A Study Guide in Organic Retrosynthesis: Problem Solving Approach

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Lecture - 49
Topological based Strategies

Welcome back students today will be trying to explore.

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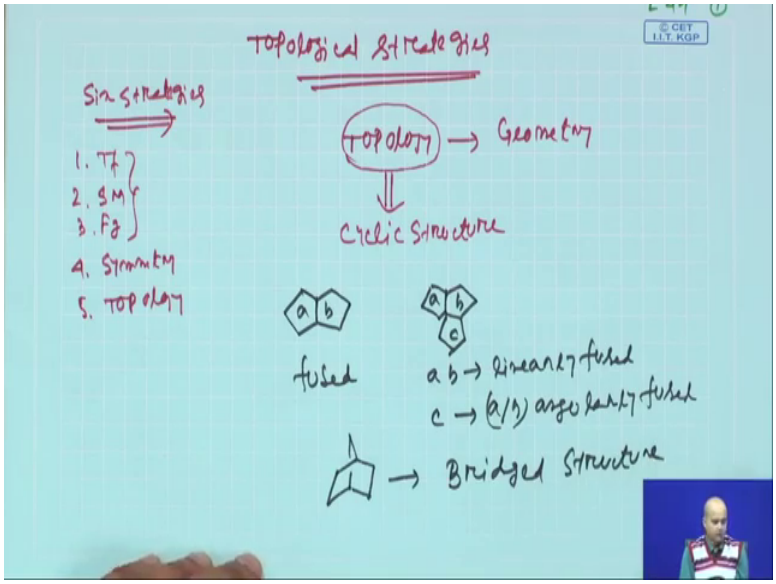

You another strategies topological strategies, now if you see the earlier lecture of the very beginning lecture is it will basically try to have a six different strategies six strategies through which will try to explore you different kind of disconnection best strategies you said. Initially, we talked about transformation, second is starting material, third is functional group this strategies we have discussed in detail number 4.

We have just talked about symmetry based strategies a number 5 comes your topology based strategies. Now, topology is a very unique terminology is usually used in a topology was often used in the particular field of geometry or mathematics, but how is topology can be used or how topology can be used in the field of organic synthesis would next talk about topology basically means that; if you are having a cyclic structure in your given molecule cyclic structure. Now, this cyclic structure can give you a nice topology or nice geometry in the target molecule. Let say for example, I will give you a few interesting cyclic structure.

Now, this structure is basically a and b ring are fused together fused together. Now, if I now draw structure optics that three rings are there. So, where a, b are linearly fused linearly fused, but a, b this ring is fused angularly with the ceiling. So, c is basically fused linearly with the b, but is fused with angularly fashion with the a, b ring angularly fused.

So, this kind of interesting topology will be always there in target molecule and normally in the nature will find that this kind of topologies are very much existing a unified topologies your bridge structure bridge structure has a unique topology, because you are having a core cyclohexane ring. And then in top of that you are having a bridge this also bridge structure gives you a very unique topological features bridge structure.

So, what I am trying to explore throughout this throughout this lecture contained, I will try to give some terminology that; what are the different kind of ring structure?

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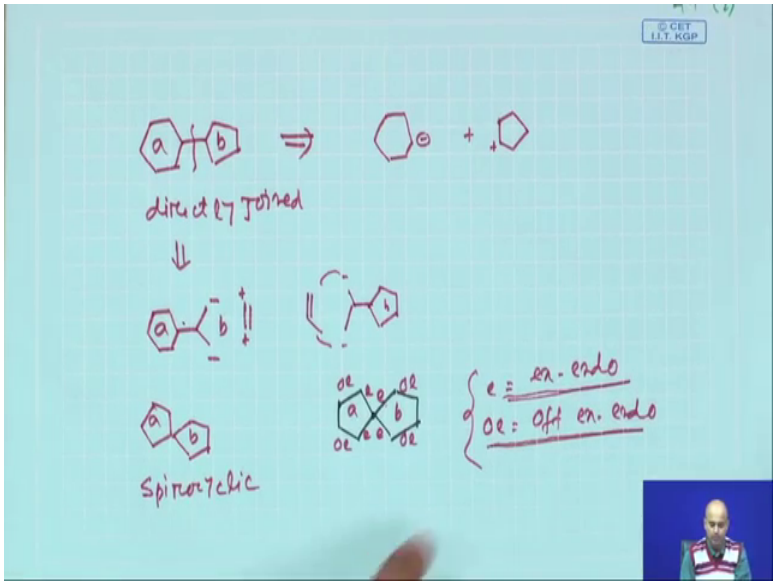

Known in the literature and how these compounds are given their nomenclature to initially, I said this two rings a, b have a unique topology, but these are basically can called it as a directly joined directly joined. Now for this kind of topologies you have to do a disconnection you can simply do a disconnection through this disconnecting bonds, it is a one of the best way to do it, if you are having a required variety concept that you can do a simple plus minus carbon cover bond formation.

This could be a good way of disconnection, otherwise other things are also basically preferred if you make any of these ring like a and then you can put a this kind of structure which gives you this ring and this bonds will give you the central b ring; or in the other hand if you are having a, b ring as a starting material you just try to do the same way minus, but here you basically I need a 3 carbon unit. So, in this way also you can do this ring contraction sorry ring construction. So, this is the how the usual guidelines, but definitely as I said there are no straightforward guidelines for this kind of molecules.

Now, this is one of the; of interesting topology there are topologies which let us see this topology this molecule is a by cyclic molecule and that particular topology is named as spirocycle the spiral cyclic molecule. So, first spirocyclic molecules there are some terminologies which you need to know for spiral cycle molecule they have a common carbon atom and the bond which was just originated are naming in a different way this particular bond is named as e e e e.

Now, e basically stands for the terminology named as ex endo. Now what is ex endo? Ex endo means that the ceiling is endo to the right hand side, cyclopentane ring ok, but is exo to the left hand side cyclopentane ring this is a and b. So, e o there are 4 bonds e 1, e 2, e 3, e 4. So, this e 1 is endo to b ring, but exo to a ring these are bonds are named as ex endo bonds is other terminology named as o e or off ex endo.

Now, off ex endo means that bond which have been generated from the ex endo bonds. So, this is a off ex endo bonds this is a off ex endo bonds this is a off ex endo bond this is a off ex endo bond. Now for statistical guidelines ex endo bonds can be a good point of this connection as well as off ex endo bonds. So, both the bonds basically can be a good strategically point of disconnection and you probably the next few examples will talk about; how this ex endo bonds and the off ex endo bonds can be a statistically disconnect you can also have a topology which have already discussed.

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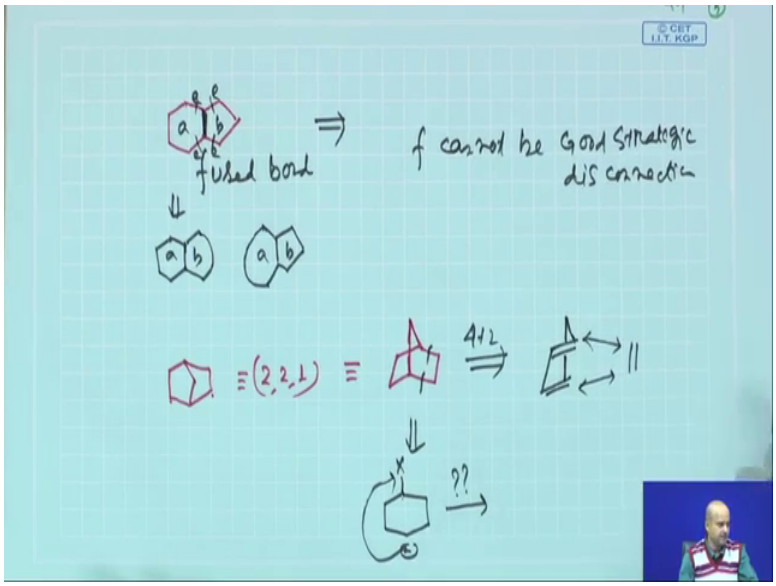

Now, this ring or this bond which is common to both the rings is called fused bond fused bond fused bonds. Now fused bond if you want to disconnect this kind of molecule; the fusion bonds cannot be a good strategy can a disconnection be a good strategic disconnection, because fusion bond is very difficult to construct disconnection. Now, in those cases you basically can think about you can take any of this primary ring or any of this ring as your core structure either a or b as a starting material then this other bonds.

So, we get the bonds these are the bonds. So, basically ex endo bonds ex endo bonds, earlier I said ex endo bonds can be a good statistical disconnection, basically you can now think about having this kind of disconnection or this kind of disconnection to make a cyclopentane ring here or a cyclohexane ring here. So, this gives b this gives a this is the point the fusion bonds you probably never touch it that is a usual way of doing the disconnection is usual route.

Now, for bridge structure I say the bridge structure is a very unique topology like this; this is named as 221, because 2 carbon here, 2 carbon here is a 1 carbon. So, if you like to write if you like to draw the structure in this way you say this is this bridge structure also probably the bridging bonds is not a good point of disconnection. Now, probably we all of you have known couple of reactions which gives very familiar disconnection of this system the best to way always we know 4 plus 2 cycloaddition reaction.

Now, what we do in this reaction you react with a dying and diana file now this 4 plus 2 cycloaddition reaction, basically makes this carbon carbon bond this carbon carbon bond. Now this carbon carbon bonds are basically not bridge bond you are making this bond. Now this bridge one is basically this as a bridge bond cannot be disconnected. So, like you can have a other disconnection for this molecule keep the course cyclo hexane let say you put x group here a minus group here.

So, I am saying that this minus can attack here to give you a bridge structure like, you basically connect here as it there are some question marks you cannot have, because this in reality these are not a close proximity group this groups are a little bit for apart. So, in those cases this is not a good strategic disconnection. So, this points you need to always always consider then, there other rings which also having unique topology I said there are rings something like this.

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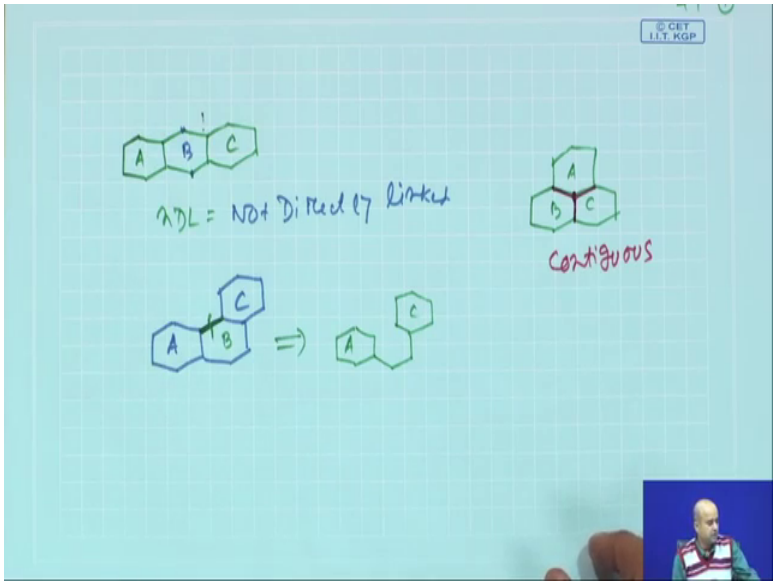

Now, ring A and ring C these are called n DL or not directly linked not directly directly linked, because you see A and C in between there is B ring, but these are not directly linked we have Michelin things here ok. So, this linearly if you used try cyclone then will find the lin some other other topology. So, ring A, ring C now you see the ring A and C is directly linked. This is also a good point that A and C are directly linked sometimes rings are directly link probably this is a good strategic point of disconnection you have this A.

So, which is now give you disconnection something like this part is there and then. So, if you have A ring and C ring you can basically construct this carbon carbon bond through this could be a good strategy point sometimes rings are having a common bond all together at this kind of structure this kind of topology A, B, C rings are basically we can call this ring are contiguous. Contiguous means like, this is the particular thing that this point this common to all the ring and this things are this rings are name as contiguous ring in a contiguous rings are also you will find many natural products which is having this kind of contiguous structure contiguous structure.

Now, now I will try to give you some structural information on different kind of topological based topological district molecule in the natural products.

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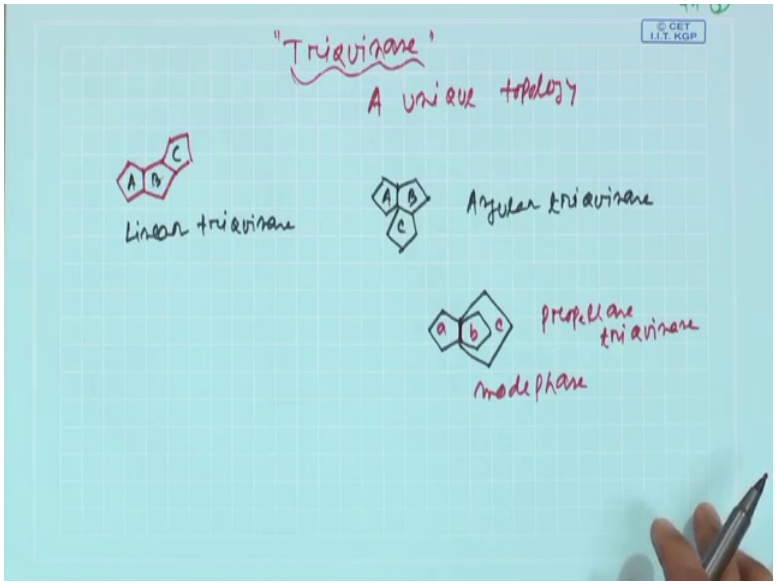

Now, eventually you will find that this one of this class of molecular named as triquinane, which you are basically a naturally occurring compound the quinane basically stands for cyclopentane network. And try means 3 cyclopentane network and triquinane always have a very unique topology very unique topology means their ring structure are very unique few structure are already have talked about.

Now, I am saying this is a linear try quinine linear triquinane and means there are three rings: A, B and C are basically linearly fused so, linear tryquinane. Then there are many natural product based on this kind of core structure. Then there are angular try quinineis

a angular try quinine will be something like having this structure where ring A and B are linearly fused ring C is angularly fused is called angular try quinine.

And definitely these are not hydrocarbons you have a different functional groups attached to this particular ring carbons angular try quinine. In addition there is a another interesting structure which have already discussed is called propylene, where you are having a common band which is common to all are 3 rings ring a, ring b, and ring c.

And there are compounds this frame work is basically named as mode phase frame work and it will go on the symmetry strategies we talked about such molecules like mode phase; large number of natural products which is basically having this kind of structure. So linear triangular, angular try quinine try quinine and this kind of try quinines are named as propellant try quinine propellant and try quinine where a propellant structure is definitely there.

Now, there retrosynthetic disconnection as well as their synthesis is very complex very complex. We probably will not to discuss all of the things in very detail, I try to pick up very simple example world find that; how this kind of this kind of compounds can easily be made sometimes you may have a of molecules like this where a aromatic nucleus was fused with a another ring.

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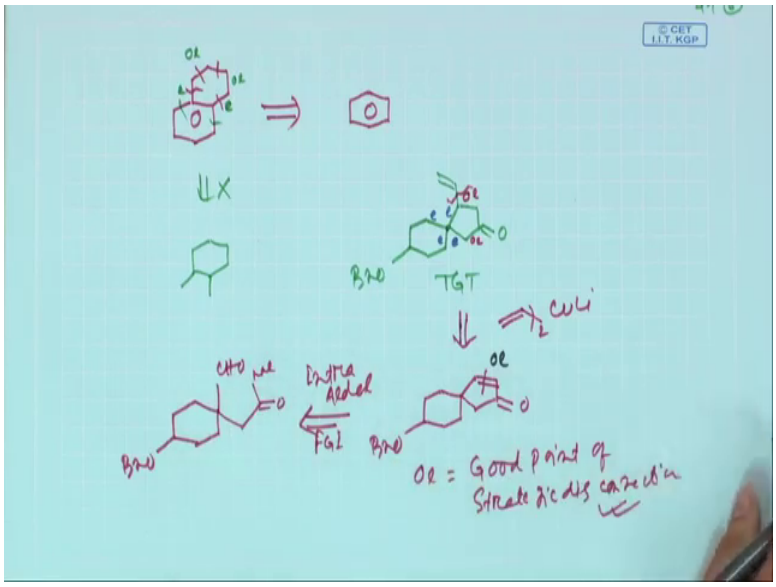

And in this case is your strategy should be always follow that, you start with aromatic compound and then, make this bond this bond which is basically ex ex endo or you can make this off ex endo bonds.

So, you always start with aromatic partner and then you do the disconnection of ex endo bonds or off ex endo bonds. But, never ever do the other way means you start with a cyclohexane thing, and then you are saying that I will be trying to disconnect here to construct the aromatic ring at a later part. This is usually not recommended, because because aromatization is a bit difficult scenario sometimes you can do it, but now it is not recommended is aromatic precursors are easily available and you can think about making these molecules quite easily.

So, now one trying to do will try to explore this I said ex endo bonds and off ex endo bonds are often a good point of disconnection. So, will try to take a example and will figure it out; how this strategy is valid? I will give you a spiro cyclo molecule as a target molecule you see the molecular 6 members rings is few to few with a 5 member ring one end you are having a benzyl appendage and another end your this cyclopentane is kind of functionalized choices.

Now, if you now see the disconnection or the strategically point the nomenclature this is ex endo ex endo ex endo and ex endo and you have this off ex endo off ex endo. Now I say that off ex endo as well as ex endo bonds are good point of disconnection. So, simple disconnection of this molecule, probably will give you a this kind of structure and I say that this off ex endo bonds this is not a off ex endo. This is basically a appendage this appendage can be constructed through a vinyl copper lithium based ok, now what I am saying that.

Now, you are having alpha beta unsaturated keytone. So, this probably can be easily made through your; now this bond is becoming a off ex endo bonds this bond is your off ex endo bonds. Now, I am saying that this off ex endo bonds you can easily prepared, if you are having it this CHO and this CH 2 CO CH 3 to a intra aldel F G I. So, intra aldel F G I. So, what we can you make you make a new off ex endo bond. So, we said off ex endo bands are good point of strategic disconnection good point of strategic disconnection.

So, now you can basically see how this rule is valid? We are basically making off ex endo bond fine, now again you do the retro for this molecule and there find how we can further disconnect it.

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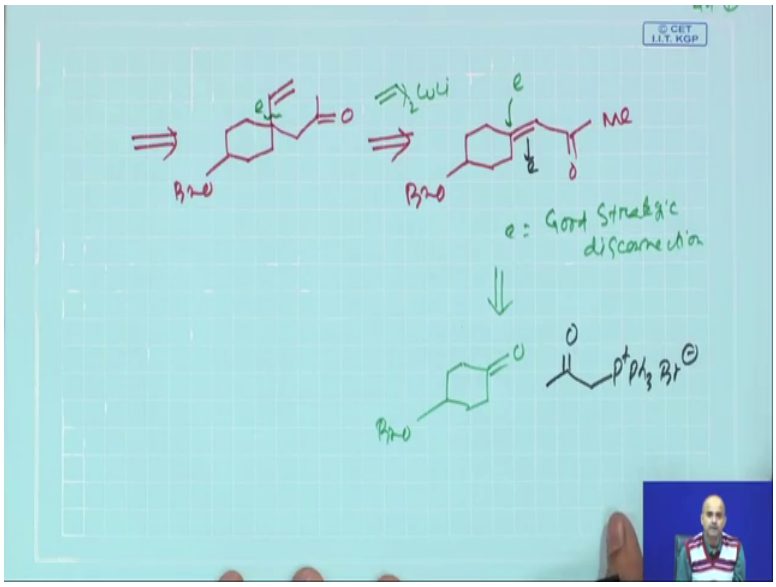

We have to basically being the aldehydes at one end and then you are saying that would be trying to do a this kind of oxidative cleavage to bring this aldehyde. Now, this was very good dishes you are very cleverly done.

Now, the next retro will be clearing your all the doubts. We are now saying that, if you are having a this compound you can do a another round of vinyl copper lithium to Gilman reaction. Now, what bond you are mean? Basically, making this bond is basically a ex endo bonds. So, you are basically making a ex endo bonds. So, ex endo bonds also good strategic disconnection we earlier said ex endo, as well as off ex endo bons are good strategical disconnection.

So, we are just trying to follow the terminology and now we are, now simplifying structure through this and here B n O c double bond. Now you are saying that if you can do a Wittig reaction with this you make this bond know this bond. After the final transformation, this bond also become to a ex endo bond is not it. So, all the throughout the retro will basically disconnected through a ex endo as well as off ex endo bonds disconnection. Now, let us do the forward synthesis of this.

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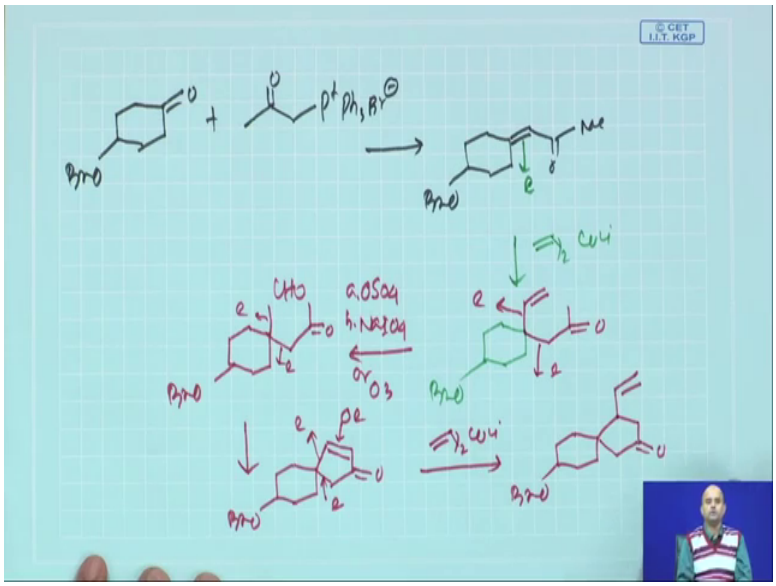

Molecule to visualise the entire pathway starting material is this one first you do Wittig reaction. With this Wittig salt basically generate the alpha beta unsaturated ketone. So, what you make basically make a new ex endo bonds.

Now, this is bond is not ex endo it is exo cyclic bond, because did not make the cycle or cyclic structure. Now is saying you do a venile, copper, lithium that will basically give you the this. So, initially ex endo bonds was made you are making another ex endo bonds ok. Now this bond in this form is not ex endo bond is exocyclic bond and now you are doing a oxidative cleavage by sodium, paragon and osmium peroxide limited diet oxidation a and b are how you can do a simple ozonolysis.

So, what will be now getting? Basically now get a CHO and CH 2 CO CH 3. Now, I am visualising it can be connected to this intra molecular aldel reaction. So, once it closes this bonds become ex endo this bond become ex endo and the newly created bonds became a off ex endo. So, that basically highlight the main thing, now see the initial formed bond is a ex endo bonds this bonds is a ex endo bond this one basically off ex endo bonds.

So, now you complete the synthesis by doing a again another round of vinyl copper lithium; and then you find that you have this BnO and get this spiro cycle with this happed to this was, basically a nice statistical disconnection of a topologically simple

molecule. This topologically basically spiro cycle molecule may would try to a go back to earlier thing if you remember.

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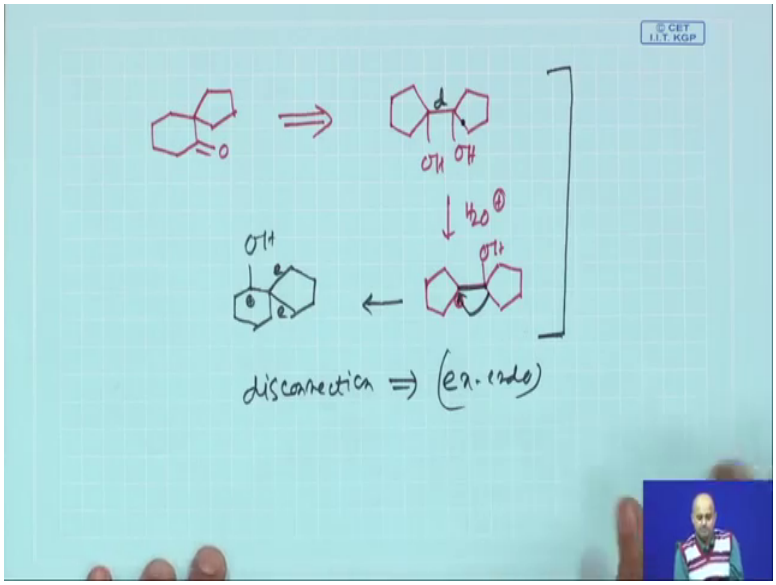

Earlier, it talked about synthesis of this kind of spiro cycle molecule to a pinnacle rearrangement; we say that this compound can easily be made through pinnacle pinnacle rearrangement of these things. Now, if your now taking this as mechanical perspective initial, what you do you basically? Generate, a carbonium ion here by water elimination now actually the rearrangement takes place here.

Now, this is basically migrates and what it will give? It basically give you the 6 member things here and basically collapses to give you the a carbocation. Now, actually this is this cannot be a simple ex endo disconnection as I said, because this bond is ex endo this bond is ex endo this bond is ex endo to this bond is ex endo, but the migration also gives you the heat, because one of the particular bond which is initially endo to one ring is basically migrating is basically basically migrating.

So, the bond which is a initially directly connected bond directly connected bond is now becoming a ex endo bonds. So, the earlier one once you said the pinnacle pinnacle rearrangement in two sense is not a ex endo bonds disconnection, but you can also figure it out we are basically going to the disconnection through a ex endo fashion, the one ex endo bonds are mainly created like this case; we said this a directly linked bond director linked bond. Now, once this goes off this goes off one of one of your bond, which is

endo to this ring endo to this ring is basically migrates, now endo to this thing is basically migrates.

So, then this directly linked bond is becoming ex endo is not it directly linked bond is becoming ex endo. So, our disconnection basically centred through a disconnection is always focus through ex endo bonds ex endo bonds and that was usually preferred; when you have a spiro cyclic compound now will be just trying to give you a one simple bridge bicycle system.

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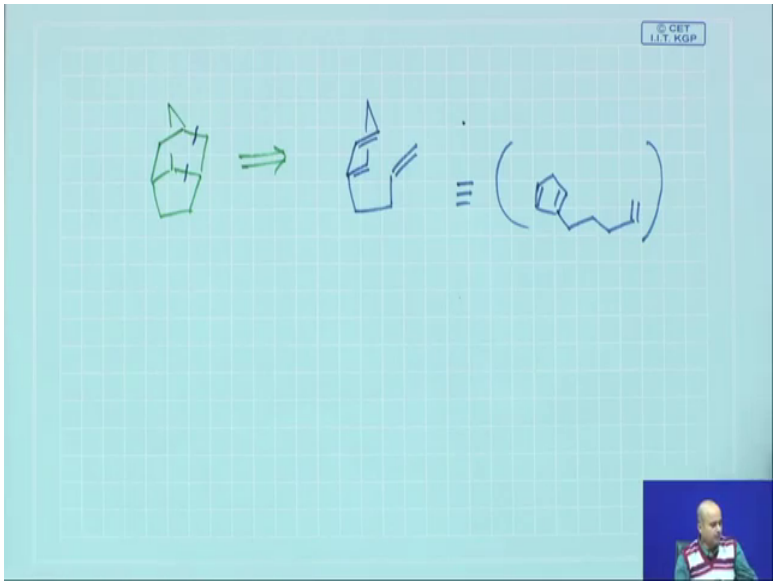

The topology was little bit difficult is like a box like molecule you have a cyclopentane bridge there and in this bottom of you having another topologies said the bridge structure. Probably, you cannot do the disconnection and normally for bridge kind of compound the cycloaddition reaction or this particular bond disconnection was always preferred. So, for this one if you do a disconnection can you make sure that every the thing was in perfect shape you probably have a intra molecular disconnection.

Now, this compound is basically a cyclopentadiene derivative or have a properly substituted pattern this things that can judiciously be done, but they said this compound may not be very easy to synthesise, because there are certain issues involved and you will try to focus it out little bit more when you talk about one another multy cyclic molecule. In the next lecture and try to try to figure it out that ex endo bonds as well as off ex endo bond are always good point of disconnection when you are having a spiro

cycle topology or related topologies. So, will continue our discussion for this topological district molecule the next lecture till then have a good time and goodbye.