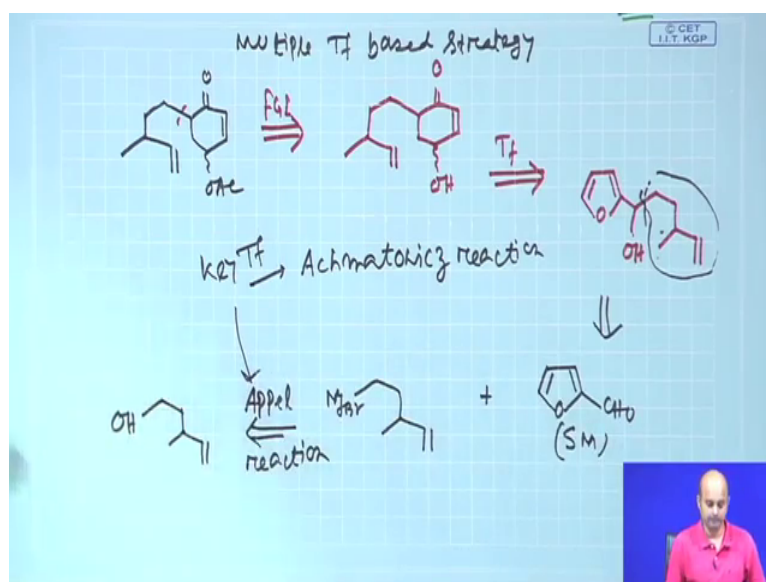


A Study Guide in Organic Retrosynthesis: Problem Solving Approach
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Lecture – 19
Selective Transformations

Welcome back students, as we are discussing several transformation based strategies. In the last class, last lecture, we talked about a very important transformation by using sulphur (Refer Time: 00:30) and the reductive desulfurization based method to access it natural products. We will try to explore the similar kind of transformation and little bit unusual transformation which you might not aware of that.

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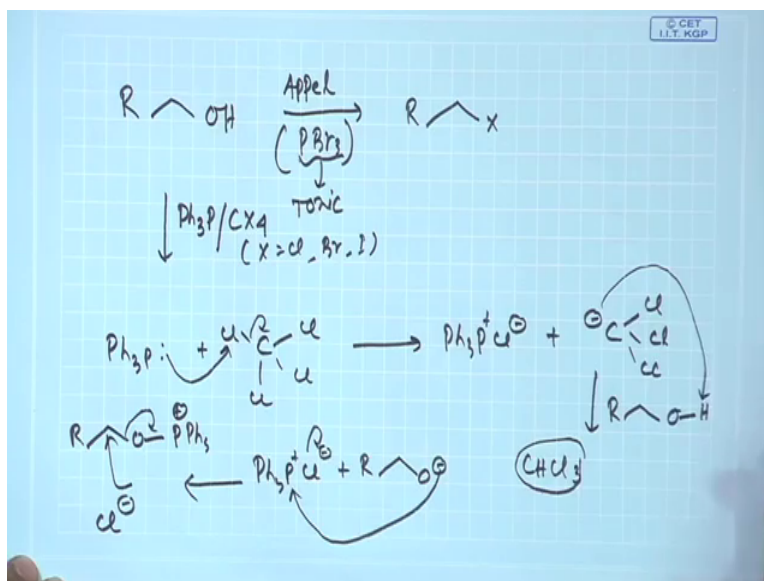
So, first will give you the target molecule, which was now we are going to access; the target molecule which I am now going to present having a structure something like this. It is based on a six member lactone, it is basically and then this lactone is having a this alkyl appendage called is a appendage. And this is the core structure of a six member unsaturated lactones. And eventually this compound we first draw the retro. The retro as it is says that this final target molecule having acetate functionality in the cyclohexane core, we probably trying to put it as a OH, because alcohol can be easily converted to corresponding acetate by a standard functional group inter conversion.

Now, next transformation which I will be drawing is a very unique transformation, you first draw the retro, draw the retro, and then we explain what is this transformation. This is the main transformation will be discussing in today's lecture. Now, it might look very strange to you definitely from a furile carbonyl, basically fluorine derived compound is a furile carbonyl. Now, if you see the appendages this particular appendage remains similar which is basically nothing CH₂ CH₂ having a methyl having a phenyl; so you need some transformation which basically convert this furile carbonyl to this six member lactone with a hydroxy group the appendage remain same.

Now, here the reaction which will be going to discuss this particular transformation is named as achmatohicz reaction or achmatohicz rearrangement. It is definitely unknown reaction to you fine we will discuss it a little bit later on now formulate how further you can do the disconnection. This is very simple disconnection, we will try to put a furfural and then we will be doing the disconnection here, we will putting a simple grignard kind of species of this Mg Br, it is a very straightforward. And this starting material is commercially available. This one you can again made it by corresponding alcohol.

Now, here is another useful transformation will be using is called appel reaction appel reaction will be now explaining. So, what is the appel reaction, what is achmatohicz reaction. So, this entire transformation is basically based on these two key transformation - key Tf, one is achmatohicz, one is the appel reaction.

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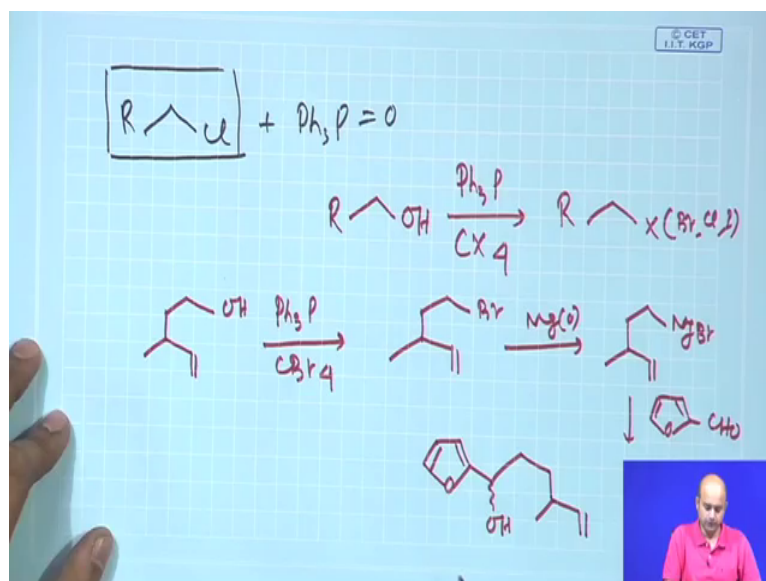
So, next trying to talk about one by one. Now, Appel reaction is a very useful reaction. Appel reaction will give you a access of corresponding halogen compound starting from a parent alcohol in a single step reaction. Normally if you have to convert alcohol to corresponding bromide you can definitely do by PBr_3 or other reagent PBr_2 or PCl_3 , but definitely handling PBr_3 and PCl_3 , this very top those were basically toxic chemical very toxic chemical.

So, do you have the mild version? The answer is yes, you can do it by Appel reaction. Now, apple reaction what is the reagent condition they use triphenyl phosphine and a corresponding $\text{C} \times 4$, x stands for chloro bromo or iodo. The mechanism is very simple to react triphenyl phosphine plus a carbon tetrachloride. I have taken a carbon tetrachloride. So, initially this Ph_3P tries to attack one of this chlorine linked to this thing this give a $\text{Ph}_3\text{P}^+\text{Cl}^-$ plus CCl_3^- .

Now, this CCl_3^- is then try to abstract the acidic hydrogen from this alcohol to become chloroform. And in the whole process, this CCl_3^- minus which is now remain here, this CCl_3^- we left becomes CHCl_3 chloroform. Then you are having this $\text{Ph}_3\text{P}^+\text{Cl}^-$ minus in the reaction mixture, and then you are having this RCH_2O^- minus because is the alcohol now donates the hydrogen to CCl_3^- to become CHCl_3 that was the main thing. Now, this O^- minus, this O^- minus, now attack to this phosphorus is attack to this phosphorus with the loss of chlorine item. And what it gives it basically gives you RCH_2OPh_2 plus fine the Cl^- minus which have been expelled by attacking this alchoxide to this triphenyl phosphine.

As I said the driving force is making a oxygen phosphorous bond. Remember we talked about Mitsunobu reaction, the alcohols are very bad leaving group. You are trying to make a oxygen phosphorous bond similar kind of mechanism we will also operate in the Mitsunobu reaction, you might have encountered in the Wittig reaction also the triphenyl phosphine oxide is a byproduct.

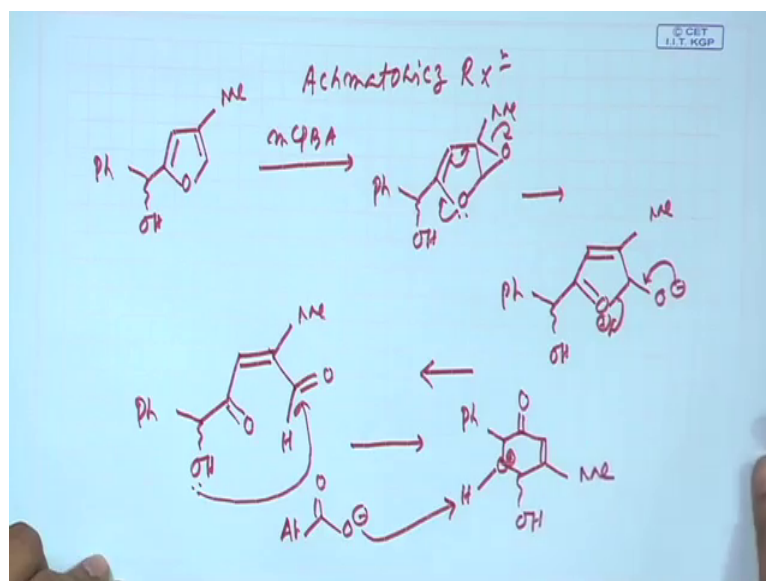
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So, now the Cl minus undergoing a standard is in two reaction to give you a corresponding halide species or CH_2Cl plus triphenyl phosphine oxide. So, this is your final product to get in the one step by Appel reaction. Now, this Appel reaction is very useful, you can take this kind of compound depending on the source of this halogen, you will basically get corresponding x, x stands for bromo chloro iodo. This is a one step reaction and I will explain the mechanism.

So, now coming to our problem which was giving to you, you are having a initial starting material $\text{CH}_2\text{CH}_2\text{OH}$. So, what you do you basically treat with triphenyl phosphine CBr_4 you will basically get the corresponding bromide react with magnesium zero magnesium metal basically. And you will get corresponding grignard react with furfural that is it if you are not familiar with this Appel reaction does not matter, you can simply do a two step displacement by using it tosyl or reacting with sodium bromide then or otherwise you can use PBr_3 . So, now, what we will get we will basically get this compound. So, this is a one of the intermediate.

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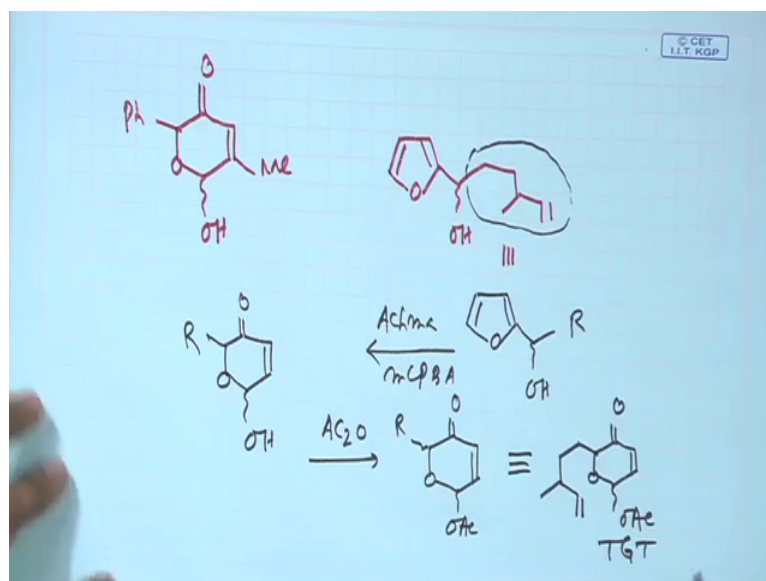
Now, next we will try to visualize what is the achmatowicz reaction. So, now, we will try to visualize what is achmatowicz reaction, because in this furan carbonyl, you have to do the achmatowicz reaction. Now, achmatowicz reaction is a very useful reaction, I will draw a furan compound substituted furan compound. And the furan must be having this kind of structure, the furan must have a alpha hydroxy is basically carbonyl structure furan carbonyl. Then you take this compound react with m Cp BA meta chloro per benzoic acid it was initially postulated that this one of this electron reach double bond in the furan fast undergo epoxidation reaction with this parent furan.

I take a simple furan like this. And then reaction something like this takes place to open up the epoxide. We will basically now opening up the epoxide, try to put the proper arrow this oxygen now becomes oxonium species and you are having this OH and phenyl here. And this epoxide basically opens up to give you this alchoxide epoxide opening simple up epoxide opening. Now, this epoxide now can open up in this way to open up the furan ring. Now, this part is crucial we will basically get a methyl here fine. And then here you basically get a aldehyde from this. This part is oxonium ion basically a ketone. So, basically a ketone and then you are having this carbonyl structure.

So, furan ring must have to open up. And then you see there is a hydroxy, there is a aldehyde, there is a hydroxy there is a aldehyde. So, this alcohol now undergoing a intramolecular nucleophilic attack which is similar like a when you form say acetyl or

Keitel. And then basically you will get a six member thing, you will basically get a six member thing you try to formulate exactly what is going on the very important transformation in the whole pathway. So, basically you try to attack there now see 1, 2, 3, 4, 5, 6, so this way basically you would get a six member things. And then it is a normal this oxonium iron species and this m Cp Ba this corresponding carboxylic acid remains here. So, this basically picks up this hydrogen. And once it picks up this hydrogen, the final product which will come will be having a structure.

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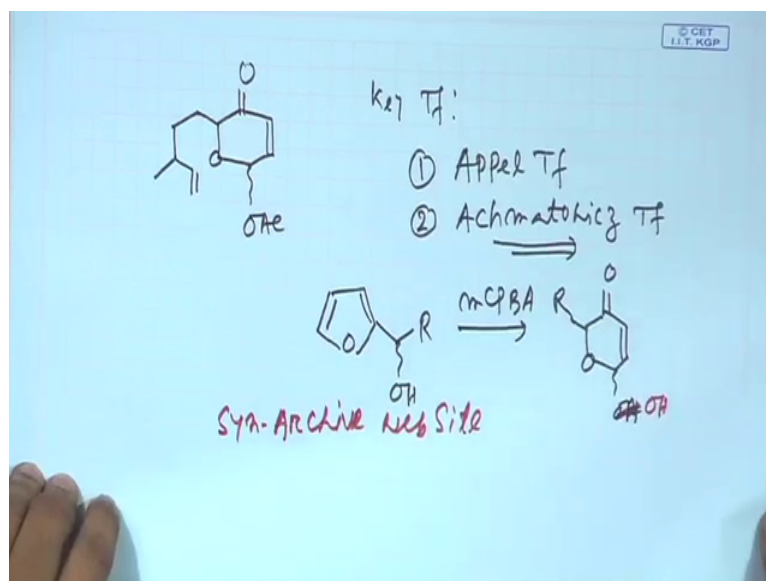


This groups remains same, we will having this hydroxy here, and you have a these things, and then for having this phenyl. So, this is basically your six member lactone, six member lactone. Now, we will come back to the original problem, where the structure of this after this appel and grignard, which is the furan carbonyl is basically these things. We will try to simplify it by putting the entire group as a r . So, we will write these things as a OH R. Now, subject to this starting material to this achmatohicz reaction, achmatohicz by m Cp BA. And then after this achmatohicz reaction, you will get the compound the six member thing as we explained earlier this R group is basically this group. So, R group is basically this group.

So, we are very close now what we will need to do you just need to do a acetylation, to put this acetic acetic group here. Now, these set if you are not familiar with these achmatohicz reaction, this will be very difficult for you to think that is why more and

more reaction you know this compound is basically nothing or target molecule you now try to put all the groups in a proper structural group point. So, this group is this group and then you have this methyl, and you have this group. So, this is the target molecule which we initially drawn. So, achmatohicz reaction is basically the main or key transformation. And in addition you are having a appel reaction.

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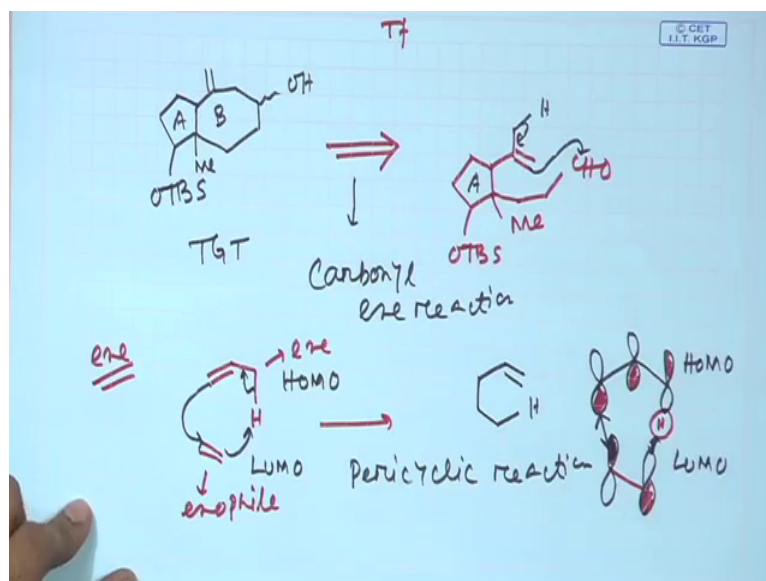


So, both the transformation we are using it here, so entire pathway if I now draw it again the entire pathway the target molecule was this and then you are having this is the target molecule. So, the transformation key transformation which we were using here first one is the appel reaction, appel transformation, the second one is the achmatohicz. Now, achmatohicz reaction was basically named by this inventor Achmatohicz who is a Russian scientist. And eventually you can use this achmatohicz reaction by treating this furile carbonyl with m CP BA. There are other reagents also which can facilitate this achmatohicz reaction and then that will be probably give you a very nice access this OH basically this kind of compound this is OH, this is OH. So, achmatohicz reaction is very useful.

And eventually you can access this kind of compounds and achmatohicz reaction if you go to the Syn-archive website you will find its mechanism and you can explore that is achmatohicz reaction was sometimes used for the synthesis of many natural product. So, this is the powerful transformation probably not known to you. Appel reaction is simple

one, but achmatovich this transformation if you are not familiar with that will give you the idea that this simple transformation. So, the starting material is pretty simple the reaction is pretty simple, but the final product which is definitely you have to think about how this furile carbonyl system reacts under this oxidative condition to give you the rearranged product which is having this pyranone structures which basically six member lactone sometimes called pyranone. Now, this is the beauty of this powerful transformation which helps you to deal with.

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We will stop today's lecture by discussing another simple problem and then we will try to analyze how this one was done. This particular compound was used as a target molecule, was given as a target molecule. And if you see the structural features, see the structural features is basically a five member ring and a seven member ring fused together fused together. Now, as I said it will be purely transformation based approach, let us first do the retro. Now, this reaction might be known to you might not be known, we will figure it out. This is the first retro which we draw is based on this kind of transformation.

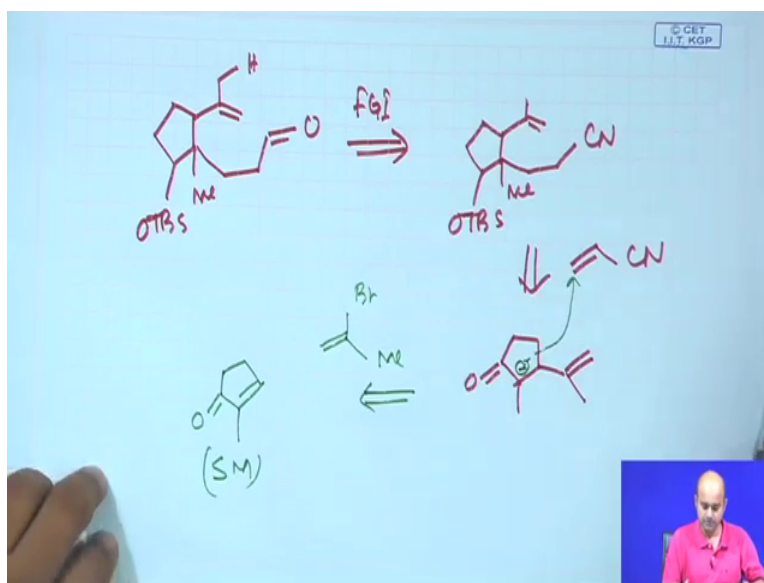
We see the ring, ring A and ring B, earlier we explained that cyclopentane containing starting materials are easily available. So, we kept out the cyclopentane containing things as a ring A. And then the reaction which we will be discussing here it is basically no one else carbonyl ene reaction. It means that this hydrogen of this compound will undergo a

hydrogen transfer from these to this carbonyl. Ene reaction is basically pretty cyclic reaction. I am just trying to figure it out what is the ene reaction in a simplified version not in detail.

So, this is a ene reaction, this is basically a called a ene, and this compound is called enophile, similar like dien and dienophile. Now, this reaction basically says that you try to close or make a, so this hydrogen which was here now have been shifted at this end, similar like this. This hydrogen is here and eventually for ene reaction is a kind of a pericyclic reaction, is kind of a pericyclic reaction is a pericyclic reaction. And we will find that effective HOMO LUMO orbital interaction is needed, you need a HOMO of the ene and LUMO of the enophile will interact in a very efficient way.

So, probably this HOMO LUMO drawing we can just now simplified it. If you are familiar with this HOMO LUMO thing, you can grow this homo of this particular ene and this is the HOMO of the ene. And then this enophile, we will trying to draw its LUMO. We have the similar kind of colored the red colored which indicates you have a maximum overlap, and this hydrogen particularly this hydrogen particularly is a have been here hydrogen, so that specifically makes this perfect overlap. And this is similar electron density, this HOMO LUMO overlap. So, that is a HOMO of this ene and LUMO of this enophile will make ene reaction. So, in principle this is the very important reactions, it is named as carbonyl ene reaction because one part you are having this carbonyl compound. Carbonyl compound as a enophile fine.

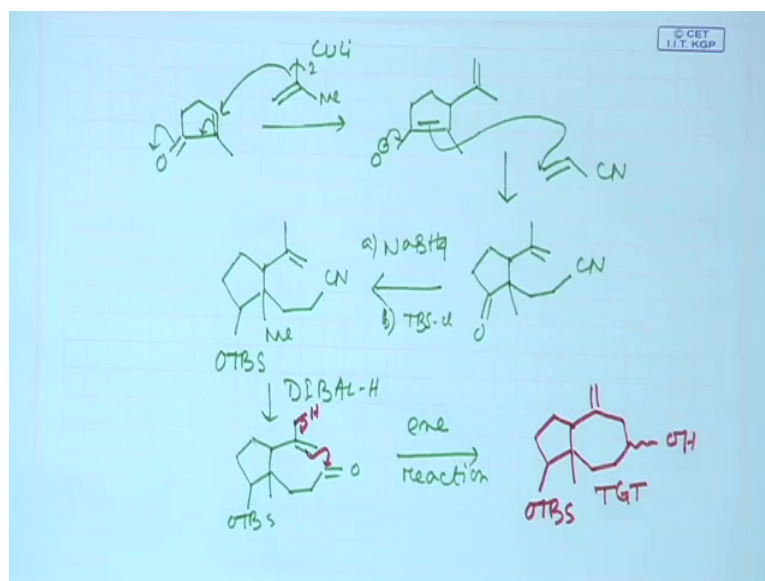
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So, now, we will explain the starting material or intermediate which you have just drawn now. We said we will be having a ene kind of reaction if you have this particular substrate, we will draw the structure in this way. So, this is the now we will simple do it a functional group manipulation or functional group inter conversion. How we will do it we will put remaining groups all similar, we will try to convert this aldehyde by a functional group inter conversion, which we explained earlier. To treat the cyanide, if you have cyanide react to it dibal, fine let us say FGI.

Next, what we will do, we will check it. If you have this compound, you have this methyl, and if you have this, it is starting material. So, basically we are trying to now figure it out, if you can think about a doing a michael reaction, a michael reaction with whom acrylonitrile. You can generate a stable thermodynamically given enolate here. And this enolate will react in one four fashion to give you this compound. Now, this was you can simplify it to a starting material a cyclo pentenon based starting material which is this. And you can think about doing a simple Gilman reaction simple Gilman reaction to put this compound. So, this is your starting material is absolutely these starting material commercially available.

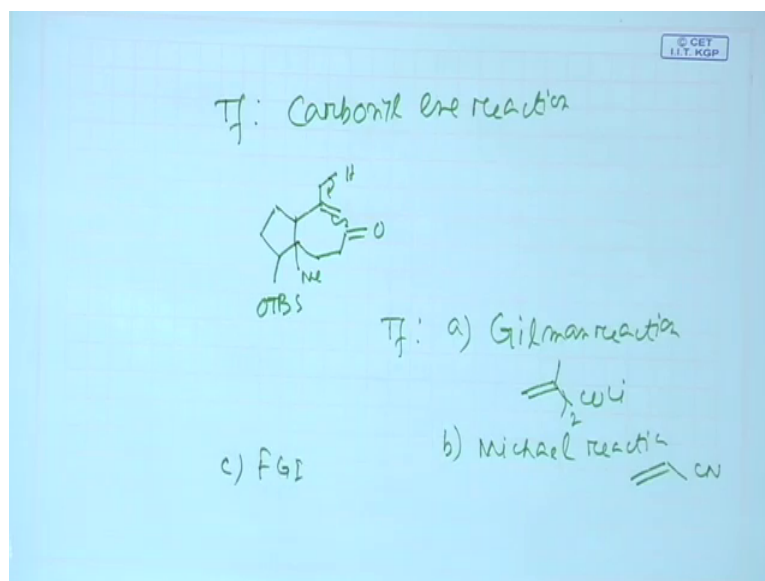
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So, now, let us draw the forward pathway. So, what you are having to have this starting material, this starting material is there with you. And you reacting with this thing corresponding Gilman reagent its methyl give a 1, 4-Gilman you can do a 1, 4-Gilman. So, means that these things we will attack here and then you come here to have these things. And now once these things will basically you have this O minus, and then you have this Gilman. This methyl is here fine. So, now, you can put this acrylonitrile as required by you. So, it can go back, it can react between one four fashion and that will basically give you this, this, this part is similar - your CH₂ CH₂ CN. And the final target this ketone was not like this, because kept as a protected. So, what you do just use a sodium borohydride, which will reduce the keytone; and step one, step b, you will just protected with tBSbs chloride. So, you can do a OTBS and then you figure it out this is.

So, next you are almost close to the carbonyl ene reaction. What you do you do a simple DIBAL reduction to convert the cyano to corresponding aldehyde. So, we will convert the cyano to corresponding aldehyde this. Now, everything is ready everything is ready. You can now visualize the ene reaction, you can now visualize the ene reaction. So, what to do as I said the ene reaction is basically thermally driven reaction. So, then you will basically have a in product, it is called carbonyl in reaction, say carbonyl in reaction and then this double bond will be generated, you have these things it is CH₂, it will basically the OH. Now, see this is your target molecular target molecule. This is the target molecule. So, a complex structure we are simplifying it by using is series of reaction.

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So, the key transformation what we use here is basically a carbonyl ene reaction. So, carbonyl ene reaction is as we explained earlier, it is basically a hydrogen shifting from one end of the molecule to another end when you have an enophile. So, this is ene, this is enophile. And then this basically undergoes these things to give you the seven member ring. So, carbonyl ene reaction one reaction and then this is the main transformation; in addition, you use other transformation which is nothing but a Gilman reaction of a suitable nucleophile.

So, in this case, we are using a Gilman something like this copper-lithium. And then we are using on the same part we are using a Michael reaction, Michael reaction with acrylonitrile that basically gives the $\text{CH}_2\text{CH}_2\text{CN}$, the CN has been converted to CHO. And then we do simple functional group inter conversion to reduce this carbonyl group to alcohol and then you convert this to a suitable protecting group TBS because our final target structure having a TBS. So, see the simplified thing was you take the target molecule, we take the target molecule, and you devise the retro this is target molecule. We have simplified the target through a ene reaction and then we have basically made your life quite simple. So, fine we will keep on discussing several transformation based strategies through this kind of problem solving approach. I hope all of you are enjoying it. And if you have any difficulties, you can definitely come to open forum, till then try to swap the assignments.

Until then have a good time, bye.