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

Lecture - 27
Strychnine (Woodward)

Yeah good morning and welcome back to the NPTEL lecture series ion Classics in Total Synthesis Part- 1 and this is Professor Krishna Kaliappan from IIT Bombay. So, we will continue our discussion on total synthesis of natural products today. In the last class we talked about total synthesis of an alkaloid called perhydrohistrionicotoxin by E J Corey which involved you know two important key reactions; one Barton reaction and the second one is Beckmann rearrangement ok.

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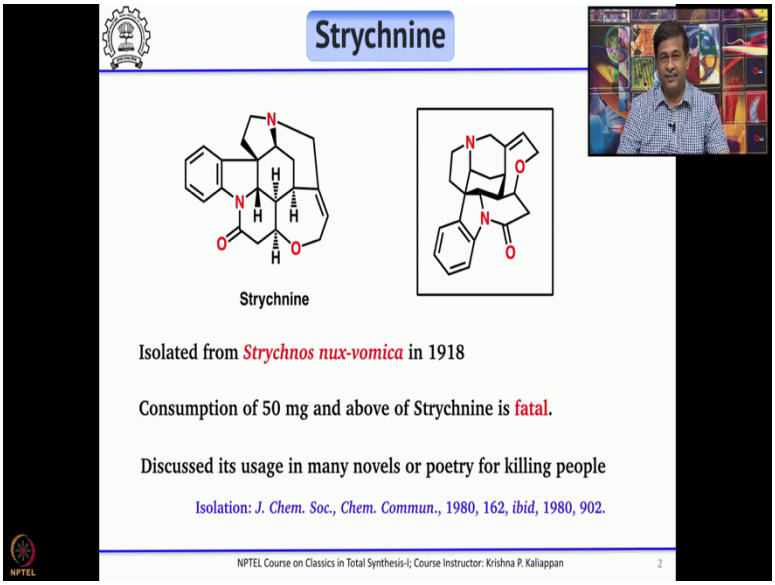

So, today we will talk about one of the most complex alkaloid synthesized in 20th century. So, that molecule is called Strychnine, I am sure many of you might have heard the name Strychnine is it was you know one of the most complex molecules isolated in the 1918. And this is the structure of Strychnine and in fact, is one of the first alkaloids to be first complex alkaloids to be isolated.

It was isolated from Strychnos nux - vomica in 1918 and it was considered as one of the dangerous natural product, because if you consume anything more than 50 milligram of this natural product it is fatal ok. It is so dangerous so bad and this poisonous material

should be handled very very carefully. In fact, many novels and poetry those who are familiar in reading English novels know that there are many stories where Strychnine was given to poison and kill people ok, it has been routinely used in many novels.

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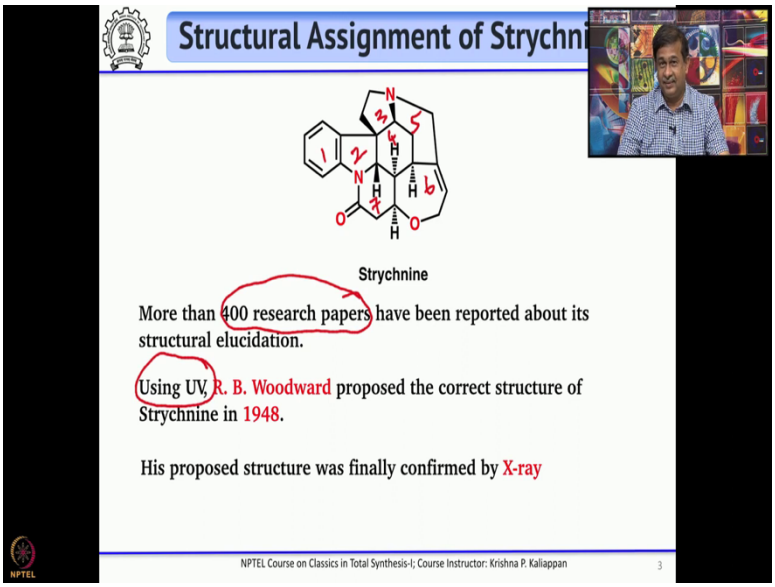

From the complexity point of view if you look at this molecule what are the challenges one can expect from synthesis point of view? First of all, how many rings are there? See; 1 2 3 4 5 6 7 there are 7 rings there are 7 rings, one can imagine you know I am talking about when the molecule was isolated in 1918. So, making a molecule of this complexity with 7 rings is not a joke and more importantly even the structural elucidations took considerably long time. It was isolated in 1918, but the correct structure was proposed by Woodward correct structure was proposed by Woodward after 3 decades ok.

It took 30 years to propose the correct structure of Strychnine, but interestingly if you look at how Woodward proposed the correct structure of Strychnine was based on using UV, you know you one should know those days NMR was not there, X- ray was not there. So, one has to depend on two important techniques one is degradation ok. Those days Strychnine was available in large quantity ok, one could isolate Strychnine in large quantity.

So, you keep on doing degradation ok until you reach a known compound ok that is how you know ok when you do a degradation you can expect what reaction it can undergo and what are the products you got based on that you can work back, work back and then

assign the structure. So, those days degradation played a very very important role in assigning the structure nevertheless the final proof for structural assignment of any natural product comes only in the form of synthesis ok, it was those days.

And you can imagine; there were 400 research papers in the 30 years 400 research papers have been published just to talk about only the structural elucidations of Strychnine ok. So, partial structural elucidations 400 research paper, I do not think any other natural product would have got that much attraction particularly about structural assignment ok that much complex this molecule was.

And finally, whatever structure Woodward proposed in 1948 based on degradation and UV was confirmed later by X- ray, then you can imagine the intuition the knowledge of various organic reactions by Woodward really stood very tall ok, exactly he proposed a correct structure without even looking at other techniques. So, that tells volumes about his knowledge of organic chemistry.

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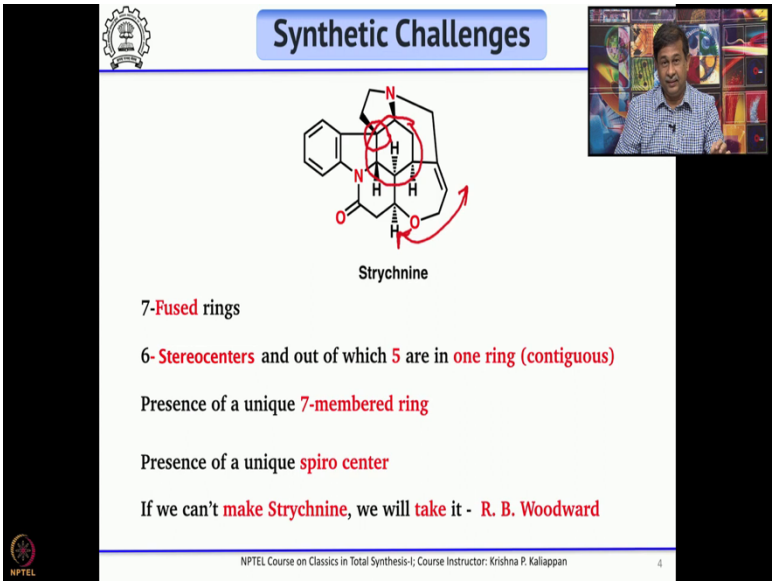

And when you talk about synthetic challenges as I mentioned already there are 7 rings ok. So, making 7 rings those days is not a joke, it was very very complex problem and one has to deal with it ok. And if you look at the number of stereocenters if you look at the number of stereocenters there are 6 stereocenters ok in this molecule. And among these 6 stereocenters 5 stereocenters are in this ring ok, 5 stereocenters are attached to one ring and next task is all the 5 stereocenters of this ring are contiguous ok.

So, this makes much more challenging because you have to introduce 5 stereocenters in one ring and these 5 stereocenters are contiguous ok. And another interesting aspect of this molecule is this seven - membered ring, this is a unique seven - membered ring which was not heard or not seen in other natural products the first time they have seen such unique 7 membered ring in an alkaloid ok.

Then there is a spiro center. So, is it possible to locate the spiro center in this molecule you can make easily you can see the 7 rings, but can you look at the spiro center there is one spiro center that is this there is one spiro center. So, these are some of the synthetic challenges one could foresee before starting working on synthesis of Strychnine ok.

After proposing the correct structure of Strychnine based on various degradation studies Woodward thought definitely this is the molecule one should make. So, the more the challenge better for synthetic chemist to work on that because they used to love challenge ok and that time he made a very very famous statement. And that statement is if we cannot make it if we cannot make Strychnine then we will take it ok.

You know if you take Strychnine what will happen ok, that is how you took this as a challenge and started working on Strychnine and as you know during his days the retro synthetic concept was not there. So, that is why I am not going to talk about retro synthesis of Strychnine by Woodward nevertheless we will see how he could go ahead and then make Strychnine in reasonably good quantity ok.

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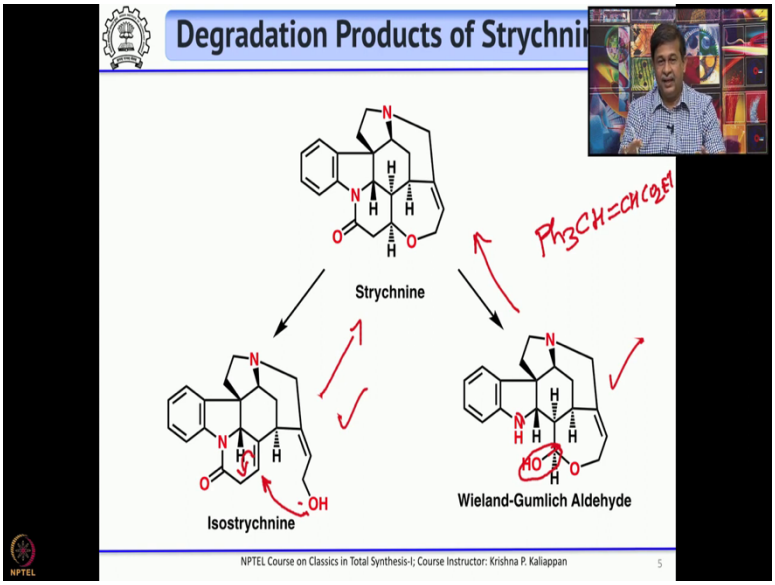

So, before that as I said the structure of Strychnine was arrived based on combination of spectral data and degradation studies. The degradation studies of Strychnine when you degrade Strychnine there are two important sub structure ok one was Isostrychnine. So, isostrychnine and Strychnine if you look at, isostrychnine can be converted into Strychnine how?

If you migrate this double bond if you migrate this double bond you become alpha beta unsaturated system followed by oxa - Michael addition will give Strychnine. So, that was the first degraded product from Strychnine. The second degraded product was called Wieland - Gumlich aldehyde. If you look at this you can see that this is a lactol, is not it?

This is a lactol if you do a stabilized Wittig reaction if you do a stabilized Wittig reaction ok, this lactol means it is aldehyde ok and alcohol. The aldehyde will undergo this stabilized Wittig reaction to get alpha beta unsaturated ester then it can form an amide and then it can undergo oxa - Michael addition to give Strychnine.

So, in one step one can convert Wieland Gumlich aldehyde to Strychnine ok. So, if you look at subsequent total synthesis of Strychnine ok subsequent total synthesis of Strychnine most of the synthetic groups either used this key intermediate or isostrychnine as a key intermediate. So, they come up to this and from here it is known ok.

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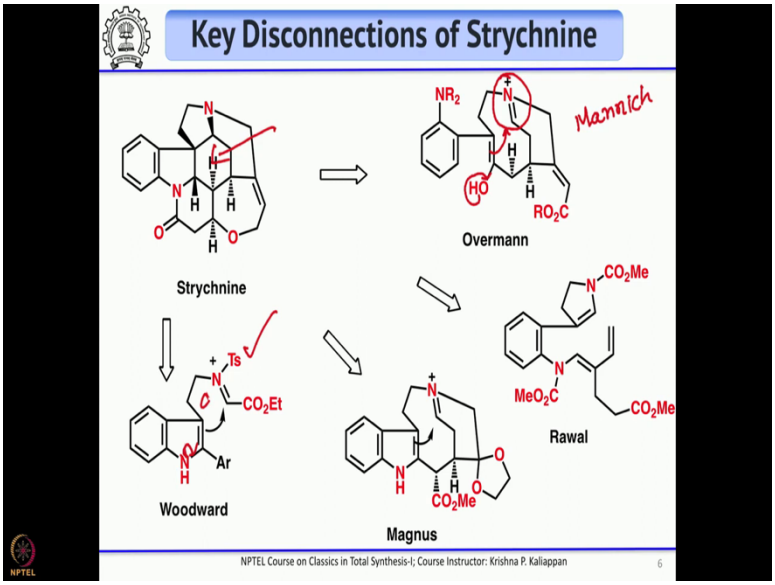

What are the key disconnections? Ok I will not go into the complete retro synthesis what are the key disconnections of some of the synthesis, there are many synthesis I will talk about only four total synthesis of Strychnine and today I will talk about Woodward's total synthesis.

So, Woodward's idea was first to construct the spiro system and the spiro system how he construct is first you make this iminium ion ok, this iminium ion then use the lone pair on the nitrogen of indole ring that will come and then neutralize the positive charge on the iminium. So, that is how you construct the spiro as well as the C ring ok.

Now, Overmann, Overmann almost followed similar trend that is the iminium ion, but what he did was the spiro system was constructed by a reaction called Mannich reaction ok. So, this enol so, now, this will come and this will attack. So, the Mannich reaction was the key reaction in Overmann's total synthesis of Strychnine.

And Magnus, Magnus also almost followed similar method of Woodward's ok. He form a iminium and the indole, indole double bond attacks and neutralizes the positive charge on the nitrogen. One synthesis which was completely different than these three approaches and was well received was Viresh Rawal's.

So, Viresh Rawal constructed this particular ring ok this is a 6 - membered ring. So, always when you see a 6 - membered ring one reaction which should come to everybody's mind is Diels - Alder reaction, is not it? Normally, when you talk about 6-membered ring 2 reactions will come to your mind one is Robinson annulations sequence the other one is Diels-Alder reaction. So, he cleverly used Diels-Alder reaction as the key reaction to construct this CD this ring ok.

So, these are some of the key disconnections used by synthetic chemist across the globe for the synthesis of Strychnine.

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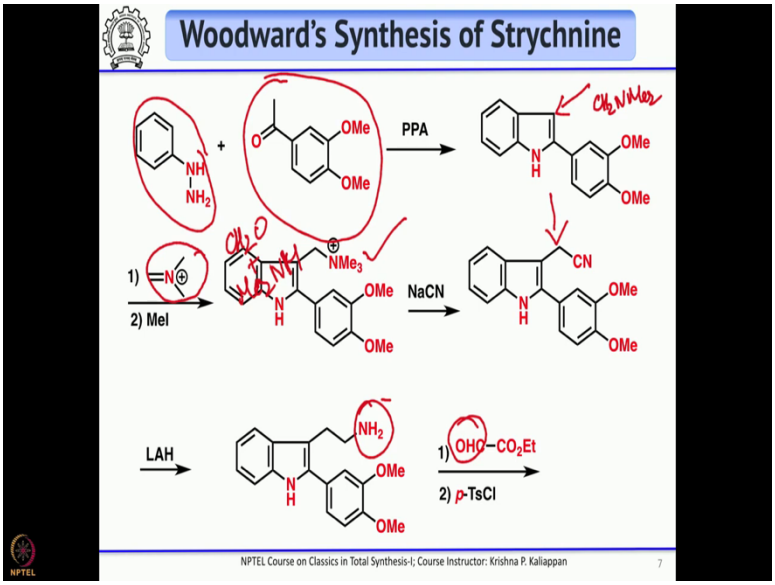

Now, let us as I mentioned let us discuss total synthesis of Strychnine by R. B. Woodward today. So, he started with Fischer indole synthesis, first he started with phenyl hydrazine and treated with this ketone this two upon treatment with polyphosphoric acid form this indole ok. So, now, what he has to do is, he has to functionalize the carbon number 3 ok he has to functionalize carbon number 3.

So, what he did? He used a Mannich reaction ok. So, this is obtained from formaldehyde dimethylamine ok and HCl ok, this is you know standard intermediate for Mannich reaction. So, he introduced first a CH_2NMe_2 here CH_2NMe_2ok afterwards he added methyl iodide so; that means, already you have a tertiary amine. The tertiary amine was quaternized ok this tertiary amine was quaternized.

So, now once you have quaternized amine it can be a good leaving group it is a good leaving group. So, if you treat with any nucleophile the NMe_3 is a good leaving group it can go. So, what he did, he took this compound and treated with sodium cyanide ok, when use sodium cyanide it underwent SN_2 displacement to get the corresponding cyanide ok. So, basically in three steps he could introduce this functional group that is CH_2CN.

Next one has to reduce the cyanide. So, that was easily done by treating with LAH that is lithium aluminium hydride. So, you could get $CH_2CH_2NH_2$ in good yield. The subsequent step was the cyclization step ok, the key step to make the spiro system. The

first step was just make the imine just make the imine you have an aldehyde and you have an amine you make the imine then you treat with tosyl chloride. What will happen with tosyl chloride? When you treat with tosyl chloride the imine nitrogen will be tosylated imine nitrogen will be tosylated ok.

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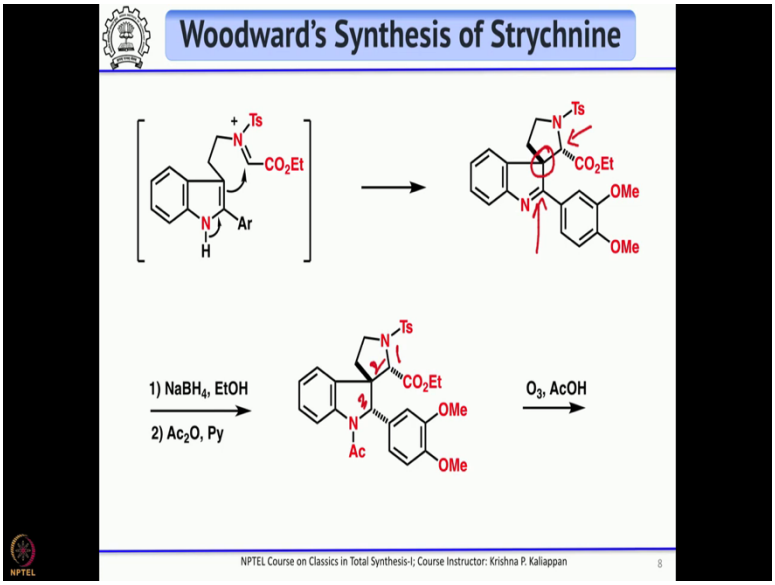

So, that is what happened, you can see first imine is formed then N-tosylation took place, then followed by cyclization all this happened when you treat with tosyl chloride to get the spiro system ok. So, now, you can see you have made the spiro system and you introduced one chiral center and in the process this became imine ok. So, once it becomes imine you have to reduce the imine, is not it? The imine was reduced to the corresponding amine by sodium borohydride and that resultant NH the indole NH was acetylated to get the corresponding N acetyl group.

So, now, you can see there are 3 chiral centers 1 2 3 were fixed using this reaction ok, all are relative ok all are relative and they are not absolute ok. Next step he did ozonolysis, guess what would happen, when you do ozonolysis of this what would have happened? Are there double bonds? No, you have 2 aromatic rings is not it, you have 2 aromatic rings more substituted double bonds will be cleaved under ozonolysis condition ok.

So, if you look at this aromatic ring and this aromatic ring, this is the double bond ok, this is the double bond which is tetra substituted, is not it? This is a double bond which is

tetra substituted. Now, if you cleave this particular double bond selectively if you cleave this particular double bond selectively what we will get is the corresponding diene.

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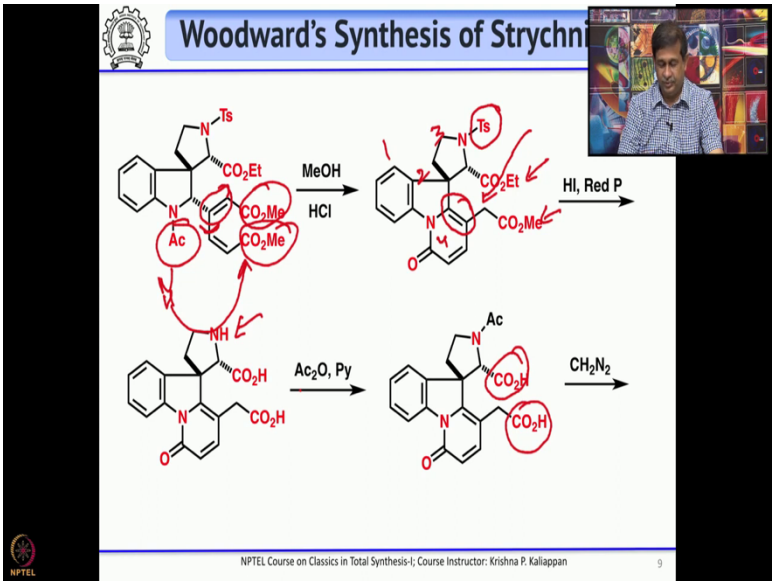

And the terminal, since you have OMe this will become ester ok so, di ester ok. So, this is a very very important and clever idea of using aromatic ring ok aromatic ring to generate the bisester using selective ozonolysis that was one of the classical thinking ok. Then you treat with HCl methanol ok, HCl methanol first it removes the acetate first it removes the acetate then what will happen? You have that NH is not it, this NH will attack this ester because if you rotate this C-C bond if you rotate this C-C bond it will come here.

So, what will happen, you get the corresponding lactam you get the corresponding lactam that is one thing. Second thing is the double bond which is outside now isomerized ok to this ring. So, two reactions happen one the N acetyl was cleaved followed by cyclization, the second the double bond isomerization to get this pyridine ring ok.

Now, if you look at Strychnine out of 7 rings 4 rings are constructed 1 2 3 4 ok, 3 more rings to be constructed the 5th ring ok, the 5th ring here was constructed using a Claisen reaction you have CO_2Me and CO_2Et one can generate anion here and attack. So, that is what happened and for that before trying to do this base catalyzed or base mediated the Claisen reaction what happened this tosyl group the presence of tosyl group created

trouble ok. The tosyl group got you know eliminated and then sometimes it created a double bond here double bond here it gave complex mixture.

So, what he thought was first let us remove the tosyl group. So, he removed the tosyl group with HI and red phosphorus, but when you try to remove the tosyl group with HI and red phosphorus the esters also will get hydrolyzed esters also will get hydrolyzed. So, that is how you get the dicarboxylic acid then no problem, the NH was acetylated with acetic anhydride and pyridine to get the diacid ok diacid can be easily converted into the bisester by diazomethane.

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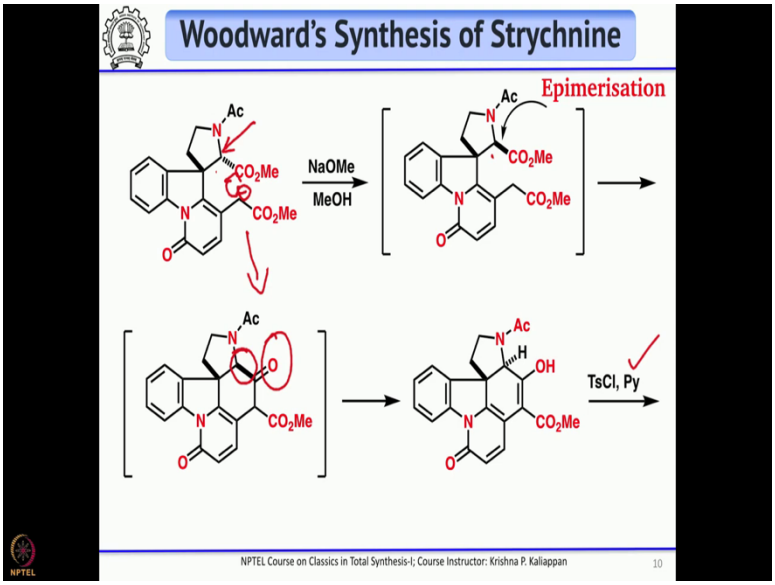

The diester by diazomethane treatment you get the diester, now if you do the Claisen reaction sodium methoxide will generate anion and attack the ester. So, you will get the corresponding beta keto ester. But when he tried to do that the epimerisation was taking place at this carbon epimerisation was taking, you can see what was the stereochemistry here and what is the stereochemistry here. So, the after epimerisation the cyclization takes place ok leading to the formation of beta keto ester ok.

So, this is what he wanted, but this C-C bond formation that is the epimerisation happened and then you got this compound ok. No problem, next what one should do is you have to remove the ketone you have to remove the ketone you do not want the ketone there you want CH_2 ok. So, the keto ester as you know the keto ester can exist in enol form ok. So, once you have this in enol form you can convert that into

corresponding enol tosylate. So, if you treat with tosyl chloride pyridine it forms a corresponding tosylate ok.

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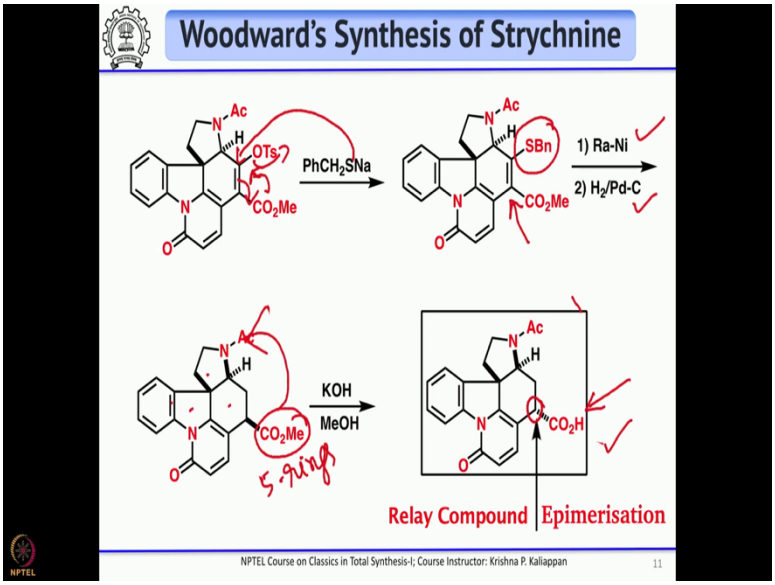

Basically he want to make this compound ok. So, now once the tosylate is there one can think of addition elimination reaction with sodium benzyl thiolate ok. So, this will give you the corresponding SBn. So, this will undergo addition and followed by when it comes back the tosyl group will go ok. So, now, SBn as you know SBn and then double bond can be reduced under hydrogenolysis condition.

First Raney nickel will remove SBn then simple hydrogen and palladium carbon will reduce the alpha beta unsaturated ester to give this compound ok. So, now if you look at this closely you have made 1 2 3 4 5, 5 rings are made ok. Now you have to connect this ester to this ok you have to connect this ester to the amine. So, first he hydrolyze the ester to carboxylic acid with potassium hydroxide methanol and that time this particular carbon also underwent epimerisation, because when you draw a conformation you draw a possible conformation of this molecule.

After epimerisation this carboxylic acid occupies equatorial position ok that is why it undergoes epimerisation when you treat with potassium hydroxide methanol to get alpha carboxylic acid ok. So, you have the alpha carboxylic acid and in fact, this is the compound this is one of the compounds prepared in large quantity from Strychnine by

degradation ok this is one of the compounds prepared in large quantity from Strychnine by degradation ok and this is also called relay compound.

What is relay compound? What is relay approach? Ok. So, before I go further I will talk about what is relay approach. So, those days when they work on total synthesis of complex molecules ok. So, they have to start from some simple commercially available starting materials and then they go further after 10-15 steps you see you will have 1 milligram or 2 milligram ok, but interestingly they will reach a very very important intermediate that intermediate they might have isolated from the natural product through degradation ok.

Suppose if X is a natural product through degradation after few steps they get Y ok. Now same group or some other group works on the total synthesis of the natural product X and they follow a certain pathway and then reach Y, Y is the compound, which from the natural product they could degrade and get it in large quantity.

Now, what they do, they have already established a method for making Y from simple starting material ok they already established the method for making Y, now what they will do instead of going back and then starting from the commercially available starting material to make Y.

What they do, they take Y which was available from natural product by degradation because it is available in large quantity by synthesis they might have made only small quantity. They will take this degraded product again from the degraded product they try to convert they try to achieve the synthesis of the target molecule X. So, that is called relay approach ok. So, what Woodward has used here as relay approach?

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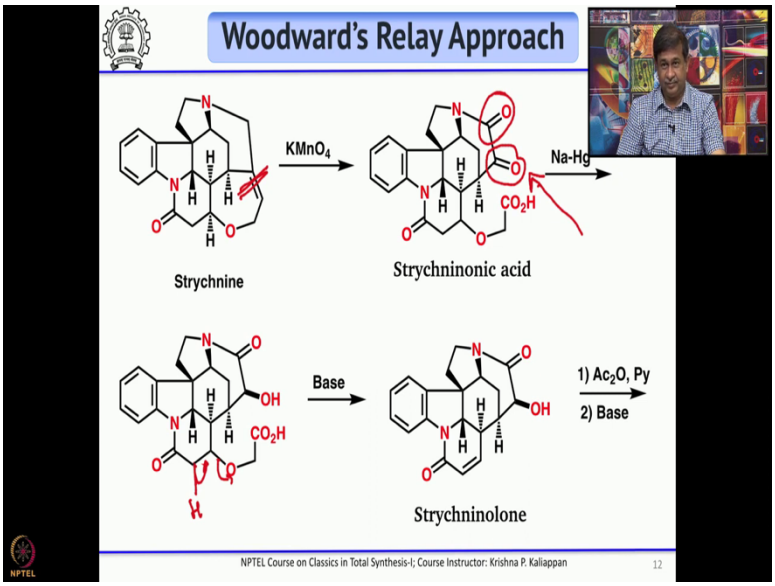

So, Strychnine is available in plenty because from natural source, now when you when you do potassium permanganate oxidation as you know this double bond gets cleaved ok this double bond gets cleaved. So, one side it becomes ketone, other side it becomes carboxylic acid and not only that not only that this becomes ketone it also oxidizes the adjacent one adjacent CH_2 to get a keto lactone ok it is a keto lactone.

The next step what he did so this is also called strychninonic acid. So, then sodium amalgam, sodium amalgam selectively reduces this ketone in the presence of two lactams it will not touch the lactam it will reduce only the ketone to get the corresponding alcohol.

Now, this alcohol upon treatment with base what happens, if you have hydrogen here see this hydrogen is acidic. So, base will pick up this proton and it undergo elimination to give this alpha beta unsaturated lactam ok. So, this Woodward and his group made in large quantity ok this is also called Strychninolone ok.

Now, if you treat with acetic anhydride, acetic anhydride pyridine. So, what you get? This OH will become OAc and base treatment also migrates a double bond base treatment you can see the base treatment migrates a double bond from alpha beta to beta gamma ok.

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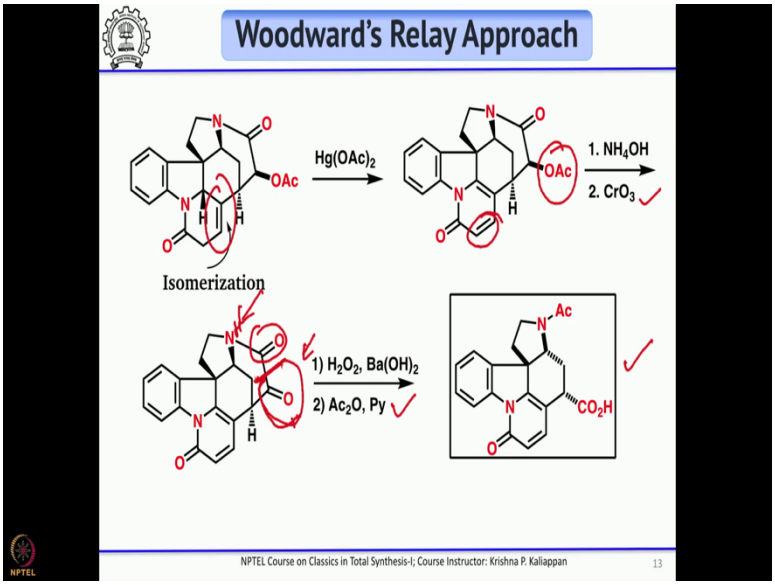

From this now he treated with mercuric acetate ok, mercuric acetate. So, what happened? It introduced another double bond ok one more double bond introduced to get the six-membered lactam six - membered lactam. What he has to do? He has to hydrolyze the acetate and then the resultant alcohols if you oxidize with chromium trioxide you get the corresponding keto lactam.

This upon treatment with H_2O_2, H_2O_2 as you know it can undergo Baeyer - Villiger oxidation here ok. Baeyer - Villiger oxidation followed by hydrolysis this becomes the corresponding carboxylic acid this becomes corresponding carboxylic acid and this undergoes decarboxylation and then you get corresponding NH.

So, this much happens in the first step that is hydrogen peroxide Baeyer Baeyer - Villiger oxidation and hydrolysis this becomes carboxylic acid and this becomes NH, that NH is acetylated to get this carboxylic acid. So, now, you know Woodward has come up to this stage starting from simple phenyl hydrazine he could come up to this stage.

The same compound Woodward also got it by degradation from Strychnine in large quantity. So, now, what he felt? This compound made from Strychnine in large quantity could be used further instead of starting from simple starting material. So, and here also you can see that ester gets hydrolyzed to get the carboxylic acid.

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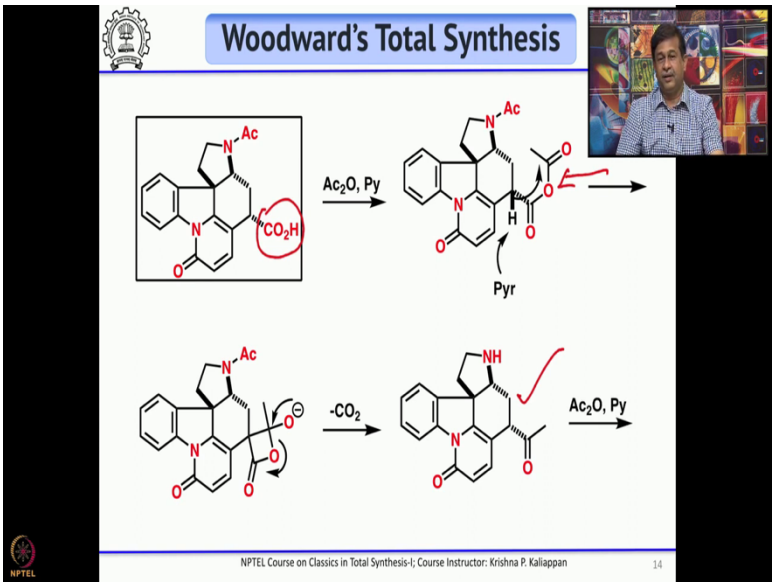

Then once you have that he treated with acetic anhydride so, basically he wants to decarboxylate this one ok and introduce $COCH_3$. So, when you treated with acetic anhydride and pyridine first the carboxylic acid was acetylated carboxylic acid was acetylated $COOCOCH_3$.

Since you are using pyridine so what happened the pyridine picks up this hydrogen pyridine picks up this hydrogen then it attacks the acetyl carbonyl group, basically when that happens you get a four - membered ring ok. The four - membered ring if you see it can undergo elimination of carbon dioxide four - membered ring can undergo elimination of carbon dioxide and when it happens then you get the corresponding acetyl group. So, this is what he wanted, he wanted the $COCH_3$ that he did cleverly by treating with acetic anhydride and pyridine.

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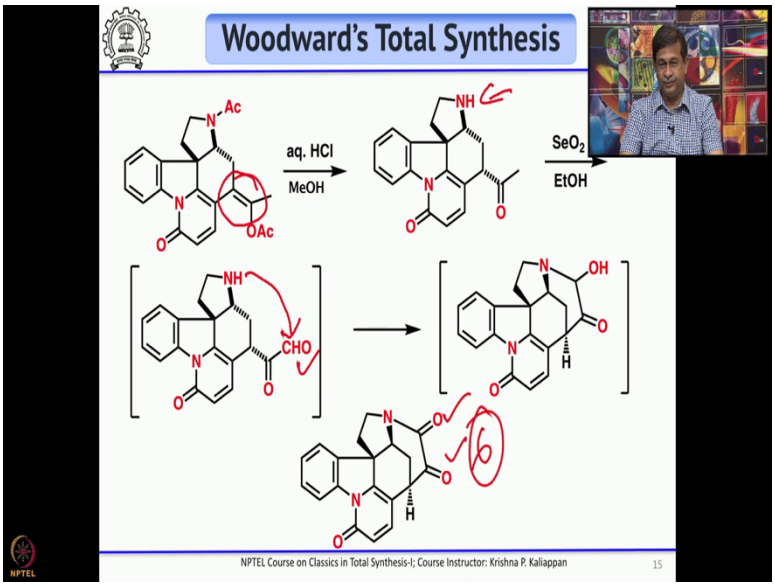

Now, again he has to treat with acetic anhydride and pyridine to get the N acetate and aqueous HCl methanol ok not only N acetate this also became enol acetate this $COCH_3$ become enol acetate. Then if you hydrolyze with HCl methanol it becomes the $COCH_3$ and also it becomes NH this becomes NH.

Selenium dioxide oxidation as you know if you have $COCH_3$ selenium dioxide oxidation will give COCHO. So, that is the first step it forms COCH CHO now this NH intramolecular will attack the CHO to form the aminol to form the aminol. Now, the aminol again will get oxidized with selenium dioxide to get the keto lactam. So, now if you look at this carefully we have made six rings ok six rings are done. So, seventh ring that seven - membered ring has to be done.

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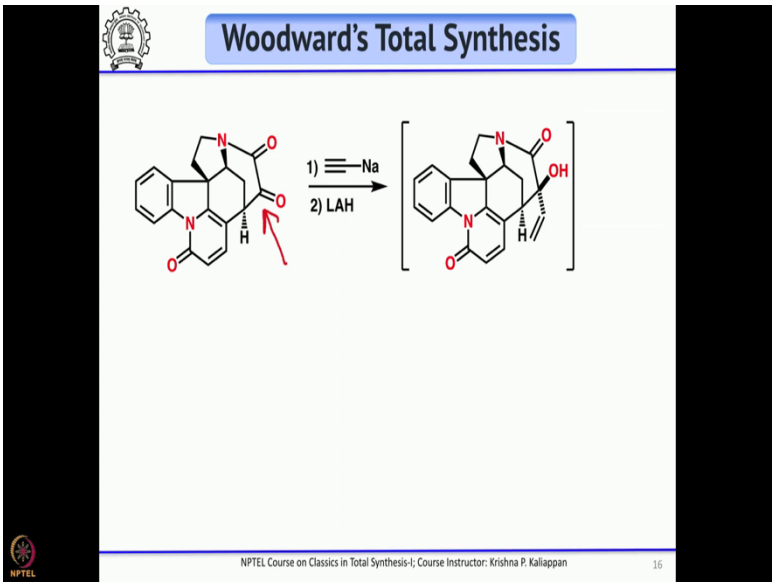

So, now you have lactam and ketone. So, you can differentiate ketone from lactam. So, he added sodium acetylide. So, that added to this ketone followed by reduction of the triple bond with LAH he got the double bond. Lithium aluminium hydride in addition to reducing the triple bond to double bond it also reduced the lactam to corresponding amine, this on treatment with HBr ok.

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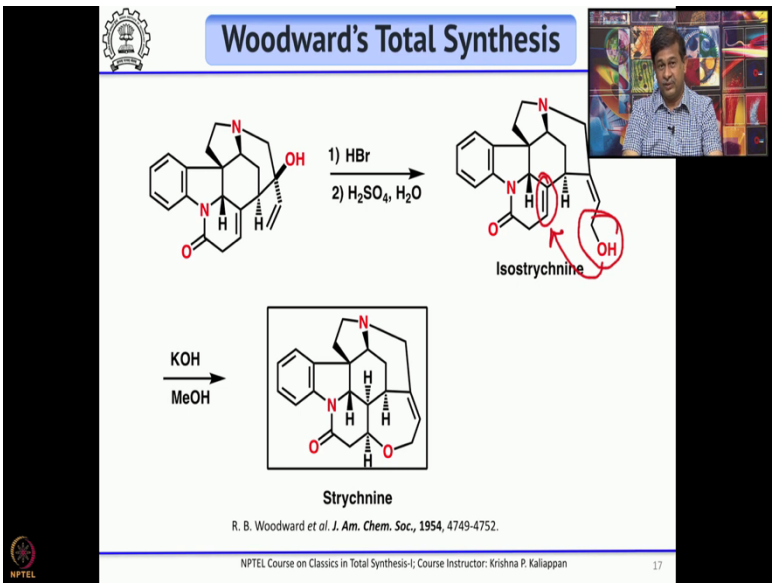

Allylic rearrangement took place and then you got isostrychnine ok, HBr it forms allylic rearrangement to get the Br allylic bromide this on treatment with H_2SO_4 water you get

the corresponding alcohol. What is this? This is nothing but isostrychnine and we all know isostrychnine has been already converted into Strychnine by base treatment. So, he simply treated this isostrychnine with potassium hydroxide methanol and it underwent first isomerisation of the double bond to alpha beta unsaturated system followed by oxa-Michael he got Strychnine.

So, this was considered as one of the most advanced and classical synthesis in 20th century and this actually opened many, many synthetic methods and there are many total synthesis of Strychnine reported since then we will discuss at least three more total synthesis of Strychnine in the next class ok.

Thank you.