Classics in Total Synthesis - I
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Lecture - 18
Triquinanes

So, good morning and welcome back to the Classics in Total Synthesis, NPTEL lecture series. In the last lecture we talked about the application of photochemical reaction in the total synthesis of Triquinanes. So, we will continue our discussion on synthesis of few more triquinanes using different types of photochemical reaction and how they have successfully used this photochemical reaction in synthesis of triquinanes.

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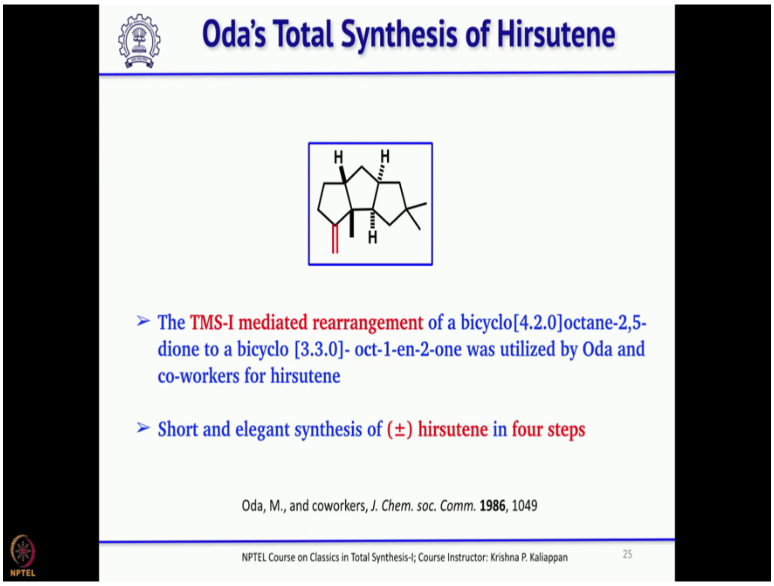

Oda's Total Synthesis of Hirsutene

- The TMS-I mediated rearrangement of a bicyclo[4.2.0]octane-2,5-dione to a bicyclo [3.3.0]- oct-1-en-2-one was utilized by Oda and co-workers for hirsutene
- Short and elegant synthesis of (±) hirsutene in four steps

Oda, M., and coworkers, *J. Chem. soc. Comm.* **1986**, 1049

So, first we will start with two total synthesis reported from Oda's group; one on hirsutene another one on capnellene. So, this is the structure of hirsutene and he again as I said he has used photochemical reaction as well as trimethylsilyl iodide mediated rearrangement of a bicyclic system as key reactions in the synthesis of hirsutene.

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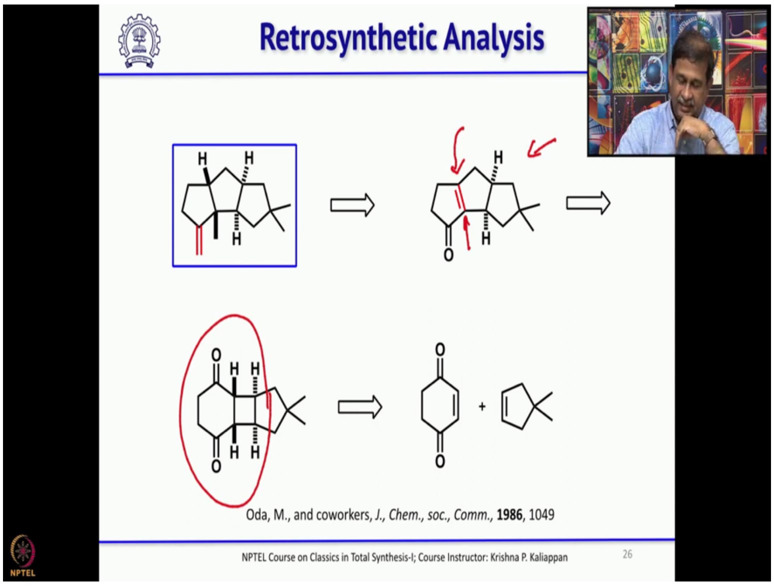

Retrosynthetic Analysis

Oda, M., and coworkers, *J., Chem., soc., Comm.*, **1986**, 1049

So, let us see how he has thought about it and according to him this molecule can be easily obtained as you can see obtained from this enone. You do a reductive alkylation at this carbon and followed by Wittig reaction one can convert this into the natural product and this can be obtained from this tricyclic compound using trimethylsilyl iodide mediated rearrangement of this bicyclic compound. The six-membered and four-membered it undergoes a rearrangement I will come back how this rearrangement takes place in a while.

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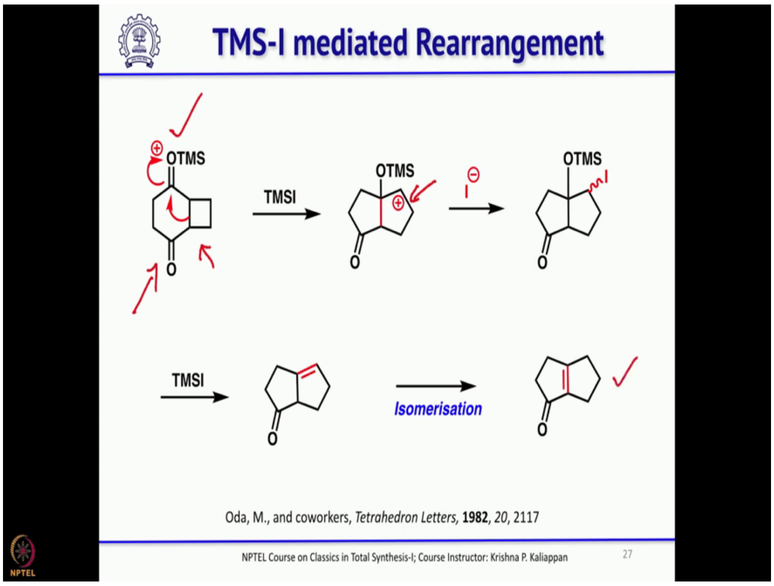

TMS-I mediated Rearrangement

Oda, M., and coworkers, *Tetrahedron Letters*, **1982**, *20*, 2117

And of course, this can be easily obtained by 2 plus 2 cycloaddition reaction. What is the trimethylsilyl iodide mediated rearrangement and how does it work? So, if you have a bicyclic system particularly a six-membered ring fused with a four-membered ring and if you treat with trimethylsilyl iodide. One of the carbonyl group will attack trimethylsilyl group and then you form the corresponding oxonium ion immediately the bond which is fusing the six-membered and four-membered ring.

So, will migrate as shown here to form a bicyclic compound where both the rings are five-membered ring. Once you have this carbocation iodide will attack and you will get the corresponding iodide this undergoes further cleavage to introduce the double bond. Both iodine and OTMS will eliminate to generate the double bond and that double bond under the same condition will isomerise to get the conjugated enone ok.

So, basically if you look at this reaction is done in two steps first a photochemical reaction 2 plus 2 to get this compound then you treat with trimethylsilyl iodide that rearranges to the bicyclic compound where both the rings are five membered rings ok.

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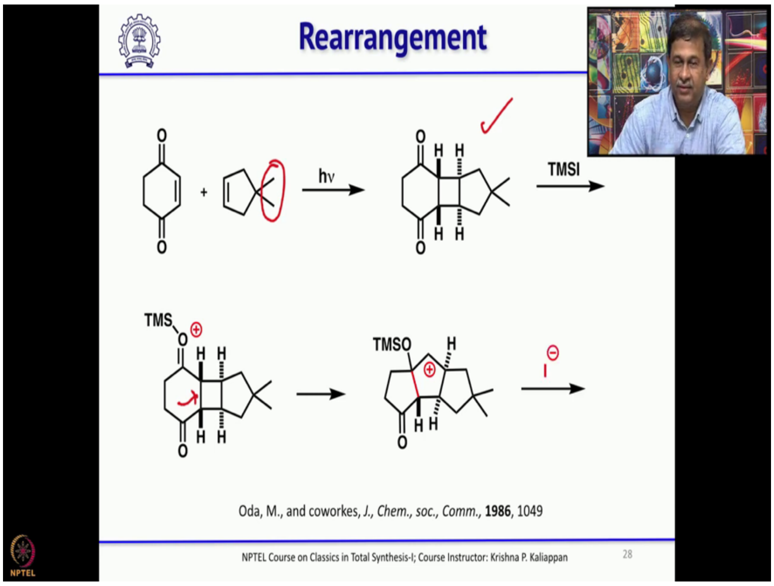

Rearrangement

Oda, M., and coworkes, J., *Chem., soc., Comm.*, **1986**, 1049

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Let us see how he has developed this for the synthesis of hirsutene. So, he took cyclohexenedione and then did 2 plus 2 cycloaddition with the cyclopentene having a gem dimethyl group to get this tricyclic compound then treat with trimethylsilyl iodide ok treat with trimethylsilyl iodide. So, which forms this intermediate followed by migration of this bond ok you get this tricyclic compound. And as I discussed in the previous slide this will be attacked by iodide followed by elimination.

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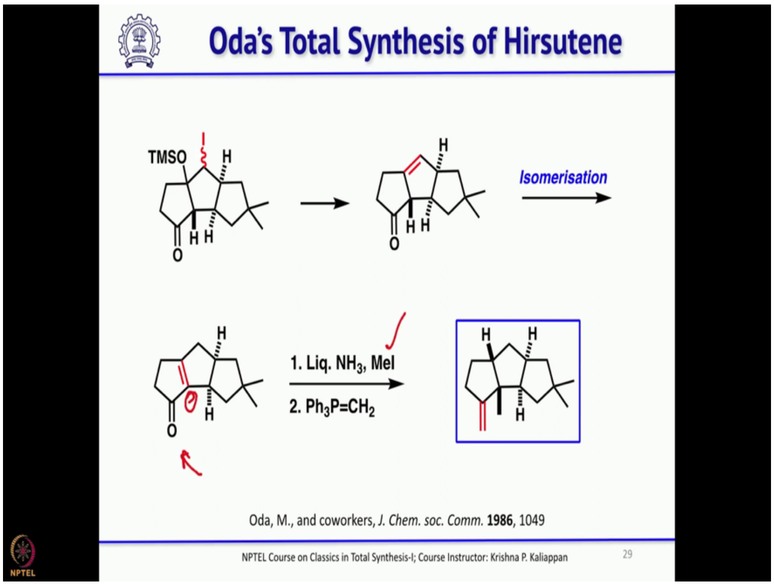

Oda's Total Synthesis of Hirsutene

1. Liq. NH_3, MeI

2. $Ph_3P{=}CH_2$

Oda, M., and coworkers, *J. Chem. soc. Comm.* **1986**, 1049

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You get the corresponding enone that undergoes isomerisation to give the tricyclic compound. So, this tricyclic compound you could easily get in two steps very interesting ok two steps. Then reductive alkylation was done with lithium in liquid ammonia.

So, lithium in liquid ammonia reduces and then you basically it reduces the double bond and generates an anion here that can be quenched with methyl iodide and followed by Wittig reaction on the ketone gives natural product. So, if you look at the synthesis in four steps Oda's group could successfully achieve the total synthesis of hirsutene.

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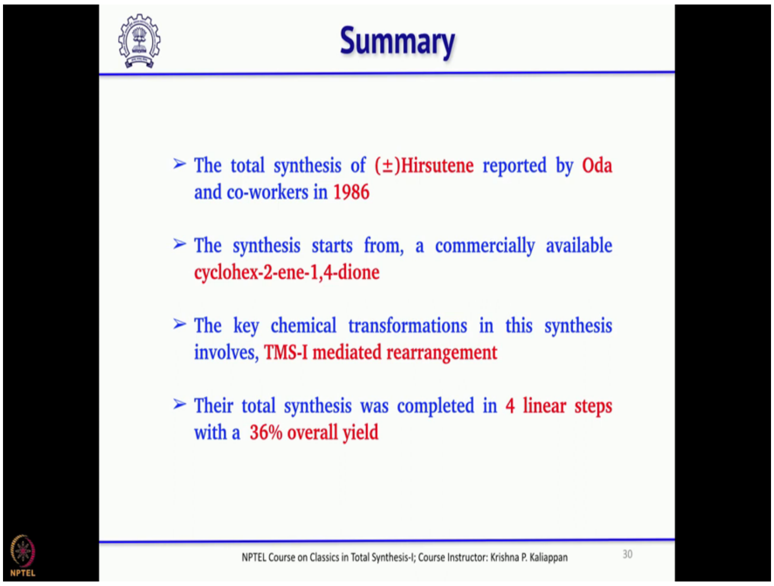

Summary

- ➢ The total synthesis of (±)Hirsutene reported by Oda and co-workers in 1986
- ➢ The synthesis starts from, a commercially available cyclohex-2-ene-1,4-dione
- ➢ The key chemical transformations in this synthesis involves, TMS-I mediated rearrangement
- ➢ Their total synthesis was completed in 4 linear steps with a 36% overall yield

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And overall yield is also very high and 36 percent overall yield for in a natural product total synthesis is considered as an excellent outcome. And that is mainly because you could do it in four steps and one of them is photochemical reaction other one is rearrangement. So, that is how he could successfully do this.

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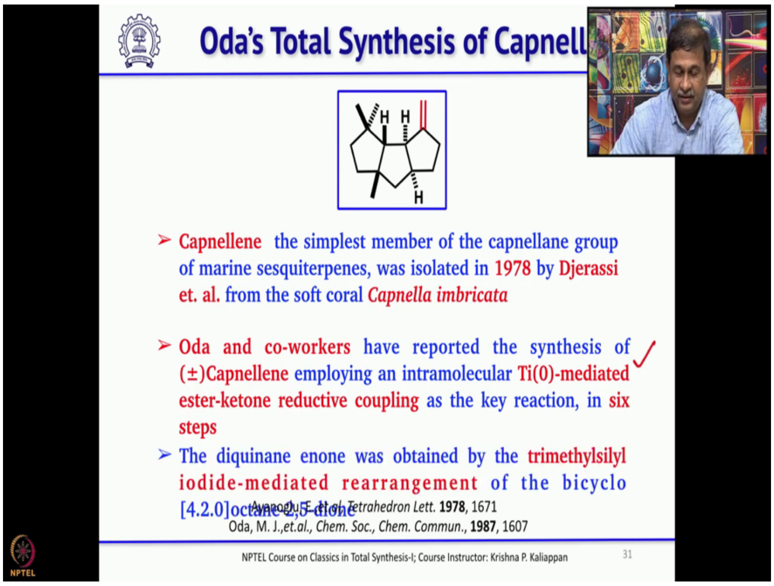

Oda's Total Synthesis of Capnell

- ➢ Capnellene the simplest member of the capnellane group of marine sesquiterpenes, was isolated in 1978 by Djerassi et. al. from the soft coral *Capnella imbricata*
- ➢ Oda and co-workers have reported the synthesis of (±)Capnellene employing an intramolecular Ti(0)-mediated ester-ketone reductive coupling as the key reaction, in six steps ✓
- ➢ The diquinane enone was obtained by the trimethylsilyl iodide-mediated rearrangement of the bicyclo [4.2.0]octane-2,5-dione

Ayanoglu, E. *et al.* *Tetrahedron Lett.* **1978**, 1671
Oda, M. J.,*et.al.*, *Chem. Soc., Chem. Commun.*, **1987**, 1607

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Then he extended the same methodology to its isomer capnellene. If you look at hirsutene and capnellene this I already discussed when I talked about initial introduction to triquinanes.

So, there is some minor modification or adjustment of alkyl groups between hirsutene to capnellene. So, he thought he could extend the same method to the total synthesis of capnellene and here he used one more key reaction that is titanium mediated ester ketone reductive coupling which later people call it as a Shapiro reaction which later people call it as McMurry coupling ok.

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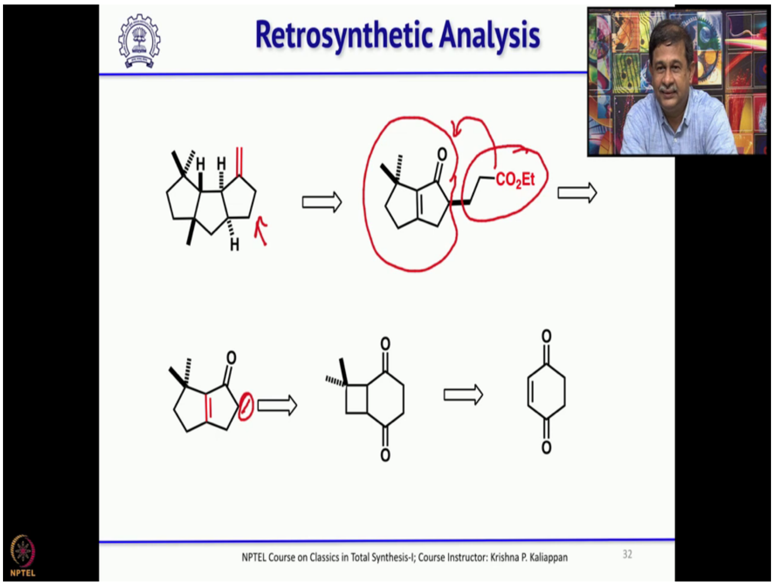

Retrosynthetic Analysis

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So, how he did this. Let us see his retro synthesis if you look at this portion as you know it comes from the TMS iodine mediated rearrangement. So, once you have that this three carbon unit can be easily introduced by Michael reaction with ethyl acrylate. And one can also cyclize this to get the corresponding ketone and then followed by Wittig reaction you can introduce the double bond this as I said one can use a Michael reaction to introduce the $CH_2CH_2CO_2Et$ and this is obtained by TMS iodide rearrangement and which in turn can be easily made from cyclohexene dione and isobutylene.

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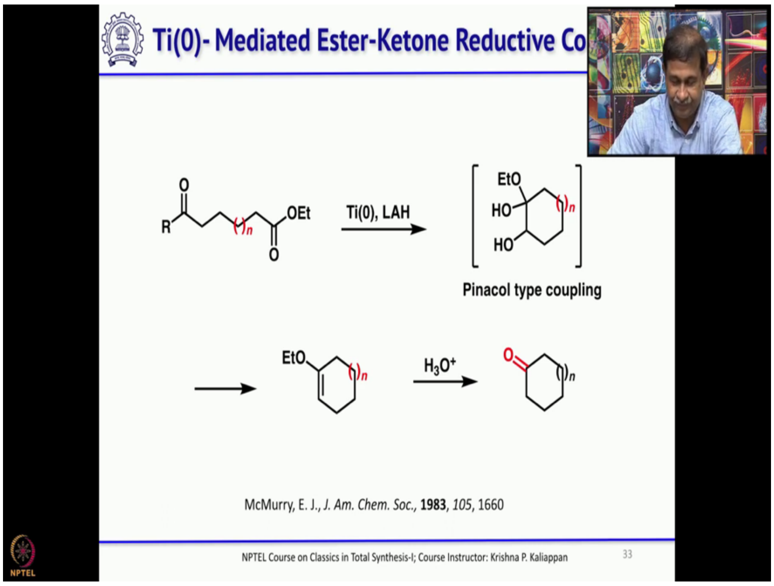

Ti(0)- Mediated Ester-Ketone Reductive Co

Pinacol type coupling

McMurry, E. J., *J. Am. Chem. Soc.*, **1983**, *105*, 1660

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And this McMurry coupling you know if you have a diketone and if you treat with titanium zero it can form either a ring with a double bond or it can form a diol ok, but if you have a keto ester same thing if you do first it will form the diol which is almost like pinacol type coupling then this will undergo elimination to get the enol ether which upon hydrolysis will give you the corresponding ketone.

So, this is what McMurry has reported if you have a ketone and an ester you will get the ketone. If you have two ketones you will get either diol or the diol will be further converted into the double bond.

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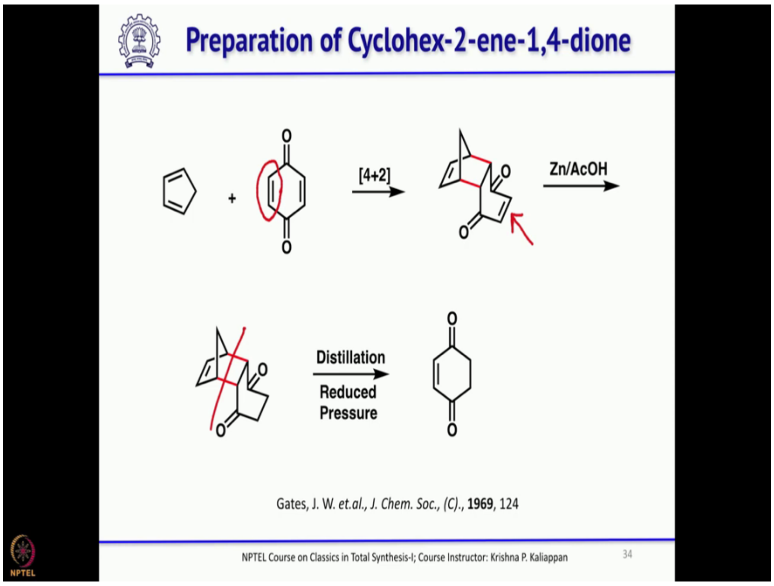

Preparation of Cyclohex-2-ene-1,4-dione

Distillation

Reduced Pressure

Gates, J. W. *et.al., J. Chem. Soc., (C).*, **1969**, 124

And the other starting material that is cyclohexene-1, 4-dione. So, that was not easy to prepare, but there are reports how one can make this in good quantity. So, this was done using a combination of Diels Alder reaction followed by reduction and pyrolysis. In three steps one can get or one can reduce one of the double bonds of benzoquinone ok.

See that is what you need is not it you take benzoquinone and reduce one of the double bonds. So, how it was done? First you do a Diels Alder reaction with cyclopentadiene and you get this tricyclic adduct then you have to selectively reduce the double bond which is in conjugation with two ketones that is very easily done by treating with zinc and acetic acid.

So, now if you do a pyrolysis if you heat it ok. If you heat it, it will undergo a retro Diels Alder reaction and this also can be done and if you heat it and then distill ok. So, while distillation under reduced pressure also one can do the same thing that is pyrolysis that is retro 2 plus 2 ok retro 2 plus 2 will give you the cyclohexene-1, 4-dione plus cyclopentadiene ok.

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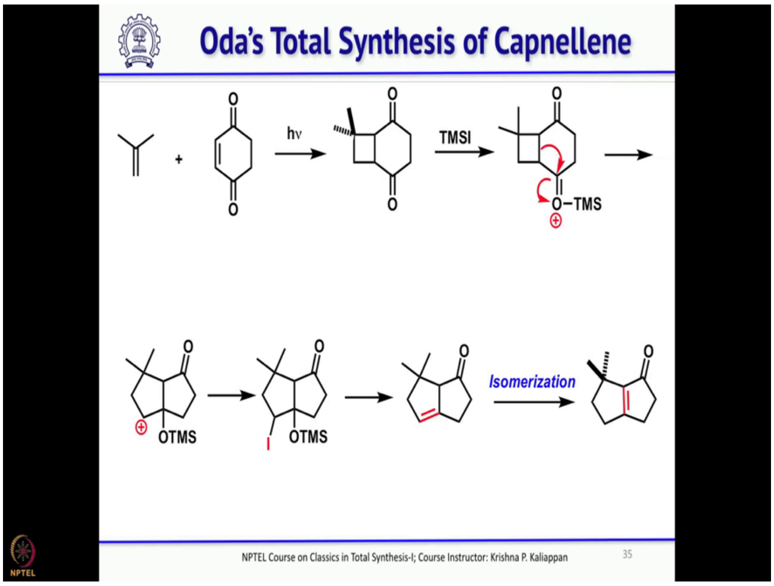

Oda's Total Synthesis of Capnellene

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So, this cyclohexene-1, 4-dione upon photochemical reaction with butylene will give you the bicyclic compound ok. This bicyclic compound upon treatment with trimethylsilyl iodide as I mentioned earlier for the hirsutene synthesis it undergoes rearrangement to give the corresponding bicyclic compound.

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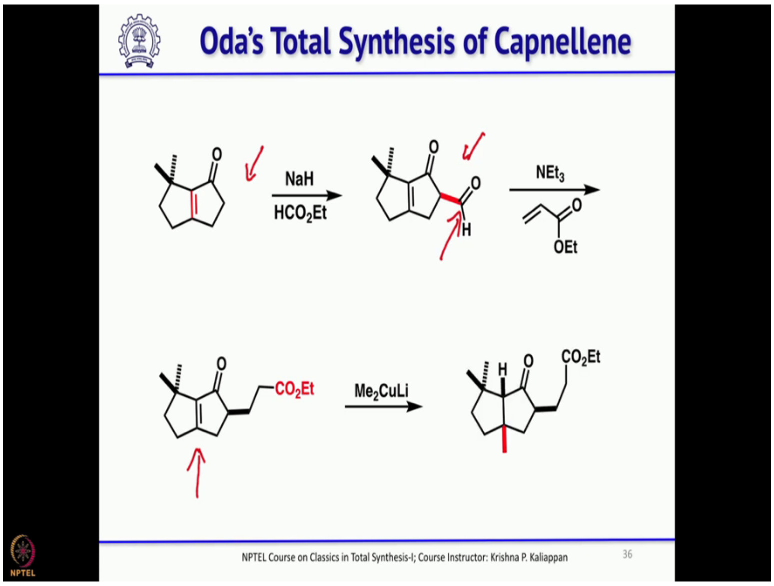

Oda's Total Synthesis of Capnellene

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This undergoes further elimination to get the bicyclic enone. Once you have this bicyclic enone then one can do the Michael addition product. For that first introduce a CHO that is normally done by treating with sodium iodide and quenching with ethyl formate you introduce the aldehyde then you do the Michael addition. So, Michael addition is done with triethylamine and ethyl acrylate. And after the Michael addition this aldehyde also undergoes a sort of retro Claisen to give only the Michael addition product aldehyde is easily removed.

Once you have that then you do the 1, 4-addition with lithium dimethylcuprate you could introduce the methyl group then you carry out the McMurry coupling reaction. You have a ketone you have an ester.

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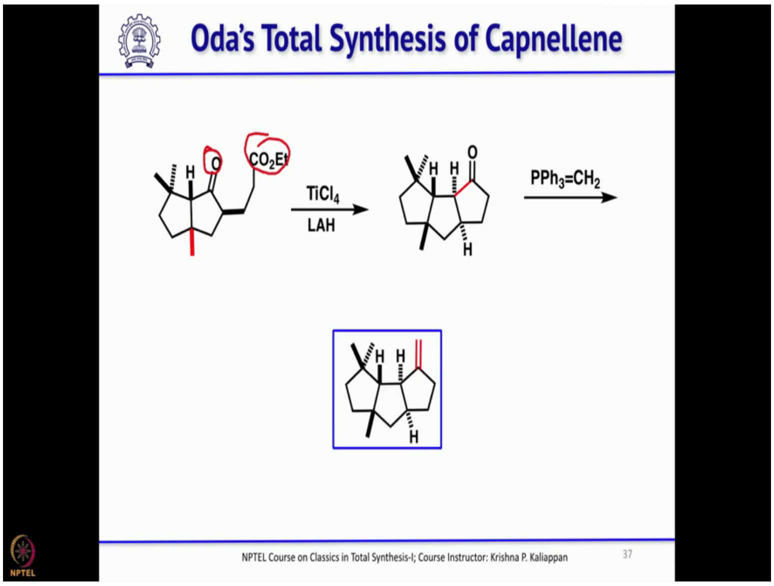

Oda's Total Synthesis of Capnellene

Then the McMurry coupling gives the five membered ketone ok forms the enol ether hydrolyzed to give the five membered ketone. The example where I have shown we formed six membered ketone here it is a five membered ketone once we have the ketone next step is just to form the double bond using Wittig reaction to get the corresponding natural product that is capnellene.

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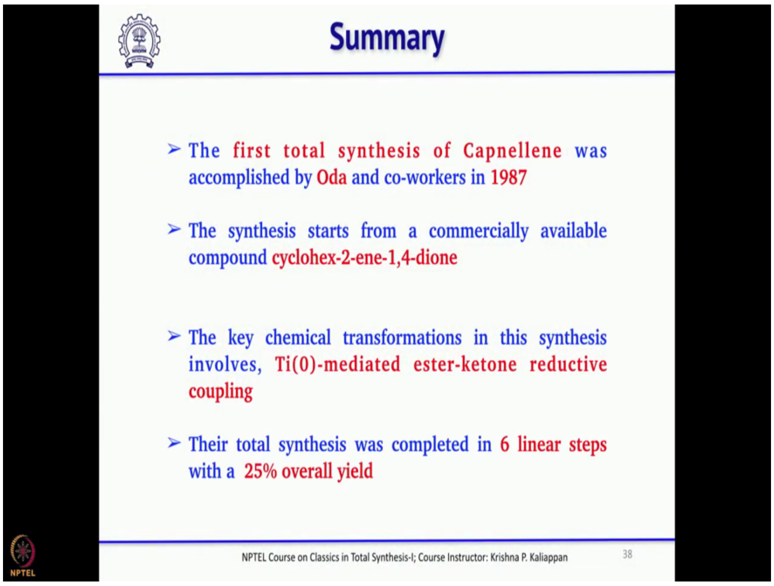

Summary

- The first total synthesis of Capnellene was accomplished by Oda and co-workers in 1987
- The synthesis starts from a commercially available compound cyclohex-2-ene-1,4-dione
- The key chemical transformations in this synthesis involves, Ti(0)-mediated ester-ketone reductive coupling
- Their total synthesis was completed in 6 linear steps with a 25% overall yield

So, to summarize Oda group could synthesize this capnellene in 1987 and the starting material was same for capnellene as well as hirsutene that is cyclohexene-1, 4-dione which is made from para benzoquinone by reducing the double bond the double bond was reduced selectively, but through three step sequence first Diels Alder reaction followed by reduction of the double bond and retro Diels Alder reaction and the second key reaction was the McMurry coupling of the ester and ketone to get the ketone.

And overall the whole synthesis was done or accomplished in 6 longest linear steps with an overall yield of 25 percent. So, 25 percent overall yield for any natural production so quite high and it was very successful one.

So, now, we will move to another very interesting photochemical reaction which has been successfully used by Paul Wender’s group and also others.

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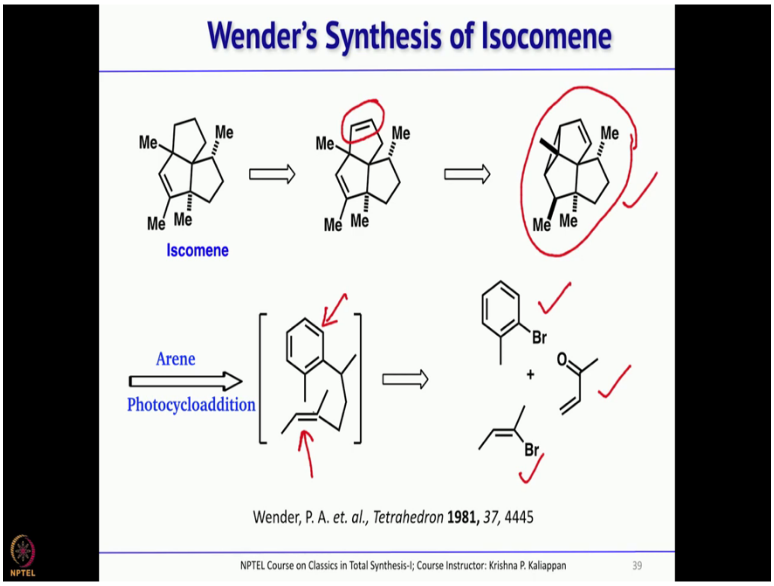

Wender's Synthesis of Isocomene

Arene Photocycloaddition

Wender, P. A. *et. al.*, *Tetrahedron* **1981,** *37*, 4445

So, here what he has used is a meta photocycloaddition reaction of an aromatic compound with a double bond as a key reaction to make many natural product belonging to triquinanes. One such natural product which we will discuss is isocomene and his idea is this is the first retrosynthesis you can see you introduce a double bond and the double bond if you reduce you get isocomene and this can be obtained by this particular tetracyclic intermediate where you can see a cyclopropane ok.

Now, let us see how he makes this cyclopropane he used a very clever arene meta photocycloaddition reaction as the key reaction. So, you can see an aromatic ring and a double bond. This under photochemical condition undergoes this arene meta photocycloaddition to give this tricyclic compound. I will come to that how this is done and this can be obtained easily in few steps starting with two bromo toluene and methyl vinyl ketone and another bromo butene ok.

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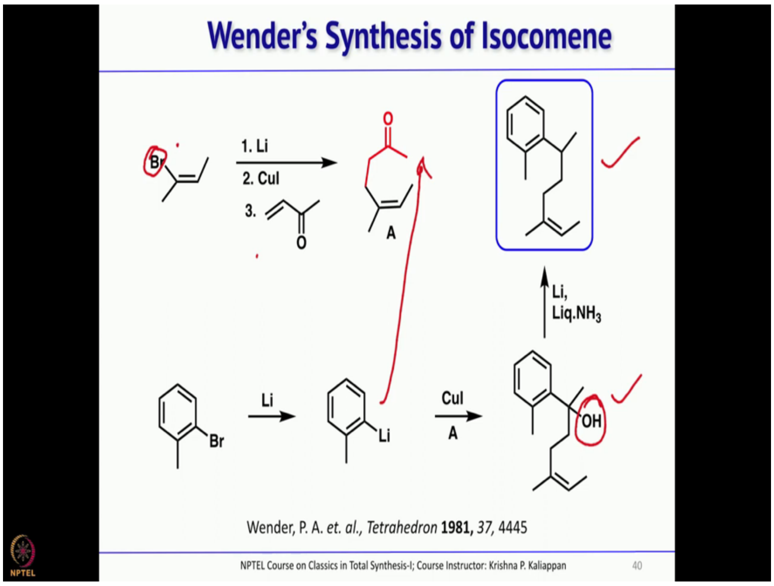

Wender's Synthesis of Isocomene

Wender, P. A. *et. al.*, *Tetrahedron* **1981,** *37,* 4445

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So, before going into the details I will discuss about this arene meta photo cycloaddition. And before that the starting material that is this aromatic compound how they made it. You take this two bromo trans butene and treat with lithium. So, you will exchange the bromine with lithium then exchange with copper and that undergoes 1, 4-addition with methyl vinyl ketone to get this intermediate.

This intermediate then you add to a lithium derivative of two bromotoluene and cuprous iodide. So, that will give you this alcohol ok. This lithium if you add to this ketone you will get this compound ok. Now again if you treat with lithium in liquid ammonia. So, this benzylic alcohol will be cleaved and you get the starting material which is required for the photocycloaddition reaction.

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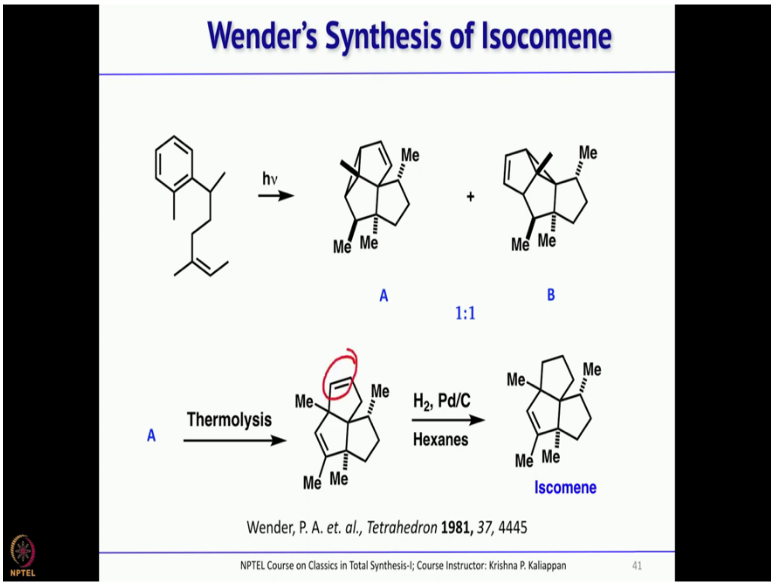

Wender's Synthesis of Isocomene

Wender, P. A. *et. al.*, *Tetrahedron* **1981,** *37,* 4445

So, this photocycloaddition reaction gives you this intermediate as well as B ok. So, A and B they are obtained in almost equal amount and if you take A and again heat it ok. So, after photochemical reaction you isolate that and then heat it this will undergo. So, opening of the cyclopropane to give this diene ok. And that if you reduce selectively only this double bond you will get isocomene.

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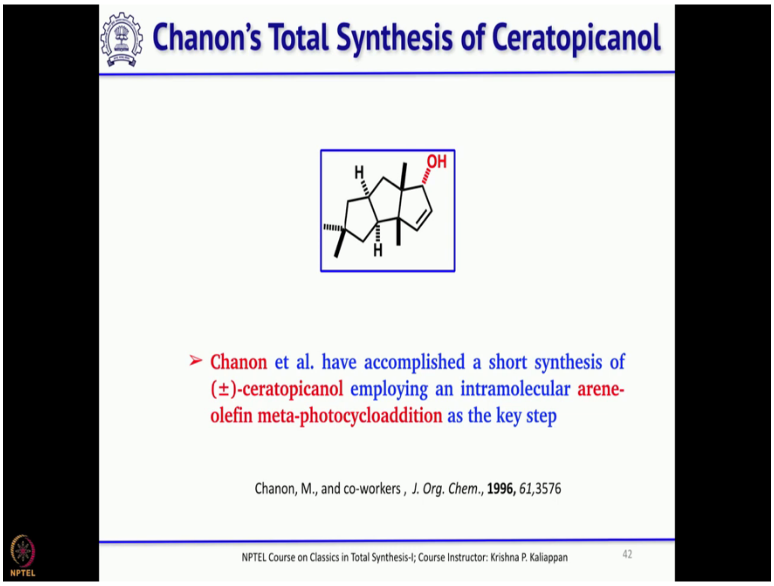

Chanon's Total Synthesis of Ceratopicanol

- Chanon et al. have accomplished a short synthesis of (±)-ceratopicanol employing an intramolecular arene-olefin meta-photocycloaddition as the key step

Chanon, M., and co-workers , *J. Org. Chem.*, **1996,** *61*,3576

And this method was extended for the total synthesis of ceratopicanol again same arene olefin meta photocycloaddition was used following what Wender has reported as you can see here.

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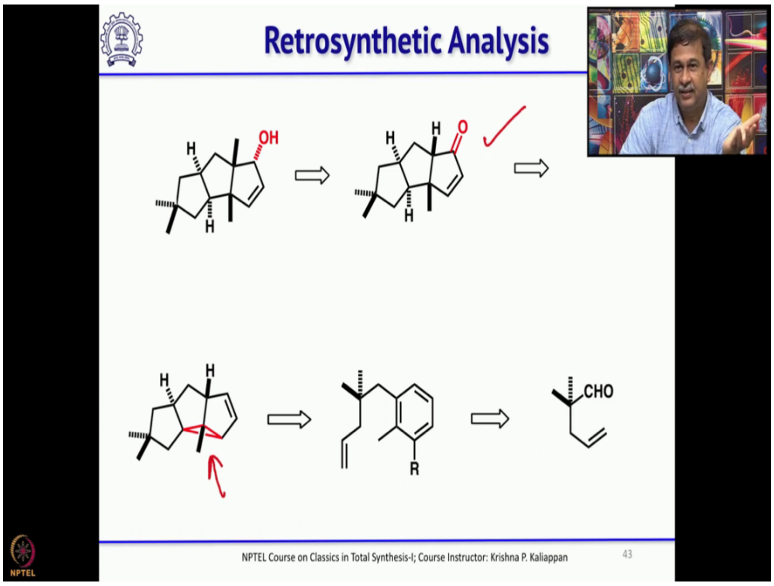

Retrosynthetic Analysis

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This can be obtained from the corresponding enone by simple reduction and this can be obtained again from this cyclopropene ok. And which in turn can be obtained from this aromatic substituted compound ok.

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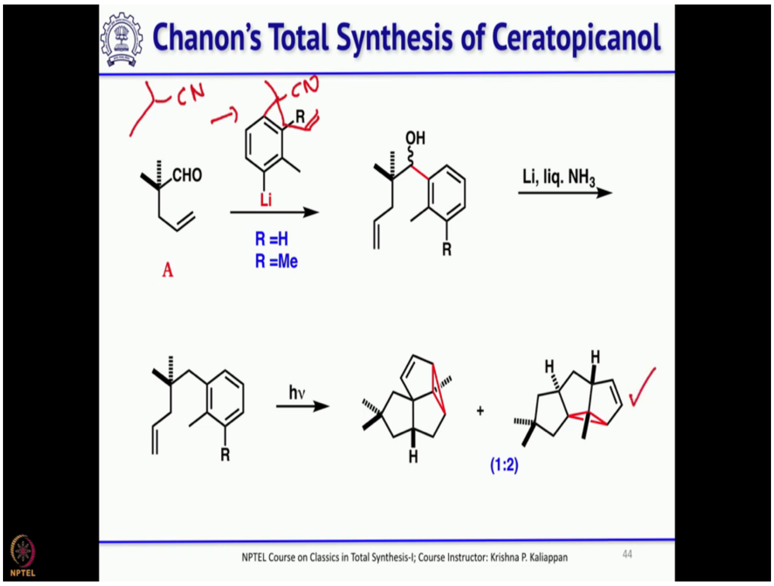

Chanon's Total Synthesis of Ceratopicanol

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How he synthesized? So, he took this aldehyde. So, this aldehyde can be obtained in two steps from isobutyronitrile you take isobutyronitrile and treat with base like LDA and quench with allyl bromide and you will get corresponding the allyl group. This upon reduction with DIBAL you get the corresponding aldehyde and this aldehyde on treatment with this lithium you will get the alcohol and further reduction gives you the precursor for arene meta photocycloaddition reaction.

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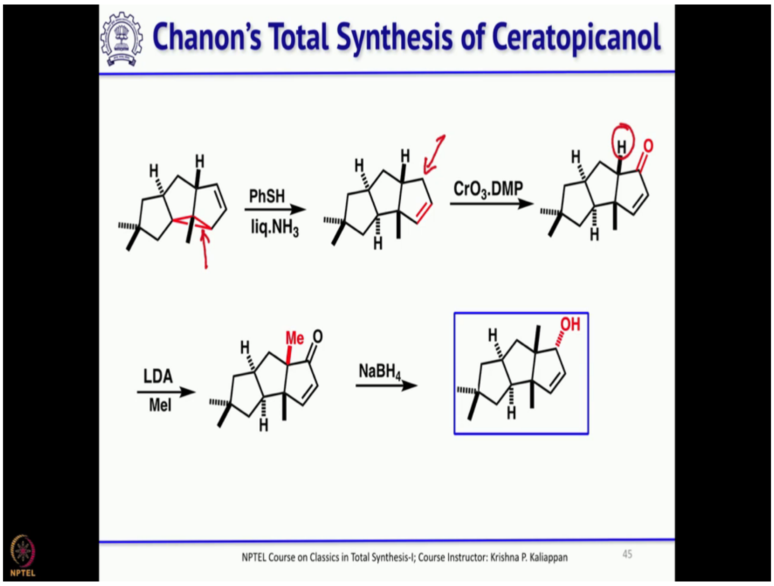

Chanon's Total Synthesis of Ceratopicanol

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So, this undergoes arene meta photocycloaddition to give these two products where this is the major product. Take this major product and then treat with benzenethiol in liquid ammonia. So, what happens in the presence of liquid ammonia benzenethiol forms PhS radical ok. So, that undergoes a 1, 4-addition that undergoes a 1, 4-addition and pushes the double bond ok. And followed by lithium in liquid ammonia cleaves the SPh. So, basically the cyclopropane is opened up with benzenethiol.

And when it opens up the double bond also migrates then the SPh is reductively cleaved with lithium ammonia to get the double bond. Now you need a functional group here is not it you need a you need a hydroxyl group there. So, that is done by treating with chromium trioxide dimethyl pyrazole to get the ketone and that was reduced to get alcohol before that you know you need a methyl group here ok. This place you need a methyl group.

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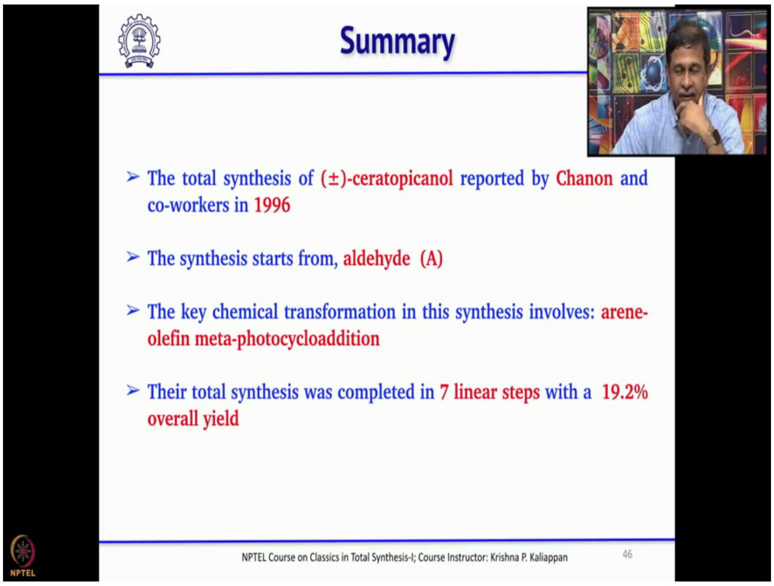

Summary

- The total synthesis of (±)-ceratopicanol reported by Chanon and co-workers in 1996
- The synthesis starts from, aldehyde (A)
- The key chemical transformation in this synthesis involves: arene-olefin meta-photocycloaddition
- Their total synthesis was completed in 7 linear steps with a 19.2% overall yield

So, you treat with LDA and quench with methyl iodide you can introduce the angular methyl group and followed by reduction with sodium borohydride you get corresponding ceratopicanol. I will complete the whole process of photochemical reactions being used at the total synthesis of triquinanes with one more total synthesis again reported by Wender and that is about total synthesis of subergorgic acid ok.

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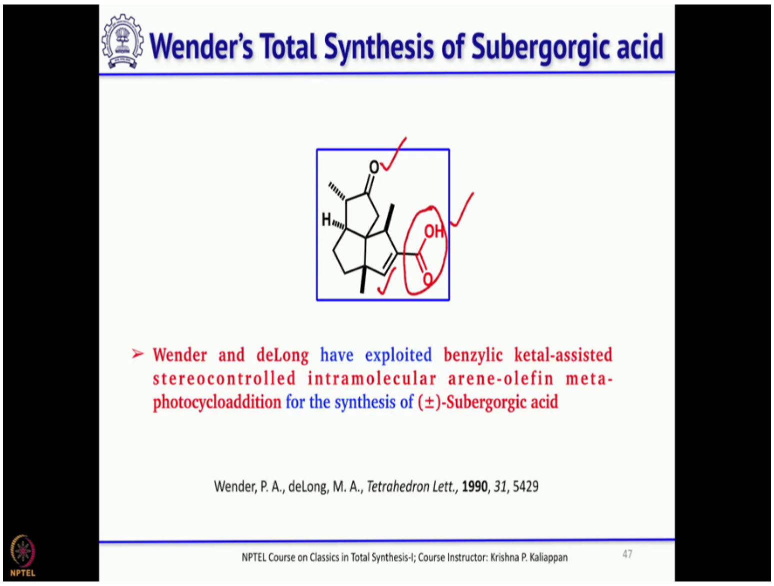

Wender's Total Synthesis of Subergorgic acid

- Wender and deLong have exploited benzylic ketal-assisted stereocontrolled intramolecular arene-olefin meta-photocycloaddition for the synthesis of (±)-Subergorgic acid

Wender, P. A., deLong, M. A., *Tetrahedron Lett.*, **1990**, *31*, 5429

So, this is an angular triquinane ok having a carboxylic acid ok. So, now, if you look at this particular compound has three functional groups. One you have a ketone then you have a double bond and third one is the carboxylic acid. And Wender could use successfully the arene olefin meta photocycloaddition reaction to get this compound.

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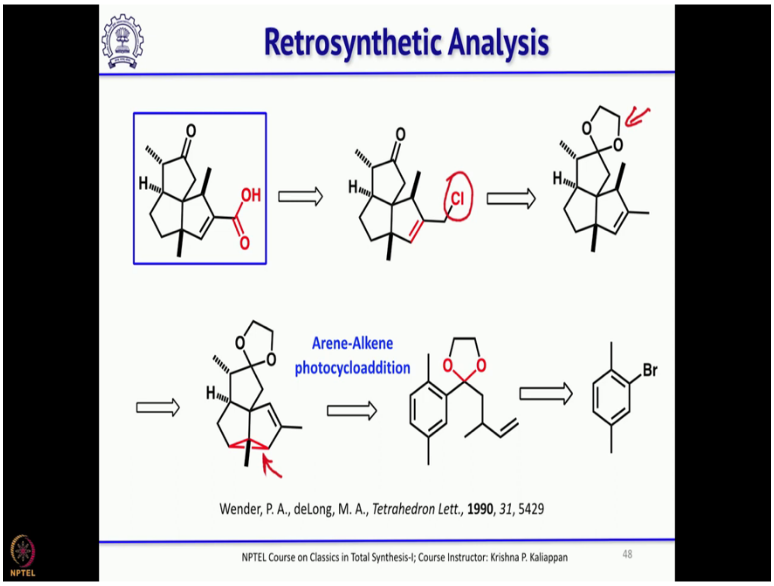

Retrosynthetic Analysis

Arene-Alkene photocycloaddition

Wender, P. A., deLong, M. A., *Tetrahedron Lett.*, **1990**, *31*, 5429

How he has devised this retrosynthetic analysis? This acid if you have a CH_2Cl or CH_3 ok that methyl group attached to the double bond can be converted into carboxylic acid ok. It can be just simple methyl also ok that can be converted into the corresponding carboxylic acid ok.

And the ketone it is better to protect it. So, that you know it will not interfere in other reactions and that can be obtained from this tetracyclic compound using the photocycloaddition reaction. Obviously, the precursor for this is this arene substituted compound and that can be obtained from 2-bromo-1, 4-dimethyl benzene ok. So, that is the commercially available starting material.

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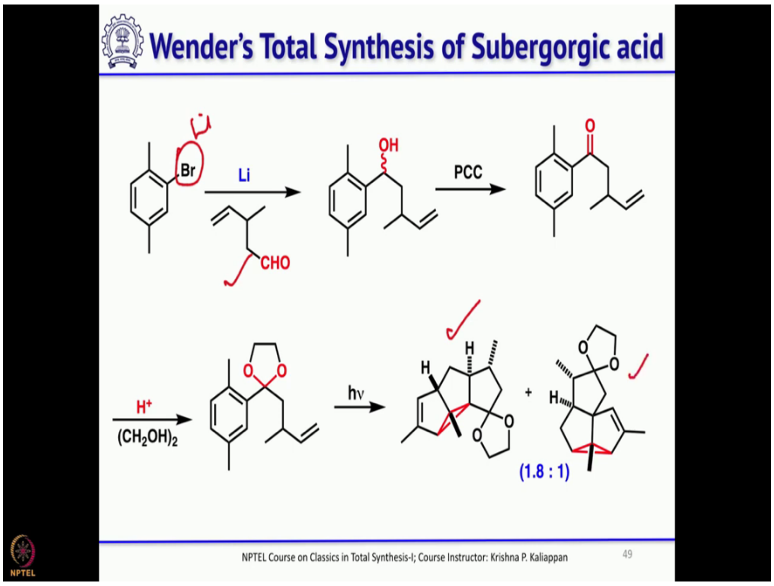

Wender's Total Synthesis of Subergorgic acid

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So, you take this 2-bromo-1, 4-dimethyl benzene and treat with lithium. So, you exchange this with lithium and then add this aldehyde ok. So, this aldehyde also you know quite easy to make you have to think about using Claisen rearrangement. This is an exercise. Think about it if you use a Claisen rearrangement you will get this aldehyde then you will get this benzylic alcohol oxidize this benzylic alcohol with PCC to get ketone. Then protect this ketone as the corresponding ketal then do the key meta photocycloaddition reaction that gives a mixture of these two.

One is the linear triquinane other one is the angular triquinane one. So, separate these two take the angular one and again use a radical condition.

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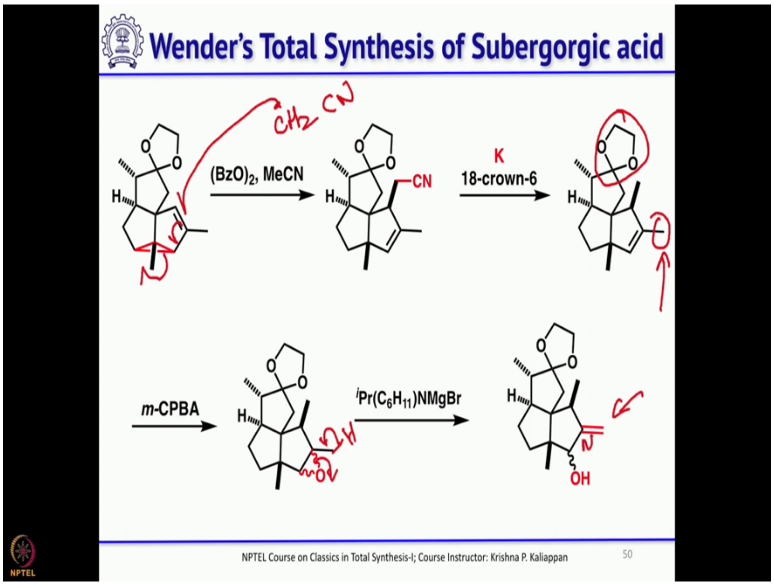

Wender's Total Synthesis of Subergorgic acid

NPTEL Course on Classics in Total Synthesis-I; Course Instructor: Krishna P. Kaliappan

You use the benzoyl peroxide and acetonitrile benzoyl peroxide and acetonitrile it forms a sort of you know benzoyl peroxide generates this CH_2CN radical. And that undergoes a 1, 4-addition like it attacks this double bond and the double bond migrates and then breaks this. It is almost like 1, 4-addition concurrently breaking the cyclopropane.

Now you do not need the cyanide ok you need you know methyl group only there. So, you can use potassium in 18 crown 6. It will reductively cleave the cyanide and you will get the methyl group ok. Now what you need? You need to remove this ketal as well as oxidize the methyl group to corresponding carboxylic acid.

So, if you treat with mCPBA there is only one double bond. So, the double bond will become the epoxide. You make this epoxide. Now if you treat with base strong base ok. You can use LDA or you can use isopropyl cyclohexane magnesium bromide. So, that is the base that will act as a base basically what you will get is corresponding allylic alcohol.

So, basically this will open up the epoxide to get corresponding allylic alcohol. So, what you need? As I said this methyl group should be converted into corresponding carboxylic acid ok. So, it took little bit more steps than what they would have expected. Then you have to functionalize this here. The double bond should be functionalized at the same time the double bond has to move here. So, this was easily done by treating with thionyl chloride

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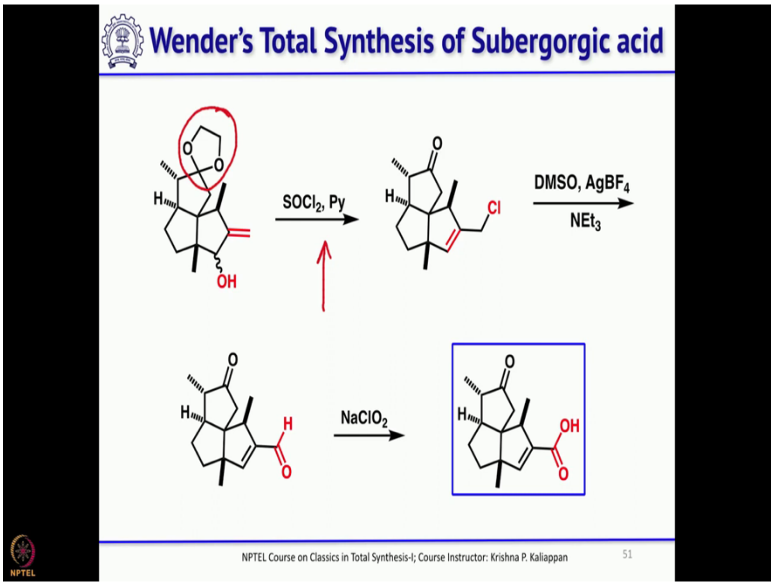

Wender's Total Synthesis of Subergorgic acid

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So, what will happen? The double bond will migrate and you will get a corresponding CH_2Cl allyl chloride. So, once you have this allylic chloride. So, you do treat with silver fluoroborate and DMSO you will get the corresponding aldehyde ok. It is a DMSO based reagent ok. So, that is very easy to oxidize a chloride to corresponding aldehyde. Then Pinnick oxidation gives the corresponding carboxylic acid. So, that is the natural product.

But what you should remember is during the thionyl chloride reaction not only the allylic alcohol was converted into the corresponding allyl chloride with the displacement in the form of SN_2I reaction, but also the ketal was cleaved because when you use thionyl chloride HCl also will be formed ok. Though use pyridine the HCl pyridine HCl also is sufficient to cleave the ketal to give ketone.

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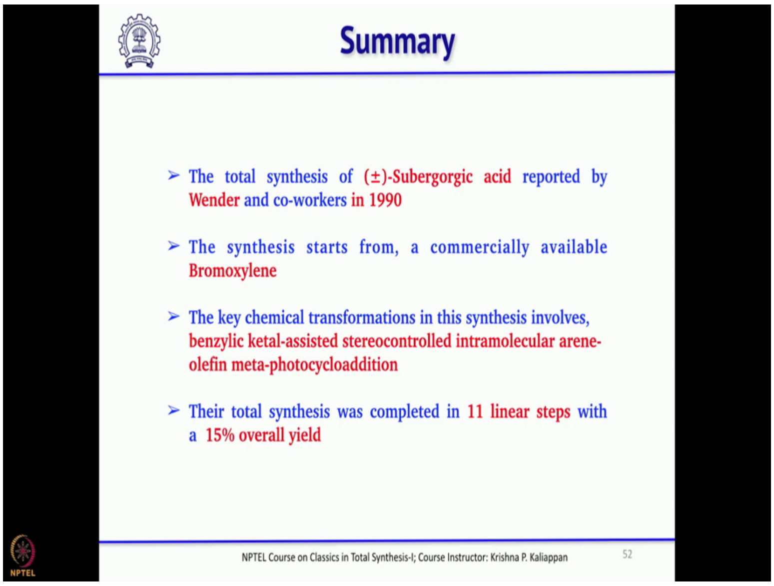

Summary

- The total synthesis of (±)-Subergorgic acid reported by Wender and co-workers in 1990
- The synthesis starts from, a commercially available Bromoxylene
- The key chemical transformations in this synthesis involves, benzylic ketal-assisted stereocontrolled intramolecular arene-olefin meta-photocycloaddition
- Their total synthesis was completed in 11 linear steps with a 15% overall yield

So, to summarize Wender’s group reported the total synthesis of subergorgic acid in 1990 using the reaction that is arene a meta arene photocycloaddition reaction and they started with bromo para-xylene as the starting material and as I said the key reaction is the arene olefin meta photocycloaddition. So, this reaction this particular synthesis took little bit longer steps. So, it took about 11 steps still the overall yield was 15 percent ok. So, that is a really interesting method to make such a natural product ok.

Thank you.