Classics in Total Synthesis-I
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Lecture - 15
Triquinanes by radical cyclisation I: Hirsutene and Capnellene (Curran)

Good morning. And welcome back to the NPTEL lecture series on Classics in Total Synthesis. In the last lecture we talked about total synthesis of few triquinanes and we will continue our discussion on total synthesis of more triquinanes today and a few more lectures we will focus on the same. And today's lecture what we will do we will take one key reaction and how this key reaction was used successfully to synthesize a few triquinanes.

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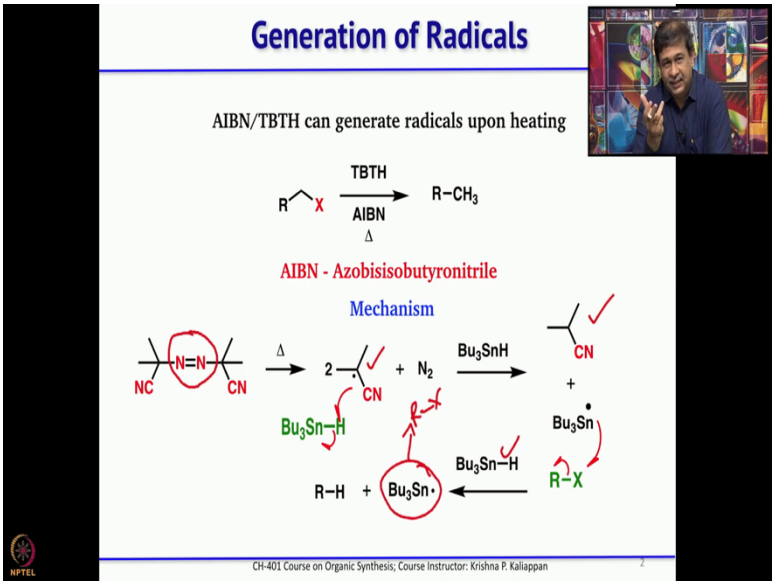

And that key reaction is radical cyclization. As you know radicals can be easily generated from corresponding alkyl halides or nitroalkanes. So, one of the most common methods for generating radicals is take an alkyl halide and then treat with tributyltin hydride and AIBN. So, the AIBN is nothing but azobisisobutyronitrile, ok. You take this compound and easily one can dehalogenate, ok if you have an alkyl halide that halide can be replaced by hydrogen.

And the mechanism is very simple when you take an alkyl halide or nitroalkane in toluene or benzene when you reflux it, ok. Then you had this azobisisobutyronitrile. So,

if you look at the structure of azobisisobutyronitrile there is a nitrogen, ok N_2 which is a good leaving group. So, easy extrusion is possible.

So, this is what you observe when you do this reaction when you take this halide in toluene or benzene and reflux it. Then when you add this azobisisobutyronitrile immediately you can see the extrusion of nitrogen bubbles you know you can see nitrogen bubbling, ok. And that will generate this radical ok.

So, this radical what will happen since you add tributyltin hydride which is 1, 1 to 1.1 equivalent of tributyltin hydride you add to this reaction mixture. So, that will immediately abstract the hydrogen of tributyltin hydride and it will form the corresponding tributyltin radical. And already you can see the azobisisobutyronitrile became simple butyronitrile.

Now, the tributyltin radical will react with your alkyl halide, ok. And then form tributyltin halide and alkyl radical, ok. That alkyl radical will pick up hydrogen from tributyltin hydride and then it form R-H. So, now, what will happen this tributyltin radical again it will pick up it will react with R-X to form alkyl radical, ok. That alkyl radical will further undergo you know hydrogen abstraction from tributyltin hydride. So, the cycle will continue, ok.

So, what you need is you need only a catalytic amount of azobisisobutyronitrile. So, that is a radical initiator ok, but you need more than one equivalent of tributyltin hydride because that is what which replaces the halide in your system.

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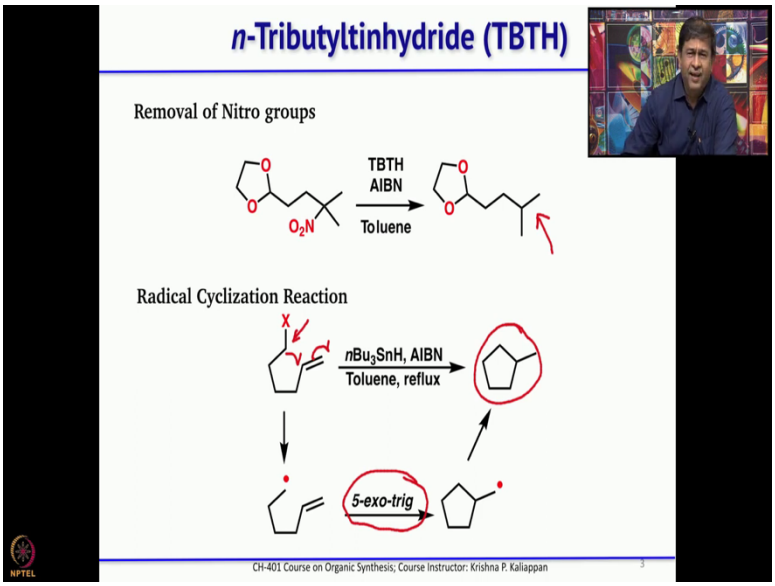

And when you use tributyltin hydride as I said you can also remove nitro group if you have a nitro group the nitro group also can be cleaved. Instead of nitro group what you get in the product is hydrogen, ok. In addition, what will happen when you have an alkyl halide and also an acceptor in the same system, ok. Also, an acceptor in the same system, then this radical instead of abstracting hydrogen from tributyltin hydride it can add to the acceptor, it can add to the double bond, it can add to the triple bond.

So, when that happens the radical will not be at this place, ok. So, once the radical is generated here, then the radical adds to this double bond and it the radical comes to now the primary carbon of the double bond, ok. At that position that CH_2 radical will abstract hydrogen from tributyltin hydride. So, in the process you can see if you start with an open chain you end up in getting a ring.

And this is the process and when you do this you also will see in many papers people write like this notation 5 exo 6 exo and some number they will give an exo an endo and then they will give trig dig and so on. And what are they?

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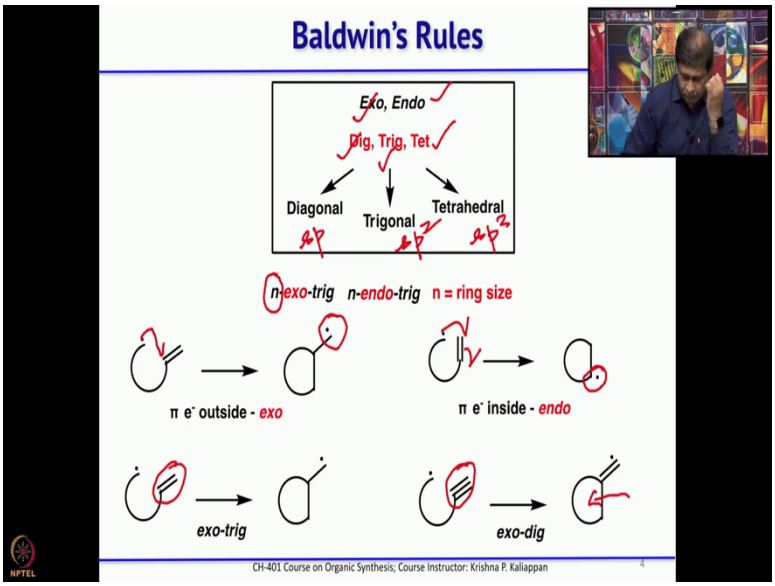

Exo you would see, endo you would see, dig, trig, tet. Dig means diagonal, trig means trig represents trigonal, tet represents tetrahedral. So that means; so, this is sp3 carbon this is sp2 carbon this is sp carbon. So, these are the carbon atoms which are accepting the radical. If your acceptor has sp carbon atom then you write dig. If your acceptor has sp2 carbon atom then you write trig. If your acceptor has sp3 carbon atom then you write tet.

Then what is exo? What is endo? And also you will see some number in front of exo or endo, ok. So, what that number means? That number means when you do the cyclization, what is the ring size. The size of the ring is represented by n. Suppose if you are forming a 5 membered ring then you write 5, if you are forming a 6 membered ring then you write 6, if you are forming a 3 membered ring then you write 3, ok.

So, the n represents the size of the ring formed after the cyclization. What is exo and endo? So, when the radical is formed, ok when the radical is formed now the radical adds to the double bond it can add in 2 ways. First way it adds like this and the final radical the final radical that is after the cyclization if it is outside the ring, if it is outside the ring then the whole process is called exo, ok.

And same thing when the cyclization takes place and the final radical if it is part of the ring, it is inside the ring then it is called endo, ok. n represents the size of the ring formed and exo means the final radical is outside the ring, endo means the final radical is inside

the ring. Then the trig and then dig as I said since we are talking about radical cyclization acceptor we will talk about only sp and sp2 carbons. So, this is sp2 carbon is not it.

The acceptor is sp2 carbon. So, this means it is trig, exo trig this is sp carbon ok, both are sp carbons is not it the acceptor has sp carbon atom. So, then the cyclization you have to write dig, ok. Depending on the ring size you put the number before the exo, ok. this is what proposed long time ago and also Baldwin proposed a set of rules where, which are the reactions allowed which are not allowed based on the literature, ok.

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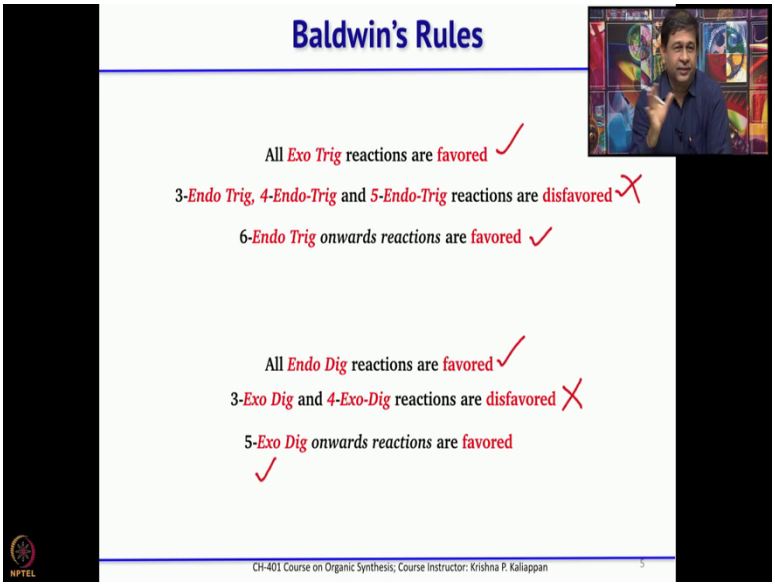

So, according to him all exo trig all exo trig reactions are allowed or favored. What is not favored is 3 endo, 4 endo, 5 endo, ok. These are not favored in the case of trig. That is if you have a double bond and if you are carrying out radical cyclization then 3 endo, 4 endo, 5 endo are not favored. The first earliest ring where endo is favored is 6 endo, only 6 endo is favored, ok.

Coming to sp carbon atoms you have exactly opposite to what trig is, all endo dig reactions are favored. All endo dig reactions are favored. But, 3 exo and 4 exo dig are not favored, ok. Only from 5 exo dig onwards all exo dig reactions are favored, ok. So, these are rules which you can remember or no problem when you carry out reactions automatically you will come to know whether your reaction works or not.

If it does not work then go back and then see why it did not work. It may be because of these rules, but though these rules are you know used extensively there are many exceptions. As is the case with many rules, ok.

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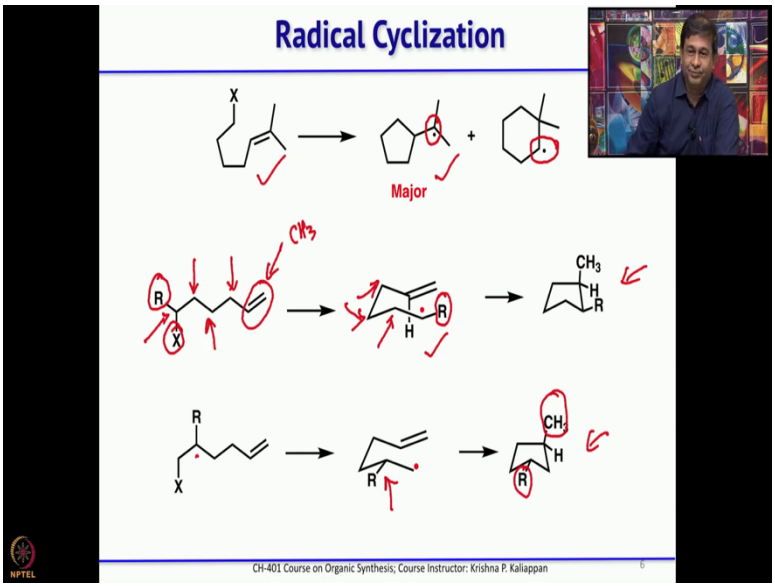

Then what about the regiochemistry? So, when exo and endo are allowed for the same substrate. Which one will be favored? Ok. Exo will be favored or endo will be favored. Then when your substrate has substituent after the radical cyclization what will be the stereochemical relationship. So, the regiochemistry and stereochemical outcome of radical cyclization can be easily explained see for example, if you take this compound.

Now, 5 exo will give a tertiary radical whereas, 6 endo will give a primary radical. So, from the stability point of view you know the tertiary radical is more stable. So, that is why this is more favored, that is 5 exo is more favored than 6 endo. Coming to the stereochemistry say for example, you have a double bond and you have a halogen.

So, it forms 5 exo trig, ok. Since you do not have substituent at the end. So, 5 exo trig is more favored. Now, you put the substituent at the same carbon as the halides, ok. When the radical cyclization takes place this will become a methyl group, is not it? This will become a methyl group. And what will be the stereochemical relationship between the R and methyl? What will be the stereochemical relationship between R and methyl?.

So, what you should do? You should draw a chair-like conformation, see this is a chair-like conformation. And when you do that you put the radical and also put the R group in the equatorial position of the chair conformation. So, you draw the chair conformation and put the R group in the equatorial position.

Now, when you cyclize, when you cyclize this is what you get, ok. What you get? R and methyl are cis to each other. Now the R group can be here, here, here, ok. What you should do? Accordingly, you have to draw the chair conformation and then put the R group in the equatorial position accordingly, ok. Accordingly, you put the R group in the equatorial position then do the cyclization.

Then you draw the cyclopentane and then look at the methyl group and your R group. So, I will give one more example. So, now, what I have done I just moved the R group to second carbon. And again, you draw the same chair conformation and this R you put in equatorial position. Do the radical cyclization and as you can see here in this case the methyl and R are trans to each other, ok.

So, these are the major products you also will get the other product, ok. So, in this case you will get trans in this case you will get cis also, ok these are the major regio and stereochemical outcome. So, the regiochemical outcome is based on stability of the radical. Whereas, the stereochemical outcome is based on putting the alkyl group or the substituent in equatorial position and drawing the chair like conformation and then see the final outcome, ok.

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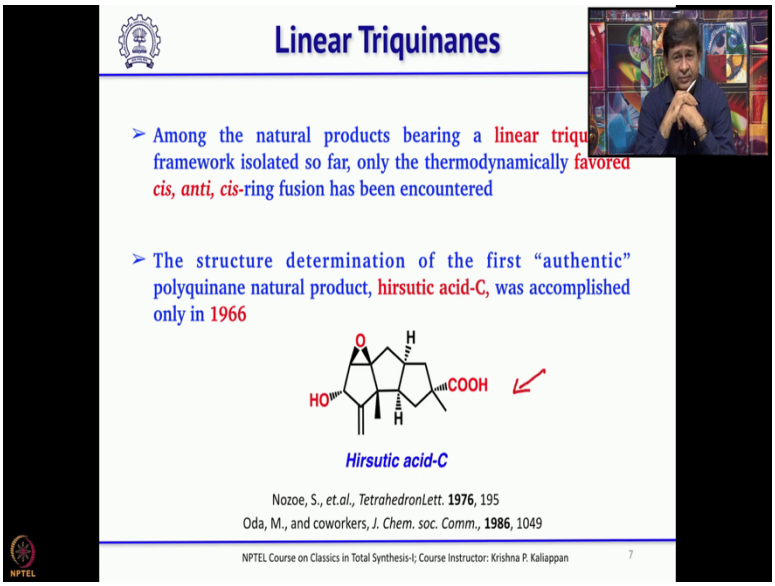

So, now we will see how this radical cyclization reaction has been successfully used in the total synthesis of natural products, as we are talking about triquinanes. I will explain how this particular radical cyclization has been used in the synthesis of linear angular and propellanes, ok. One example which we will see is hirsutanes and hirsutane belongs to you know linear triquinane.

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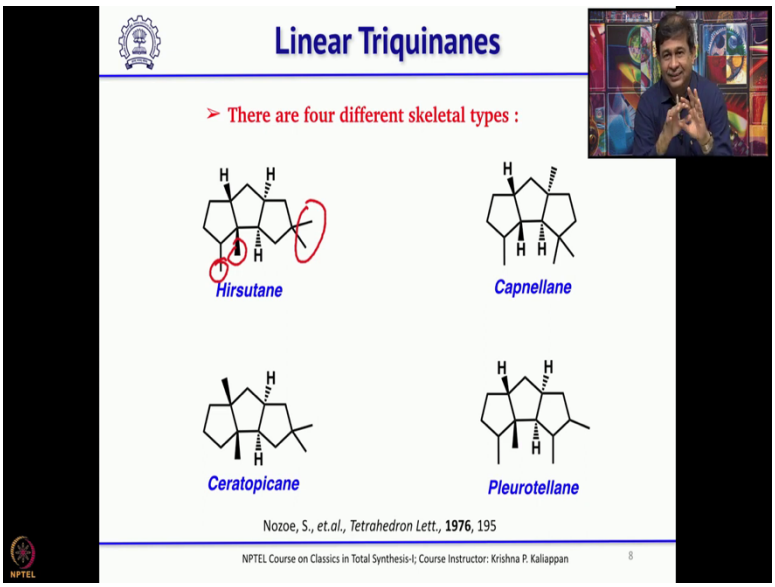

So, this is one of the earliest hirsutane type triquinanes which were isolated it was isolated in 1976. I will not go into the details of this. Because there are 4 different types

of linear triquinanes and this 4 different types vary based on the position of the 4 methyl groups, ok. The 4 methyl groups you can see here these 4 methyl groups are located in different places for these 4 different skeletons, ok.

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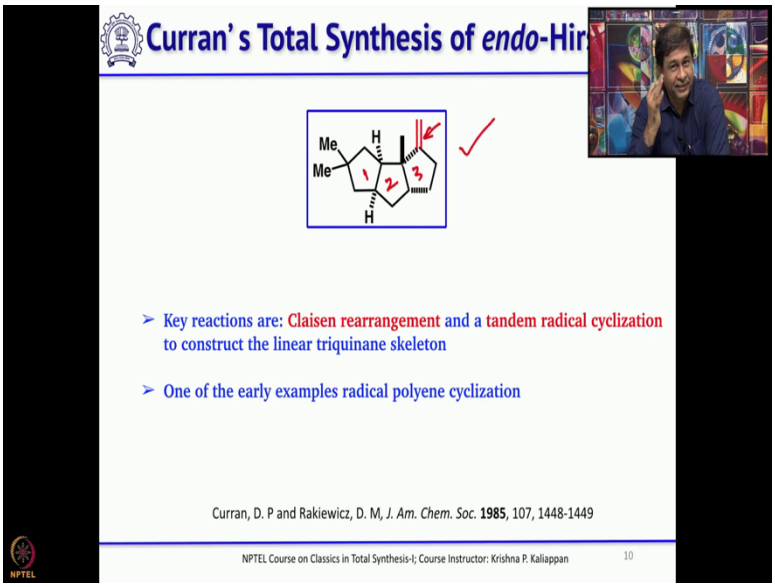

The first natural product where a tandem radical cyclization was used as the key step was hirsutene. So, this is a sesquiterpene called hirsutene. And this molecule Curran has cleverly used a tandem 5 exo radical cyclization as well as a Claisen rearrangement to prepare the starting material for the key radical cyclization. This was one of the earliest examples of polyene radical cyclization.

So, once you see a double bond here, ok. Then you also see three 5 membered rings. So, one can easily think about 5 exo radical cyclization reaction.

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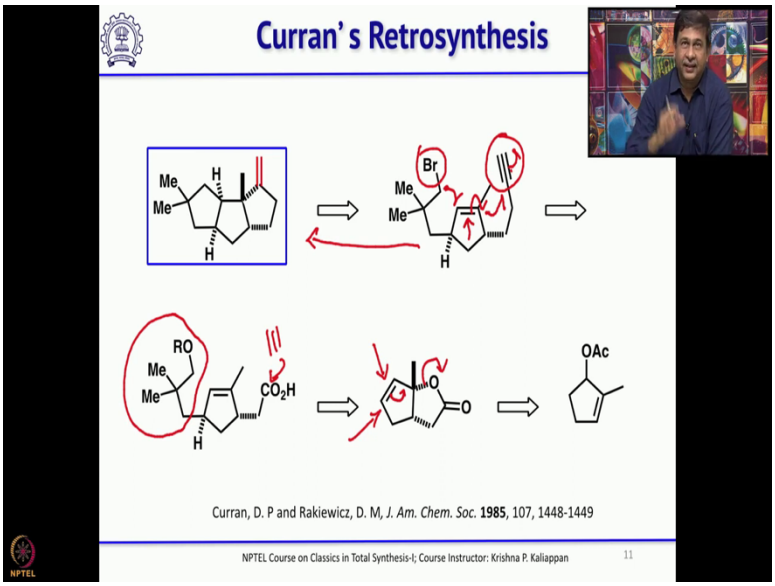

So, what he thought was this could be easily made from this precursor. So, the hirsutene can be easily made from this precursor. So, his idea was this bromine on treatment with AIBN and tributyltin hydride should generate a radical here. That radical should undergo first 5 exo cyclization to give a radical here, ok.

So, the 5-membered ring is formed and this 5 exo trig because this is sp2 this is sp2, is not it? So, trigonal 5 exo trig and then 5 membered ring is formed that leads to another radical. Now you have an acceptor this time its a triple bond so; that means, it is dig. So, that will be 5 exo dig. So, its a combination of 5 exo trig and 5 exo dig, all this happen in one pot.

So, you start from this and one pot in principle you should be able to convert this into natural products. So, that was the key reaction which Curran has proposed. Now this compound can be easily obtained by simple homologation. So, what you need is you need to add a triple bond to this, ok. So, some functional group transformation followed by adding this triple bond you will get the radical cyclization precursor.

The next key step is the nucleophilic attack, the nucleophilic attack of this whole unit nucleophilic attack of this whole unit to this lactone. So, now, the nucleophile will attack here and the double bond will migrate and this will open up, ok its like SN_2', ok. So, that will give you the carboxylic acid. And this lactone if you look at this lactone whenever

you see a 5 membered lactone one reaction which should come to your mind immediately is iodolactonization, ok.

So, now you have a double bond here. So, what can what one can do is after iodolactonization, you can eliminate. And this can be easily obtained from this acetyl through a Claisen rearrangement which I will discuss during the synthesis let us see.

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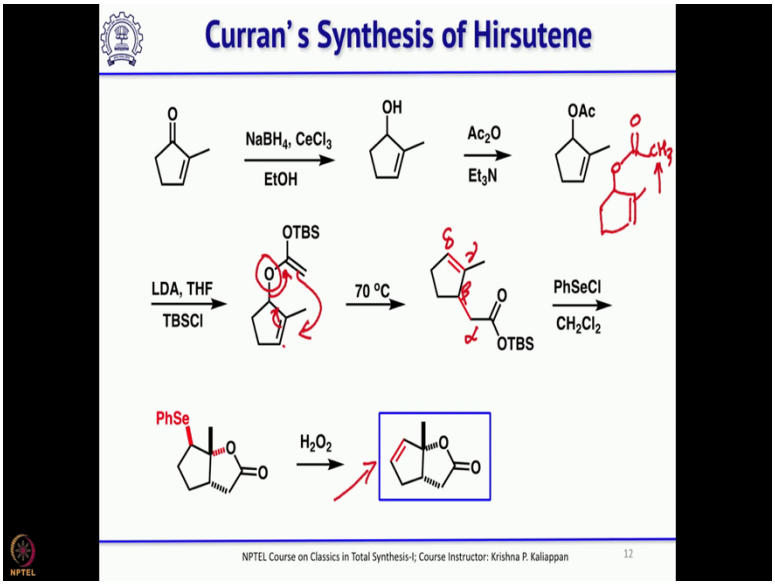

How this bicyclic lactone was made? He started from commercially available 2 methyl cyclopentenone, ok. And the first step was to use Luche reduction that is sodium borohydride, cerium chloride to reduce only the ketone of alpha beta unsaturated ketone to get the cyclopentenol. So, with the methyl group at 2 position.

Then he treated with acetic anhydride. So, which acetylated the 3 hydroxyl group to form the corresponding 2 methyl cyclopentenyl acetate. This on treatment with LDA and quench with TBS chloride. So, you can write this compound like this now you see this as acidic proton, ok. You can generate anion with LDA and if you quench with TBS chloride this is what you get, ok.

So, if you look at the substrate carefully if you look at the substrate carefully. So, this is having a 1, 5 diene ok, is having 1, 5 diene. You can see 1, 2, 3, 4, 5. So, when you have 1, 5 diene then that is the substrate for Cope or Claisen rearrangement, since you have oxygen part of this. So, this is Claisen rearrangement. So, this is easy you can see this

will undergo this 3, 3 sigmatropic rearrangement, upon heating to give the corresponding rearranged product.

Gamma, delta unsaturated ester. Alpha, beta, gamma, gamma, delta. Always you know when you do such a Claisen rearrangement you will get a gamma delta unsaturated system, ok. So, this upon treatment with phenylselenyl chloride. So, one can think about using iodolactonization or phenylseleno lactonization the phenylseleno lactonization is slightly better than iodolactonization.

Just for the reason that the introduction of double bond is much easier because it can be done at 0 degree, ok. So, that will give you the corresponding seleno lactone. As you know once we have the seleno group then treatment with hydrogen peroxide at 0 degrees, one can easily eliminate the phenyl selenic acid to introduce the double bond ok, its a cis syn elimination to get the corresponding bicyclic lactone.

So, the bicyclic lactone was obtained in 6 steps from commercially available 2 methyl cyclopentenone. And the next step is to make the nucleophile ok, to make the nucleophile and that should undergo SN_2' reaction.

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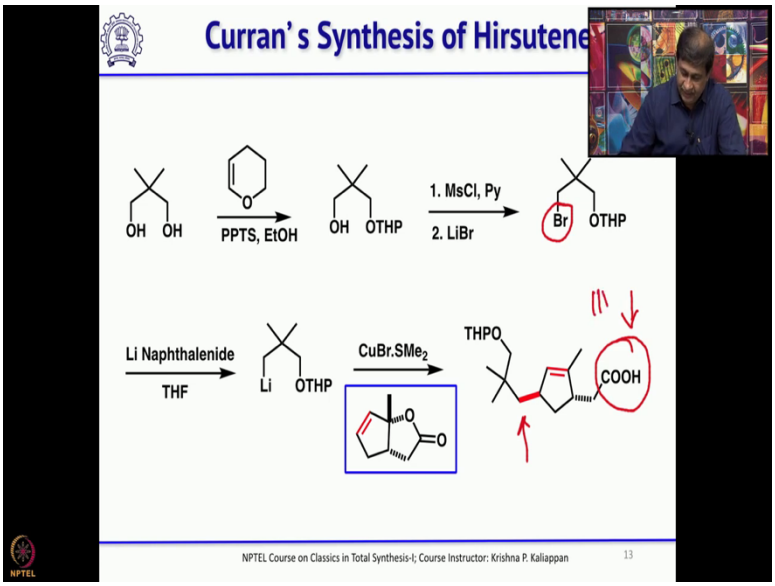

For that he started from again commercially available 1, 3 diol ok, having a gem dimethyl group. And selectively one can protect one of the alcohol because this is a

symmetrical alcohol. So, you protect one of the alcohol as corresponding THP ether. So, its also very simple and straightforward.

So, you protect this as a THP ether then the other alcohol you mesylate and convert that into a bromo compound, ok. So, this is the second precursor, ok. Now you convert this into lithium ok, convert this into lithium. So, one can treat with tertiary butyl lithium and of those days he has used lithium naphthalenide to convert that into lithium, lithio derivative and now you make it as copper.

So, that you know it can undergo you know SN_2' like reaction to give this carboxylic acid and you also introduce this 3 carbon unit, ok. So, next step is you have to homologate ok, you have to introduce the triple bond, is not it? You need a triple bond here ok, you need a triple bond here.

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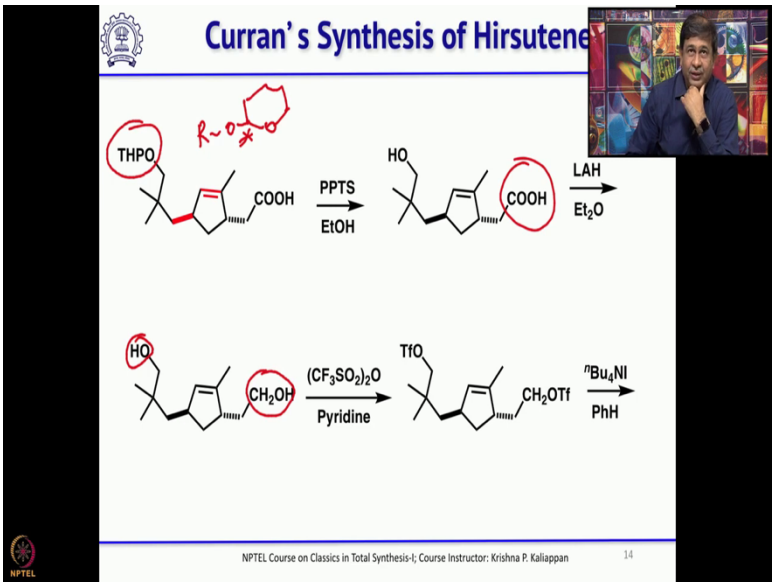

So, that can be done before that this THP group. So, the THP group has served its purpose. So, once the protecting group served its purpose it is better to remove, ok. And the problem with THP group is it will give additional stereo center. THP is nothing, but if you see. So, this is THP and then you can see there is another chiral center here. So, because of this extra chiral center, ok.

You will get a diastereomer you will get a mixture. So, that NMR would not be clean. So, whenever you use THP, whenever you use a THP ether and if you have a chiral

center in your molecule, remove the THP as early as possible. So, that you will get a good spectra, ok. So, then remove that THP and then you get the primary alcohol. Now the free carboxylic acid can be easily reduced with LAH to get another primary alcohol.

So, now, if you look at this molecule you have two primary alcohols, ok. So, both you convert into triflate and then convert that into corresponding iodide by treating with tetrabutylammonium iodide, ok.

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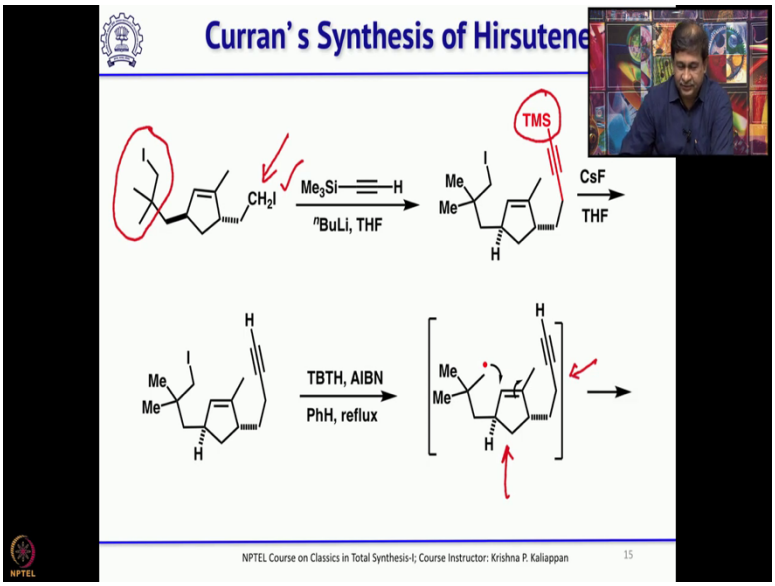

The tetrabutylammonium iodide converts these two into CH_2I here and CH_2I there. Now what you need to do is you need to homologate here with the triple bond, ok. Now when you treat with TMS acetylene and butyllithium, ok. So, this is a neopentyl system, this is a neopentyl system.

So, when you add lithium trimethylsilylacetylene, ok. The neopentyl system is not that reactive it is very very difficult. So, here this nucleophile can attack only at this carbon. So, what you get is the corresponding triple bond and TMS and for the radical cyclization you do not need this TMS. So, just remove it with the fluoride source. So, cesium fluoride will remove the TMS and that sets the stage for the key radical cyclization.

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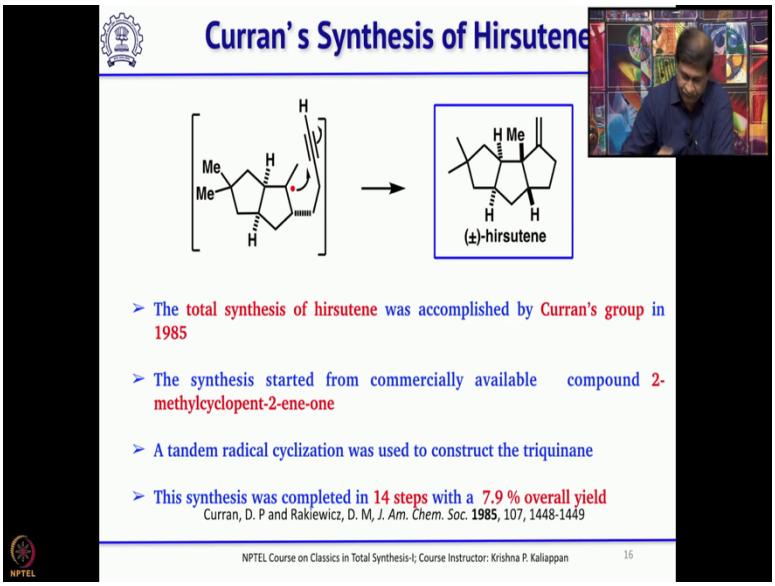

So, the radical cyclization as you can see here it undergoes a tandem 5 exo trig followed by 5 exo dig radical cyclization to give the natural product hirsutene. So, if you look at the overall process the total synthesis of hirsutene was made from commercially available 2 methyl cyclopentenone.

And it involved 3 key reactions Claisen rearrangement, SN_2' substitution and tandem radical cyclization, ok. And the yield overall yield for this whole sequence was close to 8 percent and considering that it is a 14 step process is 8 percent is a very very good deal.

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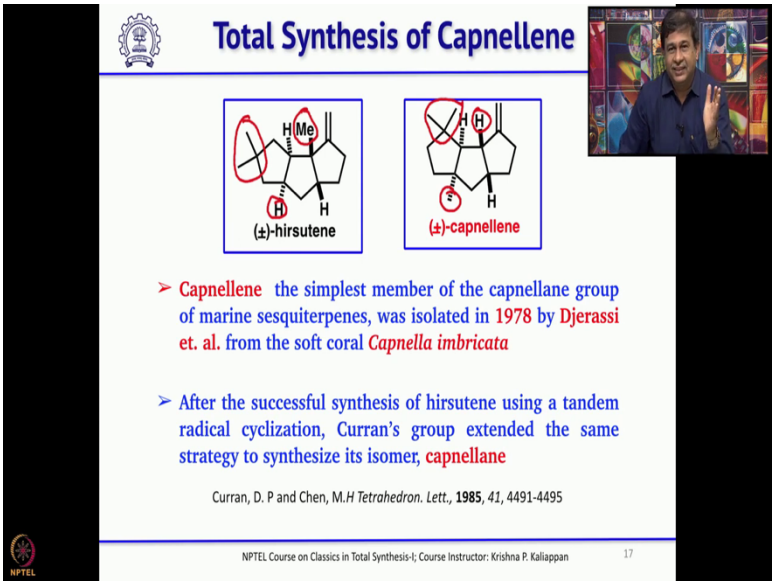

After successfully synthesizing hirsutene, he wanted to extend this methodology to another closely related natural product called capnellene. So, if you look at capnellene and hirsutene immediately first look at these 2 molecules you feel the both are same, but it is not. You need to have a closer look at this molecule. In hirsutene you have a methyl group here whereas, you have hydrogen.

In hirsutene you have hydrogen here, you have methyl group here. In hirsutene the dimethyl group is here whereas, dimethyl group is here at capnellene. So, there is there are subtle differences between these 2 natural products and what Curran wanted was he wanted to extend the same tandem radical cyclization to capnellene also.

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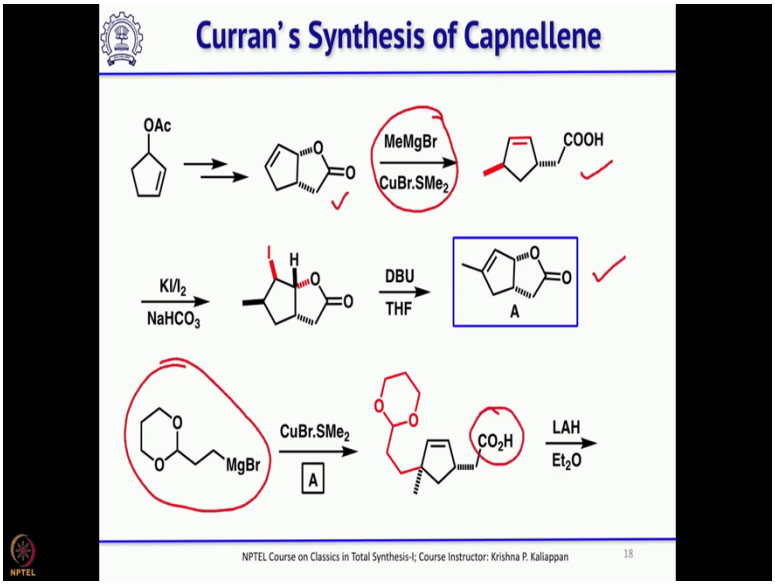

So, what he did? So, he also started from cyclopentenone. This time he does not need the methyl group here and followed the same process to get this bicyclic lactone. But he needs a methyl group here, ok. So, for that first what he did he did a 1, 4 like addition with methyl magnesium bromide and cuprous bromide dimethyl sulfide. So, it opened to give this carboxylic acid.

And then followed by iodolactonization and elimination you could get this bicyclic lactone. Then another ring opening with this Grignard reagent and copper. So, this is commercially available the corresponding bromide is commercially available.

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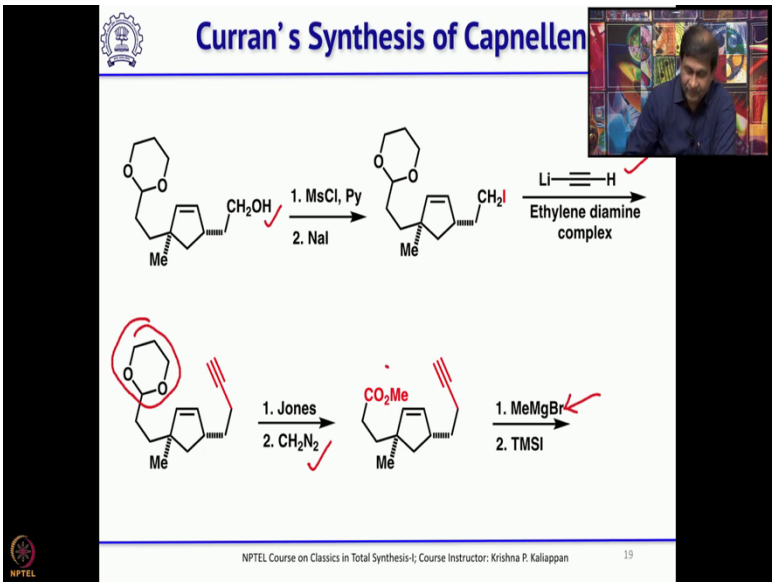

So, make the Grignard and add and you get this carboxylic acid. Reduce the carboxylic acid to get the corresponding primary alcohol then you mesylate and convert into CH_2I. And now based on the earlier experience you do not need even TMS acetylene you can directly take lithium acetylide ethylenediamine complex.

So, that will give you the triple bond required for the radical cyclization. Now what we need is, you have to remove this convert it into gem dimethyl group and also the halide. So, Jones oxidation directly oxidize the protecting group first hydrolyze the protecting group to aldehyde and then oxidize the aldehyde to carboxylic acid and then carboxylic acid was methylated using diazomethane to get the corresponding methyl ester.

Now, if you take excess methyl magnesium bromide and add to this ester it will give corresponding tertiary alcohol, the tertiary alcohol was converted into corresponding iodide by treatment with trimethylsilyl iodide.

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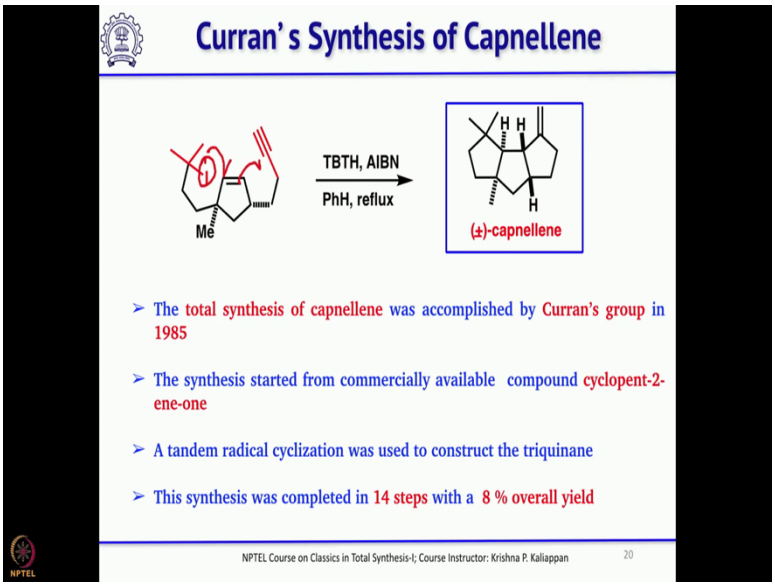

So, that is the that gives the key precursor for the tandem radical cyclization. So, you have the radical here. So, you can generate the radical from this iodo compound and then that will give 5 exo followed by another 5 exo, first one is 5 exo trig the second one is 5 exo dig. So, that gave directly the natural product that is capnellene.

So, again using the same radical cyclization same tandem radical cyclization Curran's group could successfully achieve the total synthesis of capnellane. And here they started from the commercially available cyclopentenone, 2 cyclopentenone and not with methyl group and overall yield was almost same as in the case of hirsutene.

The total number of steps was 14 steps and with an overall yield of 8 percent. So, we will continue our discussion on the radical cyclization how this radical cyclization has been successfully used in the synthesis of more triquinanes in the next lecture.

Thank you.