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

Lecture - 04
Total Synthesis of Illudin M, C

Good morning and welcome back to this course on Classics in Total Synthesis. So, far in the last 3 lectures we had a lot of introduction about organic synthesis, total synthesis and so on. So, now, we will actually go into the you know topics. First let us start with total synthesis of natural products having 3-membered ring. So, when you talk about 3-membered ring, not only natural products have 3-membered ring as core structure, but they also will have other rings.

So, what we will do, we will talk about how these 3-membered rings are made for these natural products and also other rings and as a result and in the end, how they have done the total synthesis.

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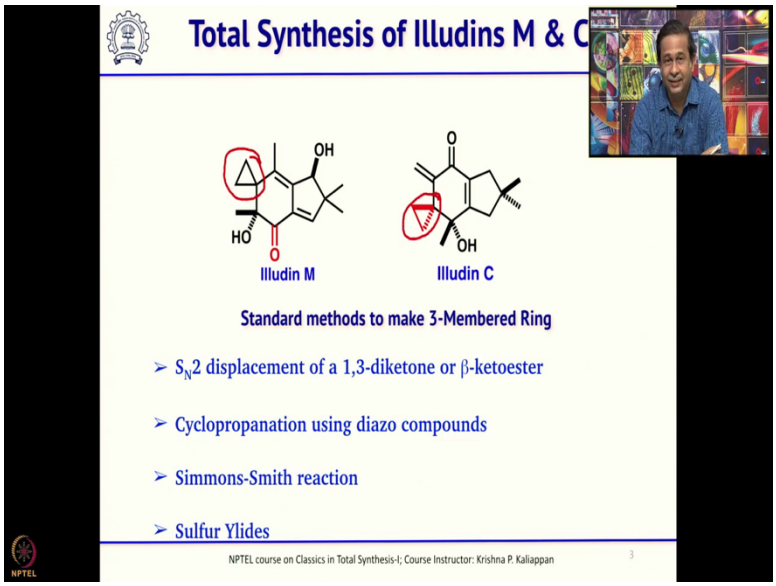

So, today's lecture we will talk about two natural products, they are called illudin M and illudin C and both the natural products, you can see here there is a cyclopropane here, there is a cyclopropane here and in illudin C you have a cyclopropane this side ok.

So, normally when you talk about cyclopropanes, what are the normal standard methods to make 3-membered ring? One is if you have a β-diketone, 1, 3-diketone or β-ketoester then one can think of SN2 displacement reaction, double SN2 displacement reaction with 1, 2-dibromo compound, 1, 2-dihalo compound ok. That is one of the easiest way to make a 3-membered ring. Then if you have a diazo compound, if you have diazo compound then you can do a cyclopropanation on a double bond ok, that is also quite simple and straight forward.

Then one can think about a Simmons-Smith reaction, so that was nicely exploited by Andrew Charette in asymmetric cyclopropanation, which we will discuss tomorrow in one of the total synthesis. And if you have an α, β-unsaturated ketone ok, if you have an α, β-unsaturated ketone sulfur ylides particularly dimethyl sulfoxonium ylide can undergo a 1, 4 addition and in the end it can form a cyclopropane.

So, these are the four standard methods in literature if you see widely used for making cyclopropanes, but as I said in this particular synthesis, we not only talk about how to make cyclopropane, but also how other rings can be made ok.

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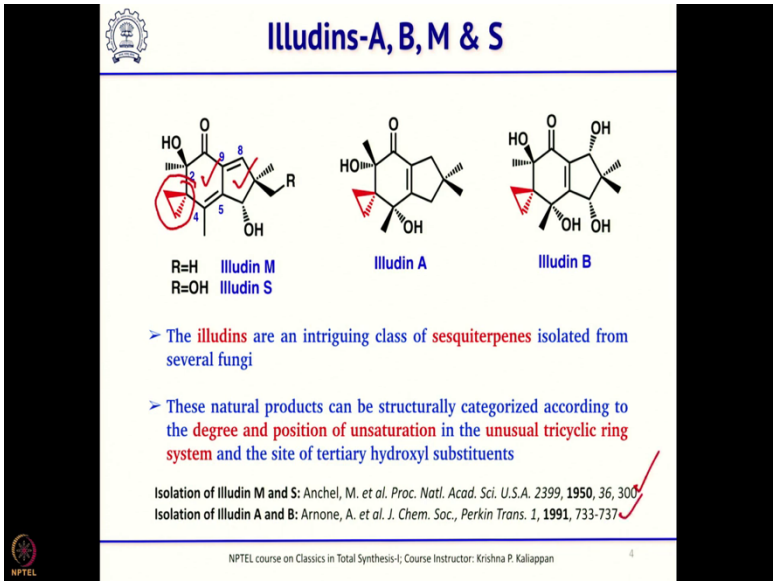

So, let us move to the real natural product. So, illudins, you know there are many illudins here I show a few illudins, like illudin A, illudin B, illudin M, and S all of them you can see having 3 rings, 2 are fused together, that is the 6-membered and 5-membered, they are fused together. And here the 6 and 5, 6 and 3, they are spiro fused together ok, spiro

fuse. And most of them you know, they are very closely related only the functional groups are you know located at different places.

Otherwise, you know they have the common basic skeleton 6-membered, 5-membered and 3-membered and they are also oxygenated. In the first case you can see there are 3 oxygens and second case also you can see 3 oxygen and whereas, in the 4th one illudin B you see 4 oxygens. So, they are all isolated from several fungi and as I said, it has several degree of unsaturation and a unique tricyclic ring: ring system. So, these are the references if you want to see how they were isolated, they are quite old.

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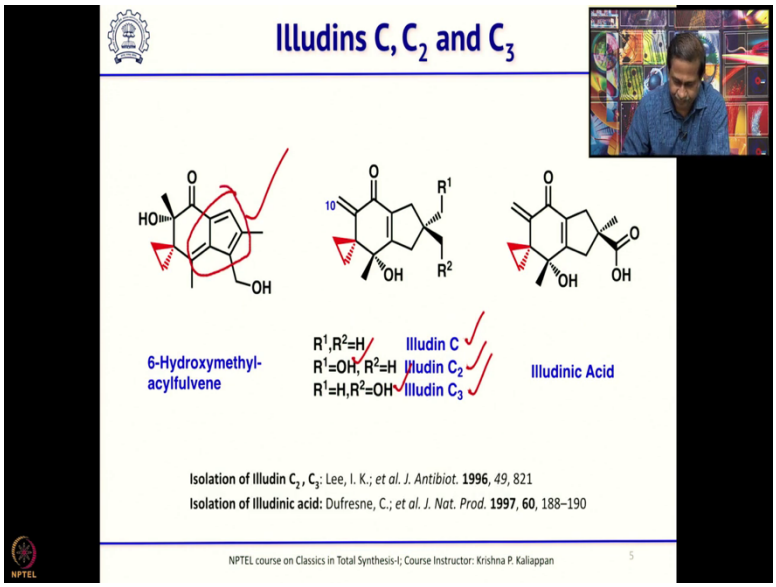

And there are few more illudins you can illudin C, illudin C2 and C3 ok, they differ by presence of OH ok. And again, they have the same structure ok, same core structure and illudinic acid where the CH2OH is further oxidized you have the carboxylic acid and this is another natural product called 6-hydroxymethyl-acylfulvene. So, the fulvene you can see here, this is a fulvene subunit of this natural product.

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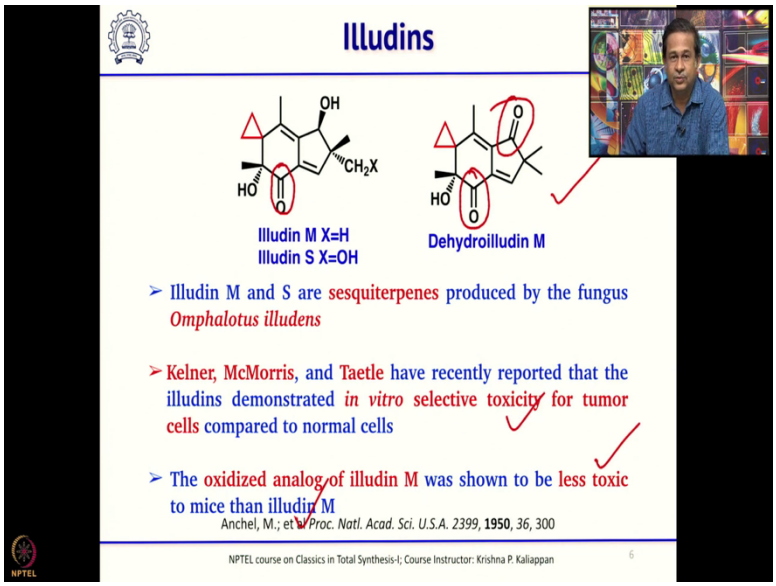

Then you also have oxidized version ok. So, you know there are 2 or 3 hydroxyl groups in illudins and some compounds these hydroxyl groups are further oxidized.

For example, here the hydroxyl group is oxidized to ketone, again you can see the same thing here, the hydroxyl group is oxidized to ketone and then they show a very good biological activity. Particularly it shows selective toxicity for tumor cells compared to normal cells and particularly the oxidized analog this is has been shown to be less toxic than illudin M to mice actually ok.

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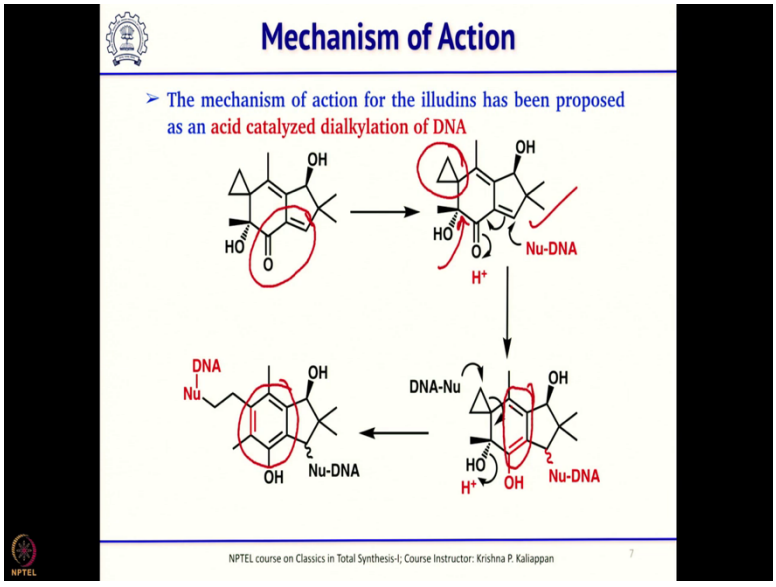

Now, let us go through directly the synthesis of illudin M and C, before that how these illudins are acting.

So, there are mechanism action for illudins one should know. So, if you know that, then it is also easy to make analogs of illudins. So, what happens, it undergoes you know 1,4 addition, basically when your compound has a Michael acceptor, you can see that there is a Michael acceptor here ok, α, β-unsaturated ketone. Then the DNA with the nucleophile can attack in a 1, 4 fashion.

You can see that it undergoes a 1, 4 fashion. Then if you look at your substrate you also have a cyclopropane and next to a carbon having hydroxyl group, you have a cyclopropane next to carbon having a hydroxyl group.

So, what will happen? Once you do this 1, 4 addition the double bond shifts here ok. You get already you see there are two double bonds ok, there are two double bonds ok formed. Now, the another DNA molecule when it attacks the cyclopropane as you know cyclopropanes are like double bonds ok, it can undergo ring opening. So, when it attacks the cyclopropane, then this hydroxyl group can come out as water thereby you make this compound as an aromatic compound ok.

So, that is the driving force for the overall mechanism of action of illudins ok. So, even when you want to design something similar to this, you should keep this in mind. It is not only for illudins, but also other natural products having similar skeleton. Now, let us start with illudin M first, the total synthesis of illudin M was reported by Frederick Kinder almost 28 years ago ok.

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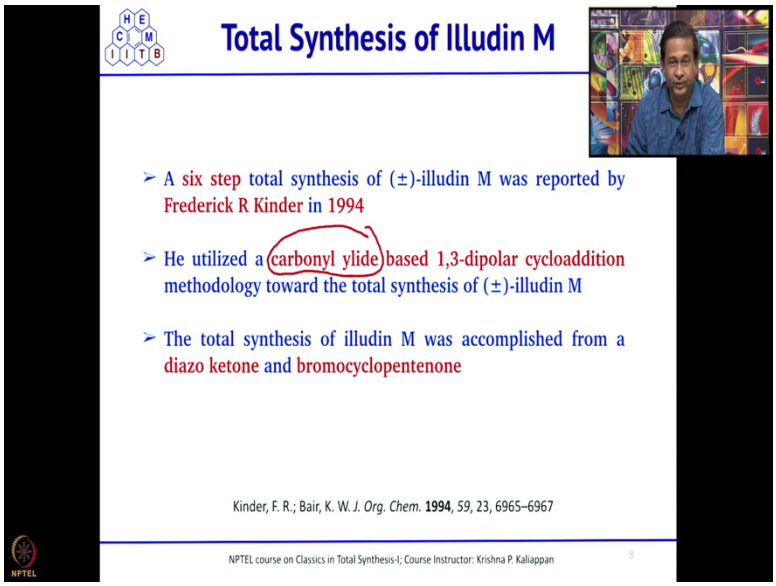

So, it was a six step total synthesis and they used 1, 3 dipolar cycloaddition between a carbonyl ylide, 1, 3 dipolar cycloaddition between a carbonyl ylide and cyclopentenone ok.

Carbonyl ylide and cyclopentenone as the key reaction to construct the tricyclic component ok, the key tricyclic compound was constructed by reaction between carbonyl ylide and cyclopentenone ok, and of course, the carbonyl ylides are normally made from diazo ketone. I will come back to that how carbonyl ylides are made and what is 1, 3 dipolar cycloaddition before we actually move to the total synthesis.

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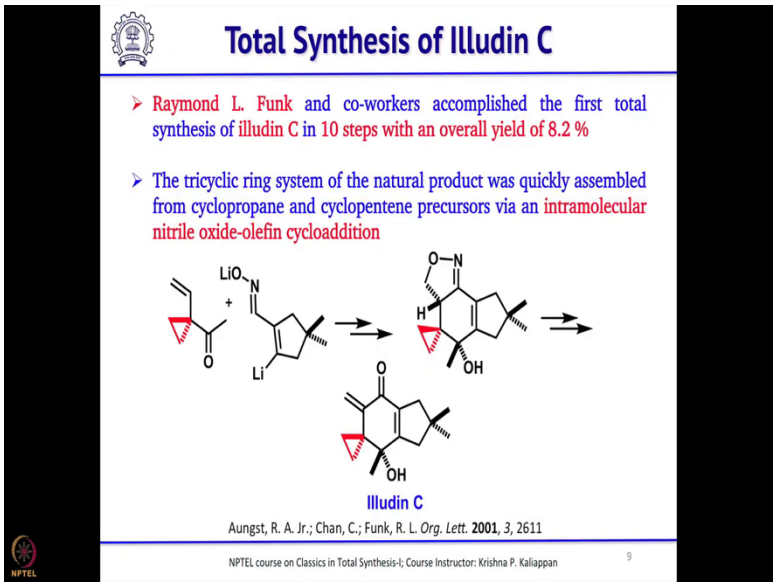

The other natural product which we will discuss under 3-membered ring is illudin C. So, this was reported 20 years ago by Raymond Funk and he took about 10 steps and with a high overall yield of 8.2 percent to make this compound ok. Here he used another 1, 3 dipolar cycloaddition, in the earlier case carbonyl ylide acted as a dipole; dipole whereas in this case a nitrile oxide. The nitrile oxide was used as a dipole and nitrile oxide olefin cycloaddition as the key reaction to make the 5-membered ring ok. So, this is the starting material.

And you can see the addition of lithium species to this ketone followed by nitrile oxide formation from this oxime and intramolecular dipolar cycloaddition gives this tricyclic compound and that can be converted into illudin C. We will discuss this in details in the subsequent slides. Before that what I want to discuss is if you look at these two natural products, there are key reactions and there are key starting materials. So, how they are made ok? That we will have some discussion so that it will be useful, when you talk about the total synthesis.

So, what is the key reaction if you look at in the both synthesis? The key reaction is 1, 3 dipolar cycloaddition ok, one. And what is the key intermediate which is used in illudin M and illudin C? In one case we have used nitrile oxide, in other case we have used carbonyl ylide. So, what we do in the next few minutes is what is one, we will discuss what is 1, 3 dipolar cycloaddition and what is carbonyl ylide. So, what can what one can

do with carbonyl ylide and we also see how nitrile oxide can be generated and what nitrile oxide can do.

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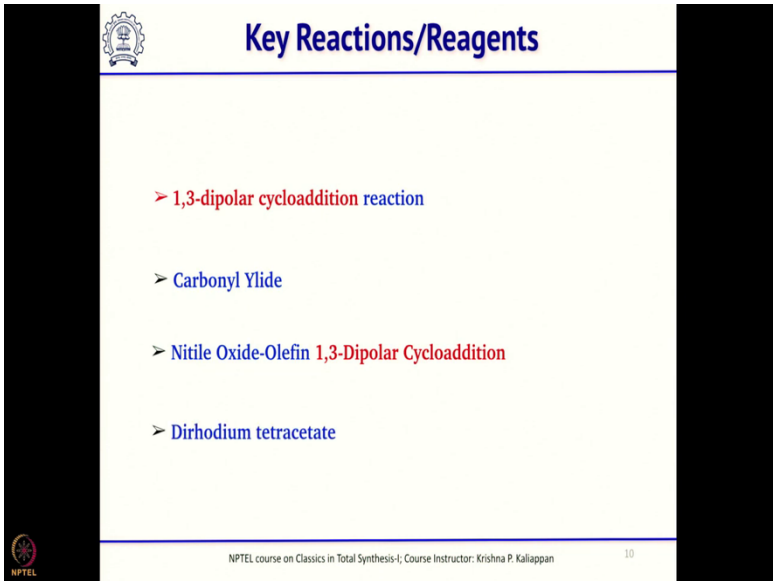

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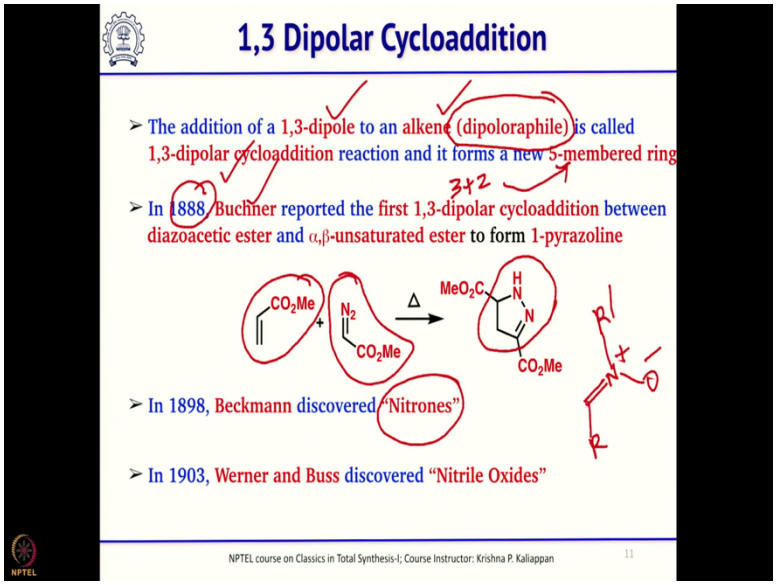

So, first let us start with 1, 3 dipolar cycloaddition reaction ok. And when you talk about 1, 3 dipolar cycloaddition reaction, it is like Diels Alder reaction. but 1, 3 dipolar cycloaddition is known before 4 plus 2 cycloaddition that is a Diels Alder reaction is known. So, 1, 3 dipole ok, it is a 3 carbon unit ok having a dipole and it adds to an alkene

ok, this alkenes are called dipolarophile ok, in Diels Alder reaction it is called diene and dienophile ok.

Here it is called dipole and dipolarophile. So, when they react together the product the reaction is called 1, 3 dipolar cycloaddition reaction; obviously, when you add 3 plus 2, you get 5-membered ring ok. So, that is a basic thing about 1, 3 dipolar cycloaddition. The first 1, 3 dipolar cycloaddition was reported in 1988 by Buchner ok. The reaction was between this α, β– unsaturated ester and diazo acetic ester ok. So, that underwent a 1, 3 dipolar cycloaddition to give this 5-membered ring that was the first 1, 3 dipole cycloaddition reported in literature.

Then 10 years later so nitrones were discovered ok, nitrones are also you know this is called nitrone ok. So, nitrones were discovered in 1898 and the early 20th century Werner and Buss discovered nitrile oxides ok.

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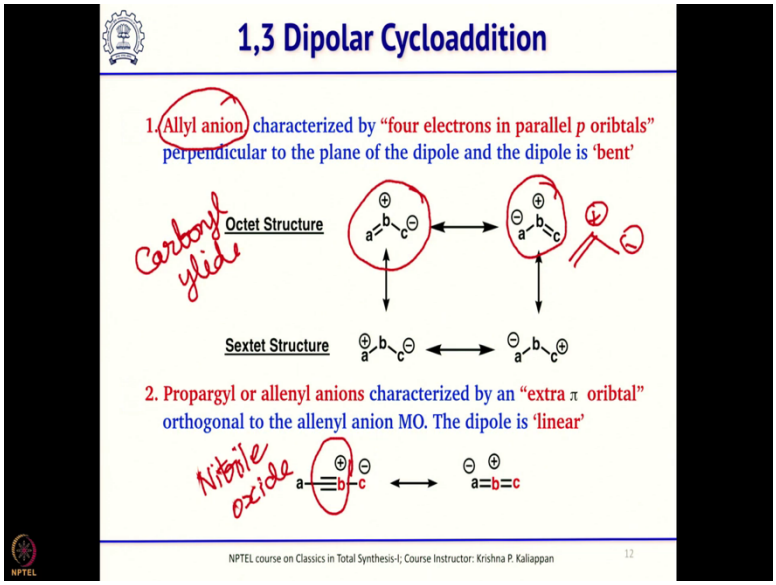

And when you talk about dipole; 1, 3 dipole see this 1, 3 dipole can exist in two forms; 1, it can be like allyl anion ok, see if you have allyl group. So, this is like allyl anion, but since it is a it is an ylide, it is a dipole you should also have a positive charge like this.

So, that is why either it can be like this or you can you know you can write another canonical structure ok. So, this is one form of dipole, another form of dipole is linear. So, that is if we have a triple bond, if we have a triple bond you can see that if we have a

triple bond, then the triple bond the atom, the atom which is attached to one of the triple bond can bear the positive charge, then adjacent oxygen or whatever I you know, it can be nitrogen, sulfur the adjacent heteroatom should be a negative charge.

So, these are the two types of dipoles one can see in the literature one is allyl anion type, another one is propargyl anion type. So, we are going to talk about carbonyl ylide and we are also going to talk about nitrile oxide. So, carbonyl ylide belongs to this and nitrile oxide belongs to this ok. So, nitrile oxide is used for synthesis of illudin C and the other one is used for illudin M ok.

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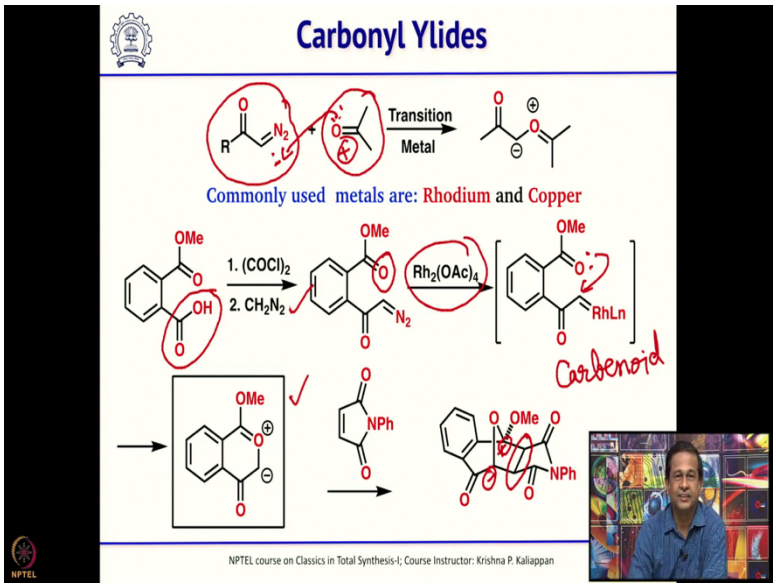

And when we talk about carbonyl ylide, how carbonyl ylides are generated? First of all what is an ylide?

Ylide is a substance where you will have carbon having negative charge and the adjacent atom, that is the heteroatom having a positive charge; is not it? Carbon atoms should have negative charge the adjacent heteroatom should have positive charge.

So, now, if you take a diazo compound and then if you have a carbonyl group either within this within the substrate or you add extra ok, then this this is basically it will form a carbene; is not it? Once the nitrogen goes it will form a carbene and immediately the lone pair on the nitrogen will attack so that it will become positive charge and this will become negative charge ok.

So, that is how carbonyl ylides are generated and for generation of such carbonyl ylides, you need transition metals ok. There are two transition metals which are used routinely to make or generate such carbonyl ylides, first it goes through carbenoids then it forms the carbonyl ylides. What are those two metals? One is copper, other one is rhodium ok. These are the two metals we can see in the literature routinely being used to form carbonyl ylides.

So, now let us see one example how carbonyl ylides are made. Say for example, if you take this carboxylic acid having an ester, now when you treat with oxalyl chloride it forms the corresponding acid chloride. Subsequently when you treat this with diazomethane it forms the corresponding diazo ketone.

Now, if you look at this it has a carbonyl group which is in the same substrate ok, and if you add a rhodium metal dirhodium tetraacetate ok, dirhodium tetraacetate it forms this rhodium carbenoid ok, it forms this rhodium carbenoid ok.

Now, what will happen? This is like carbene, but it is not really carbene rhodium carbenoid, then immediately this lone pair can attack and then form the corresponding carbonyl ylide ok. So, this is what it will form. Once the carbonyl ylide is formed, then you can do dipolar cycloaddition with various dipolarophiles. For example, if you do this with N-methyl N-phenylmaleimide, then you get this 1, 3 dipolar cycloaddition adduct you can see.

So, this is the dipolarophile and here originally you had the dipole, so that undergoes dipolar cycloaddition to give this bicyclic system ok.

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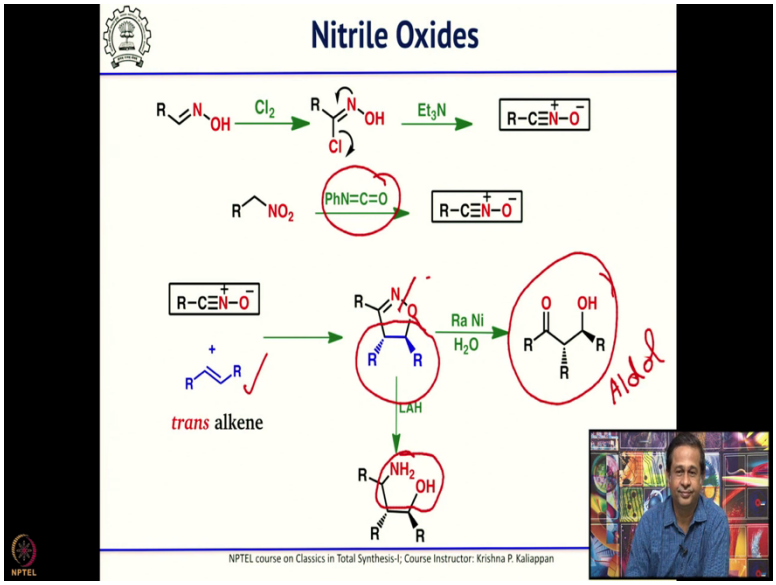

Likewise, nitrile oxide; nitrile oxide can be generated from the two different starting material, one is oxime other one is from nitro compound.

So, once you have an oxime, treat with any chlorinating agent. When you treat with chlorinating agent first a monochlorination takes place, then followed by elimination of HCl in the presence of bases like triethylamine you get the corresponding nitrile oxide. Then the second method which is also widely used is nitro alkane. Here what you need is a dehydrating agent. So, one of the most widely used dehydrating agent for making nitrile oxide is phenyl isocyanate. So, the phenyl isocyanate removes water molecule from this and gives nitrile oxide.

So, once you have nitrile oxide, then as I said you can do a dipolar cycloaddition with any alkene. So, if you use trans alkene and you can see the trans products and if you use cis alkene you will get cis product. Now, once you made this if you use Raney nickel. So, Raney nickel is known to cleave this N-O bond, Raney nickel is known to cleave this N - O bond and afterwards aqueous workup will also hydrolyze the imine to give ketone. So, now, if you look at this product. What is this product? This product is nothing but aldol ok.

So, indirectly what you are doing is you are doing an aldol reaction with starting with nitrile oxide and alkene, that is it undergoes a 1, 3 dipolar cycloaddition followed by reductive cleavage with Raney nickel ok. So, nitrile oxide and carbonyl ylides are

routinely used in 1, 3 dipolar cycloaddition. And one can also use, LAH; LAH what it does? It not only it cleaves a N-O bond, but also reduces the C double bond N. So, you get the corresponding amino alcohol ok.

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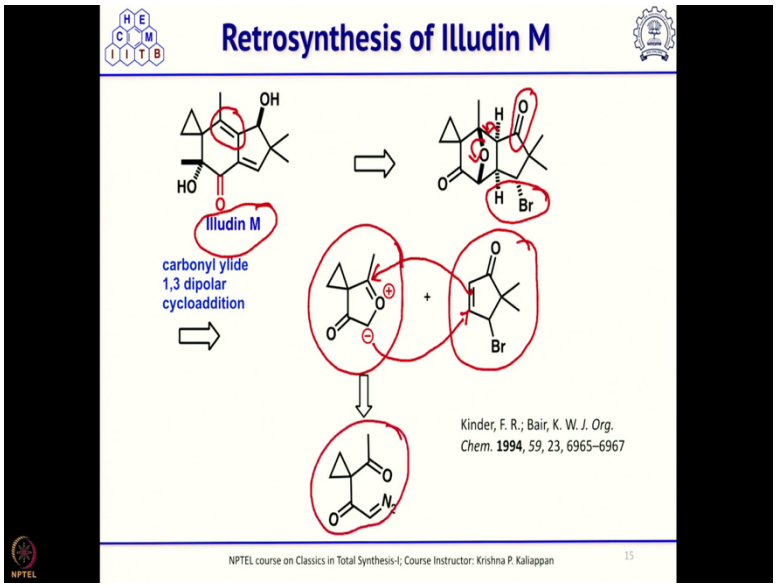

So, with this introduction on 1, 3 dipolar cycloaddition, carbonyl ylide and nitrile oxide, now we will go to the real total synthesis are illudin M and illudin C. First let us start with illudin M. So, when you look at this illudin M ok, as I said the it goes through carbonyl ylide and 1, 3 dipolar cycloaddition. So, this final target molecule illudin can be obtained from this tetracyclic compound in 2 to 3 steps ok. How? one, if you reduce this if you reduce this you get a hydroxyl group, but before that you have to open this.

How you do? If you treat with a base ok, then it can open up the oxa bridge, if you treat with the base you can open up the oxa bridge. So, you can see this double bond can be formed and this will become hydroxyl group, that hydroxyl group can be oxidized. Second the elimination ok the elimination will give you the required double bond. So, this is the precursor for illudin ok, it takes maybe 2 or 3 steps. Then if you look at this carefully this is nothing but a carbonyl ylide and a dipole ok.

So, this will attack here and this will attack. So, that will form the 5-membered ring ok. Now, your job is how you generate this diazo carbonyl ylide this carbonyl ylide can be easily generated from the diazo ketone ok. Now, let us see how this diazo ketone is prepared ok.

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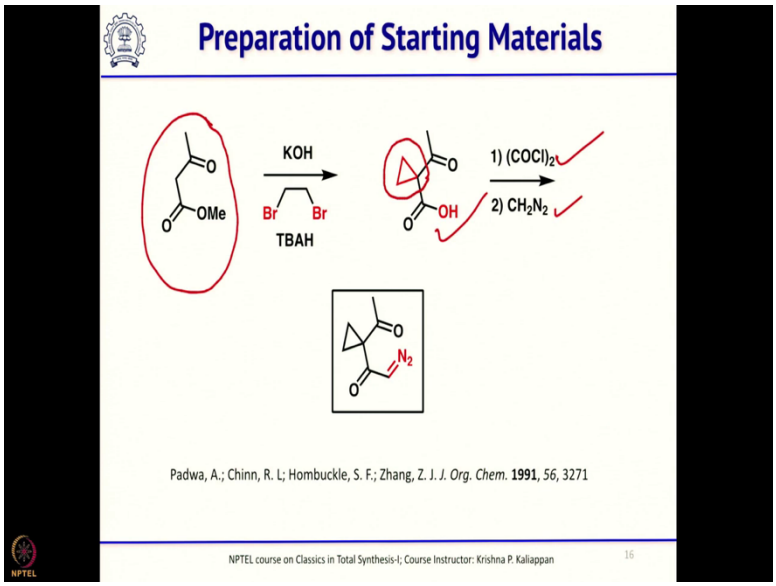

That is very easy; as I said when you whenever you have β–keto ester or 1, 3 diketones then one can use a SN2 displacement reaction. So, for example, if you take methyl acetoacetate or ethyl acetoacetate then treat with base, like potassium hydroxide in the presence of a phase transfer catalyst, 1, 2 dibromoethane will give the cyclopropane. So, it is easy to introduce the cyclopropane.

Since you are using potassium hydroxide the ester also gets hydrolyzed and you get the corresponding carboxylic acid. It is a well-known reaction and it works very well. Now, the acid, the carboxylic acid can be easily converted into diazo ketone in two steps; 1, treat with oxalyl chloride it forms the oxalyl corresponding acid chloride. Second step you treat with diazomethane, you get the corresponding diazo ketone. So, basically as you look at in the scheme this methyl acetoacetate is very cheap, it is available in you know plenty and tons scale one can buy.

In three steps one can make the starting material which is required for making the carbonyl ylide ok that is the first fragment. For the second fragment what you should do? You should start from ethyl adipate.

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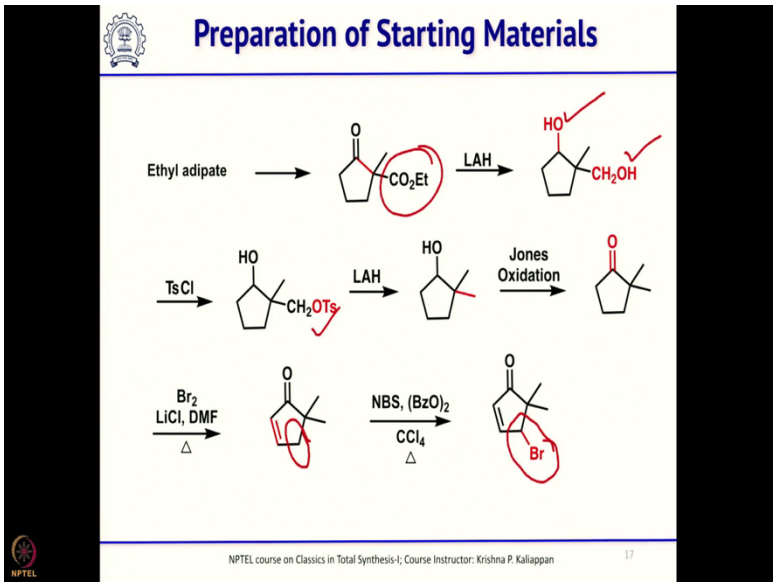

So, ethyl adipate again it is a commercially available compound and in one step one can make this 2 methyl cyclopentanone with ester at α-position. Now, you reduce the ester as well as the carbonyl group, that is ketone to get a diol, you have a primary alcohol and secondary alcohol ok. What we have seen is you need a dimethyl group. So, the CH2OH can be selectively tosylated in the presence of secondary alcohol ok, it is easy to tosylate.

Now, if you treat with LAH, the tosyl group will go and you introduce the methyl group ok. So, now, you have 2 methyl groups, what you need is you have to oxidize the hydroxyl group, introduce the double bond and also introduce the bromine. So, simple oxidation, a Jones oxidation of course, one can use other oxidizing agents then treat with bromine in the presence of lithium chloride and DMF. When you heat it bromination followed by dehydrobromination takes place, that is how you introduce the double bond.

Having introduced the double bond now you need one leaving group at this position ok because that is how you introduce the double bond. So, that can be done under you know peroxide condition, NBS and the peroxide you can easily introduce this bromine. So, now, you have made both the fragments one diazo ketone and enone, what you need to do take the diazo ketone treat with dirodium tetraacetate and cyclopentenone. So, then it will undergo first the formation of carbonyl ylide, then immediately it will undergo 1, 3 dipolar cycloaddition reaction.

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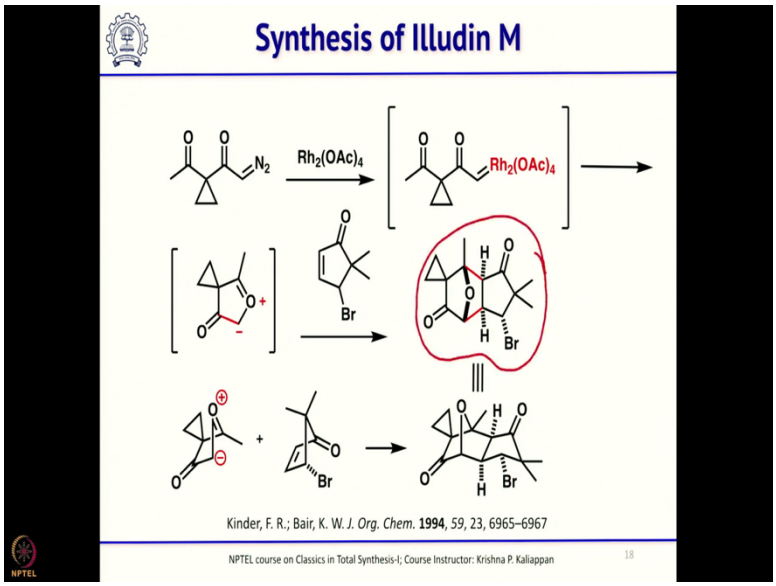

So, take the diazo ketone and then treat with rhodium acetate you get the corresponding carbenoid and then it forms the carbonyl ylide and you treat with cyclopentenone and it undergoes the 1, 3 dipolar cycloaddition to form this compound. Very simple straightforward ok, then once this is formed you need to; ok of course, this can be drawn like this also ok.

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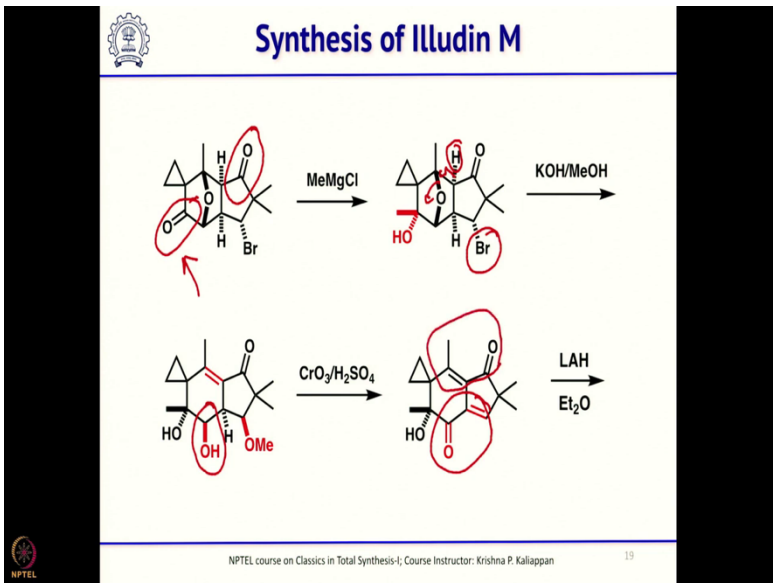

Once this is formed what you do? You have to add a Grignard reagent ok, you have to add a Grignard reagent. So, now, there are 2 ketones, one as well as here between these two this is sterically less hindered; this is sterically less hindered.

So, Grignard addition takes place at this ketone and you get the corresponding tertiary alcohol ok. Next step is the removal of not only removal of this oxygen oxobridge, but also when you treat with base potassium hydroxide and methanol. It undergoes an SN2 displacement of this compound, SN2 displacement of this bromine. So, you get a methoxy group and this one opens and you get a hydroxyl group, understand? This opens and you get oxygen bridge and the bromine undergoes SN2 displacement with methanol.

Now, if you oxidize, there is only one alcohol which can be oxidized other one is tertiary alcohol and during that condition elimination also takes place and you introduce the α,β–unsaturated ketone ok. Now, there are 2 ketones ok, I should say both are enones ok and selectively one can reduce one of them, but it is very difficult ok.

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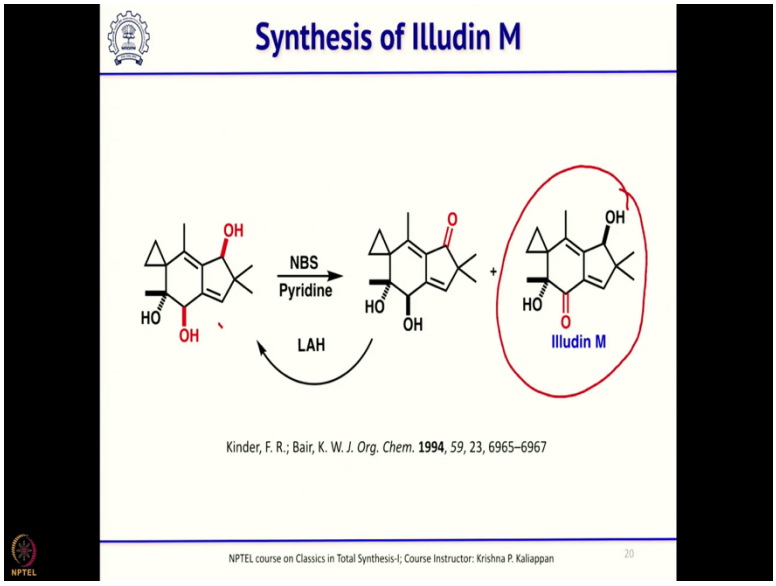

One can think of reducing one of them selectively, but it is very difficult. So, when you treat with LAH, it reduces both ok it reduces both; however. When you oxidize ok when you try to oxidize this alcohol you get illudin M as the major products ok.

And the other one can be recycled you know you can again reduce it, again you can reduce it you get the dihydroxy compound the dihydroxy compound can be oxidized

with a to a mixture of illudin M and this compound. So, that is how the illudin M was synthesized where a carbonyl ylide was used as the key intermediate and 1, 3 dipolar cycloaddition was used as a key reaction.

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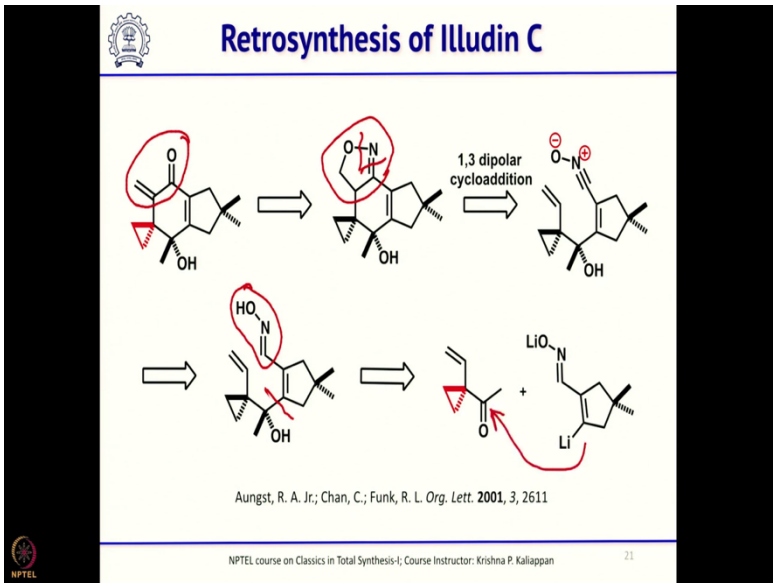

So, now we will move to the next natural product called illudin C and here the idea is to use a nitrile oxide cycloaddition. So, if you look at this compound, this enone it can be prepared from this 5-membered ring.

So, if you cleave this NO bond you get a CH2OH and this also will get hydrolyzed to ketone followed by elimination one can get this α,β–unsaturated ketone. And this one can be easily obtained by this intramolecular nitrile oxide olefin cycloaddition reaction ok. And this in turn can be obtained from the corresponding hydroxyl amine ok. So, bromine source and you get this and here these 2 fragments addition of this lithio species to this ketone will give you the precursor for the nitrile oxide formation ok.

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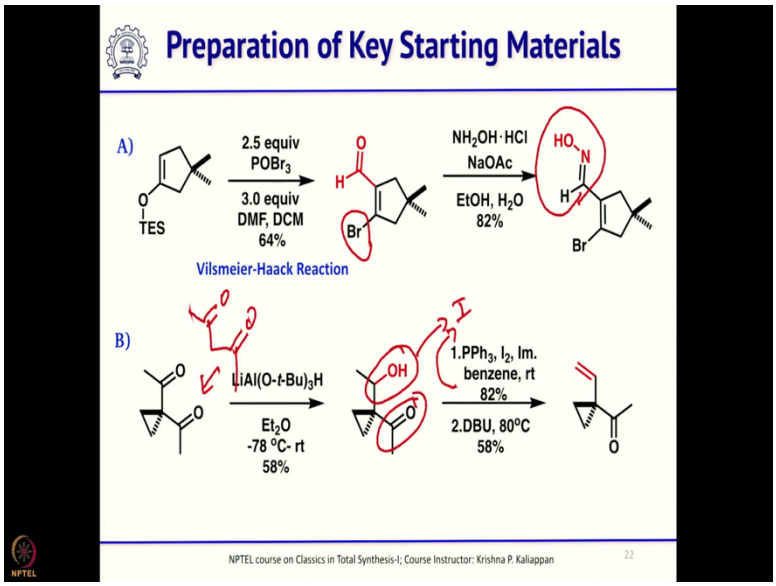

Now, let us see how these 2 fragments are made. First you can start with the corresponding ketone or you can make it as enol-t enol tes ether. Basically, what you are doing is a Vilsmeier-Haack reaction, treat with b o POBr3 and DMF and you get this α,β–unsaturated aldehyde, with a bromine atom at the β position. So, standard Vilsmeier-Haack reaction ok. Only thing is the ketone you start with enol ether, then once you have aldehyde convert that into oxime, simply by treating with hydroxylamine you get the corresponding oxime.

Now, you have bromine and that bromine should be exchanged with lithium. So, best way to do is tert-butyllithium. I will come to that later. And before that the other fragment it is very easy to make from the corresponding 1, 3 diketone, acetyl acetone ok. Then you do cyclopropanation, you get this it is also commercially available.

Then reduce one of them, since this is a symmetrical compound one of them can be selectively reduced to get the hydroxyl group. Now, this ketone can be you need a double bond, is not it? So, either this ketone can be converted into double bond or you can do dehydration to get the double bond there are two possibilities.

So, what they did? This hydroxyl group was converted into iodide ok using this reaction, then DBU eliminated that to get the corresponding double bond ok. So, this is how you know in three steps you know one could make this starting material.

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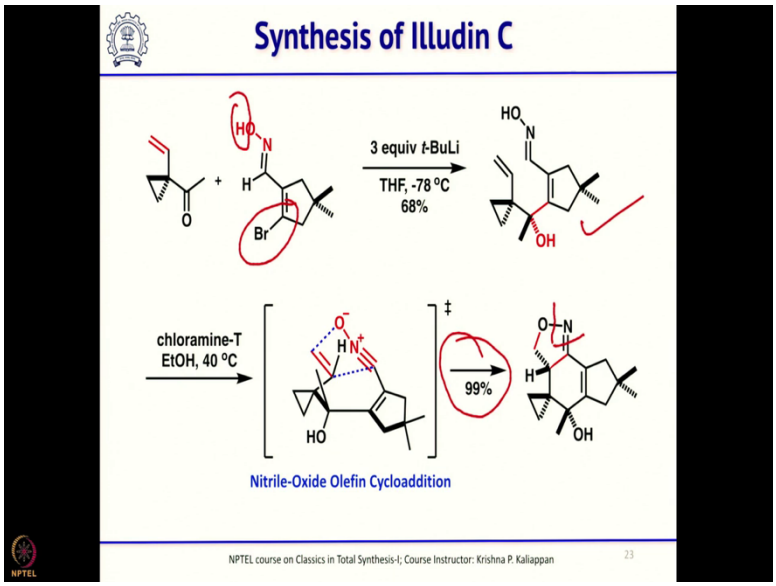

Once you have these 2 fragments the next step is to generate the lithio species and add to this ketone ok. How do you generate normally? Lithium exchange can be done with N butyl lithium or with tertiary butyl lithium. So, they used three equivalents of tertiary butyl lithium, you should know why three equivalents of tertiary butyl lithium is required.

Two equivalents are required to exchange the bromine and one more equivalent is required to remove the OH. So, it adds to this ketone and you get this compound which is the precursor for the dipolar cycloaddition intermediate that is nitrile oxide. Now, you treat this with chloramine-T ok, chloramine-T is a chlorine source. So, chlorination followed by elimination you generate this nitrile oxide. So, once you generate this nitrile oxide, then it is ideally the double bond is ideally situated for the nitrile oxide olefin cycloaddition reaction. So, that takes place to give your tetracyclic compound ok.

So, very high yielding reaction, you can see 99 percent yield ok. Then as I said you have to cleave the NO bond and hydrolyze the imine.

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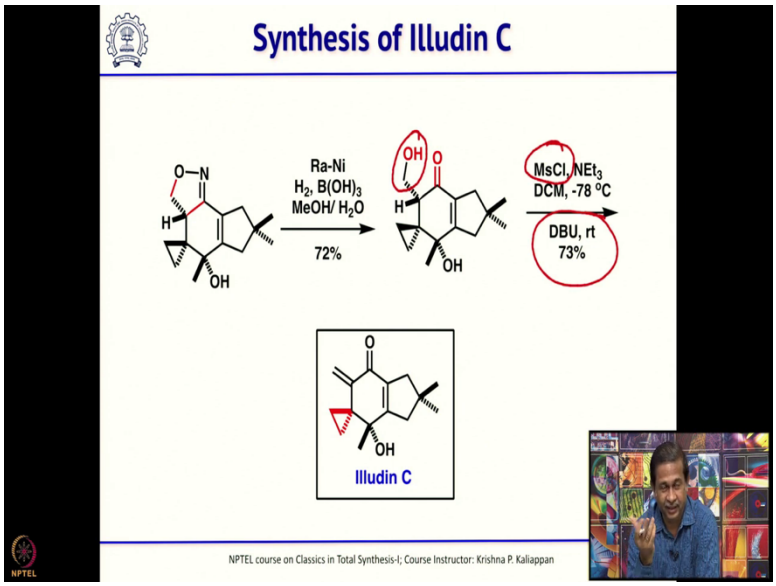

So, that can be done with Raney nickel ok, Raney nickel cleaves NO bond and hydrolysis and you get the β-hydroxy ketone ok. It is an aldehyde like β-hydroxy ketone. Once you have this β-hydroxy ketone the next step is to introduce a double bond ok. So, that is very easy convert the hydroxyl group into a good leaving group.

So, here the good leaving group is mesyl group treat with mesyl chloride triethylamine, you got you convert the hydroxyl into mesylate then upon treatment with DBU, the elimination takes place, that is how you synthesize illudin C.

Again if you look at this whole process the number of steps is only 6, in 6 steps total synthesis of illudin C is accomplished. Though in both cases the cyclopropane is formed by double displacement reaction, the focus was more on the other rings making the 5-membered and 6-numbered ring and both cases a dipolar cycloaddition was successfully used.

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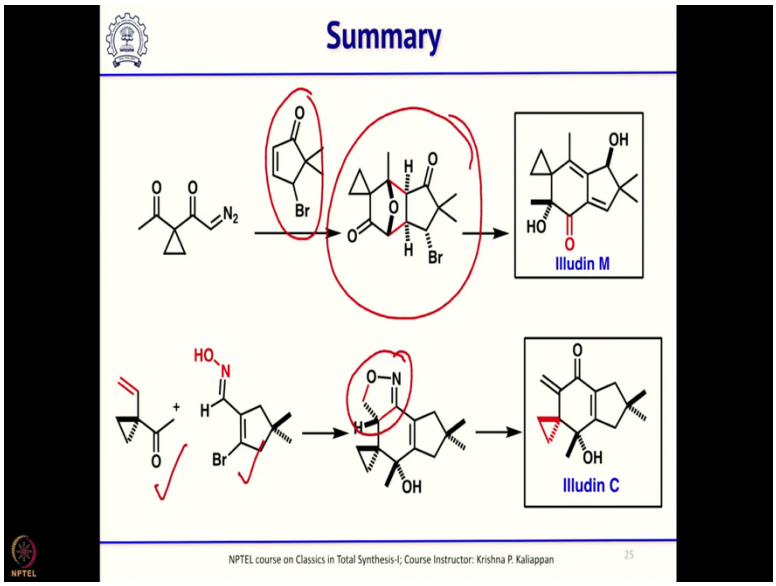

So, to summarize, if you see the first case carbonyl ylide was used as a dipole 1, 3 dipole and 1, 3 dipolar cycloaddition reaction with cyclopentenone gave this tetracyclic compound, which in few steps was converted into illudin M. In the second case where you can see here the nitrile oxide precursor was made in two steps from this ketone and the bromine and intramolecular nitrile oxide cycloaddition gave this intermediate which was converted into illudin C in a couple of steps ok.

So, these are the two natural products having cyclopropane, we discussed and tomorrow we will discuss another natural product having more cyclopropanes and then we will move to 4-membered ring ok.

Thank you.