Classics in Total Synthesis - I
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Lecture - 17
Triquinanes

Good morning and welcome back to our NPTEL lecture series on Classics in Total Synthesis part 1. So, we have been discussing total synthesis of Triquinanes and in the last week we talked about total synthesis of Triquinanes using photochemical reaction. For example, Paterno Buchi reaction as a key reaction to form Triquinanes reported by Viresh Rawal's group.

So, we will continue our discussion on total synthesis of Triquinanes where photochemical reactions have been used as the key reaction ok. So, today we will talk about maybe 4 or 5 total synthesis.

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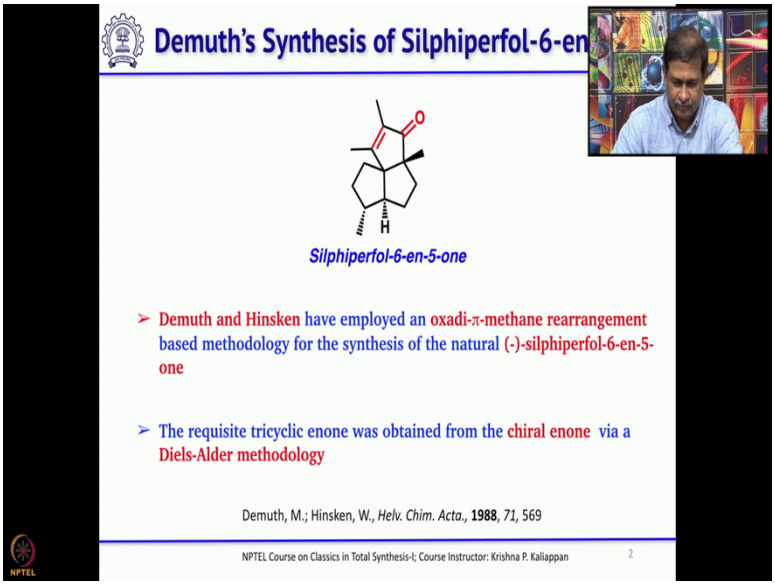

And the first one which we will discuss is the total synthesis of Silphiperfol-6-en-5-one and this synthesis particular synthesis was reported by Demuth and Hinsken and interestingly what they have used is oxadi-pi-methane rearrangement induced by photochemical condition.

And overall if you look at the whole synthesis though the number of steps are little bit more the strategy of using oxadi-pi-methane rearrangement to get the Triquinane is a unique one. And the starting material that is the diene which is required for the asymmetric Diels Alder reaction was started from chiral enone which we will discuss.

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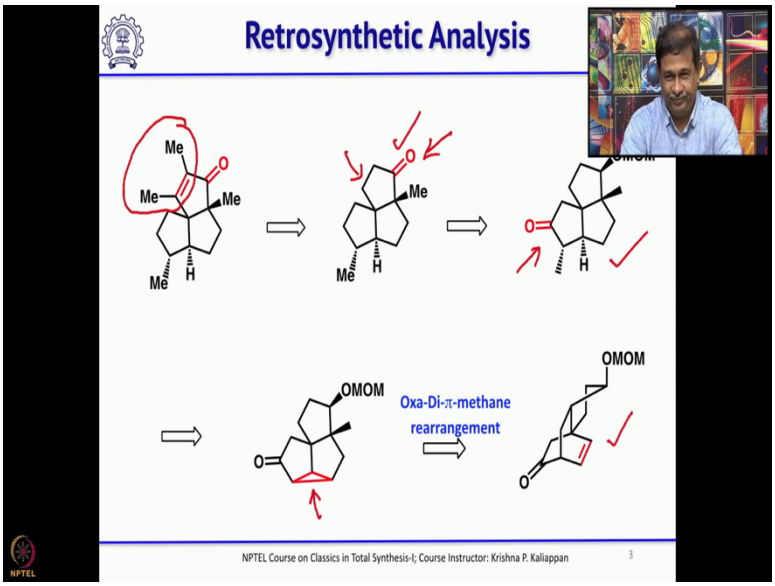

From the retrosynthetic point of view, this natural product can be obtained from this particular compound, you can see what one has to do is 2 methyl groups as well as the double bond should be introduced that can be done by first introducing a double bond here, then you add a methyl group followed by quench with methyl iodide then introduce a double bond.

So, one can do it in 3 to 4 steps and this ketone can be obtained from another ketone and why this ketone was introduced, you will know that is because for the photochemical oxadi-pi-methane rearrangement this ketone is required and before that this ketone should be reduced and protected. And this particular ketone can be obtained from this tetracyclic compound ok.

See now you can see a cyclopropane ok, so this is formed through the oxadi-pi-methane rearrangement and reductive opening of this cyclopropane followed by quenching with methyl iodide you will get this intermediate ok and the key reaction here is the oxadi-pi-methane rearrangement of this tricyclic compound.

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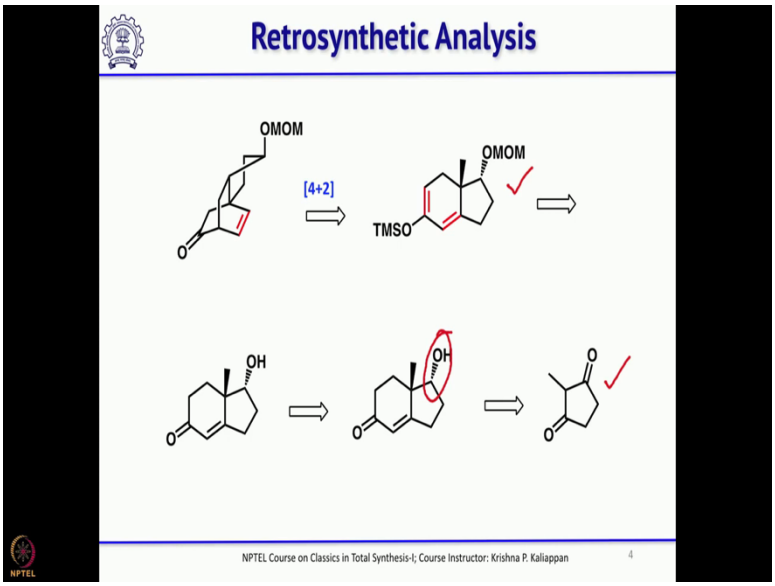

And when you look at this tricyclic compound as you know it can be obtained from a 4 plus 2 cycloaddition reaction, where in this is the diene ok. This diene can be obtained from a commercially available compound as well as one can make this in large quantity from Hajos Parrish ketone.

And that is nothing but if you have this instead of alcohol if you have ketone that is Hajos Parrish ketone and that can be obtained from 2-methyl cyclopentane-1, 3-dione using L-Proline as the catalyst. One can do a Michael addition followed by Aldol reaction which we normally call it as a Robinson annulation sequence ok.

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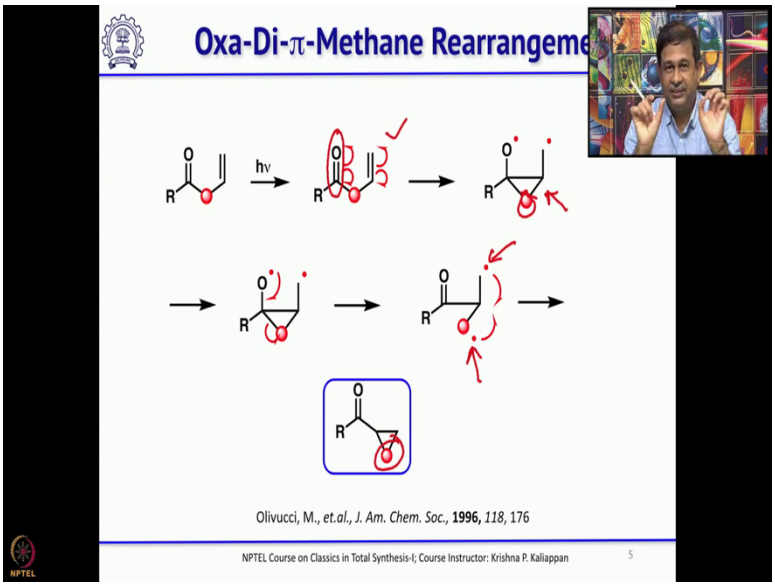

So, the starting material for this is 2-methyl cyclopentane-1, 3-dione which is commercially available. So, before we go into the details of the total synthesis reported by Martin Demuth, we will discuss the key reaction which is Oxa-Di-pi-Methane rearrangement. So, what is that? So, if you have a system like this that is you know you can call it as allyl ketone. Now under photochemical condition first this carbonyl will form a diradical same thing will happen with the double bond.

So, that can lead to the formation of this type of cyclopropane assume that this is CH_2 ok. So, this diradical what will happen next it will open up. So, how it will open up? So, they will open up like this and it will lead to the formation of original ketone, ketone we started with you will get the ketone back as well the resultant diradical.

Now you can see here this is radical this is a radical they will combine to form the cyclopropane assume that this is CH_2 ok. So, basically if you do an Oxa-Di-pi-methane rearrangement you can see the formation of cyclopropane ok.

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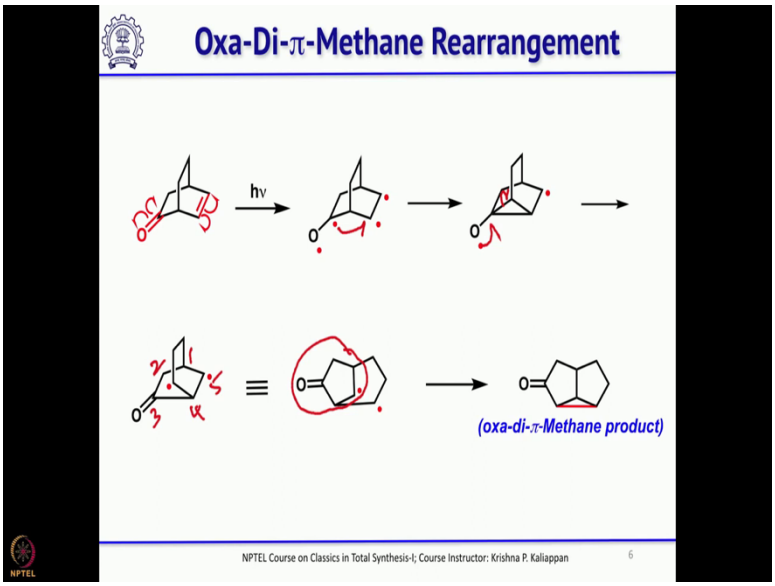

And this one can do on bicyclic system, tri cyclic system and here is an example where you where you have a bicyclic system. So, that will give like this tetra radical and then what will happen this tetra radical immediately you can see it will form a cyclopropane ok.

Then this radical on the oxygen will come back and then open this cyclopropane to give this bicyclic diradical, this bicyclic diradical one can easily redraw like this ok. You can see here this is 1 this is 2 this is 4 this is 5, so that is a 5-membered ring and the remaining is 6 membered ring. Now these 2 diradical will combine to form the tri-cyclic compound in that the third ring is a cyclopropane.

So, this is the Oxa-Di-pi-Methane rearranged product ok, this can be easily obtained from any bicyclic compound having a carbonyl and double bond at appropriate place.

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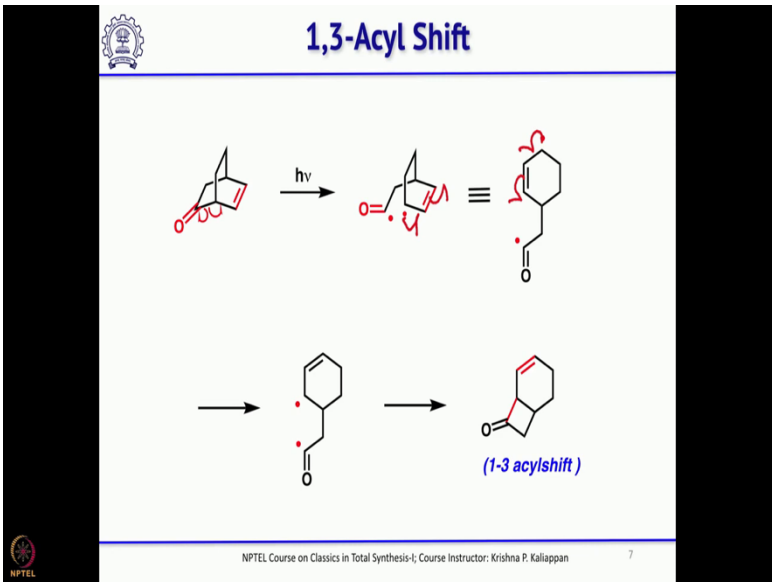

When you do that one can also expect another product which is normally minor product, that is arising out of 1-3 Acyl Shift, that is when you do a photochemical reaction on this ketone first Norrish type-I cleavage will take place. Where you have you generate this di radical followed by migration of the double bond ok. The double bond will migrate and you will get the corresponding allyl radical ok. What will happen?

Now, this will migrate or here you can write like this and these diradical will combine to form cyclobutanone ok. So, one can see using Oxa-Di-pi-Methane rearrangement you can get a cyclopropane or if you use 1-3 acylshift then you will get a cyclobutanone ok, 6 membered ring fused with cyclobutanone.

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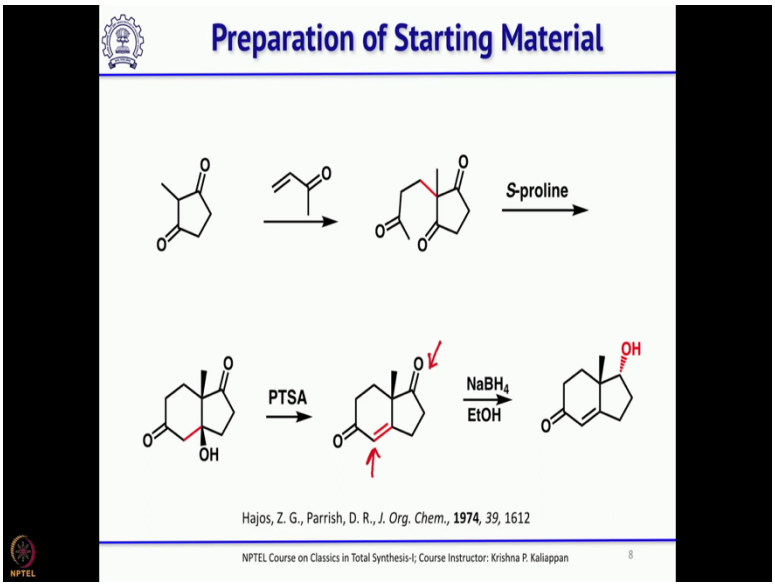

Now, let us see how Demuth synthesized this natural product, he started with 2- methyl cyclopentane 1,3-dione which we saw during the retrosynthetic analysis.

Then using the Robinson annulation sequence first Michael addition with methyl vinyl ketone followed by treatment with S-proline and dehydration you get the Hajos Parrish ketone ok. You have an enone and a ketone and the ketone can be selectively reduced with 0.25 equivalents of sodium borohydride in ethanol at 0 degrees to get this allylic or this alcohol.

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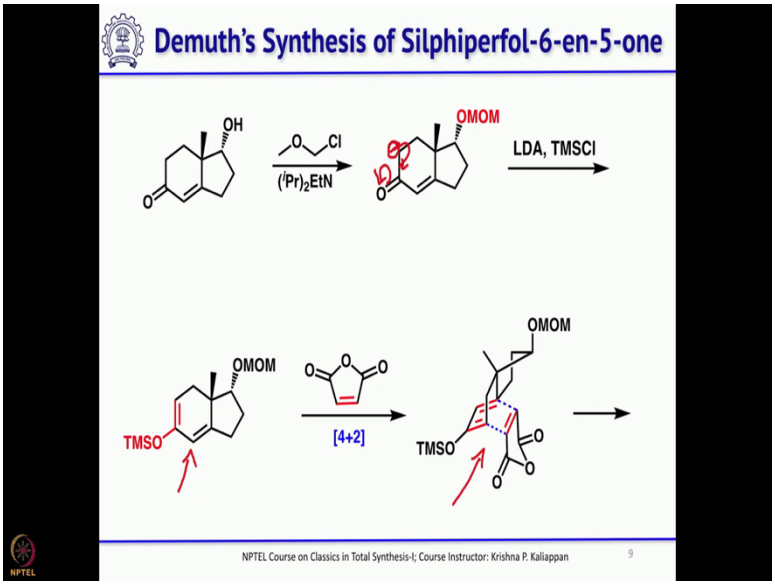

And once you have this alcohol then you can protect this alcohol as MOM ether ok and if you treat with LDA TMS chloride, if you treat with LDA TMS chloride so it will generate anion here and then it will form an enolate; that enolate will become enol TMS and this is the diene.

Now, he did Diels Alder reaction with maleic anhydride to form this tetracyclic compound ok. So, this is the intermediate and this intermediate you can see this is a transient state ok this is a transient state and this gives this tetracyclic compound.

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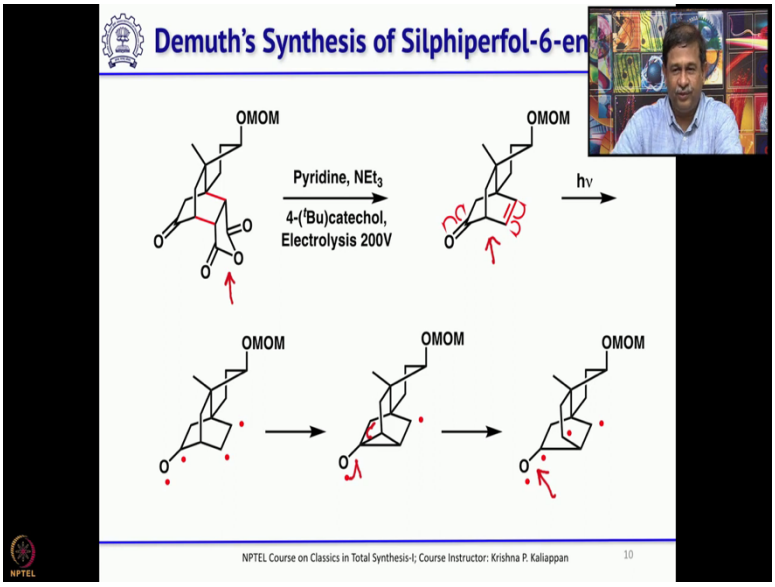

Now this anhydride if you look at this anhydride should be converted into double bond. So, he used a electrolysis method hydrolysis followed by di-decarboxylation to give the double bond and this is the key precursor for the Oxa-Di-pi-Methane rearrangement.

So, taking this compound and then shine light it undergoes Oxa-Di-pi-Methane rearrangement and as I mentioned earlier about how Oxa-Di-pi-Methane rearrangement takes place first it will form this tetra radical and followed by formation of the cyclo propane and opening of this 3 membered ring you will get another di radical and whereas, this will be a carbonyl group.

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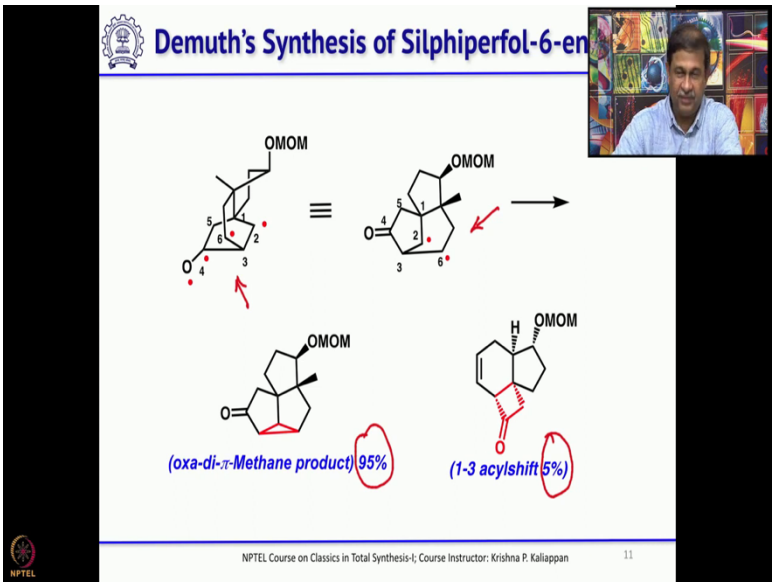

And once you have this di radical and you can number it you know for better understanding, always better you number the starting material ok you give numbering. So, the 6 membered ring you can give numbering and then see where the radicals are in the starting material and when you redraw the structure for better understanding you can give the number and then you can easily make out where these two radicals are; once these two radicals you can write and that will form the corresponding cyclopropane.

As I said there is a possibility of forming 1,3 acylshift also, of course the yield is only 5 present and the main product is only the required one that is a cyclopropane formation.

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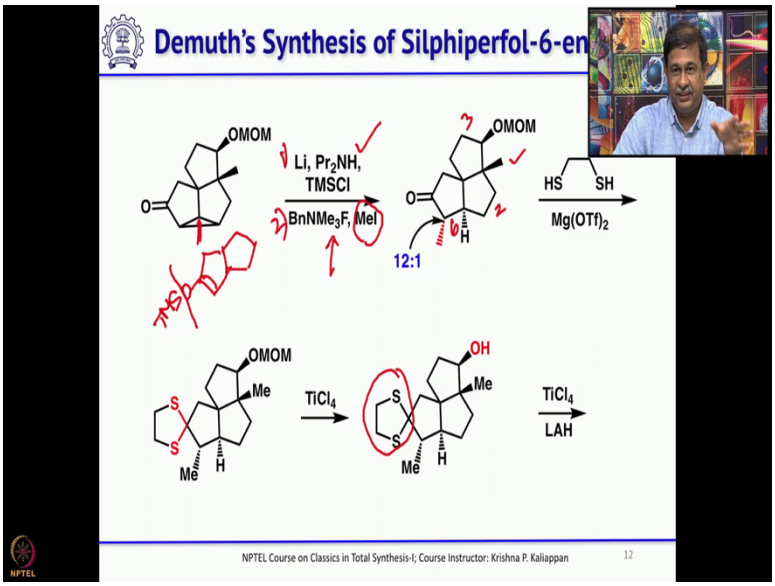

So, this tetra cyclic compound next he reductively opened ok, so lithium tri di isopropyl amine and TMS chloride. So, what happens? This will be cleaved the cyclopropane will be cleaved and then it will form it will form the corresponding enol TMS ok this will form the corresponding enol TMS, because you are using lithium diisopropyl amine and quenching with TMS chloride because that enolate once it is generated you trap that enolate with the corresponding TMS chloride.

Once we have that, that is the first step and the second step the enol TMS ether can be cleaved with any fluoride source. So, that is what they have done they have done with this benzyl tri methyl ammonium fluoride to cleave the enol TMS to generate the O minus and that O minus you quench with methyl iodide ok you quench with methyl iodide you stereo selectively introduce the methyl group ok.

So, now if you count the number of carbon atoms you will see here in this ring you have 6 here you have 2, 8 and then here you have 3 and then here you have 1 ok. Next step is to remove the carbonyl group, so you do not want the carbonyl group ok. This can be done in many ways, but what they have done is they have protected the ketone as dithiane derivative ok.

Then you remove the mom group ok, you remove the mom group using titanium tetrachloride you get the hydroxyl group at this point you can remove the dithiane using

a combination of titanium tetrachloride Lewis acid and a reducing agent. So, they use titanium tetrachloride and lithium aluminium hydride to get the corresponding CH_2.

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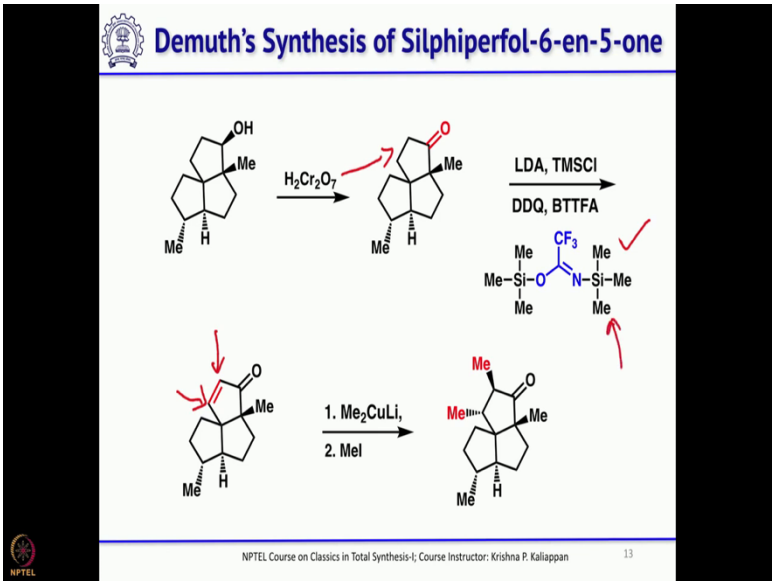

So, the deoxygenation of carbonyl group was done in 2 steps, first you protect with dithiane then remove that with titanium tetrachloride and LAH. Now what you need to do? You have to oxidize the alcohol to ketone ok, then you have to introduce the 2 methyl groups and then double bond.

So, here you use some expensive reagent. So, first he treated with LDA TMS chloride which you know it will form the corresponding enol TMS, then for introducing the double bond he used DDQ and this exotic reagent which looks like exotic reagent, but it is not it is a reagent derived from tri fluoro acetamide ok. Take tri fluoro acetamide and then you treat with tri methyl silyl chloride you get this.

So, this is the reagent you know you can get a double bond or you can introduce a double bond next to the ketone. Next you have to introduce two more methyl groups one here and one here, but at the same time the double bond should be kept intact. So, how it can be done? First you add the one four addition on the double bond with lithium dimethyl cuprate and quench the enolate with methyl iodide to get the two methyl groups and then repeat the same process repeat the same process.

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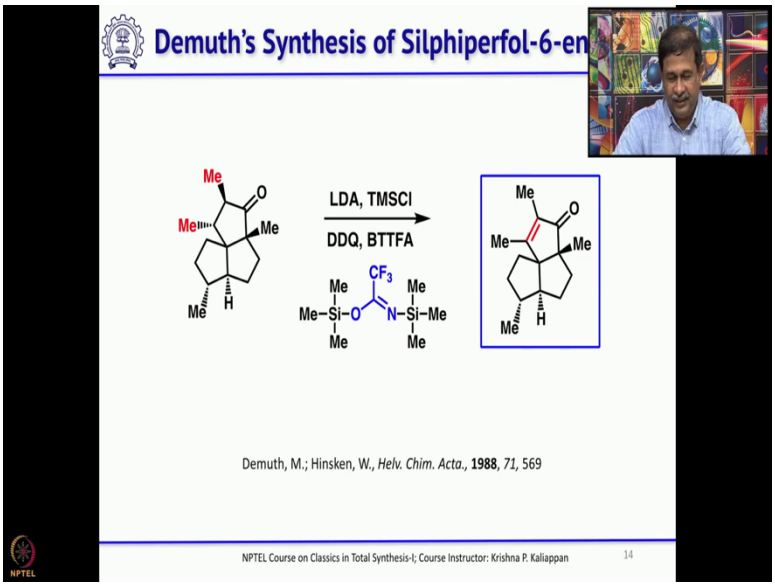

So, that is you introduce a double bond via enol TMS followed by oxidation to get the actual product ok.

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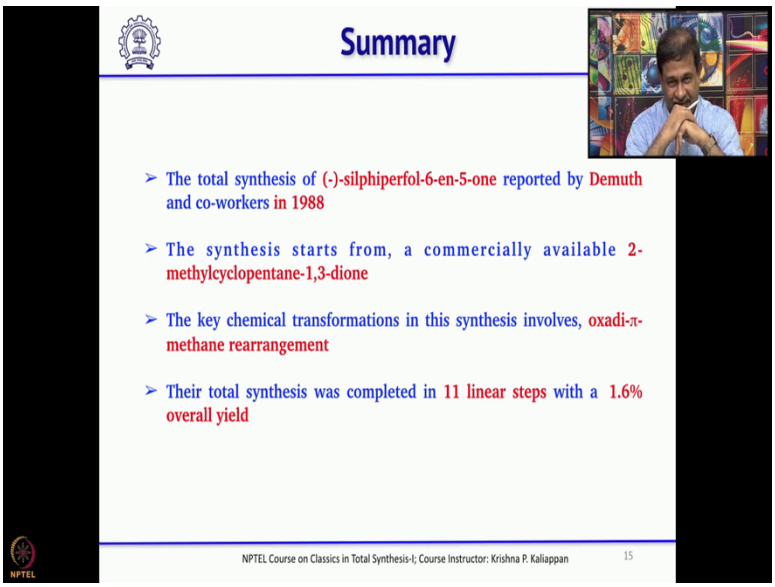

So, that way if you look at this synthesis the key step in the synthesis was the Oxa-Di-pi-methane rearrangement and they started from commercially available 2 methyl cyclo pentane 1, 3 dione and then they used Robinson annulation as a key step to make the next starting material that is Hajos Parrish ketone. And overall this total synthesis was accomplished in 11 longest linear steps with an overall yield of 1.6 percent yield.

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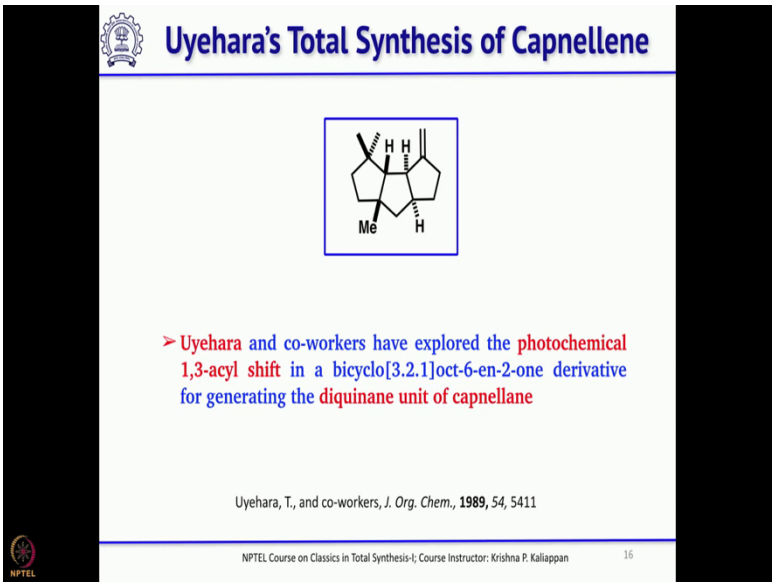

So, now we will move to another very short total synthesis reported by Uyehara ok. Here again as I said we will be discussing only the photochemical reaction which has been used as the key reaction in the synthesis of Triquinanes and what he has used in this particular synthesis is photochemical 1, 3 acyl shift.

The earlier synthesis which we saw were Oxa-Di-pi-methane rearrangement as the key reaction and there also he got 1, 3 acylshift product as a minor product. In this particular case Uyehara has used photochemical 1, 3 acyl shift as the key step and that is the main reaction to get the key starting material or key intermediate.

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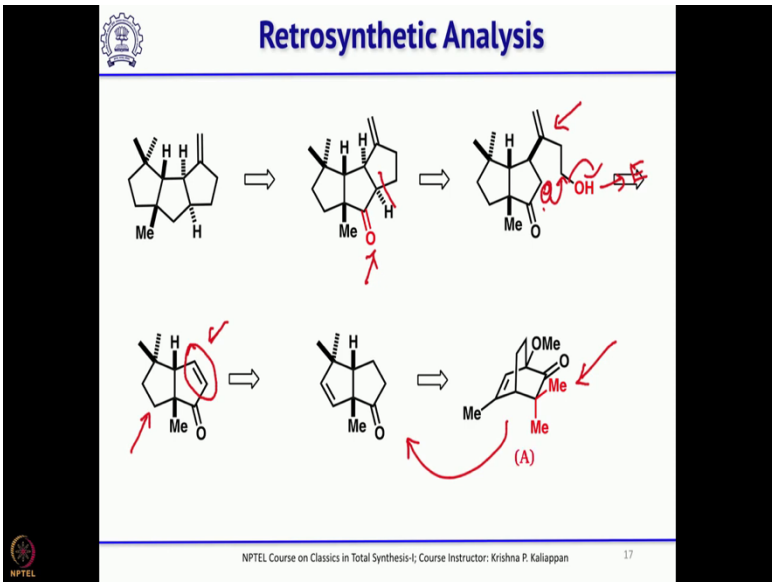

So, let us see his Retrosynthesis and when you look at this capnellene as I said whenever you have a functional group or if you do not have many functional groups you can introduce a functional group ok. So, here you have a functional group a double bond, but that may not be sufficient sometimes when you do a proper retrosynthetic analysis.

So, it is better to introduce another functional group which can facilitate the Retrosynthesis to get a simpler starting material. So, that is how what Uyehara has done he has introduced a carbonyl group at the middle ring the idea is if you introduce a carbonyl group then one can do an intramolecular alkylation ok. So, that is what he planned.

So, you can see you can if you make this as a good leaving group ok, if you make this as a good leaving group then you can generate anion and you can form the 3rd 5 membered ring is not it. So, that was the idea. So, for introducing the carbonyl group then you can introduce a double bond here, the reason for introducing the double bond is this 4-carbon unit can be added stereo selectively using a 1, 4 addition reaction.

And now if you look at this you reduce this double bond and introduce a double bond here what for that is how he can use the photochemical reaction that is 1, 3 acyl shift to get this compound.

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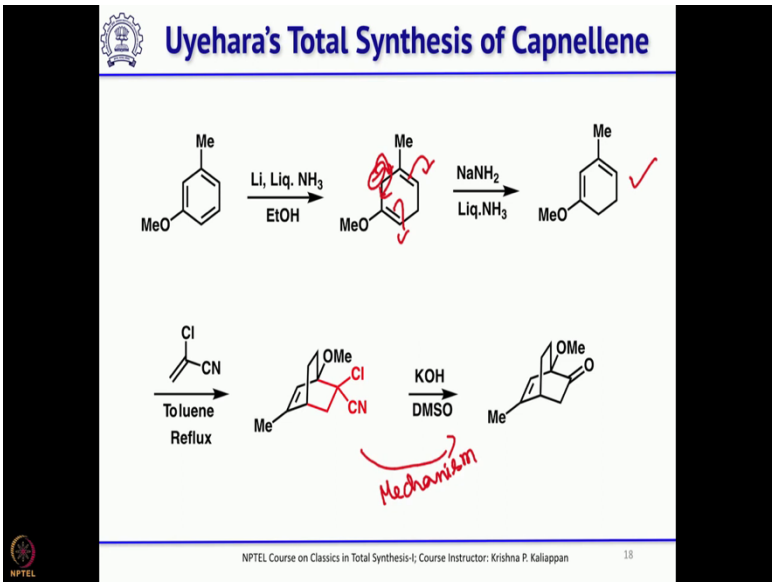

Let us see how he made this compound in the real synthesis and how from there he used the 1, 3 acylshift to get this bicyclic compound. The total synthesis start started with meta cresol methyl ether metal ammonia reduction gave the diene and you treat with sodamide, when you treat with sodamide then it will generate an anion and the migration of the double bond will take place to give this type of diene or you can this will give this type of diene, but this is the most stable diene.

So, you get this diene and this can undergo Diels Alder reaction with alpha chloro acrylonitrile, alpha chloro acrylonitrile is a synthetic equivalent for ketene ok. So, ketene normally cannot undergo 4 plus 2 cyclo addition reaction. So, that is why indirectly you have to use some equivalent which can give ketene in the product.

So, alpha chloro acrylonitrile is one of the best synthetic equivalents for ketene. So, you do the Diels Alder reaction with alpha chloro acrylonitrile. Now if you treat with potassium hydroxide and DMSO that will hydrolyse this to ketone ok try to write mechanism for this ok. So, mechanism for the hydrolysis of chloro nitro nitrile adduct to the ketone it's a very interesting mechanism.

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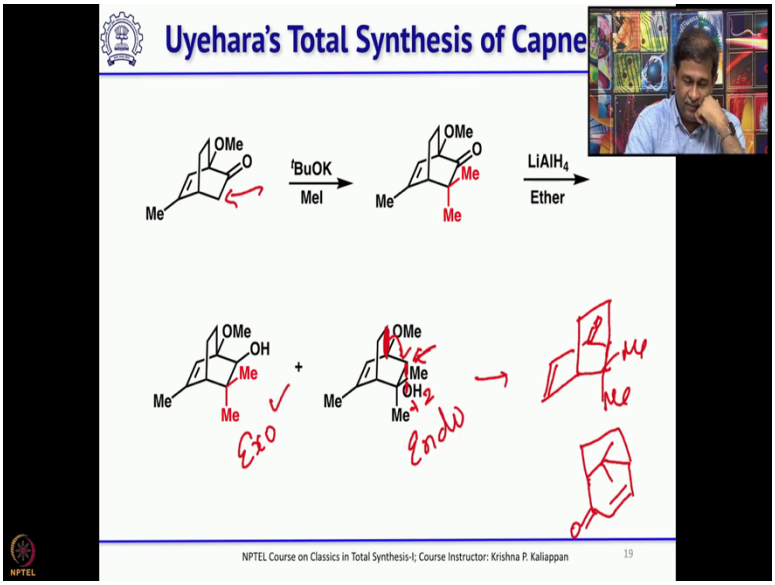

Take this bicyclic ketone and then treat with potassium tertiary butoxide, excess potassium tertiary butoxide and methyl iodide you can introduce 2 methyl groups next to the ketone ok. Then when you reduce this with sodium borohydride or lithium aluminium hydride you get a mixture of Endo and Exo alcohol. So, this is Endo and this is Exo alcohol. So, almost you get 1:1 ratio these 2 will give 2 different products upon treatment with acids.

For example if you take this Endo alcohol. So, first it will protonate the hydroxyl group and that will be a leaving group. Now the bond which is anti to the leaving group. So, this is the bond which is anti to the leaving group that is the OH bond and this is the bond which is anti to that ok that will migrate and what will you get if you use Lewis acid is ok you will get this product. So, this is nothing but if you look at you can write like this, that is because the C this C-C bond which is anti to the leaving group migrates.

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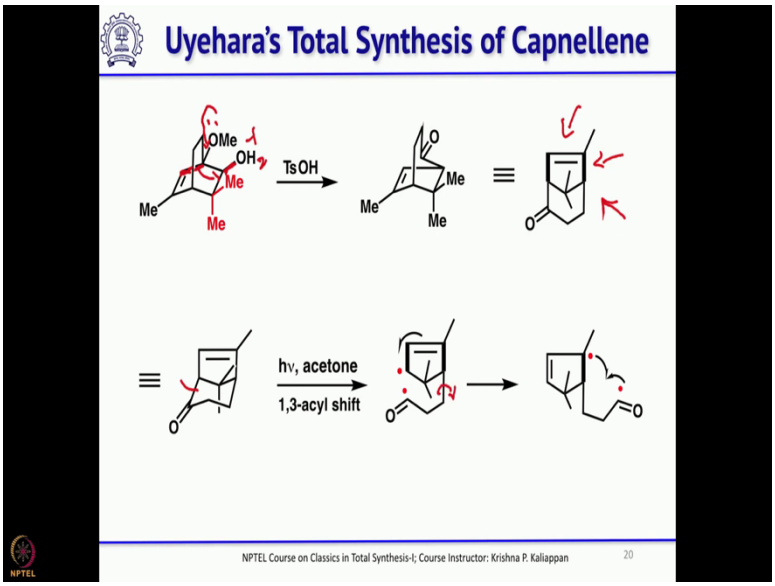

So, if you do the same thing with exo, exo alcohol now which bond is anti to that. So, this is the bond and this bond is anti to this. So, that will migrate if you treat with acid and this will migrate. So, that will give you this bicyclic ketone ok and this can be redrawn like this ok.

It is a 5-membered five-membered ring here and 6 membered ring here. So, what you have to notice in this is if you use endo alcohol you get the corresponding alpha beta unsaturated ketone. But if you use exo alcohol you get ketone and the double bond moves to the 5-membered ring other ring ok, no problem and you can also write it like this and then now you shine light.

So, what it will happen first the Norrish type-I cleavage to generate the di radical followed by migration of the double bond? Now this C-C bond can rotate is not it this C-C bond can rotate and when you rotate.

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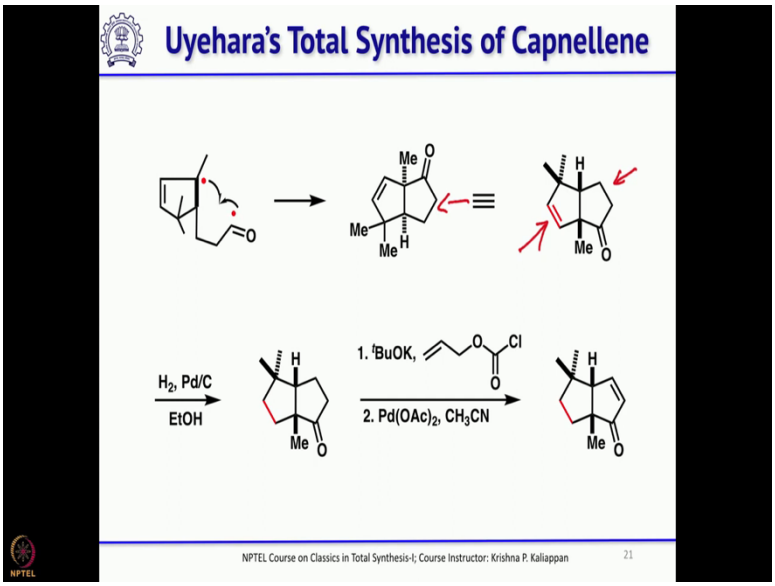

You can see this diradical this diradical will combine to form the corresponding 5-membered ring and if you rotate this by 180 degree ok you can go through this and then rotate it by 180 degree and you will get this compound ok. Hydrogenate the double bond as I said you have to shift the double bond here you do not want the double bond here you want the double bond here.

So, first you reduce the double bond then introduce the double bond. So, this is done using Tsuji Trost method, where you generate the enol, enol carbonate enol allyl carbonate and followed by treatment with palladium acetate you get the double bond. So, once you have the double bond next is to add the 4 carbon unit in a 1, 4 fashion.

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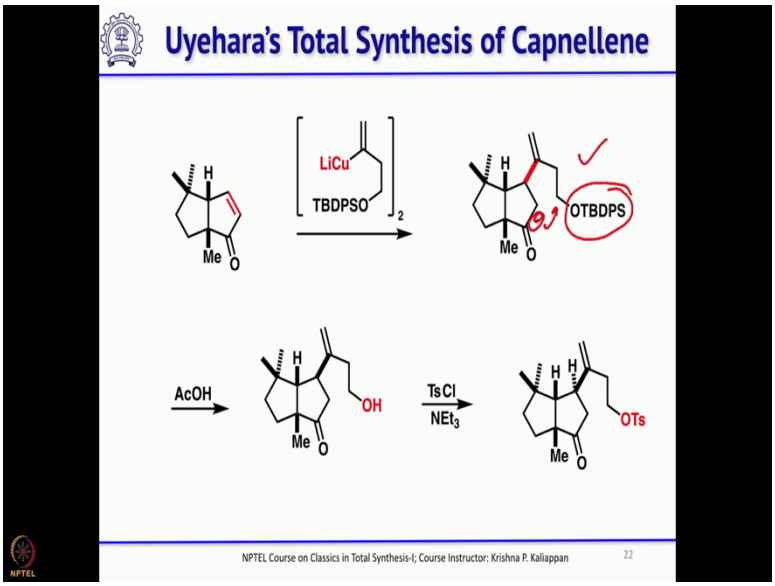

So, take this enone and add this four carbon unit you will get this product. Now as I said next you have to make this as a good leaving group generate anion and then form the third ring. So, for that you have to remove the TBDPS get the alcohol converted to good leaving group. So, TBDPS can be easily removed if you treat with acetic acid get the alcohol convert that into tosylate. So, tosylate is a good leaving group. Now you take this compound treat with lithium hexa methyl disilazide.

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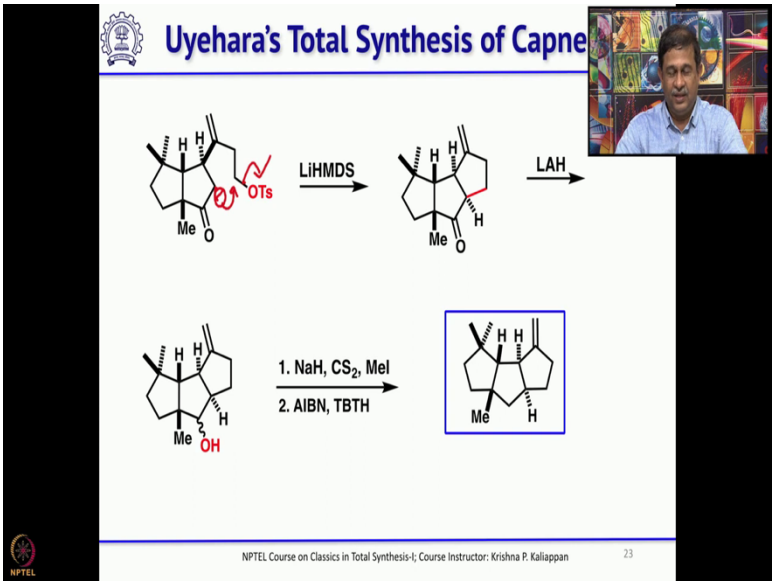

So, it will generate anion and intramolecularly attack the carbon bearing O-tosylate in a SN_2 fashion and you introduce the 3rd ring. So, what is left now is to remove the ketone. So, reduce the ketone to alcohol convert that into xanthate, sodium hydride, carbon disulphide, methyl iodide which will be converted to xanthate and the xanthate can be reductively cleaved using tributyltin hydride and AIBN.

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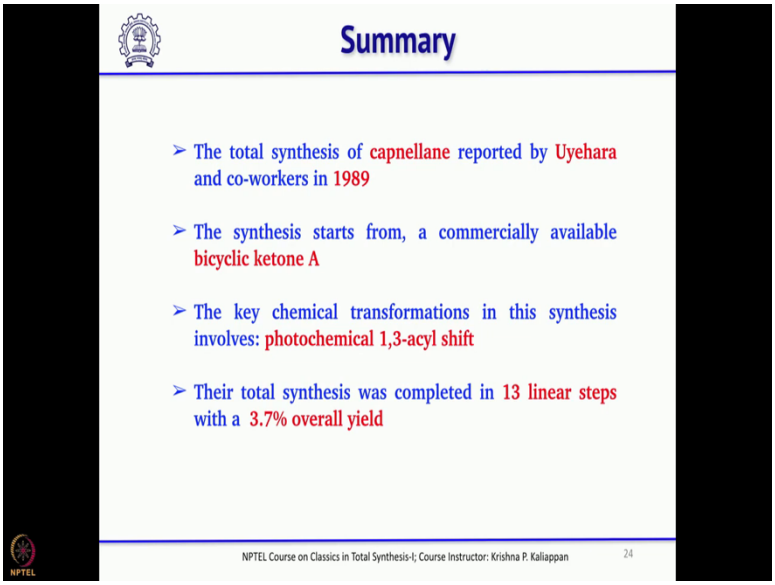

So, to summarize so if you look at the total synthesis of Uyehara and Yoshinori Yamamoto of Capnellane they started with a simple commercially available starting material that is meta cresol methyl ether. So, they did Birch reduction, conjugation, Diels Alder reaction to get the bicyclo[2.2.2] octenone.

Then the key reaction that is 1, 3 acyl shift was done under photochemical condition to get a 5 membered ring and 6 membered ring and later they do they did functional group transformation to achieve successfully the total synthesis of Capnellane. Overall they took about 13 longest linear steps; however, the overall yield is quite good about 3.7 percent yield.

So, with this we have discussed few more total synthesis based on photochemical reaction as the key reaction. We will continue our discussion on synthesis of few more Triquinanes again using photochemical reaction in the next lecture ok.

Thank you.