Classics in Total Synthesis - I
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Lecture - 28
Strychnine (1) Rawal, 2) Overman)

So, good morning and welcome back to the NPTEL course on Classics in Total Synthesis. In the last class we talked about the total synthesis of strychnine by Woodward. So, we will continue our discussion on total synthesis of strychnine by two more groups today we talk about total synthesis of strychnine by Viresh Rawal's group from University of Chicago and the second one is from Larry Overman from University of California ok.

So, when you talk about total synthesis of strychnine each group use some key reactions to construct the center 6 membered ring. Rawal's group used two key reactions one is an intramolecular Heck reaction the second one is an intramolecular Diels-Alder reaction to construct this six membered ring ok.

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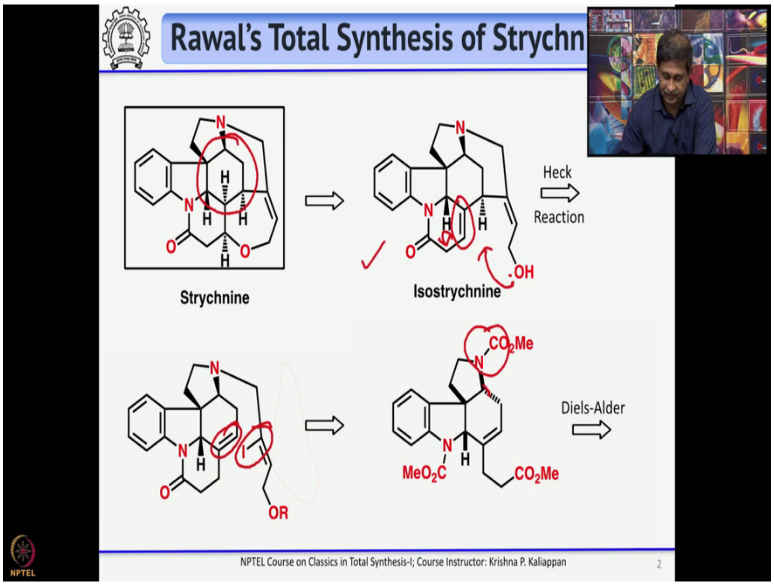

Rawal's Total Synthesis of Strychn

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So, the six membered ring they constructed using intramolecular Diels-Alder reaction. But the first retrosynthesis is they started from isostrychnine ok. So, from isostrychnine if you know as I discussed in the Woodward synthesis if you treat with base. So, the double bond the double bond will migrate and at the same time oxa Michael will take place which will give you strychnine.

So, the precursor for strychnine is normally isostrychnine or they can also use Wieland gumlich aldehyde. So, in the case of Rawal's total synthesis he has used isostrychnine route. So, how he made isostrychnine? So, this is where the first key reaction key disconnection he used was the Heck reaction an intramolecular Heck reaction so, that he envisaged from this starting material.

As you can see here you have the vinyl iodide. So, palladium insertion can take place and then you have a double bond. So, the intramolecular palladium catalyzed Heck coupling followed by migration of the double bond will give you isostrychnine ok. So, that was the first important disconnection Rawal has used.

Next he thought this can be made from this intermediate ok. So, if you see this what he has to do is remove the ester and then attach this whole side chain ok. Now if you look at this particular intermediate you can see a cyclohexene unit ok. So, whenever you see a cyclohexene unit one reaction which should come immediately is the Diels-Alder reaction ok.

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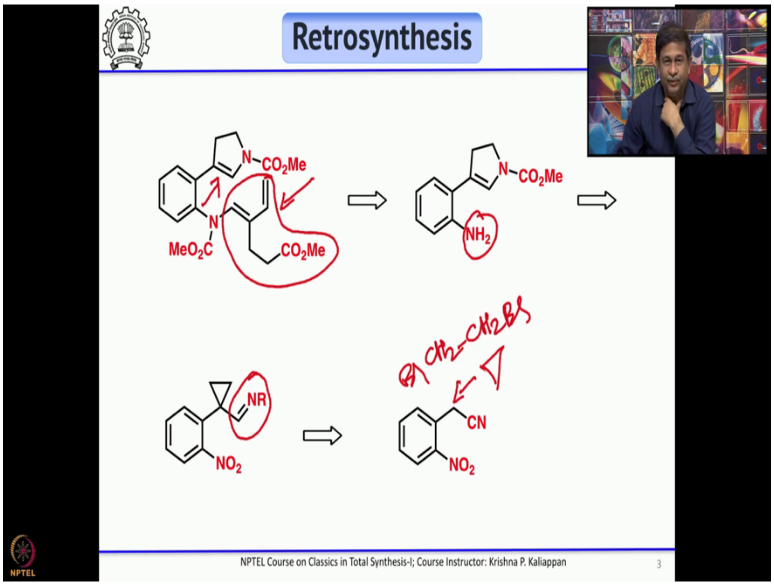

Retrosynthesis

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So, the Diels-Alder reaction so, can be easily thought of to construct this compound so, how do you do? If you see this diene ok the diene and the dienophile this is the dienophile and this is the diene ok. So, now, an intramolecular Diels-Alder reaction should give the tetracyclic compound and how do you make this compound? If you have an amine ok and an aldehyde. So, then you can couple to form an enamine ok. So, what you need is the whole unit should be an aldehyde ok.

Then the aldehyde can react with this amine to form imine and that will isomerize to enamine ok that enamine can undergo Diels-Alder reaction. This can be made from this imino cyclopropane ok the imino cyclopropane. So, we know if we have a double bond then it is called vinyl cyclopropane. So, vinyl cyclopropanes are known to undergo vinyl cyclopropane rearrangement to give cyclopentene ok vinyl cyclopropanes are known to undergo vinyl cyclopropane rearrangement upon heating to form cyclopentene.

He thought about a similar reaction instead of the double bond he wanted to use an imine ok. So, that way you can get dihydropyrrole ok. How this can be obtained? This can be obtained from this cyanide and you can treat with a 1, 2 dibromo compound, base and an 1, 2 dibromo compound you can easily introduce the cyclopropane unit here.

Then you know some functional group transformation one can easily get the starting material.

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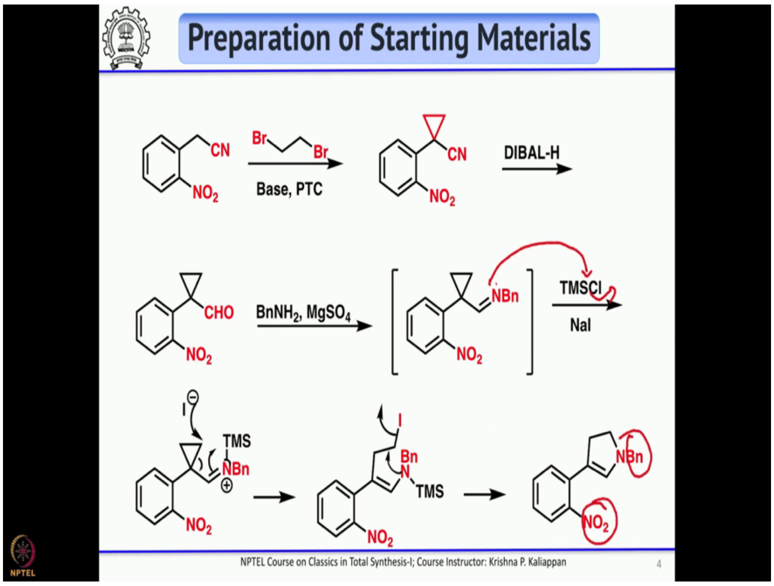
Preparation of Starting Materials

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So, now let us see how he has really carried out the total synthesis. First let us see the starting materials how he prepared. As I said first the phase transfer mediated base catalyzed the cyclopropanation took place, then you have a cyanide and that cyanide should be converted into you know aldehyde and then subsequently imine.

So, first reduce that with DIBAL. So, cyanide is reduced to aldehyde now you treat with benzyl amine ok it forms the corresponding Schiff base ok benzyl amine and then the imine this upon treatment with TMS chloride and sodium iodide ok. So, that the nitrogen lone pair will attack the TMS nitrogen lone pair will attack the TMS. And the TMS chloride and TMS iodide sodium iodide to form TMS iodide in situ ok so, that iodide will come out.

So, now you will have this intermediate. Now what will happen? The iodide which came out that will attack the cyclopropane and it will open the cyclopropane and the double bond will neutralize the positive charge on nitrogen, which will lead to the formation of this intermediate.

So, now the lone pair on nitrogen will attack carbon bearing the iodide thus forming the five membered ring and the loss of TMS will give the first starting material which is required. However, if you have looked at the retrosynthesis you do not need benzyl group here what you need is ester group that NCO_2Me ok and also this nitro group should be reduced to corresponding amine.

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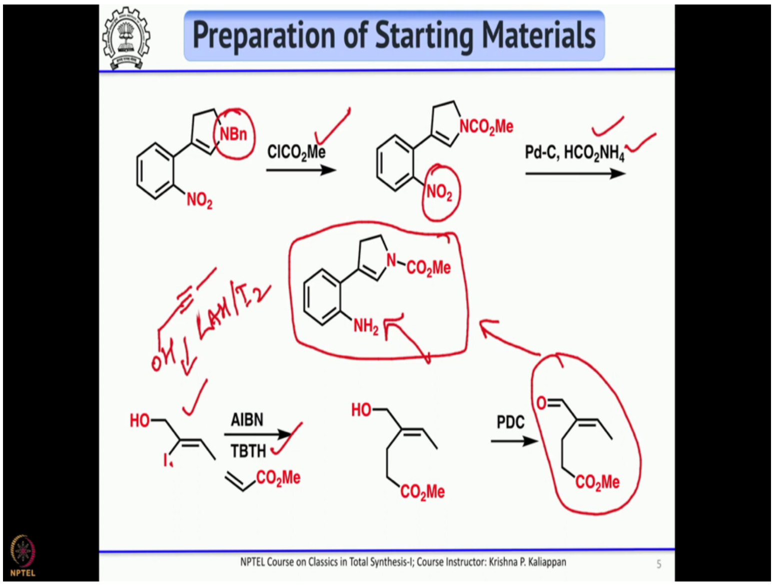

Preparation of Starting Materials

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So, both can be done easily and first if you treat this N-benzyl with chloromethyl formate easily one can replace benzyl group with ester ok corresponding CO_2Me. Now the nitro group can be reduced by transfer hydrogenation method. So, the ammonium formate in the presence of palladium charcoal in situ it will generate hydrogen, carbon dioxide, and ammonia ok. So, that will reduce the nitro group to amine to get your the first starting material ok.

So, this is fragment A we can keep it then you need an aldehyde to form an imine is not it. So, for that he started with this iodo alcohol this is normally prepared from the corresponding triple bond and then CH_2OH by treatment with LAH and the iodine ok. So, this is a standard reaction one can easily prepare from like this compound with LAH and iodine ok.

Then you do radical reaction. So, upon treatment with tributyltin hydride vinyl radical is formed that vinyl radical will add to alpha, beta unsaturated ester here it is methyl acrylate to get this compound ok. Now as I said next step is the oxidation of the allylic alcohol to get aldehyde that is what is required to form the imine ok. Now, we prepared both the starting materials the next step is to combine these two.

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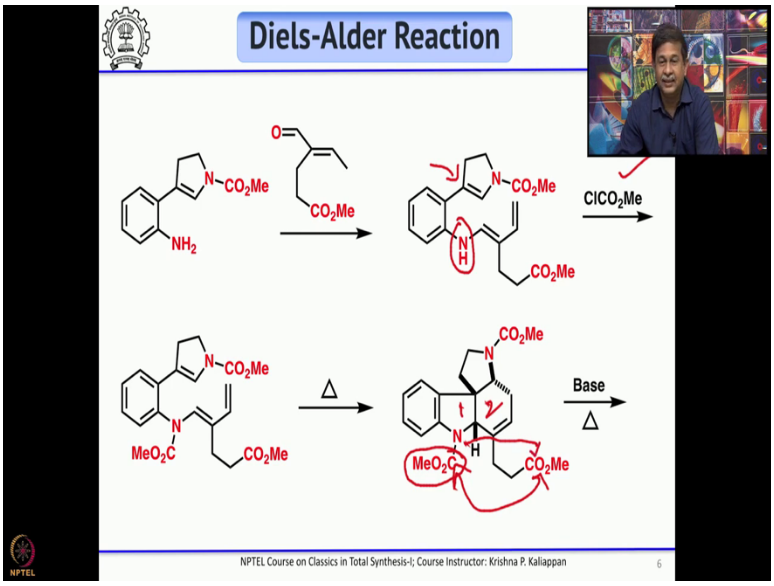
Diels-Alder Reaction

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So, when you combine these two. So, first it will form an imine Schiff base then it will undergo because you have an extra double bond it will undergo isomerization to generate this diene. Once a diene is there and already dienophile is present then it if you heat it can undergo intramolecular Diels-Alder reaction.

Before that this amino group is protected by treating with chloro methyl formate then you heat it you get the cyclohexene ring. So, if you look at carefully not only you get cyclohexene ring, but there are two rings ok 1, 2 there are two rings, which are formed using the Diels-Alder reaction ok.

So, now you see from seven membered ring because strychnine has 7 membered ring now how many rings are formed? 4 rings. So, you need two more three more rings. So, how three more rings are constructed? You can see one can easily connect these two ok if you easily connect these two that will form one more ring that is the fifth ring. So, for that you treat with base and heat it.

First when you treat with base and heat it this protecting group will go ok. Now the N minus which is formed intramolecularly will attack the ester and form the corresponding lactam ok.

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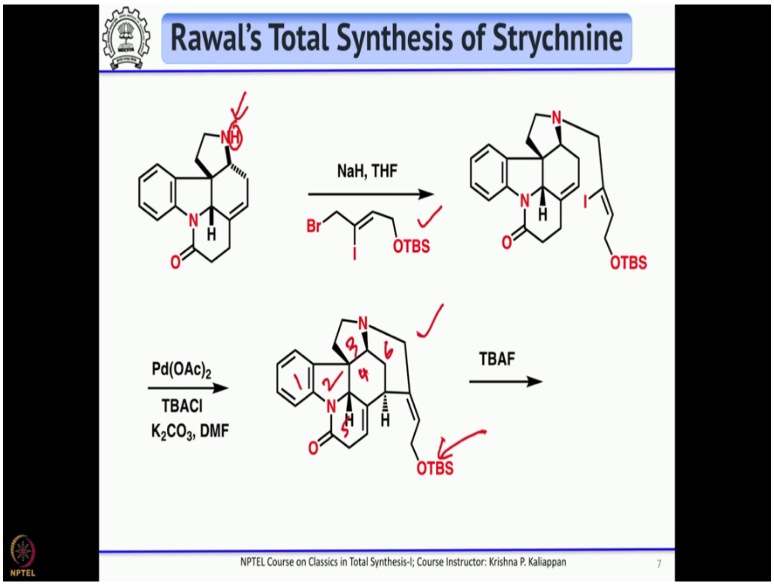

Rawal's Total Synthesis of Strychnine

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So, now the fourth ring also is formed ok at the same time that NCO$_2$Me also here NCO$_2$Me also is removed.

Now, for the Heck reaction you have to attach the side chain at NH ok. So, this is also you know very easy to make ok. So, treat with sodium hydride you pick up this proton then quench with this bromide. We can see the Heck precursor is ready now once you have this then treat with palladium acetate and tetrabutylammonium chloride in the presence of inorganic bases like, potassium carbonate it undergoes intromolecular Heck reaction to give this compound.

So, 1 2 3 4 5 6 six rings are already formed ok. So, now, only the seventh ring that is a seven membered ring should to be formed. So, that is why very easy. So, remove the protecting group remove the protecting group.

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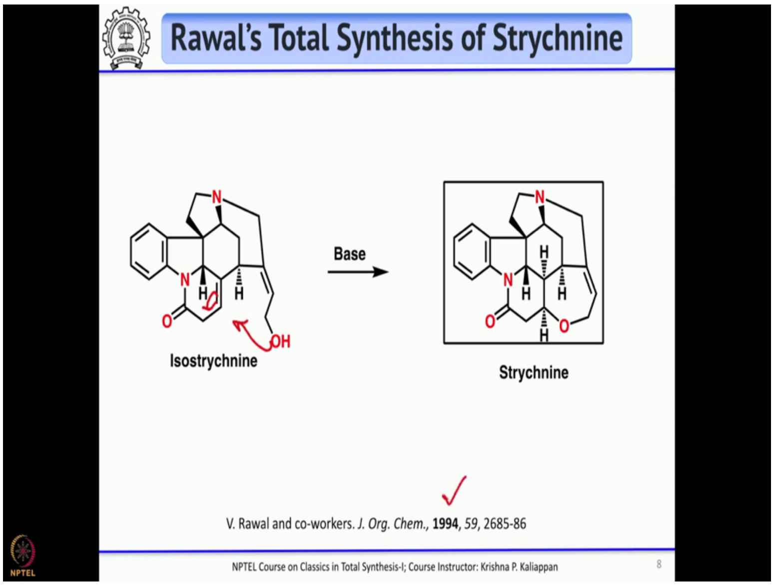

Rawal's Total Synthesis of Strychnine

Isostrychnine

Strychnine

✓

V. Rawal and co-workers. *J. Org. Chem.*, **1994**, 59, 2685-86

So, any fluoride source for example, if you use tetrabutylammonium fluoride. So, TBS group can be removed once you remove that that is isostrychnine and we all know that if you have isostrychnine if you treat with base. So, the double bond will migrate and oxa Michael will take place to give strychnine.

So, this is one of the you know shortest and clever synthesis of strychnine reported by Viresh Rawal in 1994.

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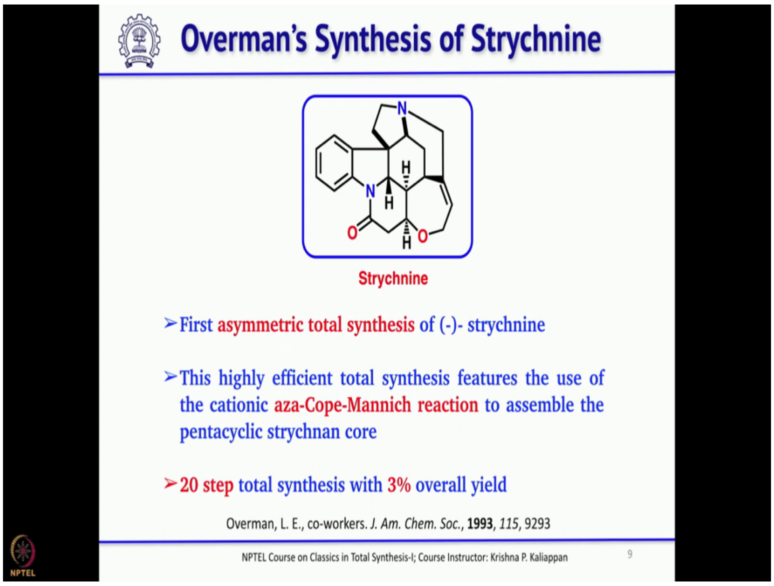

Overman's Synthesis of Strychnine

Strychnine

- First asymmetric total synthesis of (-)- strychnine
- This highly efficient total synthesis features the use of the cationic aza-Cope-Mannich reaction to assemble the pentacyclic strychnan core
- 20 step total synthesis with 3% overall yield

Overman, L. E., co-workers. *J. Am. Chem. Soc.*, **1993**, *115*, 9293

So, now we will move to the third total synthesis first was Woodward which we discussed the second one which we discussed was Viresh Rawal it is not the in the chronological order, but we whatever we discussed there are two one by Woodward second one by Viresh Rawal and third one is by Overman.

Why overman synthesis is important? Because this is the first asymmetric total synthesis of strychnine reported in the literature ok; and what are the key reactions he used? One key reaction which he has used was aza-Cope-Mannich reaction I will come to that what is the aza-Cope-Mannich reaction later ok.

And overall he took about 20 steps ok 20 steps to complete the total synthesis and with an impressive 3 percent overall yield considering the complexity of this molecule 3 percent overall yield is a very very good yielding total synthesis.

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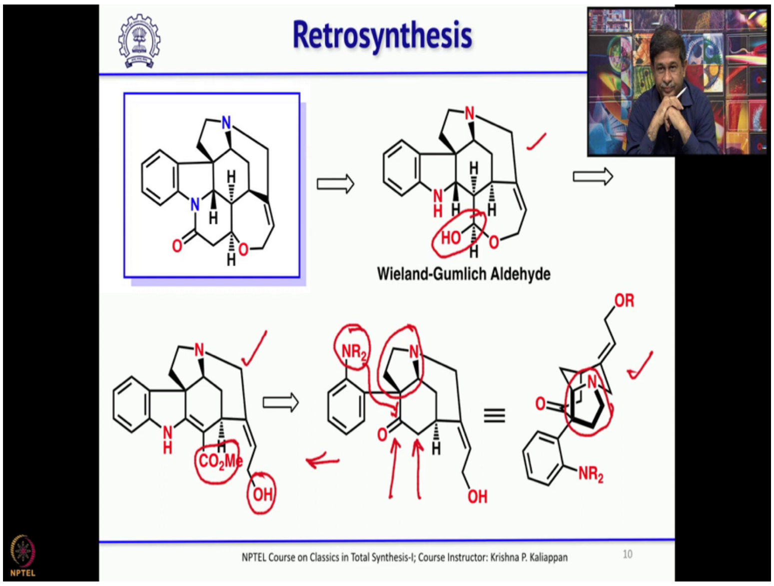

Retrosynthesis

Wieland-Gumlich Aldehyde

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Let us see how he has done the retrosynthesis. The earlier two retrosynthesis we saw went through isostrychnine ok Woodward's as well as Viresh Rawal whereas, Larry Overman's retrosynthesis went through Wieland-Gumlich Aldehyde. So, now if you have Wieland Gumlich Aldehyde if you treat with malonic acid if you treat with malonic acid and heat it this aldehyde is converted into strychnine ok.

In one step you can do that. So, either you have to go synthesize isostrychnine or Wieland Gumlich aldehyde to synthesize strychnine in one step. So, how this Wieland Gumlich aldehyde is made or thought to be made by Larry Overman? So, he thought if you look at this, this is nothing but an aldehyde is not it nothing but an aldehyde. So, you thought ideal precursor should be an ester because more stable compared to aldehyde it should be more stable. So, the precursor should be an ester and then alcohol once you reduce a ester the alcohol will immediately cyclize to form the lactol.

So, this is a logical precursor for Wieland Gumlich aldehyde. So, the next step if you see this; so, if you have a ketone ok when you have a ketone one can easily introduce the ester next to that ok one can easily introduce the ester next to that. Now this NH_2 here the protected one upon removing the protecting group you will have NH_2 that can form imine with the ketone, ok.

Then it can undergo isomerization to form enamine ok. So, basically in two steps one can make this compound from here ok. So, now, look at this. So, this compound can be redrawn like this compound can be redrawn like this I just leave it for 30 seconds for you to visualize.

So, if you see this five membered ring. So, that five membered ring is here and then you have the aromatic unit and then you have the six membered and then six membered both are behind ok just try to understand ok. This is very important when you go from here to further retrosynthesis ok. Ok

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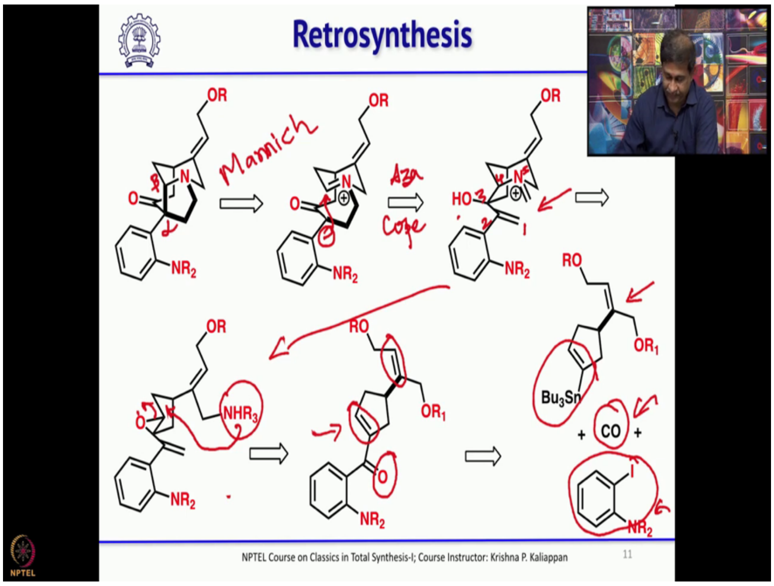

Retrosynthesis

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Now, let us see how he made this. This is whereas I said he used a very very simple, but efficient key disconnection. If you look at this intermediate ok alpha and beta the beta position with respect to ketone you have a nitrogen. So, you can call it as beta amino ketones. In literature when you want to make beta amino ketones the best reaction you will consider is Mannich reaction all beta amino ketones can be easily made by Mannich reaction.

So, the precursor for this should be this iminium ion. So, now, what will happen? You can make a negative charge that is enolate then intramolecularly attack and neutralize the positive charge on the nitrogen of iminium salt ok. Now this if you look at can be obtained by an aza-Cope rearrangement if you look at this 1, 5 diene 1 2 3 4 5 you have 1, 5 diene when you have 1, 5 diene if you heat it should undergo Cope rearrangement.

But one of the carbon is nitrogen. So, it is called aza-Cope rearrangement. So, if you heat it you will get this product this is called aza-Cope rearrangement ok this is Mannich ok. Now this aza-Cope rearrangement how will you get it? So, you have a nitrogen and an epoxide that nitrogen can come and open the epoxide ok you will get this alcohol and the nitrogen if you treat with formaldehyde you get the corresponding iminium ion ok.

So, the precursor for this is this later this can be easily obtained from this alpha beta unsaturated ketone. So, once you have alpha beta unsaturated ketone there are two double bonds one is electron deficient other one is electron rich the electron deficient double bond can be easily epoxidized by alkaline peroxide and afterwards you can convert the ketone into double bond ok. So, in two steps you can get this intermediate.

Now, this can be obtained from a carbonyl Stille coupling reaction you have a vinyl stannane and then iodoaniline. Now if you do a Stille coupling in the presence of carbon monoxide then you can get the insertion of carbon monoxide here to get corresponding alpha beta unsaturated ketone ok. So, this is commercially available this is available in cylinder now next we have to see how this can be made ok.

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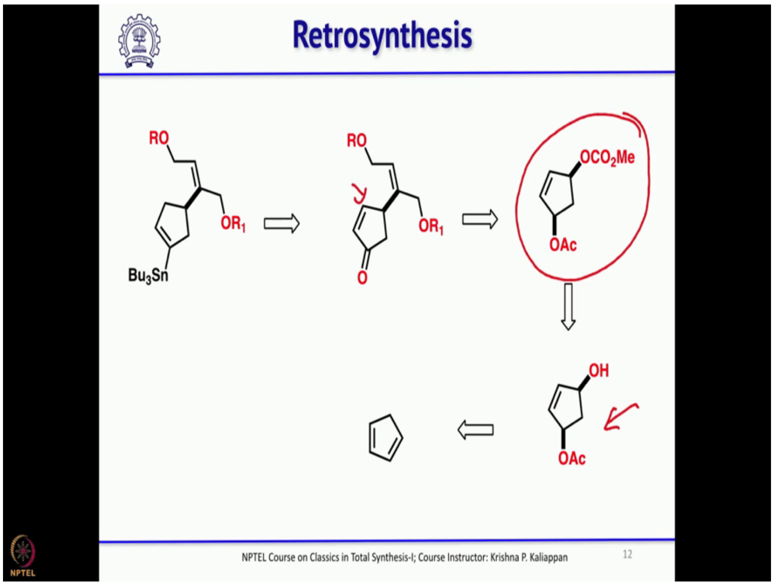

Retrosynthesis

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So, take this compound and obviously, whenever you have vinyl stannane ok whenever you have vinyl stannane it is easy to make from corresponding alpha beta unsaturated ketone.

So, you reduce a double bond and then generate the enolate ok reduce the double bond you alpha, beta unsaturated ketone reduce the double bond and generate the enolate and that can be converted into tributyltin derivative. And this alpha beta unsaturated ketone can be obtained from this cyclopentene derivatives ok.

So, this is normally done using a palladium catalyzed reaction and this can be obtained from this mono protected alcohol and that is normally obtained from cyclopentadiene ok. These are all well-known reaction ok. Now let us see how the synthesis of this compound natural product worked ok and before that I should explain so, slightly about aza-Cope Mannich reaction ok.

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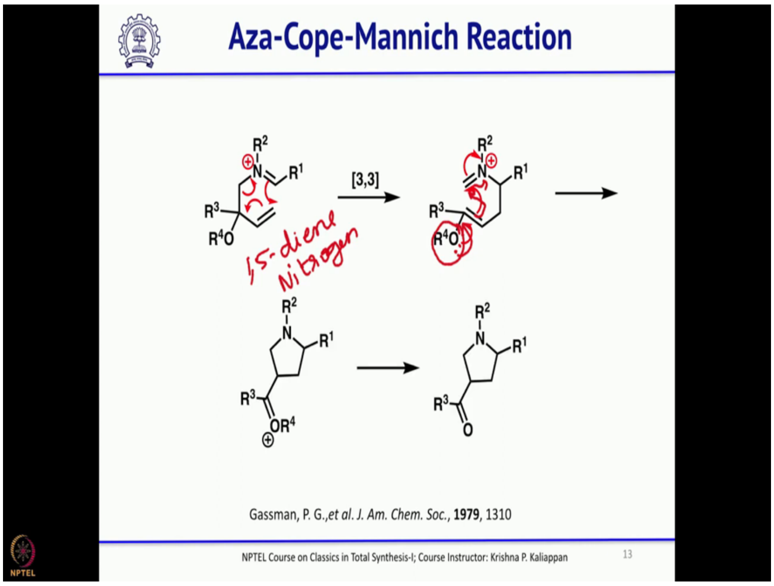

Aza-Cope-Mannich Reaction

Gassman, P. G.,*et al.* *J. Am. Chem. Soc.*, **1979**, 1310

So, this is 1, 5-diene ok and you have a nitrogen. So, you can call it as a aza-Cope ok then that should give you this compound ok. Now the iminium ion if this is oxygen ok then this can come and neutralize the positive charge. So, this is Mannich reaction. So, a combination of Cope rearrangement that is aza-Cope rearrangement followed by Mannich reaction can give a five membered compound ok. This is what exactly he has cleverly used in the total synthesis of strychnine.

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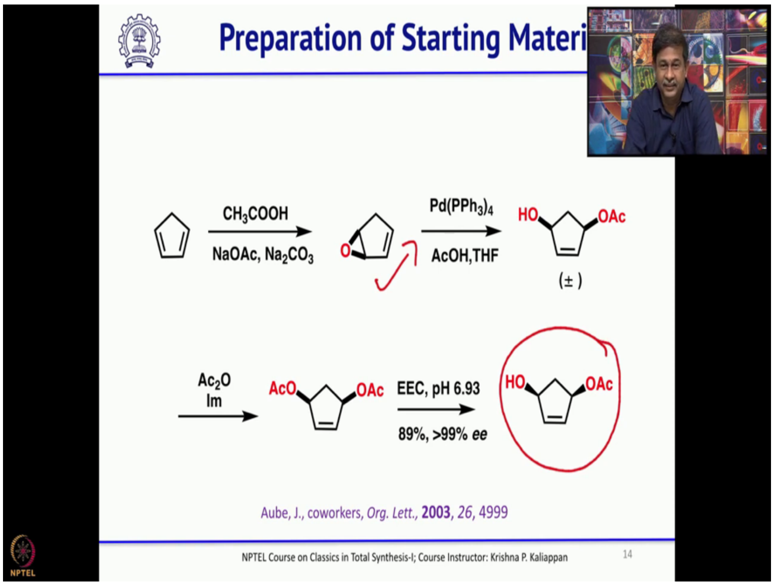

Preparation of Starting Materi

Aube, J., coworkers, *Org. Lett.*, **2003**, *26*, 4999

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Now, let us see first he how he made a starting material. The cyclopentadiene mono epoxides are well-known one can easily prepare using peracetic acid and you treat with palladium tetrakis compound and acetic acid as the nucleophile. So, one can easily open this epoxide ok to get the racemic compound ok one side you have alcohol other side you have acetate.

Now, make the second alcohol also acetate and this can be easily resolved using an enzyme and that will give you. So, only one isomer you can isolate. So, this is optically active and you get it 99 percent ee ok.

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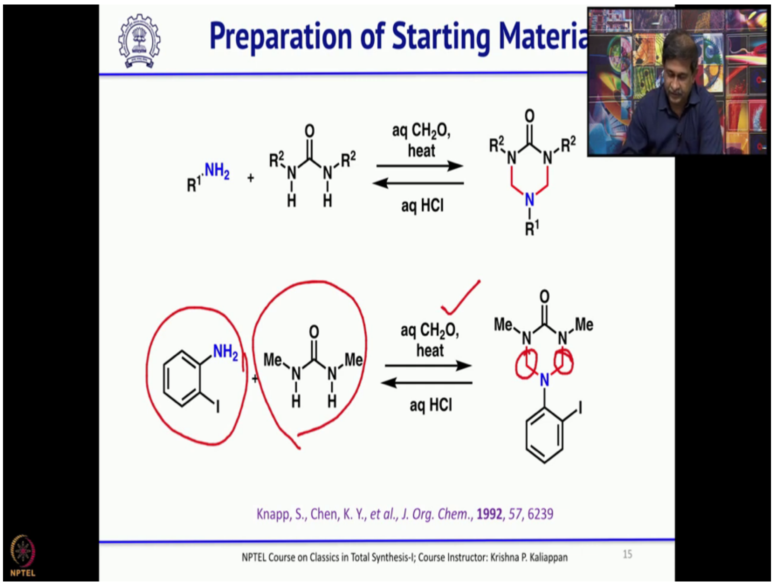

Preparation of Starting Materia

aq CH_2O, heat

aq HCl

aq CH_2O, heat

aq HCl

Knapp, S., Chen, K. Y., *et al.*, *J. Org. Chem.*, **1992**, *57*, 6239

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Now, the other portion that is the iodoaniline portion so, you can take 2 iodoaniline ok and then protect with this dimethyl urea in the presence of formaldehyde ok in the presence of formaldehyde. So, this is the formaldehyde coming from it forms basically it forms iminium ion and then nitrogen and nitrogen attacks and it undergo 1, 4 addition ok. So, this starting material is prepared the other starting material is prepared.

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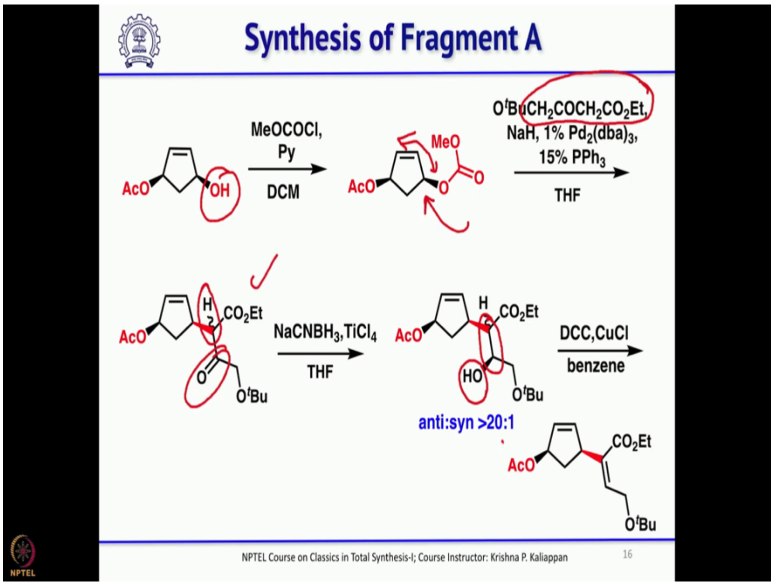

Synthesis of Fragment A

MeOCOCl, Py

DCM

$O^tBuCH_2COCH_2CO_2Et$, NaH, 1% $Pd_2(dba)_3$, 15% PPh_3

THF

$NaCNBH_3$,$TiCl_4$

THF

DCC,CuCl

benzene

anti:syn >20:1

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So, then what you do? First you protect this alcohol as carbamate because allylic carbamate is required for palladium catalyzed alkylation. So, once you have this then treat with this beta keto ester ok this beta keto ester. So, what will happen? Your pi-allyl complex will form and the nucleophile will attack here. So, that will give you this compound ok.

This chiral center is not fixed no problem one can reduce the ketone to get corresponding alcohol and at this point you know the ratio was 20 is to 1 and next is you have to introduce a double bond here; that means, you should make this hydroxyl as a good leaving group simple treatment with DCC simple treatment with DCC gives the corresponding alpha beta unsaturated ester ok.

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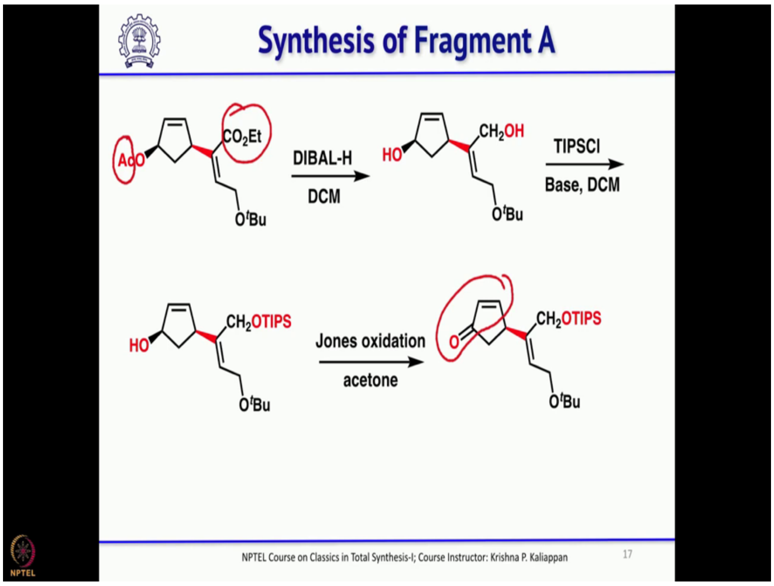

Synthesis of Fragment A

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This alpha beta unsaturated ester when you reduce with DIBAL it will do two things one the acetate also will be reductively cleaved acetate also will be reductively cleaved and then ester will be reduced to get the primary alcohol. Now the primary alcohol you protect it as tips ether ok primary alcohol is protected as tips ether and this allylic alcohol can be oxidized to get the corresponding enone ok. Any oxidation you can do, but they have done Jones oxidation.

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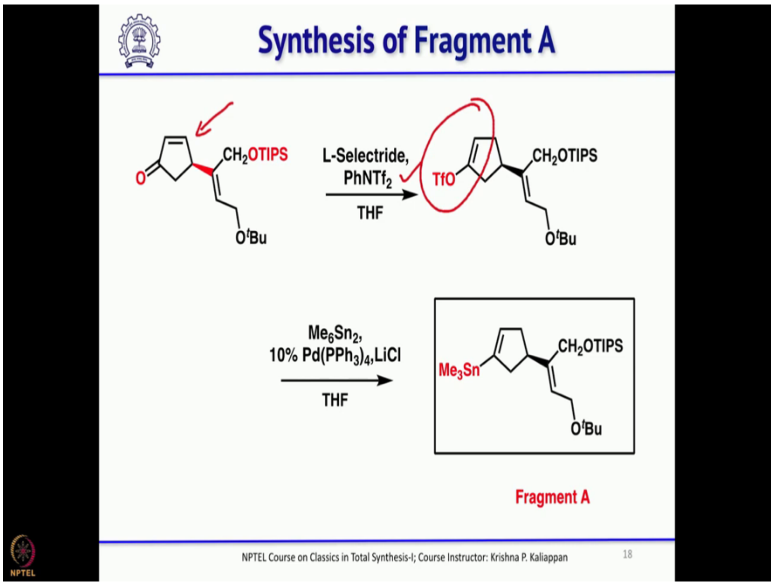

Synthesis of Fragment A

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So, once you have this alpha beta unsaturated ketone then you do treat with L selectride. So, L selectride adds as hydride in a 1, 4 fashion in this then that enolate is quenched with phenyl N triflate ok. So, this is this will give you corresponding enol triflate ok this enol triflate can be exchanged with hexamethylditin ok.

So, if you couple with palladium and then O triflatewill be replaced with corresponding trimethyltin compound ok. So, this is fragment A. So, now, you have fragment A and already you we made fragment B.

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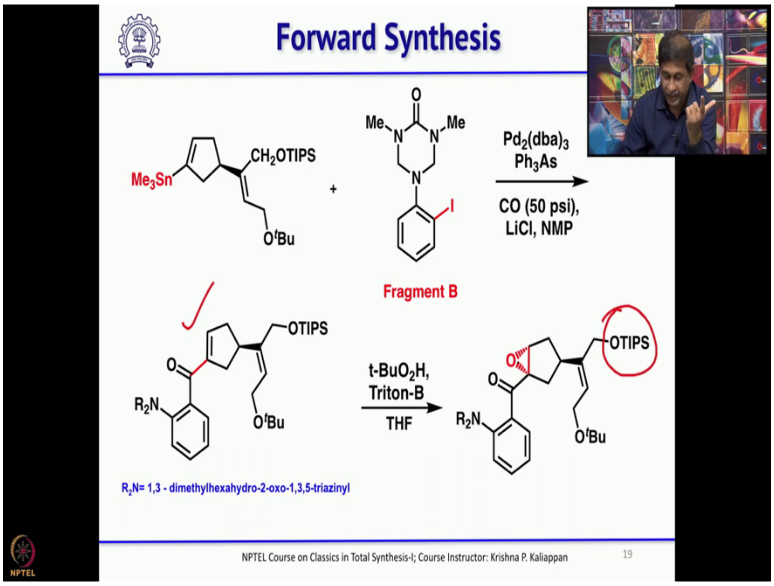

Forward Synthesis

R$_2$N= 1,3 - dimethylhexahydro-2-oxo-1,3,5-triazinyl

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So, combine these two using Stille coupling in the presence of carbon monoxide ok. So, what it give is the expected alpha beta unsaturated ketone.

Once you have this alpha beta unsaturated ketone, the next step is to introduce the epoxide. Of course, alpha beta unsaturated ketone if you want to epoxidize in the presence of other double bond then you have to treat with alkaline hydrogen peroxide. So, you can use Triton B and then tertiary butyl hydroperoxide that gives the alpha epoxide predominantly ok.

So, once you have this alpha epoxide now the next step is to remove the TIPS group ok you have to remove the TIPS group convert that into amine ok.

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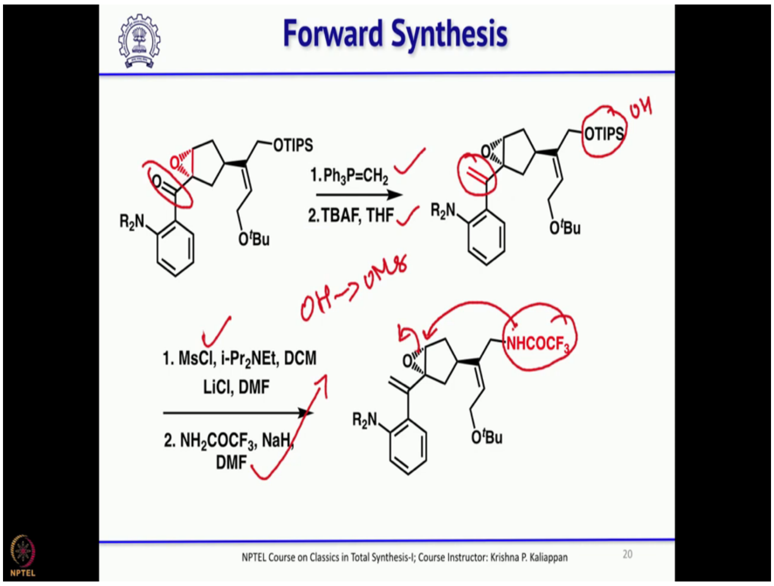

Forward Synthesis

1. $Ph_3P=CH_2$

2. TBAF, THF

1. MsCl, i-Pr_2NEt, DCM
LiCl, DMF

2. NH_2COCF_3, NaH, DMF

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So, the TIPS is removed before removing TIPS you have to convert the carbonyl into double bond ok, that is normally one can do in one step with Wittig reagent then followed by removal of the TIPS give this should be OH ok. First step Wittig gives the double bond and then second step TBAF will remove the TIPS and you will get alcohol.

Now, the alcohol is mesylated and OH is converted into O mesylate making it as a good leaving group then this amide attacks the mesylate and you introduce the $NHCOCF_3$ ok the next step is this NH the lone pair should attack the epoxide and open the epoxide to get the corresponding alcohol.

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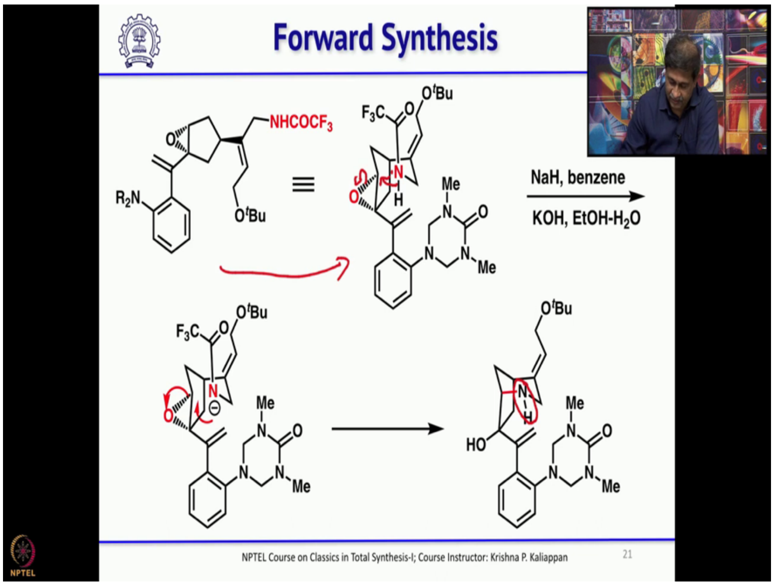

Forward Synthesis

NaH, benzene

KOH, EtOH-H_2O

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So, that is done using you know simple base this is done with sodium hydride and intramolecularly we can also draw this compound in a different way for better understanding. So, now the N minus will attack here and open the epoxide and you get the corresponding alcohol ok. Now it is all set for the aza-Cope rearrangement ok; what we should do? Only thing is this NH should be converted into N double bond ok.

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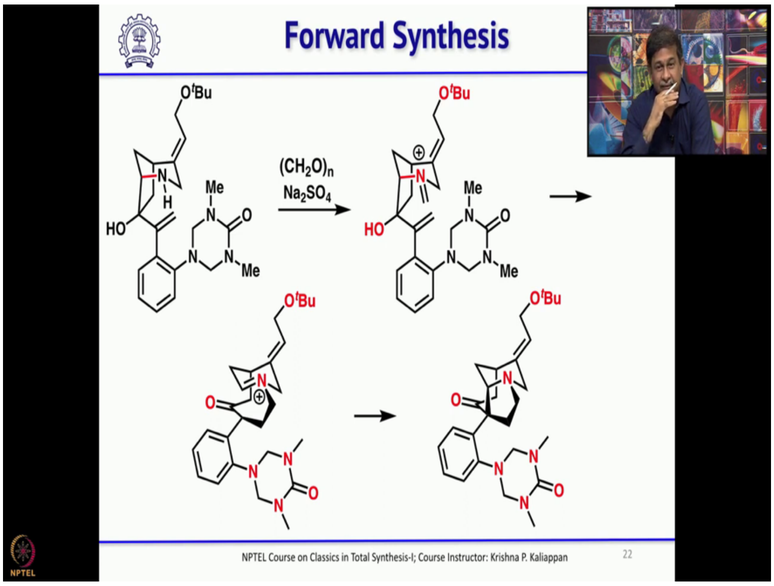

Forward Synthesis

$(CH_2O)_n$

Na_2SO_4

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So, that is very easy if you treat with formaldehyde. So, then you get the corresponding iminium and it does not stop there. So, it undergoes the aza-Cope rearrangement and followed by Mannich reaction to give this ok. So, this is as planned he could successfully use the aza-Cope and then the Mannich reaction ok.

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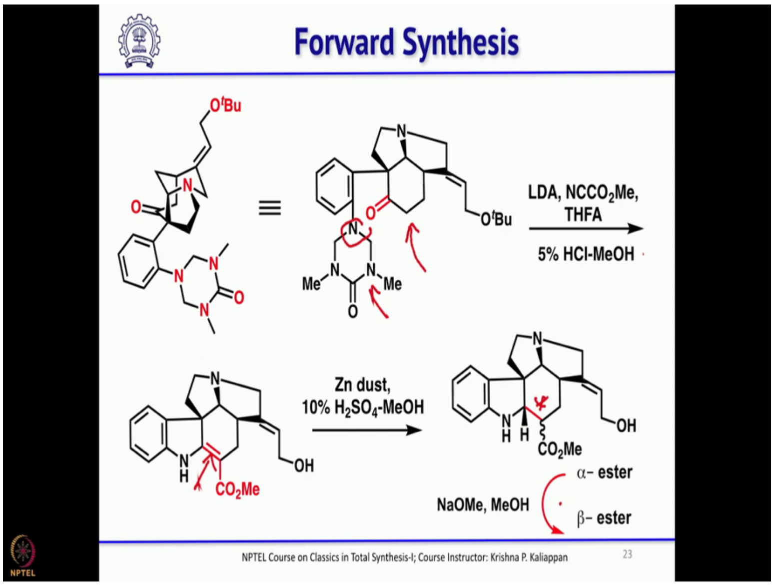

Forward Synthesis

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Now, we will redraw this. So, once you redraw this is what you got ok. So, what is left is now you have to introduce the ester here and remove this and then form the enolate ok that is the next step. So, you can treat this ketone with LDA and then Mander's reagent cyano methyl formate you get the corresponding ester and the same time after you work up with a 5 percent HCI methanol then you can remove this and it forms NH$_2$ the NH$_2$ attacks the carbonyl and it forms the enolate ok.

So, now from this particular route already you can see five rings are formed five rings are formed. So, only one more ring to form to get the Wieland Gumlich aldehyde one more ring ok. So, what you should do? You should reduce this double bond ok. So, that is straight forward you treat with zinc dust in methanol you reduce the double bond, but; however, the chiral center here is a mixture ok. So, that if you treat with sodium ethoxide and methanol then that alpha ester gets epimerized to get the required beta ok.

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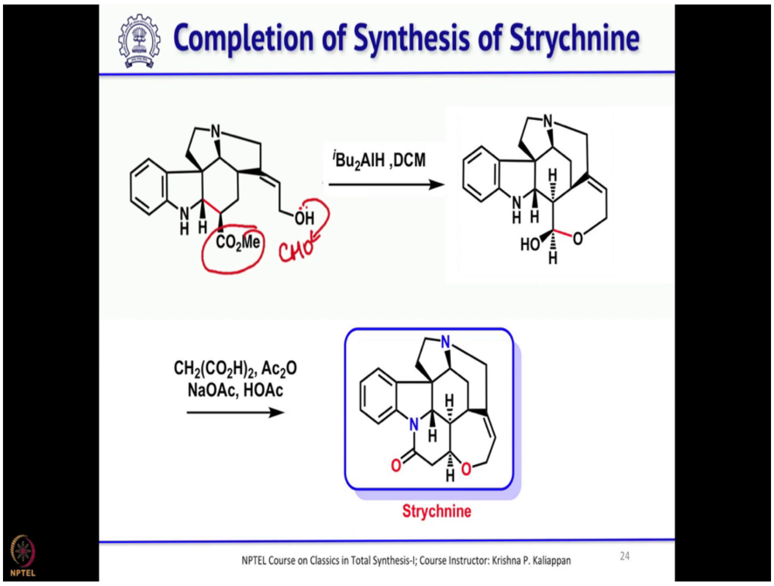

Completion of Synthesis of Strychnine

$^{i}Bu_2AlH$, DCM

$CH_2(CO_2H)_2$, Ac_2O
NaOAc, HOAc

Strychnine

Now, once you have the beta next is to reduce that with DIBAL. So, DIBAL ester is reduced to aldehyde as soon as the aldehyde is formed alcohol attacks that gives you the corresponding lactol, is not it, that gives you corresponding lactol. Then you treat with malonic acid and acetic anhydride reflux it will directly give strychnine ok in one pot you can take Wieland Gumlich aldehyde and that will convert that will be converted into strychnine in one step ok.

So, if you look at the synthesis of strychnine by Overman it involved a very very simple and important key reaction that is aza-Cope and Mannich in 1 pot the aza-Cope reaction followed by Mannich reaction to get the five membered ring with all the stereocenters in place ok. That is the beauty of this particular synthesis and second important thing is this is the first asymmetric synthesis of strychnine reported in the literature ok.

So, thank you with this, I will stop here and then we will discuss a couple of more total synthesis of strychnine in the next lecture.

Thank you.