Classics in Total Synthesis - I
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Lecture - 19
Triquinanes by Thermal Metathesis (Mehta)

So, good morning and welcome back to NPTEL lecture series on Classics in Total Synthesis. We have been talking about quite a few total synthesis of triquinanes and today also we will continue and complete discussion on more total synthesis of triquinanes.

Today we will start with our homegrown total synthesis where we discuss total synthesis of three triquinanes, actually two triquinanes and one having a diquinane moiety reported by none other than Professor Goverdhan Mehta. And first let us start with a known molecule hirsutene.

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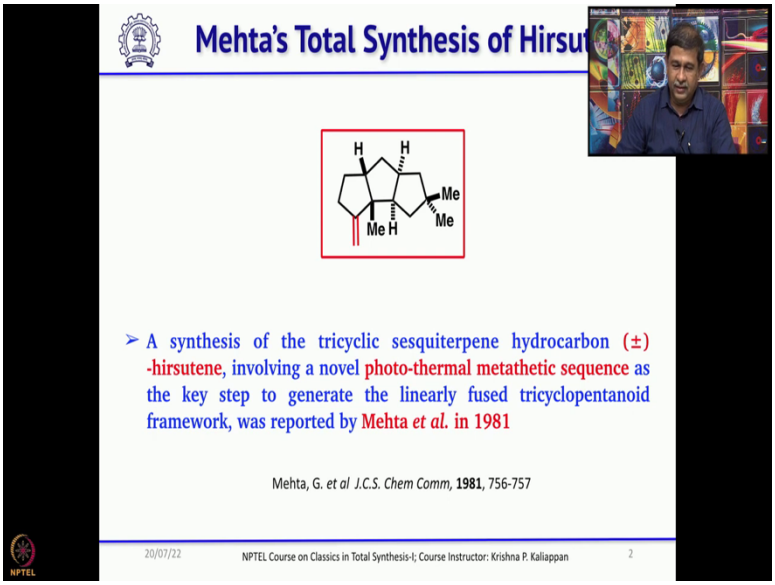

And how his group has synthesized this molecule. He has used a unique reaction now we all know what is metathesis, ring closing metathesis, enyne metathesis, ring opening ring closing metathesis all, but in 80s, but at early 80s he is the one who introduced the term thermal metathesis. So, where you know it undergoes a retro 2 plus 2 under very high temperature one can even call it as flash vacuum pyrolysis to get triquinanes. So, that is a key reaction in many of his total synthesis of triquinanes and related natural products.

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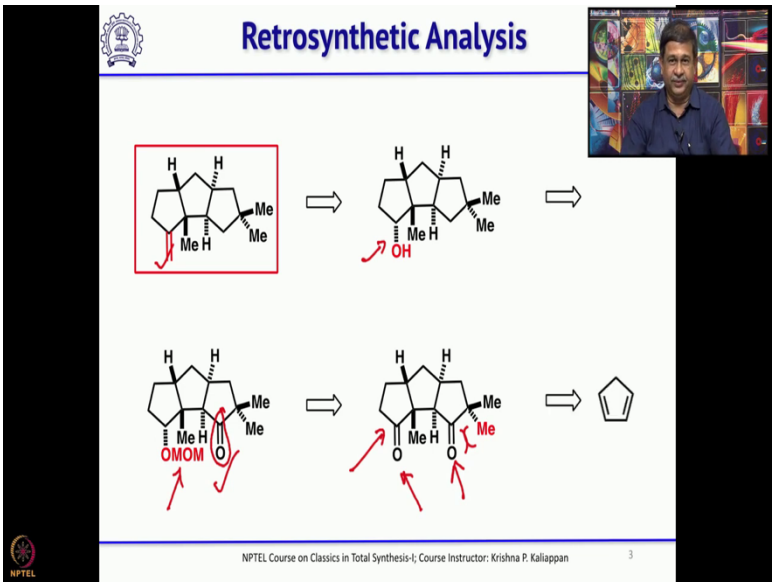

So, let us see how he did a retrosynthesis of this hirsutene molecule as you know when you have a double bond and the double bond can be obtained from alcohol via oxidation and Wittig reaction and this can be obtained from this keto intermediate; this keto intermediate is required which we will come to know when we talk about the synthesis.

So, you can remove the carbonyl group in two to three steps and at the same time after doing that we can remove the mom group to get the hydroxyl and this can be obtained from the diketone. So, you can see there are two carbonyl groups and one is you know highly sterically hindered position.

So, one can easily manipulate the other ketone. So, that is what you have seen in this retrosynthetic disconnection and this can be obtained from cyclopentadiene, ok. So, this is so well known, but I will come to that how he has done.

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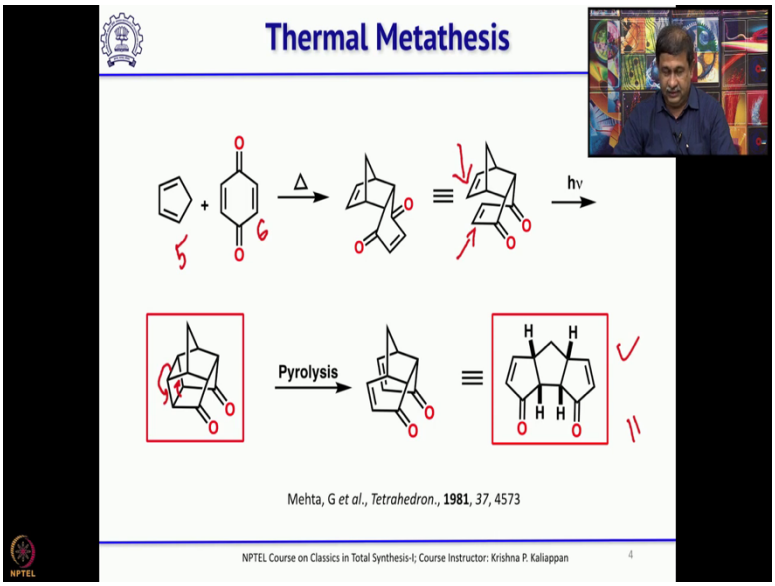

So, it involves five steps to come to the triquinane moiety. A first step is 4 plus 2 cycloaddition between cyclopentadiene and 1, 4-benzoquinone to get this bicyclic tricyclic compound. And this tricyclic compound, if you redraw like this now you can see, this double bond and this double bond they are close to each other and this upon photochemical reaction can undergo an intramolecular 2 plus 2 photocycloaddition to give this highly strained compound, ok. Basically, if you look at this in two steps one can get this highly strained compound.

So, this is this was reported by Cookson. So, it is called Cookson's dione, but what is important was Mehta's group used this Cookson dione for a very important transformation as I already mentioned called thermal metathesis. This upon flash vacuum pyrolysis if you heat it at 600 degrees this undergoes a retro 2 plus 2. So, if you do like this, you will get this tricyclic diene dione, tricyclic diene dione.

This you can also write for better understanding, better visualization you can write like this. Clearly, from cyclopentadiene and benzoquinone one can get this linear triquinane ok linear triquinane core structure basically in three steps. So, what are the key reactions and what are the key takeaway from this whole sequence. One, as I said so first time the thermal metathesis was used to get this tricyclic compound.

Two, people often talk about atom economy ok this is a buzzword in the last two decades. If you look at the whole transformation you started with 5 plus 6, 6 carbons and

you can see in the product you have this same 5 plus 6, 11 carbon atoms, all the hydrogen atoms, all the oxygen atoms, all are retained. So, it is a 100 percent atom economy reaction over three steps.

So, this is the second beauty of this whole sequence which his group exploited in the total synthesis of many natural products. Now, let us see how this core structure was taken further for the completion of total synthesis of hirsutene, ok.

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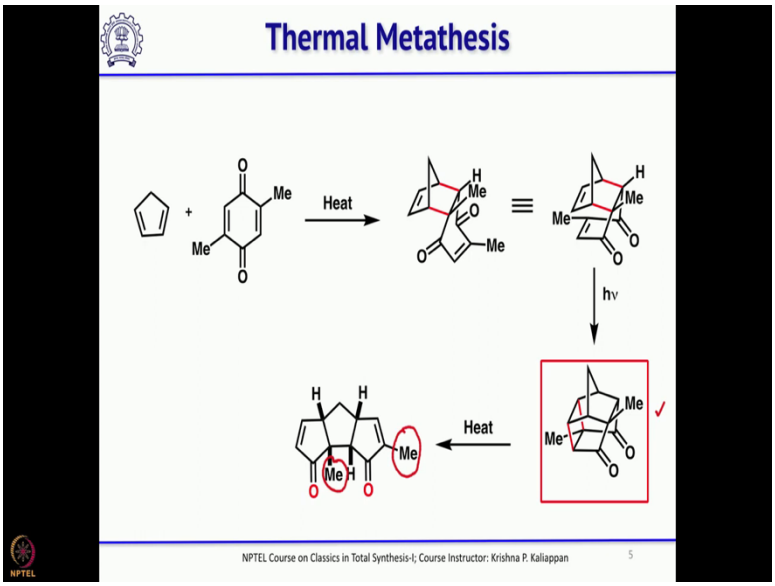

So, that was the key step. So, instead of benzoquinone if you use 2, 5 ok, 2, 5 dimethyl benzoquinone you will get this tricyclic intermediate. This upon intra molecular 2 plus 2 cycloaddition with under photochemical condition will give you the strained compound, ok. Then, you do the flash vacuum pyrolysis you get this tricyclic compound, where compared to the triquinane which we discussed in the previous slide we have two methyl groups in addition. One is angular methyl group, other one is attached to an sp2 carbon, ok.

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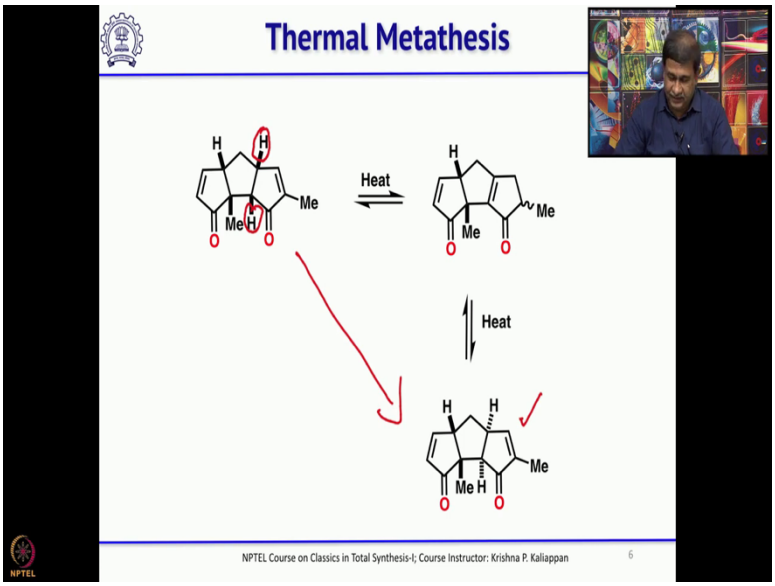

So how he took this intermediate to the final compound hirsutene, ok. So, you take this diene dione and heat it ok, basically what he wants was these two hydrogens should be alpha, ok. So, he could do this using thermal condition when you heat it the double bond migrates ok and if further heating it isomerizes to this more stable triquinane ok this is what he wants. So, by heating it for long time he could convert this into this tricyclic compound, ok.

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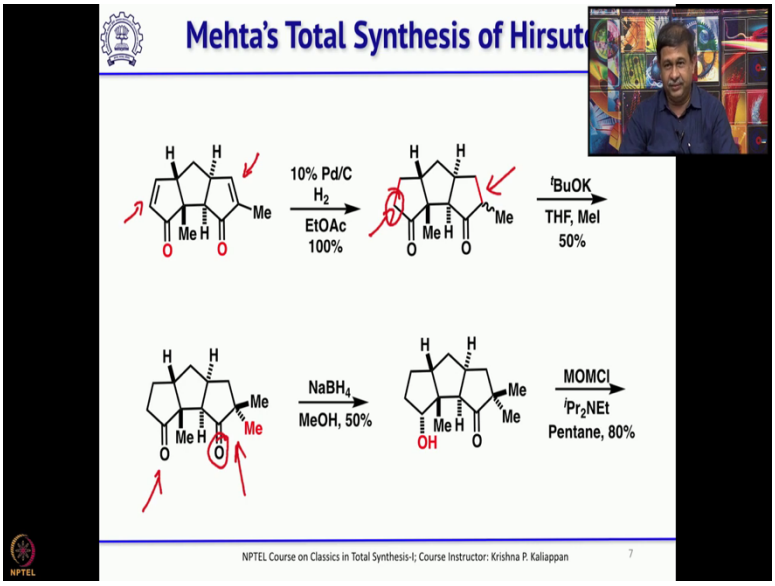

This tricyclic compound he took it and then, reduced both the double bonds ok you have two double bonds and both the double bonds are reduced to get the corresponding diketone. Next, he wanted to introduce one more methyl group here, if you look at hirsutene, you have a dimethyl group at that carbon.

So, he wanted to introduce one more methyl group; obviously, if you see there is a another ketone and then next to that is CH_2 there also one can do the deprotonation. So, what he did, he treated with potassium tertiary butoxide ok and quenched with methyl iodide. So, he could introduce the one more methyl to get the gem dimethyl group, but he got only 50 percent yield which is understandable because, one can also methylate at this carbon.

Nevertheless, he could successfully isolate 50 percent of the required product where you have the gem dimethyl group. After having this diketone, next as you know you need to remove this carbonyl group, but between these two carbonyl groups this carbonyl group is more reactive because, that is less sterically hindered compared to the other ketone. So, what one can do? You can protect that.

So, protection is done through reduction. So, first you reduce the carbonyl the left hand side five membered ring carbonyl to alcohol, then protect that alcohol as mom ether using Hunig's base you get the corresponding mom ether.

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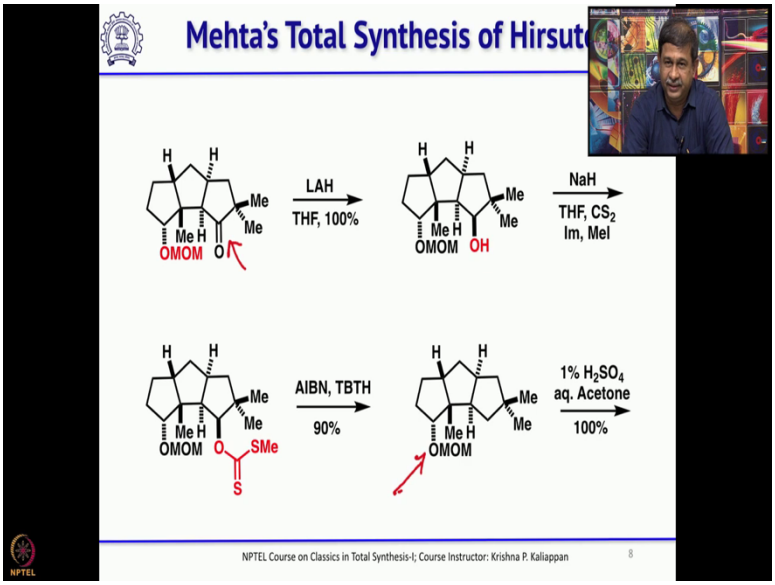

Now, you have to remove the carbonyl group. How do you remove the carbonyl group? There are many methods, but he choose a three step protocol. Where you reduce the ketone with LAH to get the alcohol then, that alcohol was converted into xanthate. A treat with sodium hydride and quench with carbon disulfide and methyl iodide you get the corresponding xanthate that xanthate you treat with tributyltin hydride, AIBN you remove the oxygen.

So, the right hand side five membered ring is fine, the middle five membered ring is fine now what he has to do he has to remove the protecting group, oxidize the alcohol and do the Wittig to complete the total synthesis of hirsutene.

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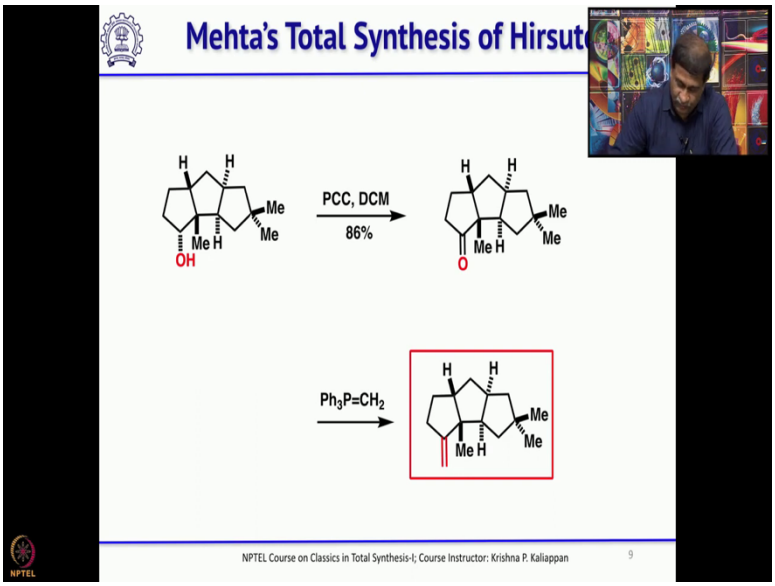

So, the mom group was removed under acidic condition to get the corresponding secondary alcohol, the secondary alcohol was oxidized with PCC to get the ketone then, simple methyl Wittig gave the final natural product that is hirsutene.

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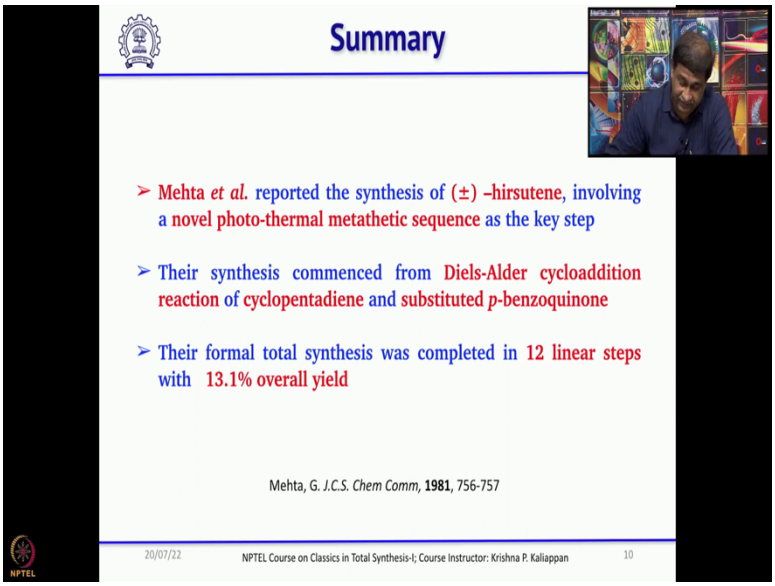

So if you look at this synthesis, overall the key step was the photo thermal metathetic sequence. So, this sequence also as I mentioned is one of the earliest 100 percent atom economy reaction. And, the starting material of course, the tricyclic compound was prepared from cyclopentadiene and 2, 5-dimethyl parabenzoquinone using Diels Alder cycloaddition reaction.

Overall his group took 12 longest linear steps to complete the total synthesis of hirsutene and the yield was about 13 percent. So, 13 percent yield for this molecule is quite competitive and that is mainly because of the atom economy 100 percent atom economy reaction.

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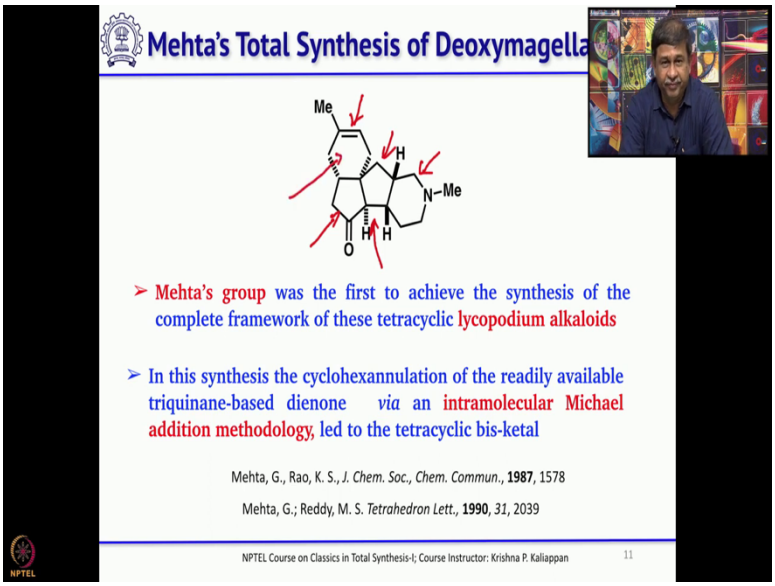

So now, we will move to another natural product which is not a triquinane, but it has a diquinane substructure plus 1 six membered ring and another six membered ring having a hetero atom. So, this molecule is called deoxymegellaninone ok you can see there are 2 five membered rings and one six membered ring and another six membered which we can call it as N-methylpiperidine, ok.

So, since we are talking about triquinanes, I just want to extend that method which professor Mehta has used I want to discuss the extension of Professor Mehta's methodology to synthesize such molecules. So, this was the first total synthesis reported by Professor Mehta and in addition to; in addition to the standard metathesis thermal metathesis reaction he has also used an intramolecular Michael addition reaction as the key reaction to construct this six membered ring, ok.

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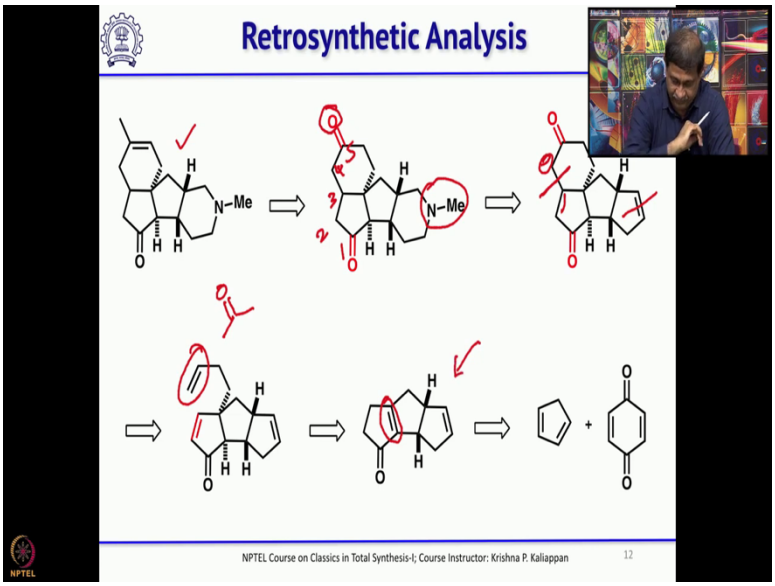

Let us see, how he has done this first let us look at the retrosynthetic analysis. So this molecule as you know you can easily obtain from this diketone. So, if we look at the diketone between five membered and six membered, six membered is a little bit more reactive. So, you can do a Wittig on this ketone followed by isomerization you will get the natural product.

And this diketone, if you look at carefully it is 1, 2, 3, 4, 5 it is a 1, 5-diketone. So, whenever you see a 1, 5-diketone in a natural product immediately the Michael reaction should come to your mind. So obviously, the precursor for this could be the corresponding diketone. So, if you remove this and if you have double bond then it can generate anion and it can undergo Michael addition.

At the same time, the other side six membered ring if you see that is N-methylpiperidine, if you ozonolyse this double bond. If you cleave the double bond and if you get a dialdehyde then, one can think about reductive methylation on this dialdehyde or you can reduce that aldehyde to alcohol convert that into leaving group then treatment with methylamine one can get this compound.

And this compound can be obtained from here, if you convert this into a methyl ketone ok normally this is done using Wacker process. So, the terminal double bond can be selectively oxidized under Wacker process to get the corresponding methyl ketone and that methyl ketone can undergo intramolecular Michael addition reaction.

And this of course, can be obtained from this tricyclic compound, where you have an enone and one can think about using another Michael addition to introduce this four carbon unit. And this of course, can be obtained from cyclopentadiene and benzoquinone. So, that is why I thought I should discuss this if you look at this whole synthesis it also goes through the triquinane moeity, ok.

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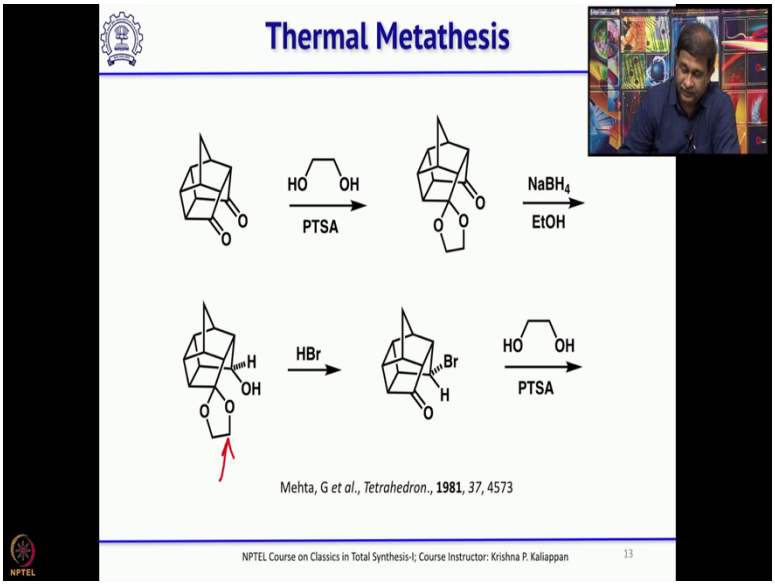

So, this compound we already discussed is not it? This is obtained from cyclopentadiene parabenzoquinone 4 plus 2 cycloaddition followed by 2 plus 2 cycloaddition you get this compound. Now, you do pyrolysis you will get the triquinane. But, you if you look at the previous example one side you do not have the ketone. So, you have to remove one of the carbonyl groups and that is best achieved at this stage.

So, this is symmetrical diketone. So, one of the carbonyl groups is protected as ketal, then the other carbonyl is reduced to get the corresponding alcohol and basically you have to deoxygenate ok the carbonyl group the keto group should be removed. So, it went through three steps reduction followed by conversion of the hydroxyl group into bromide.

And that bromide, during the conversion of hydroxyl group into bromide under HBr condition not only the hydroxyl group was converted into bromide so using a SN_2 right reaction. The ketal also got cleaved, because you are using acidic condition, ok.

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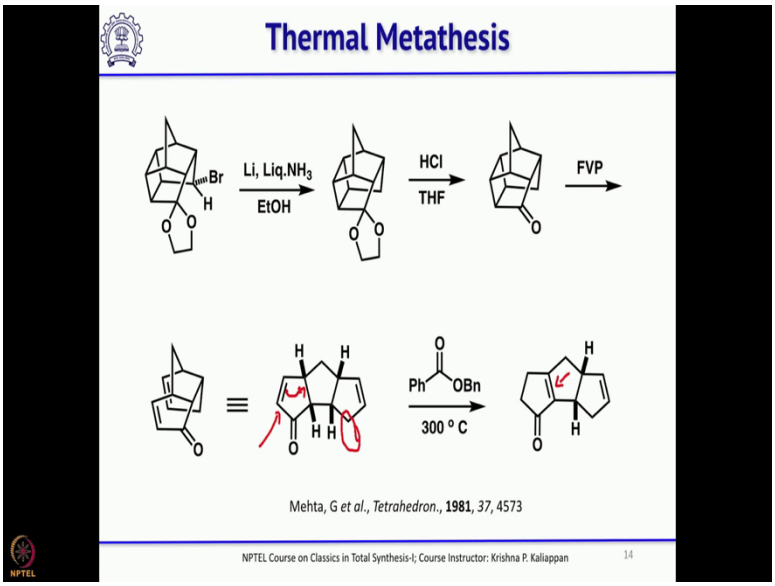

So, again he has to protect the ketone as ketal then, remove the bromide under reductive condition that is metal ammonia condition to remove the bromide so now, you have this. Remove the ketal to get the ketone then, flash vacuum pyrolysis at high temperature you get this compound and if you look at this, this is dienone, ok. Normally you get a ketone one more ketone here that ketone was selectively removed using this process. So once you have that, then the double bond should be migrated. See, basically what you need is this double bond has to come here.

So, that was best achieved by refluxing or heating in benzyl benzoate at 300 degrees the double bond could be successfully migrated to another alpha beta unsaturated ketone, but this time the double bond is tetra substituted; this double bond if you look at this is tetra substituted whereas here it is disubstituted. Next step is the key 1, 4-addition.

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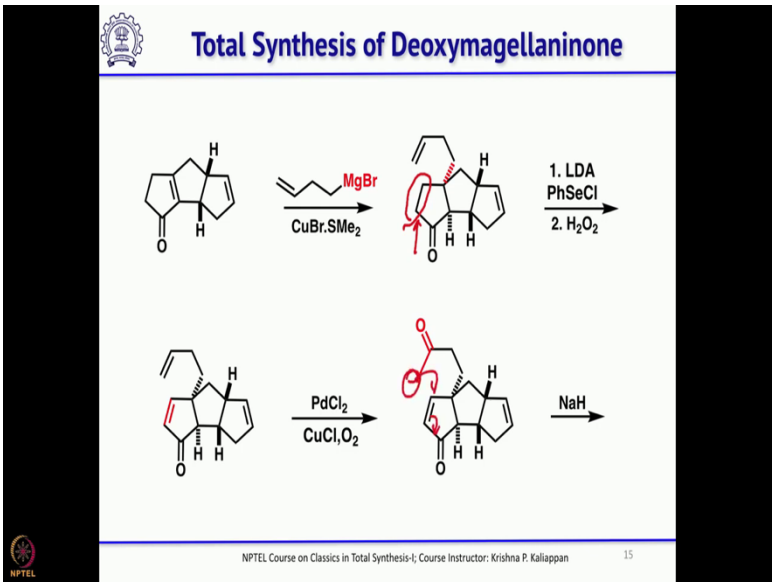

So, that was done using 4 butenyl magnesium bromide and copper bromide dimethyl sulfide complex. So, that added this 4 carbon unit and as I said this once you do this next step is the conversion of the terminal olefin to methyl ketone which is normally done using Wacker process, but before doing that you have to introduce a double bond here is not it, then only the Wacker process will give methyl ketone and that methyl ketone can undergo intra molecular Michael reaction.

So, the double bond was introduced in the step following standard protocol first LDA phenyl selenyl chloride you introduces phenyl seleno group at this carbon and then oxidation to phenyl selenyl phenyl seleno oxide and elimination of phenyl selenoxide gives that double bond. Then, you carry out the Wacker Wacker process to get the corresponding methyl ketone this on treatment with sodium hydride it generates anion and then undergoes a Michael reaction to give this tricyclic compound, ok.

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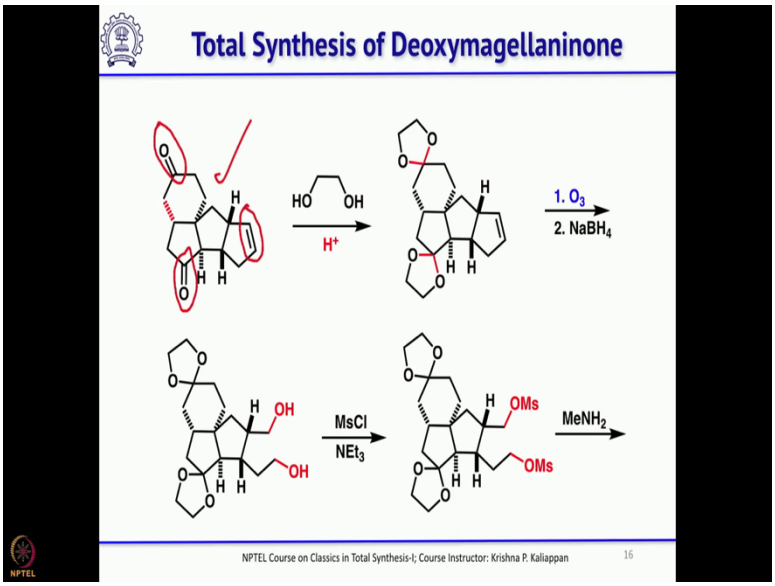

Having got that next this five membered ring should be converted into the six membered ring with hetero atom that is the hetero atom is nitrogen. And in order to do that, you need ozonolysis or you need to dihydroxylate and then cleave with sodium periodide. Before that, one has to protect these two carbonyl groups. So, that was the first step protect those two ketones as ketal then, you do ozonolysis of the double bond to get aldehyde in situ you reduce that aldehyde you get the diol.

The diol was treated with mesyl chloride to get the dimesylate. So, basically what you are doing is you are converting the hydroxyl group into better leaving group this upon treatment with methylamine.

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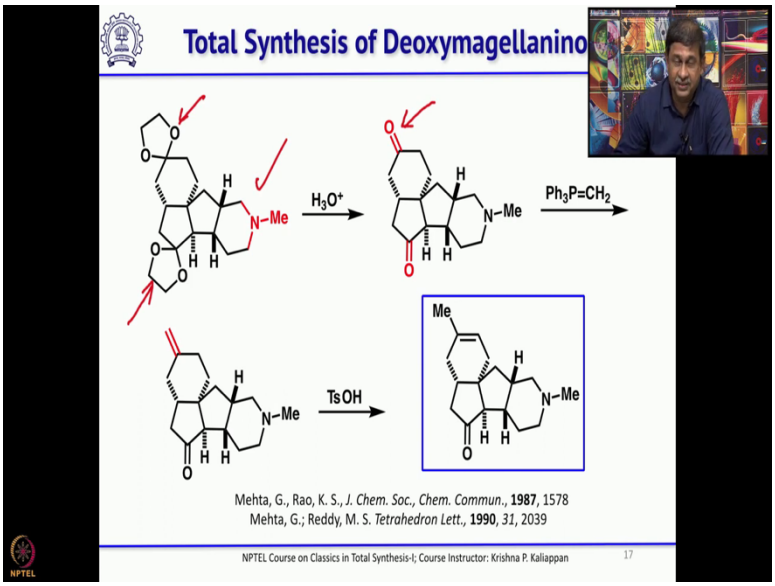

If you reflux with methylamine, it will undergo 2 SN_2 displacement to get this compound, ok. So now, what is required you have to remove both the ketal, you have to remove both the ketal to get the diketone. Yes, that was done you under acidic condition. Then, selectively you have to do Wittig reaction on the six membered ring in the presence of five membered ring yes, you can do that and basically the exocyclic double bond has to be isomerized and that was done by treating with para toluene sulfonic acid.

So, though this is not a triquinane, but if you look at the total synthesis it went through triquinane and though that triquinane also was obtained through a thermal metathesis which was developed by Professor Mehta's group.

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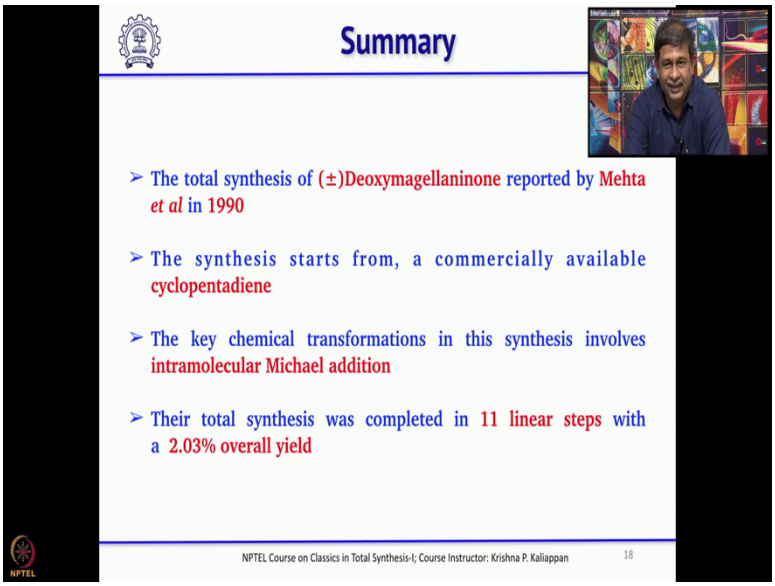

So, the synthesis was reported in 1990 and the starting material as you know it is a cyclopentadiene and benzoquinone and the key step is also intra molecular Michael addition to get this deoxymagellaninone. Overall it took 11 longest linear steps and yield was little lower, but considering the complexity of the molecule 2 percent over all yield is really good and this way he could successfully extend the methodology developed in his laboratory to extend his methodology not only to triquinane, but also to other natural products having a diquinane as a substructure, ok.

The two natural products which we discussed reported by Professor Mehta's group they are racemic. The third synthesis which is about total synthesis of another triquinane is a chiral approach where he started with a chiral starting material called limonene and the natural product which is synthesized is ceratopicanol, ok.

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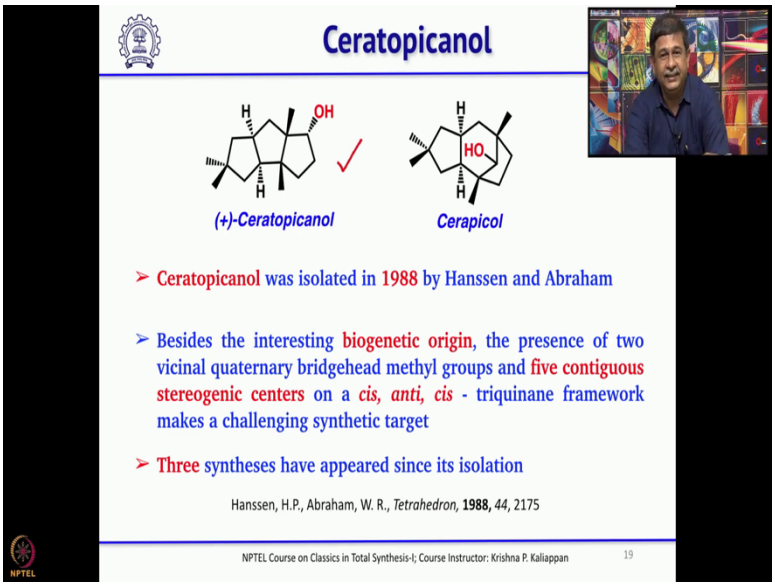

This was isolated in 1988 and it has five contiguous stereocenters as usual for a typical triquinane framework.

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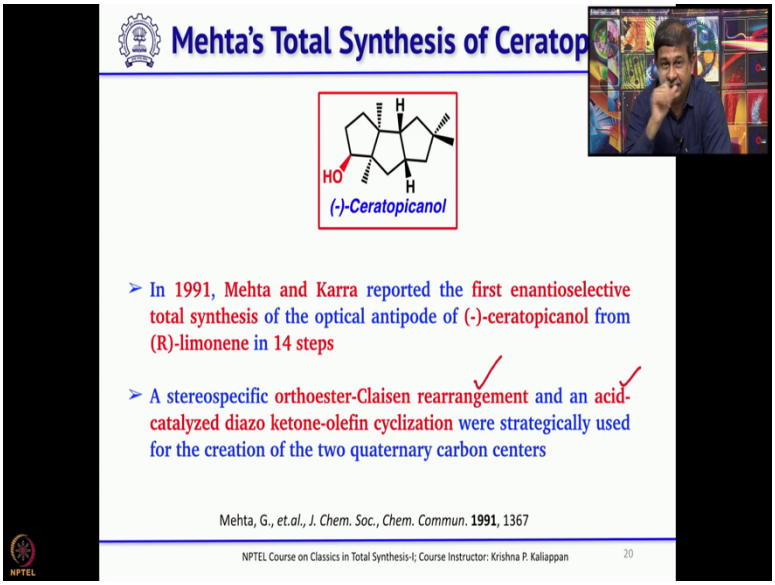

So, it has cis, anti cis configuration and for him the key step is as I said not like the earlier two synthesis where he has used thermal metathesis here it is a chiral approach and in the chiral approach he started with limonene as the chiral starting material. And he also used two key reactions. One is Johnson's orthoester Claisen rearrangement, the other one is acid mediated or catalyzed diazo ketone olefin cyclization to get a

cyclopropane followed by opening up the cyclopropane to get the five membered ring, ok.

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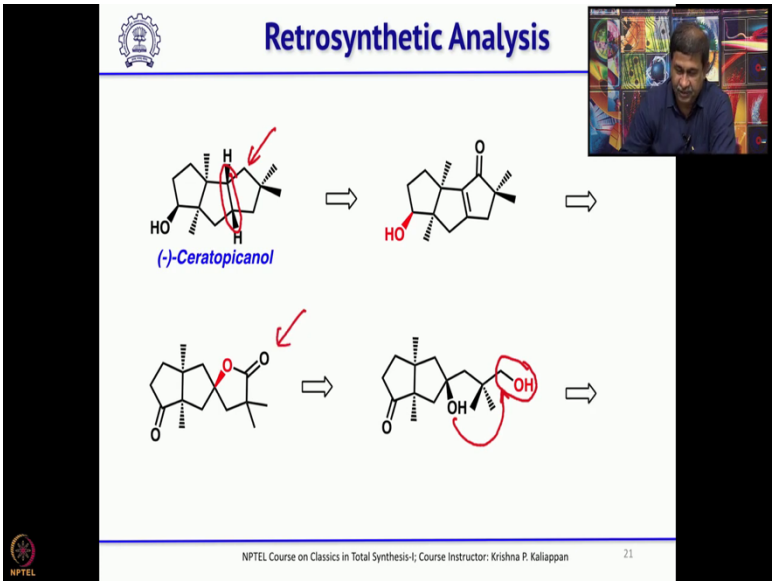

Let us see how he did. And this natural product first he wanted to introduce a double bond and a carbonyl group here. So, that he wanted to use as a handle for further disconnection and this molecule can be obtained from acid catalyzed intramolecular Friedel crafts like cyclization, ok. So, I will come to that when I talk about this how this reaction took place and this can be obtained from this diol ok. So if you look at this diol, one can selectively oxidize the primary alcohol. Once you oxidize this alcohol will attack and then it will form a lactol that lactol will be oxidized to the corresponding lactone.

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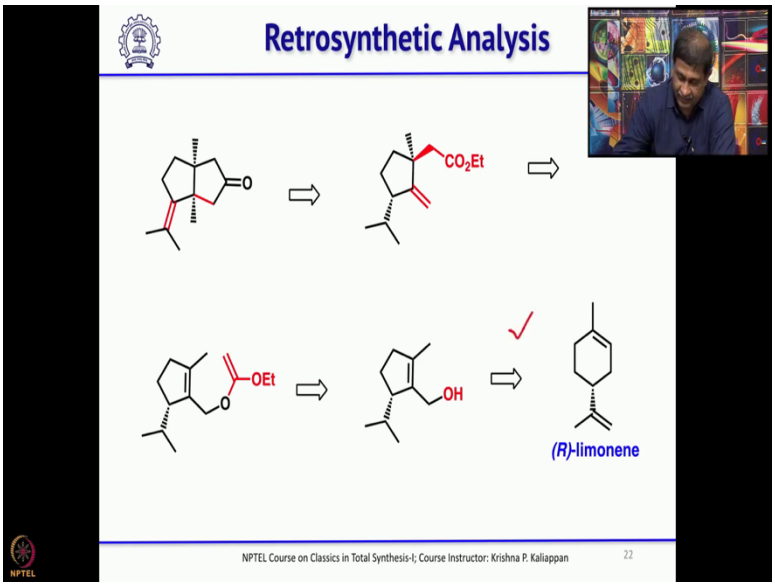

And this can be obtained from the corresponding ketone, ok. And this is where the first key step that is intramolecular diazo ketone addition to the double bond to get a cyclopropane and the opening of cyclopropane gives a five membered ring. And this can be obtained from the second key reaction that is Johnson's orthoester Claisen rearrangement that can be obtained from this alcohol which in turn can be obtained from limonene and this process is smooth ok, this process is smooth. Let us see how he accomplished this.

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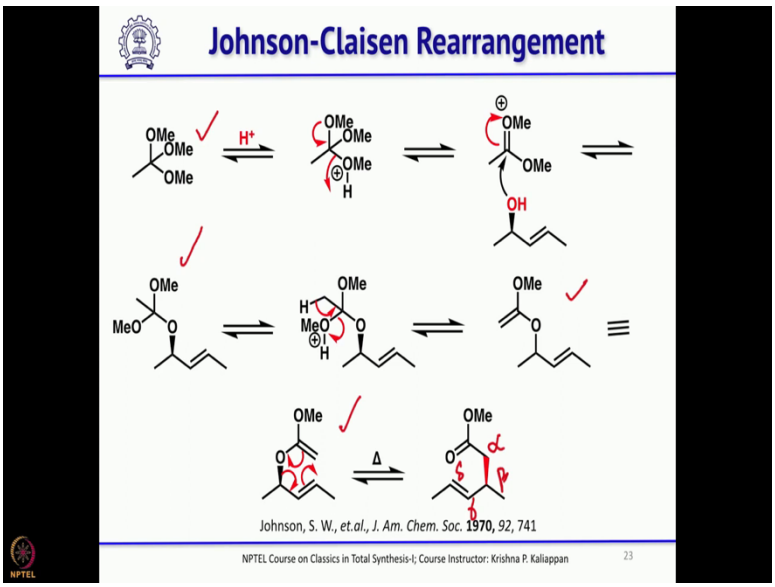

Before that, I just briefly describe the mechanism of Johnson's orthoester Claisen rearrangement. So, you can take trialkyl orthoacetate. So, for example if you take trimethyl orthoacetate if you treat with acid; one of the methoxy group will be protonated and the lone pair on one of the oxygen of methoxy group will push the methanol out. So, you generate an oxonium ion and the allylic alcohol, ok.

So, allylic alcohol normally is required for the Claisen rearrangement will intermolecularly attack this carbonyl carbon to form this intermediate. So, this again it will undergo loss of another methanol under acidic condition to give this 1, 5-diene and that can be redrawn like this and that will undergo 3,3-sigmatropic rearrangement which is nothing but Claisen rearrangement to give this alpha beta gamma delta gamma delta unsaturated ester as you know. Claisen rearrangement will give gamma delta unsaturated ester, gamma delta unsaturated aldehyde, gamma delta unsaturated carboxylic acid, ok.

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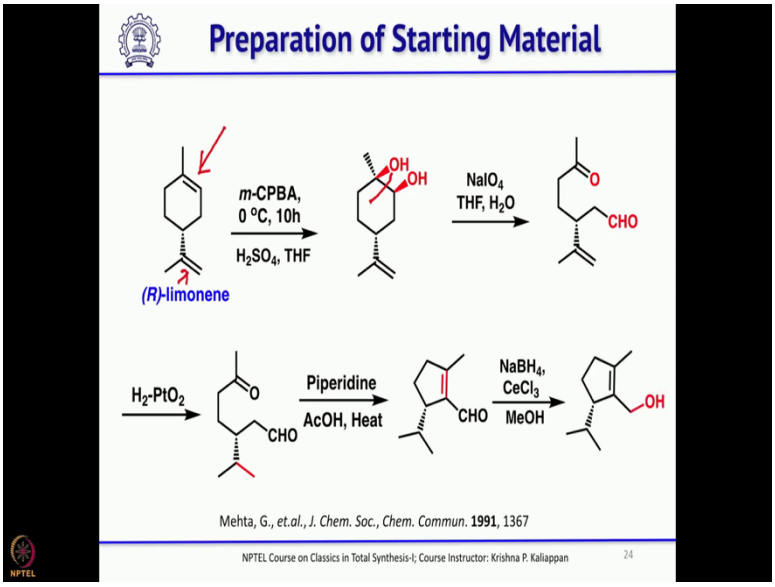

So, that is the key step and let us see how he prepared the starting material, he started with limonene and selective dihydroxylation of this trisubstituted double bond, ok. So, you have two double bonds one trisubstituted other one is 1,1-disubstituted. So, the trisubstituted double bond was epoxidized and then opened with sulfuric acid dilute sulfuric acid to get the corresponding diol and that was cleaved with sodium periodide to get the keto aldehyde because, if you cleave this you get the corresponding ketaldehyde then, reduce the double bond.

So, to get the isopropyl group and followed by intramolecular aldol reaction will give you the five membered ring with aldehyde. Then, simple reduction of the aldehyde with sodium borohydride and cerium chloride that is called Luche reduction that gives the corresponding allylic alcohol.

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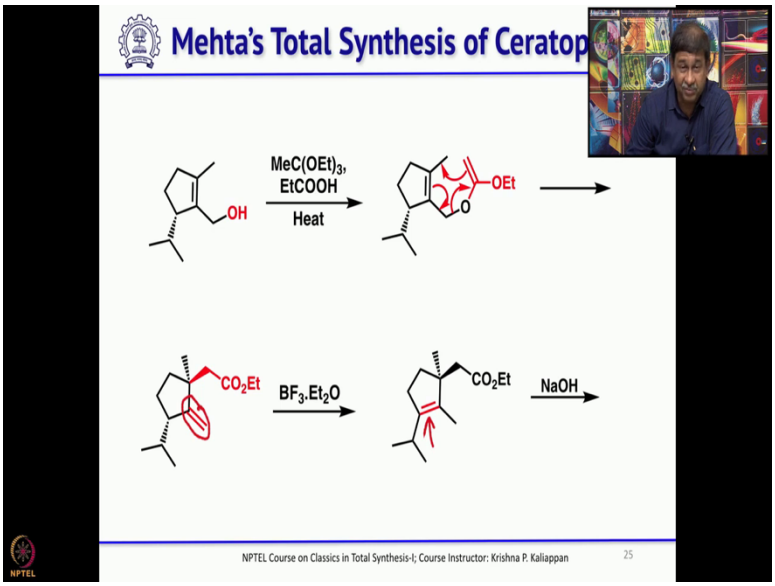

This allylic alcohol upon Claisen rearrangement will give you the corresponding gamma delta unsaturated ester, ok. This gamma delta unsaturated ester can be hydrolyzed to the corresponding carboxylic acid. Before that, as I said you do not want the double bond here. The double bond should go inside so, that the diazoketone can be added to this double bond. So, the migration of the double bond to internal double bond was done under acidic condition that is Lewis acidic condition.

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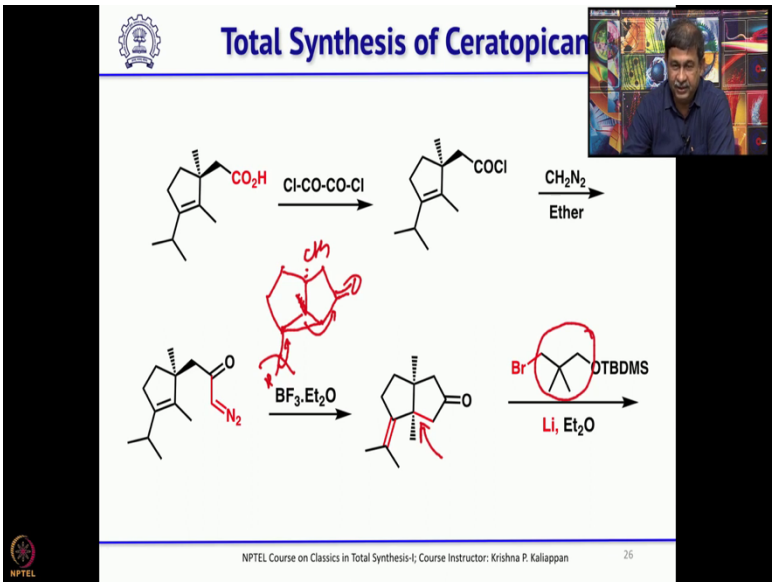

Now, hydrolyze the ester to carboxylic acid and that carboxylic acid upon treatment with oxalyl chloride, you get the corresponding acid chloride this upon treatment with diazo methane, you get the corresponding diazo ketone. This diazo ketone then on treatment with $BF_3.Et_2O$ undergoes three steps in one part. The first step is the formation of cyclopropanation ok, it undergoes cyclopropanation ok; it undergoes cyclopropanation. Now, under this acidic condition the cyclopropane opens so, you get this compound, ok.

So, in this particular step you can see, first the diazo compound form the cyclopropane and then it opened and in the process a quaternary carbon is fixed. Stereo chemically quaternary carbon is fixed and also formed a five membered ring. Then, this 5 carbon unit was added the bromine lithium exchange was done by treating with lithium and it was added to the ketone to get the alcohol.

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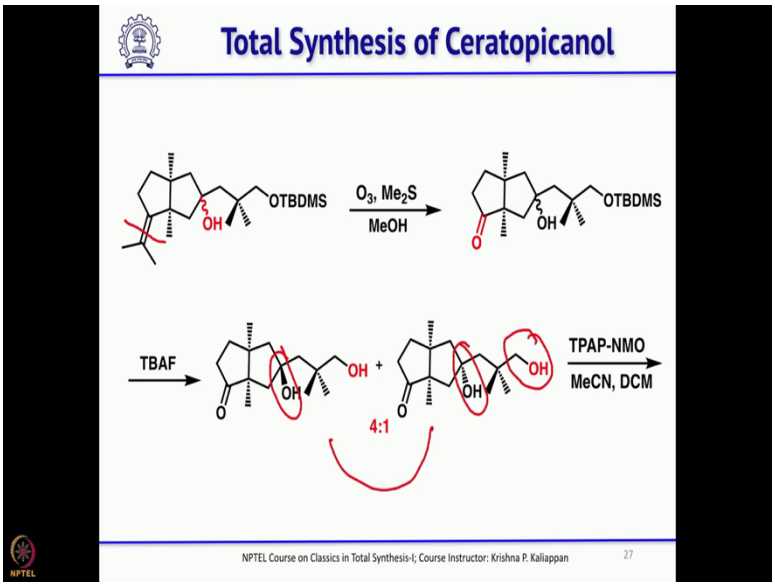

Now, removal of the TBS will give the primary alcohol and that primary alcohol can be oxidized and then cyclize, but you do not need this, you need a ketone is not it. So, do a ozonolysis, you get a ketone then, remove the TBS group; when you remove the TBS group that pull at that time one can separate these two ok. You can see a beta alcohol and alpha alcohol one can separate these two.

Now, if you treat with TPAP that is tetra N-propylammonium perruthenate NMO is a co-oxidant and use catalytic amount of TPAP. So, that will oxidize the primary alcohol to aldehyde and immediately the tertiary alcohol will cyclize to form the lactol and further oxidation gives the corresponding lactone, ok.

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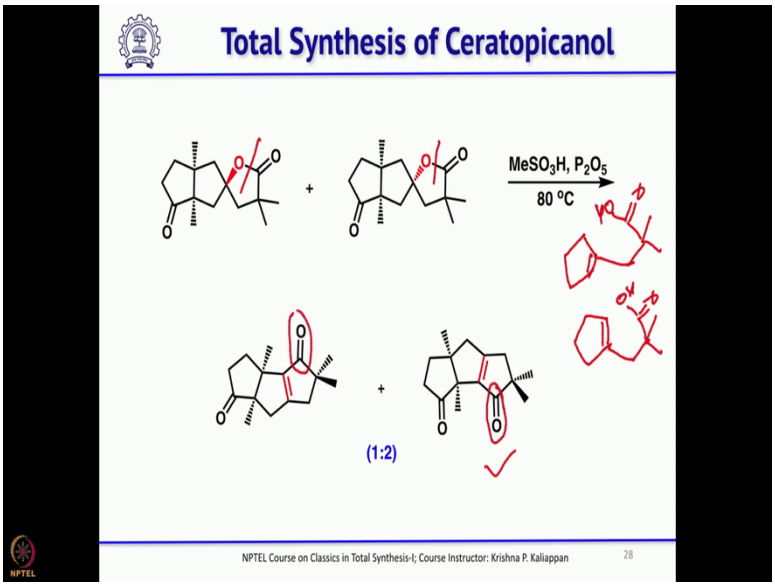

So once you have this lactone, this on treatment with methane sulfonic acid and P_2O_5. So, what will happen? It will hydrolyze and you will get a corresponding you can see either this double bond or both will undergo intramolecular Friedel Craft's like cyclization to give these two triquinanes ok, they can the only difference is the location of the carbonyl group, ok.

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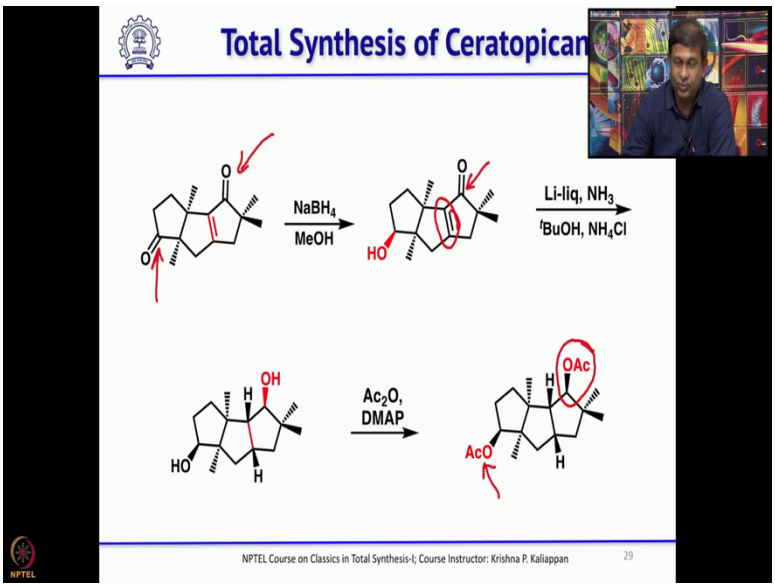

Take the required one reduce with sodium borohydride methanol so, this is enone and this is simple cyclopentanone one can reduce the cyclopentanone to get the alcohol and

now you treat with lithium and liquid ammonia. So, what will happen lithium in liquid ammonia? The double bond will be reduced and this carbonyl group also will be reduced? So, you get a diol. This diol upon treatment with the acetic anhydride you get the corresponding diacetate then, he uses the last key reaction where in one step he removes this acetate completely, but hydrolyses only the acetate to get alcohol, how did he do, he did with sodium in HMPA.

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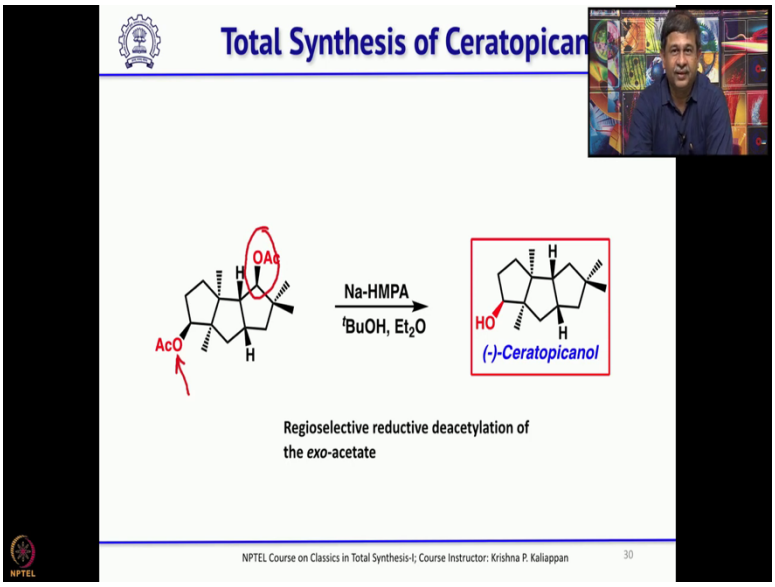

So, this is a highly regioselective reductive deacetylation. So, the reductive deacetylation takes place here, but at the same time this hydrolyzes only the acetate to give the natural product that is ceratopicanol.

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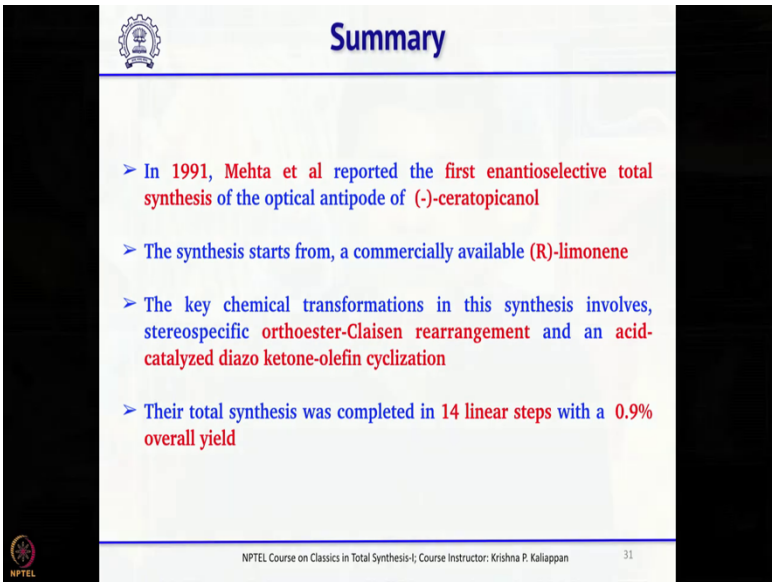

So to summarize, if you look at this total synthesis he started with commercially available R-limonene a monoterpene and then in few steps he could convert that limonene into five membered ring. And then, he used two key reactions- one is orthoester-Claisen rearrangement, then acid catalyzed diazo ketone olefin cyclization to form a cyclopropane followed by opening of the cyclopropane to construct the second five membered ring.

And then third five membered ring was constructed using acid catalysed cyclization. Overall he took 14 steps to complete the total synthesis and close to 1 percent overall yield he could successfully complete the synthesis. So, we will have one more lecture on synthesis of triquinanes we have already discussed many synthesis of triquinane because, if you look at the synthesis of triquinanes there are many ways one can make a five membered ring. So in the next lecture, we will talk about few more methods and then one more total synthesis and complete the total synthesis of triquinanes.