Classics in Total Synthesis - I
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Lecture - 16
Triquinanes by radial cyclisation: Silphiperfolene & Modhephene (Curran)

So, good morning and welcome back to the course on Classics in Total Synthesis Part-1. So, in the last lecture we talked about synthetic utility of radical cyclization in total synthesis of Triquinanes. And where we talked about synthesis of 2 linear triquinanes namely, hirsutene and capnellene; these two were reported by Dennis Curran. And today we will continue our discussion on the applications of radical cyclization to 2 more triquinanes. One is an angular triquinane, other one is an a propellane type ok.

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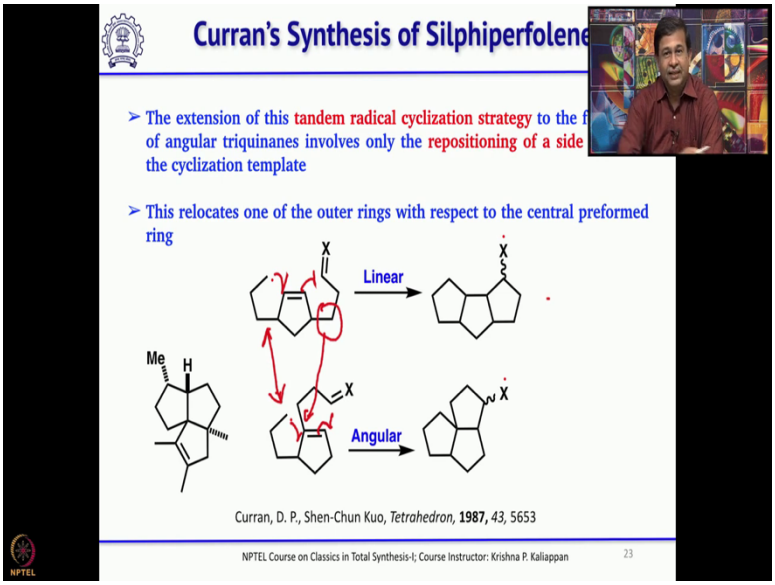

So, the first one the angular triquinane, which we will talk about today is called Silphiperfolene. So, this we already discussed via a different method. The here what Curran has done is, if you look at the linear synthesis where he has made a cyclopentene first, then he try to have an side chain he tried to have a side chain with a radical and that will undergo 2, 5 exo radical cyclization. So, for this angular triquinane again he wants to have only one 5 membered ring that is cyclopentene. Only the position of the 2 side chain differs.

So, if you look at the left hand side it remains same ok. However, this side chain comes to here ok. So, now, if you look at this carefully, the 5 exo radical cyclization on to this double bond followed by another 5 exo radical cyclization will give you the angular triquinane. So, this was the key strategy which he wanted to use in the synthesis of silphiperfolene ok.

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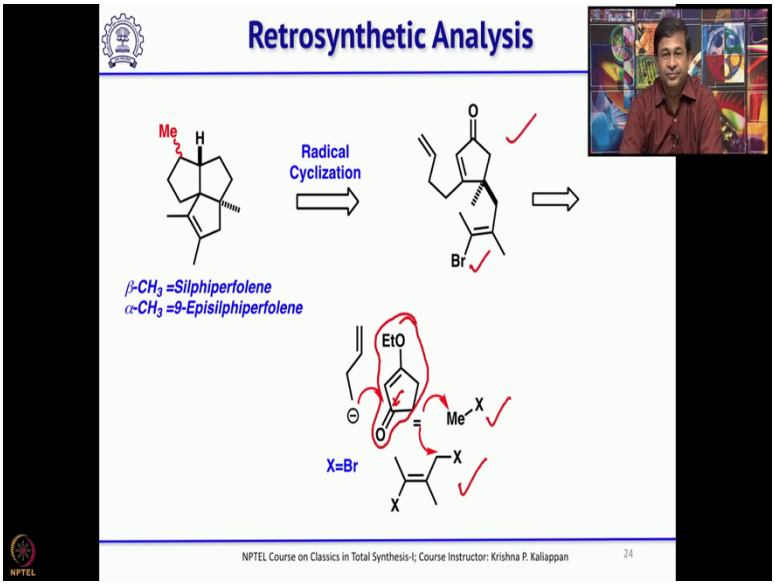

Let us see his retrosynthesis and his idea is to have this vinyl bromide. This vinyl bromide should in principle undergo 2 successive 5 exo trig radical cyclization.

Whereas in the case of capnellene and hirsutene, which are linear angular triquinanes he has used a 5 exo trig followed by 5 exo dig cyclization; here it is 2 consecutive 5 exo trig cyclization. So, this can be obtained from this particular cyclopentenone. So, if you look at this carefully, first you can do 2 alkylation ok. One is methyl, the other one with this allyl halide, substituted allyl halide. Then followed by the Grignard addition of 4 carbon unit on to this ketone and hydrolysis will give this precursor ok.

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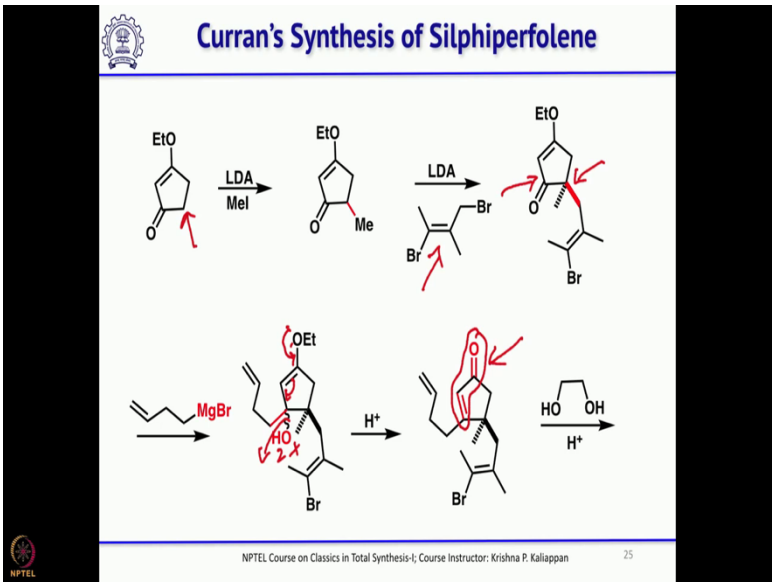

So, the synthesis actually started with 3-ethoxy cyclopentenone, which is very easy to make from cyclopentane 1, 3-dione by treatment with ethanol and HCl, one can prepare this in large quantity. Now, you do the alkylation first with methyl iodide. So, you can introduce a methyl group at alpha carbon then, again another alkylation with this substituted allyl bromide. So, you could introduce 2 alkyl groups alpha to the carbonyl ok.

Now, what you need is you need to add a Grignard reagent. So, the Grignard reagent is made from bromobutene. So, the butenyl magnesium bromide was added to this ketone in a 1, 2-fashion, to get this allylic tertiary alcohol. Now, this upon protonation ok; once you protonate, you get this positive charge. Now, the lone pair on this ethoxy group will come and then, pushes this water molecule out. So, you get the corresponding cyclo pentenone

So, this is the key precursor for the radical cyclization. So, you took this compound and one problem with this is, this is the Michael acceptor ok. If you do a radical cyclization first 5 exo trig radical cyclization will work. However, the second exo radical cyclization may not work. So, that is why it is better to protect the carbonyl group.

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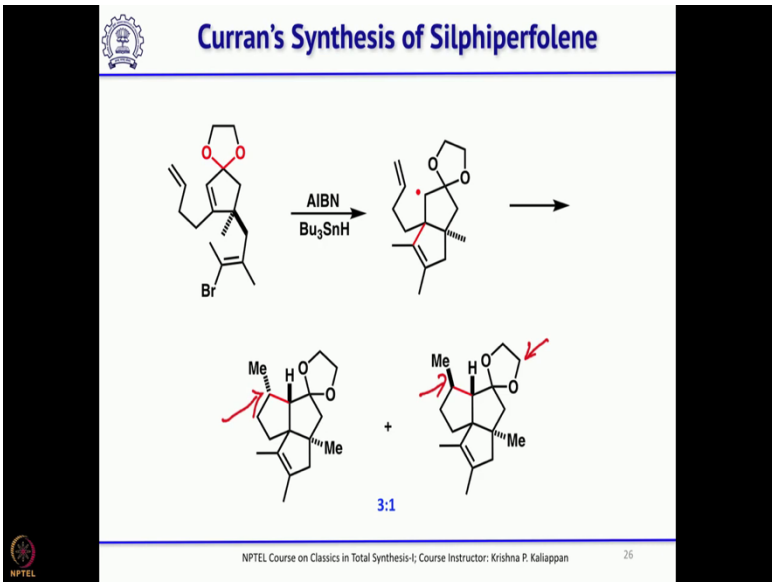

So, the carbonyl group was protected as ethylene ketal by treating with ethylene glycol and acid. So, then he carried out the key tandem radical cyclization. So, the tandem radical cyclization worked well to give a mixture of 2 diastereomers.

So, this is the required isomer, but he also got the unwanted isomer in the ratio 3:1 in favor of the required isomer ok. So, now what is required is you have to remove the ketal as well as remove the ketone.

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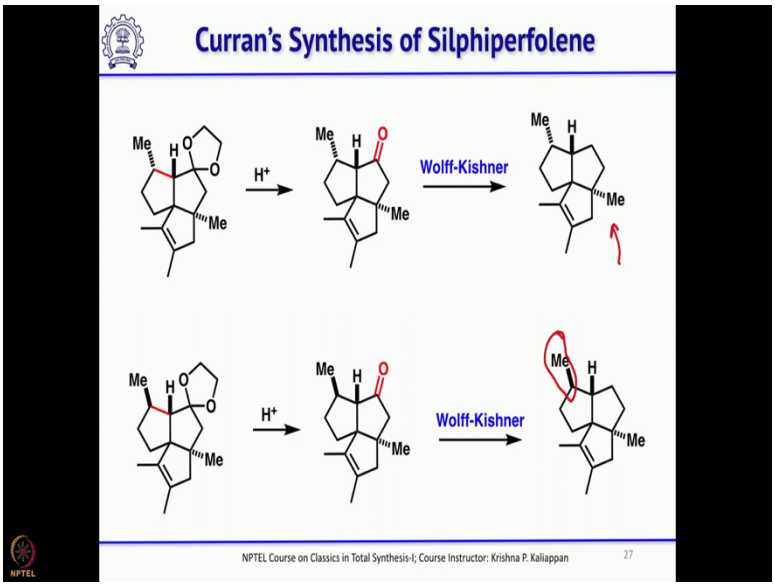

So, the ketal was removed using treatment with acid and the keto group was removed using Wolff Kishner reduction. So, that is how you could complete the total synthesis of silphiperfolene that the epimer also was you know made, where the ketal was removed and Wolff Kishner reduction gave the corresponding epi-silphiperfolene.

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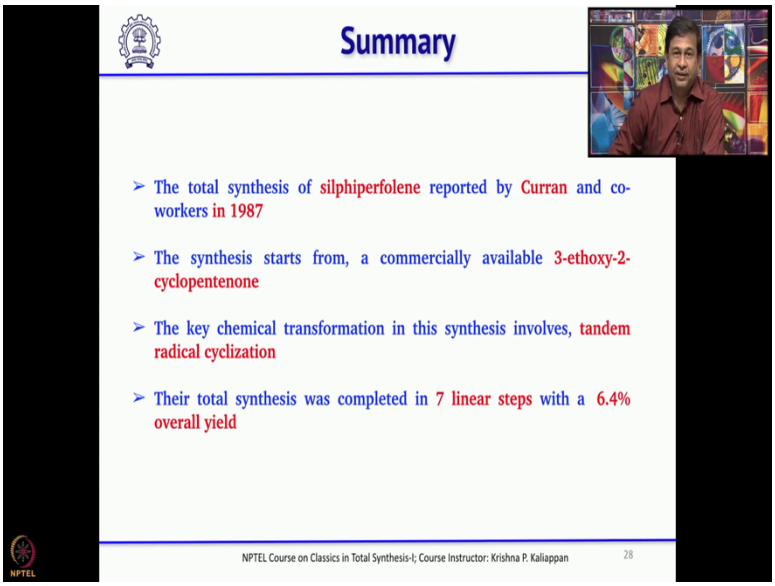

So, in summary if you look at this synthesis Dennis Curran who reported the synthesis in 1987 started with the cyclopentane-1, 3-dione and he used like in the case of hirsutene as well as in capnellene he use the tandem 5 exo trig radical cyclization to accomplish the total synthesis of silphiperfolene. Overall he took about 7 linear steps with a yield of 6.4 percent.

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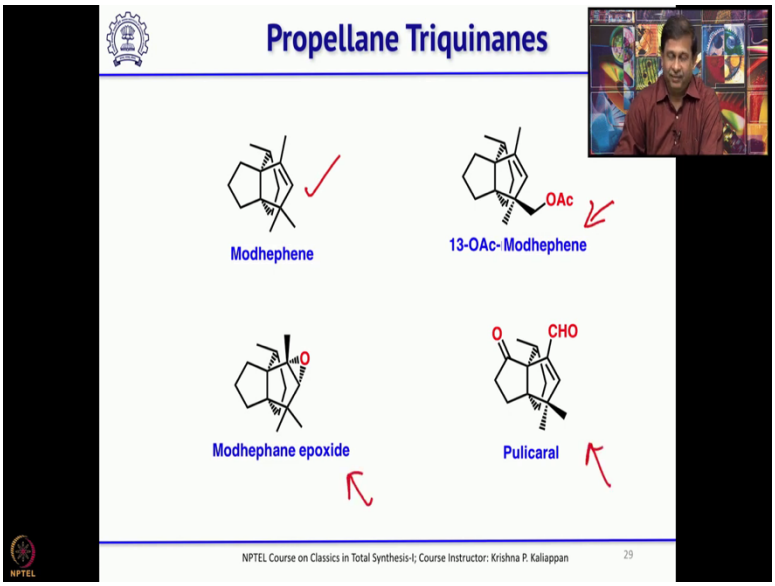

So, now from linear to angular to we will go to propellane triquinanes. How propellane triquinanes can be synthesized using radical cyclization. So, these are some of the propellane triquinanes and the basic one is called modhephene. And there are some oxygenated modhephenes, where 13-acetoxy modephene, modephene epoxide, and pulicaral.

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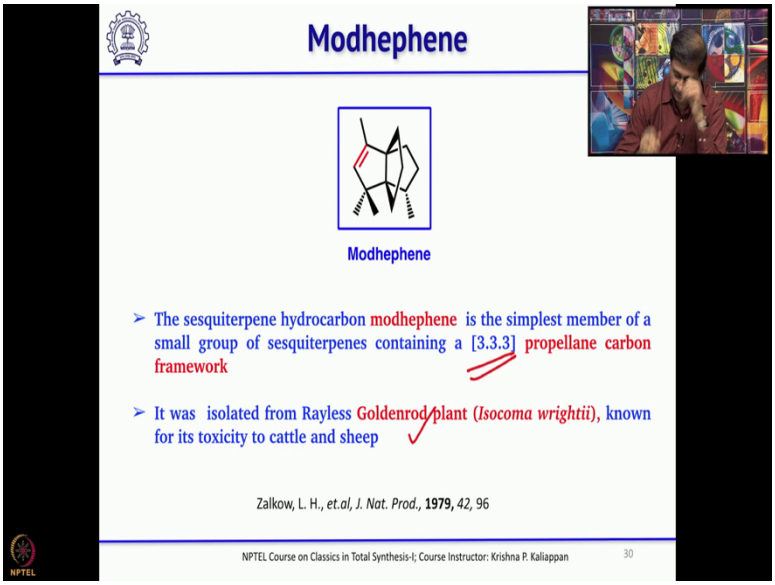

So, this modhephene first let us look at the modhephene. So, you can call this as [3.3.3] propellane system ok. 3 carbon 3 carbon 3 carbon all 3 carbon atoms are joined together

ok. So, that is why this is called [3.3.3] propellane system, and it was isolated from a golden rod plant and which was well known for its toxicity to cattle and sheep.

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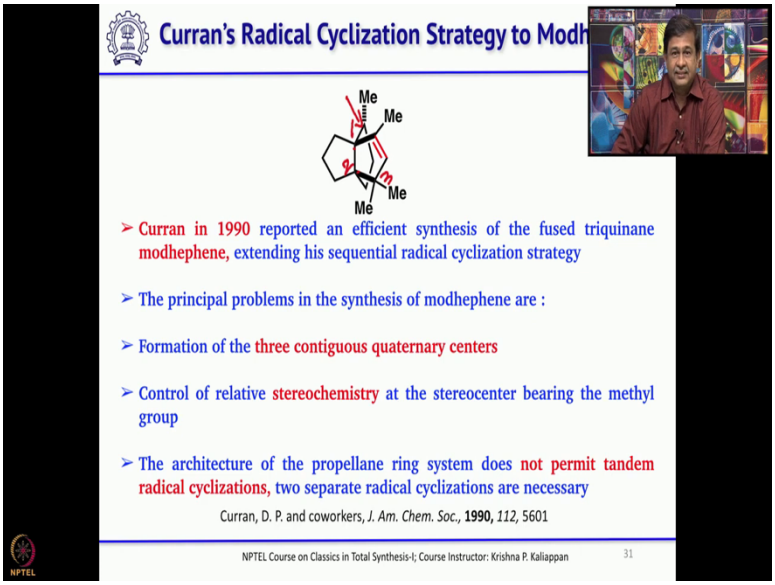

And from the synthetic point of view particularly from Dennis Curran's radical cyclization strategy point of view, he wanted to extend the same you know tandem radical cyclization. However, in this synthesis he faced quite a bit of problems - one there are three contiguous quaternary center in modhephene. 1, 2 and 3 there are three contiguous quaternary centers. So, it is not that easy to form three contiguous quaternary centers using tandem radical cyclization. This is a big challenge.

Then you also have equal number of chiral centers. 1, 2, 3 chiral centers are there ok, and particularly the chiral center with a methyl group that is not that easy to fix. And the molecular architecture of modephene is such a way that it does not allow the tandem radical cyclization to take place.

So, he has to do stepwise radical cyclization to achieve the total synthesis of modephene. So, let us see, how he achieved the total synthesis of modephene.

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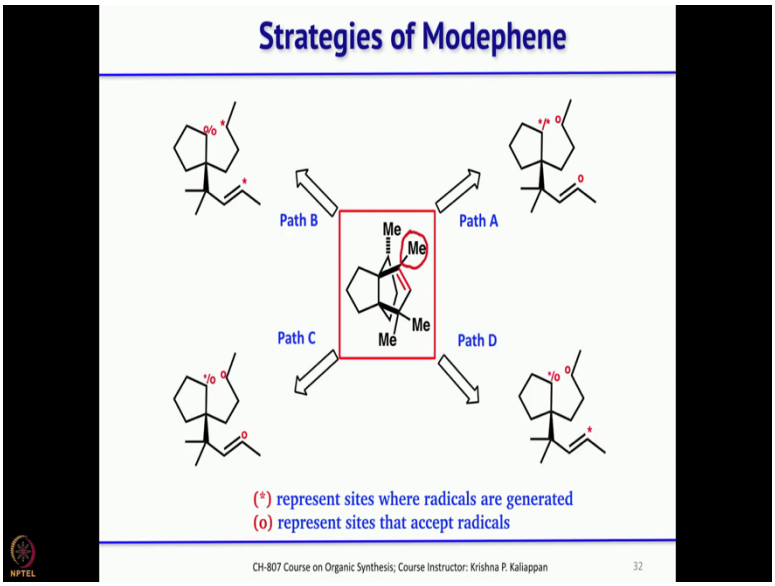

So, he thought about 4 different strategies ok. So, let us not go into the details of how these 4 different strategies he wanted to use. He wanted to make first without this methyl group.

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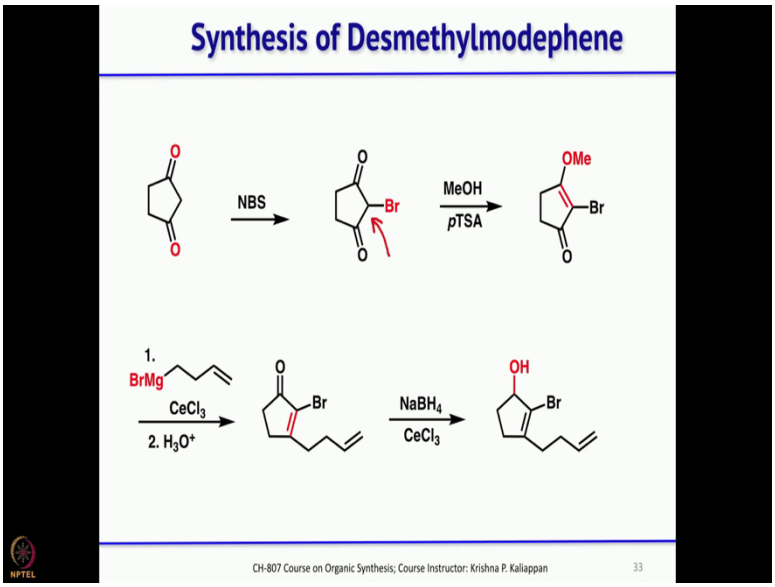

So, to check his strategy; so, that is synthesis of desmethyl modephene. So, he started with cyclohexane-1, 3-dione and then, if you treat with NBS, you can introduce the bromine at this carbon then, you treat with methanol pTSA. So, that will form the corresponding enol ether.

So, once you have this enol ether, then again you add this 4 butenyl magnesium bromide, what we have done for the synthesis of silphiperpholene followed by hydrolysis, you get the 3- homoallyl 2-bromo cyclopentenone, 3- homoallyl 2-bromo cyclopentenone. So, now, you reduce the enone with sodium borohydride cerium chloride under Luche reduction condition to get the corresponding allylic alcohol.

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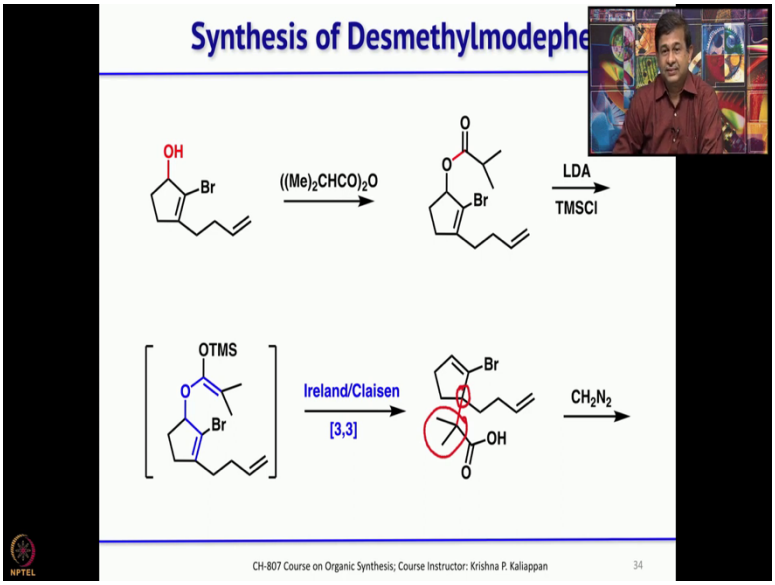

So, once you have this allylic alcohol then treat with isobutyric anhydride ok.

So, when you treat with isobutyric anhydride, it forms the corresponding ester. The idea is once you have this ester, he wanted to carry out a Claisen rearrangement, intramolecular Claisen rearrangement. So, for that he has to treat with LDA and TMS chloride, which in situ generate this enol TMS followed by Claisen rearrangement, Ireland Ester Claisen rearrangement to give this carboxylic acid ok. So, now if you see you have that dimethyl group it is a quaternary carbon, and there is another quaternary carbon.

So, 2 quaternary carbons are made, but what you need to do is to introduce the 3rd quaternary carbon followed by cyclization.

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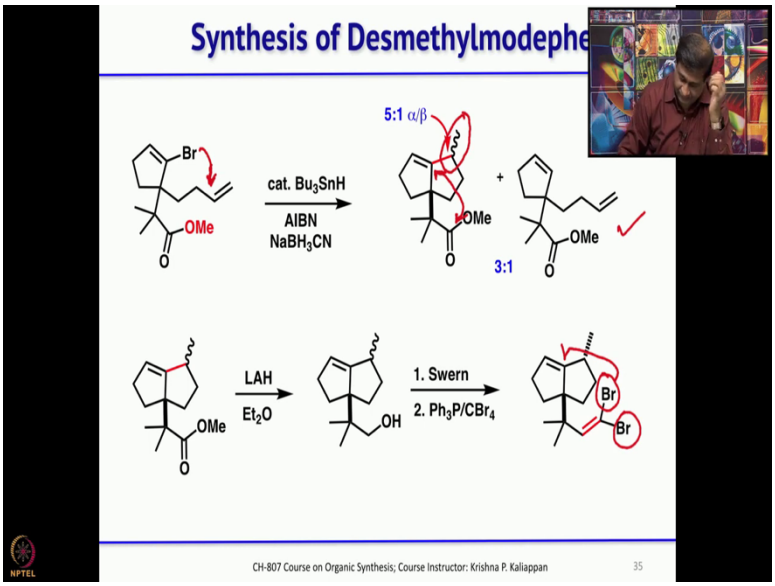

So, the carboxylic acid was esterified with diazomethane to get the corresponding ester. Then he try to cyclize this ok, using radical cyclization. You treat with tributyltin hydride and AIBN. So, here when you want to do radical cyclization, you can use stoichiometric amount of tributyltin hydride and catalytic amount of AIBN or one can also use catalytic amount of tributyltin hydride, catalytic amount of AIBN, but stoichiometric amount of sodium cyano borohydride.

So, what does it mean that is, the tributyltin halide which is formed can be further reduced with sodium cyanoborohydride or sodium borohydride. So, that is how one can use tributyltin in catalytic amount ok. So, now, this reaction works well as you can see here 3:1 ratio of the cyclized product and then, simple reduced product. And here the stereochemistry what he got was 5:1 in ratio where the required isomer alpha is the major isomer ok.

So, successfully he could carry out the first radical cyclization ok. Successfully he could carry out the first radical cyclization.

Now, what he has to do is he has to connect here these two carbon. Connect these two carbon to form the 3rd ring ok. So, for that what he did, he reduced the ester to alcohol. So, once you have the alcohol you oxidize to aldehyde and then treatment with tri phenyl phosphine and CBr_4 will give you corresponding dibromo alkene ok. So, he wanted to

use this dibromo alkene as the radical precursor ok. So, you can see you have 2 bromines ok. And if it cyclizes here so, that will give you the corresponding modephene.

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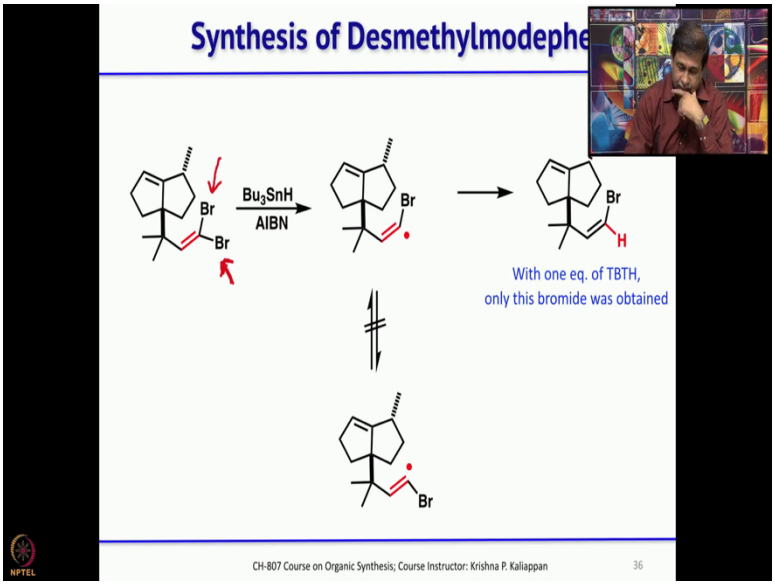

So, when we did this reaction with 1.1 equivalent of tributyltin hydride and AIBN. So, between these 2 bromides, we should know which one will form radical first. Obviously, so, this is more exposed or least hindered is not it. So, that will form the radical quickly. So, that radical was formed and if this radical is formed, then this cannot cyclize. So, what it will happen? It will take up the hydrogen and it will simply reduce. And this also does not isomerize ok. This does not isomerize.

So, he thought this will isomerize to the trans compound and the trans compound can undergo the 5 exo trig radical cyclization, but the isomerization did not take place with 1 1.1 equivalent of tributyl tin hydride and AIBN only the less hindered bromine was replaced ok; that only was reductively removed ok. The exchange did not take place.

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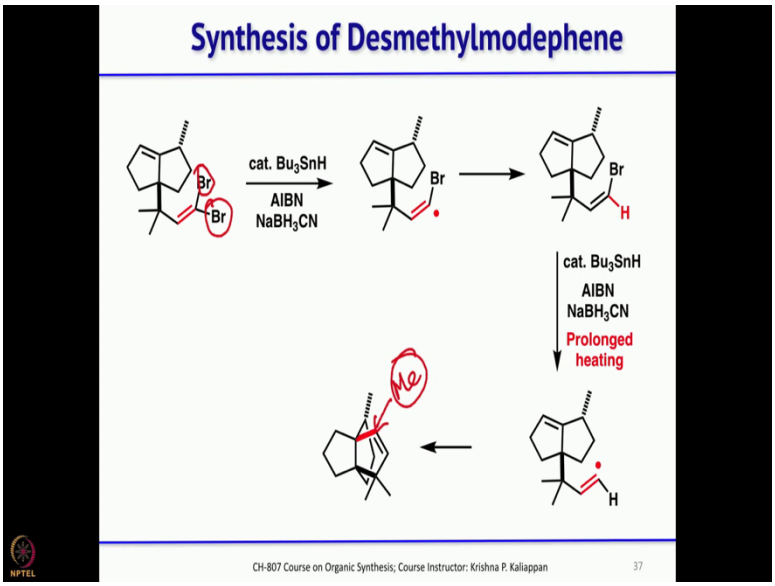

So, what he thought? So, instead of using 1.1 equivalent of tributyltin hydride, he thought he will use catalytic amount of tributyltin hydride and excess sodium cyanoborohydride ok.

And here the idea is first anyhow only this bromide is reduced ok. So, let it reduce afterwards if he add excess sodium cyanoborohydride which will in turn generate more tributyltin hydride, then this bromine will be replaced by radical and that can undergo cyclization. So, with this he tried this reaction and as expected first the least hindered bromide was reductively removed, then followed by further heating under the same condition the trans radical was formed and which underwent further cyclization to give desmethylmodephene.

So, if you look at the modephene structure, you need one extra methyl group here ok. So, based on this, he wanted to extend the same strategy to the synthesis of modephene.

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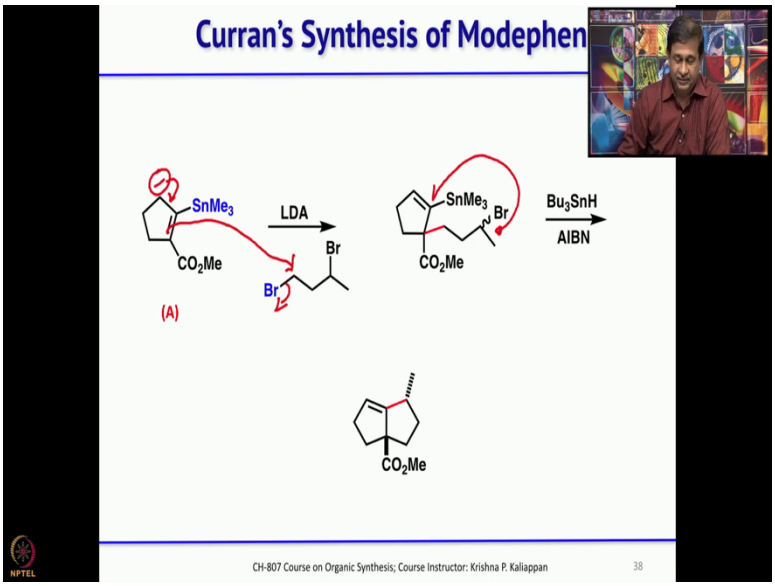

So, for that he started with this trimethyltin derivative ok. This trimethyltin derivative what he did, if you treat with LDA if you treat with LDA you can generate anion here ok. That anion will come like this and then it will attack this carbon that is a primary halide.

So, alkylation will take place at the primary halide and the secondary halide will not be affected. So, that will give you this. His idea was now, if you can generate radical here ok. That radical can undergo cyclization 5 exo and when it comes back the trimethyltin radical will come out that way you have the double bond still intact.

So, with this he treated with tributyltin hydride in the presence of AIBN. So, he got exclusively this product.

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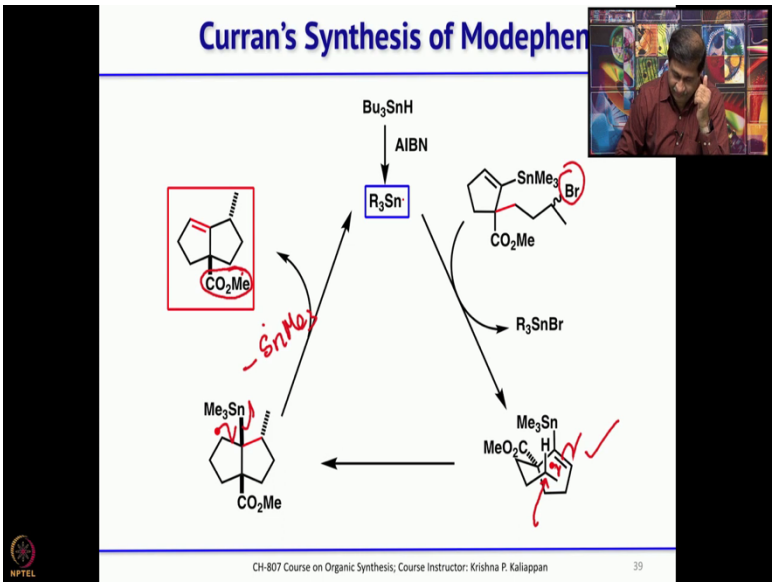

How did he get? The tributyltin hydride first generates the tributyltin radical ok. And it exchanges with bromine. So, you get the secondary radical ok. So, when I talked about radical cyclization, the stereochemical outcome of radical cyclization particularly, for 5 exo radical cyclization can be done by drawing a chair like conformation. So, exactly if you see this, we have drawn a chair like conformation.

So, the first step is the addition of the radical to the double bond 5 exo trig. So, that should give you this compound ok. I will leave it for few seconds. So, that you know you can understand this. So, this will undergo 5 exo radical cyclization to give this radical. Now, this radical will come like this and then eliminate the tributyltin radical. So, you can write like this, yeah ok. So, that is how this cyclization takes place and the methyl group, which is alpha it is because here the methyl group was put in equatorial position.

So, that is how you know the chair like conformation will help in establishing the stereochemistry of the methyl group which is formed here ok. So, once you have this bicyclic system, the next step is you have to convert this ester; convert this ester into a dimethyl group and then CH_2.

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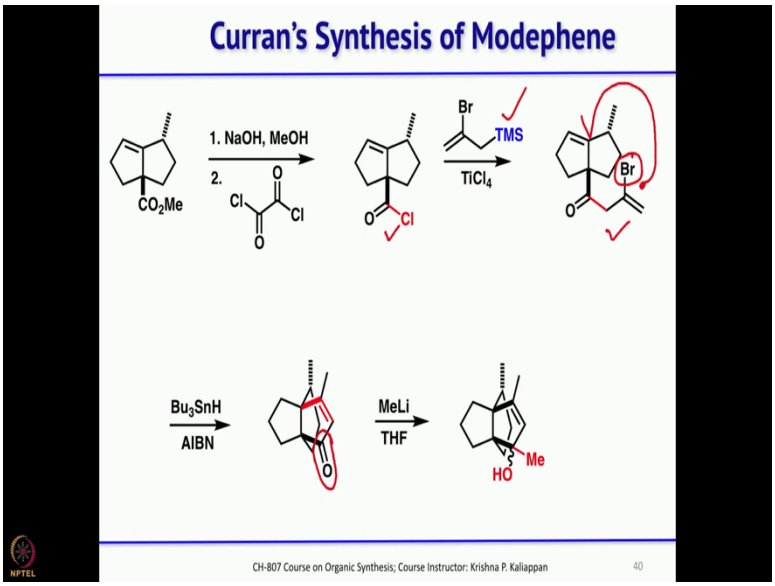

So, for that first you hydrolyze the ester to carboxylic acid and then treat with the acid chloride you get the corresponding acid chloride. So, now, what he did was he tried a Sakurai like reaction, where the allyl TMS ok. The allyl TMS was treated with this acid chloride in the presence of titanium tetrachloride to add this bromo allyl group directly to the carbonyl group.

So, now if you look at this, so, you have the vinyl bromide, which on treatment with tributyltin hydride should generate the radical and that radical should add here to form the third 5 membered ring. Otherwise, that will give that is core structure of modephene. So, when you did this reaction yes the reaction worked well and then you could get the propellane structure. So, now, what is required is convert this carbonyl group. The carbonyl group should be converted into dimethyl group ok.

So, if you look at the radical cyclization, first the radical cyclization took place followed by the migration of the double bond; internal double bond instead of external double bond you get internal double bond that is because you have a ketone after radical cyclization, because normally radical cyclization you do it at high temperature. So, the double bond exocyclic double bond migrated to alpha beta unsaturated ketone. So, what he did to introduce the 2 methyl groups. First he treated with methyl lithium to get the corresponding tertiary alcohol.

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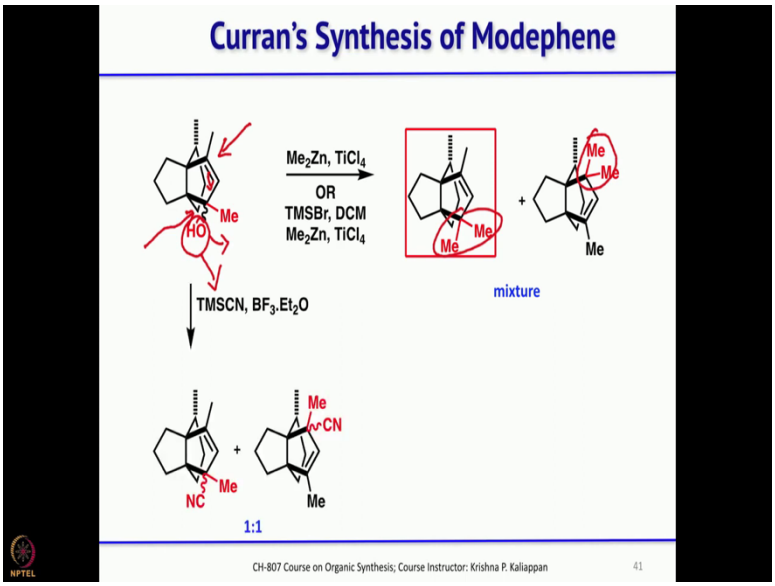

These tertiary alcohols are known if you treat with you know titanium tetrachloride and dimethyl zinc ok. It is known well known in the literature the tertiary alcohol can be converted into quaternary by treatment with titanium tetrachloride and dimethyl zinc. So, basically, you know the Lewis acid will coordinate with OH to make it as a good leaving group and dimethyl zinc will deliver the methyl group. One can also do the same thing by treating with dimethyl zinc, titanium chloride in the presence of TMS bromide ok.

So, effectively what you are doing is you are converting the tertiary alcohol into quaternary. So, this is what was the expected product, but what he got was another product that can be easily explained, when this OH goes as a leaving group the methyl group can attack this carbon or the double bond can migrate the double bond can migrate the tertiary carbocation followed by methyl group attacking here.

So, you got a mixture of 2 methyl groups ok. 2 gem dimethyl group here as well as here. So, he thought ok this is not a good method.

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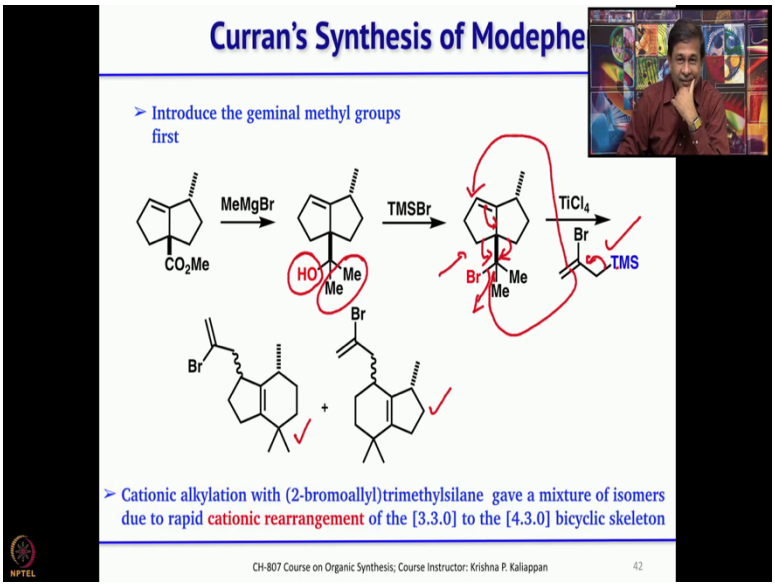

So, he wanted to introduce the gem dimethyl group first. So, for that what you did? You take ester and then convert into the tertiary alcohol. So, now, you see 2 gem dimethyl groups are introduced first itself at the right place. Now, you have to homologate. So, what he did he treated with TMS bromide to get the corresponding bromide. Now, he wanted that vinyl group.

So, he treated with titanium tetrachloride and then bromo allyl trimethylsilane, when he did this reaction he got again a mixture of 2 compounds and that again was obtained by rearrangement. So, now, when you use titanium tetrachloride this will go as a leaving group. When it goes as a leaving group ok, instead of this allyl TMS attacking this carbon either this bond of the 5 membered ring or this bond can migrate.

When the right hand side bond migrates you get this product; when the left hand side migrates you get this product. What happens, once this migrates then, this allyl TMS this will attack the double bond and the double bond will come here to neutralize the positive charge. So, ring expansion takes place ok.

So, instead of three, 5 membered ring fused you get one 5 membered ring, and one 6 membered ring fused and you get a vinyl bromide also ok. So, again he could not get what the precursor he was looking for to synthesize the modephene ok.

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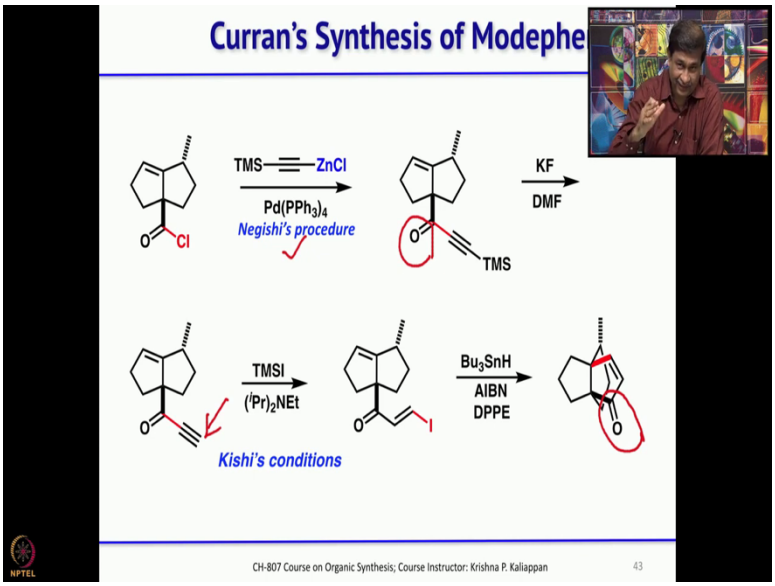

So, what he went back to the ester hydrolyzed the ester and converted that into acid chloride. So, now, what he did, he introduced a triple bond. He added a triple bond to the acid chloride. So, for that he followed a Negishi's procedure.

So, palladium catalysed coupling reaction to introduce a triple bond. So, his idea is later he wanted to convert this carbonyl into gem dimethyl group. Let us see how he has done.

Then TMS group was removed, which is not required with the fluoride source potassium fluoride DMF, you can remove the TMS to get the alkynyl ketone ok. So, once you have this alkynyl ketone; now, you have to introduce the radical precursor that is corresponding bromide or iodide vinyl bromide or vinyl iodide.

So, the treatment with TMS iodide; so, the TMS iodide this is again developed by you know Kishi. So, it undergoes a 1, 4-addition to give trans iodo compound ok, the trans vinyl iodide ok. The trans vinyl iodide is required as you know for the radical cyclization to take place you need the trans iodo compound.

So, once you have this trans iodo compound then tributyltin hydride reaction works very well to get the modephene that is the propellanes skeleton. So, once you have this propellanes skeleton, now what is required is converting this ketone into dimethyl group ok. Earlier he failed incorporating this ketone into dimethyl group and when he started with dimethyl group then cyclization did not go ok.

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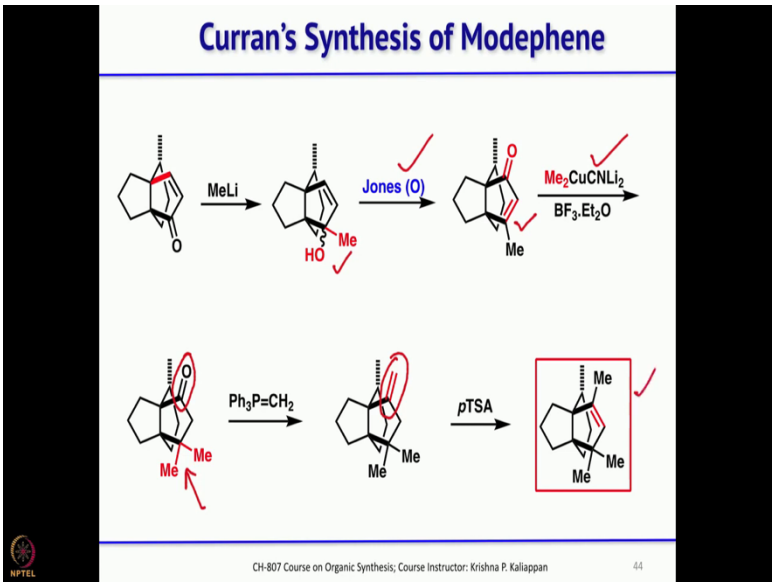

So, how we did was when you have the ketone with the double bond that is cyclopentenone, you add methyl Grignard or methyl lithium to get the corresponding tertiary alcohol.

Once you have this tertiary alcohol the next step is the oxidative transposition, oxidative transposition of allylic tertiary alcohol. So, this was reported by William Dauben using PCC. So, PCC that is pyridinium chlorochromate is well known for the oxidative transposition of allylic tertiary alcohol to corresponding enone.

So, here he use Jones reagent, Jones reagent is nothing but chromium dioxide and sulfuric acid in acetone. So, that oxidation gave the transpositioned enone. Once you have this enone, then for the introduction of one more methyl group you normally you use a Gillman's reagent. So, that way you could introduce now the gem dimethyl group ok.

What is required is convert this into a methyl group. So, treatment with Wittig salt, then you can get the corresponding exocyclic double bond, but for modephene what you need is the endo double bond. So, the exocyclic double bond on heating with para toluene sulfonic acid gave the modephene.

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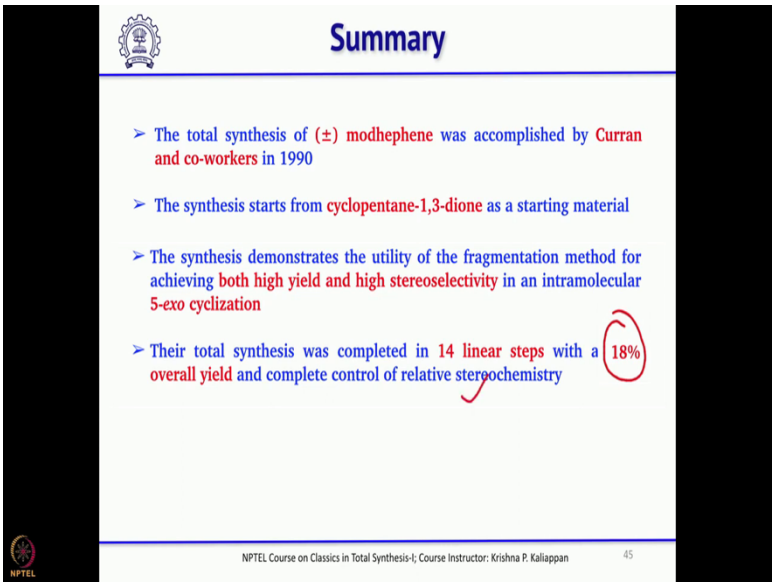

So, he has successfully used not the tandem radical cyclization, but 2 radical cyclization to form two 5 membered rings he also started with one 5 membered ring and two more 5 membered rings were added based on the radical cyclization.

A synthesis started with cyclopentane-1, 3-dione and he also used an intermediate cyclic vinyl stannane for the successful synthesis of a modephene. And overall this synthesis took little longer than the other 2.

So, it took about 14, 14 steps, but the yield is quite good. So, 14 step with 18 percent overall yield with complete control of stereochemistry is one of the key aspects of the total synthesis of modephene reported by Curran. Though it is a racemic synthesis it was one of the classical synthesis of triquinane ok. With this I will stop and we will see more discussion on synthesis of triquinanes in the next class.

Thank you.