Classics in Total Synthesis-I
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Lecture - 21
Longifolene

So, good morning and welcome back to NPTEL lecture series on Classics in Total Synthesis Part-I. So, we have been discussing many total synthesis and today we will discuss one of the classical total synthesis of a natural product called Longifolene.

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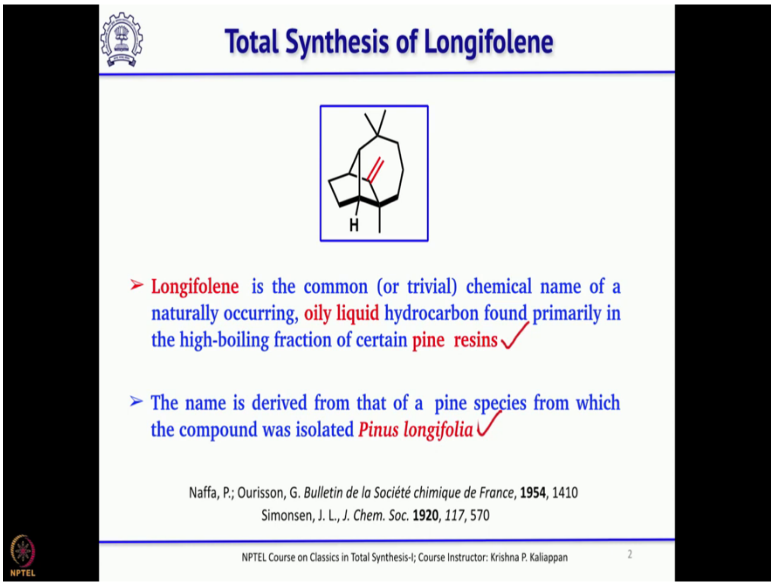

Total Synthesis of Longifolene

- Longifolene is the common (or trivial) chemical name of a naturally occurring, oily liquid hydrocarbon found primarily in the high-boiling fraction of certain pine resins ✓
- The name is derived from that of a pine species from which the compound was isolated *Pinus longifolia* ✓

Naffa, P.; Ourisson, G. *Bulletin de la Société chimique de France*, **1954**, 1410
Simonsen, J. L., *J. Chem. Soc.* **1920**, *117*, 570

So, this longifolene is a sesquiterpene as you can see here it is a hydrocarbon. And, it was obtained from pine resin as an oily liquid and the name itself was derived from where from it was isolated. It was isolated from your pine species called Pinus longifolia. So, that is why the name was given as a longifolene.

And if you look at this molecule, from synthetic point of view the major challenges are first of all it is a tricyclic compound 1 and it has 2 quaternary centers, ok. It has 2 quaternary centers and 3 chiral centers. And, what is more important was here there is no functional group other than the double bond, only you have a double bond as a functional group. Other than that, you do not have any other functional group.

And as it is a hydrocarbon, again, not only isolation of this molecule, but also synthesis of this molecule is quite difficult because of its volatility.

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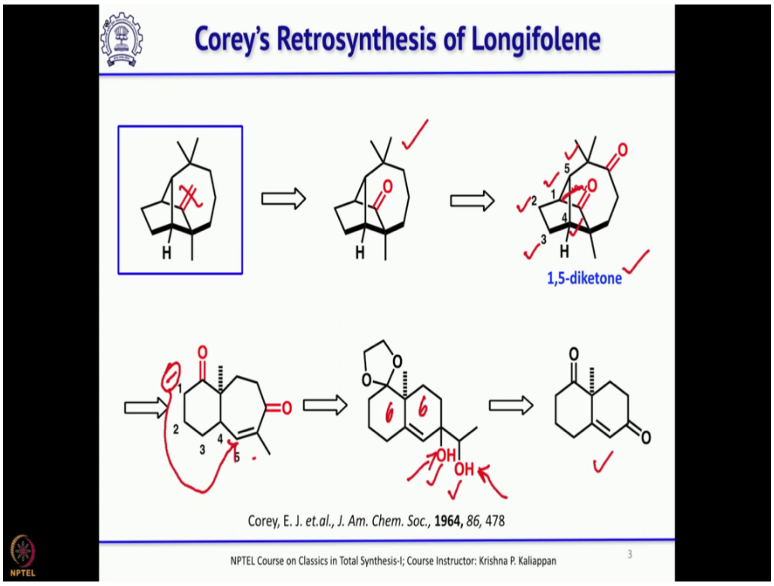

Corey's Retrosynthesis of Longifolene

Corey, E. J. *et.al.*, *J. Am. Chem. Soc.*, **1964**, *86*, 478

There are three total synthesis which I am going to discuss today on longifolene. And the first synthesis I will talk about is reported by E. J. Corey and then second synthesis I will talk about was reported by Oppolzer and the third one was reported by W. S. Johnson. First let us start with the total synthesis reported by E. J. Corey. So, how did he do? What are the real retrosynthetic disconnections he has cleverly used to make this longifolene?

So, if you look at this molecule; obviously, the first retrosynthesis, first disconnection should be to introduce the double bond. Now, it is easy is not it. So, you can easily think of making this double bond as the last step. That is if you can have this ketone, if you can synthesize this ketone then it should be possible to do Wittig reaction or you can add a Grignard followed by dehydration should give the natural product.

So, now the next problem is you have one functional group. Sometimes, when you look at a natural product, if the natural product does not have a functional group, then what one should do is you should introduce a functional group. Because, always you need a functional group in the product so that you can use that functional group as a handle for further disconnections as well as functional group transformation.

Though, this particular structure has a functional group that is carbonyl group, but still Corey felt one functional group is not sufficient, it is better to introduce one more functional group. So, that is how he introduced another functional group which is also a carbonyl group. And the reason for introducing another functional group is, if you look at this the relationship between these two carbonyl groups are 1, 5.

So, when you have 1, 5-diketones which I am sure you would have seen in synthesis of Wieland Miescher ketone and other enones. It can be prepared by Michael addition reaction, ok. It can be easily prepared by a Michael addition reaction. So, here I have given a numbering. So, you can see 1, 2, 3, 4, 5. Now, why I have given this numbering was I am going to redraw this molecule as well as do a disconnection.

So, the disconnection is suppose, if I remove this, if I disconnect this bond what you will get is this one, ok. So, now, you are going to generate an anion here, ok, that will be enolate. That enolate will add to this double bond, ok. Basically, it is a Michael reaction, ok. Now, you have 6, 7 fused ring. So, whenever you want larger ring or medium sized ring one reaction which you can think about is ring expansion reaction. See normal rings are 5-membered and 6-membered.

So, if you want to go beyond, so, one can think about ring expansion. So, what Corey thought? So, let us start with two 6, 6 fused rings, ok. So, you can see here one 6-membered and another 6-membered. Now, he wanted to carry out a ring expansion reaction to get 7-membered ring. So, what he thought you know he wanted to use a well known pinacol-pinacolone rearrangement and the problem with this diol, ok.

If you have this 1, 2-diol and if you want to carry out a pinacol-pinacolone rearrangement, ok if you want to carry out a pinacol-pinacolone rearrangement then, this tertiary alcohol only will be protonated, ok. This tertiary alcohol only will be protonated. So, what you have to do for the ring expansion?

You have to make the secondary alcohol you have to make the secondary alcohol as the leaving group. Then, the 7-membered ring formation is possible. And, this can be easily obtained from Wieland Miescher ketone, ok. So, when I discuss the real synthesis, I will talk about how this ring expansion was thought and how he successfully could do it, ok.

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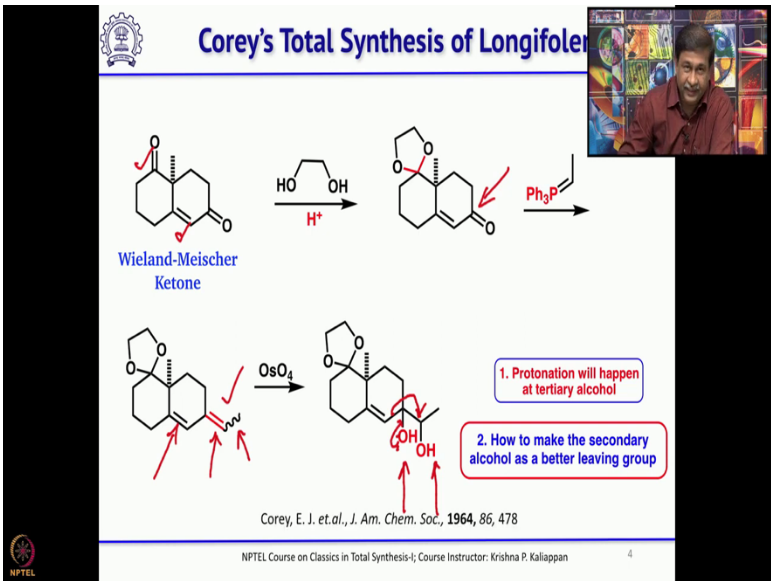

Corey's Total Synthesis of Longifoler

Wieland-Meischer Ketone

1. Protonation will happen at tertiary alcohol

2. How to make the secondary alcohol as a better leaving group

Corey, E. J. *et.al.*, *J. Am. Chem. Soc.*, **1964,** *86*, 478

So, his synthesis actually started with Wieland Miescher ketone, it is a racemic one. Then, the ketone you have 2 ketones. One is the 6-membered ketone, other one is a enone, ok. Between, enone and ketone one can selectively protect the ketone with ethylene glycol in the presence of acid.

So, now you have protected the 6-membered ketone here. So, now you can carry out the Wittig reaction on the enone. So, simple Wittig reaction gave this exocyclic double bond with a methyl group, ok. So, the stereochemistry as you know it is a mixture, does not matter. So, next step is the dihydroxylation. You have an internal double bond and an external double bond. So, one could selectively dihydroxylate the external double bond with osmium tetroxide, ok.

So, now he has got basically the key precursor for the ring expansion; key precursor for the ring expansion in three steps from known Wieland Meischer ketone, ok. So, now, the key problems which I you know mentioned, that is you have to do the ring expansion, ok. When you want to do the ring expansion as I said, the protonation will take place only at the tertiary alcohol. So, if you use any acidic condition for the rearrangement to take place then ring expansion will not take place.

So, what you have to do? You have to go you have to modify. So, what one can do is if we can make the secondary alcohol as a good leaving group, ok, secondary alcohol as a good leaving group then this bond can migrate. This lone pair will come here and this bond can migrate that will lead to the formation of 7-membered ring. So, that is what he did.

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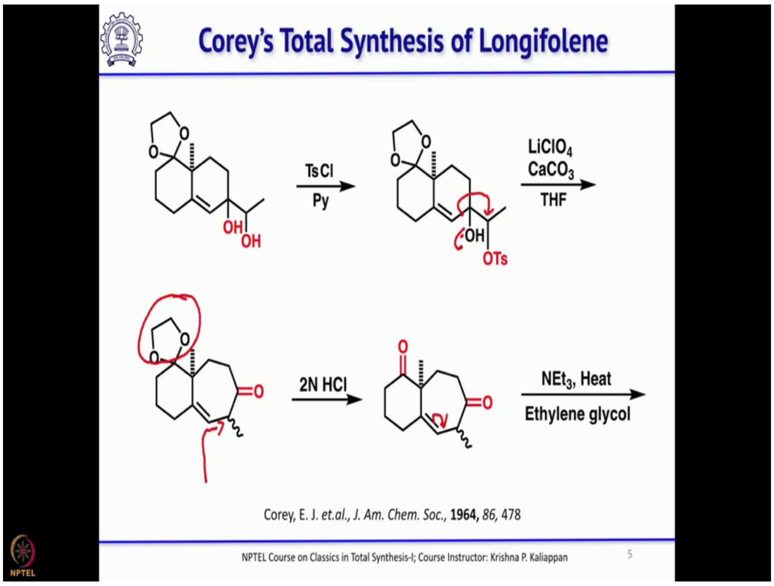

Corey's Total Synthesis of Longifolene

Corey, E. J. *et.al., J. Am. Chem. Soc.*, **1964**, *86*, 478

So, what he did was he took this diol and then made the secondary alcohol as a good leaving group. So, by converting that secondary alcohol into tosylate, ok. So, now, you have made the tosylate then it was easy. So, you treated with perchlorate in the presence of base like calcium carbonate, then as I said this bond migrated and gave the 7-membered enone, ok.

So, now, if you look at this enone, the double bond is still not in conjugation, ok, the double bond is not in conjugation. So, for the key intramolecular Michael reaction to take place for the key intramolecular Michael reaction to take place first, this double bond has to come here then you have to remove the ketal, ok. So, what he did? First he removed the ketal to get back the ketone, ok. Now, the double bond was isomerized with triethylamine and he did you just isomerize the double bond.

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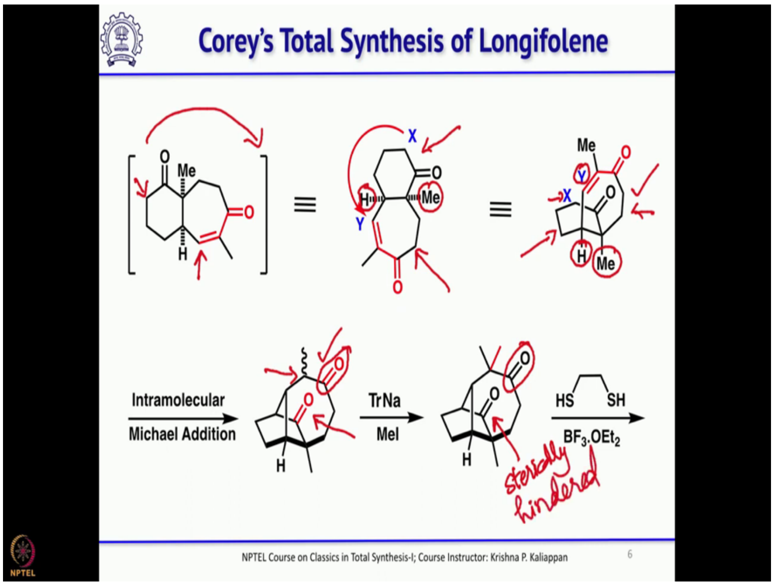

Corey's Total Synthesis of Longifolene

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So, that gave the key precursor for the intramolecular Michael addition. Now, if you look at this molecule, ok. So, we have to draw in such a way that, you can see that this carbon is closer to this carbon, ok. So, that is very important. So, I draw this in such a way now you rotate this, ok, you rotate this by 90 degree, ok, you rotate this structure by 90 degree. So, now, you have this structure. This structure, I ask you to visualize like this bicyclic system, ok.

If you look at this bicyclic system you can see here this is this is the cyclohexanone, ok. The cyclohexanone here is written like this. Now, this hydrogen is alpha you can see that is then this methyl is alpha, yes. Now, you have the 7-membered ring, yes, that is beta you have the 7-membered ring. Now, when you look at this molecule you can see carbon X. Carbon X is near to carbon Y that is the beta carbon of the enone.

So, this tells that from this conformation you can make that it is possible to carry out an intramolecular Michael reaction and that is what they did. And, treated with strong base it generated anion and Michael reaction worked very well to get this tricyclic compound, ok. So, now, you have got the core structure, ok.

So, with two carbonyl groups; so, 1, 5-diketone and as you know what needs to be done is you have to introduce one more methyl group and remove this carbonyl then you have to do Wittig reaction on this carbonyl group. So, these are three things left for the completion of longifolene.

One, introduction of methyl group; second, removal of the carbonyl group; third, conversion of carbonyl into a double bond, ok. So, first it was easy to introduce the methyl group, ok, with a very strong base sodium trityl group, then quench with methyl iodide. So, you could introduce the methyl. So, the dimethyl group was put in proper place. Next, you have to remove this carbonyl group selectively in the presence of other carbon group.

So, between these two carbonyl group, and this one is sterically you know hindered, ok. It is sterically hindered position. So, it is easy to protect the other carbonyl group.

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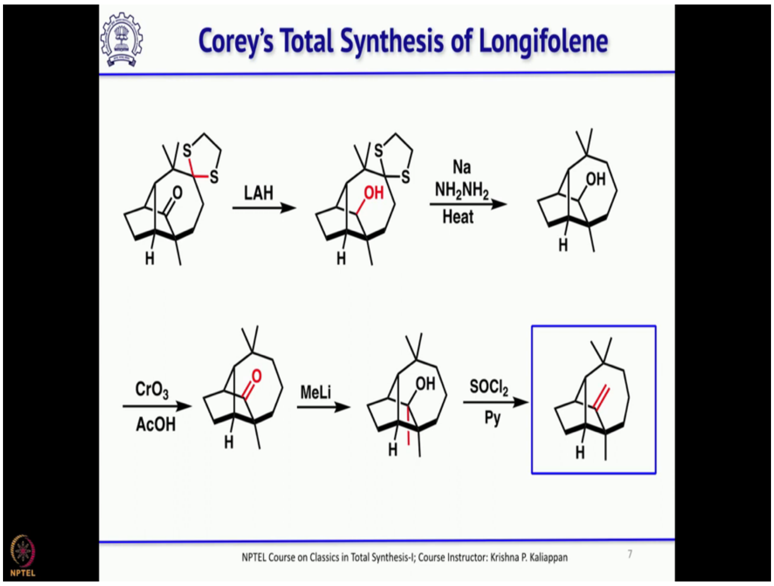
Corey's Total Synthesis of Longifolene

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So, it was protected as dithiane derivative. And, as you know when you have a dithiane derivative you can reductively remove so that you can get the corresponding CH_2. So, before that the carbonyl, the other carbonyl was reduced because that should not interfere in the removal of the dithiane.

So, once you reduce the ketone to alcohol, then the dithiane was removed with the sodium and hydrazine and to get the CH_2. So, now, what is left? You have to oxidize the secondary alcohol to ketone then convert the ketone into double bond that will complete the total synthesis of longifolene. So, that is what he did. So, treatment with chromium trioxide, oxidize the secondary alcohol to get the ketone.

So, then the Wittig reaction actually was not successful. So, he has to do the other method that is normally you can use either Grignard or organolithium species. So, he tried methyllithium addition to this ketone. So, that gave the tertiary alcohol. And, that was treated with thionyl chloride pyridine to get the exocyclic double bond and that is how he completed the total synthesis of longifolene.

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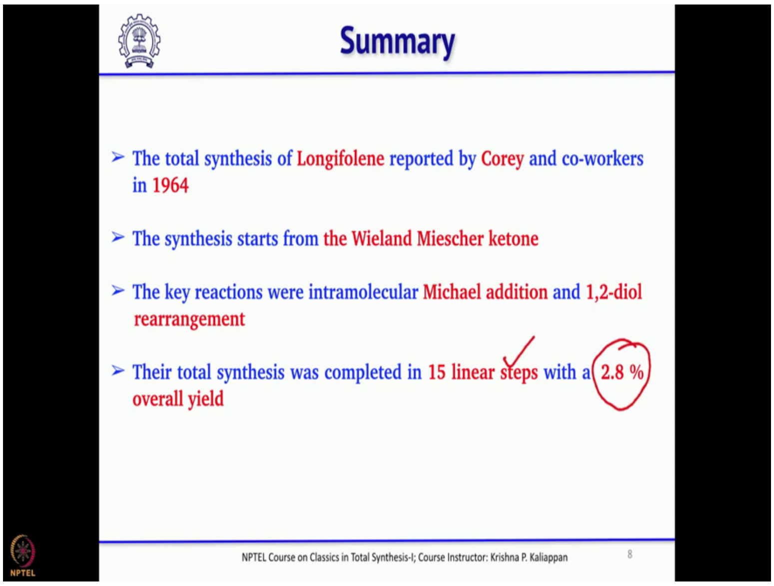

Summary

- The total synthesis of Longifolene reported by Corey and co-workers in 1964
- The synthesis starts from the Wieland Miescher ketone
- The key reactions were intramolecular Michael addition and 1,2-diol rearrangement
- Their total synthesis was completed in 15 linear steps ✓ with a 2.8 % overall yield

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So, if you look at the synthesis reported by Corey, this synthesis started with the commercially available and well-known Wieland Miescher ketone, it is a bicyclic compound. And, the key reactions which Corey used were intramolecular Michael Michael addition and the formation of 1, 2-diol. First, formation of 1, 2-diol selectively on one of the double bond, followed by rearrangement ring rearrangement of the 1, 2-diol to get the 7-membered ring.

Overall, he took about 15 linear steps with an overall yield of 2.8 percent. So, that is quite decent considering the natural product and this was the first total synthesis. So, now, we will move to the second total synthesis was which was reported by Wolfgang Oppolzer in 1978.

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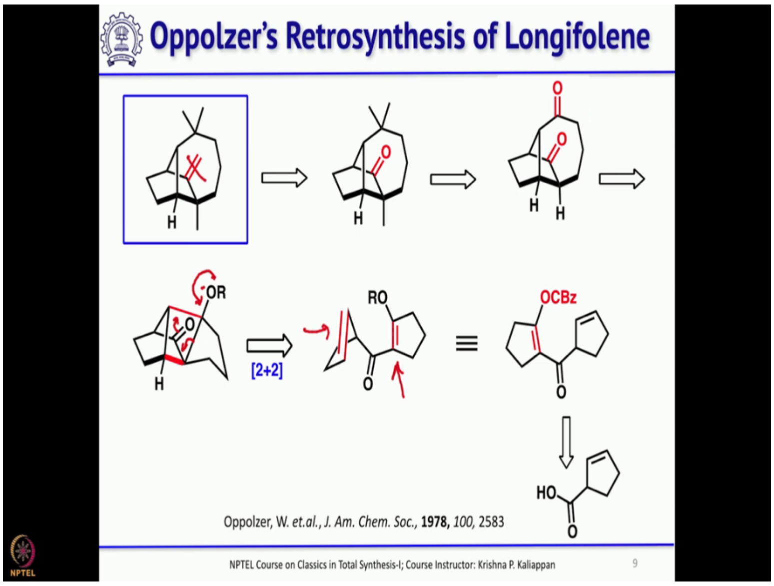

Oppolzer's Retrosynthesis of Longifolene

Oppolzer, W. *et.al.*, *J. Am. Chem. Soc.*, **1978**, *100*, 2583

And he used a very very interesting photochemical reaction followed by Grob fragmentation as key reactions to construct the core structure of longifolene. And, as usual the first disconnection was same as the case of E. J. Corey that, he disconnected the double bond and the ketone can be easily converted into the double bond using methyllithium and followed by dehydration.

And this ketone again, you can see he introduced another ketone, ok, like what E. J. Corey has done. And, the next step is the one which he literally you know is different than what E. J. Corey has done. Now, his idea is to use a Grob-like fragmentation. So, if you see this tetracyclic compound his idea is, so if we do the ring opening, ok, it is like push-pull system, ok.

When you open this 4-membered ring that will lead to the formation of 7-membered ring, ok and when you have the 4-membered ring; obviously, there is a 2 plus 2 a photochemical cycloaddition reaction only should come to your mind. And, that is what he thought as the precursor for this tetracyclic compound, ok.

So, now you can see there is one double bond here and another double bond these two should undergo an intramolecular 2 plus 2 cycloaddition to give this tetracyclic compound, ok. And, this can be easily obtained from this you know this is same compound. This can be easily obtained from the cyclopentane carboxylic acid, ok. So, his starting material is quite simple and in few steps he thought he can easily achieve the synthesis of longifolene.

Now, let us see how he really executed his retrosynthesis in the synthesis of longifolene.

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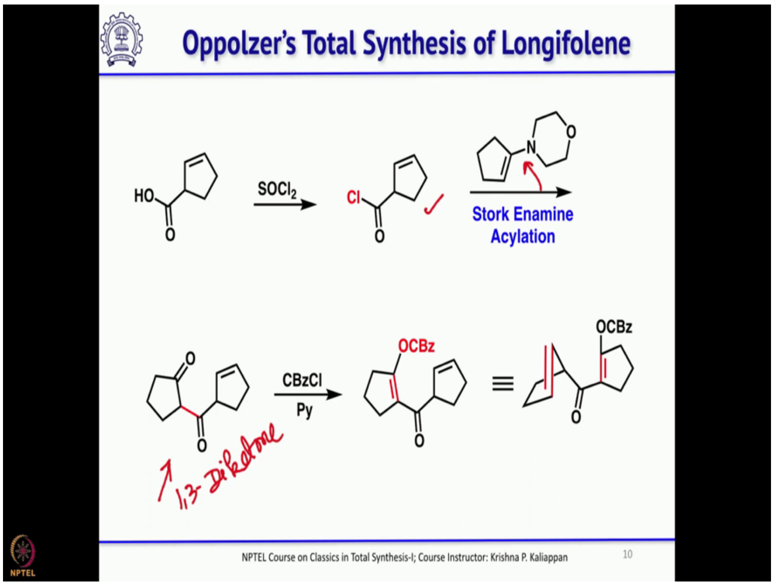

Oppolzer's Total Synthesis of Longifolene

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So, he started with cyclopentene carboxylic acid. And treatment with thionyl chloride, converted the carboxylic acid to acid chloride. And this acid chloride, upon enamine reaction with this particular enamine derived from cyclopentanone. The cyclopentanone and treatment with morpholine will give this enamine, this enamine upon treatment with this acid chloride. Basically what you are doing is you are doing the acylation reaction ok, you are doing the acylation reaction next to the carbonyl, ok.

So, once you have this 1, 3-diketone. So, this is 1, 3-diketone is not it 1, 3-diketone and this 1, 3-diketone you can selectively enolize. So, what he did? He not only enolized, but also protected the enol as CBz, ok. So, CBz is a good protecting group as you know for NH_2 and OH.

So, now, we protected that enol as enol OCBz. The CBz is nothing but, benzyl oxy carbonyl, ok benzyl oxy carbonyl, ok and that can be easily cleaved under hydrogenolysis condition later. Whenever it is required, you can use hydrogenolysis condition to cleave that Bz group, ok. So, this can be drawn like this as we have seen in the retrosynthesis. So, did the 2 plus 2 cycloaddition worked. Yes.

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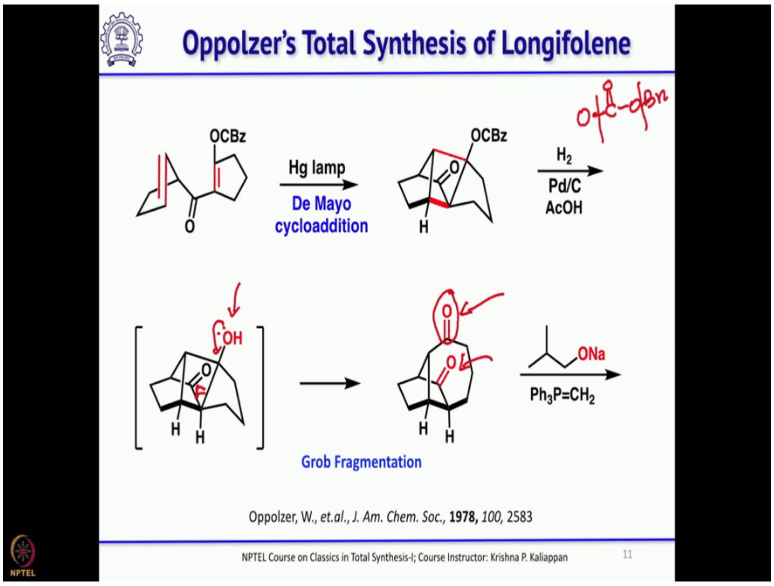

Oppolzer's Total Synthesis of Longifolene

Oppolzer, W., *et.al.*, *J. Am. Chem. Soc.*, **1978**, *100*, 2583

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So, when we tried this intramolecular photochemical 2 plus 2 cycloaddition reaction, so, which we can also call it as a DeMayo cycloaddition reaction. So, this reaction worked well. So, exactly as planned he got this tetracyclic compound, ok. So, now, what is left is, to cleave the protecting group the CBS, CBz should be cleaved and then followed by Grob fragmentation should give the 7-membered ring. So, it was cleaved under hydrogenolysis condition as I said. It is nothing but, this OCOObenzyl, ok.

So, as you know hydrogenation, it will cleave the benzyl and then carbon dioxide will also will go and you get the corresponding OH. Now, this will open up to give the 1, 5-diketone. Again, as we planned, the 2 plus 2 cycloaddition De Mayo cycloaddition worked well. And also, the ring expansion the Grob fragmentation also worked very well to get the core structure.

Now, if you look at this tricyclic compound, this is the core structure of longifolene. So, what is required is, this should be converted into dimethyl group. And this should be converted into CH_2, ok. So, it is easy. Now, you do a Wittig on this particular less exposed carbonyl group. As you know this is, the other carbonyl is slightly hindered. So, it is easy to do a Wittig reaction on the less exposed carbonyl group.

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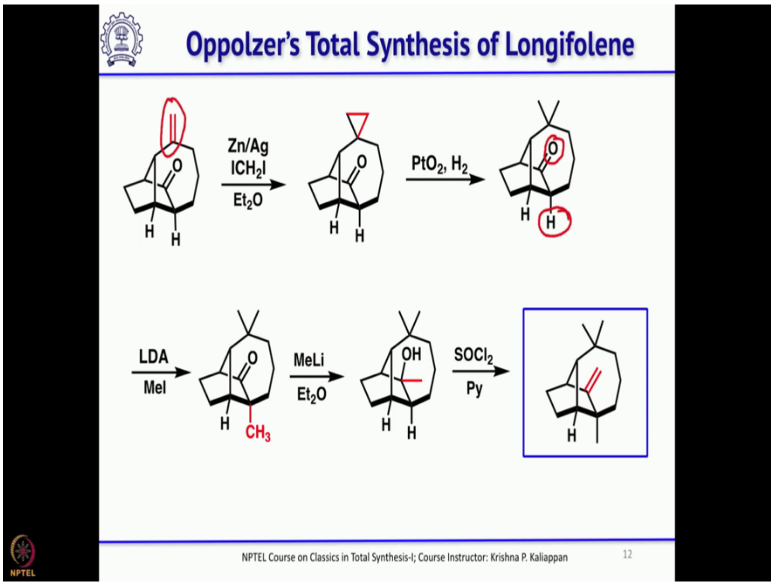

Oppolzer's Total Synthesis of Longifolene

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So, you get the double bond. Then you do the cyclopropanation. You do the cyclopropanation on this double bond to get the cyclopropane. Once you have the cyclopropane as you know you can hydrogenate to introduce the dimethyl group. Cyclopropane is converted into the dimethyl group, ok. Now, only two reactions are left one this hydrogen.

This hydrogen should be converted into methyl group. Then, you have to remove the carbonyl group. So, simple treatment with LDA and methyl iodide. So, that is the only place it can go. So, methyl group was introduced. Then as reported by Corey do a methyl lithium addition to the ketone to get the tertiary alcohol and then treat with thionyl chloride pyridine, you get the corresponding double bond and that is the natural product.

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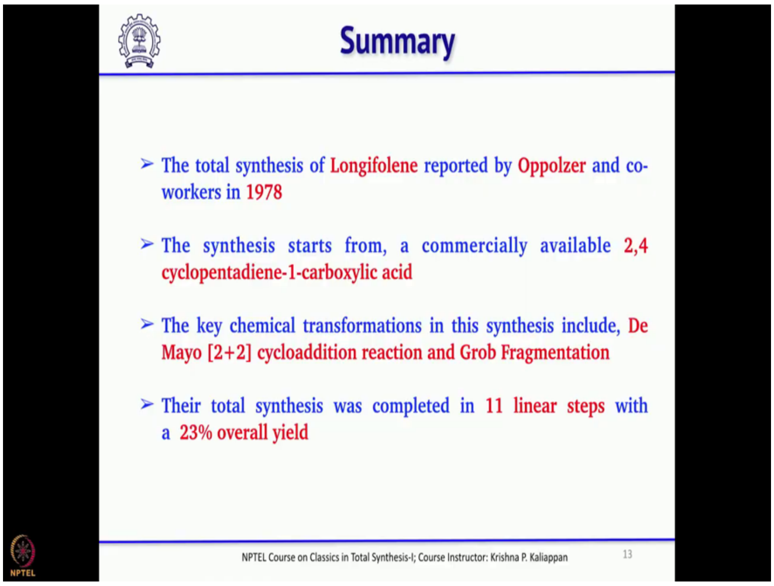

Summary

- The total synthesis of Longifolene reported by Oppolzer and co-workers in 1978
- The synthesis starts from, a commercially available 2,4 cyclopentadiene-1-carboxylic acid
- The key chemical transformations in this synthesis include, De Mayo [2+2] cycloaddition reaction and Grob Fragmentation
- Their total synthesis was completed in 11 linear steps with a 23% overall yield

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So, that is longifolene synthesis. And if you look at the synthesis reported by Oppolzer, it started with commercially available cyclopentadiene 1-carboxylic acid, but what is more important was, two key reactions which actually assembled the natural product core structure quickly; one was De Mayo photochemical 2 plus 2 cycloaddition reaction and the second was Grob like fragmentation.

Overall yield was 23 percentage, which is very good. And, the number of steps taken to complete this molecule was 11 steps. So, 11 steps with the overall yield of 23 percent is really very very high. So, this is one of the best synthesis of longifolene reported so far.

Now, we will move to the third of third synthesis which was reported by W. S. Johnson. Actually, here his total synthesis based on his serendipitous observation of his polyene cyclization. Johnson has reported several polyene cyclization which is like biomimetic cyclization he was inspired by nature's many cyclizations. So, he has developed many biomimetic cyclization.

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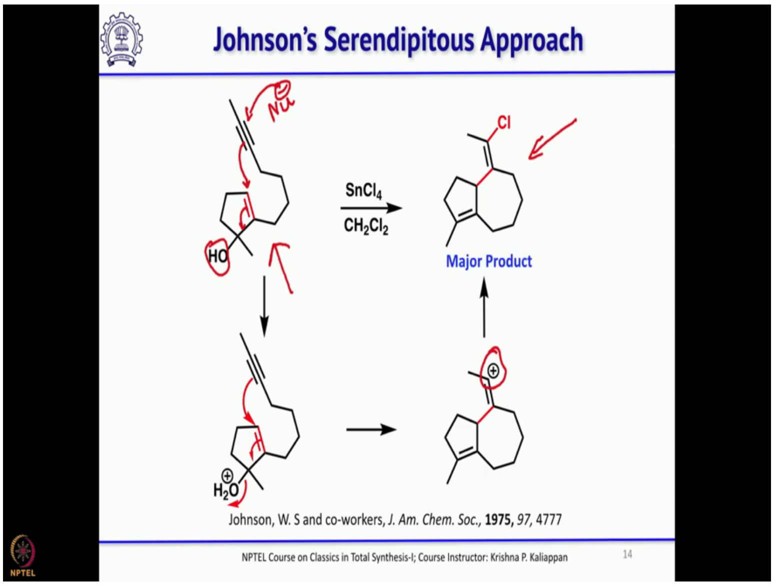

Johnson's Serendipitous Approach

Johnson, W. S and co-workers, *J. Am. Chem. Soc.*, **1975**, *97*, 4777

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So, during his report, when he was working on this polyene cyclization. So, he was trying to cyclize this particular enyne. So, his idea is this OH will be a good leaving group, ok. So, then, this double bond will migrate and this will attack and finally, a nucleophile, nucleophile will neutralize the positive charge generated here. So, when he treated this with stannic chloride, what he got was as expected this cyclised product.

So, the mechanism is simple. As I said the OH was protonated. So, now, the water is a good leaving group and, followed by migration of the double bond and the triple bond. So, you can get the bicyclic compound. So, bicyclic compound with a vinyl carbocation. Now, the Cl minus which is formed insitu, so can attack and then get this bicyclic compound with a exocyclic double bond, ok.

Interestingly, in addition to this product, he also got another product, in addition to this product he also got another product.

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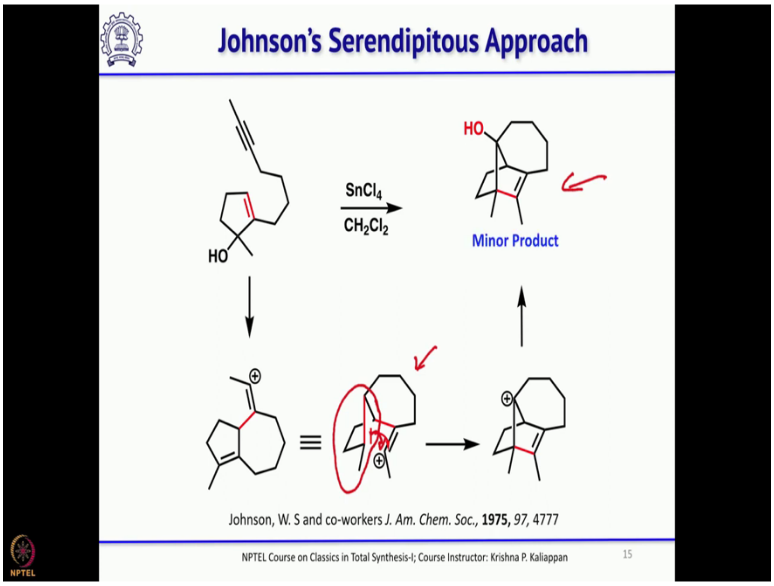

Johnson's Serendipitous Approach

Johnson, W. S and co-workers *J. Am. Chem. Soc.*, **1975**, *97*, 4777

So, that product is like this, that product is like this. So, he proposed a simple mechanism for this. So, first it forms the vinyl carbocation. So, before the chloride attacks before the chloride attacks, what happens? If you redraw this molecule if you redraw this molecule like this you can see here.

So, this is the 5-membered ring, ok you can see this is the 5-membered ring and this is a 7-membered ring. And, you have exocyclic double bond with a carbocation. What he proposed was this double bond if it migrates and neutralizes the vinyl carbocation, ok. Then, what you get is this carbocation, ok.

Now, once you have this carbocation, simple attack of water on this carbocation should give this compound, ok. Now, if you look at this structure if you look at this structure, so, this is a core structure of longifolene, is not it? This is the core structure of longifolene. So, then he thought by choosing proper starting material it should be possible to synthesize longifolene using this serendipitous observation, ok.

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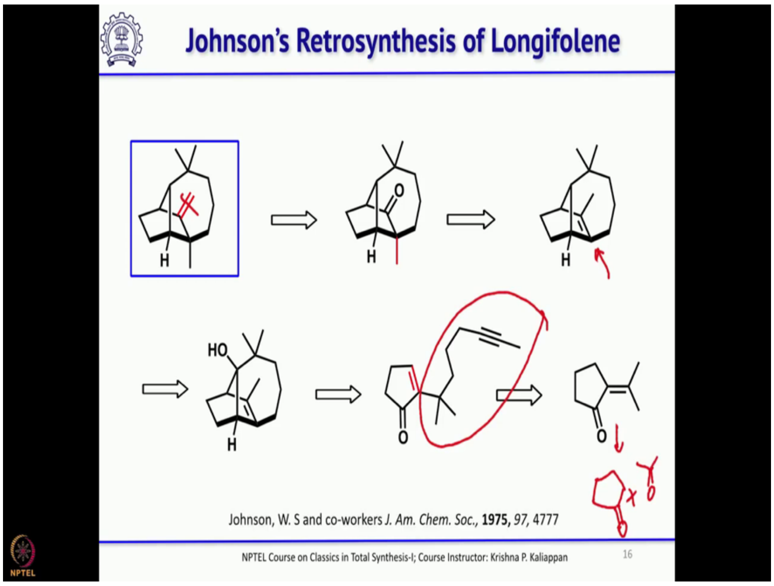

Johnson's Retrosynthesis of Longifolene

Johnson, W. S and co-workers *J. Am. Chem. Soc.*, **1975**, *97*, 4777

So, with that he wrote a proper retrosynthesis. As usual the first disconnection was to have the carbonyl group. And this can be obtained from this internal double bond, ok. So, through functional group transformation which I will discuss while talking about the total synthesis and this in principle can be obtained from this alcohol. So, if you look at the previous slide. So, this is what is the intermediate, ok.

And, now, if you look at this, this can be obtained from this cyclopentanone with this appended side chain, ok. So, this can be easily obtained from the substituted cyclopentanone, ok. The cyclopentanone can be easily obtained from cyclopentanone and aldol reaction with acetone, ok. So, that is the starting material.

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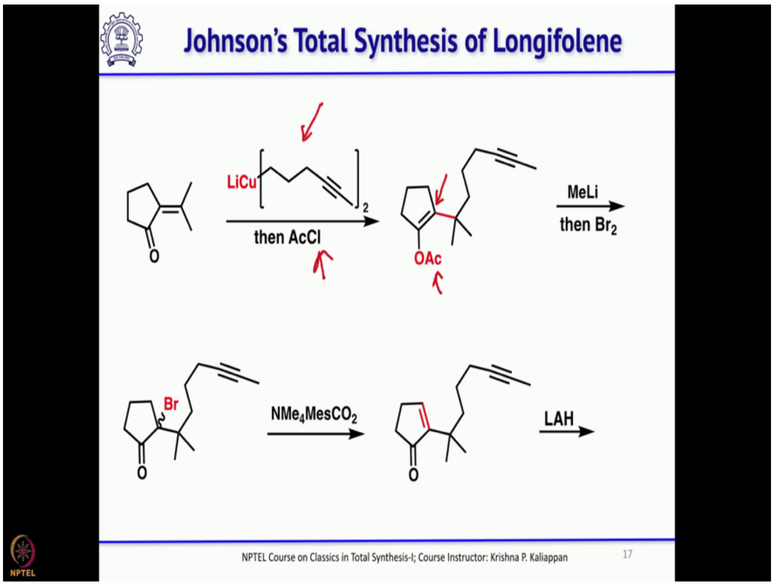

Johnson's Total Synthesis of Longifolene

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So, he started with this compound then carried out a 1, 4-addition, ok 1, 4-addition with this derivative, ok. After the 1, 4-addition the resultant enolate was quenched with acetyl chloride the resultant enolate was quenched with acetyl chloride to generate the enol acetate, ok, or in other words the enolate was trapped as enol acetate. So, after trapping the enol acetate, if you want to generate the enolate, what you can do? One can treat with methyllithium.

So, methyllithium will attack the acetate and generate the lithium enolate species, ok. Then, when you add bromine, that bromine will be quenched here. So, that is what happened. So, first you generate the lithium enolate by treating with methyllithium; then you add bromine you introduce the bromine next to the carbonyl group. So, once you have the bromine, introduce next to carbonyl group, one can easily introduce the double bond through elimination. So, it was easily done under mild condition.

So, now the key starting material is ready. So, what you should do? You should reduce the carbonyl group selectively to get only the allylic alcohol; not fully reduced compound. So, LAH reduce that enone to the allylic alcohol and that set the tone for the key Lewis acid-mediated cyclization to get the longifolene core structure.

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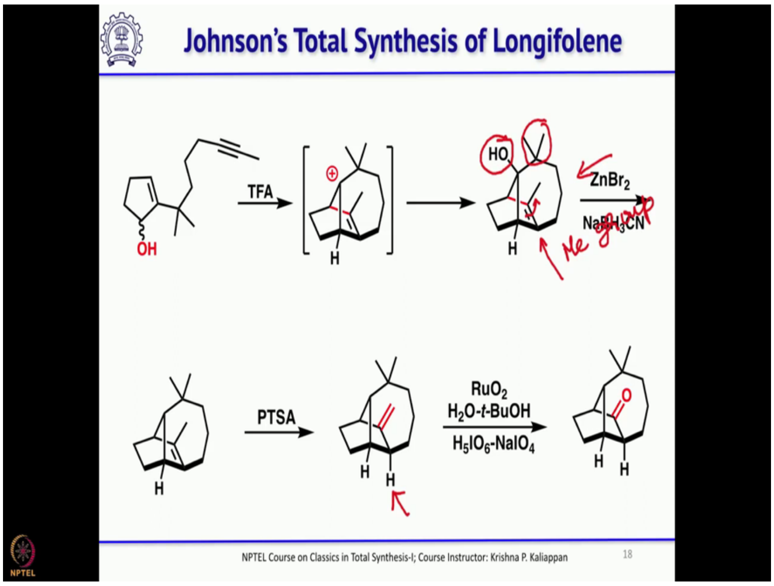

Johnson's Total Synthesis of Longifolene

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Then, he treated this compound with trifluoroacetic acid and as expected he got this carbocation and that was quenched with water to get the corresponding tertiary alcohol. So, this compound is very simple. You can see already has a dimethyl group. You have to remove this hydroxyl and somehow you have to migrate this double bond to here, as well as you have to introduce a methyl group. So, it was very easy for him to synthesize the core structure.

Now, his challenges are remove the hydroxyl group, push the double bond to exocyclic and introduce a methyl group. So, these are three more things to do in the synthesis of longifolene. So, first he removed the hydroxyl group with zinc bromide and sodium cyanoborohydride. So, that was done easily. Next, he has to migrate the double bond. So, that was done by treating with para-Toluene sulfonic acid refluxed to get the exocyclic double bond.

Now, you have exocyclic double bond. But, how will you introduce a methyl group here? It is not straightaway possible from the double bond you have you can introduce a methyl group; however, it is possible if you ozonolyse or if you cleave the double bond to ketone. So, with ruthenium oxide and sodium periodicacid, he could get the ketone. Once you have this ketone, the next step is to introduce the methyl group LDA and methyl iodide.

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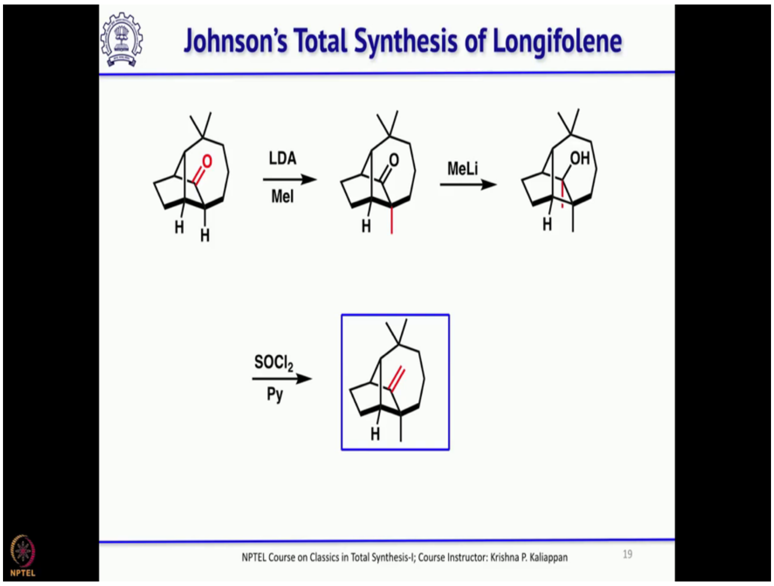

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You introduce a methyl group and followed by like, what Corey and Oppolzer has done, add methyl lithium to get the tertiary alcohol followed by treatment with thionyl chloride and pyridine. So, he could accomplish the total synthesis of longifolene.

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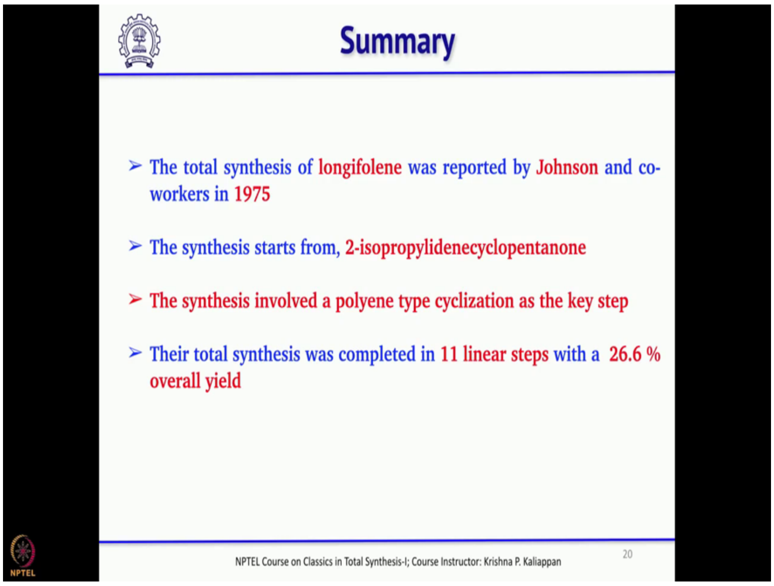

Summary

- The total synthesis of longifolene was reported by Johnson and co-workers in 1975
- The synthesis starts from, 2-isopropylidenecyclopentanone
- The synthesis involved a polyene type cyclization as the key step
- Their total synthesis was completed in 11 linear steps with a 26.6 % overall yield

So, if you look at the total synthesis of longifolene, it was though it was reported in 1975 he started with simple commercially available cyclopentanone which upon aldol reaction with acetone it gave 2-isopropylidenecyclopentanone that was used as the key starting material. And, what is important was, the serendipitous observation during the polyene type cyclization to give a minor product was used as a key step to construct the tricyclic compound in one step, ok.

One step formation of the tricyclic compound using this polyene-type cyclization was the key step. And, overall, his synthesis was achieved in 11 steps and with an overall yield of 26.6 percent. So, the overall yield of 26.6 percent is very impressive and all the three synthesis are really unique and classical in nature. And, these three synthesis reported in 60s and 70s considered as real classical total synthesis. So, with this I will stop here. And, then we will discuss more total synthesis in the next class.

Thank you.