A Study Guide in Organic Retrosynthesis: Problem Solving Approach

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Lecture – 44
Symmetry based Strategies (Contd.)

So, welcome back students basically we were discussing symmetry based strategies which we have started in the last lecture and, we said that if you have a symmetrical molecule, might be a designed molecule, might be a natural product, you try to disconnect the molecule, in a such a way that maintenance of symmetry or the sigma V element should be there. So, that basically gives you a symmetrical intermediate or symmetrical starting material which is often easy to get. Now, we will try to continue with this kind of thing.

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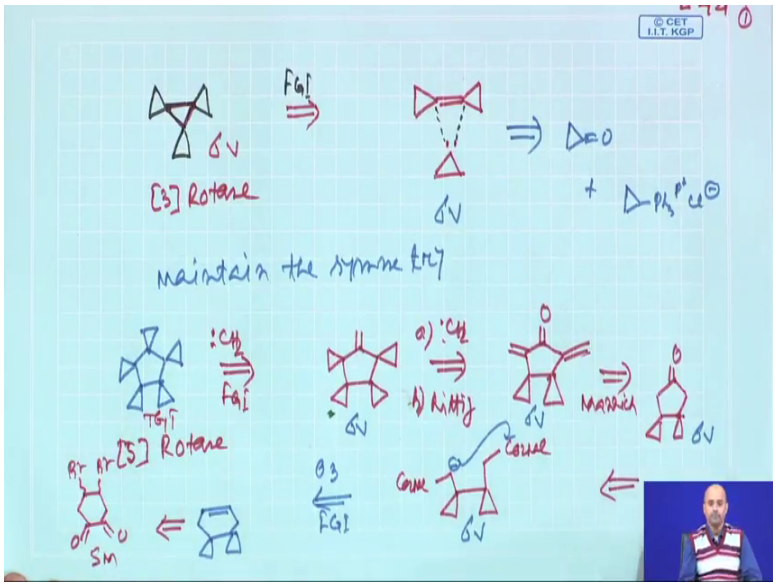

And then we will give a simple target which is basically a symmetrical molecule, and you see it structure is absolutely nice to look the structure; the molecule name is 3 rotane.

Now, if you see the structures basically a triangle means the cyclopropane. Now each point of the cyclopropane is another cyclopropane attached to it, but it is a very much symmetrical molecule it is basically designed molecule, eventually if you try to do this retro which is having a sigma V the retro was absolutely simple we initially spot that probably this kind of cyclopropane based olefin, if you can have it and you have a simple

cyclopropane based carbine probably, you can do a 2 plus one cyclo addition reaction, to construct the core cyclopropane ring that is a pure FGI.

ah now I set this cyclopropane carbine can easily be generated and, then this initial starting material cyclopropane based olefin, you can also create it if you have a cyclopropane, or suitable precursor, with a cyclopropane based betic salt like PH 3 P plus Cl minus.

So, this way basically you can you can think about doing this kind of synthesis, the only thing is the intermediates are basically all sigma V. So, maintain the symmetry is very important.

Now, the set is molecules are probably designed molecule. So, the main target was how you can make this molecule in it efficient to I. Next we will trying to have a similar kind of molecule and, then we talk about data bit different molecule. This a cyclopentane based molecule, the cyclopentane all the cyclopentane carbon atoms are basically linked with a cyclopropane, and this molecule name is 5 rotane.

There are many other molecules we will just pick a few molecules and will say how this molecule, can be synthesized. Now if you see this molecule I will give you a the clue how it can be done, I said let us start with the this molecule, step wise will keep on a doing it. Initial we say if you have this olefin, you can do a carbine addition, simple carbine addition to this FGI this is fine.

Then I say if you having this particular carbonyl compound and this exocyclic double bond, you can basically construct it through a carbine addition on both this 2 double bond and, you can do a Wittig transformation of this carbon group to construct the exocyclic bond fine.

Now, we are trying to simply the structure, we say this compound can be easily made. If you having a this carbonyl compounds, basically you can do a manic reaction. Now manic reaction we have not discussed, but probably all of you know the manic reaction, manic reaction basically you react with formaldehyde. And dimethyl amine which will give CH 2 N Me 2 here, and then you can basically extra methylate it, by methyl iodide do a half band elimination to get this exocyclic double bond here by a manic transformation.

So, now your compound is here, now we are saying that will be doing this cyclo pentane pentanone synthesis, using a kind of dieckmann reaction which probably all of you know, we say dieckmann reaction of symmetrical species. So, now if you try to analyze, this specie is sigma V so, sigma V is sigma V sigma V.

Now, you saying that you analyze this carbon to react with here will give with the dieckmann thing and, then finally, this particular precursor which was basically coming from this kind of cyclopropane containing cyclohexane by a ozonolysis related FGI. Now still you can do the disconnection because, you have to come back to simple molecule, you can basically come back to simple molecules like probably, you can have a ketone like this or you can put a dibromo species, it might be might be possible. So, you can do a double Wittig, then put the cyclopropane, then remove this double bromine to get the double bond.

So, eventually you can basically simplify the starting material. So, starting from this target, if this is the target this starting material now looks pretty simple. So, in this way basically you can analyze this symmetrical molecule, the next symmetrical molecule which I will be trying to explain is that importance symmetrical molecule, and you have a very good key transformation which is also very useful.

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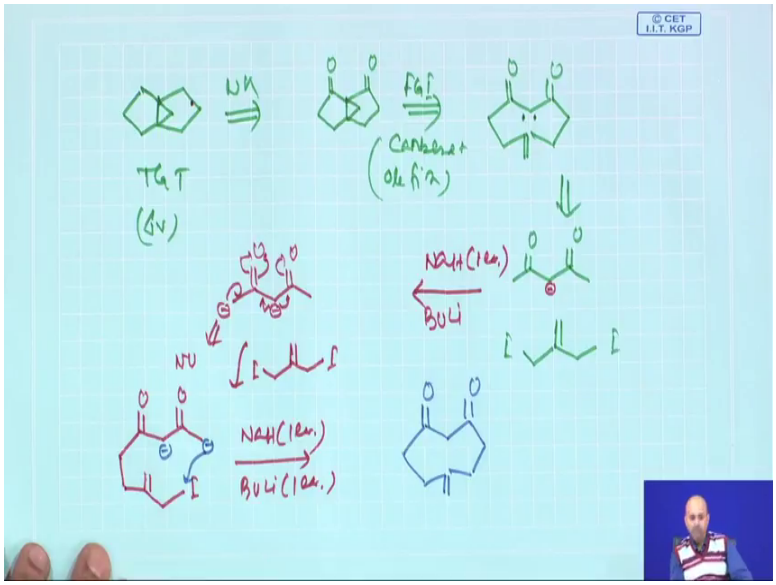

So, next target which I am going to discuss here I have 5 member ring 5 member ring, in addition you have a 3 membered ring fused to it, it is taken a designed molecule having

perfectly sigma V. The retro which one now, doing here initial I say if you have a this carbonyl compound you can basically do a double Wolff Kishner reduction with the help of this redundant functionality fine.

Now, I will try to construct this cyclopropane ring by designing this intermediate and I am saying that, if you have this intermediate and this carbine, you can basically intra molecularly trap this carbon with this olefin by a simple cyclopropanation or carbine addition. So, you have a carbine carbine plus olefin cyclo addition which probably all of you know now. This carbine how to generate this carbine how to generate, this carbine is normally been generated from a this compound with a double electrophile something like this.

Now, acetyl acetone this is the starting material, it is a very good starting material it is a bit commercially cheap starting material. So, initial what reaction was done, initial you react with a equivalent of sodium hydride, 1 equivalent of sodium hydride, that basically picks up this hydrogen and, then you put another base butyl lithium, you will basically get the double anion of this compound this minus and this minus.

Now, out of this 2 minus charge which one is more nucleophile, the the minus charge which is fanked by 2 carbonyl the charge is much more dissipated. In this case it was not it was only dissipated with only this carbonyl, like this like this but in this case it is with this with this as well as with this with this. So, this one is much more nucleophilic and, then now we will be what we will doing, we will be using this particular electrophile in one case first we do the reaction here, you get CH 2 CH 2 CH 2, then you have this double bond CH 2 I.

You do the same sequences by assuming that again sodium hydride 1 equivalent and butyl lithium, 1 equivalent you basically have this di anion one is here one is here then you close this thing. So, basically you can now get a compound which is having this structure fine.

Now, I am saying how you can generate a carbine.

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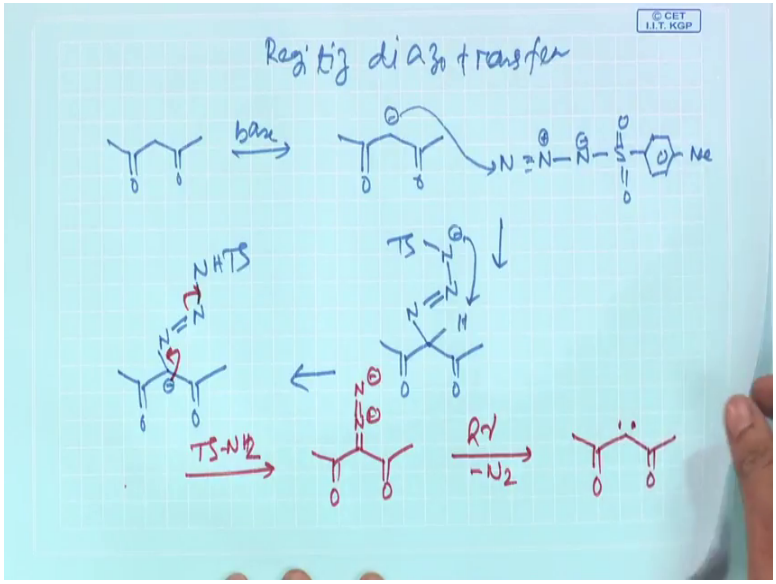

Now for to carbine generation, you need to now a reaction which is very important it is reaction name is regitz diazo transfer. Now what is this reaction says this is the array, if you having a corresponding di ketone you react with a base first any base that basically gives you a carbon ion and, then you react with tosyl azide the tosyl azide structure is basically a tosyl group is attached with the say azide functionality and, then it is a azide rejuvenate structure you can write in different way.

So, this basically this negative charge, attacks this terminal thing and, then what will get you basically get this m e c o this c o m e, then 1 of this hydrogen is here, and then basically azide structure you can now write N minus TS so, just with simple attacking of this nucleophile to this electrophilic azide in this fashion.

Now, if you see this terminal azide is n minus, it is also having another acidic hydrogen. So, this n minus now act as the base to pick up this hydrogen and, then what it will basically give it gives you a it gives you a minus here after this hydrogen goes and, then you have this N double bond N N H TS NHTS.

Now this minus comes this here, at basically now (Refer Time: 12:46) to release this tosyl high tosyl amine as a bi product, and in then what you get you basically get a diazo species N plus double bond N minus.

So, basically it is a diazo species. Now this diazo species can easily be generated from a corresponding 1 3 di carbonyl compound, which is named as regitz diazo transfer. Now then these cases basically sign light. So, nitrogen elimination takes place and you get the carbine this carbine basically you generate. So, now coming to the problem which you were discussing, if you have the if you have this particular di ketone which is the one of the intermediate the structure of the di ketone, if you remember from the earlier paper is this.

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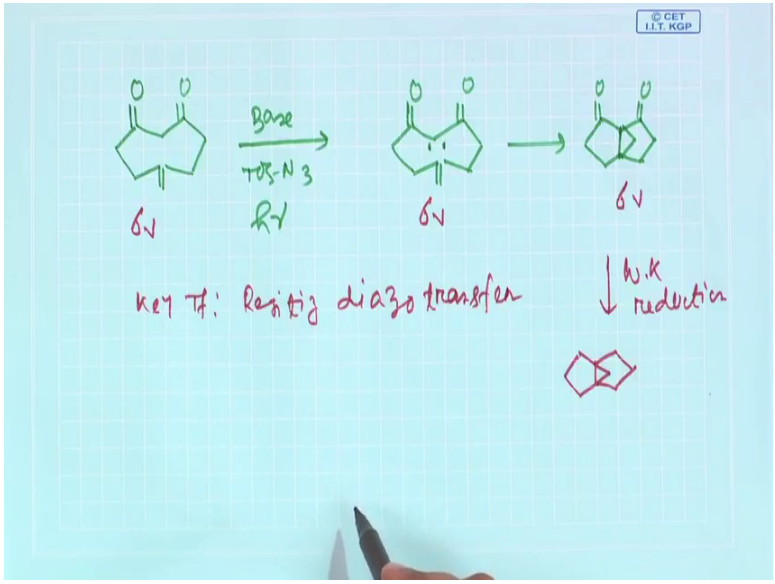

So, now you do the, you treat with base and tosyl azide and then sign light. So, basically you will generate the carbine the carbine you will generate here. Now this carbine will now react with this olefin to give you the this di carbonyl compound, that perceive the symmetric concept, this one is symmetrical intermediate, this one is symmetrical intermediate, this one is symmetrical intermediate, now do the Wolff Kishner reduction with this redundant functionality, what you will get you basically get this fine.

So, by adapting a simple function group based interconversion, you can efficiently synthesized a designed molecule designed symmetrical molecule, which was given to you only key reaction which you have now learnt is a Regitz diazo transfer which is a it is first in invented by this scientist Regitz. So, it is also very useful reaction which helps you to generate a diazo species adjacent to the corresponding carbonyl group and, this diazo species of Regitz diazo transfer is very important.

Now, next probably you would not do some synthesis will just try to give you some symmetrical structure of some intermediate. The one of the structure is very important.

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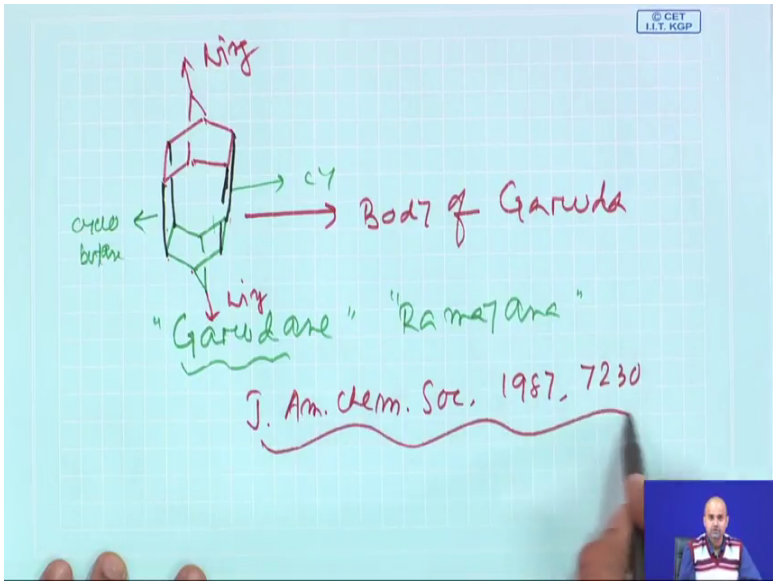

Let us try to draw the structure, this structure if you draw it and will find that so, we first drawn a norbornene skeleton. And now I am saying that I will be drawing another norbornyl skeletal, in the bottom part of this top norbornene which was drawing here.

Now, this drawing is pretty important because, this drawing will give you the sense, how you can now how I connecting this 2 norbornene is very important. I am correcting this norbornene to this black bond. Now this particular this particular visualization is important because, the drawing was little bit titled. So, I set if you have this drawing, now what I did this we basically did a top edge we did a norbornene system, this is another norbornene system. And if you fuse the black colored thing basically we connect that 2 norbornene in through a 4 membered ring. So, this is a 4 member cyclobutane the cyclobutane this is also a cyclobutane the visualization.

Now, this compound it was basically a designed molecule, which was first synthesized by a Indian scientist, it is molecule name is garudane. Now why this molecule named is garudane it is basically reminds you the garud the demi god which have been which was been described in the Indian mythology Ramayana.

So, Ramayana the garud basically a god which is having a basically having a 2 wings now the entire part of this thing this top cyclohexane ring this 1 2 3 4 5 6 and the back this considered as the body of the garud. So, this part is body of the garud, or body of the garuda god. And these particular things, this and this are considered as the wing wing.

Now, this molecule is basically designed molecule this molecule was first synthesized a Indian scientist named professor Goverdhan Mehta and this was it was reported in general of American chemical society, a very prestigious general, if you are interested I can send you the references it is a very nice demonstration of how a design symmetrical molecule can be considered very efficient, but I will try to give you a hint, that how this molecule has been basically basically basically considered.

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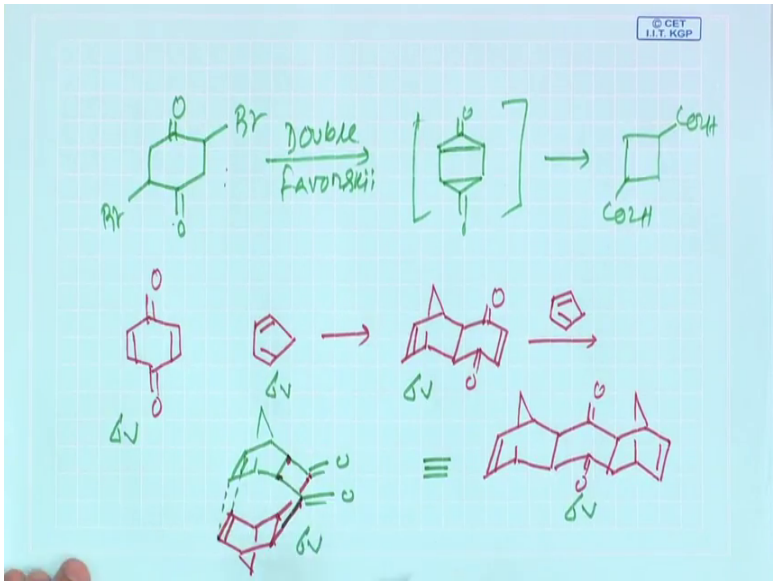

What I am if you if you see the structure, you see that the left hand side is a cyclobutane ring. The right hand side is cyclobutane ring; the norbornene part is there norbornene part is there. So, 2 norbornene are basically fused through a cyclobutane network.

Now, I am saying that probably, if you have this intermediate this intermediate you do a double favorskii reaction, double favorskii favorskii reaction was explained to you right, then basically what you will get the through the intermediate you will basically get this right and, then this intermediate will basically collapses, you will get this cyclo butane.

So, this was the key reaction used by professor Mehta in it is design. Now I will I do not do the entire retro probably it will be little bit complicated for you, what I am trying to do I will do a initial starting material which was explore, it is started with a cyclic dienophile which is para benzoquinone and a diene cyclopentadiene.

So, initial diels alder reaction basically gives you this compound, I have drawn it this way, then another round of cyclo pentadiene was reacted. And then basically what it gives it, gives you a linear dienophile I mean linear tricyclic compound whose structure is so, this part is there and the this. Now act as a dienophile and react with this to basically give you .

Now, the approach was absolutely absolutely interesting, (Refer Time: 22:01) he what he proposed that the central cyclohexane ring is your main ring, which you can basically think about to the favorskii reaction because, this cyclohexane ring is your cyclo this cyclobutane ring which you can think about this particular cyclohexanone .

Now, the left hand cyclobutane ring what it defines you said that basically cyclobutanes can be easily done by a 2 plus 2 photo chemicals cyclo addition reaction. Now you see this molecule 1 end having 2 pi, 1 end 2 pi. So, if this molecule react this molecule intra molecularly react, this will basically probably we will draw the structures in a different way this give me little bit time I will try to draw it..

So, that it is basically visible to you I am saying this way and, then what I am saying I said that , you try to do the middle cyclohexane or draw the middle cyclohexane ring in this way.

So, it is basically this visualization will be bit difficult, I will just drawing the molecule in different way and, then I am saying that this could be visualized in this way . So, now this bridge is here. Now this 2 cyclohexane basically needs to be joined. So, 1 2 there are 3 4. So, this part is basically joining with this part and this part is joining with this part. So, basically the central cyclic sending 1 2 3 4 5 6 same structure

now, if you see we are almost there. So, now if you do the 2 plus 2 cyclo addition reaction and it gives here, it gives here, and then here you try to introduce the bromine this way and this way, you do the double favorskii, you can get the molecule named garudene is probably one of the nicest demonstration of synthesizing a symmetrical

molecule. Now you see the intermediate sigma V, this is sigma V this is also kind of sigma V absolutely sigma V.

Then you make another sigma big molecule. Now what you do you keep this core cyclohexadiene, you twist the entire part. So, get another sigma V intermediate so, the the visualization was brilliant perfect visualization how this molecule can be visualized and that basically gives you the entire story.

So, we will try to continue this kind of symmetrical molecule, in respective lectures and, will give you a particular demonstration how concept of redundant functionality was the key transformation we often use and, then we also say that the maintenance of symmetry is very important.

We is always advisable to start with a symmetrical intermediate, so that the symmetry or sigma V is maintained for the throughout synthetic pathway, because the final target is symmetrical molecule which is having sigma V. So, will try to continue and then please go through the lecture notes and the assignments till then, have a good time and good bye.