Classics in Total Synthesis - I
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Lecture - 36
Methylhomosecodaphniphyllate and Secodaphnyphillane

Yeah, good morning. Welcome back to the lecture series on Classics in Total Synthesis. So, we have been discussing about synthesis of alkaloids, and today also we will continue our discussion on the total synthesis of one more alkaloid.

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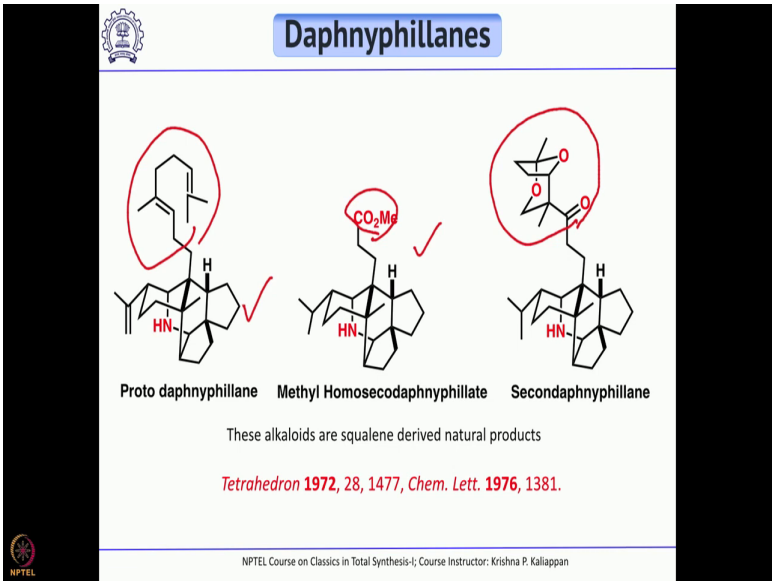

And these alkaloid actually is a combination of many alkaloids. They are basically derived from squalene. As you can see here they are quite complex. So, this is called Proto Daphnyphillane, and if you remove this portion, ok, so, you can see here Methyl Homosecodaphniphyllate. I will repeat, Methyl Homosecodaphniphyllate and instead of Ester if you have this bicyclic moiety, ok it is called Secodaphniphyllane, ok.

So, these were isolated in 70's. Today, what we will do, we will talk about the total synthesis of these two natural products, ok.

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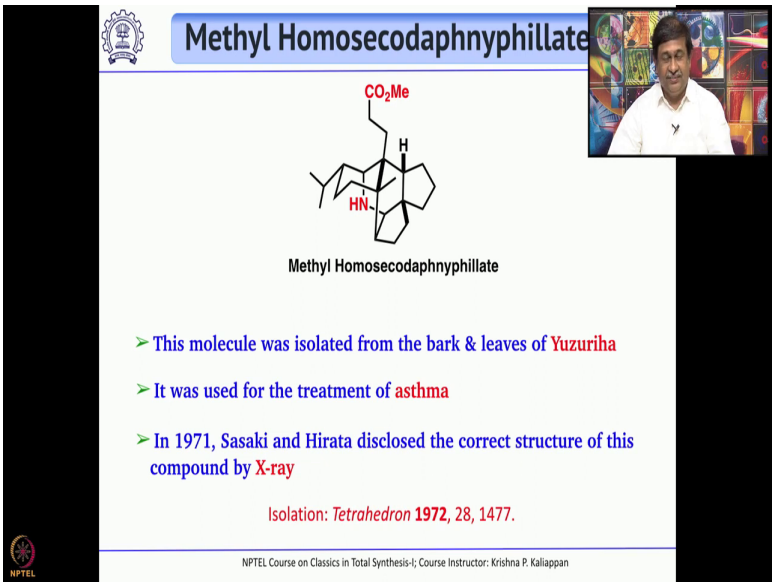

First, let us start with methyl homosecodaphniphyllate. So, this was isolated in 1971-72 and it was isolated from the bark and leaves of Yuzuriha tree which was found in plenty in China. Basically, the extracts of this bark as well as leaves were used for the treatment of asthma, ok, it is herbal treatment.

And this has been going on for centuries in China. And the crystal structure of this particular compound as you can see here, it is a quite complex natural product. So, you need crystal structure to find out the correct structure. So, it was done in 1971. Due to its complex structure, many synthetic groups were interested in the total synthesis of this particular alkaloid.

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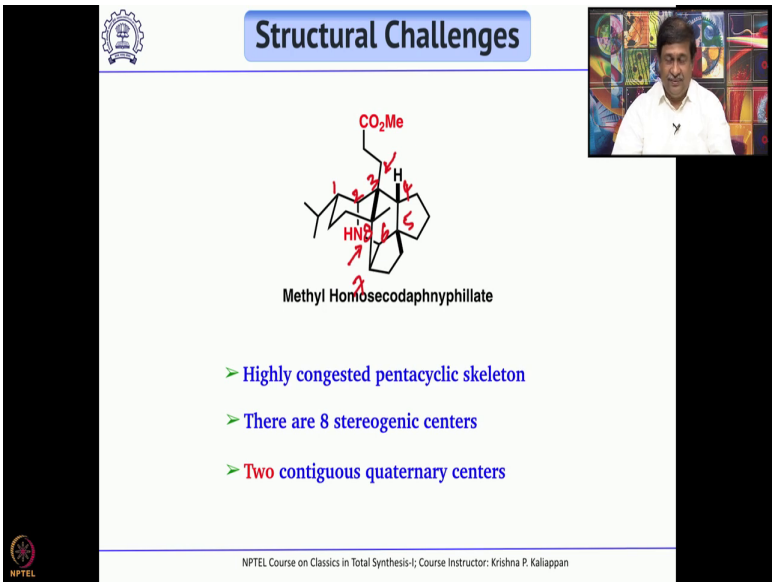

And from structural point of view, if you see this molecule you can find it is a penta cyclic compound, not only that it is highly congested, ok There are 5 rings in this molecule, then there are 8 contiguous stereo centers. There are 8 contiguous stereogenic centers. You can see 1, 2, 3, 4, 5, 6, 7, 8, 8 contiguous stereogenic centers. In that if you look at 3 and 8, ok if you look at 3 and 8, they are contiguous quaternary centers.

So, presence of 8 stereogenic centers, in that two contiguous quaternary centers coupled with a complex pentacyclic skeleton, really provided enough synthetic challenge for synthetic chemist to attempt the total synthesis of this molecule.

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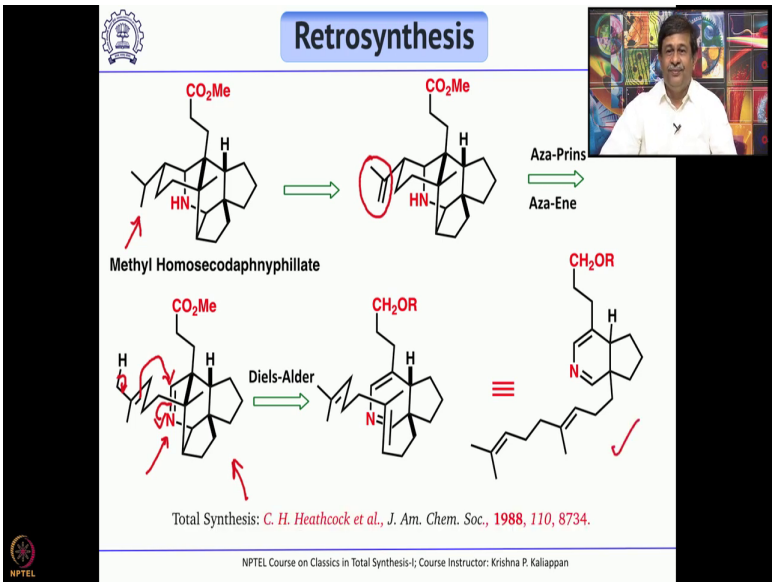

The first total synthesis was reported by Clayton Heathcock and he used a combination of two key reactions, one an intramolecular Diels-Alder reaction followed by Aza-Prins reaction. So, this is a combination of two reactions in one part. And before that he used a sequential Michael Addition followed by alkylation, ok.

The first key disconnection was here, what he did was cleverly he introduced a double bond here, ok. He cleverly introduced a double bond. So, when we talk about retro synthesis. We always look at a functional groups and strategic bonds. So, that disconnection will be easier.

But sometimes what will happen, you may not have functional groups or you may not have a proper strategic bond for further disconnection. In such cases, as I had already mentioned you need to introduce a functional group. Occasionally, you will also see that you will have functional groups, but those functional groups are not sufficient for proper retro synthesis. In such cases also, one can think about introducing a functional group, ok

So, that is what he has done. If you look at the natural product you could see an isopropyl group at equatorial position, ok. So, what he did? He did one minor change that is instead of isopropyl group he put two propenyl group that means, he introduced a double bond, ok.

Why he introduced the double bond? Because that brings lot of flexibility and also that brings sea change in the thinking of how to approach this natural product, ok. Let us see how he has done and what he has done and why this double bond was introduced and how it helped in the retrosynthesis.

What he thought was the moment he introduced a double bond, then he can think about what we call Aza-Prins or Aza-Ene reaction. What is that? You can see here, if you have an imine, ok if you have an imine, then you can think about carrying out an Aza-Prins reaction or Aza-Ene reaction. So, what will happen?

This C-H bond will come and this will attack here, attack the imine and it will undergo cyclization to form a 6-membered ring. Basically, what you have done in this retro synthesis you have removed one ring and this ring is constructed via Aza-Ene or Aza-Prins reaction. And if you look at this molecule, you can see a cyclohexene, but with a hetero atom.

Normally, when you see a cyclohexene, the key reaction which will come to your mind is Diels-Alder reaction, is not it. Here instead of cyclohexene what you have is a hetero atom. Nitrogen is present in the double bond, ok. So, this also can be obtained by a Diels-Alder reaction. Only thing is you will have a heterodyne. You should start with a heterodyne. So, that is what he proposed.

So, this could be obtained by an intramolecular Diels-Alder reaction, ok by an intramolecular Diels-Alder reaction. One should be able to obtain this tri-cyclic compound in one part, ok. And this in principle, ok, so it of course, it can be redrawn for the sake of better understanding. So, this could be redrawn like this, ok.

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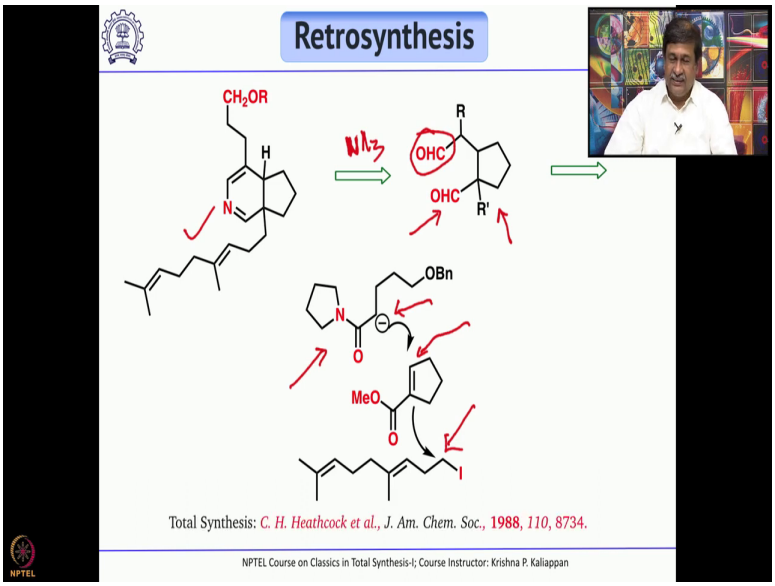

Now, if you look at this molecule, ok this bicyclic compound, this can be obtained from this dialdehyde. When you treat this with amine, for example, ammonia, ok if you treat with ammonia, first what will happen? It will react with this aldehyde, it will form imine. Since, you are treating with ammonia and it is forming imine, it can undergo isomerization to form enamine, that enamine can react with this aldehyde and to get this compound, ok.

So, one part reaction. You treat this dialdehyde with ammonia, you will get directly this dihydropyridine, substituted dihydropyridine derivative. And this dialdehyde as you know can be obtained from corresponding lactone or diol. But the next key reaction is the Michael Addition the 1, 4 addition followed by alkylation with an alkyl halide, ok.

So, what he proposed was, here the anion generated by treatment of this amide with lithium hexamethyldisilazide or LDA can undergo a 1, 4 addition on to the α–β unsaturated esters, 5 membered α–β unsaturated ester. This upon alkylation with this electrophile, that should give directly the precursor to the dialdehyde, ok.

Now, let us see how he has accomplished the total synthesis of methyl homosecodaphniphyllate using these two key reactions.

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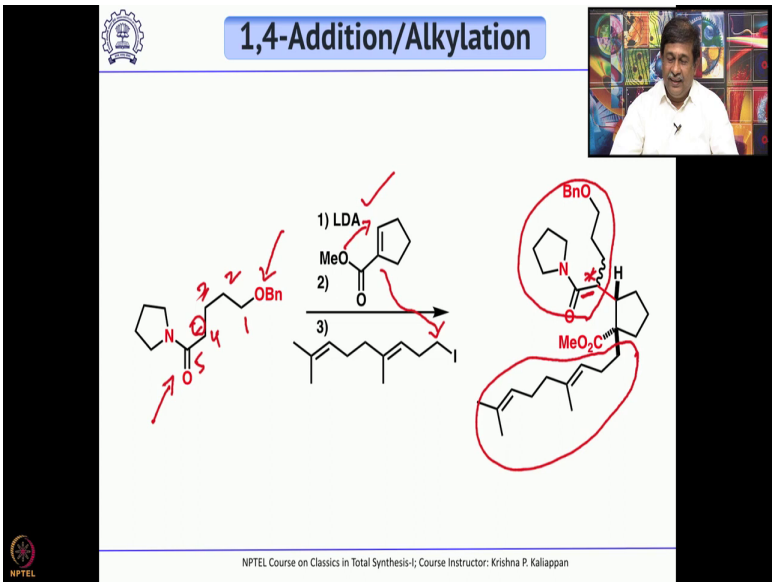

So, first you started with this amide. This can be easily obtained from the corresponding diol, ok. You see 1, 2, 3, 4, 5. You can start from 1, 5 pentane diol and selectively protect one of the alcohols as benzyl ether, and oxidize the other alcohol, other primary alcohol to carboxylic acid and convert that into amide, ok. In 3 steps, one can make this compound.

Then, you treat with LDA. So, LDA what it will do? It will generate anion here. Then as depicted in the retro synthesis, it will undergo 1, 4 addition and followed by quenching with this iodide you get this compound. Here if you look at this, particularly this whole portion and this electrophile they are trans to each other, ok.

They are trans to each other. However, this stereo center, they got mixture, but does not matter. The reason is anyhow if you look at the intramolecular Diels-Alder reaction precursor, you will have a double bond here, is not it. That dihydropyridine. So, this stereo center is immaterial. So, once you have this the next step is you have to reduce the ester, ok.

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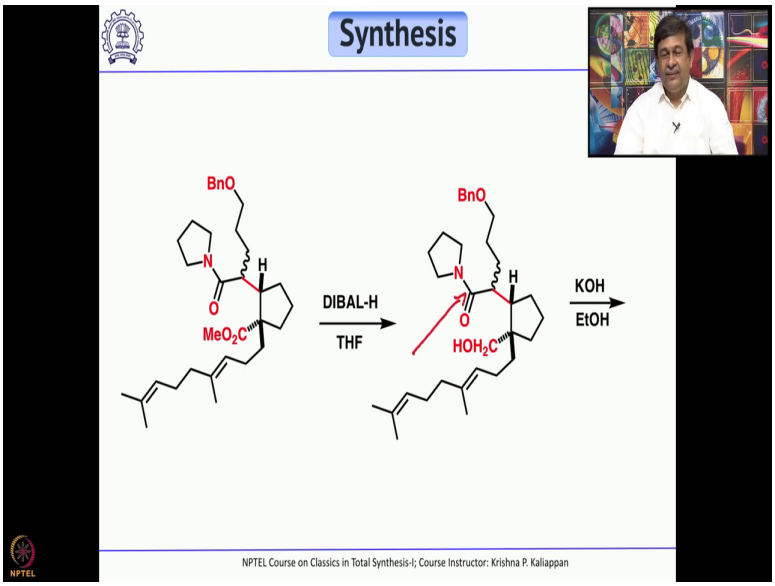

The ester could be easily reduced with DIBAL. I mean is when you do that the ester will get converted into the primary alcohol. Now, the primary alcohol if you treat with potassium hydroxide and ethanol. So, basically hydrolysis and followed by lactonization you get the corresponding 6-membered lactone, ok.

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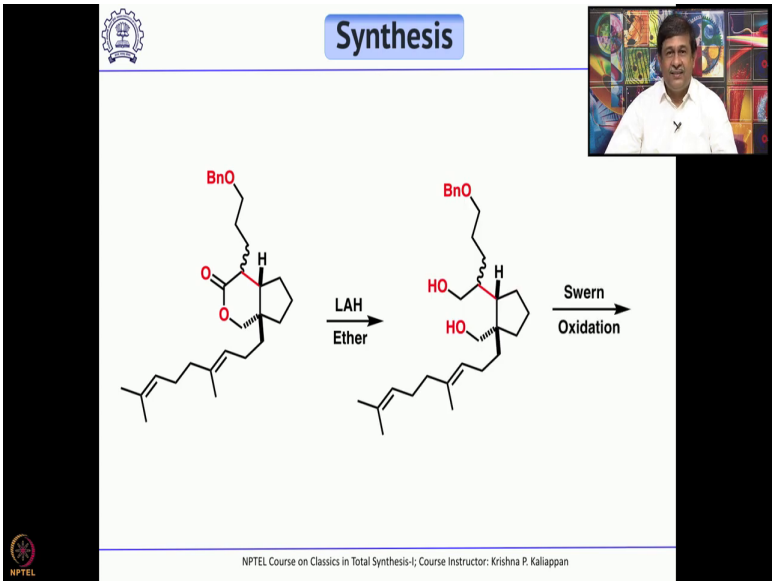

Now, from the 6-membered lactone you have to convert into dialdehyde which is a precursor for making dihydropyridine. This lactone was reduced completely with lithium

aluminium hydride to get the diol and the diol was oxidized under Swern condition to get the dialdehyde.

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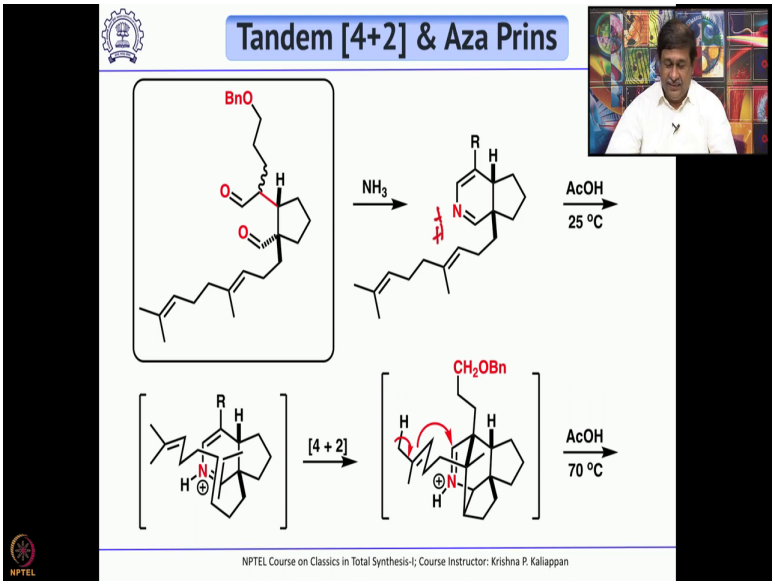

So, this is the key precursor for the subsequent tandem [4+2] as well as Aza-Prins cyclization, ok. Now, you take this aldehyde and treat with ammonia. And as I said, immediately it forms the corresponding substituted dihydropyridine, ok. Once you have this dihydropyridine, next the key step is the Aza-Prins cyclization.

And for that he treated with acetic acid at ambient temperature. So, the first step is the intramolecular Diels-Alder reaction. So, acetic acid protonates the imine, ok, the protonation takes place here, and immediately it undergoes the intramolecular [4+2] cycloaddition reaction, ok.

Now, at that temperature, at that temperature, the next step that is the Aza-Prins cyclization did not work. So, he has to slowly increase the temperature from ambient to 70°. Now, the next step the key Aza-Prins cyclization took place to give the pentacyclic skeleton.

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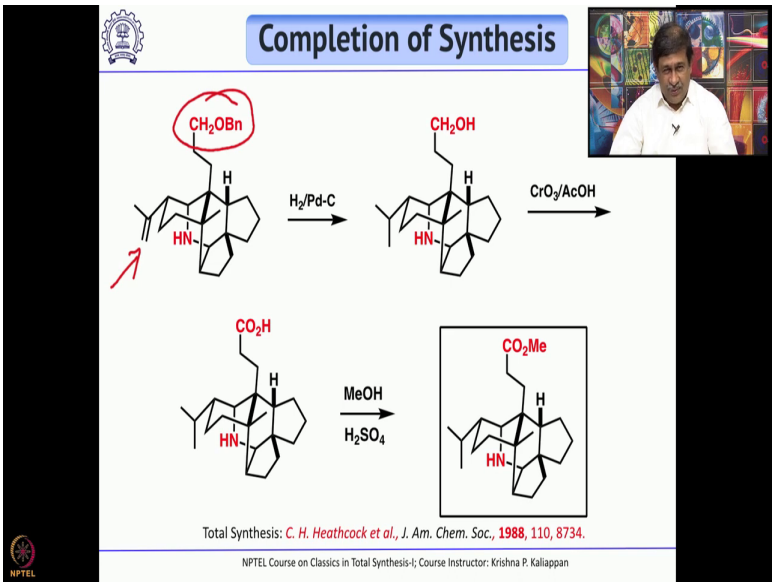

So, basically if you look at the whole synthesis, the two key steps, one, sequential Michael Addition followed by alkylation, two, tandem [4+2] and Aza-Prins cyclization, could give straight away the complex pentacyclic skeleton of methyl homosecodaphniphyllate.

Now, what needs to be done? You have to reduce the double bond and convert this C-H two -OBn into ester, ok. So, it was simply reduced, while reducing under hydrogenolysis condition, the double bond also got hydrogenated and debenzylation also took place to give the corresponding primary alcohol.

Then, the primary alcohol was completely oxidized, fully oxidized to carboxylic acid and esterify to get the natural products, which is methyl homosecodaphniphyllate. To summarize if you see, the whole sequence of reactions were very straightforward. If you look at the whole synthesis the key reactions are tandem [4+2] and Aza-Prins cyclization. And the first key reaction is the Michael Addition followed by alkylation.

He also later reported asymmetric synthesis of this compound. Now, if you look at this, this is scalemic synthesis, racemic synthesis. So, for asymmetric synthesis, what he did? He started with a chiral starting material, he attached a chiral auxiliary, ok.

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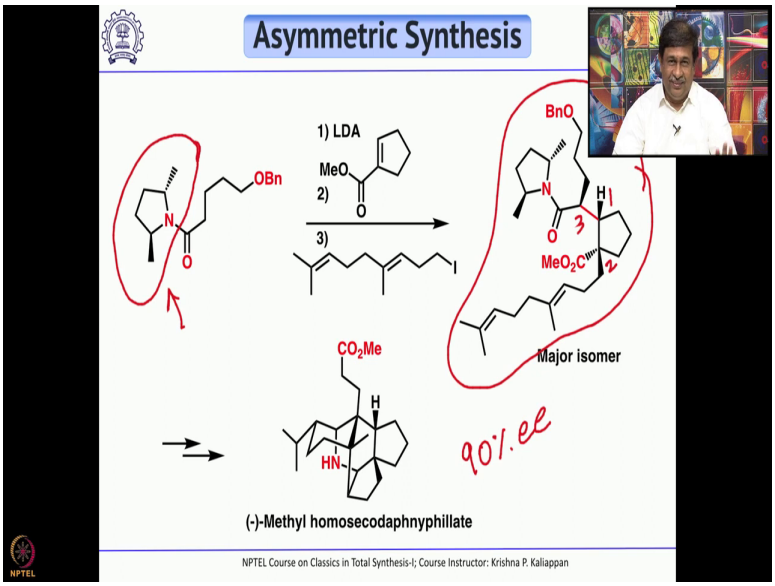

So, this chiral auxiliary helped introduced the chiral centers in the next step. So, you can see in this product, ok 1, 2, 3, three chiral centers were established by the use of this chiral auxiliary. Same set of reactions, ok same set of reactions; instead of simple pyrrolidinone he used the 2, 5 dimethyl pyrroline, ok. So, that is all. So, that took care of you know the synthesis of the same molecule, but chiral one, ok.

So, and he followed the same strategy, same route and he could achieve the asymmetric synthesis of methyl homosecodaphniphyllate. And it was almost showing 90% ee, the final natural product, the synthetic natural product showed 90% ee compared to the naturally isolated methyl homosecodaphniphyllate, ok.

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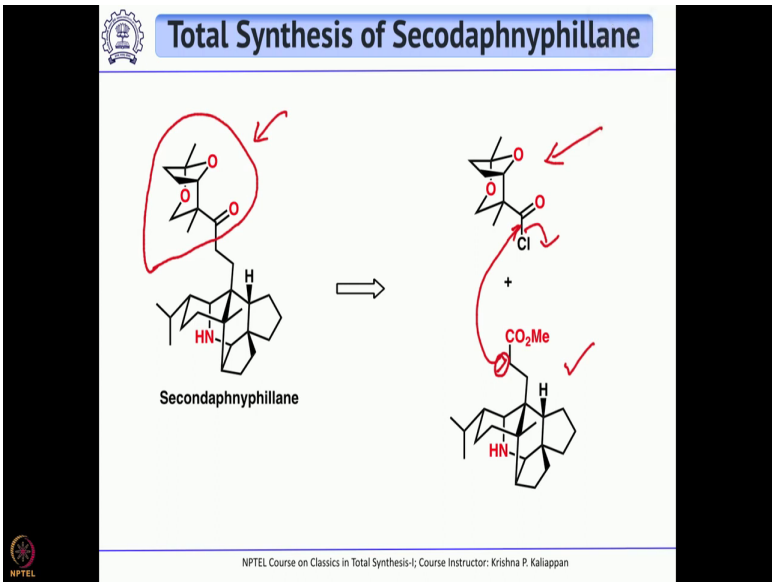

Having succeeded in that, he wanted to use a similar strategy for the synthesis of the related natural product secodaphniphillane. For secodaphniphillane what is additional is this particular bicyclic compound, ok. So, according to the retrosynthesis, this can be obtained by a Claisen type reaction.

So, already you he has successfully made methyl homosecodaphniphyllate. Now, if you can generate anion here and then attack on this acid chloride, ok, you will get a β-keto ester, ok then once you have the β-keto ester you can decarboxylate, ok. The decarboxylation will give the natural product secodaphniphillane.

So, for the synthesis of secodaphniphillane, what is required is the synthesis of this acid chloride, in optically active optically pure form, ok.

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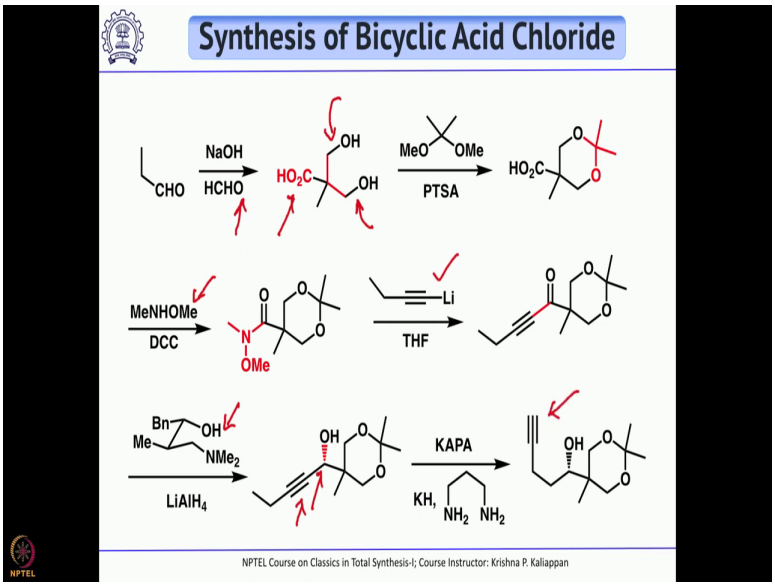

So, how did he do? So, he started from propanol, ok propionaldehyde, and then did a Cannizzaro like reaction, ok. So, he treated with formaldehyde. So, once he treated with formaldehyde, it underwent two aldol reaction with formaldehyde to introduce two - CH_2-OH group and at the same time the aldehyde was oxidized to get the carboxylic acid, ok.

Then, the two primary alcohols were protected as ketol. Now, the carboxylic acid was converted into Weinreb amide, ok by treating with Weinreb amine and DCC he made the corresponding Weinreb amine. Now, he took this lithio butane one lithio butane and added to this Weinreb amide.

As you know when you have Weinreb amide, if you add any argon lithium species or argon magnesium reagents, you will get corresponding ketone. So, that was the idea. So, you could get the corresponding ketone. Now, to introduce the chiral center, he used a combination of lithium aluminium hydride and this amino alcohol. It is a chiral one, ok. So, that helped in getting or introducing the chiral center, ok. This chiral center was introduced.

Now, once you have that he used another key reaction, ok. So, this is called Zipper reaction. So, the Zipper reaction is nothing but when you have an internal alkyne, this internal alkyne when you treat with potassium hydride and 1, 3 di-amino propane, ok if you treat with potassium hydride and 1, 3 di-amino propane the internal alkyne will

move to the terminal alkyne. So, that is called Zipper reaction. As you can see here when you do this reaction, this internal alkyne goes all the way to the terminal.

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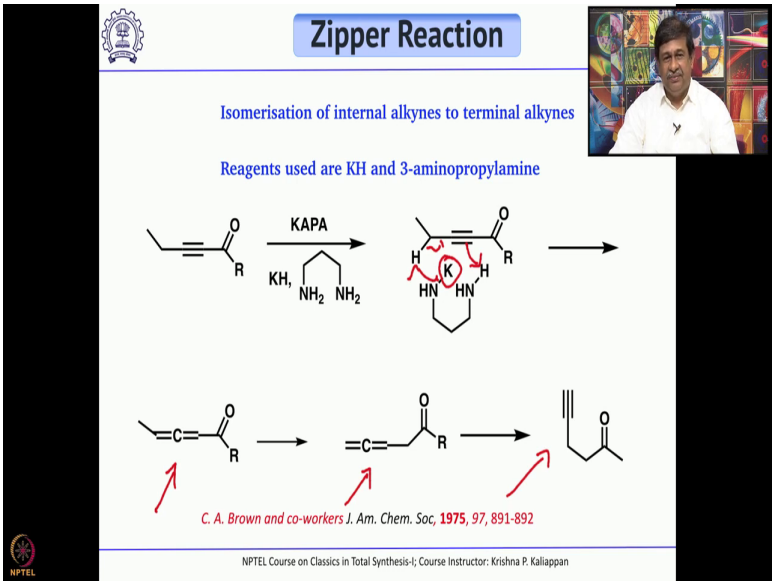

How does it do? Ok. So, this is the mechanism, ok. So, basically, as I said it is nothing but if you have an internal alkyne, if you treat with potassium hydride and di-amino propane it isomerizes the internal alkyne to the terminal alkyne. So, first, so you have this one of the hydrogen is picked up and then you have the potassium salt. So, that will pick up this hydrogen, ok and it will form an allene, it will form an allene.

Then, similarly that allene will migrate. The same process, same way this will migrate to terminal allene. Once the terminal allene is formed then again it will migrate and then you will get alkyne. So, basically it is a series of migration from internal alkyne to the terminal alkyne, ok.

So, one side it will pick up the proton, other side it will give the hydrogen, ok. So, that is how the migration of triple bond goes through allenes, ok. This was reported in 1975 by Brown and co-workers.

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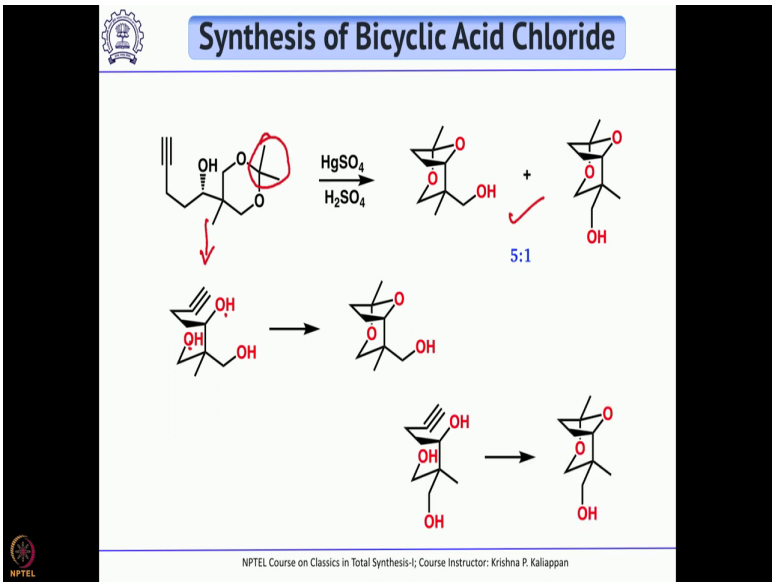

So, once you have this terminal alkyne, so, now, you can treat with mercuric sulfate and sulfuric acid, ok. So, this is again another interesting reaction. If we have a triple bond and alcohols two alcohols at appropriately placed, they can form an intramolecular ketone. How it forms? The first step is the oxymercuration, ok. See under acidic condition this ketol is cleaved. So, you have primary alcohol.

Now, this undergoes first oxymercuration followed by just hydration, ok mechanic addition of water. So, that will give you a mixture of these two alcohols, ok. As I said if you can redraw this, if you can redraw this molecule like this, then you can see here one oxymercuration followed by this alcohol and this alcohol, ok, this alcohol and this alcohol. One will undergo oxymercuration, the other one will undergo simple addition of water, ok.

First one will undergo oxymercuration to the triple bond, the second one will undergo addition of hydroxyl group to the double bond. So, that is how you get this ketone, ok.

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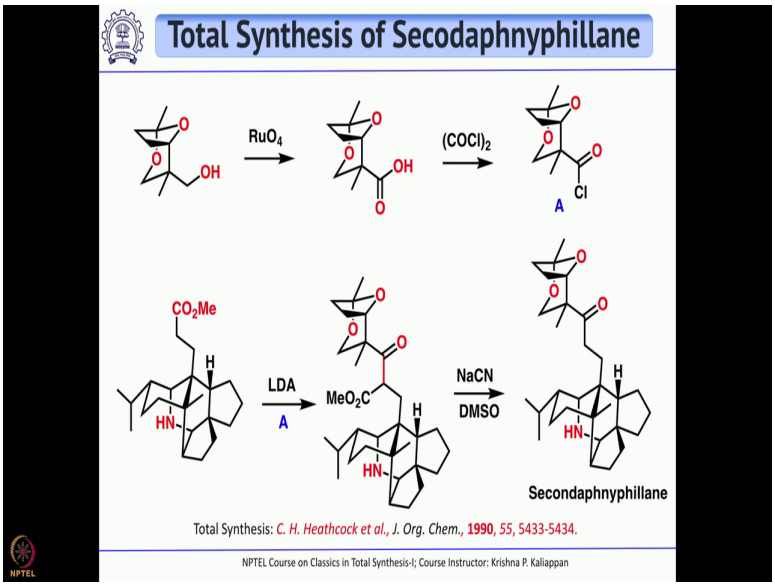

This upon oxidation, the primary alcohol, if you oxidize with ruthenium tetroxide, you get the corresponding carboxylic acid. And once you have the carboxylic acid convert that into acid chloride using oxalyl chloride. Now, you take this methyl homosecodaphniphyllate, already he has made this compound in chiral form, mix these two, ok, you treat with LDA and then quench with the acid chloride you get the corresponding β-keto ester, ok.

Then this β-keto ester can be decarboxylated by treating with sodium cyanide and DMSO, if you reflex this compound that directly gives secodaphniphillane, ok.

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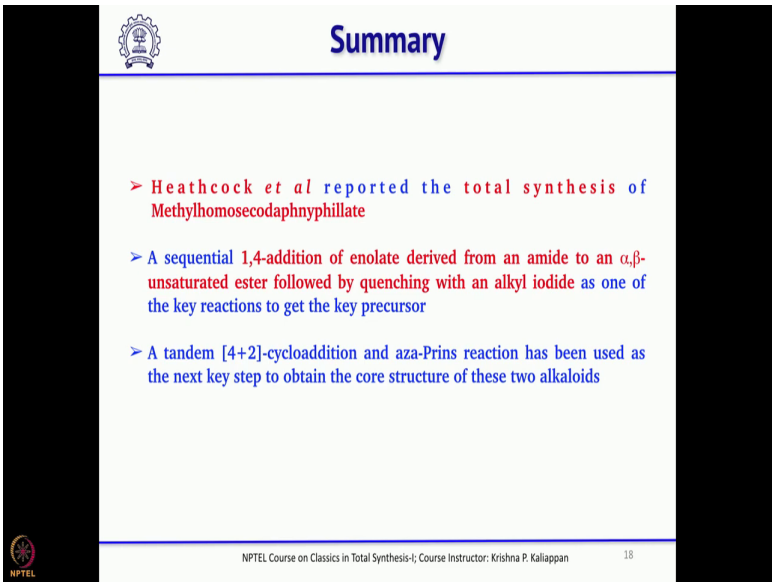

So, to summarize, Heathcock was the first one to report the total synthesis of methyl homosecodaphniphyllate. And his synthesis of methyl homosecodaphniphyllate involved a sequential 1, 4 addition followed by quenching of the enolate by an alkyl iodide. And the second key reaction was an intramolecular [4+2] cycloaddition between a heterodyne and dienophile followed by Aza-Prins reaction to construct the pentacyclic skeleton of this compound, ok.

Overall, the number of steps were very less and the total synthesis of methyl homosecodaphniphyllate as well as the secodaphniphillane were achieved in very few steps using these two important and key reactions by Heathcock, ok. So, with this, we have completed the total synthesis of methyl homosecodaphniphyllate and secodaphniphillane. And we will continue our discussion on some more synthesis of alkaloids in the next few lectures.

Thank you.