A Study Guide in Organic Retrosynthesis: Problem Solving Approach

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Lecture – 50
Topological Strategies

So, welcome back students we are basically discussing the topological base strategies and we said that topology plays a very unique role topology for organic molecular organic compound is basically, how different rings are arranged in a particular structure. So, you will be having a quite distinct topology if you have some cyclic structures in your in your compound in your given target. There could be a linearly fused cyclic structure angularly fused propellant kind of fuse there are bridge cyclic structures there are spiro cycle. So, the very unique topologies and today would be trying to talk about similar kind of things.

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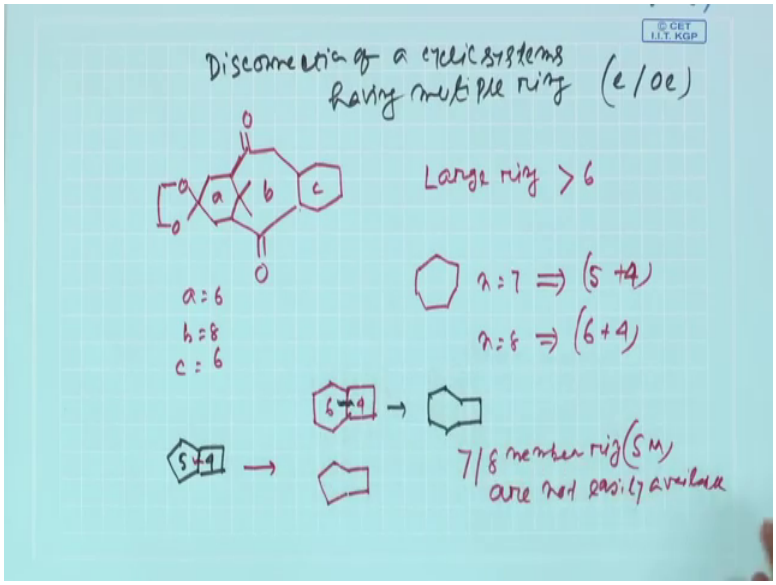

But will give a heading this disconnection of a cyclic systems having multiple ring having multiple ring multiple ring and we have already talked that; if you are a spiro cyclic compound normally exendo or off exendo bonds are good statistical point of disconnection.

Now, the target molecule which I am now going to discuss is having a multiple structure sorry multiple ring structure, and if you see the structure this structure is having a 6

member ring at the left hand side then the 6 member is. So, there are basically three rings I mean three main rings we are trying to avoid this ketole moiety this also ring, but it is the is basically a protecting group for this carbonyl. So, ring a, ring b, ring c ring a and b is basically a bridge fused, because you are having a dimethyl bridge 6 member ring. So, a is 6 member ring now b 1, 2, 3, 4, 5, 6, 7, 8 is basically eight member ring so, 1, 2, 3, 4, 5, 6, 7, 8. So, b is a 8 member ring and c is again a 6 member ring.

Now, this particular structure this 686, is the core framework of taxane based natural products. And here it is always advisable, that if you having a large ring large ring if you having a large ring whose structure is greater than 6 like, if you having a 7 member ring or 8 member ring always it is advisable that 7 member ring. If you having a n 7 member ring you try to construct the 7 member ring through a 5 member ring plus 2 member ring sorry 5 member ring and 4 member ring. I will show how and if you having a n 8 member ring try to make a 6 plus 4 now how is coming. So, I say if you are having a structure something like this a 6 member ring and 4 member ring fuse together.

Now, this 6 member and 4 member, 6 members ring, 4 member ring. Now, if some reaction allows you to break this bond. So, basically what we will now get this ring size is now start from 1, 2, 3, 4, 5, 6, 7, 8. So, 6 member and 4 member if it is linearly fused basically, you can you can cut the fusion bond you can cut the fusion bonds by some reaction to get 8 member ring. Now, similarly if you have a 5 member ring and 4 member ring, 5 member and four member you disconnect the fusion things you get a 7 member ring by similar analogy this is now a 7 member ring.

So, now I am saying that normally 7 member rings or 8 member rings often constructed through a retro synthetic pathway or real synthetic analysis, In this way because 7 member rings and 8 member 8 containing starting materials are not easily available. The 7 member rings and 8 member ring containing starting material 8 member ring starting materials are not easily available, that is our main message, but on the contrary 5 member ring and 6 member ring containing starting materials are easily available. So, now, coming to this particular problem which have just now drawn will be drawing it again you are having a 6 member ring then your this part is your protection here you are having this bridge.

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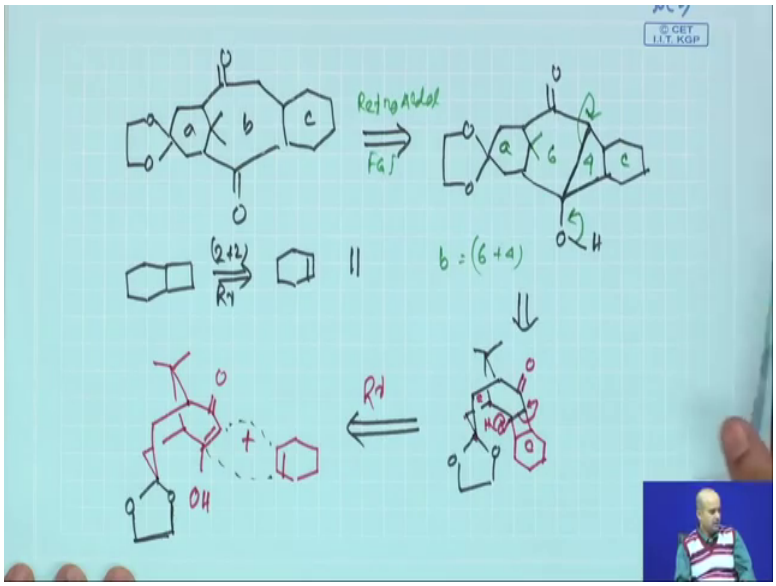

Now, if you now analyze the ring a is 6 member, b is 8 member, c is 7 member. So, now, I am saying that the central 8 member ring can probably be constructed through a 4 member 6 member and 4 member ring fusion which we have just now talked. So, now, the retro which I will be drawing as I the central 7 member ring central 8 member ring. I will try to formulate in this way you have a CH 2, you have a another CH 2.

Then basically you have this 6 member ring and then ok. Now, I am saying that I will try to make this ring in this fashion are you putting a OH here. Now, this ring a, is there, ring c is 6 member, now the middle ring which is 8 member ring. Now, I have disconnected o1, 2, 3, 4, 5, 6, a ring 6 member ring and a 4 member ring. So, ring b is now make a 6 member ring and a 4 member ring.

Now, what is the reaction the reaction which I propose that is a retro aldol fragmentation I say if you having a OH something like this it basically opens up in this way in a retro aldol fashion. So, retro aldol was the reaction which is target as a F G I fine. So, retro aldol basically the reaction which were trying to trying to figure it out; now you need to do the next round of F G I.

So, will know draw this structure in little bit bridge fashion to visualize the entire thing. Now, what I am trying to do? I am trying to draw the bridge structure in this way. So, the central ring which is there and this part is your oxygen linked. So, the ring the drawing is basically needs little bit practice. So, is a bridge structure I put the bridge structure is the

original fashion. So, 1, 2, 3, 4, 5, 6 is basically makes the 6 member ring and then you have to make the 6 member ring as well as this 4 member ring.

So, now, what I am trying to do it? I put a 4 member ring here, and here I am fusing the 6 member ring. So, this structure is basically nothing the structure which you have earlier drawn this 1. So, the basically the retro aldol goes in this way and opens up this bond. So, this is your ring c and this part is 1, 2, 3, 4, 5, 6 this part is your ring a. So, visualization is basically pretty important.

Now, the 6 member and 4 member ring fusion how you can make this kind of structure the answer was basically, we can do a simple 2 plus 2 photo cycloaddition. So, if you have this compound and this compound you can simply do a photo cycloaddition, which is the main reaction was done. Now, here if you can now do a this 4 plus 2; sorry, 2 plus 2 cycloaddition. You find that how this retro will know look like the structure is definitely complicated.

But, nevertheless it is a good exercise for you draw the structure couple of times and then you find there is a this kind of 1-3 diketone in the enolization form and then you react this compound with a cyclohexene in a 2 plus 2 fashion. So, this will gives you the 4 member ring with this connection with this connection, then the alcohol part will undergo the retro aldol reaction this oxygen this ketone is basically protected as its ketal.

So, now what we trying to do will now do the forward synthesis now for the forward synthesis I am saying that will start the forward synthesis very simple.

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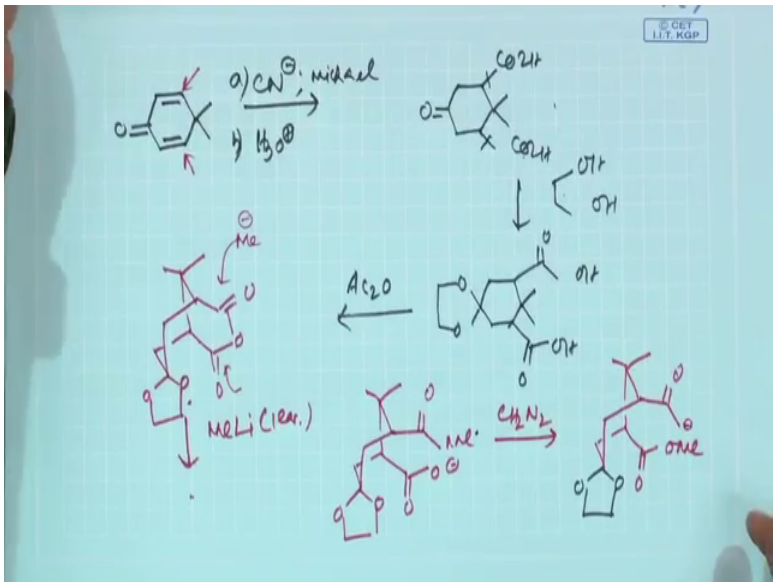

Straight forward molecule structure is this structure. Now these methyl basically serve as the bridge dimethyl, now though we have done the retro that now if I do this forward synthesis it will be quite clear. So, I am saying initially we need to do to round of Michael addition with this cyanide nucleophile. So, you do a double Michael reaction on this Michael acceptor followed by you do a cyanide hydrolysis by acidic treatment.

So, after this thing you basically get this CO 2 H, CO 2 H, this things you now protect this carbon compound with ethylene glycol. So, this will be giving you this ethylene glycol as it is your carboxylic acid is here carboxylic acid is here, sorry; C double bond O H and you have this dimethyl. Now this dicarboxylic acid was basically treated with acidic anhydride to give you the corresponding anhydride.

Now, what I do? I will try to draw this anhydride in the bridge fashion. So, that basically get this anhydride. So, this is the anhydride you will get right by this reaction now anhydride so, basically cyclic ester. So, next this compound I will be reacting with methyl lithium, because these anhydride you need to make the corresponding diketone as the retro synthesis demands will treat with one equivalent of methyl lithium.

So, is symmetrical anhydride this part your this is there symmetrical anhydride. So, it will react with one equivalent of methyl lithium and it will give you the corresponding ketone. Now draw the structure of this molecule, basically now you will be having this CO 2 Me and CO 2 O minus actually are you can have this acid. Now, eventually if this

compound you treat with diazomethane you get the corresponding methyl ester and this methyl ester your structure will be this and then you have your CO Me and C double bond O Me.

Now, this compound will again draw it in the other structure and the remaining place I mean this particular place will again draw the structure.

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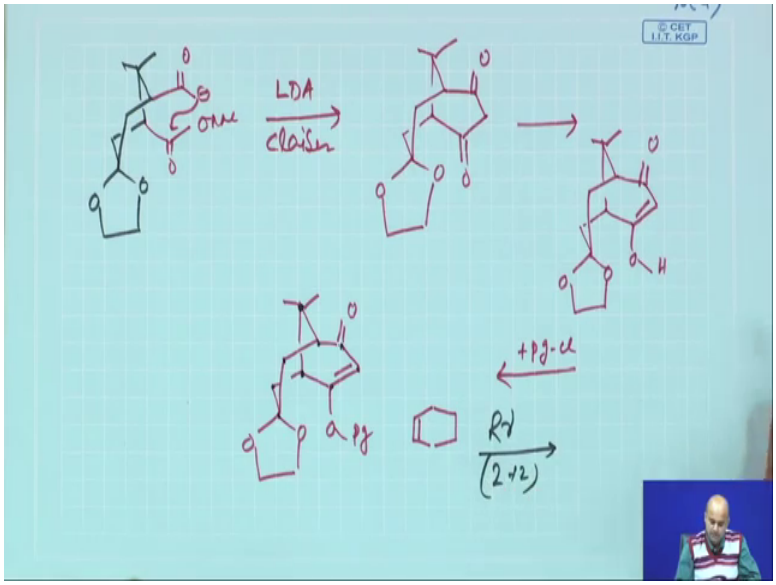

The structure drawing is bit important and then you find that this compound is having a methyl ketone as well as ester. So, if you treat this compound with a base it basically picks up this hydrogen will undergo intramolecular claisen reaction intramolecular claisen type of thing. So, minus attacks here O Me goes of you basically get the corresponding diketone which is required as a intermediate.

So, now if you see you basically have this 1, 3 diketone. Now these all symmetrical diketone symmetrical diketone find, now this diketones can be easily be enolizable. So, it basically can give you a enolizable thing and this enolization will give you a structure of this; now this enol is probably you cannot keep it as a enol you can simply do a protection here this alcohol normally as where not discussing about this production group here. So, we can put it any protecting group just by doing a production and now we will see how this structure then looks like which is ready for the next round of reaction.

So, your this part is remaining there. So, you are having is diketone here and you are having this O P g and you go to the retro basically have said that you have this 2 pi. Now we are reacting with a cyclohexene. So, you are this ring is 6 member ring is a 1, 2, 3, 4, 5, 6. You are basically having a 6 member, 6 member bridge structure this is 1, 2, 3, 4, 5, 6 and the left hand side 1, 2, 3, 4, 5, 6 is bridge structure 6 members is bridge structure. Now you are reacting with this compound with cyclohexane in a H nu is a 2 plus 2 reaction.

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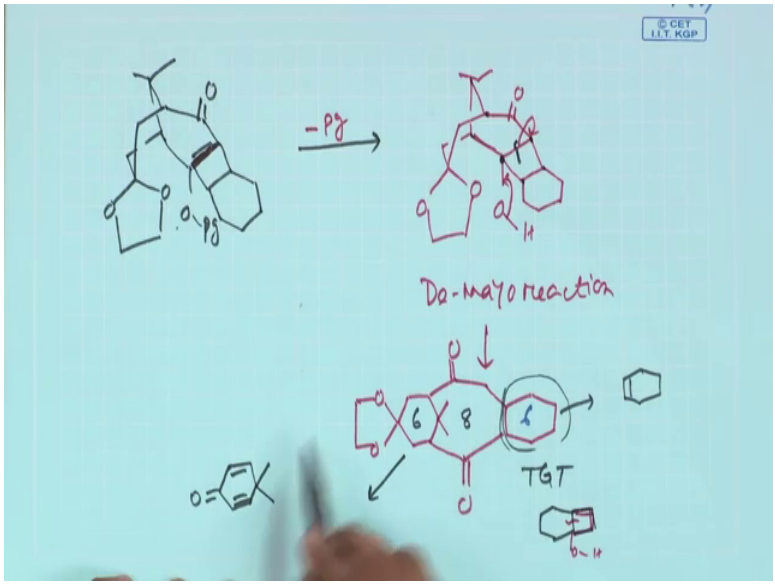

So, next will try to draw the structural part again your bridge structure is there, and then you will be having this C double bond O and this O Pg is definitely there, but now this 2 plus 2 reaction will give you a 4 member ring and this 6 member ring is there. So, now, you make this particular connection.

So, now, see this is 1, 2, 3, 4, 5, 6 and this is 4 member ring. So, now, we are saying that now what you do you remove the protection group. So, if you remove the protection group, now this drawing is taking little bit longer time, but we can basically gives you a good exercise their how you can draw different structure

So, now what will give it to you it basically gives you a OH here, and then you are having this cyclobutane and then it having this cyclohexene now your retro aldol is switched on. So, retro aldol basically goes here and your this bond clips; now this reaction we have start it this reaction is basically a de mayo reaction that photo chemical

2 plus 2 reaction followed by retro aldol reaction for making large number of rings. So, this reaction and principle we have started earlier, but now we are applying to a complex system.

Now, if you now make this ring cleavage, will now try to draw in the linear fashion the molecule which you have earlier drawn as a target molecule your (Refer Time: 21:28) bridge is there now this ketone is basically this now you are getting a CH 2 here you are getting a CH 2 here. Now you are cyclohexene is here and then, basically you get this ketone.

So, this ketone is there this ketone which is come from the retro aldol and this ketone also already there. So, only thing is you clip this bond you clips this bond and then now you count. So, 1, 2, 3, 4, 5, 6, 7, 8 so, central 8 member ring was now met this 6 remains in a molecule from the very beginning and then this 6 we are using the cyclohexene part this also prevents. So, this is a your target molecule.

Now, if you see the entire disconnection is a very useful and strategically useful disconnection, because what we exactly do you use a de mayo reaction. So, de mayo reaction you already earlier explained de mayo reaction we say that if you are having a this kind of compound you react with something like two member compound normally, the structure of this compound should be a enolether enolether.

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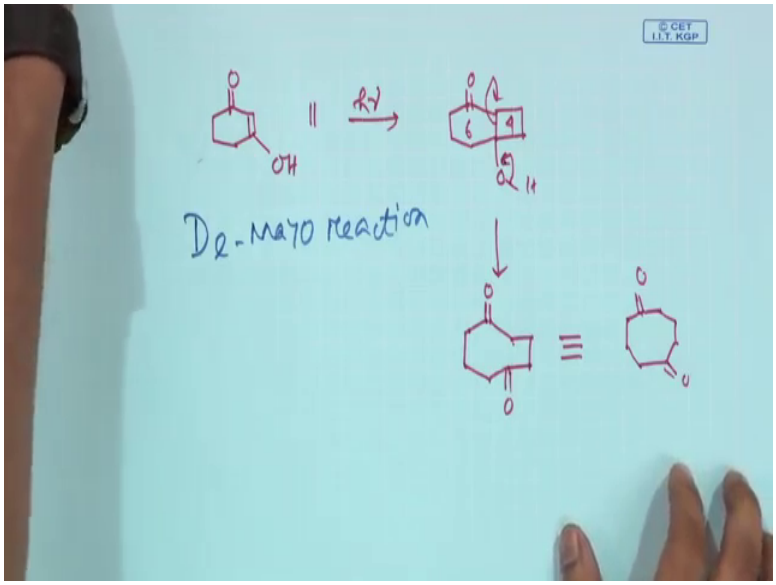

So, do you the similar kind of reaction we do a H nu mediated reaction. And then you see that the after this de mayo reaction you basically having this 6 and 4 together. Now, this 6 and 4 as a 4 member ring is strain you try to open it up in the retro aldol fashion and in reality, what will get you will basically get this compound this compound is nothing, but a 8 member compound it is a 8 member the carbonyl position is 1, 2, 3, 4, 5; 1, 2, 3, 4, 5. So, this is the 1, 2, 3, 4, 5 1, 2, 3, 4, 5.

So, in between basically you are having a three methylene groups. So, this is the main strategical view point and this reaction we have already studied is a de mayo reaction. Now, if you now see the entire synthesis we have basically started from a very simple starting material like this particular starting material this particular starting material. Now, when you talk about the initial cyanide addition this cyanide addition, basically gives this two carbon carbon bonds.

Now, this carbon carbon bonds are basically once you make this final ring here it basically x o 2 cyclohexane ring initial ring and endo 2, 1 ring. So, this is also a exendo mode of disconnection or you make this different like once you make think about this compound. So, this particular rings are ex exendo sorry exo 2, 1 ring endo 2 another thing this is exo 2, 1 ring endo 2, 1 ring. Now, what you basically considered, we start with a cyclohexanone derivative where this point we add a carbon this point we add a carbon now this is initially coming from the cyanide nucleophile.

So, once you make this CO 2 H, CO 2 H, this CO 2 H. Now becomes endo to the 8 member ring which is now later on will be will be constructed and exo to the cyclohexane ring. When reality is not a spiro cycle, but is the bridge structure, but the bonds are in come on terminology exendo bond. So, exendo bonds are always good starting point of disconnection as you said the remaining transformation is very straightforward will still explain it once you have this dicarboxylic acid the dicarboxylic acid can be easily cyclide to give you the cyclic anhydride on refluxing with acetic anhydride now anhydrides are basically esters. So, react with methyl lithium 1; equivalent symmetrical things so, methyl lithium acting as a, Me minus it will attack here or attack here.

So, it will basically give you O minus Me, then back fires it opens up to give you the ketone and the corresponding carboxylate anion. Now, immediately trap with dith

diazomethane to give you this CO Me CO 2 Me. Now, this carbolic compound having a acidic hydrogen it can undergo simple claisen kind of condensation to basically clip this, I mean it can undergo simple simple claisen kind of condensation you put a minus, here it reacts with this to give you the diketone. So, once this diketone was done this diketone basically you can easily analyzable and you can get this corresponding enol ether which will be we have earlier talked yeah. So, this once you have this diketone is there.

Now, if you see this diketone this bond and this bond these are basically exo to this parent cyclohexane ring parent cyclohexane ring, but these are also endo to the ring which is newly constructed this is also again a 6 member ring 1, 2, 3, 4, 5, 6 now is diketone symmetrical diketone. So, we simply enolizes them to give the enols and enols are basically just protected with this a one protecting group then do the 2 plus 2, cycloaddition then you can remove this protecting group and do the retro aldol reaction.

So, in principle is de mayo reaction. So, de mayo reaction is in a is applied as the key transformation then finally, you get this 686. So, this 6 is coming from the starting compound which was taken as a this starting material this 6 is coming from the cyclohexane and this middle 8 member ring is coming from the a 6 member ring and a 4 member ring your basically disconnecting through a retro aldol reaction.

Now, this four member ring is basically formed with a 2 plus cycloaddition. Now the 6 member ring which we have generated in the reaction sequence is a very nice demonstration, the structure might be little bit complex to you, but if you try to visualize it with a fresh mind I think you will be able to analyze or try to draw the structure couple of times. Once you see the video try to draw it in your exercise book with a simple piece of paper and a pen and try to draw the bridge structure very correctly and there will find that if you draw it correctly everything will be in proper shape to give you the desired thing which you are looking.

So, I think will now stop and the topological base strategies will basically try to give you only one example in the next lecture, then you try to focus more on the stereochemical strategies the strategies which is remaining left. So, out of 6 strategies transformation based strategies: number one functional group, number two starting material, number three is combined together, number four is symmetry based strategies.

we have discussed then topological based strategies, we are continuing we will probably continue remaining one lecture for the topological based strategies, then you pick up the stereochemical based strategies and will explore the stereochemical based strategies and then at the end probably will pick up one little bit complex molecule and do it is very effective way how we can retro synthetic the disconnect and how to plan the forward synthesis in a sequential manner. So, have a good time till then goodbye.