Classics in Total Synthesis-I
Prof. Krishna P Kaliappan
Department of Chemistry
Indian Institute of Technology, Bombay

Lecture - 14
Triquinanes: α, β-Isocomene and Silphipherfol-6-en-5-one (Rawal)

So, good morning and welcome back to the NPTEL lecture series on Classics in Total Synthesis Part 1. And the last lecture we talked about total synthesis of natural products there we talked about total synthesis of isocomenes by Michael Pirrung's group and Fitjer's group. Today we will continue our discussion on again total synthesis of isocomenes. This synthesis is reported by Viresh Rawal.

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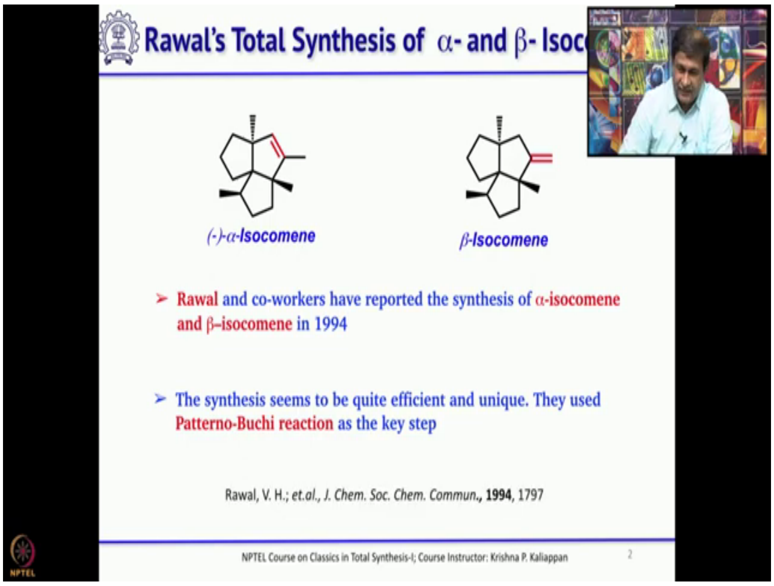

Rawal's Total Synthesis of α- and β- Isoc

(-)-α-Isocomene

β-Isocomene

- Rawal and co-workers have reported the synthesis of α-isocomene and β-isocomene in 1994
- The synthesis seems to be quite efficient and unique. They used Patterno-Buchi reaction as the key step

Rawal, V. H.; *et.al., J. Chem. Soc. Chem. Commun.*, **1994**, 1797

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So, Viresh Rawal had reported the total synthesis of both alpha and beta isocomenes and he reported this in 1994. His total synthesis involve three or four key reactions one Paterno-Buchi reaction, as you know Paterno-Buchi reaction gives an oxetane with four membered ring. And that is an intramolecular Paterno-Buchi reaction to get oxetane as the key step.

Second opening up the oxetane to get homoallylic alcohol ok. Highly regioselective opening of the oxetane to homoallylic alcohol followed by a simple fragmentation reaction which converts the bridged system into fused system. So, these are three key reactions which Rawal has used in the total synthesis of isocomenes.

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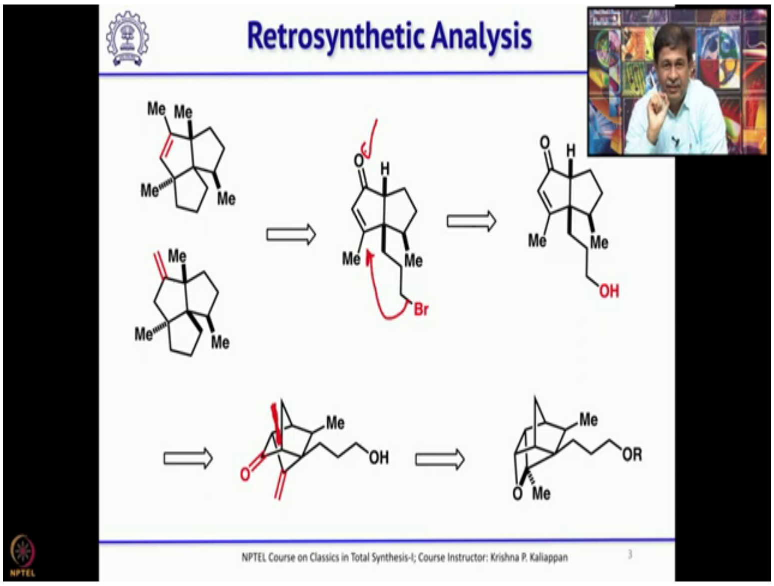

Retrosynthetic Analysis

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Let us see what he has done and from retro synthetic point of view, so these are alpha and beta isocomenes both can be obtained from one common intermediate. And this is enone and it is very simple the 5 exo radical cyclization can be used successfully to construct the 3rd five membered ring already there are 2 five membered rings and the 3rd five membered ring can be easily constructed by this 5 exo radical cyclization.

So, once it is done then simple Wittig will give one isocomene and isomerization of the double bond to in the olefin will give the other bond. And of course, the bromide can be easily obtained from the corresponding alcohol and the first key step is this fragmentation.

Fragmentation of the bridged system to the fused ring is the first key reaction from retrosynthetic point of view. So, this is the bond which is broken during this fragmentation ok. And this can be obtained from this oxetane using regioselective opening of the oxetane followed by oxidation of the secondary alcohol, you get this beta gamma unsaturated enone.

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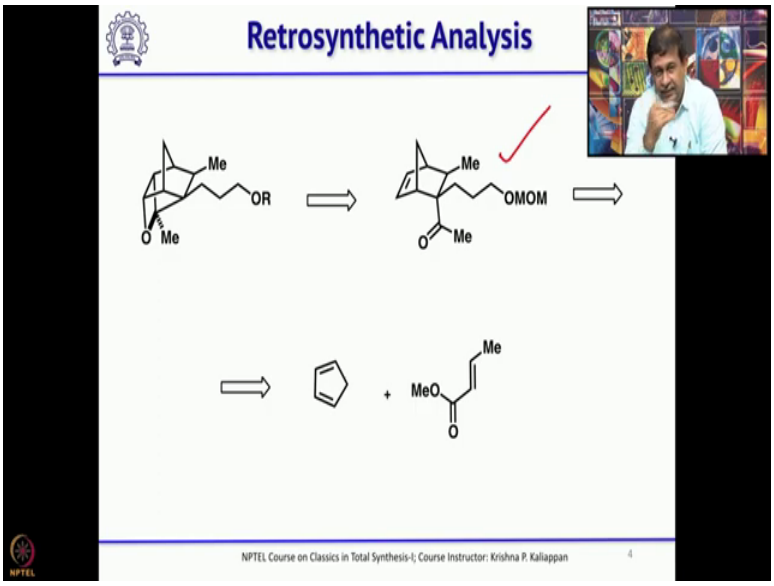

Retrosynthetic Analysis

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And this can be easily obtained from this bicyclic compound by another key reaction which is Paterno-Buchi reaction. Paterno-Buchi reaction is nothing but photochemical reaction between an alkene and a carbonyl group, so this is an intramolecular Paterno-Buchi reaction.

And this can be obtained from cyclopentadiene and this enone followed by alkylation. So, in two steps one can get this interesting bicyclic compound starting from cyclopentadiene. So, before we start discussing the total synthesis of isocomenes reported by Rawal.

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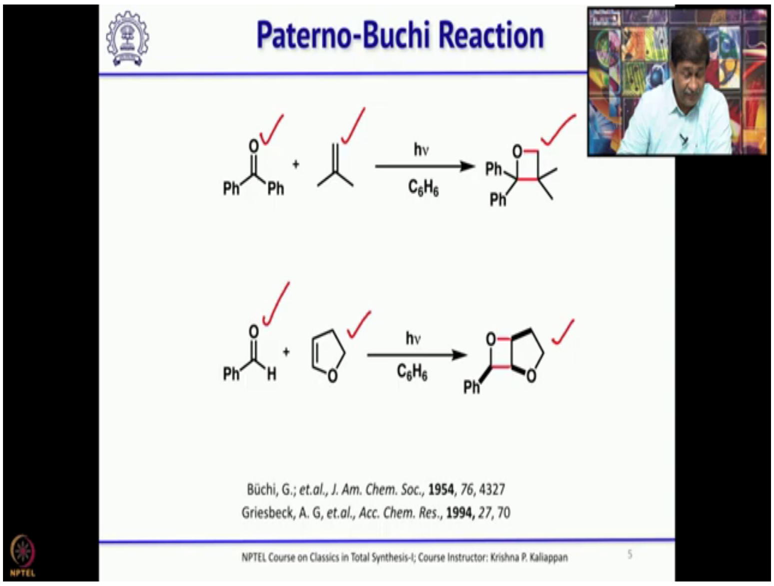

Paterno-Buchi Reaction

Büchi, G.; *et.al.*, *J. Am. Chem. Soc.*, **1954**, *76*, 4327
Griesbeck, A. G, *et.al.*, *Acc. Chem. Res.*, **1994**, *27*, 70

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As I said there are three key reactions and we will briefly discuss about these three key reactions. First it is a Paterno-Buchi reaction Paterno-Buchi reaction is nothing but it is a photochemical reaction 2 plus 2 reaction between an alkene and a carbonyl group.

Suppose if you start with benzophenone and isobutylene under photochemical condition you get this four membered ring. And one can also do the same thing with an aldehyde ok basically its a reaction between a carbonyl group and a alkene. So, if you do the same thing with benzaldehyde and dihydrofuran you end up getting this bicyclic compound ok. And this was cleverly used in Viresh Rawal's total synthesis.

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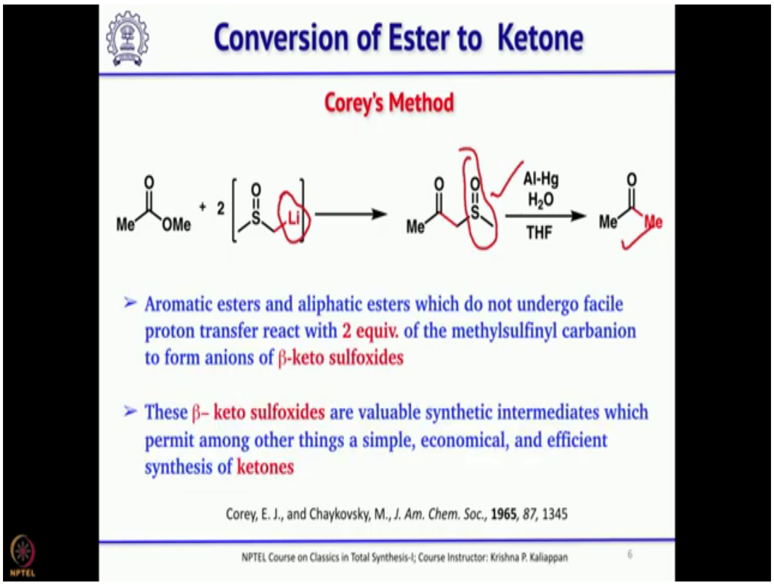

Conversion of Ester to Ketone

Corey's Method

- Aromatic esters and aliphatic esters which do not undergo facile proton transfer react with 2 equiv. of the methylsulfinyl carbanion to form anions of β-keto sulfoxides
- These β- keto sulfoxides are valuable synthetic intermediates which permit among other things a simple, economical, and efficient synthesis of ketones

Corey, E. J., and Chaykovsky, M., *J. Am. Chem. Soc.*, **1965**, *87*, 1345

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The second key reaction is the conversion of an ester into methyl ketone. So, this was reported by E J Corey where if you have an ester and then treat with this lithium dimethyl sulfoxide ok. You take dimethyl sulfoxide and then generate anion here this can add to your ester to form this beta keto sulfoxide. This upon reduction with aluminium amalgam ok that will give you the corresponding ketone ok. This can be easily cleaved under this condition, radiation condition ok.

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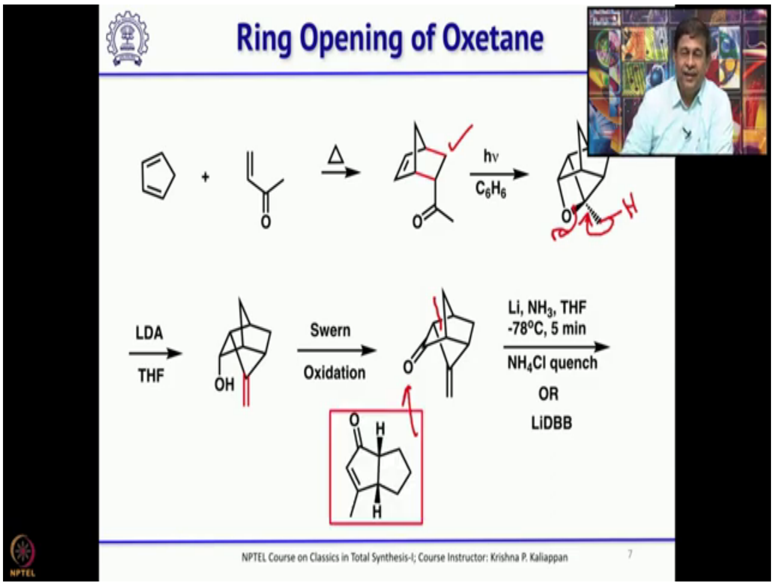

Ring Opening of Oxetane

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The third one which is very important from the point of view of synthesis of this isocomenes is the opening of the oxetane ring. How this oxetanes can be successfully opened? So, I will give one example which was reported by Viresh Rawal before we go to the total synthesis.

If you do a Diels Alder reaction between cyclopentadiene and methyl vinyl ketone you get this endo product. Once you have this endo product then shine light to carry out the intramolecular Paterno-Buchi reaction to get this tetracyclic compound ok. This oxetane can be opened by strong base ok it can be opened by strong base, like LDA to get the corresponding alcohol ok.

Once you have this alcohol then you can use any oxidizing condition for example, Swern oxidation will give you the corresponding ketone ok. So now, in four steps one could get successfully this tricyclic compound. Now what you need is you need to remove or break this bond to get a diquinane skeleton ok. So, that was successfully done with one of the two reagents one either with lithium ammonia or with LiDBB.

LiDBB is nothing but Lithium Ditertiary Butyl Biphenyl; Lithium Ditertiary Butyl Biphenyl. So, basically both regions give one electron, so one when one electron is added to this carbonyl group you get a radical anion ok. Then the radical opens up to give this required skeleton ok.

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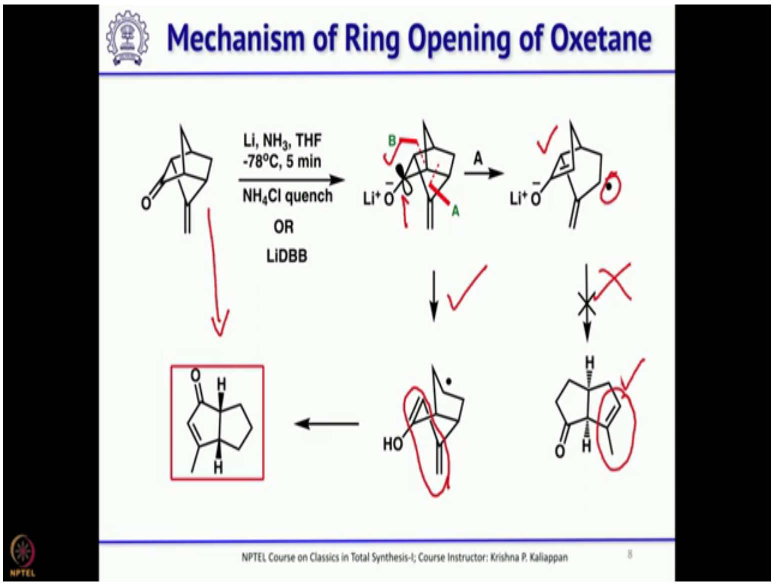

Mechanism of Ring Opening of Oxetane

Li, NH_3, THF
-78°C, 5 min
NH_4Cl quench
OR
LiDBB

So, let us see how does it work. So, once you have this enone and when you add this one electron as I said it forms this radical anion. So, the radical anion is not stable ok, so it has to open up. So, if there are two ways a bond can break to give more stable compound or more stable intermediate you should know whether bond A breaks or bond B breaks ok because once you have that radical here, so it can easily break. If bond A breaks if bond A breaks you will get this enolate and an allylic radical ok and that should give you this enone.

So, you have a diquinane with the ketone. So, if you look at this automatically the double bond goes inside, it is a more stable compound, so you get internal alkene. But this is not the product you get, what you get is based on the cleavage of bond B if the bond B breaks ok.

Now, if you see this there is a conjugation that enolate or enol which is formed is conjugated. So, that is why this is more favourable than this bond A breaking. So, when the bond B breaks you get this dienol that tautomerizes to give this conjugated enol ok. So, in one step you can convert this into bicyclic enol ok, this is the key step ok. There are three key step Paterno-Buchi reaction and conversion of ester to ketone then opening of this.

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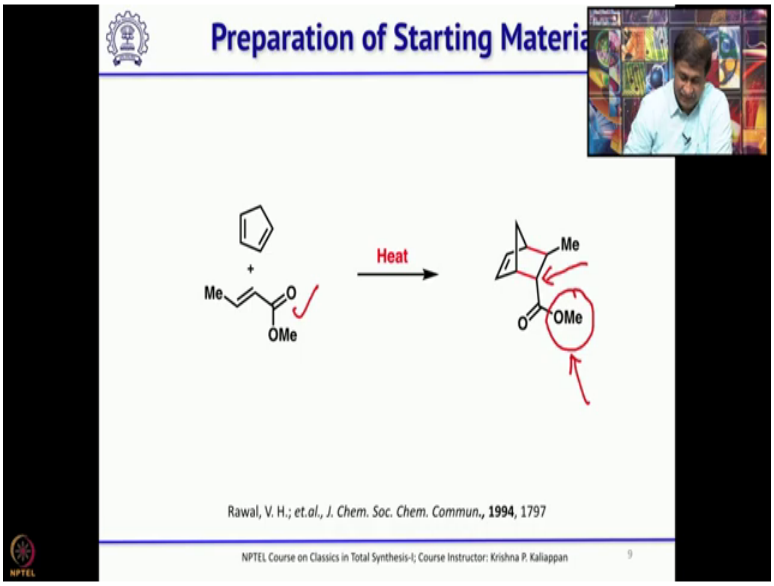

Preparation of Starting Materia

Rawal, V. H.; *et.al., J. Chem. Soc. Chem. Commun.*, **1994**, 1797

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Now, let us see how he achieved the synthesis of isocomenes. So, he started from cyclopentadiene and then did a Diels Alder reaction with this dienophile, methyl crotonate, and you heat it you get this compound. Now the next step should be to remove the methoxy with methyl, but before that you need to do alkylation at this carbon ok. Because you need a three carbon unit which should be attached here that, three carbon is required for intramolecular radical cyclization.

So, before you convert this methoxy into methyl what you should do is, you should alkylate here. Because if you convert this methoxy into methyl then the alkylation can go to the methyl group. So, that is why alkylation should be done at this stage.

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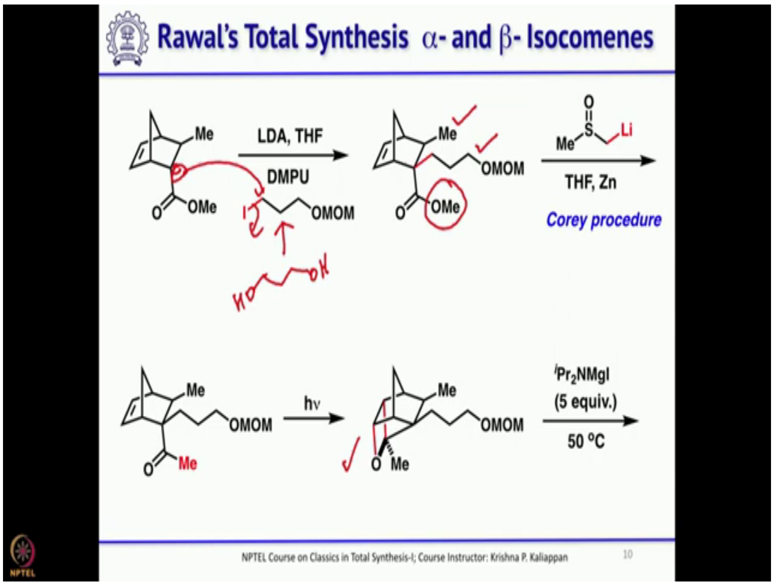

Rawal's Total Synthesis α- and β- Isocomenes

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So, you take this ester then treat with the LDA and then quench with this iodide. So, this iodide is prepared in three steps from this propane-1, 3-diol ok.

So, you protect one of the alcohol as mom ether, then convert the other alcohol as mesylate and then treat with sodium iodide, you get this iodo compound. Now you generate anion here and then quench with this iodide and it goes stereoselectively it goes to the exo position. So, now, what you can see here is the methyl group here and this side chain that is a three carbon unit they are cis to each other, because this stereo chemistry will be maintained when you do the next step ok.

Next you have to convert this methoxy into methyl group as I said you can follow Corey's procedure. So, that reaction worked well to get the corresponding methyl ketone. So, Diels Alder reaction is over you introduce the three carbon side chain and you also converted the methyl ester into methyl ketone which is required for intramolecular Paterno-Buchi reaction.

So, the intramolecular Paterno-Buchi reaction is also worked very well to give the corresponding oxetane. So, once you have these oxetane next you have to open the oxetane. So, either you can use LDA or strong base to get the corresponding homoallylic alcohol.

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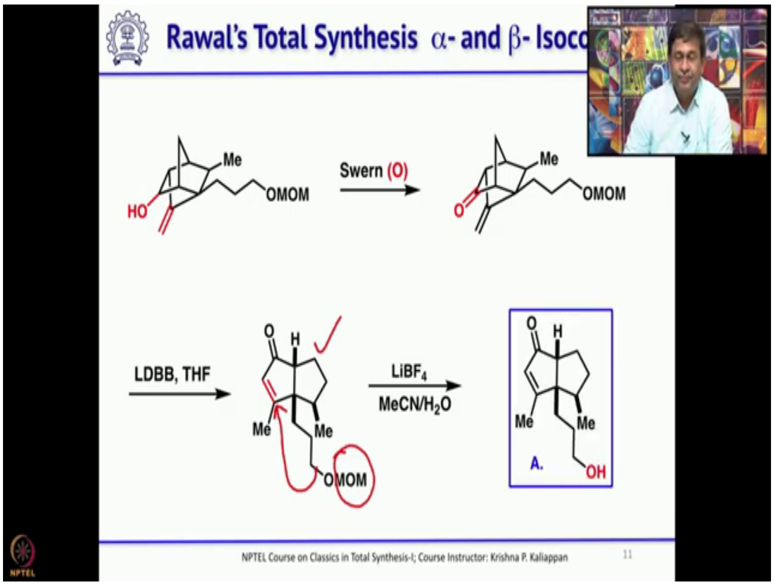

Rawal's Total Synthesis α- and β- Isoc

Swern (O)

LDBB, THF

$LiBF_4$

$MeCN/H_2O$

So, this homoallylic alcohol upon oxidation under Swern condition gave this enone. And now upon treatment with LiDBB the reaction worked very well and opened the tricyclic compound to the bicyclic compound. So, now you have already the diquinane ok. So, what you need to do is you need to cyclize here that will give the third ring which is required. So, that way you will achieve the synthesis of angular triquinane core structure, then it is just the functionalization of the carbonyl group. So, for that first you have to remove the mom group.

So, the mom group can be easily removed using lithium fluoroborate. So, that will give the alcohol. And this alcohol for the radical reaction, you convert that alcohol into corresponding bromide by treating with NBS and triphenylphosphine.

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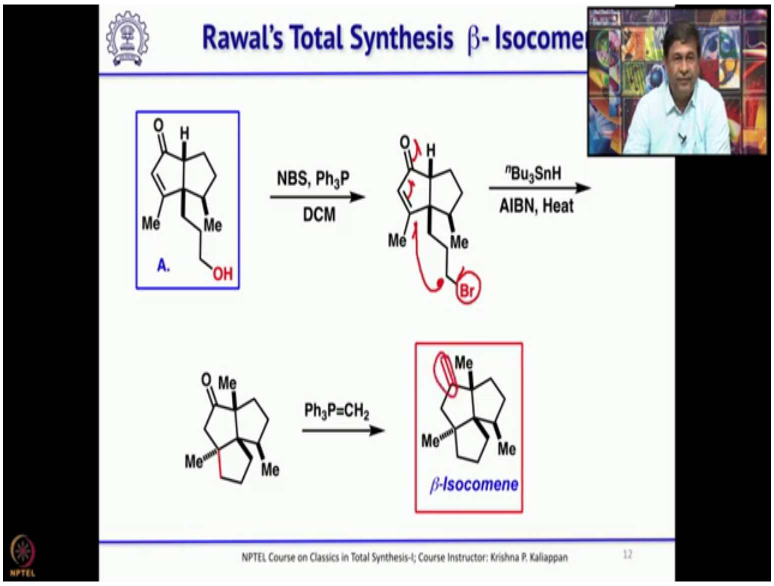

Rawal's Total Synthesis β- Isocome

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So, NBS and triphenylphosphine gives you the corresponding primary bromide. Once you have the primary bromide then treat with tributyltin hydride and AIBN that will give you theradical here. So, this will go and you form a radical that will attack here in a 5 exo fashion and give you the angular triquinane.

So, now, once you have the angular triquinane simple Wittig, simple Wittig will give you beta isocomene ok. So, for the synthesis of alpha isocomene. So, basically one can isomerize this double bond, but what he did.

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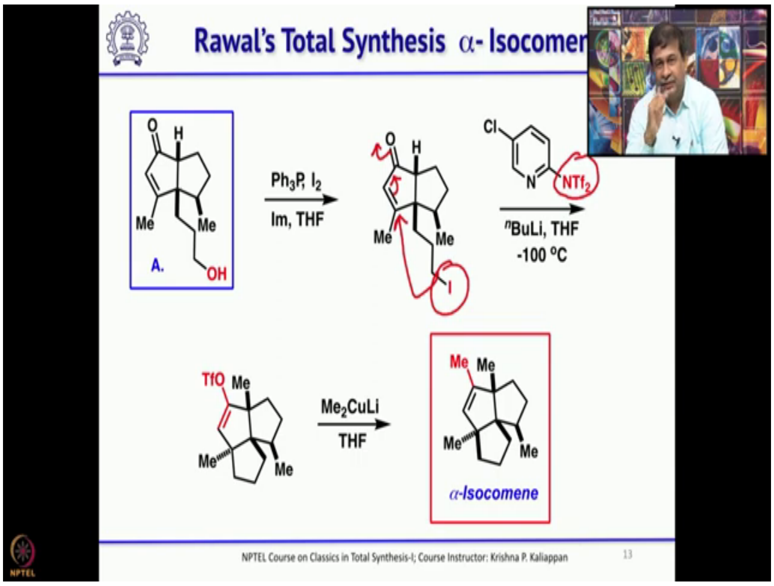

Rawal's Total Synthesis α- Isocomer

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He went back to the alcohol ok and converted that alcohol into iodide ok, using triphenylphosphine and iodine one can easily convert the primary alcohol into corresponding alkyl iodide. This on treatment with butyl lithium ok N-butyl lithium you can exchange this lithium.

Then that lithium undergoes a 1, 4 addition to this enone and once that happens it forms an enolate it forms a five membered ring followed by enolate formation that enolate is quenched with this reagents called Commin’s reagent that will give you the corresponding enol triflate us.

So, once you have the enol triflate then you couple with Gilman reagent that is lithium dimethylcuprate that will give you corresponding isocomene. So, he used cleverly the Diels Alder reaction, Paterno-Buchi reaction, and opening of the oxetane and also opening of the bridged system to fused system to synthesize both alpha and beta isocomene.

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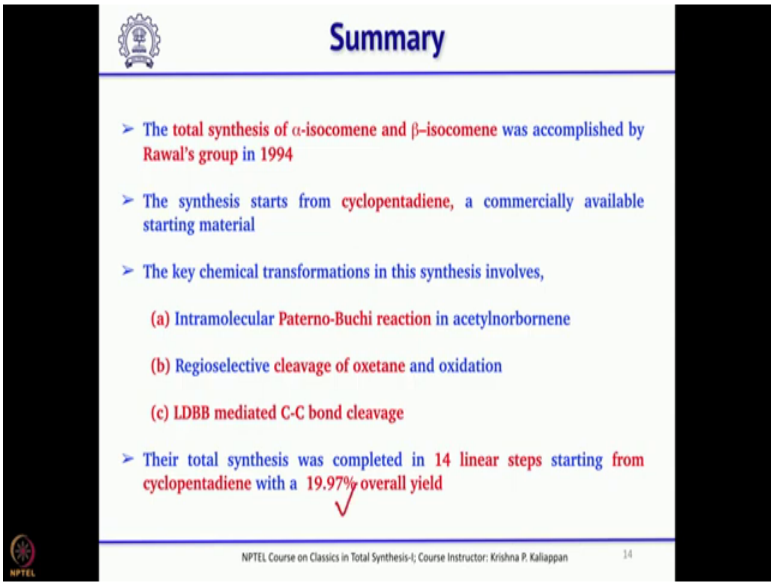

Summary

- The total synthesis of α-isocomene and β–isocomene was accomplished by Rawal’s group in 1994
- The synthesis starts from cyclopentadiene, a commercially available starting material
- The key chemical transformations in this synthesis involves,
  - (a) Intramolecular Paterno-Buchi reaction in acetylnorbornene
  - (b) Regioselective cleavage of oxetane and oxidation
  - (c) LDBB mediated C-C bond cleavage
- Their total synthesis was completed in 14 linear steps starting from cyclopentadiene with a 19.97% overall yield ✓

And the synthesis started with commercially available inexpensive cyclopentadiene and these are the key reactions which he used to synthesize both beta and alpha isocomene.

Overall the total synthesis was done in 14 linear steps and the yield was close to 20 percent. So, 20 percent overall yield is really very good considering the triquinane complexity. Now since we are talking about this Paterno-Buchi reaction and application of Paterno buchi reaction in the total synthesis we will continue our discussion again reported by Viresh Rawal in the synthesis of another triquinane called silphipherfol-6-en 5-one ok.

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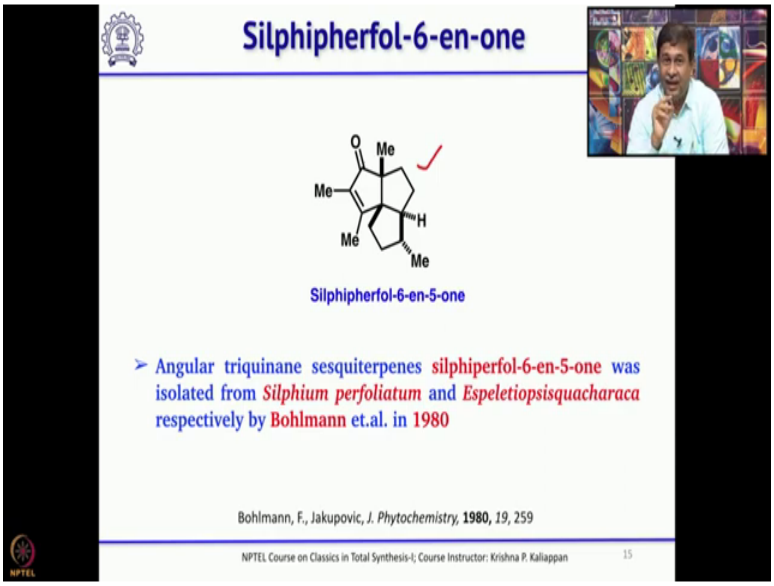

Silphipherfol-6-en-one

Silphipherfol-6-en-5-one

- Angular triquinane sesquiterpenes silphiperfol-6-en-5-one was isolated from *Silphium perfoliatum* and *Espeletiopsisquacharaca* respectively by Bohlmann et.al. in 1980

Bohlmann, F., Jakupovic, *J. Phytochemistry*, **1980**, *19*, 259

So, this was isolated in 1980s by Bohlmann and if you look at this molecule it this is also an angular triquinane ok an angular triquinane and here yet again Viresh Rawal use their use the same sequence. That is Paterno-Buchi reaction opening of the oxetane and followed by opening of the bridge system he could successfully synthesize this compound.

But importantly he could achieve this in five steps ok. So, that is significant improvement compared to what he had earlier reported for the total synthesis of isocomenes.

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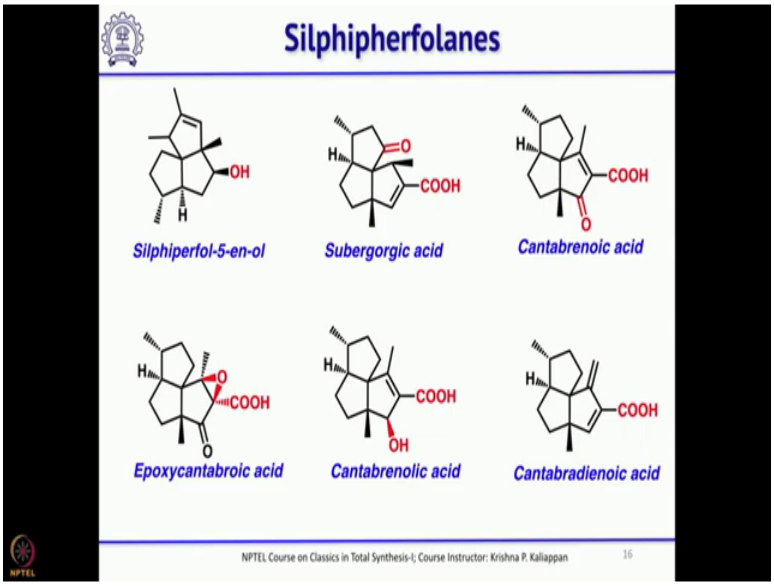

Silphipherfolanes

Silphiperfol-5-en-ol

Subergorgic acid

Cantabrenoic acid

Epoxycantabroic acid

Cantabrenolic acid

Cantabradienoic acid

So, let us see how he has done not only you know a silphiperfolanes. There are so many other natural products which are having almost similar structure with some minor modification in the functional groups ok here are some.

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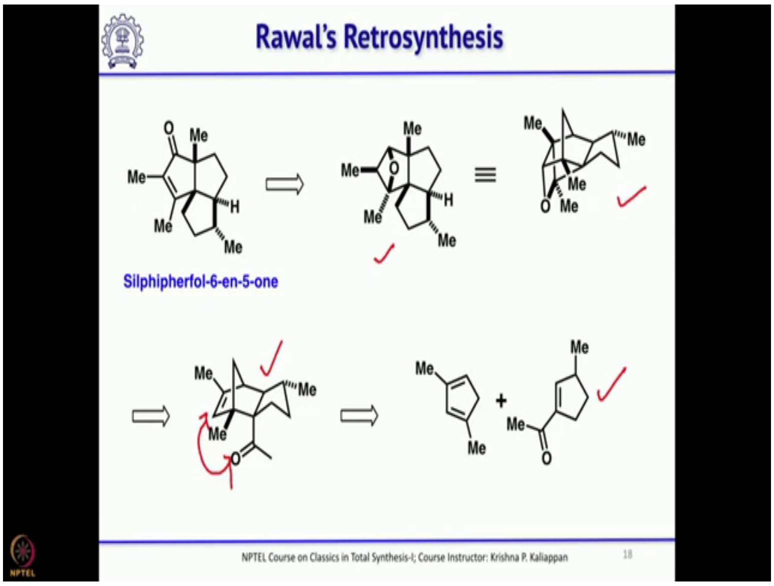

Rawal's Retrosynthesis

Silphipherfol-6-en-5-one

His retro synthesis actually started with you know this oxetane as you know already we discussed, how oxetane is the key intermediate in the synthesis of isocomenes. So, his precursor is this oxetane that oxetane can be redrawn like this ok now this oxetane as soon as you look at this oxetane you know what should be the precursor the precursor is nothing, but this tricyclic system.

So, one can do an Paterno-Buchi reaction to get this intermediate ok and this can be easily synthesized from Diels Alder reaction if you start with 2, 4-dimethyl cyclopentadiene and this cyclopentene having a carbonyl group as dienophile this Diels Alder reaction will straight away give this tricyclic component.

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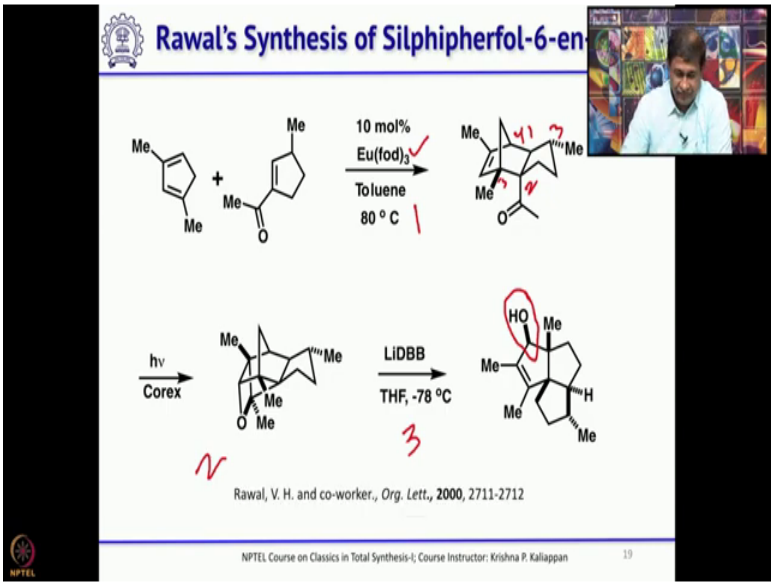

Rawal's Synthesis of Silphiperfol-6-en

10 mol% Eu(fod)$_3$, Toluene, 80 °C

hν, Corex

LiDBB, THF, -78 °C

Rawal, V. H. and co-worker., *Org. Lett.*, **2000**, 2711-2712

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So, he started this synthesis with 2, 4- dimethyl cyclopentadiene and the cyclopentene having a carbonyl group for the Diels Alder reaction he used a europium salt ok this is 10 mol percent actually helped in getting exclusively the endo isomer ok. So, now, if you look at this he got how many chiral center though it is a racemic synthesis.

So, 1, 2, 3, 4, 5 ok. So, all these chiral centers are fixed in one step that is Diels Alder reaction ok. So, it is a relative stereochemistry, but still you get only one relative isomer. Once we have that then you carry out the intramolecular photochemical 2 plus 2 cycloaddition that is Paterno-Buchi reaction to get this oxetane ok.

This also worked very well though you can see this slightly congestive system, but photochemical reactions are known to give sterically as well as you know ring strained compounds ok. So, once you have that then using the LiDBB you could easily open the oxetane to get the allylic alcohol ok.

How many steps? 1, 2, 3 in three steps you could get the core structure of this natural product and what is left for the synthesis of silphipherfol-6-en-5-one is just oxidation if you oxidize this that is a natural product.

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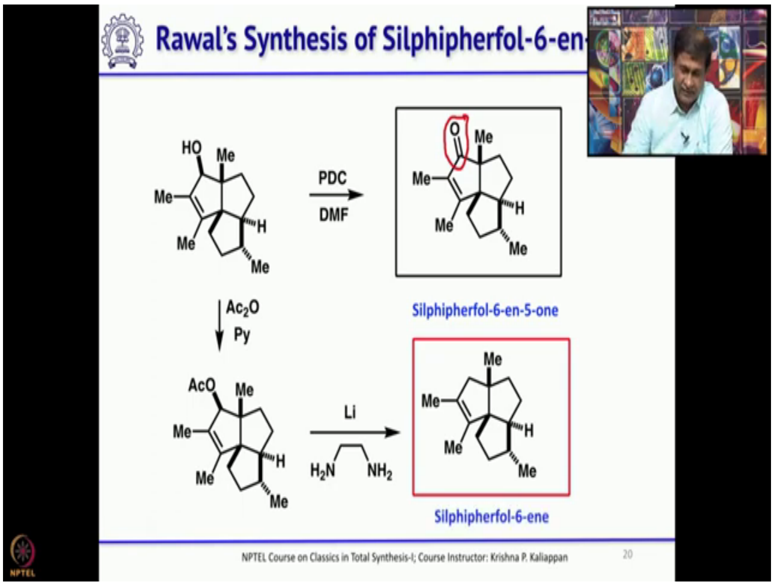

Rawal's Synthesis of Silphipherfol-6-en

Silphipherfol-6-en-5-one

Silphipherfol-6-ene

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So, simply he took this compound and oxidized with PDC he got the natural product, for the other compound other natural product one more natural product that is without the carbonyl group that is called silphipherfol-6-ene. He needs to remove this carbonyl group.

So, he tried several conditions to remove this carbonyl group, but all of them gave poor yield of the required compound plus complex mixture. So, he has to go via a two step process first he acetylated the allylic alcohol to get the corresponding acetate then he treated that with lithium in 1, 2- diaminoethane. So, that gave the other natural product which is silphipherfol- 6- ene ok.

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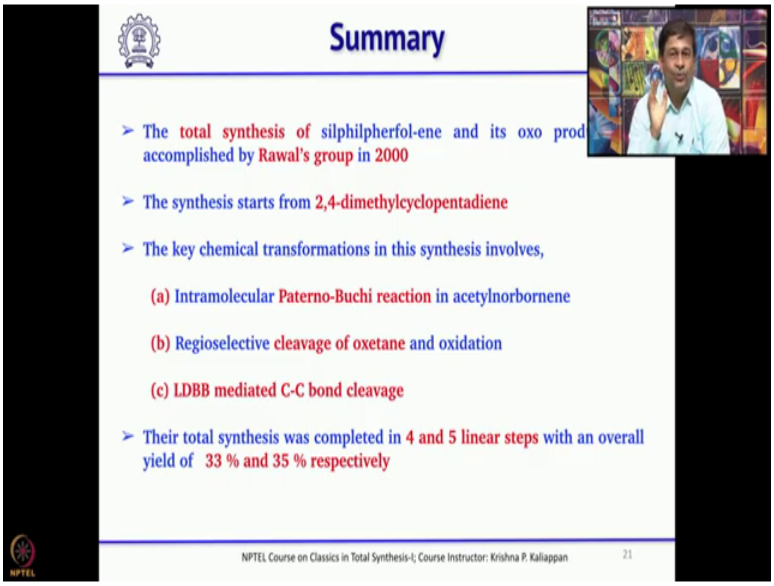

Summary

- The total synthesis of silphilpherfol-ene and its oxo prod
  accomplished by Rawal's group in 2000
- The synthesis starts from 2,4-dimethylcyclopentadiene
- The key chemical transformations in this synthesis involves,
  - (a) Intramolecular Paterno-Buchi reaction in acetylnorbornene
  - (b) Regioselective cleavage of oxetane and oxidation
  - (c) LDBB mediated C-C bond cleavage
- Their total synthesis was completed in 4 and 5 linear steps with an overall yield of 33 % and 35 % respectively

If you look at the synthesis as I said both the natural products are made in four steps and five steps. The first one was made in 4 step and the second one was made in 5 steps and this was reported by Viresh Rawal group in 2000 and synthesis started from 2-4 dimethylcyclopentadiene as in the case of isocomenes.

Here also the key reactions are intramolecular Paterno-Buchi reaction and the cleavage of oxetane and cleavage of the C-C bond using lithium ditertiary butylbiphenyl. And more importantly if you look at the total synthesis it involved on only 4 and 5 steps ok. The first natural product it took only 4 steps and for the second natural product it took only 5 step.

And the overall yield is extremely high 33 percentage and 35 for synthesis of angular triquinane is extremely high, one of the very efficient synthesis of angular triquinane reported by Viresh Rawal. So, with this we have completed the total synthesis of 4 triquinanes and we will continue our discussion on the synthesis of more angular triquinanes followed by linear triquinanes ok.

Thank you.