Classics in Total Synthesis-I
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Lecture - 53
Periplanone

Good morning and welcome back to NPTEL lecture series on Classics in Total Synthesis. So, we will continue our discussion on total synthesis of natural products. So, today, talk about total synthesis of a natural product called Periplanone B. So, this is a very interesting natural product actually, it was isolated from American cockroaches ok. This is a sex pheromone and why this particular compound was important, because very minute quantities of this pheromone was obtained, less than milligram was obtained from these cockroaches.

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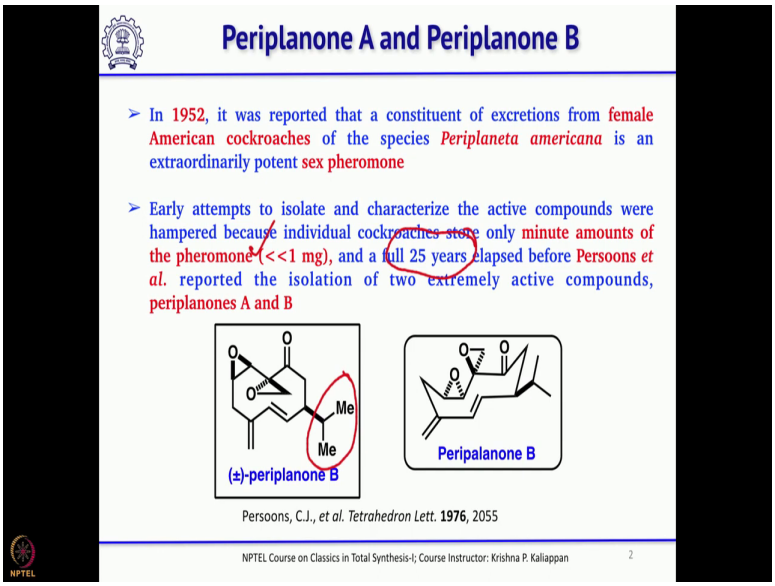

And it took about 25 years, it took about 25 years to report the isolation of two pheromones periplanones and periplanones A and B. And if you look at their structures ok. So, first periplanone A - It is little bit complex ok. So, it has two epoxides, two double bonds, one carbonyl group and one isopropyl group ok.

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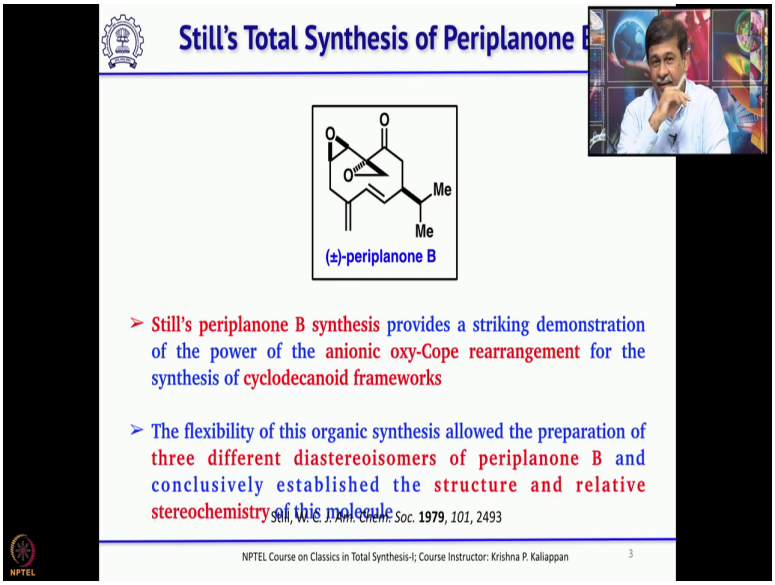

The first synthesis of periplanone B was reported by Still in1979. Actually, before he completed the total synthesis of periplanone B, initially he made 2 wrong isomers, before he completed the total synthesis the reaction which he used as a key reaction, in the total synthesis of periplanone B. Still used anionic oxy-Cope rearrangement as a key reaction to form this cyclodecanoid units ok. It is a 10 numbered ring, you can see. So, this 10 numbered ring was cleverly formed using anionic oxy-Cope rearrangement ok.

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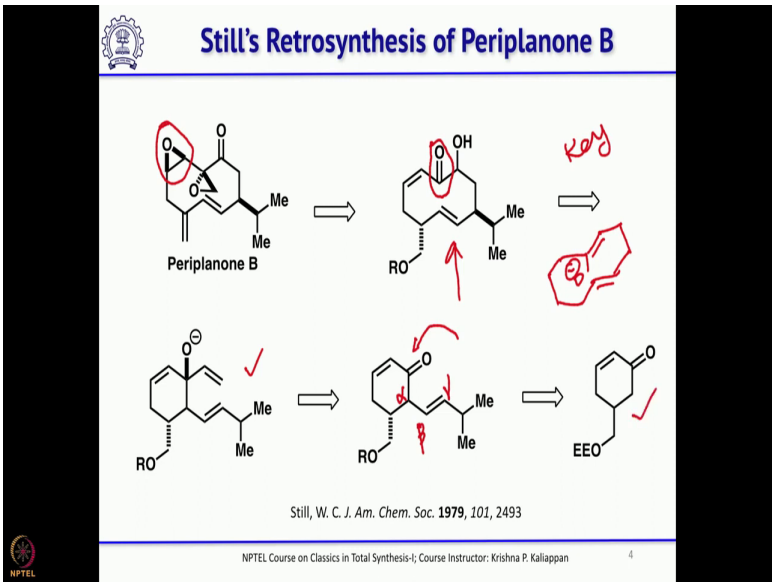

And according to him, if you look at this molecule, he thought the two epoxides can be made by two different methods. One epoxide that is this epoxide can be made directly from the double bond, using mCPBA or nucleophilic epoxidation agent. Whereas, the

other epoxide can be made from the carbonyl group directly, using sulfonium ylide or sulfoxonium ylide ok.

Basically sulfur based ylides, if you treat with carbonyl group it can form epoxide. So, that is how he planned ok. And this if you look at this, this particular cyclodecanone, his idea was it can be made using anionic oxy-Cope rearrangement. So, this is the key reaction, this is the key reaction. Anionic oxy-Cope rearrangement followed by when you do the anionic oxy-Cope rearrangement what will happen?

You will get like this ok. That enolate again, if you add mCPBA, then you will get corresponding α hydroxy ketone ok. So, that is called Rubottom oxidation. So, a combination of anionic oxy-Cope followed by Rubottom oxidation will give this corresponding α hydroxy ketone. So, that was his idea. And this as you can see, if we have the β–γ unsaturated ketone, see α–β–γ.

So, β–γ and such are ketone, then simply you can add vinyl lithium or vinyl magnesium bromide you will get this intermediate or precursor required for anionic oxy-Cope rearrangement. And that can be obtained from the cyclohexane, which is commercially available or well known in the literature.

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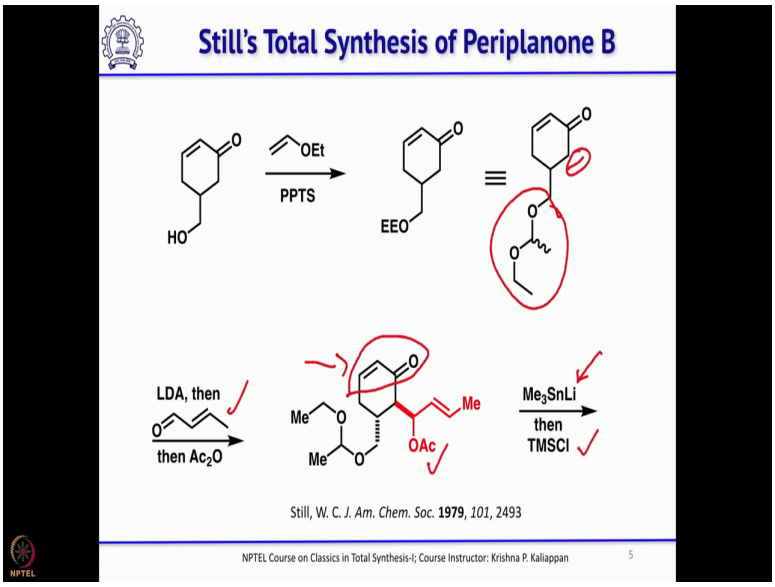

So, he started with this compound, then the primary alcohol was protected with ethyl vinyl ether and then PPTS. So, you protected this alcohol as ethoxy ethyl ether, which is

nothing but this one ok. So, normally primary alcohols are protected as TBDPS, TMS and also people in olden days they used to protect it as THP ether ok. They treat with trihexyphenidyl ok. So, this was prior to the TBD, TBDPS ether era. Then you generate anion.

And then quench with this aldehyde and that aldehyde was then entrapped with acetic anhydride to get the corresponding acetate ok. Next, this is the enone ok, if you treat with trimethyl tin, trimethyl tin hydride and butyl lithium that will generate the corresponding lithium ok; lithio trimethyl stannane derivative. So, that can undergo a 1, 4 addition to this enone and which can be trapped as the TMS ether.

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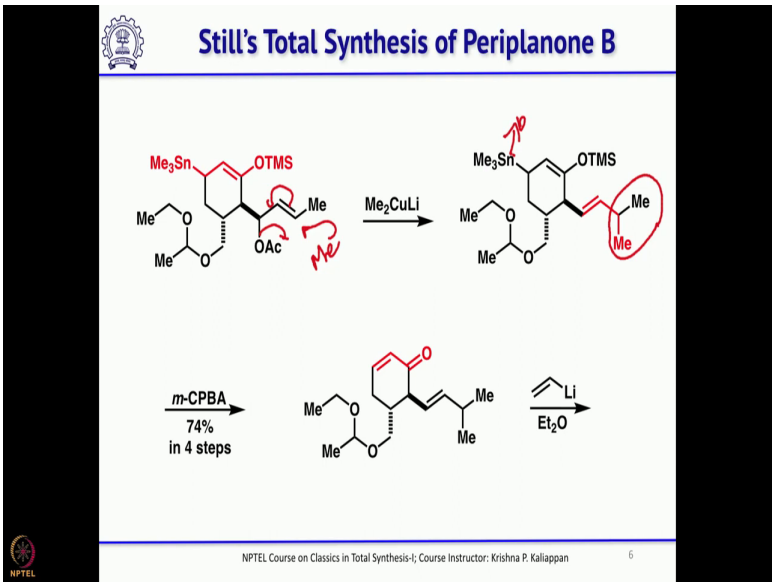

So, that is what he did ok. So, when you add this lithio trimethyl stannane, it will undergo 1, 4 addition, the resultant enolate was to happen is the enol TMS ether. At this stage he used a lithium dimethylcuprate. So, lithium dimethylcuprate is known to undergo a 1, 4 addition like on allylic acetate. So, what will happen? The methyl group will attack and the double bond will come and then your acetate will go ok. So, that is how we introduced the second methyl group, which is required for making the isopropyl group ok. So, right hand side is done.

Now, he has to generate the ketone. So, for that first he treated with mCPBA. So, mCPBA you know, it forms this and then elimination takes place, you get the

corresponding cyclohexenone. So, once we have the cyclohexenone now, we have to add the vinyl grignard or vinyl lithium species.

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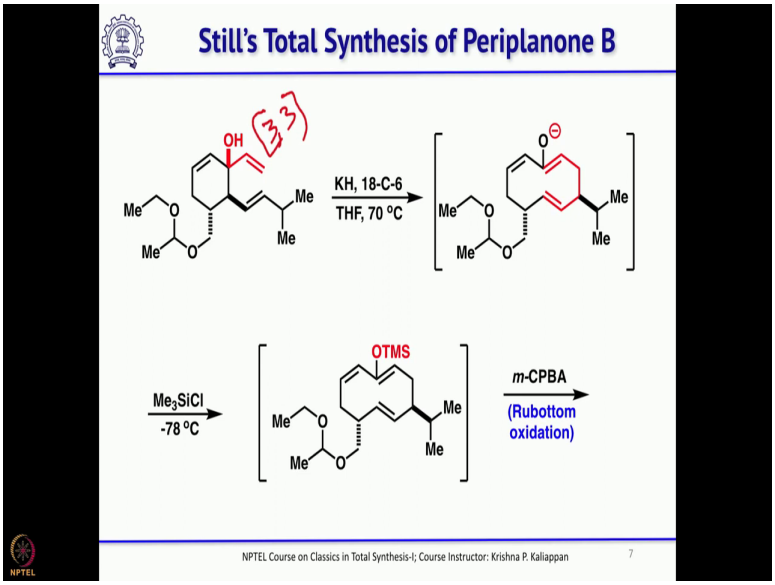

So, addition of vinyl lithium gave the precursor for anionic oxy-Cope rearrangement ok. As you can [3,3] nicely located to get the corresponding anionic oxy Cope rearrangement. So, this was treated with potassium hydride and in the presence of [18 crown 6]. So, it underwent the anionic oxy-Cope rearrangement and if you quench with TMS chloride, you get the corresponding enol TMS ether. Then you add mCPBA ok, that mCPBA as I said its nothing but, it will undergo Rubottom oxidation to introduce a hydroxyl group next to the carbonyl.

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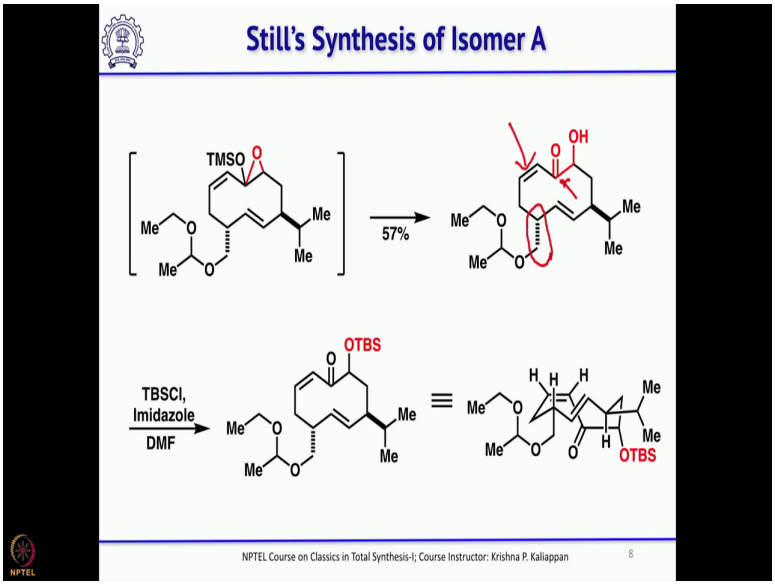

So, that is how he could introduced the hydroxyl group next to the carbonyl ok. So, he thought he is very close, what needs to be done. You have to make a epoxide here and then sulfonium ylide will make epoxide here and basically, he also has to eliminate this to introduce the exocyclic double bond.

So, he protected the secondary alcohol as TBS ether. So, then you can see the confirmation. So, this is how the molecule looks, because it is a 10 membered ring. So, 10 membered ring can form several packard shape. So, this is one of the stable confirmation on that he did first the epoxidation ok.

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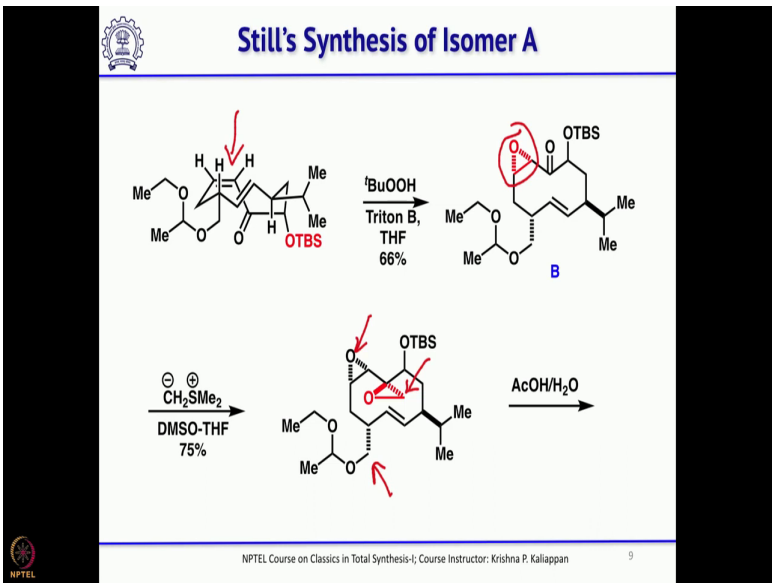

So, epoxidation you know it is a electron deficient double bond. So, you can use tertiary butyl hydroperoxide and triton B. So, when you look at this compound, the epoxide will come from the back side ok. Epoxide it will come from the back side. So, in the product you can see that it is α epoxide. But, for periplanone B the epoxide should be β ok. What you are getting is α, nevertheless he went ahead.

And then he treated with the corresponding sulfonium ylide ok, trimethyl sulfonium ylide to get the epoxide. So, again if you look at this compound, one this is opposite stereo chemistry, second this is also opposite stereo chemistry ok. But nevertheless it is good to make more analogs of the natural product. So, for that what should be done, you have to introduce the exocyclic double bond ok.

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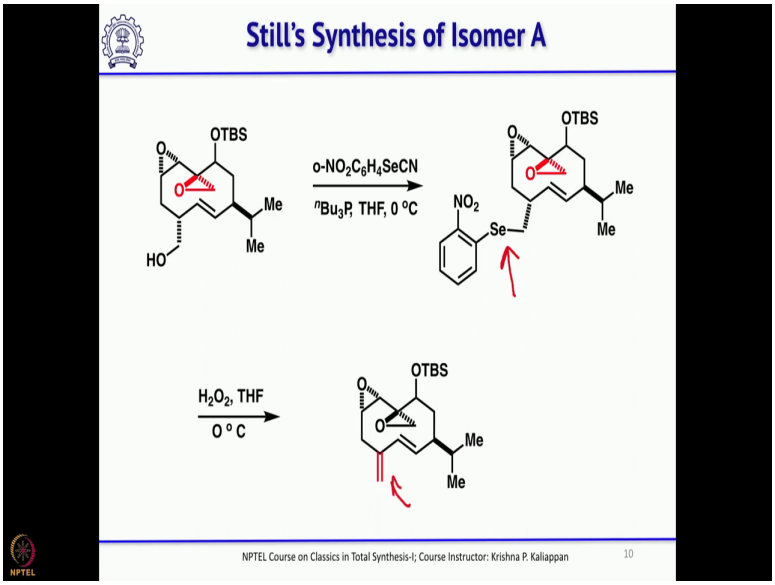

So, you remove the ethoxy ethyl protecting group with acetic acid water. So, you get the primary alcohol and that primary alcohol, if you treat with o-nitrile phenyl selenocyanate. So, you get this particular intermediate, it is well known this upon treatment with hydrogen peroxide or mCPBA; it will form the corresponding selenoxide as well as later it will undergo elimination to introduce the double bond. So, that is how he could introduce the double bond.

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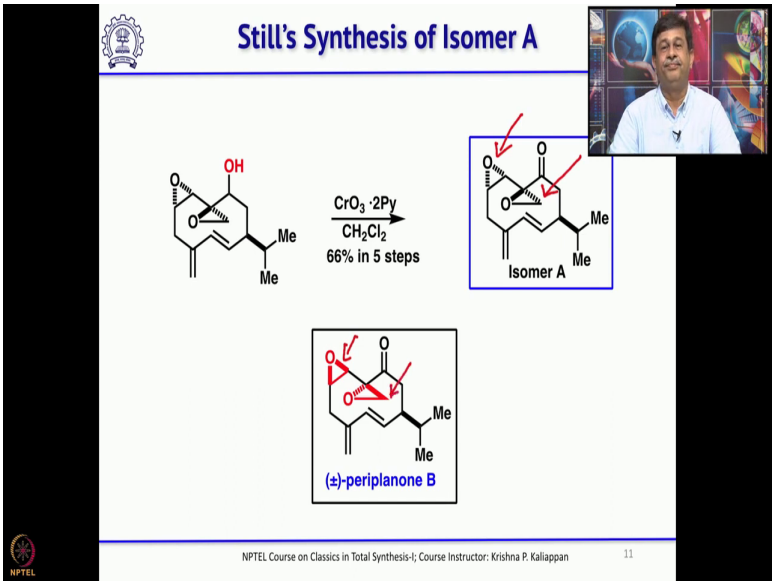

And removal of the TBS group, release the secondary alcohol which upon oxidation gave the ketone. And these ketone none of the spectral data are matching with periplanone B. So, that is obviously, because of these two epoxides are opposite to the natural periplanone B ok, you can see that. So, here it is β and here the CH_2 is β.

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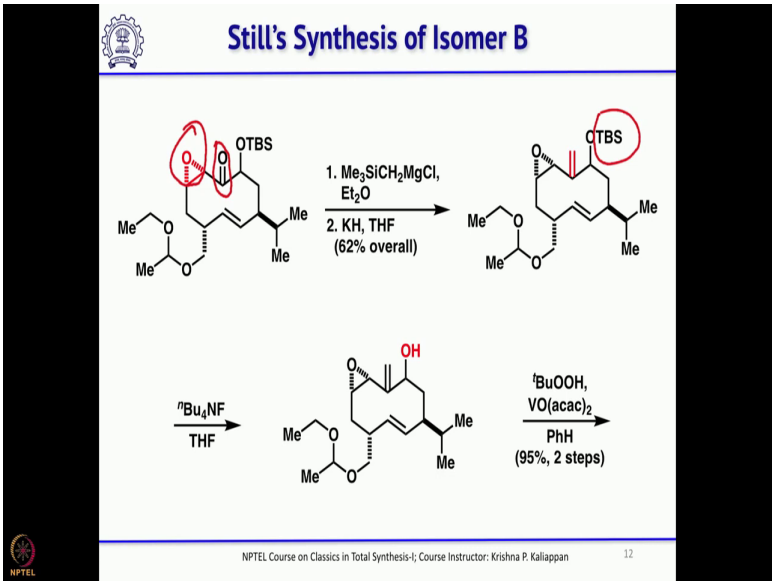

So, he went back ok, he still did not know whether the epoxide here is the correct one or not. So, he thought he can work around and then get epoxide arising from the ketone. So, first he did the Peterson olefination, introduce the double bond. Then on that he wanted to selectively do the epoxidation. So, for that it is better to remove the TBS group, so that

you will have allelic alcohol, which can direct the epoxidation ok. So, he removed the TBS group, then treated with vanadium acac and then tertiary butyl hydro peroxide.

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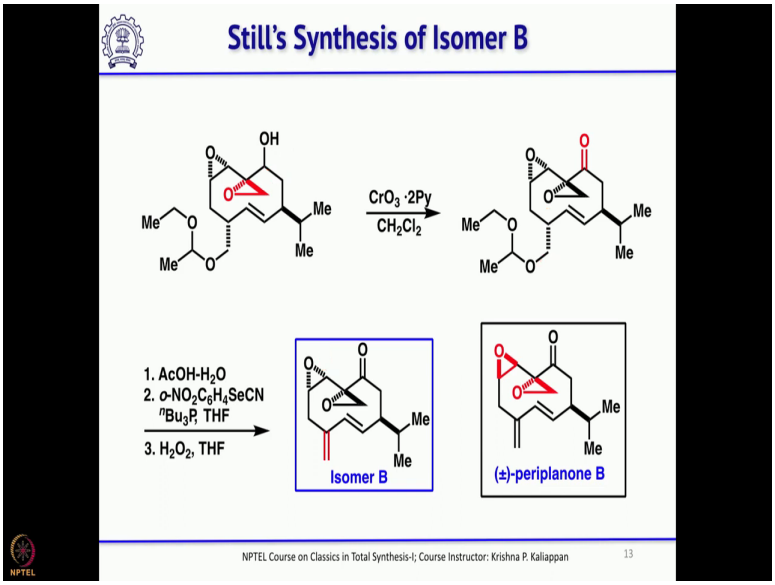

So, now, you could get this CH_2 is β ok. Then oxidation a ketone and followed by the same 3 steps protocol to convert this into double bond. Now, if you look at this isomer, you can see all are same except this epoxide. Here the epoxide is exactly opposite to periplanone B.

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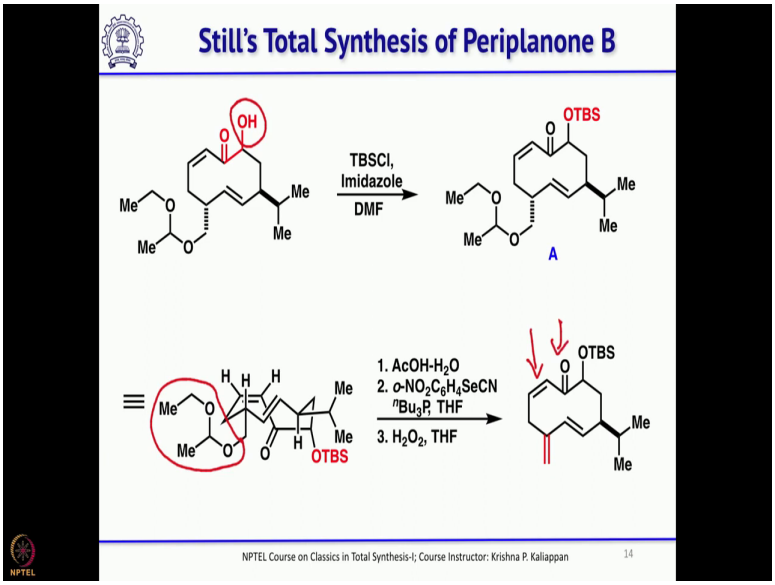

So, again he has to go back. So, at this point what he thought was he will protect this hydroxyl now, as TBS ether. And at this stage that is the ethoxy vinyl group he wanted to remove and then convert that into exocyclic double bond first. So, he did that. Now, you can see you have everything except that these two epoxides ok.

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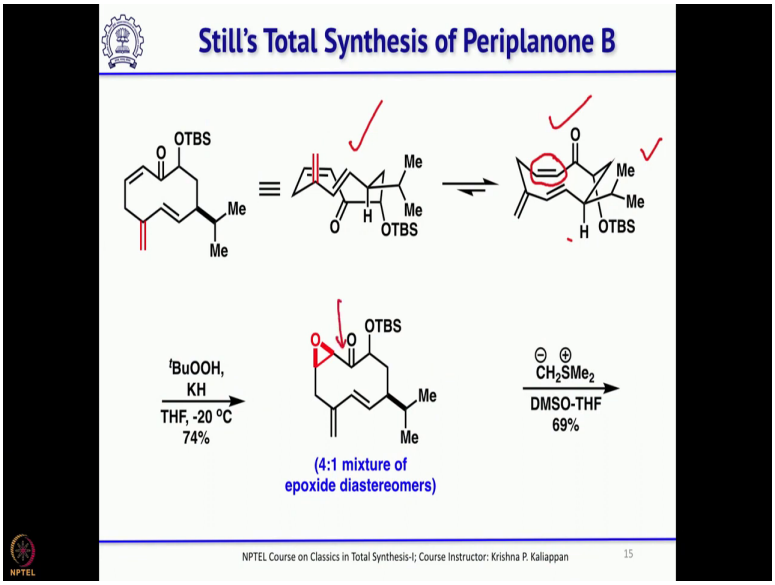

So, he took this compound and the low energy confirmation if you look at. So, there are two confirmations you can write. And this can flip to this confirmation and now, if you look at this is the low energy confirmation and if one has to do epoxidation of this double bond that will become β ok. So, at this stage, he did the epoxidation of the α–β unsaturated ketone selectively. So, he got the β epoxide as the major isomer ok. You could separate and then on that he did the sulfonium ylide treatment to get the epoxide here.

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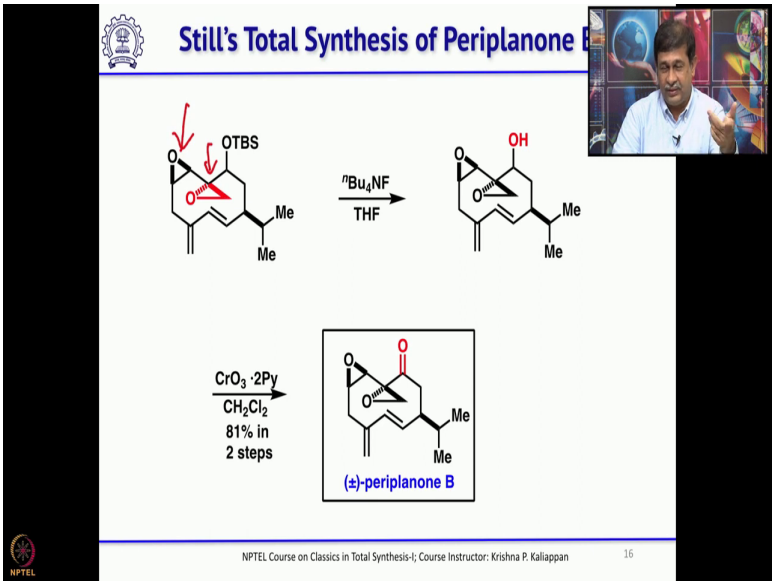

Now, the left hand side epoxide also β and the right hand side also that is the middle carbon also he got epoxide, where the oxygen is α ok. Then remove the protecting group with TBAF.

So, TBS was removed and then oxidation with chromium trioxide pyridine that is Collin's reagent, you could get periplanone B. So, before he made periplanone B, he made 2 isomers. In one isomer both the stereo centers of epoxides were opposite and the second one was correct the other one was not ok.

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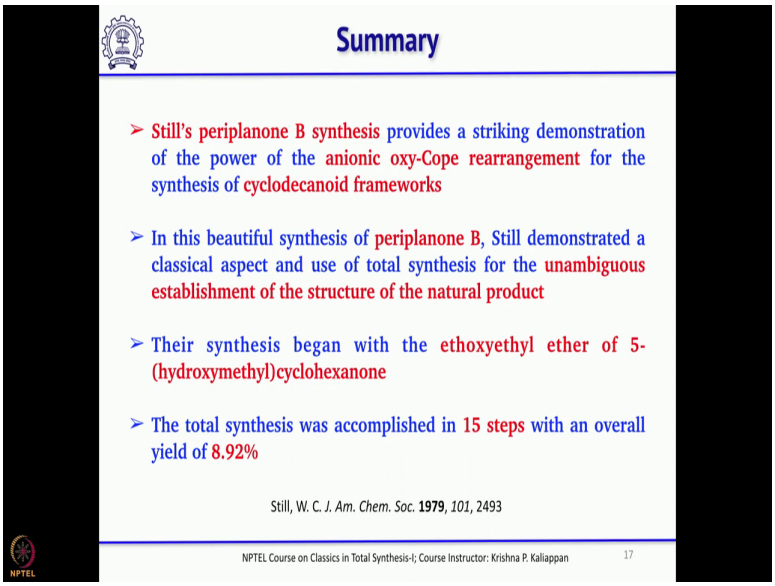

So, overall if you look at the synthesis of periplanone B that was the first total synthesis reported by Clark Still, he used anionic oxy-Cope rearrangement followed by Rubottom oxidation as the key reaction to introduce α hydroxy ketone. And overall, he took about 15 steps and the yield, the combined yield is about 9%, which is really remarkable considering this dense functional groups present in the natural product.

The second total synthesis of periplanone B, which we will discuss was reported by Stuart Schreiber's group in 1984. He also used anionic oxy-Cope rearrangement, but on a different substrates ok.

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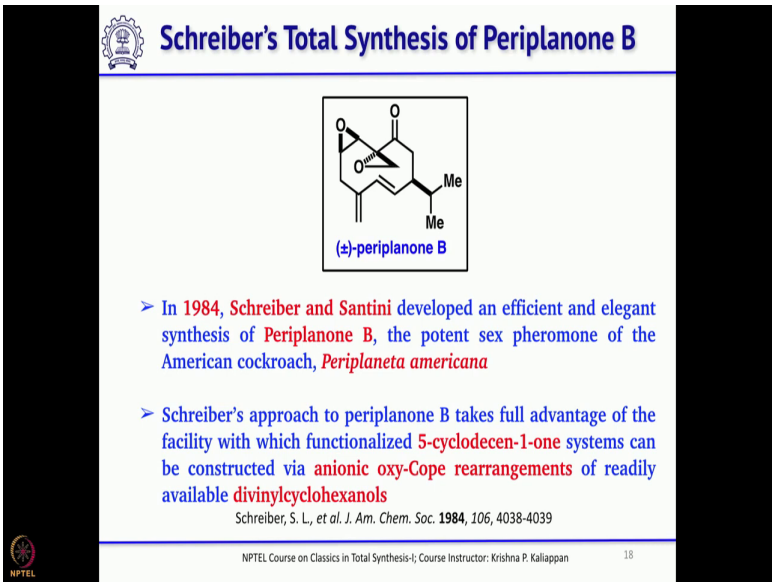

He used anionic oxy-Cope rearrangement followed by the electro cyclic ring opening as key reaction to introduce the diene present in this molecule ok.

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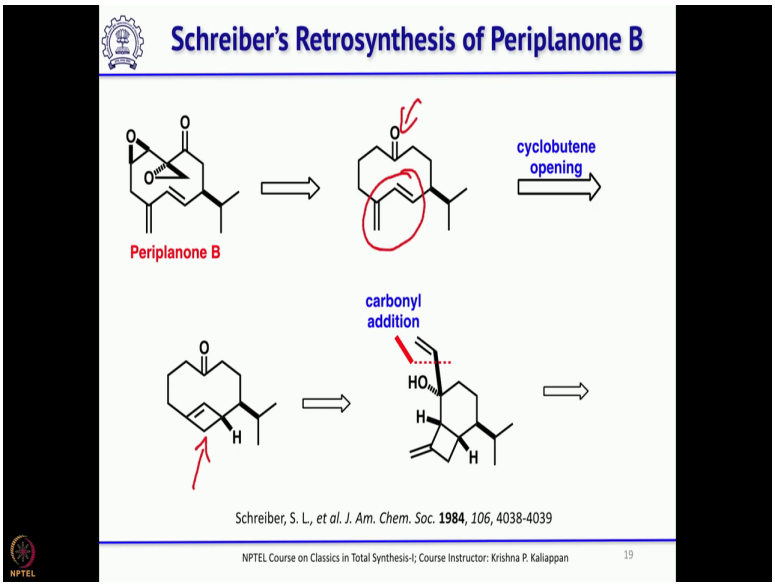

Let us see, how he has done. So, his idea was ok, both the epoxides can be introduced starting from this ketone. And if you look at this, this diene he wanted to use electro cyclic ring opening to get the diene ok. So, electro cyclic ring opening of the cyclobutene will give this diene and that can be obtained by a anionic oxy-Cope rearrangement. Say so, you can see both groups used anionic oxy-Cope rearrangement, but both are using on different substrates.

So, that is how in synthesis, when you want to work on total synthesis one molecule, the same reaction can be used on different substrates and essentially they can make the same natural product ok. So, that type of flexibility and creativity can be seen in many total synthesis.

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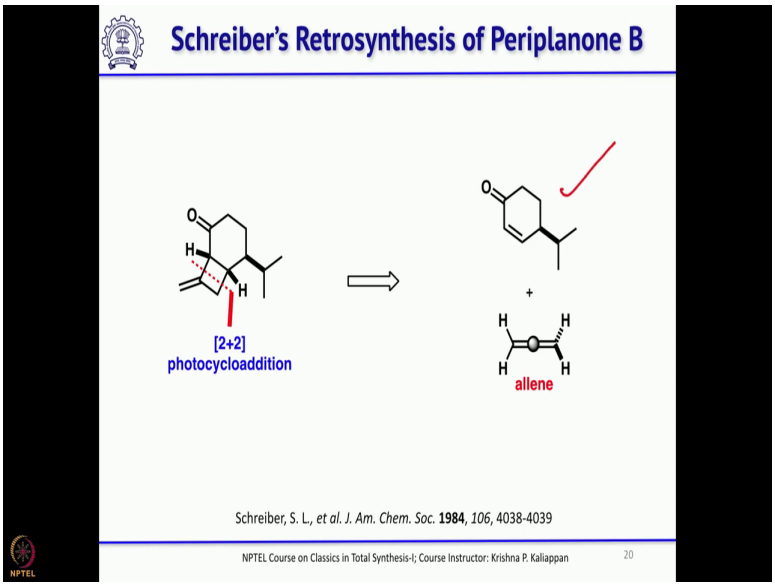

And this can be obtained from this bicyclic ketone and this bicyclic ketone can be obtained from this natural product, which is commercially available with allene through a [2+2] cyclo addition reaction ok.

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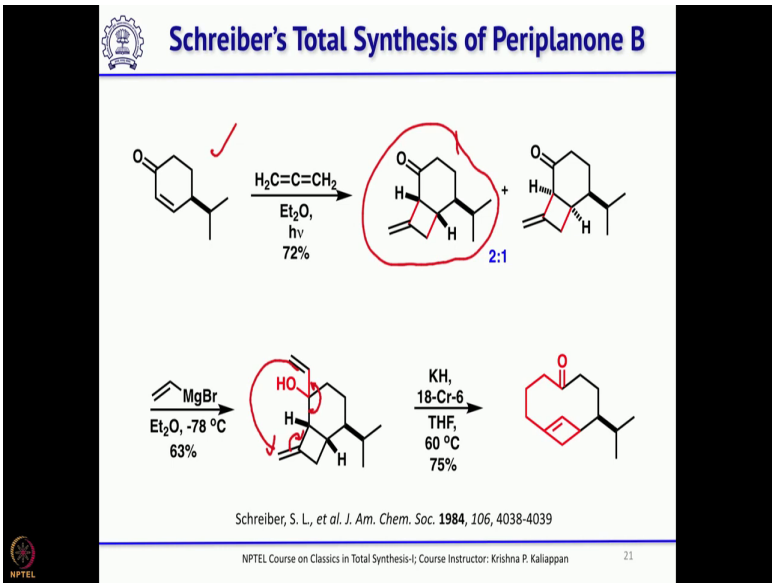

Let us see how he has done. First, it was a two plus two cyclo addition between the cyclohexenone and allene. So, he got a mixture of two is to one and of course, the major isomer is the required one. He took that compound and then treat it with vinyl magnesium bromide. So, the vinyl magnesium bromide gave the alcohol, the allylic

alcohol. So, this upon treatment with potassium hydride and [18 crown 6], it underwent the anionic oxy-Cope rearrangement as you see you can write like this. So, now you have the 10 membered ring, also the 10 membered ring is fused with a 4 membered ring ok.

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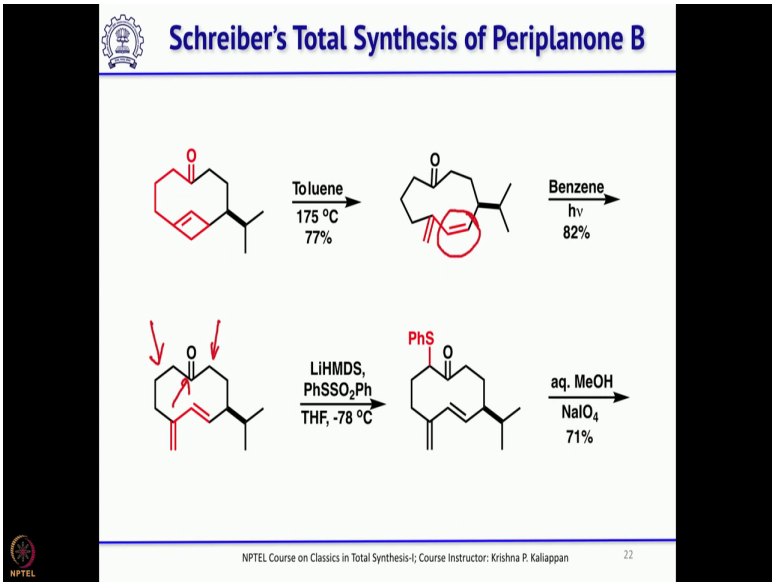

And this 4 membered ring that is cyclobutene; if you heat it, it forms the diene, but unfortunately, this is the cis double bond ok. When you do this ring opening reaction, what he got was exocyclic double bond and the internal double bond was *cis*, but in the natural product the internal double bond was trans. Of course, *cis-trans* isomerisation can be easily done under photochemical condition.

So, he tried the photochemical condition. So, he could easily isomerize the *cis* double bond to trans. So, now, one epoxidation, another epoxidation and you have to introduce a ketone. So, these are three things left. So, first he introduced a SPh group at the α position and then oxidized with sodium perborate to get the introduce the double bond ok, sulfoxide.

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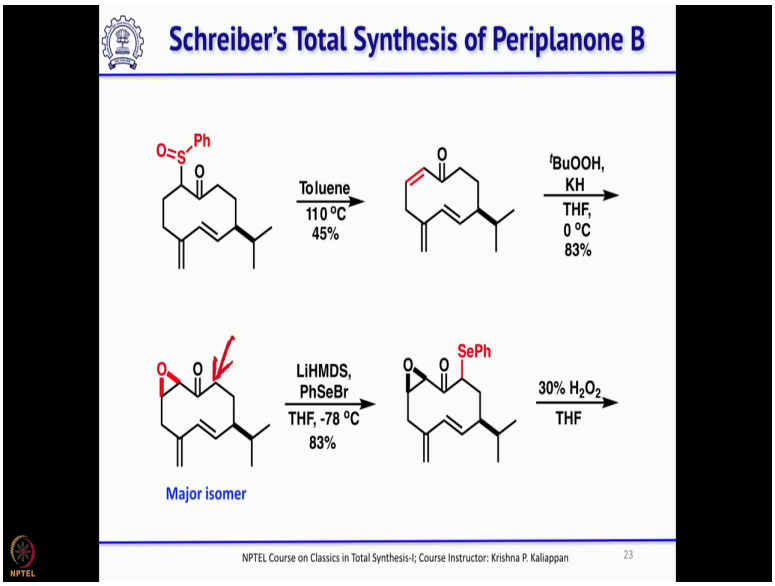

And then sulfoxide was eliminated to get the double bond ok. So, once you have the double bond, you make the epoxide. So, it is α-β unsaturated ketone electron deficient. So, you have to use nucleophilic epoxidating agent. So, potassium hydride and the tertiary butyl hydroperoxide gave the β epoxide. So, that is the major isomer. Now, he introduced the double bond on the other side.

So, that is this side, again using lithium hexamethyldisilazide followed by quenching with phenyl selenenyl bromide and instead of introducing the double bond ok. Here so, here what you need is you need to introduce a hydroxyl group, is not it. First you need to introduce a hydroxyl group. So, what he did he used a seleno Pummerer rearrangement to introduce a hydroxyl group. So, for that first he introduced a phenyl seleno group by treating with lithium hexamethyldisilazide and phenylselenyl bromide.

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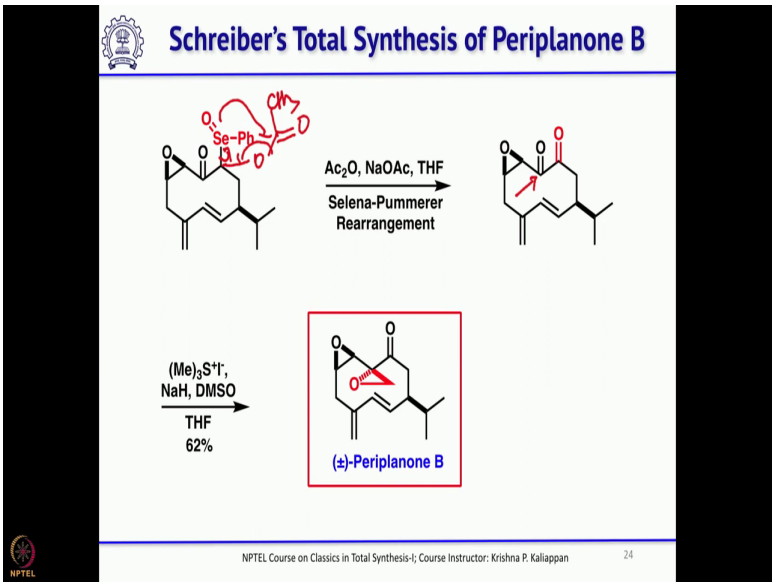

Then you oxidize the phenyl selenyl with hydrogen peroxide to form the phenyl selene oxide, then you treat with acetic anhydride. So, when you treat with acetic anhydride. So, what happens you get this -OC=OCH_3 ok. So, then intramolecularly, you know this will attack and then this will come and then you will get the carbonyl group. So, you get 1, 2 di ketone ok.

So, this is the seleno pummerer rearrangement. Now, you have 2 ketones and selectively the trimethyl sulfonium ylide added to this ketone, not only region, it is stereo selective to get 62% yield of the required natural product periplanone B.

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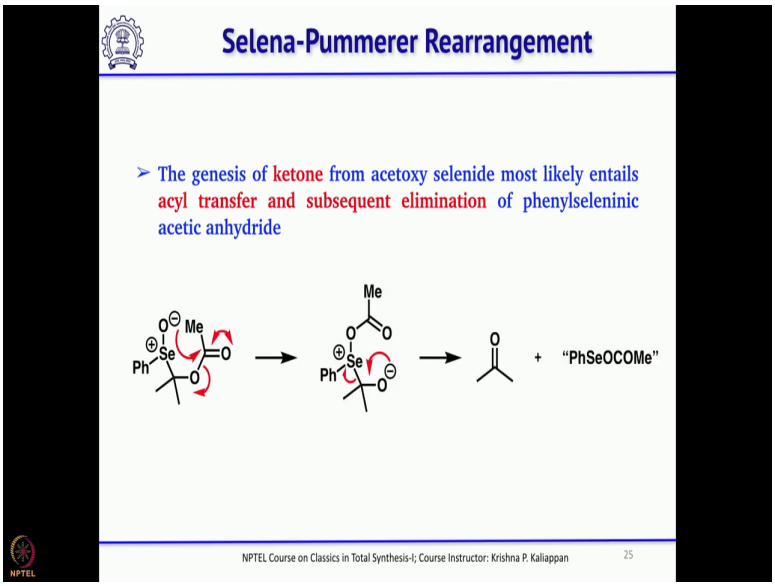

So, it is one of the shortest synthesis of periplanone B, which involved again an interesting anionic oxy-Cope rearrangement.

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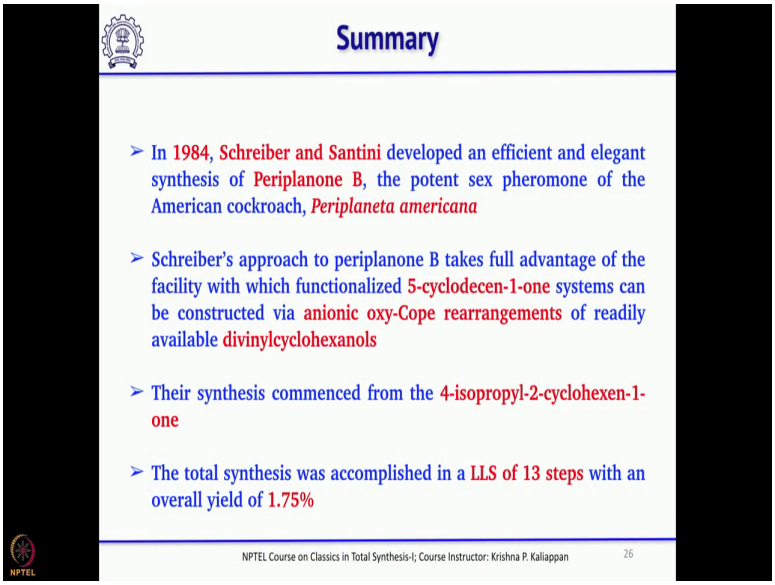

So, this is the mechanism of Pummerer rearrangement and also [2+2] cycloaddition to get the precursor for the anionic oxy-Cope rearrangement. Then he also used electro cyclic ring opening of cyclobutene and then seleno Pummerer rearrangement to introduce a ketone next to the ketone and a highly stereo and regioselective epoxidation of ketone using trimethyl sulfonium ylide. Overall, it took about 13 steps and the yield

was close to 2% ok. So, with this I will stop here, and then, we will talk about more natural products in the next week ok.

Thank you.