolysis, then what will happen? It will open the epoxide. So, when it opens the epoxide, from the less hindered side if it attacks, you get the thermodynamic products ok or it can also attack this carbon ok. One will give five-membered ring, the other will give a six-membered ring ok. Correct? One will give this is five-membered, this is six membered.

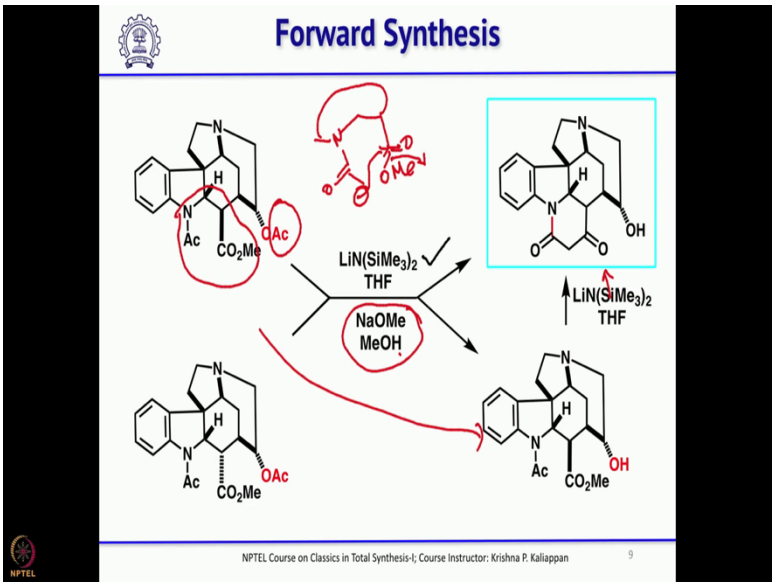
(Refer Slide Time: 06:56)



So, you take the thermodynamic product that is the six-membered which is required, then that can be controlled to get only one as the major product. Now, if you remove the benzyl group ok, benzyl group can be easily removed under hydrogenolysis condition. Then, the double bond you know I mean the push pull double bond can be reduced with sodium cyanoborohydride; but you get a mixture at this carbon, you get a mixture at this carbon.

No problem. The free hydroxyl, now you have the free hydroxyl that should be acetylated ok. So, when you acetylate; at that stage, you should be able to separate these two ok. So, you have this beta ester and alpha ester in the ratio 3 is to 1 ok.

(Refer Slide Time: 07:52)

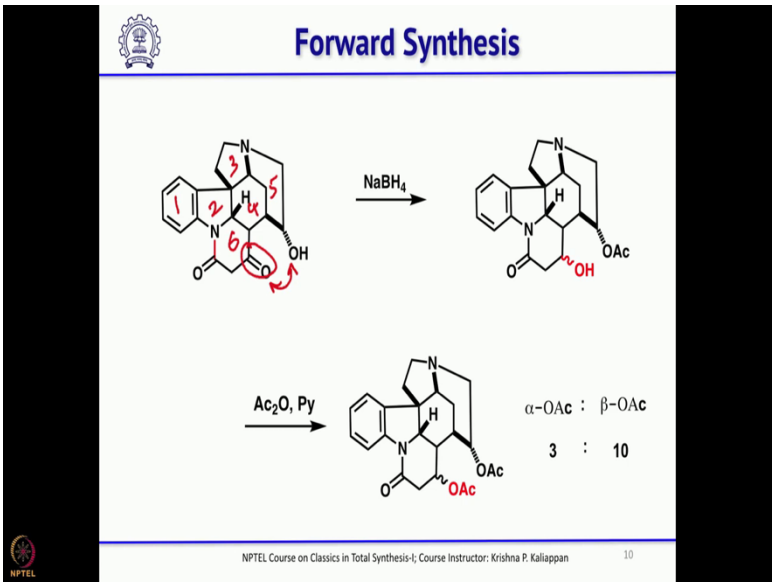


You can take both beta and alpha, you can take both beta and alpha ester and treat with two reagents successfully; one is lithium hexamethyldisilazide. Say what is lithium hexamethyldisilazide or what it what will it do? It is a base; hindered base. So, you have N acetate; is not it? That N acetate, what it does?

Here, you can see ok I have written only this portion; LiHMDS; lithium hexamethyldisilazide will generate anion here and it can attack this and your OMe will come out. So, that way you will get a six-membered 1, 3 dicarbonyl compound; six-membered 1, 3 dicarbonyl compound and followed by treatment with sodium ethoxide methanol.

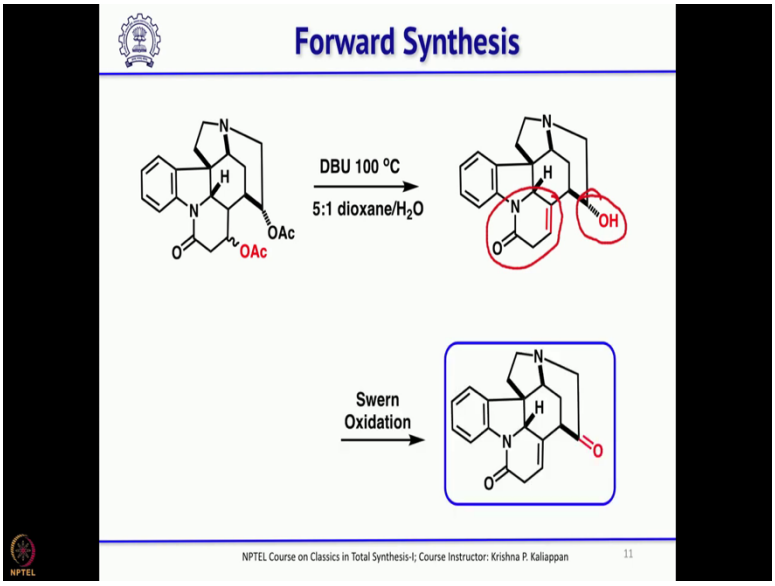
The sodium ethoxide methanol will hydrolyze the acetate and you get this ok. So, both will give; but the second one that is this, the first step, it does not work. So, it hydrolyzes only the acetate and in the second step, you treat with lithium hexamethyldisilazide and you can get this ok.

(Refer Slide Time: 09:25)



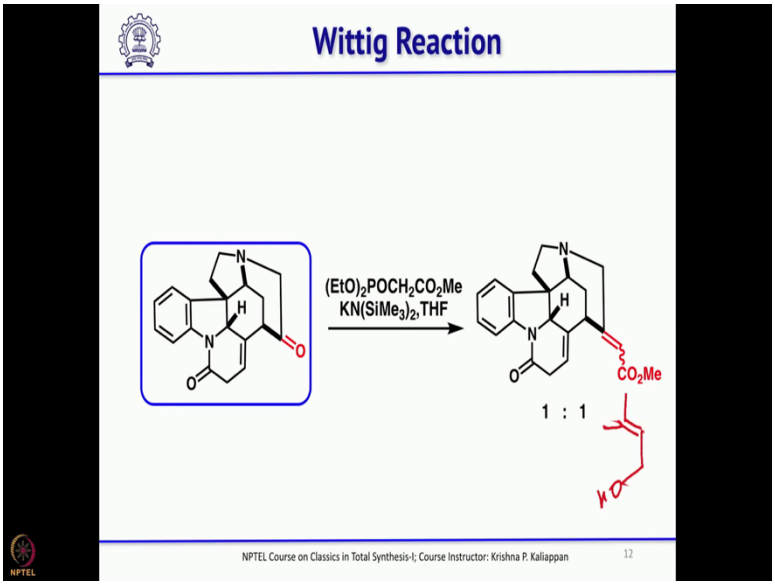
Once you have this, now you can see how many rings you have made; 1 2 3 4 5 6 ok. What is missing? You have to connect the seventh ring that is a seven-membered ring, you have to connect. How do you do it? You reduce the ketone, you reduce the ketone to alcohol; basically you have to introduce a double bond, you have to introduce a double bond. Now, you treat with acetic anhydride, you get a beta alpha acetate ok; does not matter.

(Refer Slide Time: 10:03)



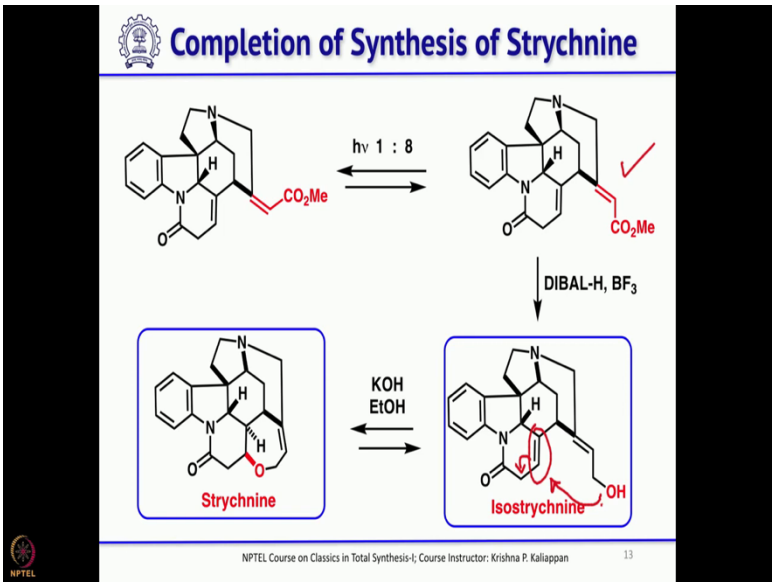
Then, you treat with DBU ok. When you treat with DBU, you get this intermediate ok. So, if you look at other synthesis, you will see this intermediate you would have seen. Now, what you need is you have to homologate this; you have to oxidize this hydroxyl and do the homologation. So, how will you do? First you oxidize with Swern; Swern condition to get the ketone.

(Refer Slide Time: 10:30)



Then, you do the Wittig reaction. So, when you do the Wittig reaction that is stabilized Wittig, you get the corresponding alpha beta unsaturated ester both E and Z in 1 is to 1 ratio ok and you know you need this isomer; is not it? You need this isomer for the cyclization to get the seven-membered ring.

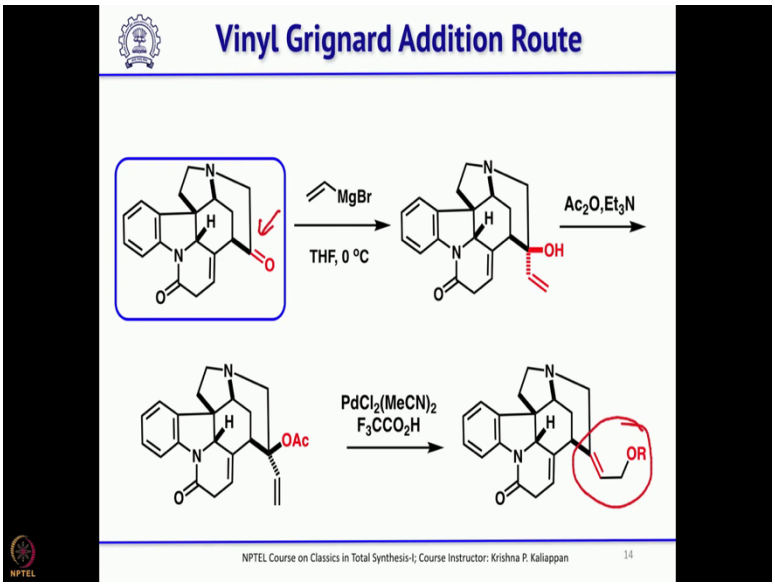
(Refer Slide Time: 10:57)



No problem. So, this can be isomerized. So, one isomer can be isomerized to required one through a photochemical condition. So, photochemical is you know very well the double bond can be isomerized; cis-trans isomerization or trans-cis isomerization can be done under photochemical condition. So, once you have this alpha beta unsaturated ester with the right regiochemistry, then reduce it with DIBAL. Once you reduce it DIBAL that will give you the isostrychnine. As you know isostrychnine has been converted into strychnine in one step by treatment with base ok.

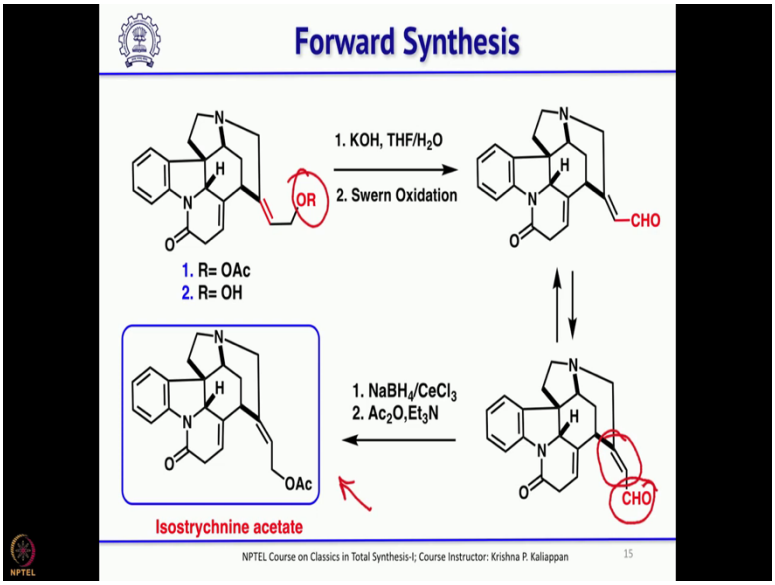
The base first it will isomerize, the double bond here; then, followed by oxa Michael addition, you will get strychnine ok. So, this was a very simple straightforward synthesis. However, the key step was one pot Mannich, 3, 3- sigmatropic rearrangement and another Mannich reaction.

(Refer Slide Time: 12:59)



Then, he also used another route instead of homologating using Wittig reagent, he used a Vinyl Grignard addition. So, on this ketone they added vinyl Grignard to get the tertiary allylic alcohol. Then, he did the palladium catalyst rearrangement. So, after making the tertiary alcohol as acetate he treated with palladium catalyst to get the allylic rearrangement; allylic rearrangement to get this protected allylic alcohol ok.

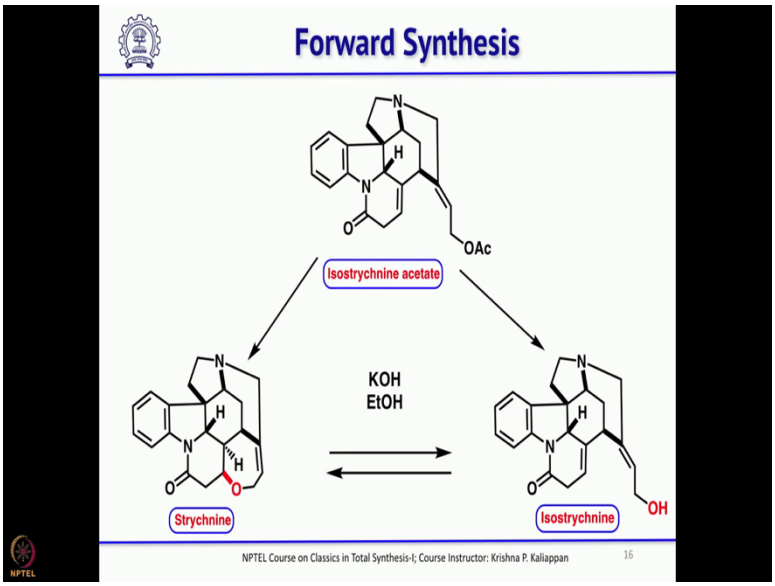
(Refer Slide Time: 12:34)



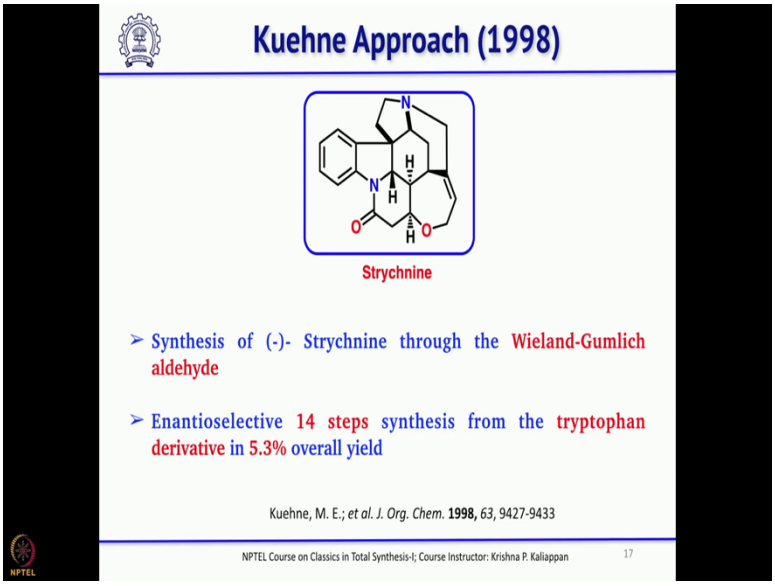
So, once you have that, if you treat with potassium hydroxide THF that the acetate is hydrolysed, then you oxidize, you get the corresponding aldehyde ok. That aldehyde can

be isomerized to get this iso particular isomer. Then, sodium borohydride, cerium chloride; sodium borohydride, cerium chloride reduces the aldehyde to corresponding alcohol that was acetylated and that is called isostrychnine acetate and that alcohol itself, if you treat with base that will convert the isostrychnine into strychnine.

(Refer Slide Time: 13:14)

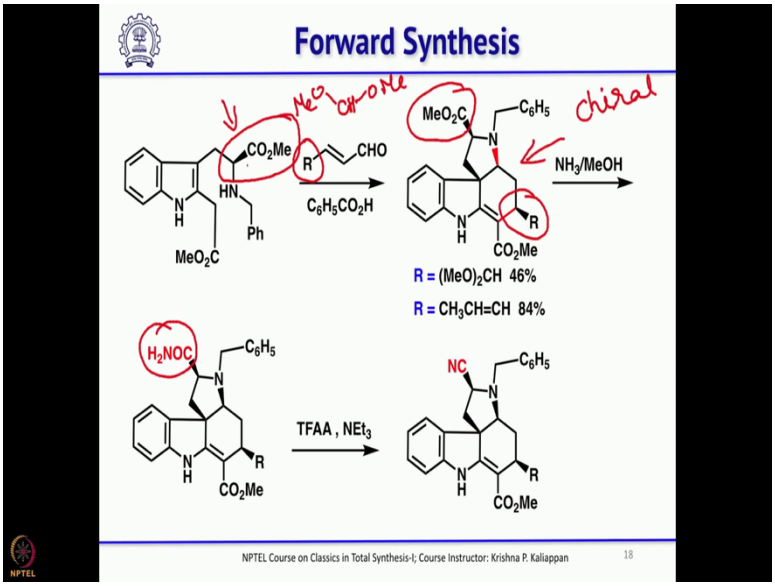


So, these are the two strategies, he used to make isostrychnine and strychnine ok. But if you look at these two approaches by reported by Corey, both are racemic synthesis.
(Refer Slide Time: 13:30)



He also tried and reported an asymmetric synthesis and in this asymmetric synthesis, he started with tryptophan derivative ok, chiral one and he also took about 14 steps; the same number of steps which he took for the synthesis of racemic strychnine ok.

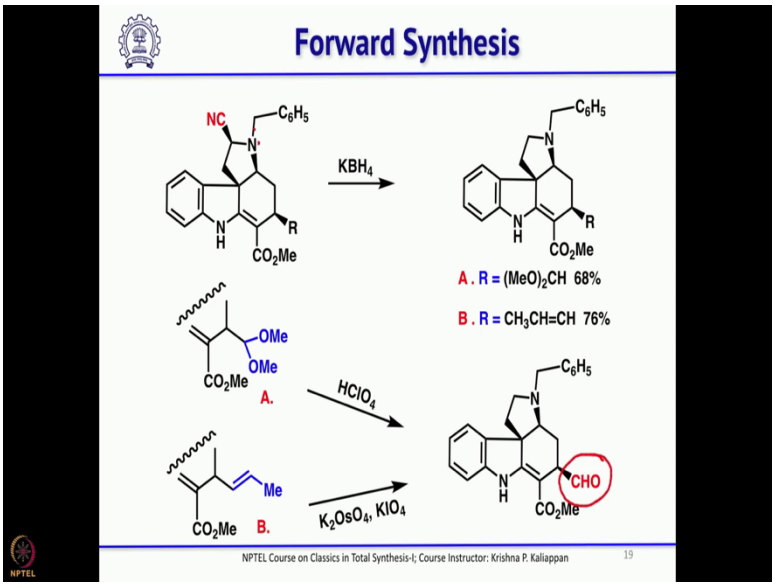
(Refer Slide Time: 13:47)



So, now, the difference between the earlier one and now is this chiral centre ok; everything else is same, except this additional chiral centre. Then, he treated with this alpha beta unsaturated aldehyde and R being CHOMe and OMe ok. So, you do the same reaction and you get the same product and here, this is CHOMe CHOMe, the main difference is this compound is chiral. So, because of one chiral centre present, you can make now three chiral centres ok. Once you have that, then you do not want this ester; is not it?.

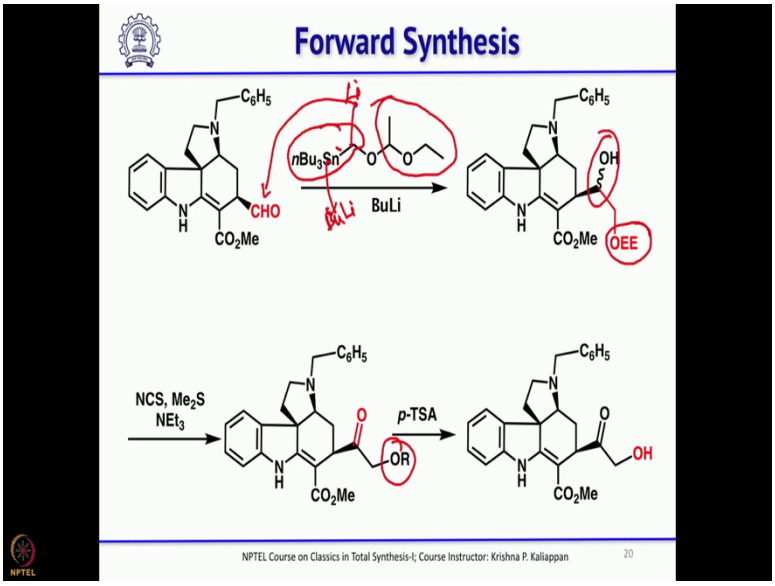
You do not want this ester ok. The ester it did its purpose; it introduced three new chiral centres. So, once that is done, you have to remove that. So, first, you convert that ester into amide. So, that is normally done by refluxing with ammonia. Then, the amide to cyanide was done with trifluoroacetic anhydride dehydrating agent amide to cyanide can be done that basically you are removing water; you are doing with trifluoroacetic anhydride

(Refer Slide Time: 15:10)



Once you have the cyanide, the cyanide group can be removed because you have lone pair here. So, the lone pair will help. So, potassium borohydride, you get the corresponding pyrrolidine ring without the cyanide ok. Next it is straight forward. So, what we have done earlier? So, this is aldehyde, you remember this is aldehyde we had.

(Refer Slide Time: 15:34)

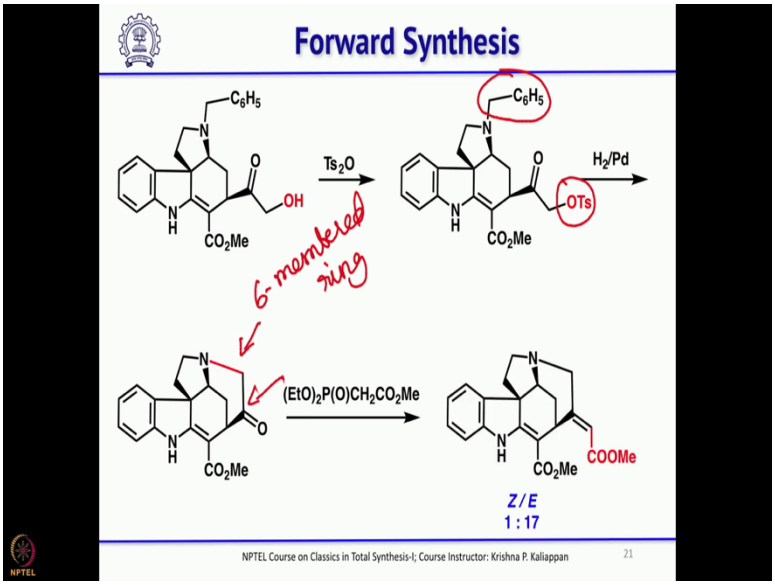


And once you have this aldehyde, what he did? He treated this with the corresponding tributyltin methanol; tributyltin methanol. But that alcohol was protected at protected with ethyl vinyl ether ok. So, now, if you treat with butyllithium; butyllithium what will

happen? It will exchange, it will exchange this and then you will get a lithium here that lithium will add to this aldehyde. So, you what you get is this compound. Basically, you have the CH_2 and the alcohol is protected as ethoxy ethyl ether; ethyl vinyl ether and ethoxy ethyl ether ok.

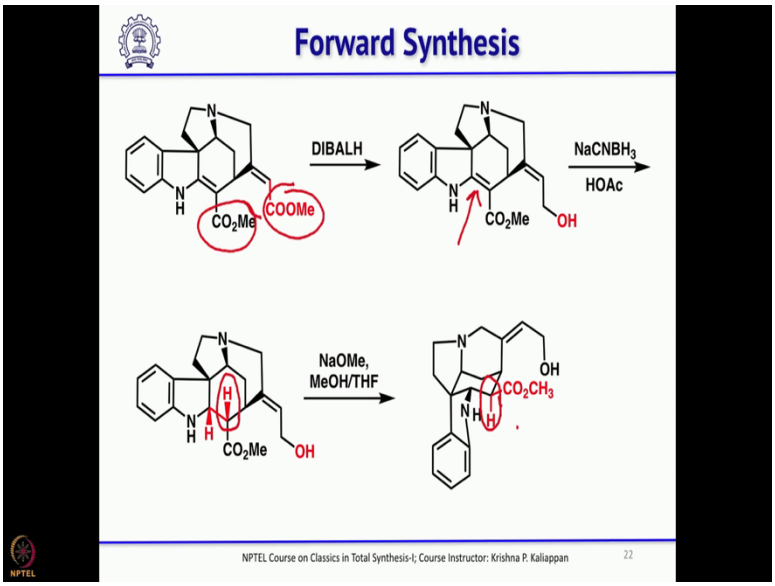
Then, you oxidize the secondary alcohol under Swern like condition to get the ketone, then remove the protecting group that is ethoxy ethyl group under acidic condition; you get ethoxy ethyl is like THP protection ok. So, you remove that and then, you get the corresponding CH_2OH.

(Refer Slide Time: 16:40)



Once you have the CH_2OH, convert that into tosylate ok tosylate. Now, if you remove this benzyl group, automatically it will undergo SN_2 reaction and then, this tosylate will go and you will get this six-membered ring ok. So, now, you have made pentacyclic core structure of strychnine. So, what is required? You have to add the 2 carbon unit and then, cyclize and then, you get the isostrychnine structure or Gumlich aldehyde. So, what he did? He did a Wittig reaction ok; the Wittig reaction gave a mixture.

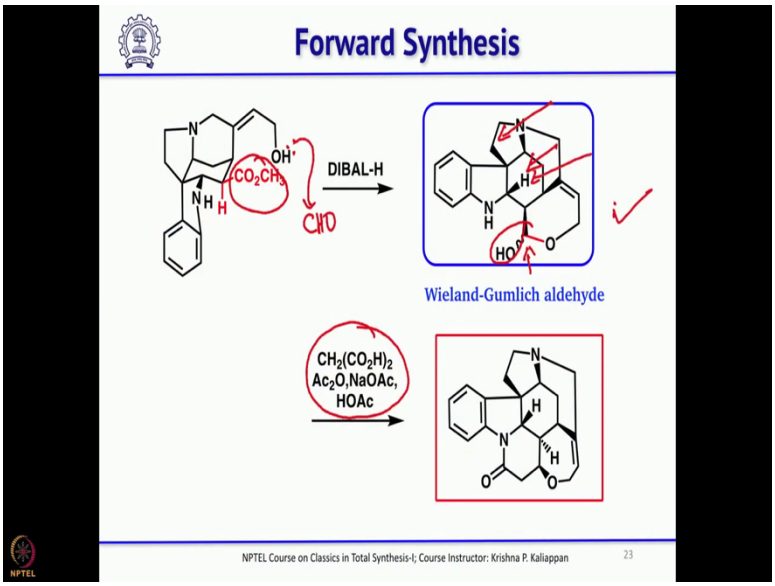
(Refer Slide Time: 17:30)



Then, the required one, he took and then, treated with DIBAL ok. When you treat with DIBAL it forms; the one is. So, this is not as reactive as this. So, one can selectively reduce that to get the alcohol. Now, you reduce this double bond selectively, using sodium cyanoborohydride acetic acid, you get this compound ok.

You can see the double bond is reduced and it gives only one isomer; sodium ethoxide methanol in THF, sodium ethoxide methanol in THF, this compound you can write like this ok. The compound can be written this way. So, what is happening? Sodium ethoxide methanol, look at this chiral centre. Hydrogen is beta; whereas, here alpha. So, the epimerisation takes place. The epimerisation takes place to give alpha hydrogen.

(Refer Slide Time: 18:34)



So, once you have that, then DIBAL will give this ester will be converted into aldehyde, as soon as the aldehyde is formed this alcohol will attack the aldehyde to give Wieland-Gumlich aldehyde. As you know when you talk about total synthesis of strychnine, there are two key intermediates; one is Wieland-Gumlich aldehyde, other one is isostrychnine. So, you can make either isostrychnine or Wieland-Gumlich aldehyde.

If you make isostrychnine which he made ok that is in the racemic synthesis of strychnine, Martin Kuehne made isostrychnine ok via Wittig reaction. He did a Wittig reaction, he also did Wieland-Gumlich followed by palladium catalyst rearrangement, then he made the corresponding isostrychnine.

Here, in this case, he what he made was Wieland-Gumlich aldehyde; what he made was Wieland-Gumlich aldehyde. The Wieland-Gumlich aldehyde is also known to be converted into strychnine in a single step. You have the lactol; the lactol on treatment with Wittig reagent ok or you can use malonic acid, acetic anhydride and acetic acid.

So, you will get the alpha beta unsaturated ester ok. This aldehyde will react; aldehyde and alcohol. The aldehyde will form alpha beta unsaturated acid and also, cyclize with this NH and then, same process the Oxa Michel addition also will take place. All will take place in one step. The Wieland Gumlich aldehyde can be converted into strychnine successfully by treating with malonic acid acetic acid sodium acetate and acetic anhydride ok.

So, this is again another interesting total synthesis. So, we talked about four total synthesis of strychnine. We started with total synthesis of Woodward ok. So, Woodward used a very nice classical method to synthesize strychnine. Then, we talked about Viresh Rawal.

So, Viresh Rawal used a very nice intramolecular Diels-Alder reaction to construct the six-membered ring here. Then, we talked about Larry Overman used a cleverly a Claisen rearrangement ok; Ireland ester Claisen rearrangement to get the six-membered ring and he also used a Mannich reaction, a combination of Mannich reaction and Claisen rearrangement to get the five and six-membered ring.

Here, in this case in Martin Kuehne's total synthesis of strychnine he used domino Mannich and 3, 3 sigmatropic rearrangement followed by another Mannich. So, three reactions in one part to construct the C and D ring ok. So, with this, we will stop and then we will talk about more alkaloids and other natural products in the next few lectures.

Thank you.