A Study Guide in Organic Retrosynthesis: Problem Solving Approach

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Lecture – 11
Tf/Sm/Fg based strategies and it is exploration

So, welcome back last week we have discussed a very important reaction named stator reaction and it is a very powerful transformation to accessing 1 4 di carbonyl compounds and also we have discussed couple of related examples and I am sure that you will find this information very useful.

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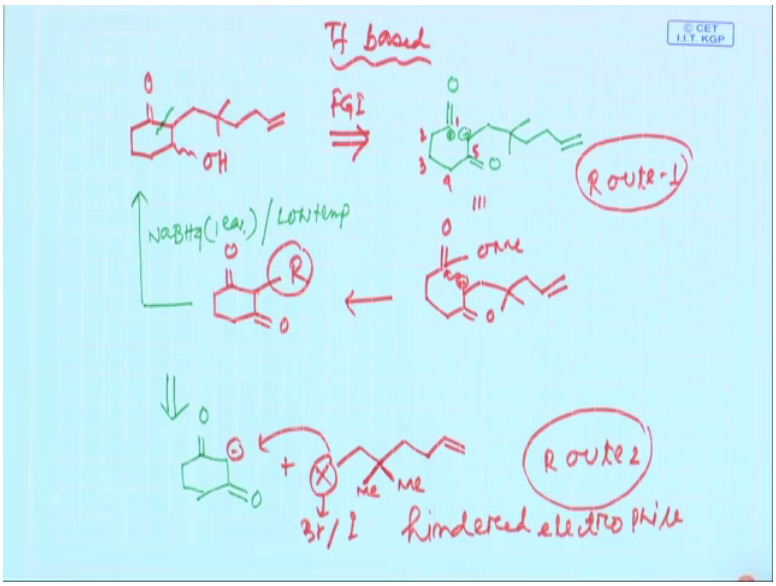

We will continue our discussion based on the transformation based strategies as a main headline, but remember we are trying to put other latest strategies like; functional group strategies as well as starting material based strategies, we will try to explore the similar kind of problems here I will give you a problem whose structure is something like this; it is having a cyclohexane based compound cyclohexanone rather and then it is a having a carbonyl functionality at one end, it is having hydroxyl functionality and then in between it is having a long chain alkyl appendage at the one end is having a pi unsaturation.

The starting material I am not giving it, I am rather asking you that you cut short or make a disconnection so that molecule can be suitably made, at the very beginning I am trying to

focus it on FGI or functional group based information as i said, now this kind of FGI if I do it can you see the how much powerful is this FGI is basically very straightforward and why this FGI has been used? This FGI is logically very much feasible. I am saying I will be doing a FGI something like this where we know the carbonyl is a delta positive I am not talking about ump lung and this end could be a minus as it is alpha to carbonyl, so basically a intramolecular reaction can takes place in reality if you have a; this is 1, this is 2, this is 3, 4, 5.

So, means if you have a properly substituted 1 5 di carbonyl compound you can do a intramolecular displacement reaction, this transformation if you have a very close look it is nothing; it is basically a dieckmann type of reaction or dieckmann condensation more precisely, so 1, 2, 3, 4, 5 and then we will try to put the entire alkyl group as it is this is a perfect examination dieckmann condensation definitely you have a ratio chemistry issue you could generate anion from here you can get anion from here that can be discussed little bit later on, but eventually this compound was subjected to a base you have a possibility that this anion will be generated and you do a dieckmann reaction. So, dieckmann reaction is a very powerful reaction and once you get the dieckmann product then what is the dieckmann product? Dieckmann product is basically your 1 3 cyclohexanedione this entire group I am putting it as a R for sake of simplicity.

The target molecule is a 1 carbonyl is reduced so here is a trick you can simplify or simple way you can do it by using sodium borohydride 1 equivalent, you can reduce the temperature you can do a low temperature reaction, but that might not be always very successful, but eventually you can get some amount of product that may not be very high yielding because carbonyl groups are symmetrically substituted but definitely both the carbonyl groups have similar reactivity, the stoichiometry might play a role otherwise you can selectively protect one carbonyl group do the reduction here and remove the carbonyl group that is another issue, you also have other possibility as the starting material was not given so starting material was not given means that your options random you can choose any random starting material but the logic must be clear, next time or next route I will be giving I am trying to provide you another route where i said that if I have a 1 3 dicarboyl compound like this and I will be choosing a electrophile which basically satisfied the entire thing.

So, I will say this electrophile which is yeah this electrophile the starting material structure basically you can look it out based on this particular things and I said if you have electrophile

X is basically bromo or iodo, now this carbanion is easily generate it because it is 1 3 dicarbon system and then you can do a electrophilic ejection, this in principle is fine but sometimes probably this electrophile is sterically crowded due to presence of this geminal dimethyl. So, this reaction might not operate and this is theoretical possibilities until and unless you do in the lab you are not sure, so till you can give it a try the other the route 1 is trying to be a little bit positive approach where you can do a dieckmann reaction, where route 2 could be a viable route but eventually you a little bit problem here when you talk about this electrophile is basically hindered electrified is a sterically hindered electrophile. So, you might have little bit difficulties, but eventually you are not sure that whether you will face real difficulties or not until and unless you do this particular reaction.

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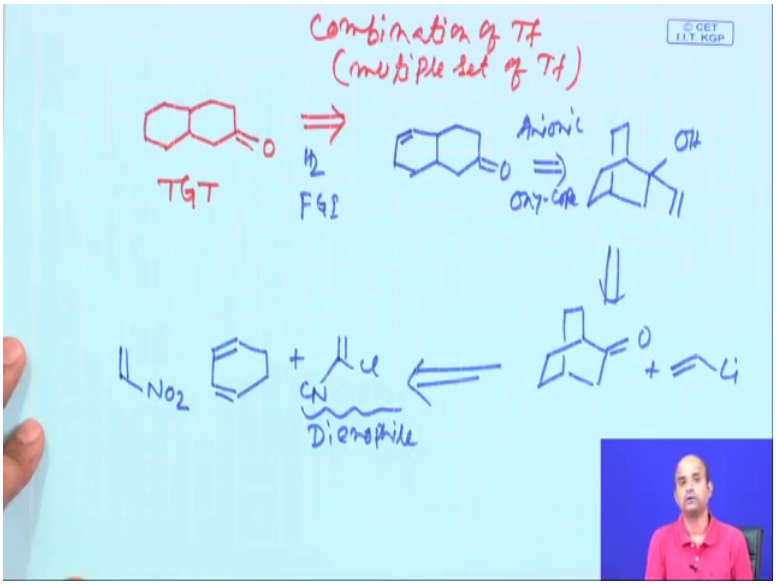

Well we will come back to a similar problem which is basically we discussed earlier, if you remember the introductory session lecture we have given you some retro quiz and during this retro quiz we have discussed this problem we said we will be use synthesizing this target molecule is a bicyclic ketone and we said sometimes you need a combination of transformation combination of transformation or multiple set of transformation which is operative to access a target molecule, now eventually if you remember the earlier introduction quiz answer we device the retro for this molecule is something like this we said we will be doing hydrogenation here which is basically a simple function of inter conversion if we have the starting material.

Now, we focused on that this compound in reality can be prepared from a anionic oxy cope rearrangement that was already taught to you anionic oxy cope fine, next we go back we said that this compound can easily be prepared by a this reaction is vinyl lithium is commercially available this bicyclic ketone we said we can be prepared by this nucleophile this is already done. I am saying that this nucleophile is fine or this dieno so this is dienophile this dienophile is absolutely fine, but this dienophile is very expensive this alpha sin of alpha chloro alpha acrylonitrile is very expensive. I am trying to give you a another alternative where you can use a vinyl nitro compound as in (Refer Time: 09:57) dienophile now how the pathway will be very similar and the transformation you are already familiar with.

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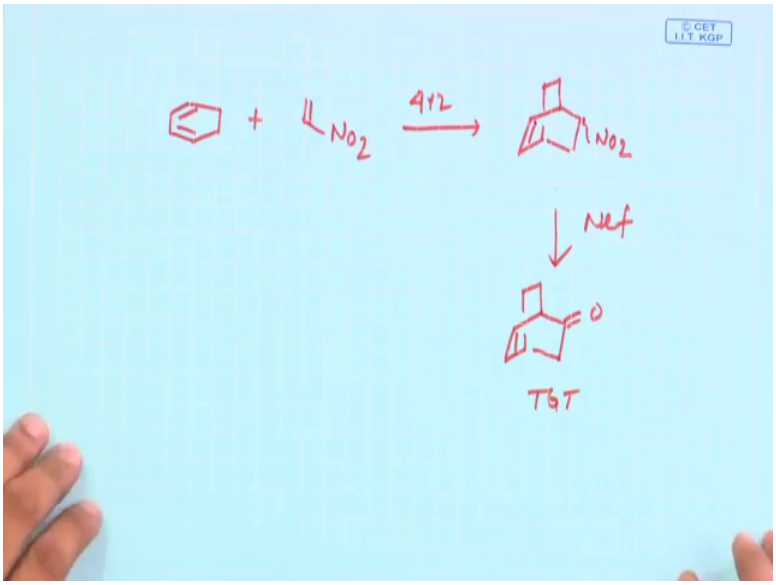

So, what we do? You take this dyne and react with vinyl nitro compound. So, 4 plus 2 thermal cyclo addition and you will basically getting the product the stereo chemistry I did not mention, but normally this is the cyclo addition always will get end product in 4 plus 2.

So fine, now you have a another double bond definitely there this will be definitely all the cases you will be having this double bond because you need anionic oxy cope rearrangement 1, 2, 3 yeah so this is a oxy cope network 1, 2, 3 this everywhere you have this double bond fine.

Now, let me know whether you know this reaction or not I am sure you know it because we have talked about this reaction many times. So, if you just do a Nef reaction you will be

accessing this target. So, the knowledge of particular transform is very important and until and unless you are quite familiar with all this function of go inter conversion or a single step transformation and make sure that this transformation gives you this kind of functional group axis your job is almost like 90 percent done and that was the main crucial factor to memorizing all the synthetically useful transformations in your memory and that would basically help you in a larger scenario. I will try to give you a very unusual transformation which probably if you would not find in any text book but that is very useful, but will explain in terms of retro synthetic analysis is it you have a target molecule something like this target molecule is giving to you.

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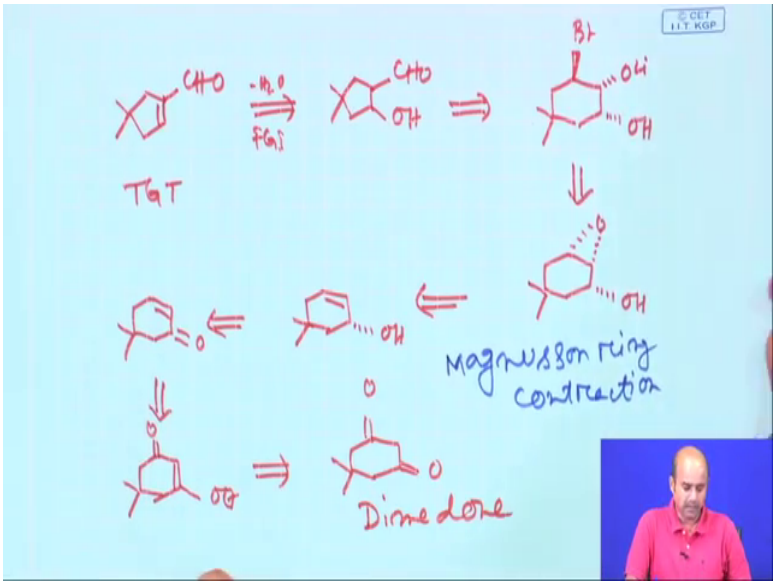

We will do a retro we will do a FGI based retro, the starting material I am not disclosing right now which is the this compound can be simple done by 1 2 elimination of a water molecule. So, you can if you have a hydroxy aldehyde you can easily make it that was the main idea, now eventually this hydroxy aldehyde this hydroxy aldehyde probably you have to prepare in different way, but the transformation which I am now going to talk to you it is a very unique transformation and this transformation I am sure is not known to many of you, the transformation will basically will give you a starting precursor which is a bromo compound with a two adjacent dihydroxy the stereo chemistry was basically given in this way, now once you do the forward pathway probably things will be quite clear just now follow the

conventional retro this kind of these compounds can be easily be prepared from the corresponding epoxide.

Now this epoxides can easily be prepared from the corresponding allylic alcohol and this allylic alcohols this allylic alcohol can easily prepared by a luche reduction by luche reduction which all of us already know and this compound can easily be prepared by this and these can be now easily be prepared from a this compound, now this is a starting material which were coming this is named as; dimedone, it is commercially available now this said this transformation the whole sequences is named as Magnusson ring contraction we will try to explore the every detail of this particular reaction let us go one by one.

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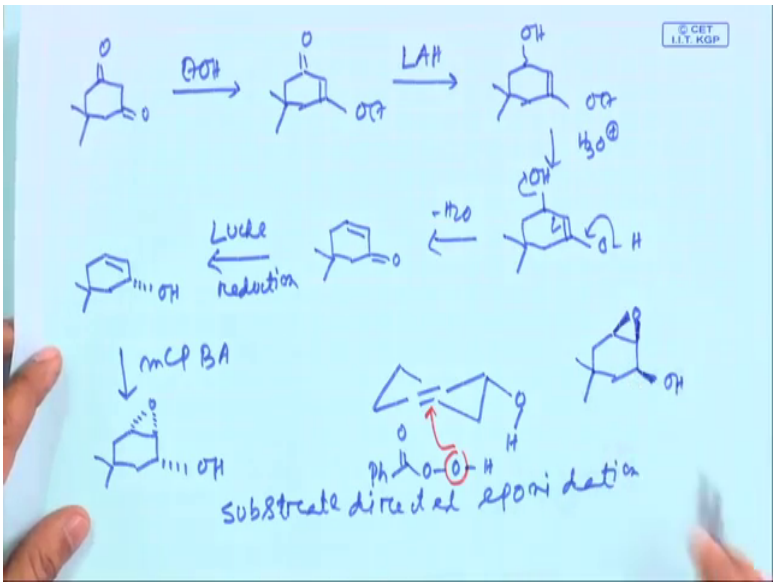

Initially your starting material is dimedone is a very simple compound, dimedone if treat with ethanol it will be instantly (Refer Time: 15:34) and forms the phenyl ether this phenyl ether you react with lithium aluminium hydride what we will get? We basically get OH OET, now subject to aqueous workup remember earlier cases when you hydrolyse the vinyl ether it is very easy and this case we just use the hydride nucleophile and then subject this vinyl set to hydrolysis will basically will give you a water elimination and will get a alpha beta unsaturated ketone, now you see this is one of our starting material in our retro pathway fine.

So, now you do a luche reduction which is already explained to you; sodium borohydride, sodium chloride in principle you will get both the enantiomers means this OH above or this

OH below, you can basically take both the enantiomers depending on your choice I will take only one enantiomer now this compound when subjected to MCPBA epoxidation you will end up with hydroxy directed epoxidation, now this is a very interesting reaction normally the stereo chemistry can be explained through a chair type of geometry, we set the hydroxys below so it is having a this kind of geometry and MCPBAis basically ph c double bond to O H par acid. So, this hydrogen bonding with this par acid basically helps this particular electron deficient oxygen to deliver to this 5 face of the double bond through bottom face, that is why you get the hydroxy is below so epoxide will be below the plane that was the main reaction, basically a substrate directed epoxidation and that will be given here.

Now, if you take the OH above says for if you have then another compound then you will basically get the above epoxide this is also another product depending on which enantiomer you start with.

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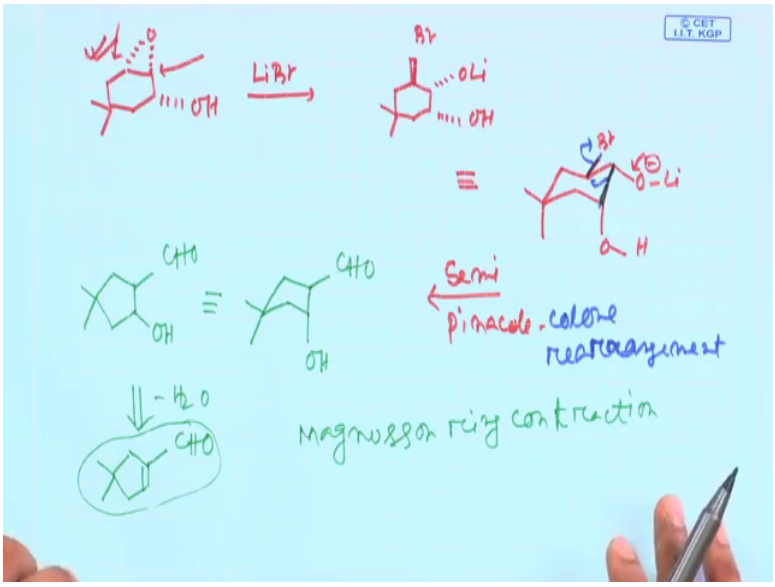

So, fine we are now here I am explaining how this Magnusson ring contraction takes place, next step is lithium bromide opening lithium bromide is the nucleophile it basically can attack the epoxide through an entire transmission state now Br minus nucleophile try to attack either from this side or this side this side attack is much more facile it is sterically less crowded this side you have a hydroxyl group. So, then you will get a product this side epoxide is below so Br minus or nucleophile will attack from the opposite face opposite face attack means Br will be above.

Opening epoxide you will get the o Li and this stereo chemistry is now OH, fine this is a 2 dimensional geometry for this compound we will now draw a 3 dimensional geometry to explain certain things; we say, Br is above try to put Br is bulky group in equatorial this o Li is below we will try to put in equatorial and this 1 2 is cist, so this OH is axial this is a real 3 dimensional geometry. Now this is O minus and all of us know; 1 2 entire geometry will undergo a semi pinacol type of semi pinacol pinacolon rearrangement now how? This comes here and this bond is this bond is and type, so this entire bond will migrate means that 6 membered ring has been contracted and then bromine will knock down, so this is semi pinacol pinacolon rearrangement will takes place. Why is called semi pinacol pinacolon rearrangement? Because in the original pinacol pinacolon rearrangement you have a OH and OH here we have a o h and Br.

So, then once this reaction takes place means that; this red coloured bond or you can write it a green coloured, this green colour bond will basically migrate so it will be open up and will give you 5 membered ring, so 5 membered ring we will just write it in this way this you will get a 5 membered ring and here your OH and the this part you are having extra carbon that will basically give you a CHO so which is nothing, but your this compound OH and CHO, now you can simply do a water elimination to close the entire reaction cycle or rather to say you can do a series of reactions together to finally come up with this potentially useful target molecule and this reaction is basic is named as Magnusson ring contraction, now as i said this is not very popular reaction which is explored during the tarpon synthesis and this kind of aldehyde (Refer Time: 22:26) as a very good intermediate or very good building block for tarpon synthesis.

Now, Magnusson ring contraction is not a name reaction it is a very useful reaction very powerful reaction because particularly this Magnusson ring contraction you will be seeing we have learnt many reaction or many strategically useful reaction what are those? Some of the reactions we already known.

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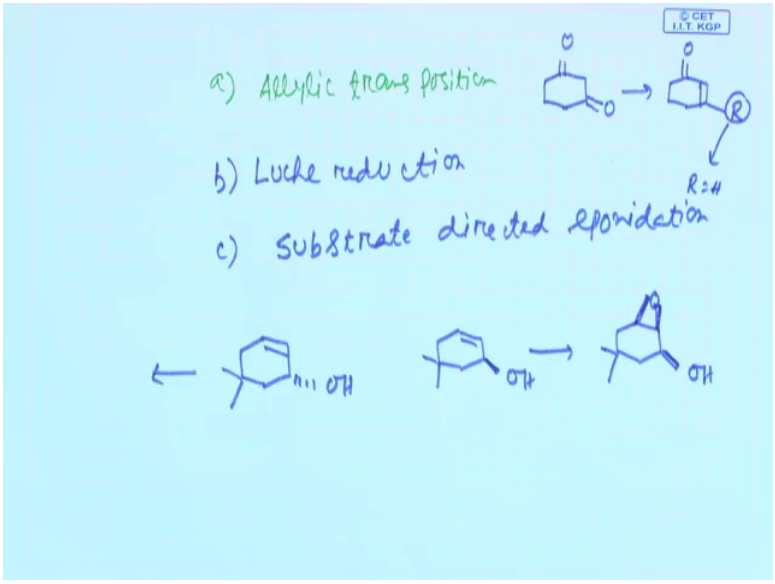

This kind of allylic transposition we are already familiar with, now what is that? We have explained it many times if you have a diketone compound or something like that you can basically fine tune this reaction to get this compound, now here we are not using any external nucleophile we put R equal to hydrogen to a lithium aluminium hydride.

Then we doing a luche reduction which is very useful reaction which is very useful transformation and then see you are doing a substrate directed epoxidation and this particular reaction basically we will be discussing when you talk about stereo chemical strategies, means just now for this particular case when you talk about this Magnusson ring contraction you are basically having 2 olefinic compounds either this enantiomer or this enantiomer, we have taken out only one enantiomer for sake of simplicity this one we have explained now if you take this one also similar kind of result you will expect only thing is you take this thing and then you will basically get the epoxide which is above the plane.

I have explained the epoxidation goes through a; hydrogen bonding directed method, where the depending on the stereo chemistry of the hydroxy group you can basically think of the whether epoxide will be above or epoxide will be below.

So, this is some unusual transformation which is named as Magnusson ring contraction and I am sure this is bit unusual reaction, but this has a very nice implication.

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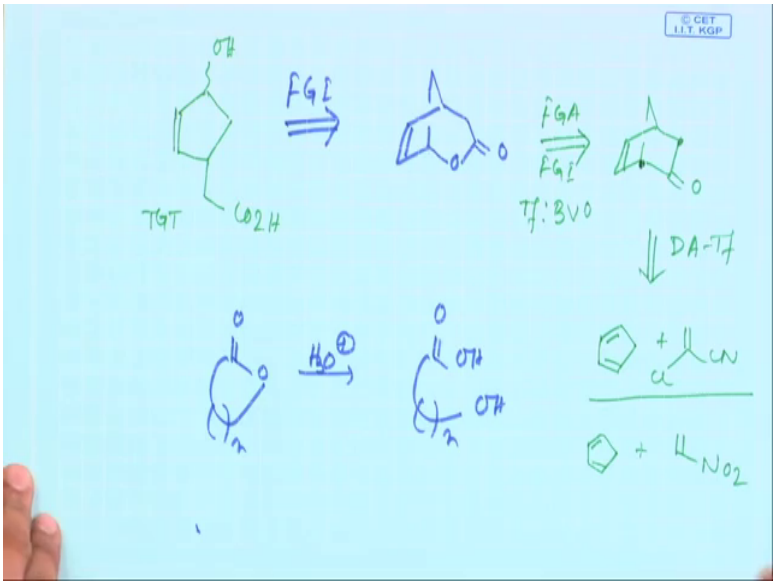

The next problem is again based on a similar kind of thing, but I will give you a molecule something like this; it is a 5 member molecule cyclopentene based molecule it is having a OH and CH2 CO2H the target, retro as I said the retros are basically based on transformation functional group as well as starting material in together. So, we will be doing trying to bring FGI now see this is hydroxy and this is acid, so which compound after hydrolysis give a hydroxy acid? My answer is lactones if you are hydrolyzing this in aqueous basic aqueous acidic or basic medium we will basically get a hydroxy acid compound no matter what is the chain this length. So, this information you need to keep it in your mind, so then try to draw the lactone which will basically give you the this hydroxy acid after and i figure it out this could be the starting material this could be the starting material which after hydrolysis will give it this things, now what is this? This is basically lactone internal lactone.

And, now we will put on some more reaction you can call FGA or FGI this is also again a probably a name reaction which all of us I am sure is known is known, this is the reaction is basically named as Baeyer veliger oxidation this Baeyer veliger oxidation the transformation will be using it now Baeyer veliger oxidation is strategically very useful reaction where a migration towards electron deficient oxygen takes place and the more substituted carbon basically migrates here if you see the more substituted carbon basically both are similar only thing is this is more substituted than this, so this is more substituted this is a secondary and this is a primary so this will migrate.

Now, this compound you can easily prepare by a Diels alder cyclo addition which was explained earlier, you can choose an this kind of dienophile or you can take a altogether a defined dienophile this chemistry was already explained to you fine. So, this is similar kind of reaction you already talked about so this is a Diels alder transformation. So, to access this molecule you need a first cyclopentadiene as a dyne take either this acryl this chloroacrylonitrile all this vinyl nitro compound Diels alder after Diels alder basically you have to remove this either cl or CN or this nitro by Nef reaction or other reaction.

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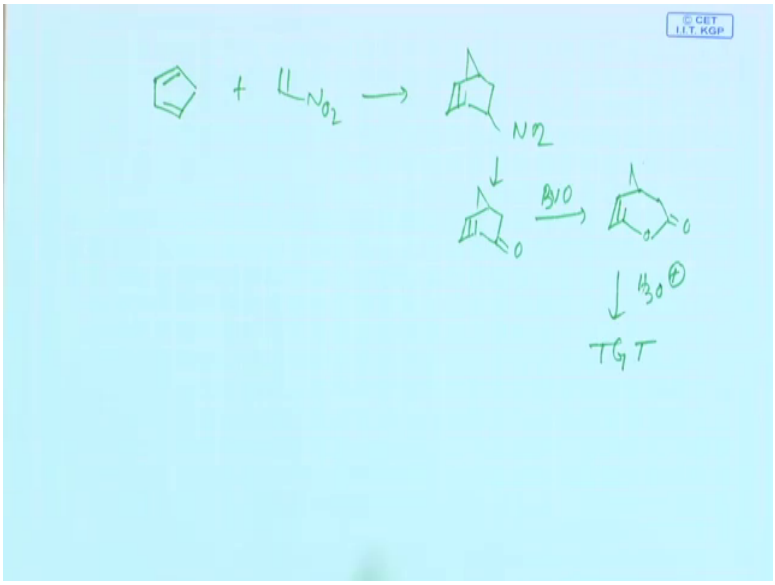

So, probably this will be a most direct way; you take this compound, take this nitro get the Diels alder adduct do the Nef reaction will get the carbonyl then do the Baeyer veliger oxidation which will basically give you the migration for more substituted carbon and then you do the hydrolysis as desired to give you the target molecule.

So, based on the target structure you can basically think of a different strategically useful important reaction and probably the next week we will talk about some more examples and some more strategies more transformation till then goodbye have a good time, bye.