Classics in Total Synthesis-I
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Lecture - 42
Manzamine A

Good afternoon and welcome back to NPTEL lecture series on Classics in Total Synthesis Part-I. And we have been discussing about total synthesis of many alkaloids and today we also continue to discuss one more complex alkaloid called Manzamine.

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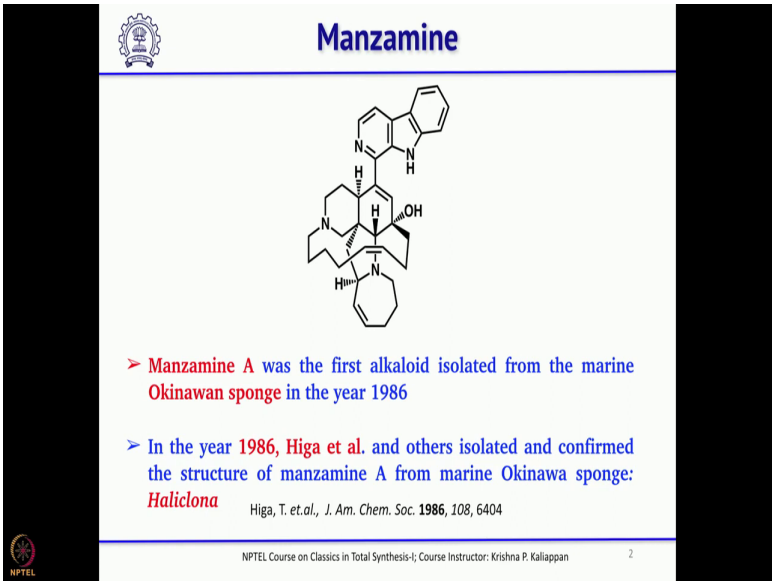

So, manzamine as you can see from here it is quite a complex molecule and it was isolated in 1986 from marine sponge called Okinawan sponge.

And from the structure one can easily make out how many rings are there? And how many chiral centers are there? It is a quite challenging molecule and because of its complex molecular architecture several groups were interested in the total synthesis and the first person to complete the total synthesis was Jeffrey Winkler and today we will talk about the total synthesis of manzamine by Winkler's group.

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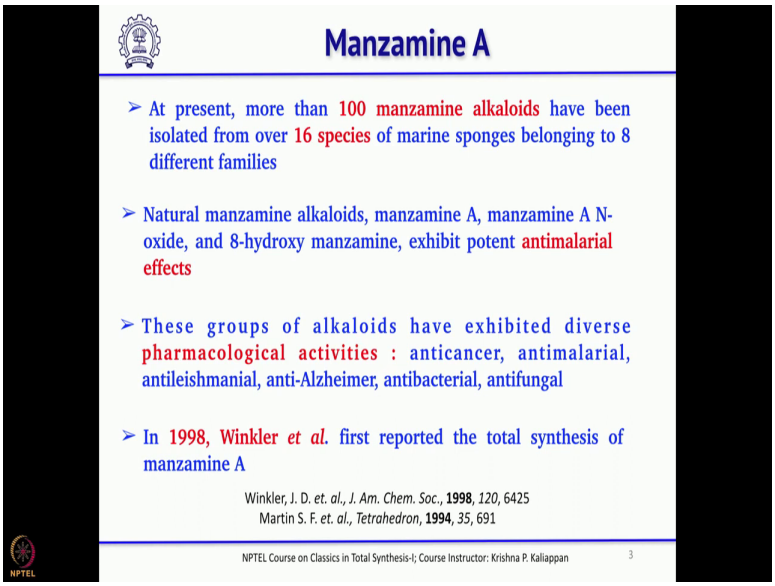

After the isolation of manzamine there were 100 manzamine alkaloids which were isolated from various species belonging to 8 different families and they generally show a very good activity against malaria. And as I mentioned Winkler was the first one to report the total synthesis in 1998 and there are other synthesis afterwards.

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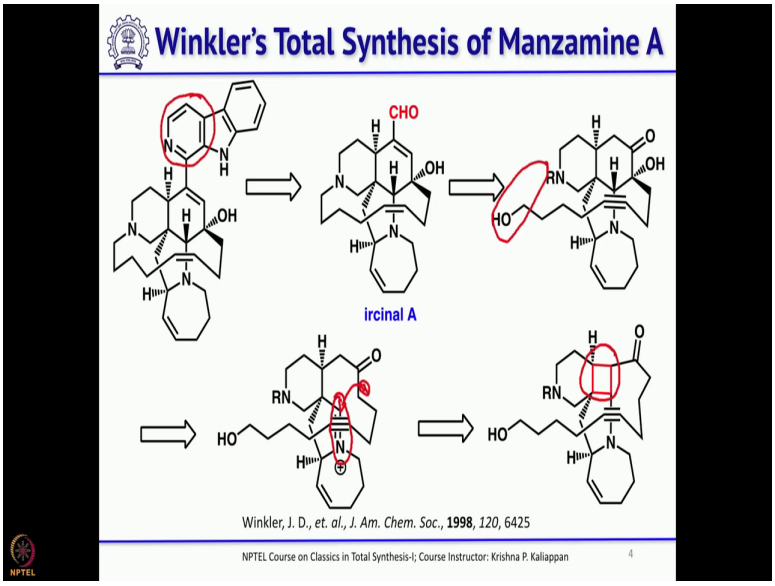

But today we will talk only about the total synthesis of manzamine by Winkler's group. So, each group the retrosynthesis of manzamine was based on 3 or 4 key reactions 3 or 4 key reaction. The first key reaction was the Pictet-Spengler reaction to construct this ring

ok. Pictet-Spengler reaction ok. So, we will come to that what is Pictet-Spengler reaction.

And then the second key reaction was you know the cyclization and to form the macro cycle ok. That is also very important from the size of the ring which is being formed during the synthesis. And the third key reaction which is of course, you know combination of 3, 4 reaction is an Intramolecular Mannich reaction.

You can see you have an iminium ion here ok. And a anion generates here and then attacks and then neutralize the positive charge on the nitrogen which as you know it is a Mannich reaction. This is an Intramolecular Mannich reaction and this is obtained this iminium ion is obtained by a series of rearrangement and that started from this cyclobutane ok. So, here it undergoes a Retro Mannich reaction and followed by Mannich reaction ok.

So, when I discuss the total synthesis you will know.

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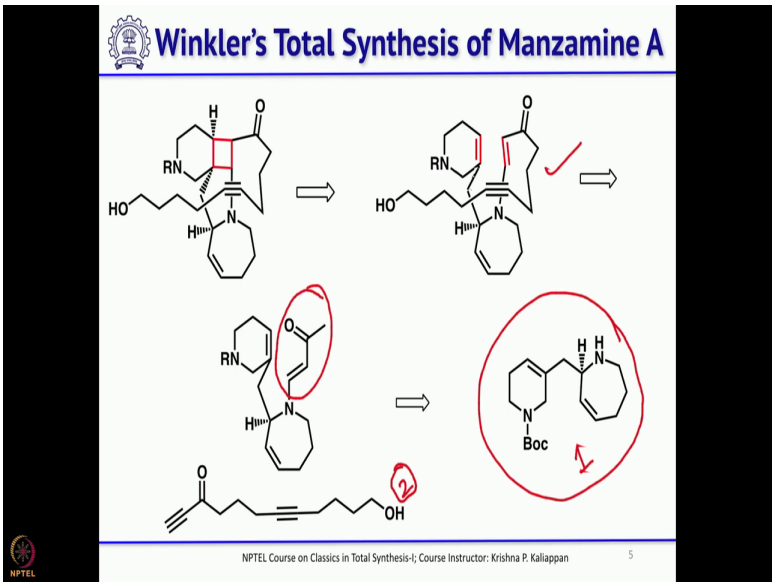

What exactly I mean ok. So, once you can see the Cyclobutane. The simplest reaction one can use to make Cyclobutanes is a photochemical reaction. So, this can be disconnected into this compound where you have two double bonds and under suitable photochemical conditions it should be possible to make the Cyclobutane using intramolecular [2+2] cycloaddition reaction.

And this can be obtained from this enone ok. And if you look at this carefully this can be obtained from this bicyclic compound ok. So, these are the key fragments. This is a fragment 1 or starting material I would say starting material 1 and starting material 2 in the synthesis of manzamine by Jeffrey Winkler ok.

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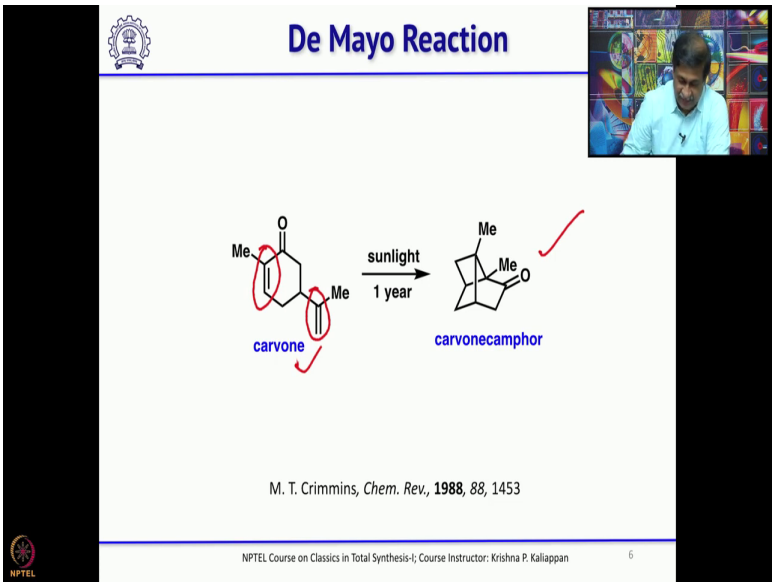

Now, as I said there are three four key reactions which Winkler has used in the total synthesis of manzamine.

The 1 key reaction is the intramolecular [2+2] cycloaddition. Which is also called de mayo reaction. One of the oldest reaction known in the literature photochemical reaction known in the literature is de mayo reaction. Carvone a commercially available monoterpene can undergo an intramolecular [2+2] cycloaddition reaction between this alkene and other alkene.

One is electron rich other one is electron deficient. And in fact, under sunlight also this can undergo. If you keep it for long time to see these [2+2] cycloaddition to take place ok.

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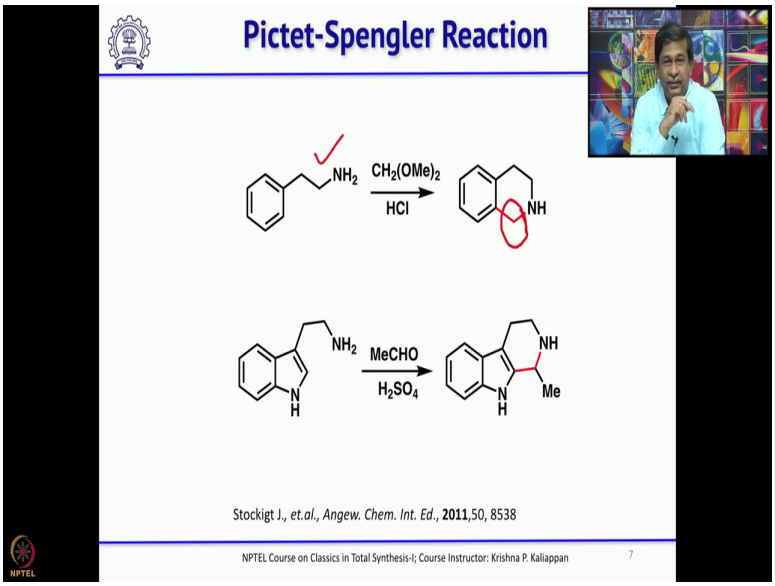

And the Pictet-Spengler reaction is if you have phenyl ethyl amine ok. Then this on treatment with aldehyde or protected aldehyde in the presence of acid it can undergo cyclization. Basically what you are doing is you are introducing the CH_2 or CH, if you are using aldehyde ok.

So, this is how one can cyclize ok. Cyclize to form a six-membered ring ok.

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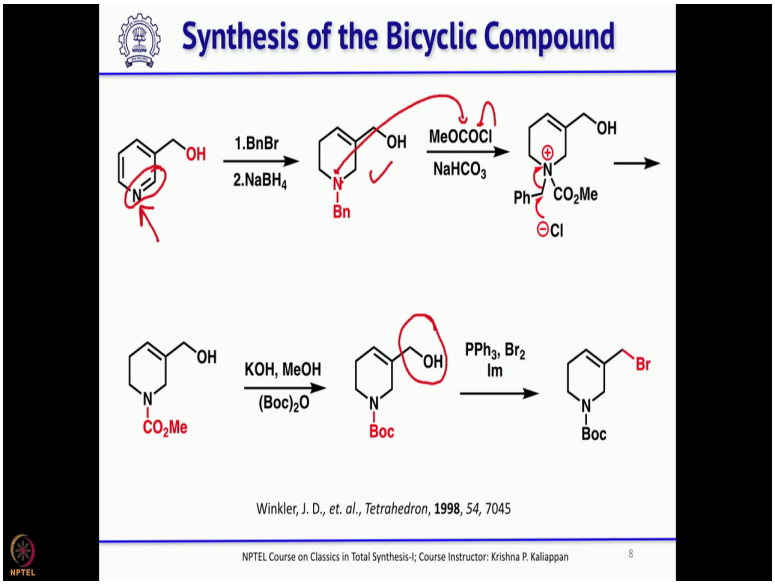

Now, let us see how the starting materials are prepared. Before we actually go into the complex total synthesis. How the starting materials are prepared for the complete

synthesis? The first the pyridine nitrogen was benzylate ok. When pyridine nitrogen was benzylated becomes quaternary ammonium salt ok. Then one can reduce this iminium with sodium borohydride.

So, 2 such successive reaction one can remove two double bonds of pyridine ok. So, that leads to the formation of this allylic alcohol ok. So, very simple reaction first you have to benzylate followed by reduction of the successive iminium ions with sodium borohydride you get the corresponding alkene ok. Only one double bond is there.

Now, he wanted to remove the benzyl and then protect it as a Boc. Now, for that he has to do a two step process. First he treat it with chloro methyl formate. So, what happens the lone pair on the nitrogen attacks the carbonyl and then chlorine comes out first. So, this is the intermediate. Where this is the first intermediate the nitrogen attacking the carbonyl and chlorine coming out.

Now, the chloride which comes out attacks the benzylic carbon attacks the benzylic carbon and breaks the -CN bond. So, that nitrogen will be now neutralized. So, in the process what happens the chloro methyl formate removes the benzyl group ok. Removes the benzyl group as benzylic benzyl chloride. So, now, you have removed the benzyl and $-CO_2Me$, as said he wanted to protect the nitrogen as Boc protecting group.

So, again he treated with potassium hydroxide methanol and followed by a treatment with Boc anhydride you could get N-Boc ok. So, the next step is to make this as a good leaving group. As you know which should be converted into bromide or mesylate or tosylate or triflate. So, that an SN_2 reaction can take place at that carbon. So, here the hydroxyl was converted into bromine using a standard triphenyl phosphine bromine imidazole treatment.

So, to get the corresponding allylic bromide ok. So, now, one small fragment of manzamine is ready.

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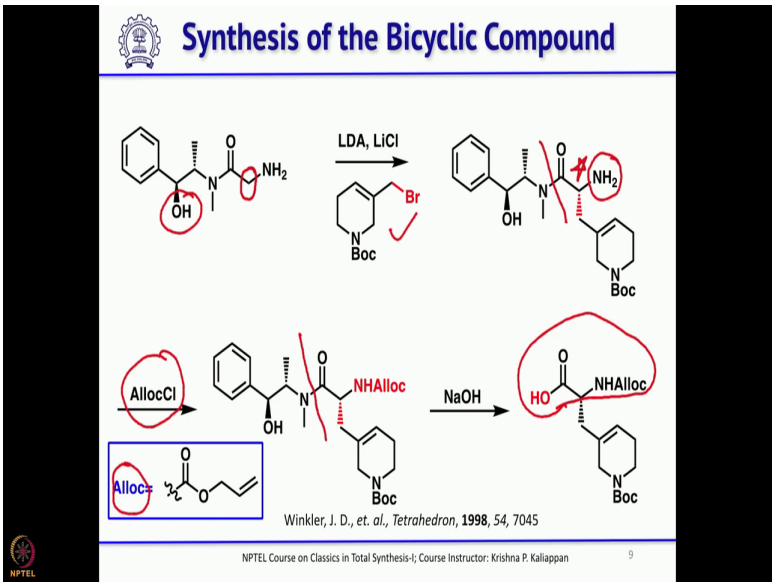

Next, how you can introduce the chiral center ok? How you can introduce the chiral center? So, for that he started with pseudoephedrine ok. So, now, this carbon has 2 acidic protons ok. One can treat with LDA. Of course, you need excess LDA because you have free hydroxyl group then quench with this allyl bromide ok.

So, that is how you introduce this chiral center ok. So, now, you could see one new chiral center has been introduced. Once the chiral center is introduced then you have to cleave the chiral auxiliary ok. So, cleaving the chiral auxiliary can be done, but before that the free -NH_2 should be protected. So, the -NH_2 was protected as allyl oxy carbonyl group. This is called alloc, alloc is allyl oxy carbonyl group.

So, the corresponding chloride you take and treat with base you get the NH protected as alloc protecting. So, now, as I said you remove the chiral auxiliary. Once you remove the chiral auxiliary you have the corresponding carboxylic acid. Now, if you look at this carefully this is a substituted amino acid is not it. This is substituted amino acid, but unnatural. It is not a naturally occurring compound. It is an unnatural amino acid ok.

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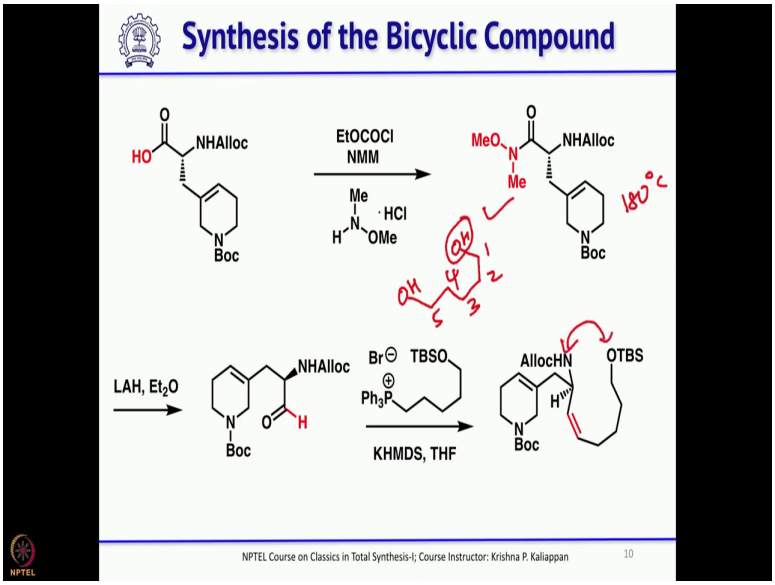

So, now one fragment is ready. What you do? You convert that carboxylic acid, convert that carboxylic acid into a Weinreb amide. So, why Weinreb amide is required? Because once you have Weinreb amide if you treat with the Grignard reagent or if you treat with reducing agents like LAH or DIBAL you will get only corresponding aldehyde. If you treat with Grignard reagent you get corresponding ketone.

So, here what they want was they wanted an aldehyde ok. For that once they made this Weinreb amide treatment with either DIBAL or LAH gave the corresponding aldehyde ok. So, I have written this structure and I rotated this 180 degree. So, just I leave it for a few seconds. Just see this carefully ok. Just I rotated this by 180 ok. So, here if this is α this is β ok.

Then once you have aldehyde then this long chain compound ok. A Wittig reaction was done on this aldehyde to get the corresponding cis alkene. So, this is Wittig reagent can be easily prepared from the corresponding diol. So, if you have this diol ok. What is this diol? 1, 2, 3, 4, 5 pentane diol.

If you have pentane diol you can selectively protect one of them as TBS ether ok. Then the other alcohol you convert it into bromide and then make the Wittig salt then you do this Wittig reaction ok. So, what is left now? You have to do this cyclization here. You have to do the cyclization here ok.

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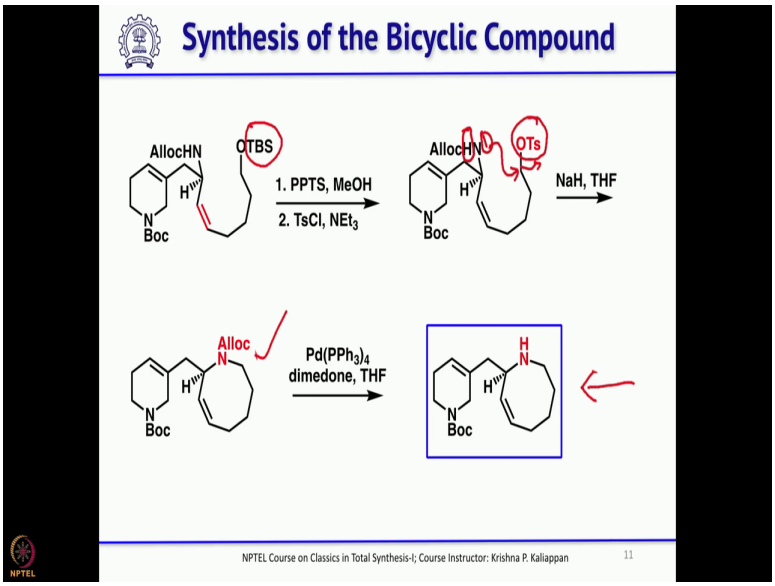

So, for that first you have to remove the TBS group ok. The TBS group primary TBS was removed using PPTS methanol.

Then converted that alcohol into a good leaving group that is tosylate ok. Now, sodium hydride and THF what happens? This -NH acidic proton ok. So, sodium hydride will remove that proton. So, you form N^- that N^- will intramolecularly attack the carbon bearing tosylate. So, that SN_2 reaction will give this ring ok. So, now, we have made the bicyclic compound ok. You know we have to make 2 more rings ok.

Once you made this that Alloc group the protecting group should be removed. So, that is normally done under palladium catalyst. So, tetrakis palladium removes the allyl oxy carbonyl group. So, that is how we get the free bicyclic compound which is ready for further transformations ok.

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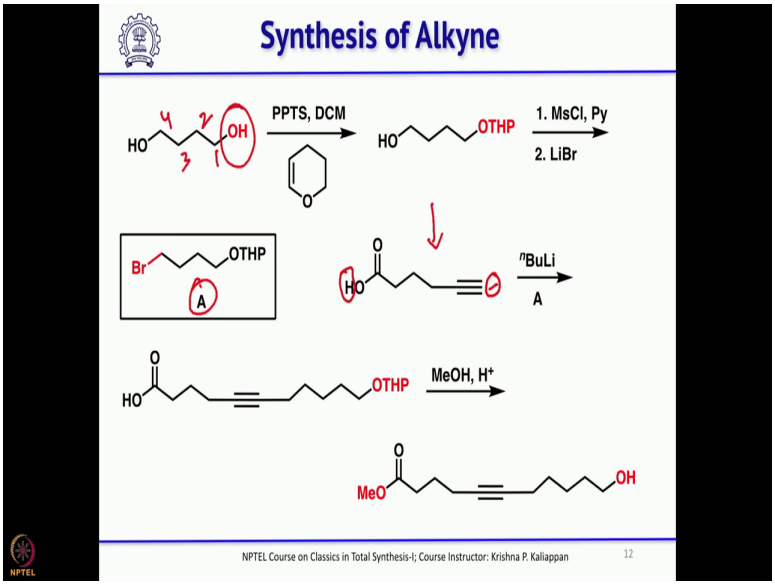

Now, the other fragment ok. Which is required for the for making the macro cycle that alkyne.

For that again you started from a diol ok. You can see 1, 2, 3, 4 butane diol. 1, 4 butane diol and the hydroxyl group one of the hydroxyl group was protected as THP ether and the other hydroxyl group was converted into bromide in two steps by treating with mesyl chloride followed by lithium bromide ok. So, now, this alkylating agent is ready. Then you have to start with the triple bond ok.

So, the triple bond and the carboxylic acid. This also can be easily made in few steps from known starting material. Now, if we treat with butyl lithium. So, more than two equivalents of butyl lithium is required. One to generate anion here other to remove this proton. So, once you do that then quench with this halide ok. So, that will give you this long chain ok. Now what you need? The ester you have to that carboxylic acid you have to convert into ester.

So, that was done. By reflexing with methanol in the presence of acid.

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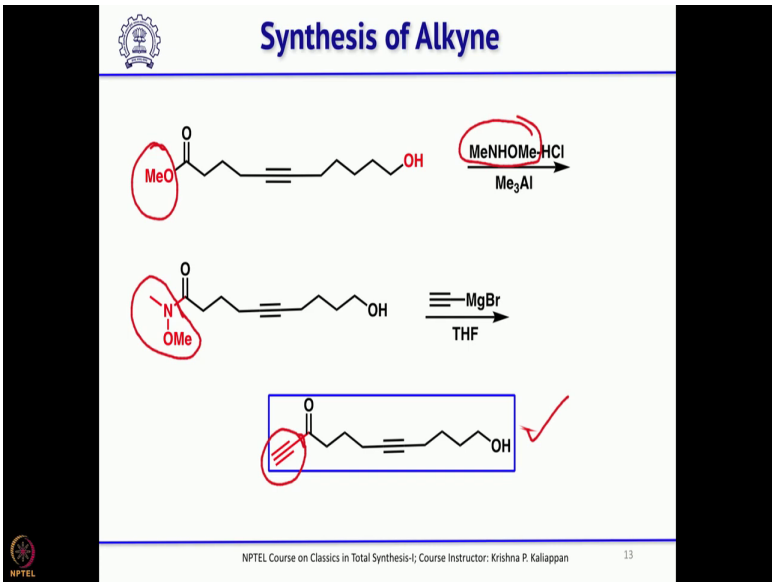

So, now as I said the second fragment which you need is this alcohol. So, use the ester you treat with Weinreb amine in the presence of tri methyl aluminium. So, these OMe will be replaced with this compound ok. So, now, you have got the Weinreb amide ok. So, if you see here the required compound has a triple bond and here you have the Weinreb amide.

So, basically what you need is you need to add a triple bond to that. So, the simplest one is the corresponding acetylenic Grignard ok. Acetylenic Grignard in THF directly will give you the second fragment, which is required for the total synthesis of manzamine.

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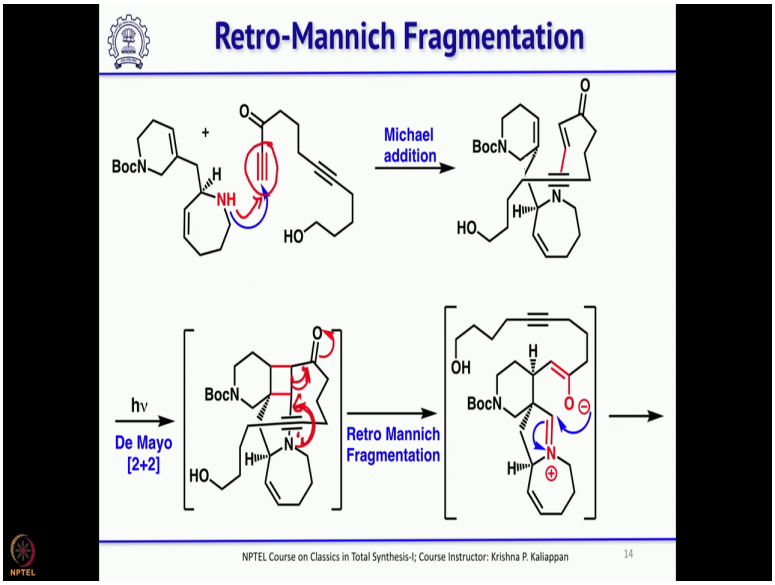

So, now, we have these two fragments. The next step is to carry out the intermolecular Michael addition reaction. So, you have the Michael acceptor and here you have the nucleophile.

So, intermolecular Michael reaction takes place. First and that gives you this product that is the one which is ready for intramolecular de mayo reaction. That is [2+2] cycloaddition reaction. So, you can see when you looked at manzamine. The molecule was looking very very complex is not it.

So, you disconnect the molecule in such a way that you cut into two simple fragments. Once you have these two simple fragments, what you have done? You are doing now an intramolecule intermolecular Michael reaction. Intermolecular Michael addition gives you the precursor for the photochemical reaction. Once you have that carry out the intramolecular [2+2] cycloaddition reaction. That gives this intermediate.

And this intermediate actually it does not stop there. You do not get this intermediate. You do not isolate. What happens? As I mentioned when I talked about retrosynthesis it undergoes a Retro Mannich fragmentation. So; that means, you can see this lone pair comes here and opens up that opens a cyclobutane to give this product ok. The lone pair opens lone pair on the nitrogen opens the cyclobutane to give this intermediate.

Now, what will happen? The O^- the O^-can directly neutralize the iminium ion ok. The enolate can neutralize the iminium ion ok.

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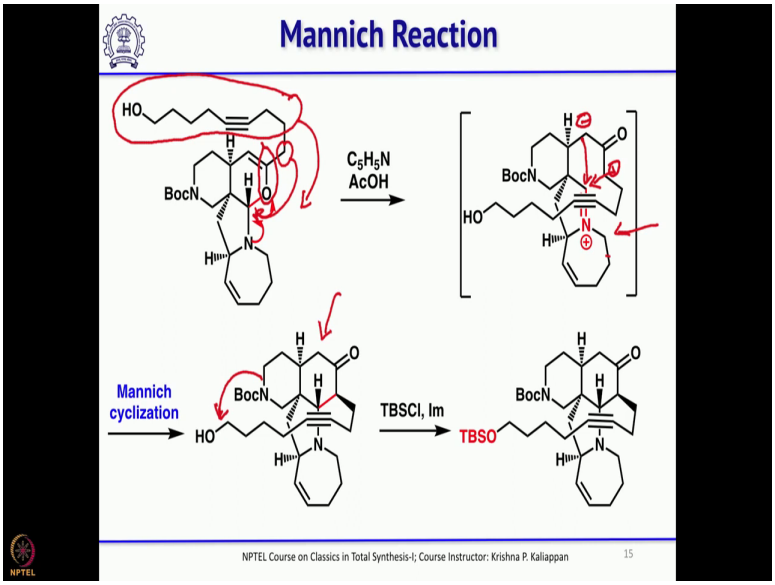

If that takes place what you will get is this tetracyclic compound ok, but what you want is not this ok what you want is cyclization at this between this carbon and this carbon. So, how to do? Again you have to open up, again you have to open up this amino. How do you do? You treat with pyridine and acetic acid.

When you do that again it opens up ok. When it opens up this becomes the bottom portion becomes iminium ion and the top is ketone ok. Just I will leave this for few seconds, because it is important for you to visualize. What happened? This became ketone ok; this became ketone and the whole side chain the whole side chain I have brought it down ok. The whole side chain I have brought it down ok. You can see whole side chain I have brought it down.

Now, once the iminium ion is formed then you can see it can generate enolate on this side as well as the other side ok. If it generates on the top that will give you a four-membered ring if it undergoes Intramolecular Mannich reaction. If this undergoes Intramolecular Mannich reaction. It will give back the original [2+2] cycloaddition product.

But if this undergoes Intramolecular Mannich reaction that will give you four-membered ring which is actually required for manzamine. So, between four-membered and six-membered which one will be favoured? The four-membered will be favored. So, that is what happens and that Mannich reaction gives rise to the required six-membered ring. So, now if you look at this intermediate carefully.

So, what we have done? So, we have used a [2+2] cycloaddition, Retro Mannich reaction followed by Mannich reaction to construct the four-membered ring. So, 4 rings are made. Now, what is left is we have to connect these two this nitrogen and this carbon we have to connect then we have to introduce the heterocycle here ok. Let us see one by one. How we introduce or how we form this macro cycle?

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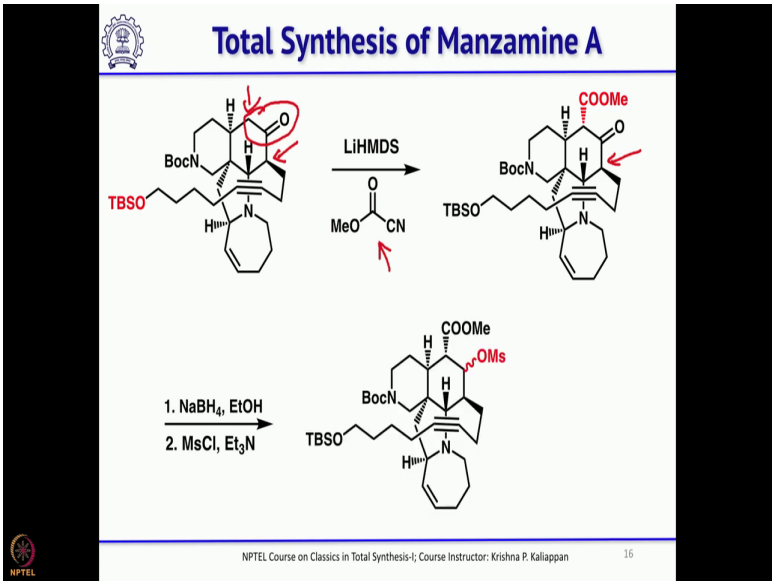

So, the primary alcohol you can protect it as TBS and before that what is important is you also have to introduce a hydroxyl group. You need to introduce a hydroxyl group here ok. How will you introduce a hydroxyl group ok? One you can straight away treat with base, you can straight away treat with base and then treat with you know m-CPBA, there are many methods to introduce hydroxyl group.

But at the same time you also have to introduce an aldehyde here. Then only you can introduce the heterocycle on the top ok. So, what he did? So, he treated with lithium hexamethyldisilazide which will generate enolate here ok. It will generate enolate here.

And then quench with manders reagent. Manders reagent is a reagent which is used for introducing ester group next to ketone.

So, the ester was stereo selectively introduced ok. Then as I said you also have to introduce a hydroxyl group here. You have ketone and you have an ester and then keto group can be easily reduced in the presence of ester. Sodium borohydride will reduce ketone to alcohol that alcohol can be converted into mesylate.

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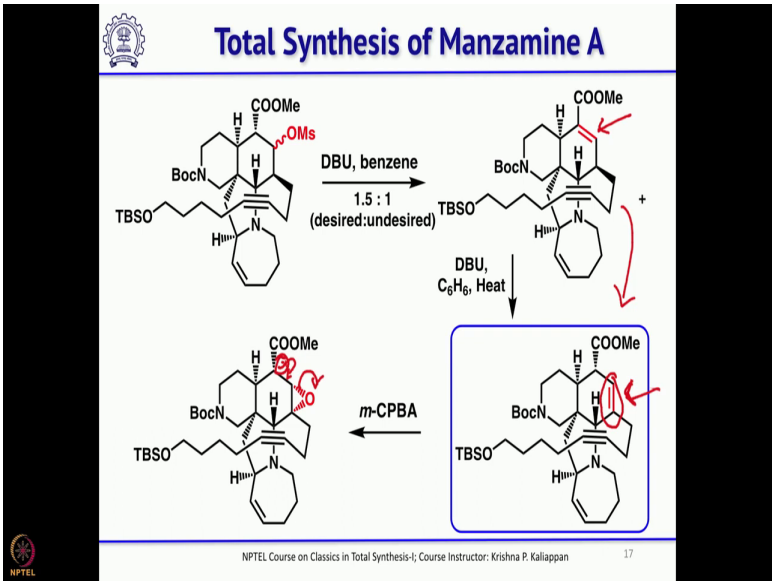

And mesylate you know is a good leaving group that can be on treatment with base can be converted into the double bond.

So, now when you do that; obviously, you will get a mixture of alkenes. 1 is the α-β unsaturated ester. Which is obvious. The other one the β-γ unsaturated ester ok. Both eliminations are possible ok, but what is required is this one, because you need to introduce a hydroxyl group here; that means, you should try to explore the functionalization of this double bond.

How do you do? Now, you isomerize the α-β unsaturated ester to the β-γ unsaturated ester. Then treat with m-CPBA that m-CPBA will give the corresponding α epoxide. Now, it is very easy the ester one can generate enolate here is not it. Then the enolate can open the epoxide. So, what you will get is? A double bond as well as a hydroxyl group at γ position, yeah.

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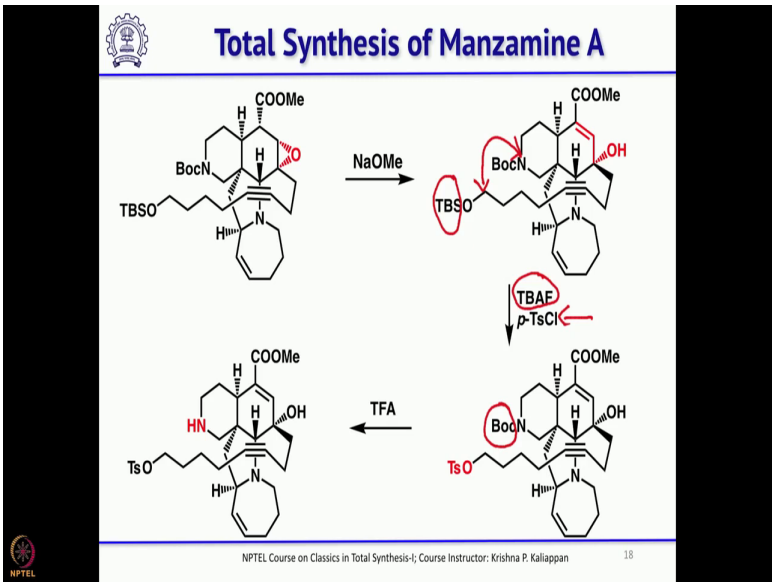

So, sodium methoxide here, acts as a base and then opens the epoxide and that is how you introduce the hydroxyl group ok. Then as I said now it is time to construct the macro cycle. So, first you have to remove the TBS group. The TBS group can be removed with any fluoride source. So, TBAF removes the TBS group to get the corresponding alcohol then the alcohol can be converted into good leaving group ok.

So, you treat with tosyl chloride. So, alcohol is converted into the corresponding tosylate ok. Then what needs to be done is to remove the Boc. So, Boc can be easily removed, if you use trichloroacetic acid and you get the corresponding amine then treatment with base ok.

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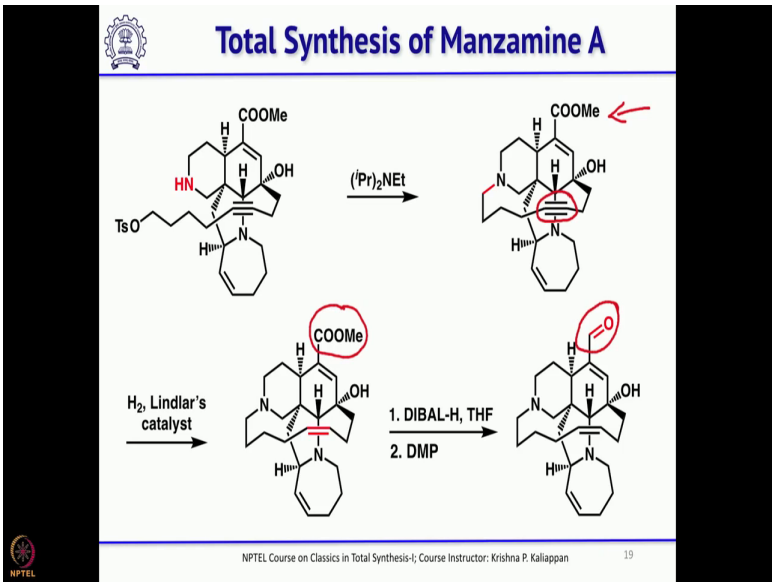

Like Hunig's base. Di-isopropyl ethyl amine will facilitate the intramolecular cyclization. So, now, if you look at this compound we have made pentacyclic compound ok.

So, now if you look at this compound they have made the pentacyclic compound. So, what is now required? Is to attach the indole and form the required six-membered ring. Before that you have a triple bond ok. The triple bond in manzamine is a double bond. So, one can easily reduce a triple bond in the presence of double bond using lindlar catalyst condition ok. Lindlar's catalyst reduces the triple bond to cis double bond.

Then you treat this ester with DIBAL to get the primary alcohol and then oxidize with DMP to get corresponding aldehyde. Now, you know you can recall why we need aldehyde was as I mentioned one of the key reactions in the total synthesis of manzamine is Pictet-Spengler reaction is not it. So, you have all for that you need aldehyde.

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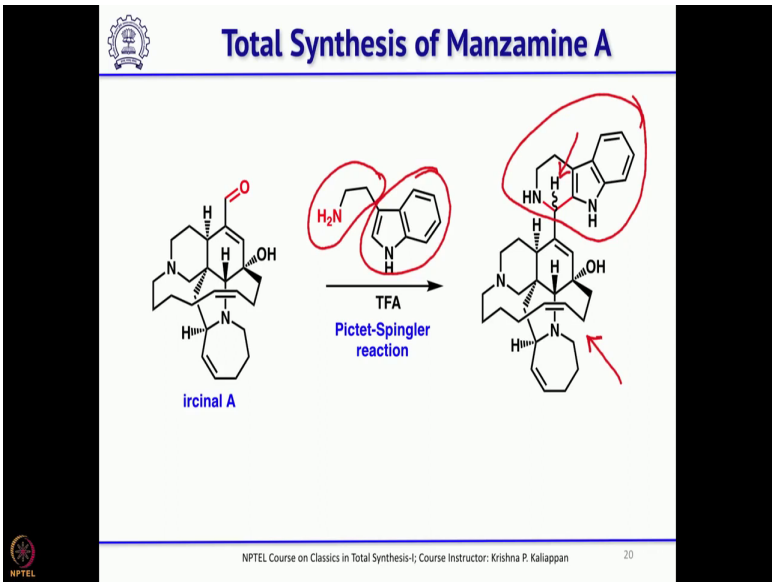

And then what you need for manzamine synthesis is this I mean. So, you have indole you have -CH_2-CH_2-NH_2 ok.

So, now with this if you if you do the Pictet-Spengler reaction by treating with trifluoroacetic acid. What happen? You will get the corresponding six-membered ring ok. Now, what needs to be done in the total synthesis of manzamine. Now, everything is there everything is there you have the core 5 rings then you also introduce the heterocycle, but this particular ring is also aromatic this particular ring also aromatic.

That means you have to oxidize or you have to aromatized this compound.

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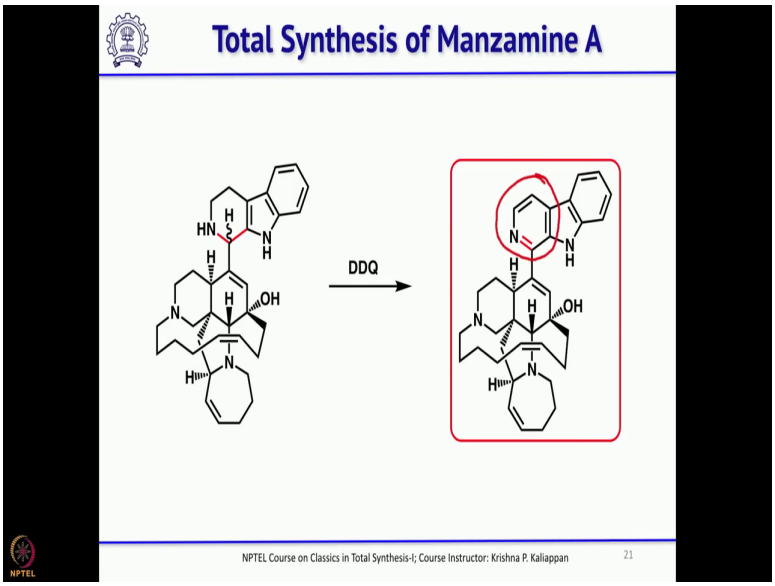

So, the best way to do is take this compound and then treat with DDQ ok. So, DDQ will aromatized that particular ring to get the pyridine ringing ok. What you need is a pyridine ring here. So, that is how the total synthesis of manzamine was complete.

So, if you look at this total synthesis of manzamine reported by Winkler. There are few key reactions one the [2+2] cycloaddition. Second sequential Retro Mannich followed by Mannich reaction ok. Sequential Retro Mannich followed by Mannich reaction. The Retro Mannich actually opened the cyclobutane ring and the next Mannich reaction converted that into a six-membered ring. Then we had this Pictet-Spengler reaction to construct the pyridine ring from indole ethyl amine ok so.

Thank you.