**A Study Guide in Organic Retrosynthesis: Problem Solving Approach**

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**Lecture - 17**
**Specific Tf such as Barton's nitrile ester photolysis**

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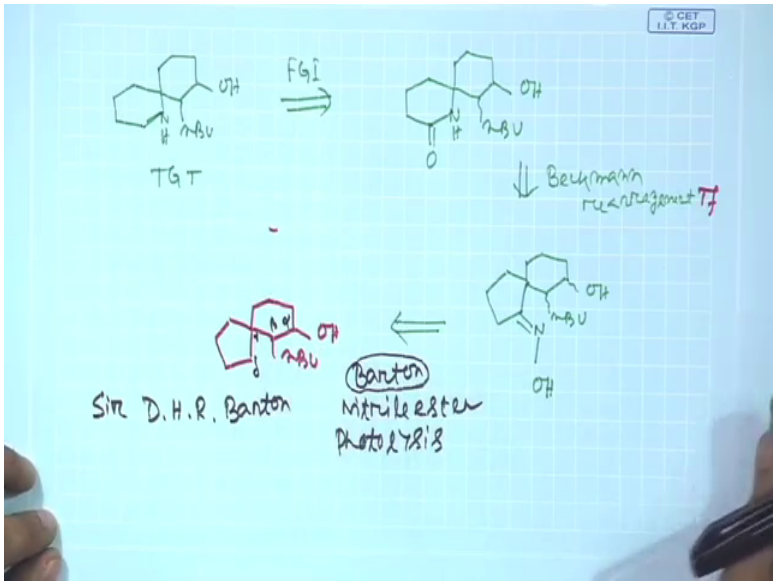


Ok students welcome back. So, in the last lecture, I have given you a problem based on a spiro cyclic compound and I said this is one of the intermediate for a natural product which saturated from is South American frog. Now, if you see the retro which was discussed in the last lecture, we come back to this Beckman rearrangement transformation. And I said Beckman rearrangement is basically a transformation where a cyclic hydroxylamine or cyclic oxime, cyclic oxime basically undergo a ring in expansion reaction to go to the higher ring. If we have a five-member oxime that will undergo a ring expansion to be give a six member amide.

So, now how you can make these oxime, next will be the very interesting reaction which probably we need to spend some time we have a OH here we have a n butyl here. Now, if I draw a intermediate something like this say that said this left end ring is absolutely unfunctionalized, then how we are planning to introduce a oxime or a keto group into this. I said there is s there are OS. And this is a very interesting reaction say alpha, beta, gamma, delta. Now, this particular reaction or this particular transformation is basically

named as Barton nitrile ester photolysis this will be explaining nitrile ester photolysis what exactly this reaction is and how it takes place.

Now, Barton nitrile ester photolysis was first invented by Sir Derek Barton, who got the Nobel Prize in chemistry working on the conformational aspects of several steroid molecules. Now, if you see it is this reaction is basically a removed functionalisation of a molecule. Now, here I said that is alpha beta, gamma, delta is a delta functionalization and nitrile ester means that you need to have a nitrile ester of the corresponding alcohol. So, now try to analyze what is the Barton nitrile ester photolysis.

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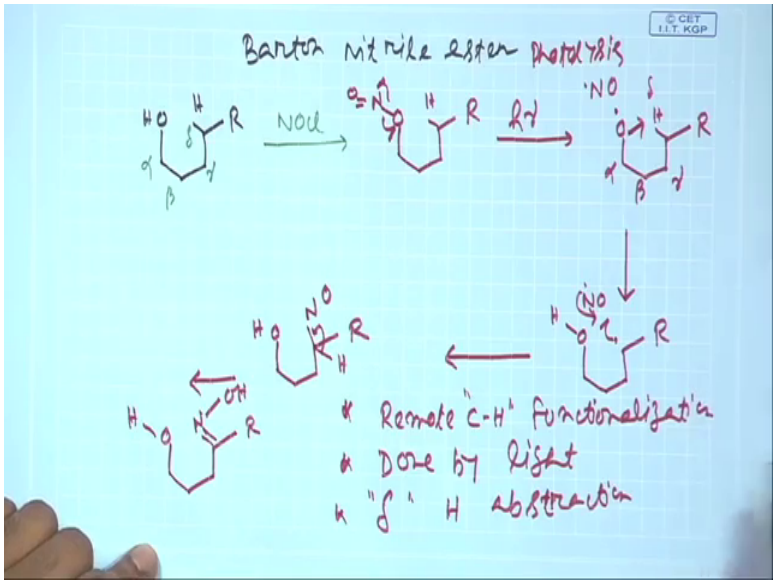


So, we will be explaining what is Barton nitrile ester. So, we will be having a starting material alcohol something like this. And now we say it will analyze the alcohol is the alpha, beta, gamma these have to in its delta. So, initially what was done if you have this kind of alcohol you react with NO Cl nitrosyl chloride. The nitrosyl chloride will basically react with this alcohol to give you a nitrile ester. Nitrile ester that is called Barton nitrile ester photolysis.

And the name implies photolysis means some where we have to use a photon source a light source. Now, this light will basically give you a heterodic cleavage of this O nitrogen bond. So, once this thing takes place, you will basically have the O dot actually this is going by this way and is a half arrow and you get a O dot and you basically get NO dot. So, this hypnotic oxygen hydrogen is clearing. And then this oxygen dot now

abstracts the delta hydrogen alpha, beta, gamma, delta through a six member transition state. So, one, two, three, four, five, six the closed functions to it.

And once it abstracts it this O now become OH and then it puts a radical here now this NO radical is sitting idle. So, NO radical is basically here. So, what it does this radical are repairing sorry pairing radical-radical pairing. And once this radical-radical pairing takes place will be this is now OH and this will be long having this NO after this radical-radical pairing. Now, this compound is having again a hydrogen, and this is kind of a (Refer Time: 05:52) will takes place to basically give you the corresponding oxime. So, this is the nutshell the Barton nitrile ester for photolysis the key feature is the remote functionalisation the remote CH functionalistion. It is very important reaction; this is done by light. And normally delta hydrogen abstraction takes place delta hydrogen abstraction . So, now you try to fit it in this our model. We will be now doing it.

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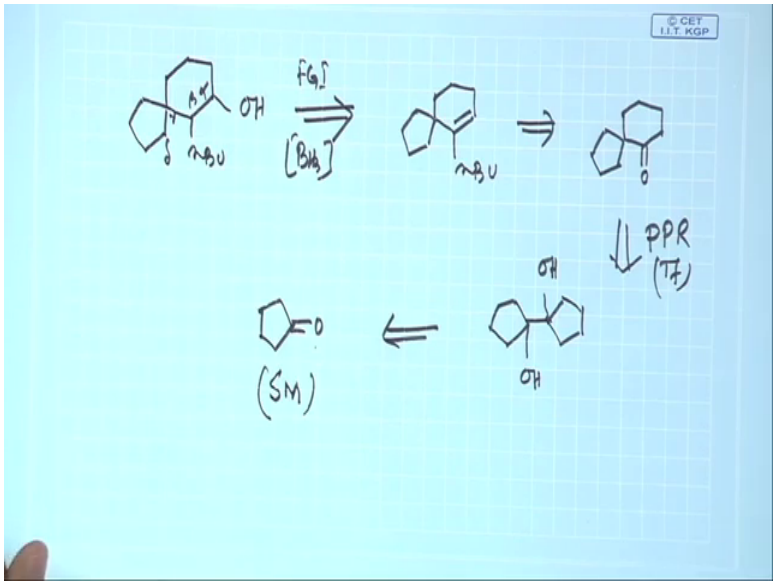


So, next if you apply this Barton nitrile photo analysis the intermediate which we have earlier figured it out, it is basically you are having it a n butyl, you are having a OH here. So, we will put a nitrosyl group here O NO then this alpha, beta, gamma, delta. Now, eventually you are having if you go back this way again alpha, beta, gamma, delta this is also another delta now as I said this molecule has a unique chemistry. So, we did not discuss it to make your life simpler; in reality we will find that only distilled the

hydrogen is in close proximity with this OH because a three-dimensional structure we did not consider fine.

So, now this compound you have to prepare this compound basically you can prepare by simple functional group addition by a functional group inter conversion through a hydroboration chemistry hydroboration simply all of you know very standard hydroboration chemistry. And then the chemistry which was of the retro which was drawn here probably all of you know this intermediate we are discussing the retro quiz try to remember. So, this is basically would be coming from a pinacol-pinacolon type of rearrangement which we all discussed previously and this compound is it pinacol-pinacolon on rearrangement transformation. And this one it is a simple coupling of two equivalent of cyclopentanone.

So, we now trying to come back to the original starting material which is cyclopentanone this is very cheap cyclopentanone starting material was not giving to you, but the point is until and unless you will know the Barton nitrile ester photolysis, the whole pathway is impossible for you to design.

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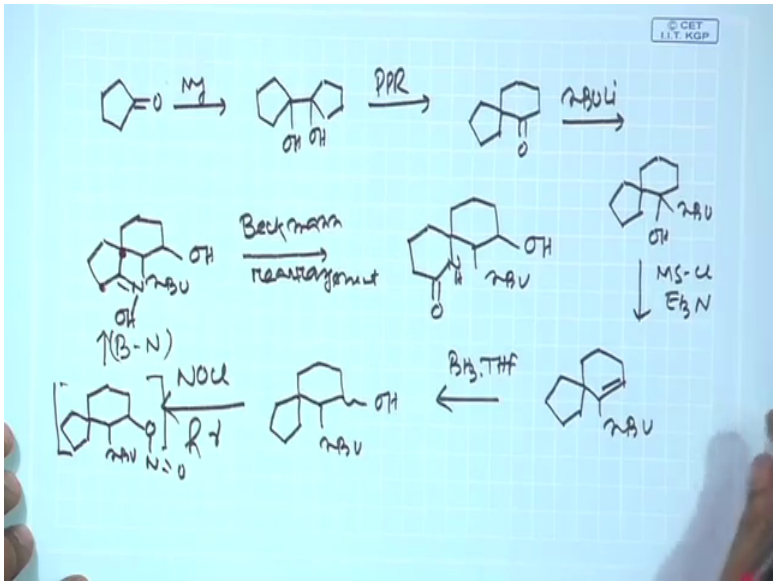


So, next what we will do we will try to go back to the forward pathway. Starting material is this, you do the initial magnesium mediated coupling, this is very simple. So, all know, it will be Pinacol-pinacolonone rearrangement and that will basically give you the spiro cycle thing then you do a n butyl lithium reaction here that basically give you a addition

of OH and n butyl neutrophilic addition. You make corresponding missile chloride by treating this alcohol missile chloride. And do a 1, 2-elimination that basically give you the corresponding olefin which is required. Then you do the hydroboration by borane THF to this hydroboration we will then give it to this compound.

To this compound, now you react with nitrosyl chloride and sign light. So, nitrogen chloride an light will basically give you the intermediate O N double bond O, N butyl is here to draw the spiro circle remaining part. Now, I say is the intermediate as I now do the Barton's reaction nitrile ester photolysis. So, alpha, beta, gamma, delta the oxime in will come here. So, what basically you will get basically get away OH here and butyl and this side cyclopentane ring will be now having the oxime. And then you do a Beckman rearrangement, Beckman rearrangement based transformation that is also very standard reaction, and your n butyl will be remain here.

Now, here in basically get the ring expanded thing, you will get the ring expanded thing. And normally Beckman rearrangement is basically a migration towards electron diffusion nitrogen. Now, more stabilized or more substituted carbonyl is basically migrate. Now, out of this, these things basically there is a possibility either this carbon can migrate this carbon can migrate. Now, this carbon is more substituted so this will be migrate and that is why this carbon is having direct nitrogen bond. So, once Beckman rearrangement is done, your next job is very simple.

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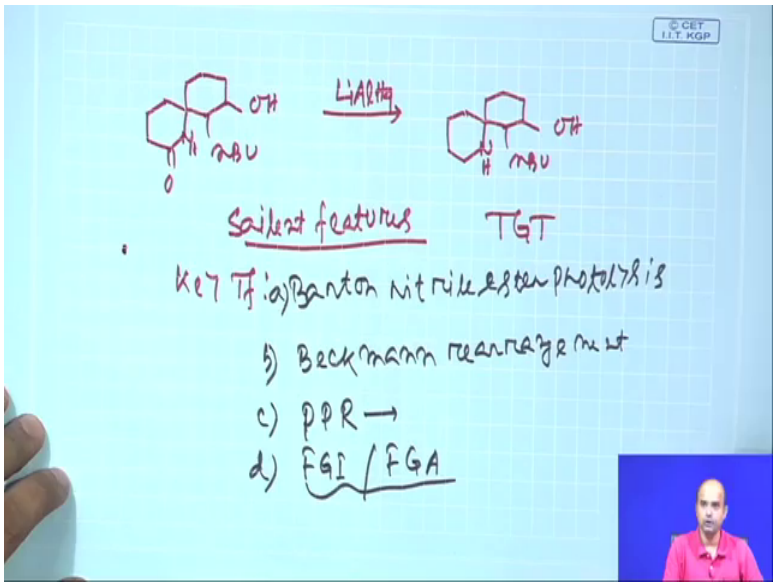

So, now, try to correlate the final target structure, you are having here n butyl, and then is a NH double bond O. You are doing a reaction with lithium aluminium hydride as I said reductive cleavage, not cleavage reductive transformation. And then you basically get the amide NH. So, this is your final target. Please try to remember. So, the salient feature, salient features of the whole synthesis was couple of interesting reaction we talked about, but definitely the key transformation key transformation is the Barton's or Barton nitrile ester photolysis is absolutely brilliant reaction nitrile ester photolysis that was the main key reaction key transformation. That the remote delta CH functionalisation through a photo chemistry photochemical path way.

In addition, you are also doing couple of interesting transformation the key is Beckman the Beckman reaction or Beckman rearrangement was used in the final stage. And then pinacol-pinacolonone rearrangement, which was, very crucial was used, and then you do couple of functional group interconversion or functional group addition. So, you would mean synthesis is basically combination of all those things what I said we would are non famine with this Barton nitrile ester pholysis that is very difficult to design the entire pathway; Beckman rearrangement and other things are basically coming into picture at a later stage. So, this will basically give you the how different powerful transformation can be applied in a sequential manner to give you a complex or medium complex size molecule.

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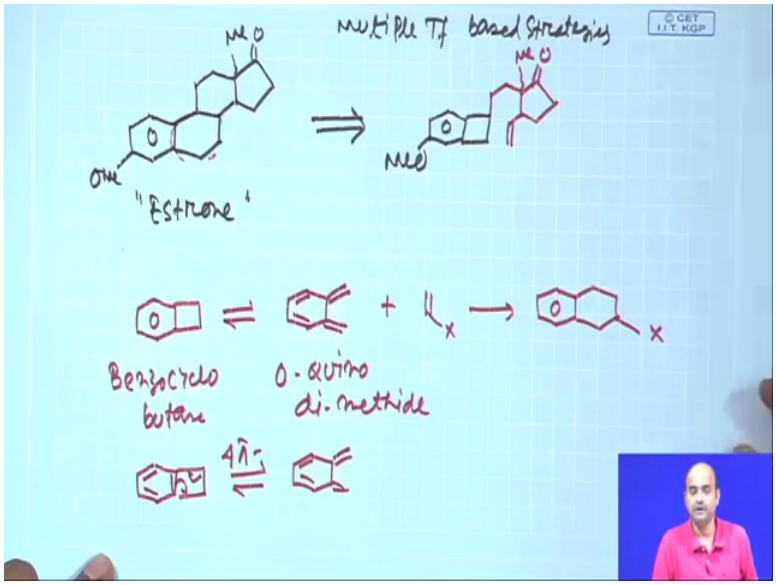

Next, we will draw a target, but eventually this case you would not discuss the forward path. We just say this molecule can be constructed through this pathway and what is the possible transformations you can think about. If there is a new transformation we will definitely discussing this transformation. Now, as I said the stereo chemistry was not discussed, this is a natural product is basically a the stone hormone. And now this compound was the synthesized long ago. Now, we are trying to use multiple transformation based strategies, how multiple transformation combine together to give you a target molecule which is desired by you.

Now, for this molecule to see that how we disconnect the molecule; in the very beginning the disconnection looks very complex (Refer Time: 16:40). It gives a five member ring at this right end. And then you put a cyclo butane ring fused with a benzene ring. And definite this was very judicious cleverly done means that there might be some transformation available. Now, what can be taught off, the idea was basically the central cyclo hexane ring, central cyclo hexane ring can be devised through a (Refer Time: 17:23) kind of transformation. Eventually, which is very difficult to assume at this stage.

Now, if we have this kind of intermediate which is basically named as benzo cyclo butane now benzo cyclo butane under thermal condition here basically undergo electro cyclic ring opening to give you this intermediate which is nothing this is benzo cyclo butane. Benzo cyclo butane is basically give you intermediate whose name is ortho quino dimethide. Now, these ortho quino dimethides are powerful dime. If we have a suitable dimo files, it immediately undergoes ring closing things because the final left side ring is getting the aromaticity. So, benzo cyclo butanes in principle the structures will be something like this, and basically this part you can think about a 4 pi electro cyclic ring opening, 4 pi electro cyclic ring opening that basically gives you the benzo cyclo butane. Now, as I said it is very easy to write in the paper, but whenever in reality you do the practice then it is ok.

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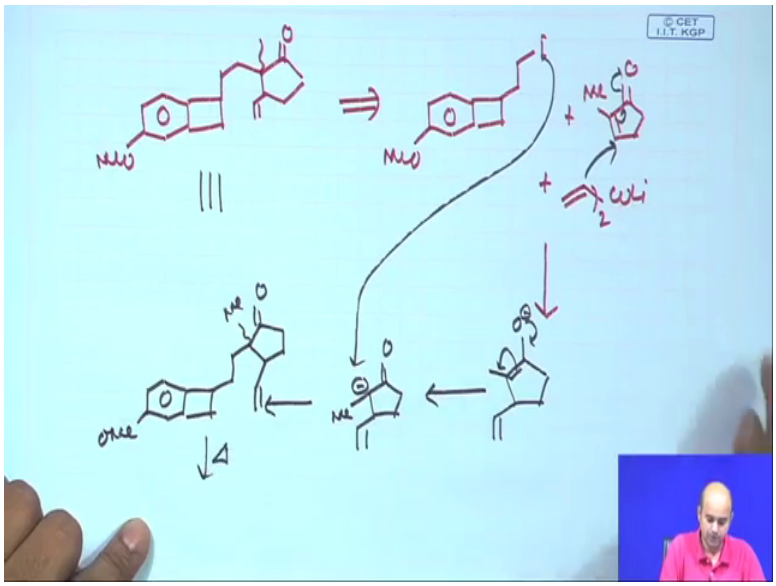

So, come back to the intermediate which we have earlier done based on the benzo cyclo butane and ortho quino on dimethide chemistry. You see there right end path remains similar. So, now, we say that this compound you can basically visualize from this type of primary ro species, and this cyclopentanonee as a michael acceptor as well as will be using a vinylic copper lithium as gilman reagent.

Now, how this is takes place is basically the three component reaction all together is a michael acceptor, it is a nucleophile finally, copper lithium. So, first case is 1, 4-addition takes place. So, once this 1, 4-addition take place we basically have this final group here now this double bond basically shifted or the anon has been shifted. So, initial nucleophile which is come here this electron has been shifted the has been delayed from here to there, this will be explaining when you talk about anon rely chemistry fine.

Now, this is basically a phenolate. So, this phenolate come back put the negative charge here and this is now going to be trapped by this electrophile which is here. So, so we will basically get the electrophile and all the things will now react in a your cyclopentanone these things. So, here obviously, you methyl is there, another methyl is there. So, you are having a methyl here. So, you are having a methyl here. So, now, see this is the vinyl, this is the vinyl, this is the vinyl. So, this is now same these two compounds are known same. So, only thing is now you need to heat it, you just need to heat it. So, once you heat it again write it down in the next slide.

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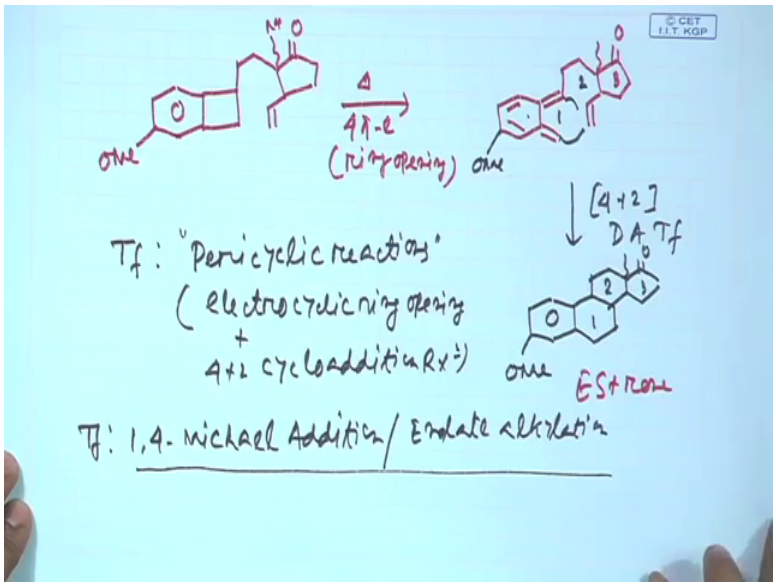


How the final reaction takes place. This is your benzo cyclo butane, benzo cyclic butane or write it in this way. This is the methyl; this is the fine. Now, this vinyl group was basically appended acting as a appendage and latter part this is hardening as a dimo file in (Refer Time: 22:19) reaction. So, next your thermal as I say 4 pi electro cyclic ring opening ring opening takes place to give you the ortho quino dimethide structure your methyl. Now, see two rings basically we are making together. If you see the target molecule, the target molecule is having this structure. So, there are four rings together actually the left end side is a benzene ring, you can call this is a ring one, this is two and this three ring is coming from the cyclo pentenon which is the use as the starting material. So, ring one and two, so this part aromatic part is here. And this is the ring three or the cyclo pentene ring which came from the starting material.

Now this ring one and this ring two how it has been now coming is the dying part this and this. So, 4 plus 2 once it close it gives you two ring together that is the very interesting. So, 4 plus 2 or gives in the transformation takes place and then basically you get the first ring one, the second ring is this and then finally, we will be having the other ring. So, all together this is 1, 2, 3 your methoxy remains as it is methoxy remain as it is. So, transformation wise this synthesis of this is estrone as a target molecule a simple definitely very simple. And then, but the only thing is you need to know exactly what is happening here, the transformation what we use here is a basically combination of a peri cyclic reaction.

Peri cyclic reactions all you have to study because in the retro synthetic pathway you were not will talk about more of the reaction that we have a restricted time. So, we use a electro cyclic ring opening as well as we use a 4 plus 2 cycloaddition reaction cyclo addition reaction and then at the end to basically use this 4 plus 2 cycloaddition reaction. The beginning what you use you basically use a 1, 4 michael addition with a properly substituted gilman reagent. So, 1, 4-addition one four addition or micheal addition type of reaction with enolate alkylation. So, all these proper combination of this different reaction making these whole process very useful and a very successful.

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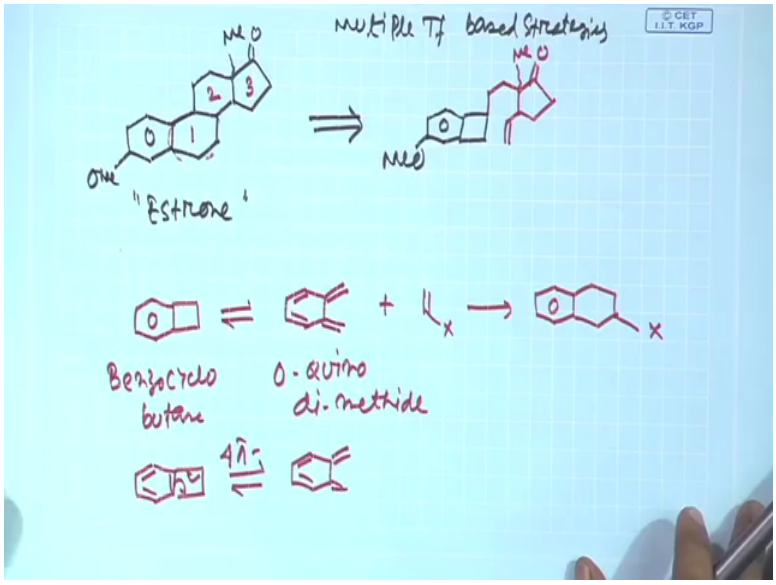


Now, if you see the target molecule which was the ace estrone part which is the estrone or the real target molecule. Again go back to a retro as I said, the retro is basically very simplified retro. We design the podcast to circulate the injection, but if you know that benzo cyclo butane this kind of compounds opens up to give the ortho quino dimethide then the job is quite easier until unless you would know this transformation, you will probably happen tough time to formulate the entire pathway.

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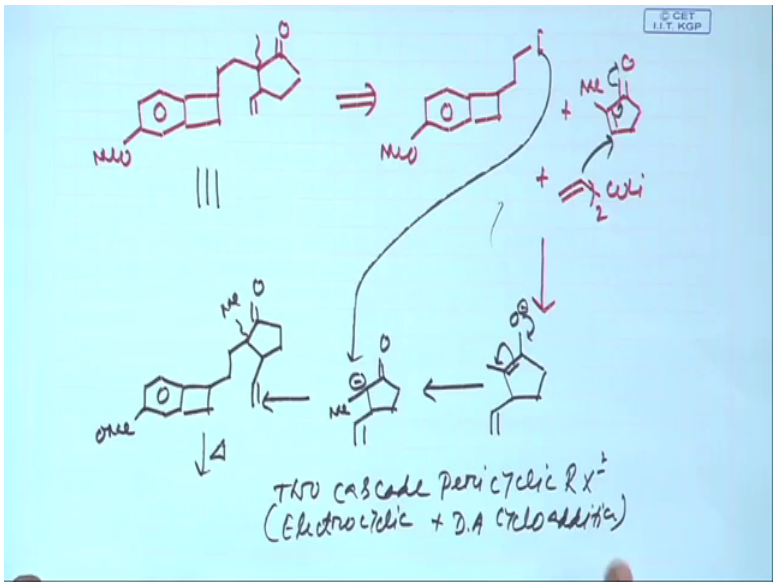


Now once this benzo cyclo butane has been chosen as the intermediate your next steps is basically you have think of using this as a electrophile. And the starting material is two methyl cyclo hexinon which is very cheap. And now react with a vinyl copper lithium is the vinyl gilman reagent. So, it is basically 1, 4-addition of this vinyl gilman in the michael fashion. and then this electron basically undergoing regulating things to put a in enolate around this enolate now undergo anolate alkylation with this electrophile.

Now, this electrophile once it attacks, it is basically a three components reaction together one-component, two-component, three-component sometimes divisions termed as multi component reaction. So, now, you are basically here the ones you are here then basically you have two cascade peri cyclic reaction we called two cascade peri cyclic reaction two cascade cascade means one after another two cascade peri cyclic reaction. As I said peri cyclic reactions, we are not discussing in detail here. The peri cyclic reaction which were talked about here is a electro cyclic reaction electro cyclic ring opening of this benzo cyclo butane and a deals alder cycloaddition.

To these two reaction is a key transformation of which was used as the penultimate stage or the final stage. And in the very beginning, we use this multi component reaction to access the core intermediate. So, we will try to continue our discussion based on this topic as I said and so try to analyze all the problems which was discussed till today, try to go to any standard textbook, try to take the help of this internet, scene archive website.

So, just try to accumulate as much knowledge as you can and then we will catch you in the next lecture.

So, till then good bye.