Classics in Total Synthesis-I
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Lecture - 13
Triquinanes: Isocomene 1) M. Pirrung 2) Fitjer

Good morning and welcome back to the NPTEL lecture series on Classics in Total Synthesis Part- 1 and today what we will do, we will move to a new class of natural products called Triquinanes and after a brief introduction, we will talk about total synthesis of at least one such triquinane and the next few lectures we will discuss more about various total synthesis of several triquinanes.

So, what are these triquinanes? As you know we have seen many natural products having 5 - membered as one of the key rings in the natural product.

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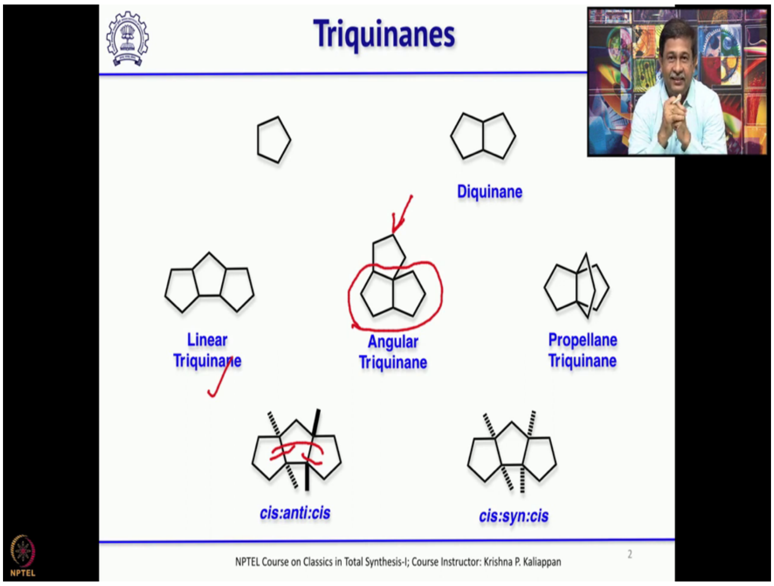

Triquinanes

Diquinane

Linear Triquinane

Angular Triquinane

Propellane Triquinane

cis:anti:cis

cis:syn:cis

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And this 5 - membered ring can be called as quinine there are 5 carbon atoms so you can call that as quinine. If two 5 - membered rings are fused then you can call that as diquinane ok two 5- membered rings are fused so, you can call them as diquinane.

And if three 5- membered rings are fused ok, if three 5- membered rings are fused then there are three possibilities ok. One they are fused in a linear fashion ok if they are fused in linear fashion then they are called linear triquinane ok and on the diquinane if you add one more 5 - membered ring in an angular fashion you can see this is the diquinane and you are adding one more 5 - membered ring in an angular fashion then they are called angular triquinanes.

Then the third ring third 5 - membered ring if you attach in such a way that if they if they look like propellane. So, then that is the third category propellane type triquinanes. And when you talk about linear triquinanes then there are two types; one cis: anti: cis, if you look at the relationship between these two rings they are cis.

However, the relationship between the first and third ring that is anti; however, the relationship between the second and third ring is cis. So, that is why this is called cis anti cis and then you also have cis: syn: cis system ok. So, when you look at many natural products belonging to linear triquinanes you will see both skeleton present ok.

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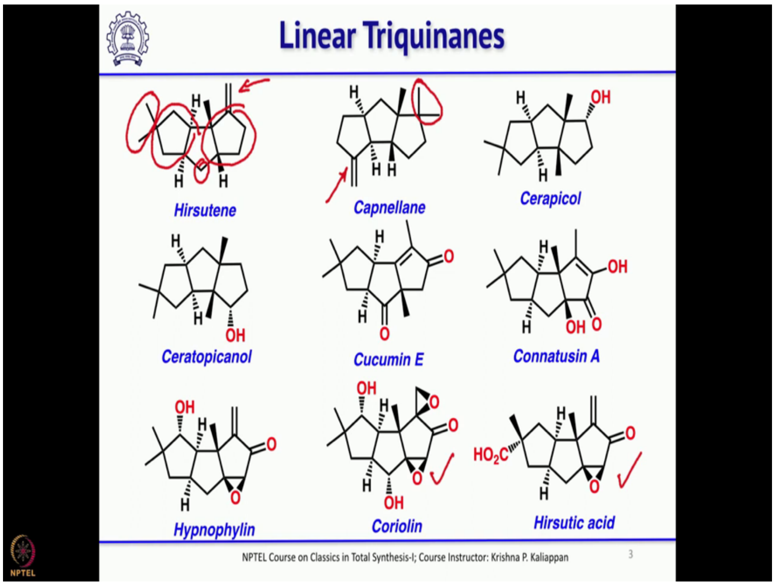
Linear Triquinanes

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Likewise, you can see if you look at the Linear Triquinanes closely the core structure has 11 carbon atoms, this is a 5 - membered ring and this is a 5 - membered ring and there is one extra carbon atom which is also part of the 5 - membered ring. So, there are 11 carbons which forms the core structure of any triquinane.

So, the remaining 4 carbon atoms because they are sesqueterpenes. So, the remaining 4 carbon atoms are distributed across this 11 carbon atom. The way they are distributed, way you have oxygen functionalities, you can see several linear triquinanes. See, if you look at the difference between hirsutene and capnellane ok. The hirsutene has exocyclic double bond here whereas, capnellane has here and then hirsutene has a dimethyl group here whereas, it has dimethyl group here.

So, like this subtle changes will lead to different natural products, this is based on their way they cyclize during the biosynthesis and accordingly you know you see different natural products and quite a few are highly oxygenated as you can see in hirsutic acid, coriolin, there are 3 to 4 oxygen atoms present in such natural products.

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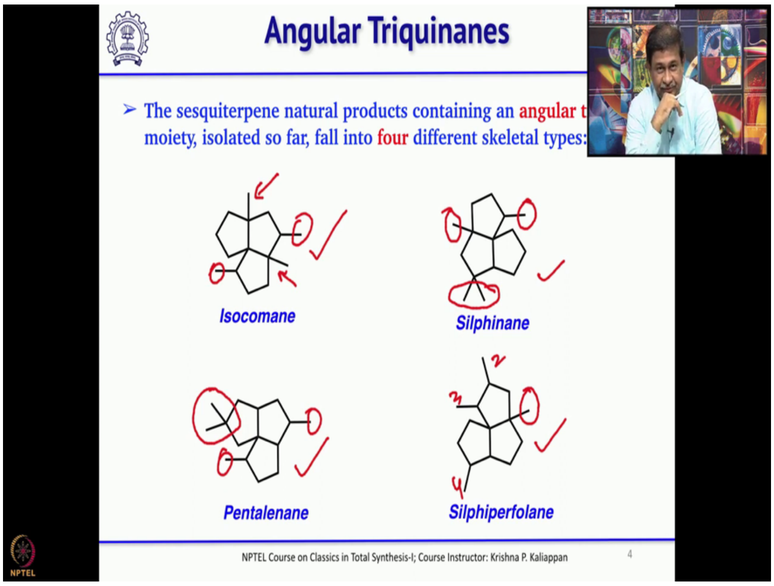

Angular Triquinanes

- The sesquiterpene natural products containing an angular t moiety, isolated so far, fall into four different skeletal types:

Isocomane

Silphinane

Pentalenane

Silphiperfolane

Coming to Angular Triquinanes, again angular triquinanes of a skeleton wise they are of four types: one for example, if you look at this isocomane angular triquinanes. There are four methyl groups in that two are angular methyl group ok, two are angular methyl groups, the remaining two they are attached to a tertiary carbon atom they are attached to tertiary carbon atom.

And in the case of silphinane, we have one angular methyl group, one methyl group which is attached to tertiary carbon atom and then you have two methyl groups they are gem dimethyl and they are quaternary ok. Same way pentalenane you can see two quaternary methyl groups and two methyl groups which are attached to tertiary carbon atom two methyl groups which are attached to tertiary carbon atoms.

And silphiperfolane type angular triquinanes it has only one angular methyl group the remaining three methyl groups are attached to tertiary carbon atoms ok.

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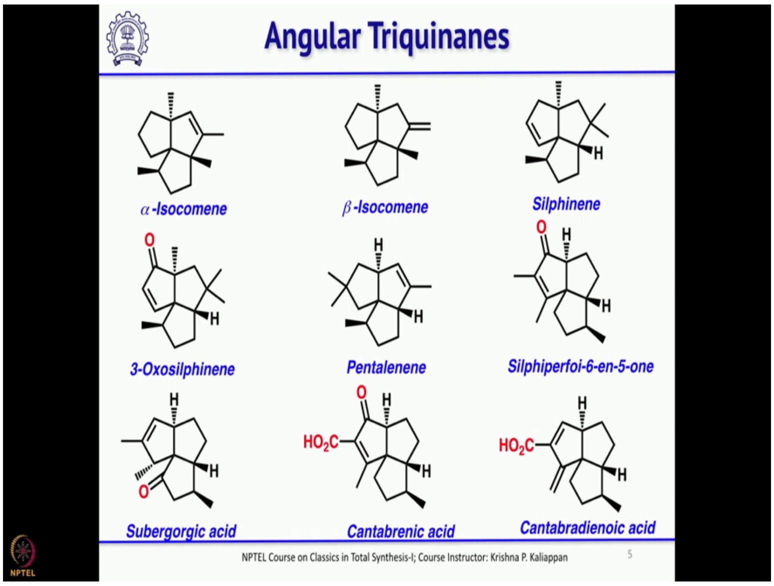

Angular Triquinanes

α-Isocomene

β-Isocomene

Silphinene

3-Oxosilphinene

Pentalenene

Silphiperfoi-6-en-5-one

Subergorgic acid

Cantabrenic acid

Cantabradienoic acid

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And there are many angular triquinanes here are some alpha isocomene, beta isocomene, silphinene and so on ok. We will try to cover total synthesis of some of them and as you know each group would have used different key reactions to make these natural products. So, over a period while talking about various total synthesis of triquinanes you also will know or you also will get an idea, how such molecules can be synthesized using different key reactions and different key strategies.

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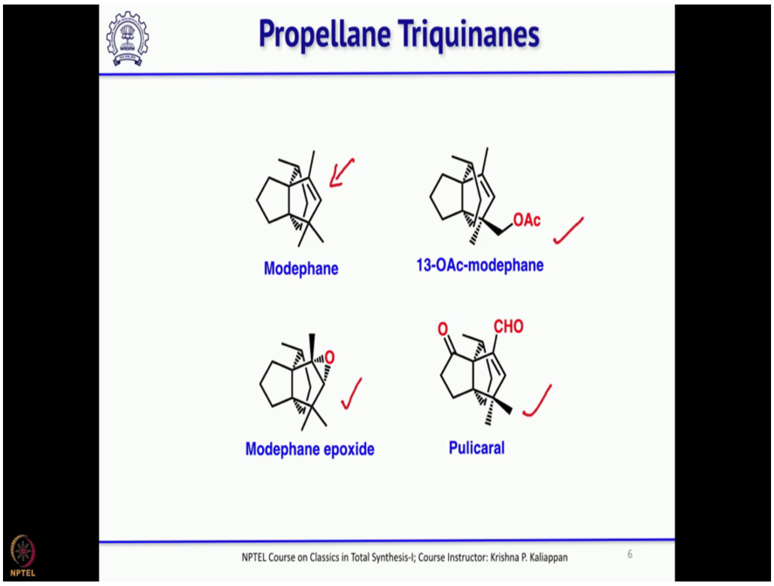

Propellane Triquinanes

Modephane

13-OAc-modephane

Modephane epoxide

Pulicaral

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Coming to the third one that is a propellane type triquinanes, the third ring ok, you can see first the basic diquinanes almost same only the third one is different and some of them are oxygenate ok.

So, for example, this one a modephane epoxide and pulicaral. So, these three are oxygenated, the basic one which is just modephane having only a double bond ok.

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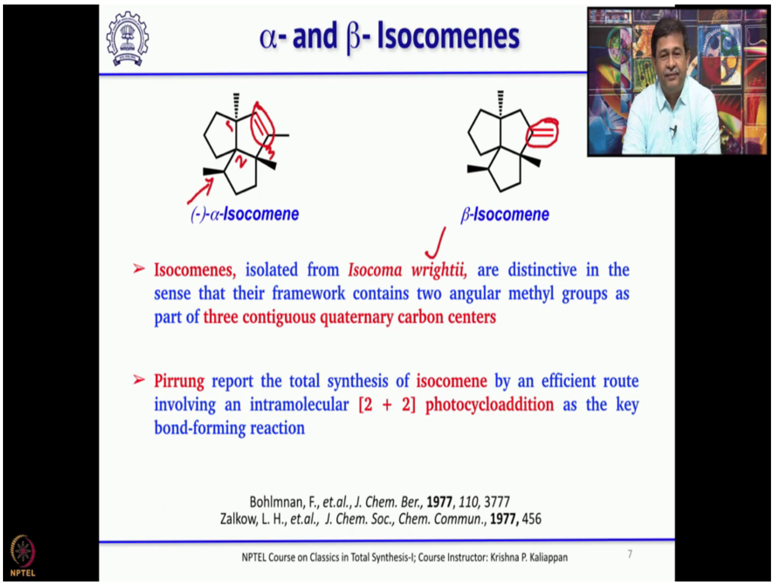

α- and β- Isocomenes

(-)-α-Isocomene

β-Isocomene

- Isocomenes, isolated from *Isocoma wrightii,* are distinctive in the sense that their framework contains two angular methyl groups as part of three contiguous quaternary carbon centers
- Pirrung report the total synthesis of isocomene by an efficient route involving an intramolecular [2 + 2] photocycloaddition as the key bond-forming reaction

Bohlmnan, F., *et.al., J. Chem. Ber.,* **1977**, *110*, 3777
Zalkow, L. H., *et.al., J. Chem. Soc., Chem. Commun.,* **1977**, 456

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Now, what we will do, we will talk about the total synthesis of alpha and beta isocomenes today. And this isocomenes were isolated from Isocoma wrightii and a closer look at these molecules, you can see that there are three contiguous quaternary center ok 1, 2, 3 there are three contiguous quaternary carbons ok.

So, always construction of quaternary carbons is not easy ok and particularly if you have to construct stereo selectively it is really a tough job and in addition you have one chiral center, the difference between alpha and beta isocomene is the position of the double bond. In the case of alpha isocomene you have internal double bond whereas; in the case of beta isocomene you have external double bond.

So, first let us start with the synthesis of isocomene by Michael Pirrung and Michael Pirrung used an intramolecular 2 plus 2 photocycloaddition as the key step.

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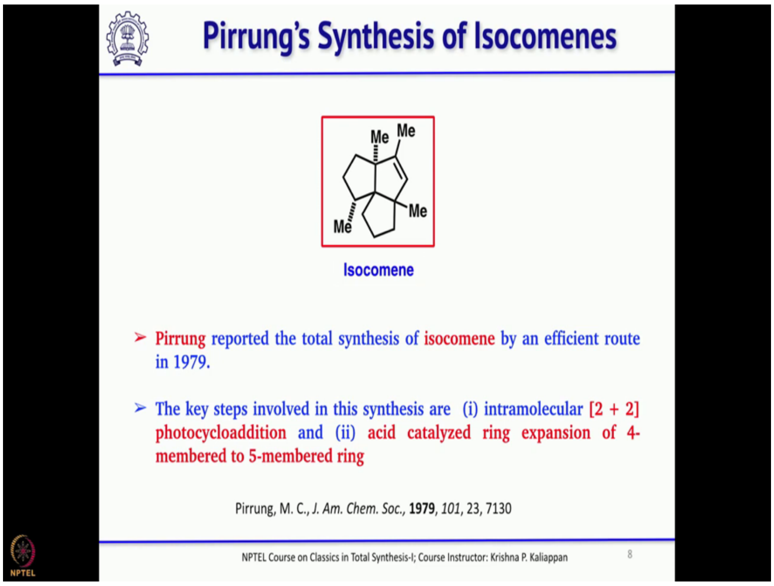

Pirrung's Synthesis of Isocomenes

Isocomene

- Pirrung reported the total synthesis of isocomene by an efficient route in 1979.
- The key steps involved in this synthesis are (i) intramolecular [2 + 2] photocycloaddition and (ii) acid catalyzed ring expansion of 4-membered to 5-membered ring

Pirrung, M. C., *J. Am. Chem. Soc.*, **1979**, *101*, 23, 7130

And this is the structure of isocomene he also used one more key reaction that is ring expansion under acidic condition. The first key reaction is intramolecular 2 plus 2 photocycloaddition and the second one is acid-catalyzed ring expansion of 4 - membered ring to 5 - membered ring.

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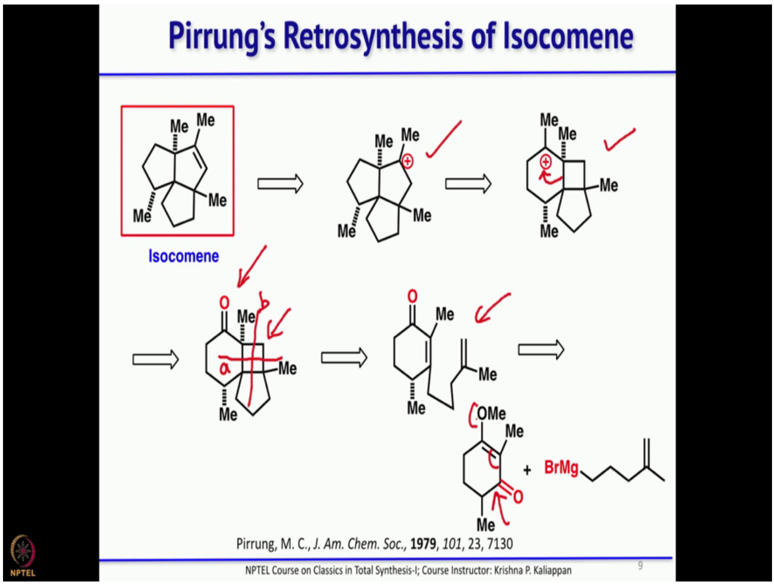

Pirrung's Retrosynthesis of Isocomene

Isocomene

Pirrung, M. C., *J. Am. Chem. Soc.*, **1979**, *101*, 23, 7130

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So, according to Pirrung, isocomene can be easily obtained from this carbocation. So, if you can generate this is a intermediate ok it is not a you know precursor, this is an intermediate this carbocation if you can generate that should lead to isocomene ok. He thought this carbocation normally what we would have thought this carbocation can be obtained from a tertiary alcohol or a double bond is exocyclic double bond ok.

Simply you know from synthetic point of view it is easy to think that this carbocation can be generated from the corresponding alcohol, but what he thought was that is a key thing that if you have like this system. Then you know Wagner - Meerwein type rearrangement can occur this four, this bond can migrate if this can migrate that will lead to this angular triquinane with a carbocation.

Once you have this carbocation; obviously, loss of proton will give the natural product. Then how do you generate this carbocation suppose if you have a ketone, then the ketone you can add either methyl Grignard or you can do a Wittig followed by protonation would should generate that tertiary carbocation, is not it. And how do you get this tricyclic compound.

So, when you look at this 4 - membered ring immediately you should think about 2 plus 2 photocycloaddition, again there are two possibilities one you can break this way ok that is if you call this as breaking a bonds, the other one you can break the vertical one so, vertically, so that you can call it as breaking b bonds. So, what he did was he broke the bonds b to form the 4 - membered ring. So, that way this became the precursor.

Now, if you look at this, this can be easily made by simple acid catalyst rearrangement again. So, if you have this enone ok, if you have this enone then you add this Grignard. So, this Grignard will add 1, 2 and then you will get an alcohol here. Then simple acid catalyst hydrolysis will transposition the oxygen ok. So, that way you can easily get this product in two steps from this ok. So, this was the you know simple retrosynthesis planned by Pirrung and let us see how this synthesis worked out.

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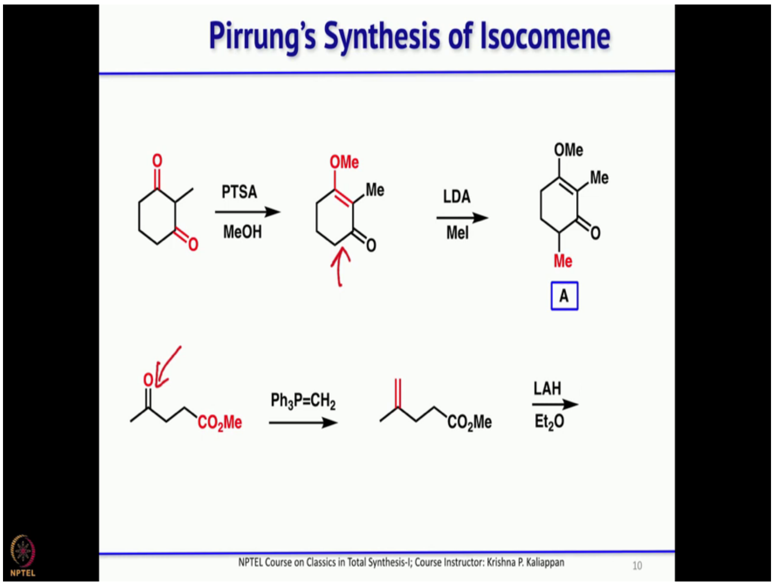

Pirrung's Synthesis of Isocomene

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He started with the commercially available 2 methylcyclohexane 1,3 dione, he started with 2 methylcyclohexane 1, 3 dione, this on treatment with para toluene sulfonic acid and methanol. It will give enol ether this is as you know when you have 1,3 diketone 1, 3 diketone also can exist in corresponding enol form. So, that is basically he methylated that ok the enol is methylated under acidic condition.

Now, if you do LDA methyliodide treatment, you can introduce a methyl group here because that is the only place it can generate anion and then quench with the methyl iodide ok. So, the fragment A is ready, now what you need is, you need to make the bromide and then add that Grignard to this enone. So, for that you started from this gamma keto ester then you do the Wittig. So, Wittig will go selectively to the ketone to get the double bond and reduction of ester with LAH you get the corresponding alcohol.

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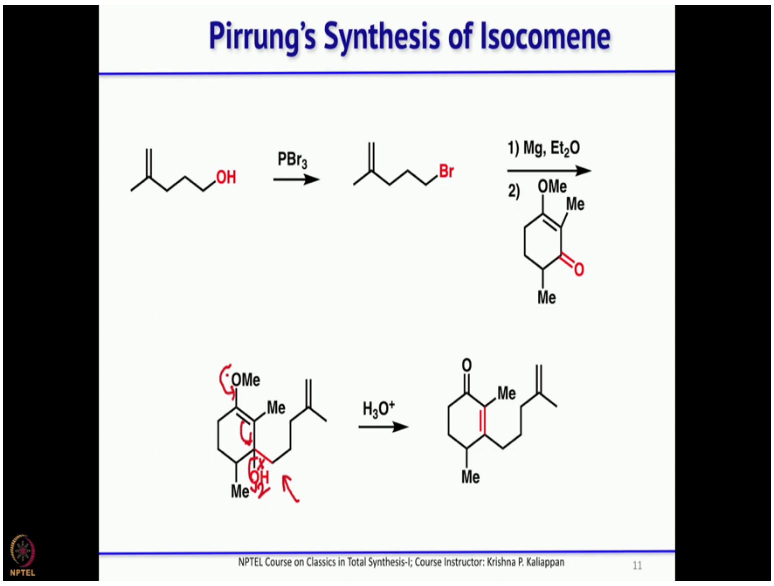

Pirrung's Synthesis of Isocomene

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Now, convert that into bromide and then make Grignard of that bromide and add to this enone. So, that will give you the tertiary alcohol. So, now, simple acid treatment, first it will make this as a good leaving group, then this lone pair will come and the water molecule will go that will lead to the key precursor which is required for the intramolecular 2 plus 2 photocycloaddition ok.

So, now once you made this key precursor what he did, he tried the key photo photochemical 2 plus 2 cycloaddition reaction.

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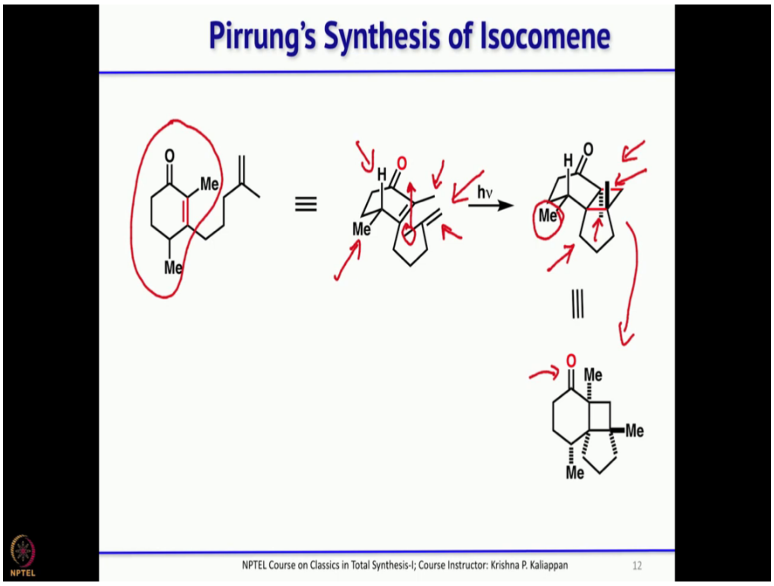

Pirrung's Synthesis of Isocomene

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And this molecule also one should draw in such a way that one can easily explain the stereochemical outcome of the 2 plus 2 photocycloaddition. So, you draw the cyclohexenone in such a way that put the methyl group in pseudo equatorial position ok.

Now, when you bring this when you bring this appended side chain for 2 plus 2 photocycloaddition, this methyl group should point upwards ok. That way if you keep this properly then you will get this stereo chemistry ok. If you look at this compound, this methyl group is in equatorial position and when this double bond comes, this methyl group goes to beta because that side only hydrogen is there, is not it that side only hydrogen is there. So, methyl group will try to go to axial or beta ok.

And during the 2 plus 2 cycloaddition this methyl group will go to alpha and this molecule can be redrawn like this ok. I will leave it for a few seconds for you to visualize how I have drawn this structure into this, is it easy to visualize? So, this 5 - membered ring is alpha, this methyl group is beta and this methyl group is alpha ok.

So, the first key reaction he could do successfully that is the intramolecular 2 plus 2 photocycloaddition worked very well to give that tricyclic compound. Now, what he needs to do is, you have to add a methyl Grignard or methyl lithium to get the tertiary alcohol followed by acid treatment should generate the carbocation, then the carbocation will undergo Wagner Meerwein type rearrangement to give isocomene.

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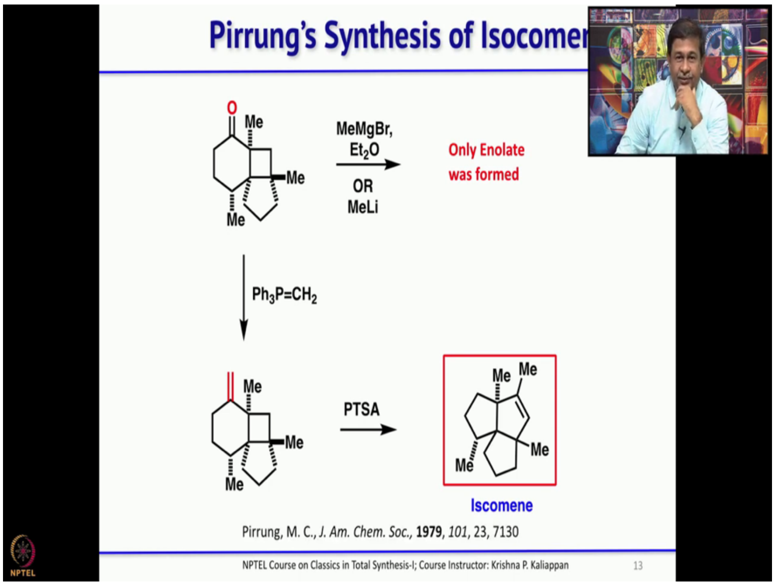

Pirrung's Synthesis of Isocome

MeMgBr, Et_2O OR MeLi

Only Enolate was formed

$Ph_3P{=}CH_2$

PTSA

Iscomene

Pirrung, M. C., *J. Am. Chem. Soc.*, **1979**, *101*, 23, 7130

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So, he took this ketone and treated with methyl magnesium bromide and also methyl lithium. Unfortunately, these two did not give the corresponding tertiary alcohol, what happened? Methyl magnesium bromide and methyl lithium they both acted as base and they did not act as a nucleophile, only enolate was formed in while treating with methyl magnesium bromide and methyl lithium.

So, alternatively it is very easy, you can do a Wittig reaction. So, simple methyl Wittig gave the precursor to Wagner - Meerwein rearrangement. So, once you had the double bond treat with para toluene sulfonic acid that gives straight away isocomene ok. Now, let us see the mechanism how this was rearranged to isocomene.

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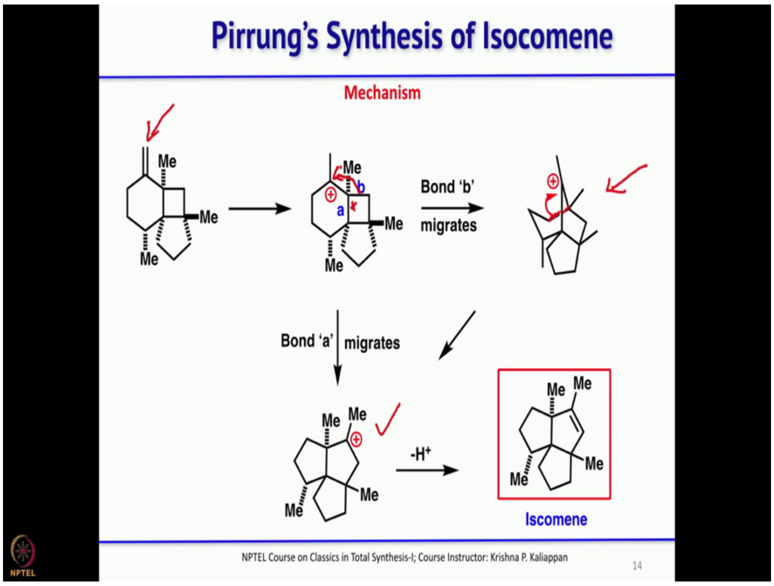

Pirrung's Synthesis of Isocomene

Mechanism

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First the protonation of this double bond took place to give the tertiary carbocation ok. Now, you have two bonds which can migrate one is bond a, the other one is bond b, if bond a migrates that will lead to isocomene, if bond b migrates that will lead to some other natural product ok. Assume that bond b migrates then you will get this skeleton ok. We can see this bond migrates here and that will lead to positive charge here ok. Now, if bond a migrates it is very simple that will straight away give the isocomene skeleton and simple loss of proton will give you isocomene.

However, if you look at this intermediate ok, which is obtained by the migration of bond b ok. Now, again this particular bond this particular bond if it migrates if it migrates what will you get is you will get the same intermediate. So, essentially it does not matter whether bond a migrates or bond b migrates, what you get is the same intermediate which upon loss of proton will give the natural product which is isocomene ok.

So, this is one of the real classical total synthesis and it is a single author paper by Michael Pirrung on the total synthesis of isocomene.

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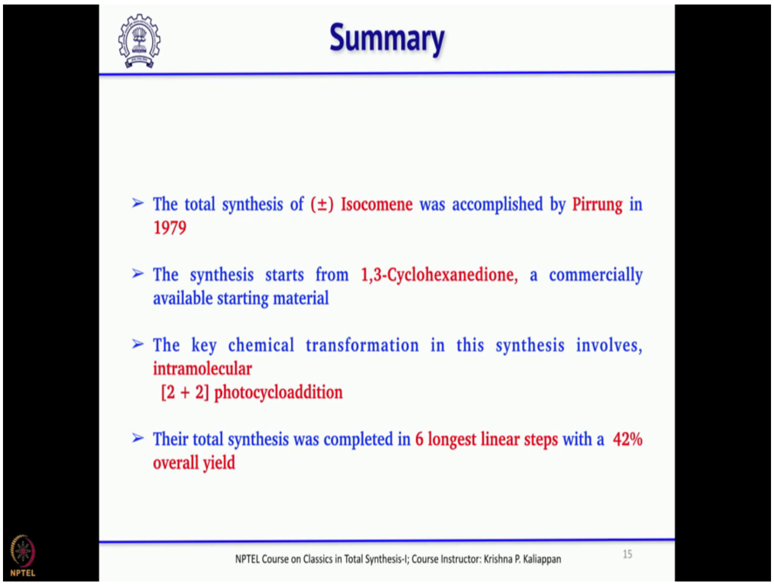

Summary

- The total synthesis of (±) Isocomene was accomplished by Pirrung in 1979
- The synthesis starts from 1,3-Cyclohexanedione, a commercially available starting material
- The key chemical transformation in this synthesis involves, intramolecular [2 + 2] photocycloaddition
- Their total synthesis was completed in 6 longest linear steps with a 42% overall yield

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So, in the total synthesis which was reported in 1979, he started with commercially available 2 methyl cyclohexanedione and the key reactions involved are 2 plus 2 photocycloaddition and Wagner - Meerwein rearrangement. Overall the total synthesis involve 6 longest linear steps 6 longest linear steps and the yield was 42 percentage which is quite high considering this angular triquinanes. The second synthesis which was reported by Fitjer.

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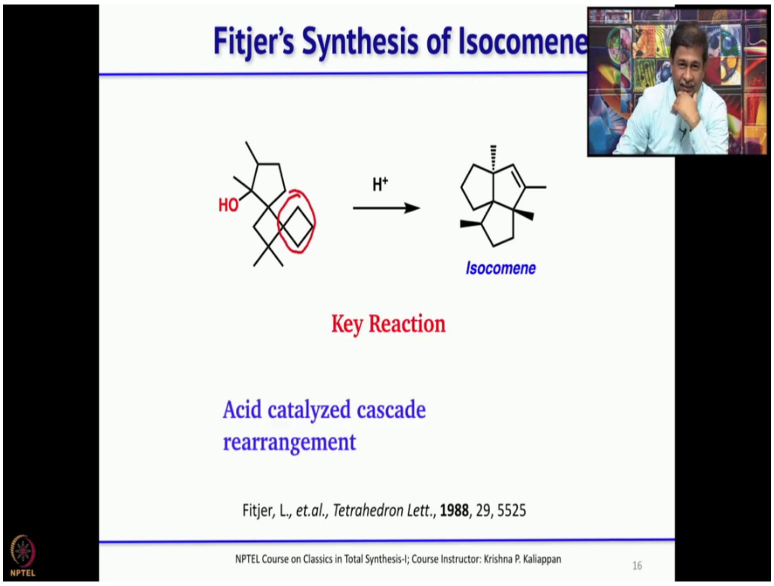

Fitjer's Synthesis of Isocomene

Isocomene

Key Reaction

Acid catalyzed cascade rearrangement

Fitjer, L., *et.al.*, *Tetrahedron Lett.*, **1988**, 29, 5525

And here again the key reaction was ring enlargement and also Wagner - Meerwein type rearrangement. This is the key reaction so, if you look at this molecule you can see two 4 - membered rings, is not it. Two 4 membered rings spiral fused and one of the 4 membered rings is spiral fused with a 5 membered ring this upon treatment with acid ok this upon treatment with acid gives isocomene ok. These are very very interesting sequence of reaction involving Wagner - Meerwein type rearrangement ok.

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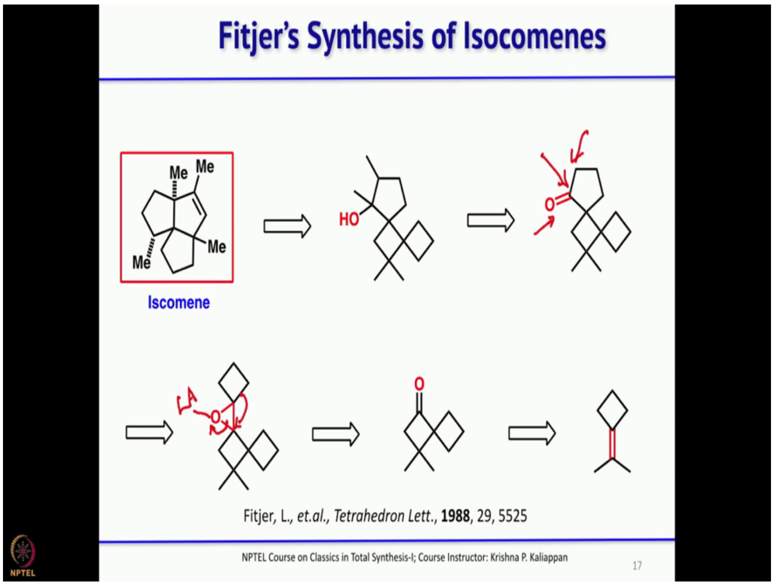

Fitjer's Synthesis of Isocomenes

Iscomene

Fitjer, L., *et.al.*, *Tetrahedron Lett.*, **1988**, 29, 5525

Let us see how he achieved this, the retrosynthesis wise you know isocomene can be obtained in one step from this tertiary alcohol and this as you know if you have a ketone ok if we have a ketone we can introduce a one methyl group here by treating with LDA methyl iodide and if you add a methyl Grignard to this ketone you get the corresponding tertiary alcohol. So, in two steps we can get the precursor for the acid catalysed rearrangement.

Now, how you get this cyclo pentanol? As you know if you have an epoxide if you have an epoxide epoxides are known to undergo ring enlargement or ring enlargement rearrangement ok. So, a 4 - membered ring with an exo epoxide can undergo rearrangement under acidic condition to give 5 - membered ring.

See for example, if you use a Lewis acid here. So, what will happen, this can open up and this bond can migrate to get the corresponding 5 - membered ketone ok. And epoxides can be easily made from the corresponding double bond and the double bond can be made from the ketone using Wittig reaction and finally, the starting material for the whole scheme on total synthesis isocomene by Fitjer is cyclobutane having an exocyclic double bond with 2 methyl groups ok. So, this is a starting material.

Let us see how he successfully achieved the total synthesis of isocomene using this acid catalyzed ring rearrangement.

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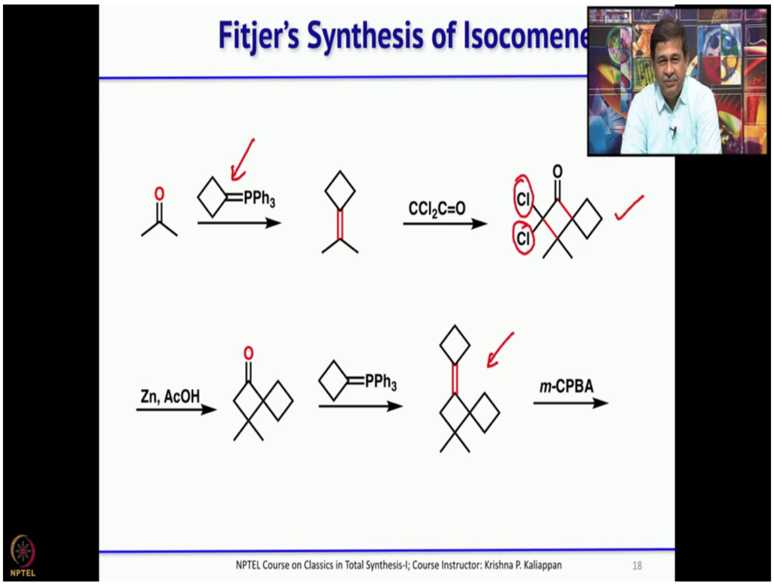

Fitjer's Synthesis of Isocomene

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First he started with the acetone, you can imagine for the synthesis of isocomene this starting material is acetone ok. The simple acetone which is a solvent, now you do a Wittig reaction with cyclobutane derived ylide you get the first starting material ok. Next, you have to do, the another 2 plus 2 cycloaddition reaction this time you do 2 plus 2 cycloaddition with dichloro ketene. So, if you look at Pirrung's total synthesis also there was a 2 plus 2 cycloaddition reaction, here also 2 plus 2 cycloaddition reaction.

In Pirrung's isocomene synthesis he has used intramolecular 2 plus 2 cycloaddition reaction, here it is intermolecular 2 plus 2 cycloaddition reaction with dichloro ketene, as you know dichloro ketene can be easily generated from either dichloro acetyl chloride by treating with triethylamine or dichloro trichloro acetyl chloride, if you take trichloro acetyl chloride and treat with zinc that also will give the dichloro ketene. So, this will give you the spiro fused bicyclic system.

So, now, you have two 4 membered ring two 4 membered rings spiro fused, next what you do not want is these 2 chlorine is not it. The chlorine was used to keep the ketene stable ok. So, once that served its purpose the chlorine should be removed. So, normally it is done by treating with zinc and acetic acid. So, you have the spiro-fused bicyclic ring.

Next, again do another Wittig with the same cyclobutane bromocyclobutane and treat with triphenylphosphine and then butyllithium, you get the Wittig product. This looks very cute, this molecule looks very nice you can see three 4 - membered rings and 2 are spiro fused and then 2 are interconnected with a double bond 2 are interconnected with a double bond. Then, what you have to do is just treat with m-CPBA ok, just m-CPBA will give the corresponding epoxide.

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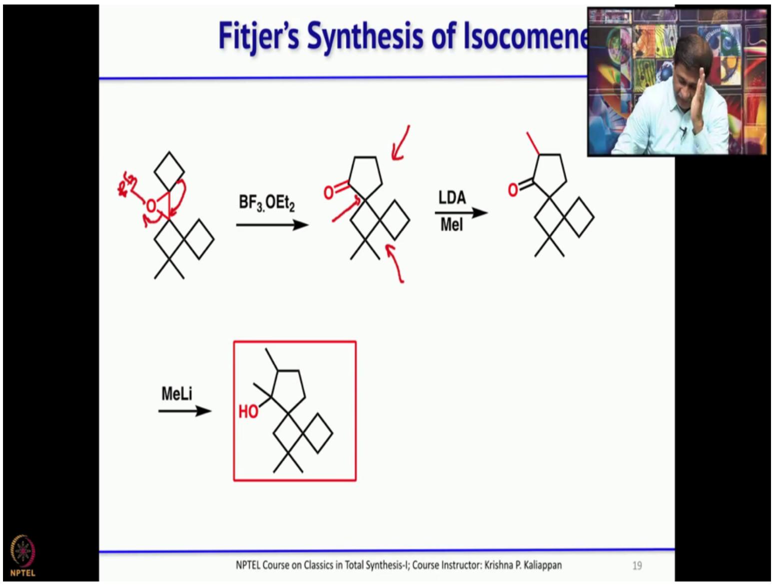

Fitjer's Synthesis of Isocomene

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This epoxide as I said when you treat with Lewis acid ok, when you treat with Lewis acid it undergoes. So, first it will coordinate with BF$_3$ ok, then it will open up and this bond migrates. So, that will give you the corresponding 5 - membered ring. If you look at this molecule now there are 3 spiro fused rings 2 are 4 membered rings and here if you see the spiro system as a 4 and 5 membered fused system very interesting system ok.

Next, you have to introduce a methyl group, next to ketone then add either methyllithium or methyl Grignard. So, LDA methyl iodide you can introduce a methyl group then followed by addition of methyl lithium will give the tertiary alcohol. So, this is the key precursor just before the acid catalysed rearrangement.

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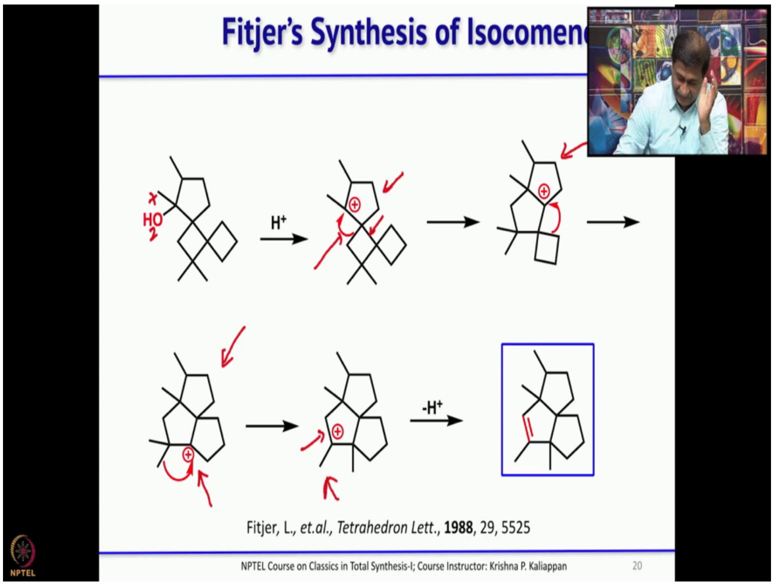

Fitjer's Synthesis of Isocomen

Fitjer, L., *et.al.*, *Tetrahedron Lett.*, **1988**, 29, 5525

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So, when he did carry out the acid catalyzed rearrangement he got the isocomene as well as another product. So, how isocomene was formed? First as you know protonation will take place when the water goes you get the tertiary carbocation once the tertiary carbocation is formed then automatically one of the bonds of the spiro fused 4 membered ring should migrate and this migration of this bond will give you another 5 membered ring.

So, now what happens, earlier this 5 membered ring and this 4 membered ring are spiro fused now after this they are linearly fused. So, that leads to another carbocation that also can trigger the migration of the bond from 4 membered ring. As you know 4 membered rings are not that stable, so that is the key thing which trigger the migration of bonds. Once that happens now you can see what you got is angular triquinane system angular triquinane system.

But still it is not leading to isocomene you are getting an angular triquinane structure, but it is not the isocomene. So, once you have a tertiary carbocation here you have a quaternary center adjacent position, from the quaternary center one of the methyl groups can migrate. So, when one of the methyl group migrates what you get is another tertiary carbocation ok and if it loses a proton if it just loses a proton. There are two possibilities that it can lead to exocyclic double bond or endocyclic double bond of course, since it is treated with acid then possibility of getting exocyclic double bond is high. So, that is how he got isocomene as the major products ok.

So, this is a very very interesting total synthesis starting with you know acetone and then do Wittig reaction with bromocyclobutane derivative ylide and you get spiro fused 3 spiro fused ring and then simple acid catalyst rearrangement gives you the natural product, Wagner - Meerwein rearrangement and 2 plus 2 cycloaddition as key reactions.

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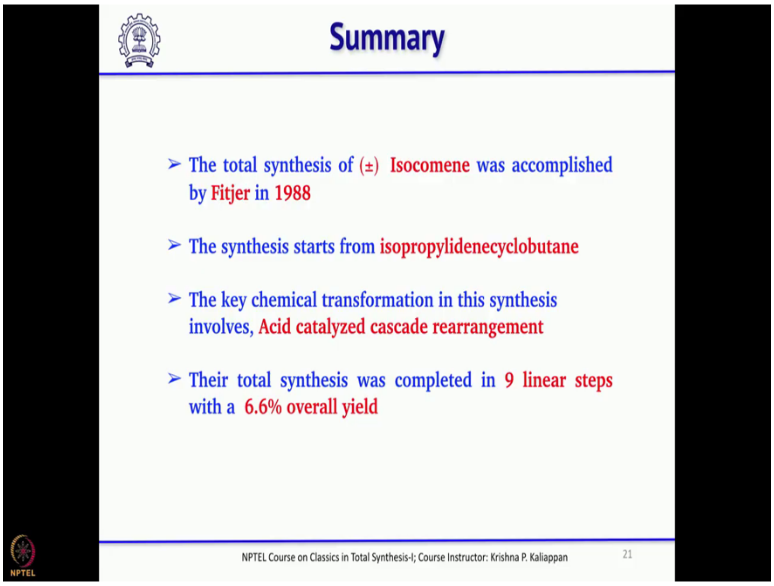

Summary

- The total synthesis of (±) Isocomene was accomplished by Fitjer in 1988
- The synthesis starts from isopropylidenecyclobutane
- The key chemical transformation in this synthesis involves, Acid catalyzed cascade rearrangement
- Their total synthesis was completed in 9 linear steps with a 6.6% overall yield

So, in summary so, this total synthesis was reported about 10 years after Michael Pirrung’s total synthesis of isocomene and it started with acetone and the key reactions involved in this are 2 plus 2 cycloaddition and acid catalysed Wagner - Meerwein type rearrangement. Overall this whole synthesis took 9 linear steps and overall yield was about 6.6 percent ok.

So, I will stop here and then I will continue our discussion on total synthesis of various triquinanes in the next maybe 7 to 8 lectures because there are many total synthesis of triquinanes and each synthesis use at least two key reactions, some of them are completely different than the other total synthesis. So, this way when we talk about total synthesis of various triquinanes we will learn lot of new chemistry ok.

So, Thank you.