A Study Guide in Organic Retrosynthesis: Problem Solving Approach

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Lecture – 25
Fg based Strategy (Contd.)

So, welcome back. We are basically discussing several strategies of based on protection and consequent deprotection of this several functional group based approaches, then the protecting group chemistry we said that you need to put it particularly chemical labial protecting groups or chemically labial functional groups with the help of some chemical reagents.

Now, this protection gives you two extra additional steps because you need to protect it or put a mask on it and then subsequently you need to damask it. Though two steps are required is very useful and advantages at certain times because many of the functional groups have similar kind of reactivity and if you want to do a selective FGI on a particular protecting group without touching the other protecting group, you need to put a mask on that particular group or particular sorry particular functional groups.

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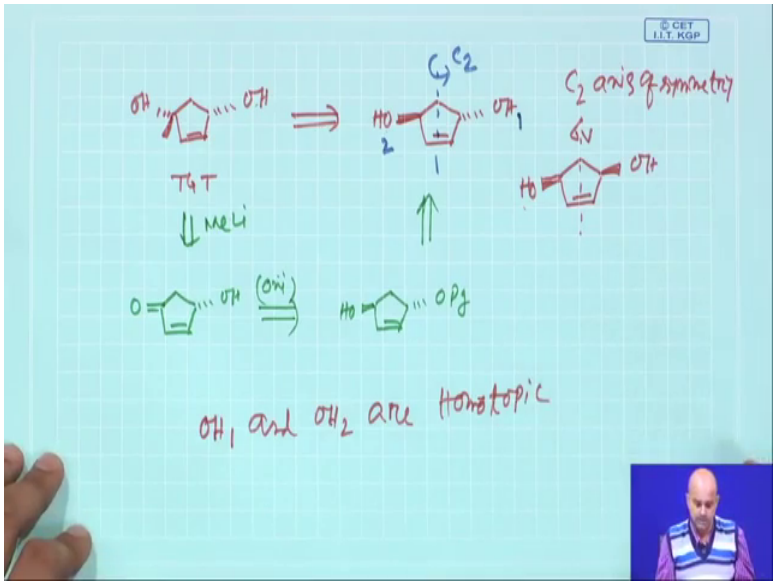

So, as we are basically discussing several problems, the next problem which is again based on a protection group chemistry the target molecule which was given to you is something like this. The structure of this target is a cyclopentane based pentane based

compound and you will find the structure is basically this. Now, if you analyse what you basically need? You basically need a addition of a methyl lithium on this carbonyl compound. The stereo chemical aspects also will be basically considering, you see both the OH are below of this cyclopentane ring and the methyl which is coming is above the plain. Now, we said you basically need a intermediate of this. How this intermediate can be constructed from this compound? There are two OH, two hydroxyl and then one of this hydroxyl needs to be selectively oxidized means that out of this two OH you need to put it one of the OH selectively.

So, basically what you need to do? You need to do or you need to put it one of this OH as a OPG and keeps the other OH as three and then you do a oxidation here and then you can basically correlate this things with this. Now, here, a certain point needs to be considered. The particular starting material which we are discussing here, having two different OH or two OH group, OH 1 and OH 2, if you consider this molecule is basically having a nice C two axis of symmetry. I am not sure how many of you have quite familiar with topicity or topicity parameters. Now, this two OH are basically in principle equivalent to each other.

The other consequence is you might have if you have a compound like this were both the hydroxyl here above the plain. These two compounds having a sigma V. Now, sigma V means you can put a mirror in the centre of the compound. So, left hand and right hand is basically having mirror image symmetry. Mirror images are basically we called non super imposable mirror images are enantiomeric to each other. So, that is why this two OH are basically enantiotopic to each other and these two OH which are C 2 symmetry is homotopic to each other.

Now, C 2 symmetry means this compound you put a rotation 180 degree around this axis you get a same compound that is what this two OH are basically chemically equivalent and they are termed as homotopic. So, I say OH 1 and OH 2 are homotopic. Now, homotopic means they are identical. We will be discussing this strategy little bit later on when you talk about stereo chemical strategies.

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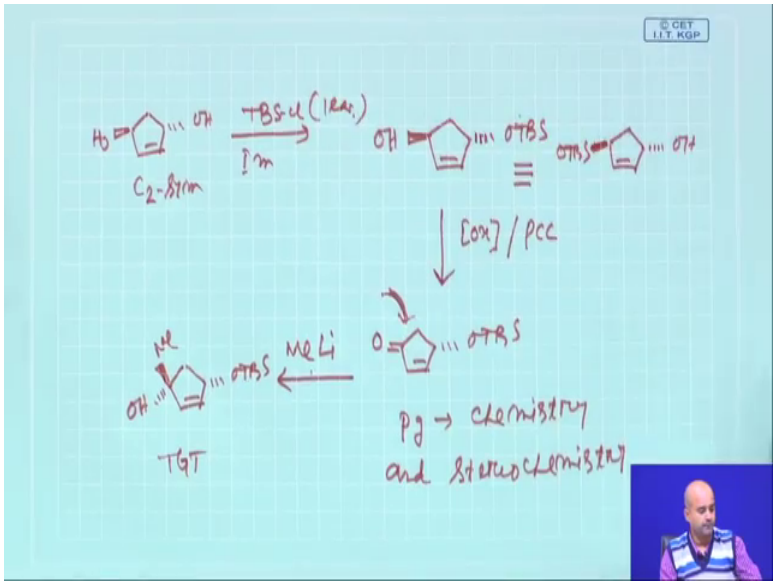

So, now, what we say you have this starting material OH and this OH, you react with 1 equivalent of TBS chloride with a imidazole. I say let us react initially I say you might thought that which OH will be reacting, first say the right hand OH is been protected in the other compound, the left hand compound left hand OH will be protected. Now, in reality both these compounds are similar is not it. You just rotate it both these compounds are similar. That is the beauty of C 2 symmetry as both the parent OH are homotopic, no matter which OH are basically protected. So, both the compounds are similar.

So, now try to do the same thing you basically put it this OH as it is bulky TBS group. Use a oxidising condition by pyridinium chlorochomate or PCC you basically get a alpha beta unsaturated ketone. Now, the next synthetic reaction is using a one equivalent of methyl lithium. This is a alpha beta unsaturated carbonyl is a basically flat sp 2 carbonyl. Now, methyl lithium can come from top phase or from the bottom phase of the cyclopentane ring. It is a basically a cyclopentane is here it can come from this top phase or the bottom phase.

Now, see TBS basically, blocked the bottom phase. So, bottom phase basically blocked by this bulky TBS group. So, methyl lithium has to come from the upper phase of this molecule, as the bottom phase is blocked by this bulky TBS group and finally, you see the product which was given to you as a target were methyl was above the plain. There is no way methyl can come below the plain. So, that is why the target molecule was given

in this way. I said this is a nice demonstration of protecting group based chemistry Pg based chemistry and it also give you a idea that how stereo chemistry is very important in designing a synthetic pathway when you are talking about inertia molecularly pure molecules and particular this discuss is very important as this starting material is having a C 2 symmetry we will be discussing this part little bit later on when you talk about stereo chemical strategies.

Now, as you discussing the protecting group basic chemistry and how protection and deprotection helps in effective designable synthetic pathway.

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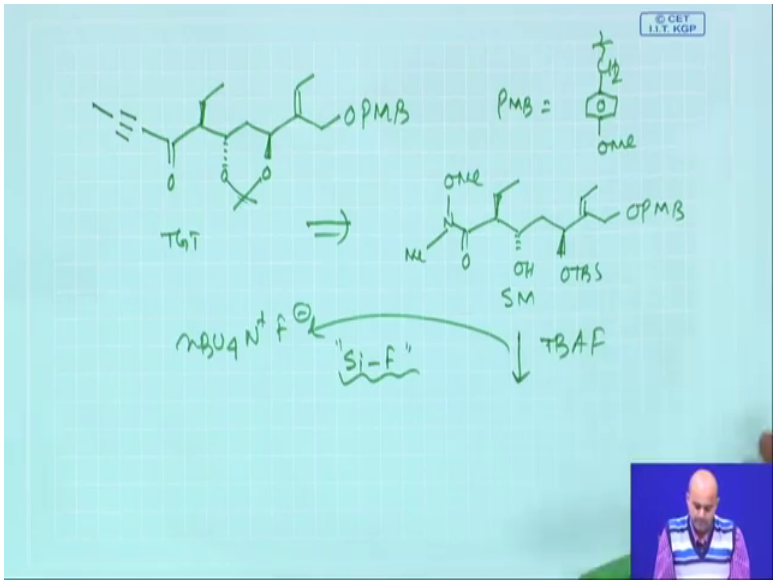

Next target which will be now, given to you is basically a target molecule were you will find, this is the target molecule is given to you. Now, remember this is basically the protection group which we already discussed is called acetonide means that acetone is reacting with this diol to give this cyclic kettle. Now, PMB, what is PMB? PMB is basically a protecting group which is abbreviated as para methoxy benzyl is also a alcohol protecting group. The structure is CH 2, this is called para methoxy benzyl group.

Now, the starting material which was this is the target molecule. The starting material which was given to you for your synthetic exercises we have basically discussed this transformation kind of thing earlier. Probably, just by seeing the structure of the left hand side you can easily find it out how these structures have been correlated with this target

molecule by simple FGI. What is this? This part is your Weinreb amide. So, basically this ketone introduction will be using a Weinreb ketone synthesis, that is why the starting material was given and then you see this one of this secondary alcohol group has already having a TBS protection group, but then the this alcohol is 3, but as I said the in the Weinreb ketone synthesis you need to have a grignard or lithium. So, which is a basic condition probably you need to put it the free hydroxyl group which might hinder in this Weinreb ketone synthesis.

So, what you do? You need to basically put it this diol as it acetonide usually in reality what was done you treat this is a TBS. TBS means (Refer Time: 11:05) containing protecting group. The best way to treat this or remove this thing, first we need to remove it. So, that it become a free OH then you protect with acetonide. The best way the (Refer Time: 11:18) can be removed is TBAF, its called tetra butyl ammonium fluoride, nBU4 N plus F minus. The fluoride ion have a tremendous affinity towards silicon. The silicon fluorine bond is very strong, that is the driving force. So, normally if I have fluoride which can clip oxygen silicon bond. So, first you treat with TBAF.

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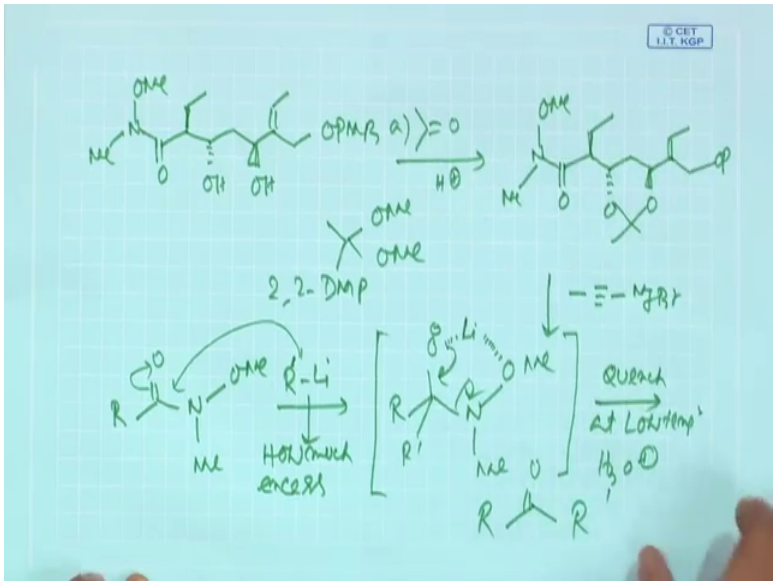

And, once you treat with TBAF you will find that the compound which will be immediately deprotected the silicon is our will be deprotected and will give you the free alcohol. The remaining portion of the molecule will not be affected. So, we are basically getting a free 1, 3 diol. Now, you react with acetone even if you do not have a acetone

you can react with another protecting group which is now I am talking to you is called this reagent, which is abbreviated as 2, 2 DMP – 2, 2 dimethoxy propane which is basically a ketal or dimethyl ketal of acetone. Now, what is happening, if you take this compound pairs of H plus this compound releases acetone with the loss of methanol is a trans ketalization reaction. So, this methanol goes off gives you acetone now, this acetone reacts with this 1, 3 diol.

So, remaining part of this molecule all similar and basically you will now getting this 1, 3 acetonide. This is OPMB and you are having these things and next you basically react with this corresponding alkynyl Grignard or lithium in the Weinreb ketone synthesis. Now, only is a time that to explore that why Weinreb ketone synthesis is so selective. I say the Weinreb amide is basically a amide, now you react with a any alkali lithium species or any Grignard species. So, initially what happen you basically will be having this alkali lithium will come here and you basically get this O this R prime is coming here, your N and methyl will be here.

Now, see you are using a lithium or any metal, so, what happen this particular methyl lithium will makes a cyclic chelate with this O Me and this O minus, now this cyclic chelate is very stable. So, it cannot further react with another equivalent of lithium or Grignard species. No matter how much excess you used, if you use 10 equivalent excess also it would not react. So, that is the beauty of using a Weinreb amide. Now, you can basically quench the whole reaction mixture at low temperature through acidic work up.

Now, basically what happen it comes here gives to back and basically you get the corresponding ketone back without getting the tertiary alcohol normally if you react with ester and acids you will basically end up with this first you will get the ketone then it reacts with the another equivalent of the Grignard or lithium to get with the tertiary alcohol, but Weinreb amide as I said once you get the cyclic chelate was rock stable. No matter how much excess Grignard or lithium react, it will always stop this reaction here then you just hydrolyse this intermediate to get back the corresponding ketone. So, this is the Weinreb ketone syntheses which have been used very efficiently.

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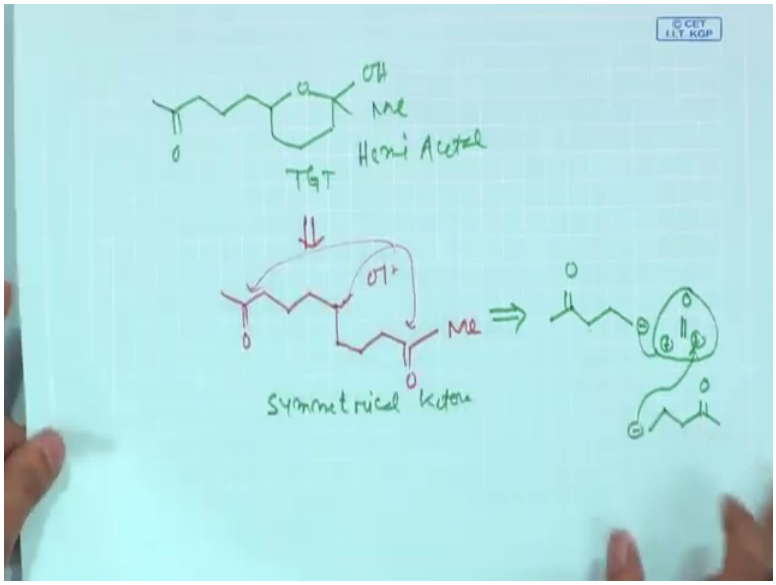

Now, coming to our similar problem we will now discussing another problem which was let us talk about with the structure is also a protecting group based strategy. The compound which was given to you is a target molecule having this structure. Now, if you closely analyse the structure you will find that this structure basically you is a cyclic acetyl. So, what you do, you just now do a retro three CH 2; 1, 2, 3. Then you see you put a OH here and then you put another three CH 2 because you need 1, 2, 3. So, I say that if you disconnect the molecule in these way, it is basically a symmetrical di ketone you have a 3 CH 2 left hand side you have 3 CH 2 right hand side. So, 3 CH 2 CO Me 3 CH 2 CO Me and (Refer Time: 17:17) you have secondary hydroxyl group. So, one of this hydroxyl will react either this way or this way, it gives you a cyclic hemi acetal. Now, this compound is basically a hemi acetal.

So, now I said this is a symmetrical ketone. So, now, if I need to disconnect this particular compound we will be using a reagent something like this will put a 1, 2, 3 because you need a secondary alcohol here and then you see that if somehow you are having a a some species which is a di acceptor of a carbonyl and then you have a another exactly the same species of this, this, this. So, this reacts here, this reacts here, you basically get this things. So, now, what kind of chemical compound or reagent will give you a double acceptor of this a 1 type, is a basically again explosion of a synthetic equivalents, but in addition you need to also find it out there are some protecting groups.

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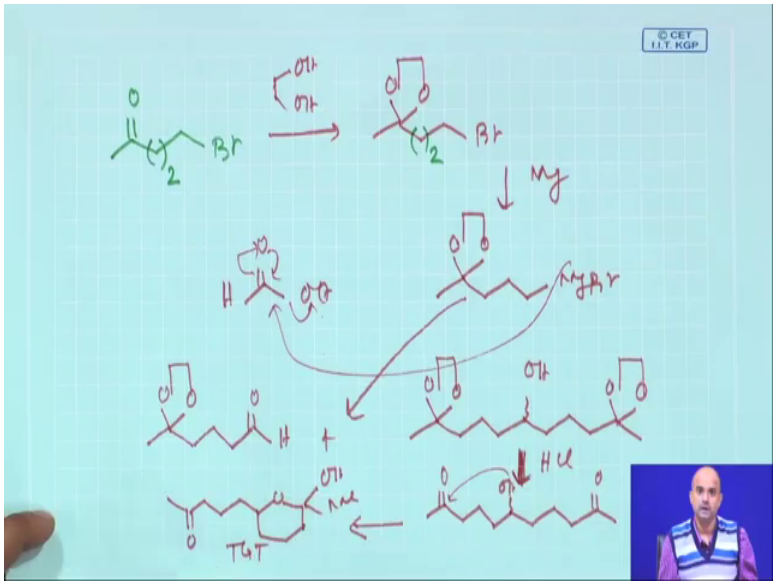

In reality, the synthetic groups or the synthetic exercises was done with this way. This starting material was easily available and then as I said this starting material you are trying to have a some reaction on this side. So, you first protect this ketone group with a ethylene glycol. So, basically you protect the ketone. So, this is the protection of ketone and you get CH 2 CH 2 Br, I think you need 1 carbon extra is it not? Here, you basically need a you have a CH 2. So, you basically need a 2.

So, the now you react with a magnesium. So, what basically you will get? You basically get this CH 2 CH 2 CH 2 MgBr. Now, this is what? This is basically the as I talked about earlier this is a CH 3 CO CH 2 CH 2 minus is a MgBr species or lithium species. And, now you are reacting this species with a ethyl formate. Ethyl formate, how it reacts? The fast equivalent of Grignard will come here goes, basically come back and it goes up and eventually you basically initial Grignard what it comes it will give you CH 2 3 CH 2 remains CH 2 CH 2 CH 2 and basically get this aldehyde.

Then, another equivalent of Grignard, again attacks here and then basically you get this this OH and then you get this CH 2 O O. This now see this intermediate which we are talking about is almost arrived, only thing is you need to damask this ketal group. You just treat with do a forward arrow HCl you basically get CH 3 CO CH 2 CH 2 CH 2, put a OH here and then with double bond O CH 3. Now, any one of this ketone will be reacting with this OH you give a target molecule which is a cyclic hemi acetal. What are

the target molecule structure if you can again rewrite, it basically gives you this OH and Me. So, 1, 2, 3 CH 2 1, 2, 3 CH 2, this OH reacts with either this or this you get the target molecule.

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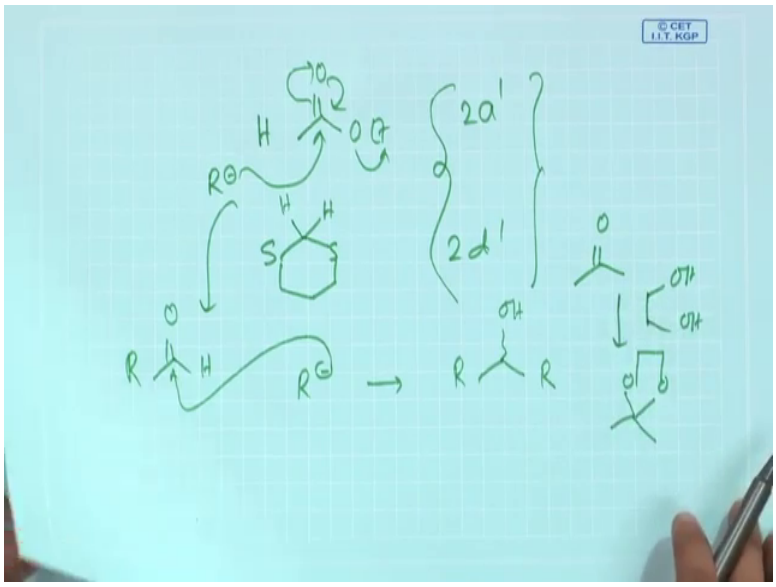

So, this particular example you have focused about some of the nice chemistry which not only explains the use of protecting group as well as we talked about a ethyl formate which basically serves as a HC double bond O O Et which served as a 2 acceptor species two a 1 earlier talked about it 2d 1 species which is this one, 2d 1. Now, this can act as a 2a 1. This is also nice demonstration of synthetic equivalents and ethyl formate, you can basically react with a nucleophilic species by this way, by this, by this it goes. It basically give you R CHO.

Now, another equivalent of Grignard or any nucleophile species come here and basically you can finally, get of this corresponding alcohol. So, this is a very nice way of talking about synthetic equivalents coupled with functional group based approaches and in addition, you have a protecting group chemistry were a ketone particularly was protected as its cyclic acetyl with ethylene glycol. We basically use this chemistry you protect the ketone as its ethylene glycol you make a cyclic ketal.

Now, combination of all this strategies make the overall pathway every efficient and very nice to look actually. So, I mean if you combine the entire pathway your pathway should be very much elegantly designed and you will find the chemistry which you write in the

two dimensional piece of paper should be visible to you and then it gives the feeling that this chemistry looks are fully fantastic, you have carry on the entire steps.

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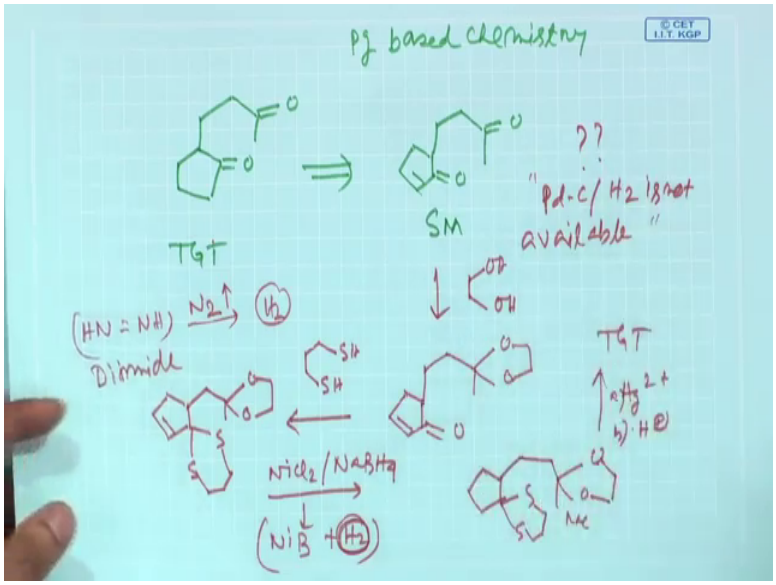

Now, similar kind of a problem which I now picked it up will find this one is on the similar line, but the target molecule was something like this. The starting material I have also given to you this is also falls under protection group based chemistry Pg based chemistry. We talked about protection group based chemistry how different protection groups helps. The starting material which I have given you here is again is this. So, in reality, if you see closely, analyse this 2 compound, you will find that the target molecule is basically 1 2 3 4 5 - 1, 5 dicarbonyl compound and the starting material which was given to you also a similar dicarbonyl compound, but only one double bond is there which needs to be removed from starting material to come to the target molecule.

Now, as I said this kind of transformation can be easily done if you do a simple paradigm charcoal immediator hydrogenation. Now, I put a note that I said paradigm charcoal and hydrogen probably is not available to you too then, will you stop this reaction in your lab or you will try to find it out some other alternative? I will probably prefer the second alternative whether some other reagents can be used to access this target. Now, I say the starting material is having alpha beta unsaturated ketone as well as a saturated ketone. So, their reactivity basically differs. So, what we first try to do, I will put it the saturated

ketone with some reagents something like this. Now, this reagent is basically 1, 3 dithiane which we earlier explored or explained, give you this.

Now, I say you this ketone is still there this. So, this alpha beta unsaturated ketone now you need to protect with corresponding 1, 3 dithiane. So, is basically a protection and deprotection because you only need to touch the double bond, without touching the both the carbonyl groups. Now, you have this double bond which is remains free and the both the ketone groups have been protected. I say that paradigm charcoal is not available to you. The best way you can do this reaction if you having a nickel chloride and sodium borohydride in your lab. Now, nickel chloride and sodium borohydride combination basically gives you a nickel boride and hydrogen gas.

Now, nickel boride is a nice black nano particle, is a blackish material and hydrogen will be evolved in this reaction from sodium borohydride and this reaction is very nicely can be carried out if you do not have a hydrogen gas in the lab also you can do this hydrogenation by mixing with nickel chloride and sodium borohydride which gives you nickel chloride and hydrogen gas. And, then it attacks double bond to hydrogenate and then you finds that remaining other part which is basically there are 2 CH 2. So, if some CH 2 are missed probably, I am little bit sorry, but that does not make any differences altogether. So, your trial part remains similar.

So, next what you want to make? You remove this cyclic ketal as well as cyclic 1, 3 dithiane you first treat with mercury. Mercury will remove this one and then you remove this ketal, cyclic ketal by acid treatment to get this target molecule which was shown here. So, you probably in this synthetic pathway, we have seen that if certain reagents which is not available to you you have to find alternative pathway and probably this is very environment friendly pathway because paradigm charcoal hydrogen is sometimes can causes fire because paradigm charcoal is very difficult to handle in the lab if your glass apparatus, your set up contains little bit of moisture, paradigm charcoal causes instantly fire and it basically is a explosive things I mean you instantly it catches fire and the hydrogen is very flammable. So, this needs to be little bit cautious. The point is if you do not have paradigm charcoal hydrogen we have alternative. You can use nickel chloride, sodium borohydride system which gives you hydrogen. There are other ways also, you can reduce this compound through diimide reduction. This is also a source of hydrogen, diimide.

Now, diimide basically this compound is diimide which under the reaction condition gives you nitrogen as a gas and that the hydrogen was there, this hydrogen is causing the hydrogenous and reaction and the diimide you have to be is not again commercial available you can easily make it the lab. You take the hydrogen hydrate and you can treat with some particular reagents, you can generate the diimide. These are basic alternatives reagents if you do not have paradigm charcoal and hydrogen.

So, we will try to continue our discussion on this functional group and protecting group based strategies. In the next week, we will talk about chemo selective protection and deprotection and how you can functionally manipulate two different chemically similar chemical reactive functional groups by suitably protection and FGI, then deprotection. So, till then good bye, have a good time.