A Study Guide in Organic Retrosynthesis: Problem Solving Approach

Prof. Samik Nanda
Department of Chemistry
Indian Institute of Technology, Kharagpur

Lecture – 43
Symmetry based Strategy

So, welcome student. As discussed in the last lecture today we are going to talk about our guideline 4 which we have discussed in the very earlier lecture.

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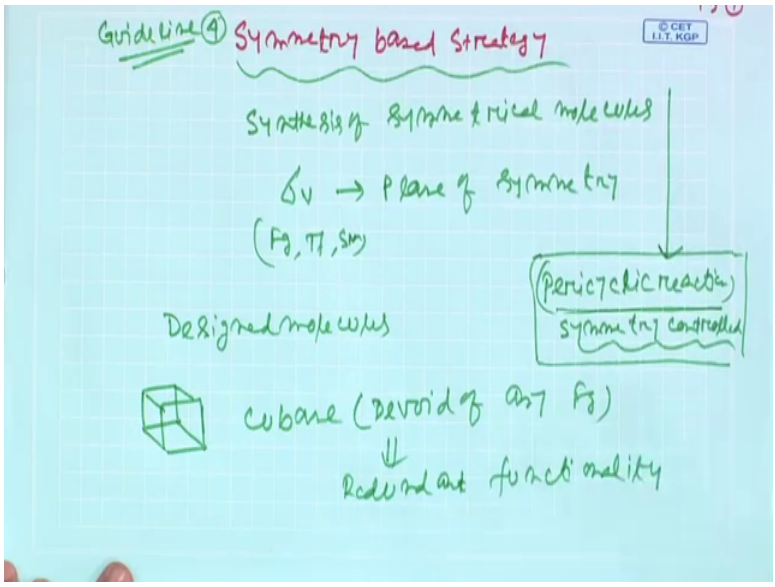

We set our entire topic will be divided into 6 different guideline. Transformation, static material, functional group based strategies which covers the 3 initial guidelines.

The guideline 4 will be talking about symmetry based strategies. Now, symmetry based strategies will trying to focus our discussion only for synthesis of symmetrical molecule, synthesis of symmetrical molecule. Now actually in the nature there are many natural products which have been found perfectly symmetrical perfectrical symmetrical in the sense that they have a nice sigma v plane of symmetry. So, in those cases what will be your guideline or what will be your strategy the initial strategies all these Fg Tf and static material will remain as it is only thing is you have to consider the symmetry element.

Now, you have to talk about the symmetry based strategies one particular aspects we are basically not discussing here we are not discussing the pericyclic reaction. So, pericyclic

reactions are basically symmetry driven reactions or symmetry controlled reaction, but as we do not have that much time. So, probably pericyclic reaction is in two sense they are symmetry controlled reaction, but this reactions we are not discussing at this moment.

So, symmetry controlled reaction will be trying to exclude this topic we will not cover this topic at this moment or in this course one. Now for molecule which will trying to have a perfect sigma v there might be a natural product as well as designed molecule designed molecule. There exist many design molecules which are perfectly symmetrical in nature. If I say now I drawing a molecule now this molecule its name is cubane its cubane molecule.

Now, this molecule is basically a hydrocarbon molecule its having only carbon and hydrogen. Now, this molecule as it looks like a cube it is called cubane. Now, probably this is a design it is basically designed molecule and at this kind of molecule also can be synthesized which our standard knowledge of (Refer Time: 03:03) on their disconnection. Now, if you see the cubane molecule does not have any active functional group means is devoid of any functional group. So, in this case our guideline is you have to explore the redundant functionality, redundant functionality.

Now, at this this kind of designed molecule like cubane or other molecules are purely synthesized in terms of academic academic pursuit. They basically do not have any biological significance as these molecules are devoid of any active functional group. There are molecules like cubane, prismane, garudane, housane probably we are not going to discuss all the structures. Now, for symmetry based molecule will often find that there are also certain guidelines or prerequisite which will be mainly following.

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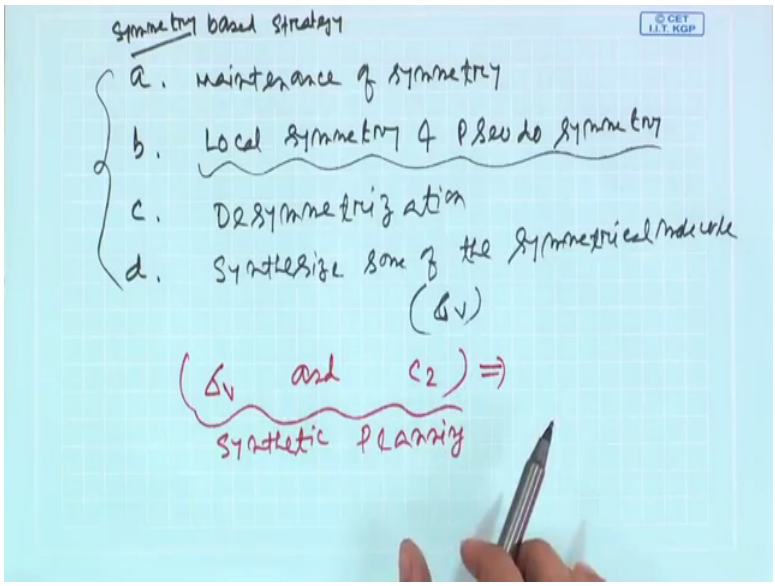

Normally we follow 4 different guidelines for symmetry based strategies for symmetry based strategies symmetry based strategy. And we say that the guideline basically focusing on 4 different point.

Now, what are the 4 points? If you are trying to do a symmetry based strategies you always maintenance of symmetry or it is always advisable that if you start with a symmetrical intermediate maintenance of symmetry is very important. You are going to make a symmetrical molecule its always advisable you start with a simple symmetrical static material. And then we always will be talking about this particular terminology local symmetry and pseudo symmetry this two are very important terminologies. And sometimes you will find that that the entire molecule is not symmetrical, but part of the molecule is symmetrical.

So, there is a local element of symmetry in the structure and due to this presence of some different functional group the entire molecule now becomes pseudo symmetrical means it looks like symmetrical because one part is having local symmetry, but the entire molecule is pseudo. Means this from the very beginning or just by looking it looks like symmetrical, but due to (Refer Time: 05:33) of that functional group content it is pseudo symmetrical, while talking about some molecules where the local symmetry and pseudo symmetry is included, and what are the strategies then will find that particular

desymmetrization is a also very important strategical guideline which falls under symmetrical based strategies.

What are desymmetrization? We will be trying to having a very brief idea very brief idea of desymmetrization based strategies. And then point d, point d will try to explore the whole this 3 different guideline and we will try to synthesize some of the symmetrical molecule. So, this will be our main point of discussion synthesize some of the symmetrical molecule.

Now, as I said the symmetry is basically we are talking about only sigma v mainly sigma v and for for information this particular two symmetry element mainly sigma v and c 2, c 2 and sigma v plays a very important role in synthetic planning. And this particular two symmetry element how it plays a very important pathway in the synthetic planning, we will talk about in stereo chemical strategies. In addition also these two symmetry element is very important in symmetric control pericyclic reaction as we are not discussing it, but for information we will come to know that the sigma v and c 2 plays a very important role for predicting the selection rule in pericyclic reaction which is purely symmetric controlled.

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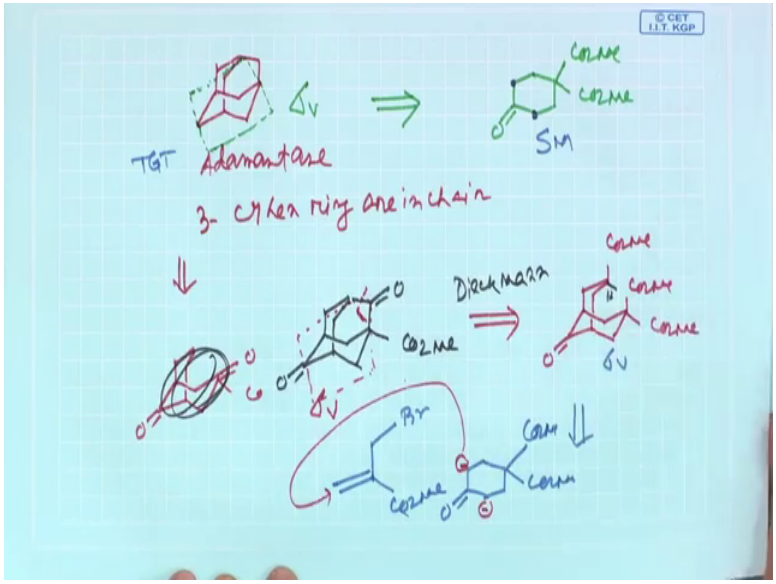

So, now we will try to explore the things we said that it is always advisable to start with a symmetrical intermediate.

Now, we will talk about some case studies. We will first try to do a retro for a symmetrical molecule this molecule we have discussed in the introductory video lecture. This molecule it is named as adamantane it is a basically a hydrocarbon it is a hydrocarbon.

Now, adamantane if you see its structural features is the purely hydrocarbon it does have a 3 cyclohexane ring in a condensed fashion. And all the 3 cyclohexane rings are 3 cyclohexane rings are basically chair, cyclohexane ring are in chair, chair form. So, that gives a very nice structural network.

Now, if you see the adamantane a nice plane of symmetry if you try to draw the plane which basically goes through this and then you basically yeah you can basically have a nice bisecting into 2 equal halves of this molecule. Now, you can basically visualize the molecule if you have a nice 3 dimensional model, so this molecule having a nice sigma v.

Now, I say we will try to maintain the guideline one that throughout the pathway if it is possible we try to disconnect that the symmetry maintenance was done. Now initial guideline or initial I will try to give you a hint that the static material was something like this static material was giving to you, giving to you.

Now, actually our strategy will be similar, similar based on the exploration of redundant functionality will be using heat transformation. Now, let us do the initial retro. The initial retro which was proposed by keeping the core structure similar it is a little bit wrong structure. So, as I said that drawing needs to be perfect we will try to we will put a carbonyl group here and as well as we will put a this carbonyl group here.

You say that if you can deoxygenated both the carbonyl groups you can get the adamantine. Now, this is nothing this is basically a beta keto ester which you can easily hydrolyzed to get the beta keto acid which you can heat which will decarboxylate to give this compound.

So, initially this is now a again a sigma v because the plane goes with this. So, this sigma v visualization is very important. So, sigma be the intermediate. So, next what I am saying I am saying that will try to have a Dieckmann kind of transformation which will basically give you this intermediate whose structure is now like this will put a Co 2 Me

here and will put a Co 2 Me Co 2 Me here. For saying that this Co 2 Me having a hydrogen here which will basically forms this carbon ion and then it will undergo Dieckmann reaction is one of the Co 2 Me group to give this thing.

So, this transformation is your Dieckmann reaction which is very obvious fine. Now, this molecule does have a sigma v fine. So, now, if you find that it is a cyclohexanone based compound 4 position is having Co 2 Me Co 2 Me Co 2 Me Co 2 Me the static material is basically now we are trying to visualize the static material also symmetrical static material. The only thing is what you need to do, you basically need to do one carbon carbon bond formation here one carbon carbon bond formation here to close the cyclohexane ring.

Now, the way it has been done you take this static material Co 2 Me Co 2 Me and take this compound this compound. Now, this compound is very unique this static material of this compound basically having a Michael acceptor at one end in addition it is having an electrophilic, allyl, bromide at one end.

Now, this initial cyclohexanone based compound what it can be done it can be first generate a carbon ion and then it can basically undergoing a Michael addition here, ok.

And then in addition this compound also can be generated a carbon ion here to trap with this electrophile. So, this compound served as a double electrophile and then this compound served as a double anion doubly charged anion then basically you get this particular compound.

So, in now let us do the synthesis which was proposed as the forward pathway.

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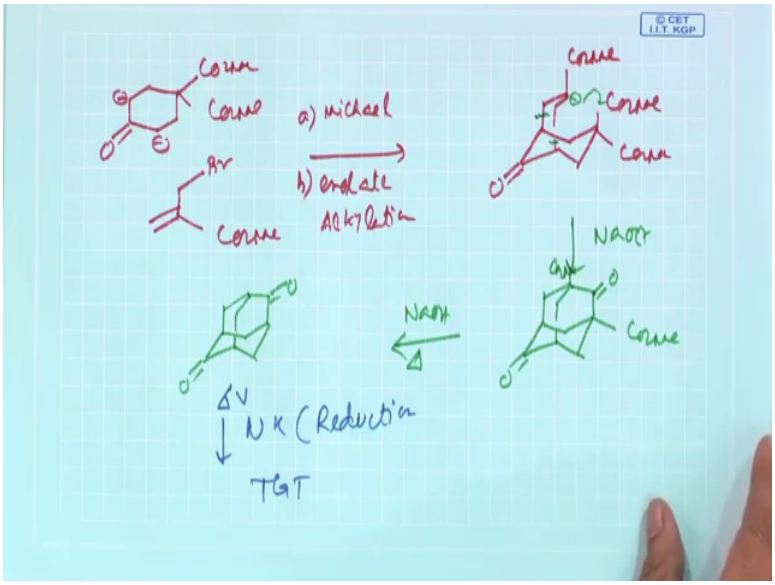

So, initial static materials Co 2 Me Co 2 Me you react with double bond C H 2 Br Co 2 Me. Now, I am saying basically a Michael and a alkylation. So, it is a Michael as well as enolate alkylation.

Now, pathways operate and then we now try to write the core structure in the chair form this part will remain similar Co 2 Me Co 2 Me. Here one of the C H 2 group is now coming here and this C H 2 is basically giving you this another Co 2 Me. So, you see it is basically now absolutely done. So, with this minus attacks here, this minus attack this huge two and you get this Co 2 Me this C H 2 be here attacks here. So, basically what are the bonds you made you made this bond you made this bonds.

So, now, next you treat with sodium ethoxide for the Dieckmann reaction this anion is generated, it reacts here, and then it basically gives you the another 6 member chair form. And so, it is basically minus it will be having double bond o it will be having another Co 2 Me also here.

So, now you just basic hydrolysis and heat, decarboxylation from here decarboxylation from here, then after this decarboxylation basically you will get the the ketone here, you get the ketone here. Now, all the intermediates are essentially symmetrical it is a sigma v and then you do a Wolff Kishner reduction by exploration of redundant functionality you get the target molecule.

So, if you now see the entire pathway we strictly followed the symmetry maintenance. You said the symmetric was maintained very perfect way.

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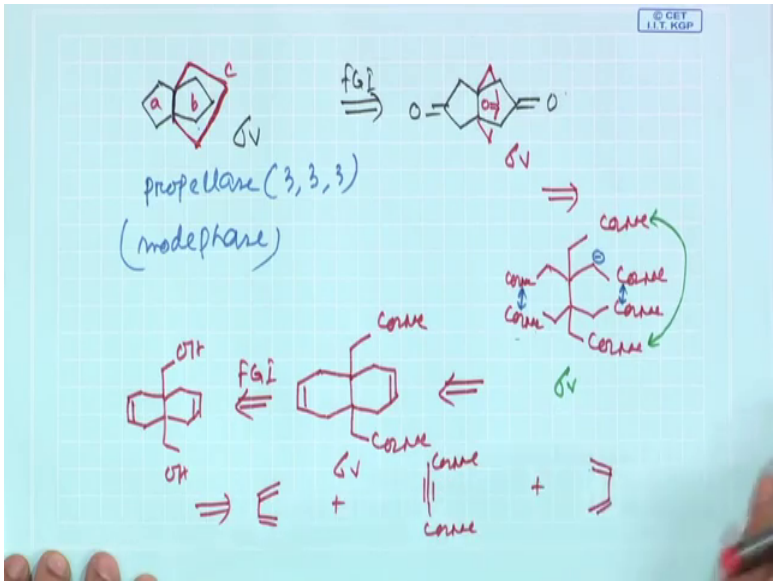

Now, try to analyze this similar kind of molecule this molecule is bit unique structure. It is a two 5 member ring fused in linear fashion and the another 5 member ring another 5 membered ring was basically fused in this way. The structure was basically drawn in these way because in a two dimensional form.

So, this is a ring a, this black is ring b and this red is ring c all our 5 membered rings. Now, this kind of compounds which basically poses a common carbon carbon bond through a particular vertex from this compounds are basically false in class of propylene you probably have seen the propeller which have a common axis then you have the cycle.

So, basically you have this cyclic structure through a carbon bond and this particular site 5 5 5 framework it is normally named as modephene. Now, normally modephene kind of compounds it is also named as 3 3 3 propylene because 1 2 3, 1 2 3, 1 2 3, 3, 3 propylene.

Now, this modephene class of compounds or this kind of compounds are available in the nature. There are basically naturally occurring compound this core framework. But the

compound which have now given or drawn here it is sigma b containing compound is it perfectly symmetrical.

Now, the retro will be trying to analyze it and you say that this retro is purely based on maintenance of symmetry element and exploration of redundant functionality was the main key transformation for accessing this molecule. So, this thing was and you are having this Co. So, 3 symmetrical carbonyl has to be reduced by Wolff Kishner reduction to give you a this molecule this molecule is having sigma v.

Now, your disconnection was bit I interesting because now where we what we now do it will put a linear or acyclic structure and you propose that that 3 round of dickemann cyclisation takes place with the help of this gives one round of Dieckmann means this minus with this. So, this is one round of Dieckmann this is one round of Dieckmann.

So, give this 5 member ring 5 membered ring and this is another round of Dieckmann with this 2 C H 2 Co 2 Me basically this alpha carbon ion reacts with this another carbonyl. So, it is basically Dieckmann now this one is also can be called as a sigma v fine. So, now, try to again simplify how these compounds can be met. This compound we propose that can be made starting from this compound by simple ozonolysis, ok.

Now, this we said you can is this is also sigma v. So, symmetry was basically maintained symmetry was maintained. These we say if you have this diol you can simply do the FGI normally FGI and then this retro we are now closing here we said if you having a diene, and if you having a dienophile like a triple bond mediated dienophile and another round of diene.

So, now we will do the forward synthesis to see how this pathway looks like. So, you have a diene plus acetylene di carboxylate.

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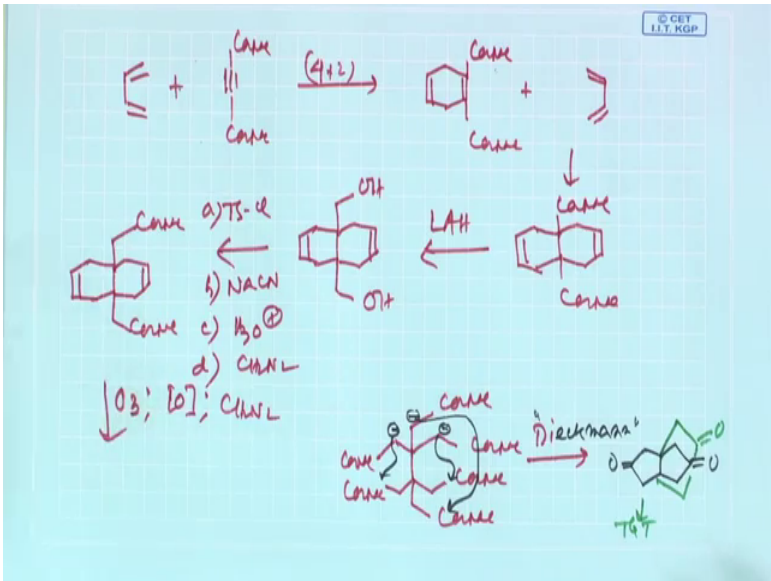

So, first round of 4 plus 2, you basically come here. Another round of cycloaddition with this diene and then basically you will get this compound.

So, next you reduce the compound with lithium aluminum hydride excess to get the corresponding diol which is one of the intermediate for this, is alcohol you need to now convert to corresponding ester by simple FGI you do a tosylation followed by sodium cyanide do the cyanide hydrolysis and then put the diazomethane. So, basically you do the diazomethane that basically gives you the compound C H 2 Co 2 Me C H 2 Co 2 Me.

Now, here what you do? You now next do the ozonolysis that will give you the aldehyde here. So, ozonolysis aldehyde then you can oxidize the aldehyde to corresponding acid followed by another round of diazomethane. So, ozonolysis oxidation of this aldehyde to corresponding acid followed by another round of diazomethane you basically get the symmetrical acyclic compound which was proposed as one of this intermediate. Now, this intermediate will now undergo Dieckmann reaction as discussed earlier.

So, basically how this reaction will takes place? This minus will react with this carbonyl, this minus will react with this carbonyl, this minus will react with this carbonyl. Naturally there is a different complex situation may arise if there are cross reaction might takes place. That is why probably the yield of this reaction will be not very good and probably you have a difficult scenario if the cross Dieckmann takes place.

So, probably we assume that the Dieckmann reaction is a done in a very perfect way and you can close the a ring as mentioned in the target molecule. So, after this Dieckmann and decarboxylation you basically will end up with this linear thing and then here will write these things as this ring. So, now it is a Dieckmann followed by decarboxylation is obvious and then you complete the target.

So, eventually this kind of aspects of a given symmetrical molecule is very important and you need to consider it when you talk about. And you remember that symmetry maintenance was the main criteria we always keep it in our mind.

So, we will continue our discussion for this perfectly symmetrical molecule in the next week also. We will see you in the next week.

Till then good bye, have a good time.