A Study Guide in Organic Retrosynthesis: Problem Solving Approach

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Lecture - 13
Tf/Fg/SM based approaches and its exploration

So, welcome back students. We are basically discussing different strategies and different transformations or different problems.

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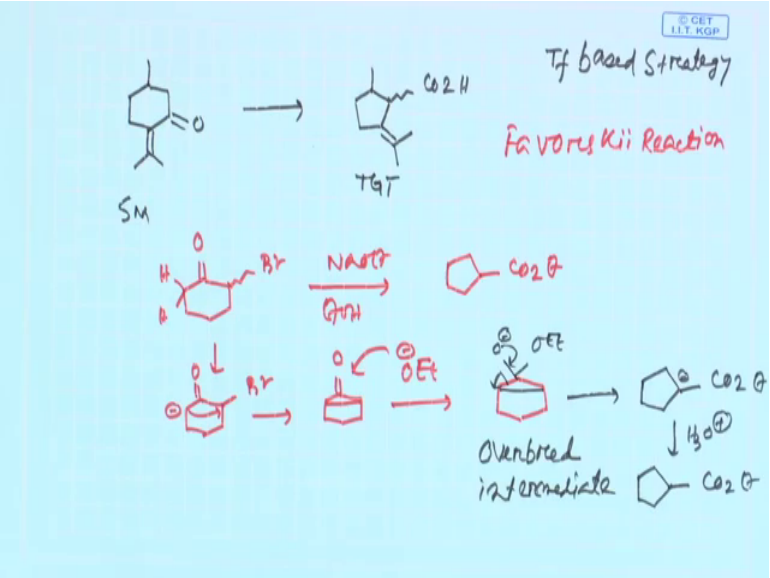

So, today we will be trying to little bit simple problems and I am sure all of you know this particular transformation. We will try to do a different approach. We give you a Starting Material; give you a starting material and then, we say that from this starting material, how you can access this particular product? It is basically similar. We are always talking about reverse way. Now, I am saying this is your starting material was given to you and the target molecule is given to you, given this one.

Now, I say this is really pure transformation based strategies, this one. This one is absolutely transformation based strategies and if you are not familiar with this particular transformation; you will be having a little bit of difficulties. But nevertheless we will talk about it and I am sure this transformation is very unique; very unique, very useful transformations.

Let me know, how many of you know this reaction named as Favorskii Reaction. I am sure all of you know this reaction Favorskii Reaction or Favorskii Rearrangement. Exactly this is the main reaction, which we will be using here. In conventional Favorskii reaction, what we do? We will basically take a compound something like this; you subject it to Sodium ethnocide and ethanol. Then you basically get a ring contracted carboxylic acid ester.

The mechanism you might be knowing it; the mechanism goes through initial step. This Hydrogen, one of the Hydrogen has been abstracted to give you this Carbon anion here. This carbon anion then, undergo intra molecular SN 2 reaction, to give you a 6 member and a 5 member, sorry 3 member ring together; this is highly strange.

Now, this strange thing is now attacked by a Nucleophile which is present in this reaction mixture, Ethoxide. This Ethoxide attack here and once it attacks, this Ethoxide basically will be giving a tetrahedral intermediate. But a 3 member ring remain same. Now we say 3 member rings are usually very strain, very strained. The strain releasing will be the main factor. So, this O minus we will try to come back and then, it will try to keep this bond clipped; anyone of this bond will try to whether this or this does not matter.

So, basically these things comes here you keep this point and then, you will be basically having this Co 2 Et, it is minus. This will be basically taking the proton from this aqueous workup and we will get this as a final product.

In latter part of our discussion, we will say that this kind of strain intermediate are often named as over bred intermediate. But eventually this is another time to discuss it. Now this is the Favorskii Rearrangement or Favorskii Reaction. So, in context to the current problem, you can easily formulate that how Favorskii Rearrangement, it is useful.

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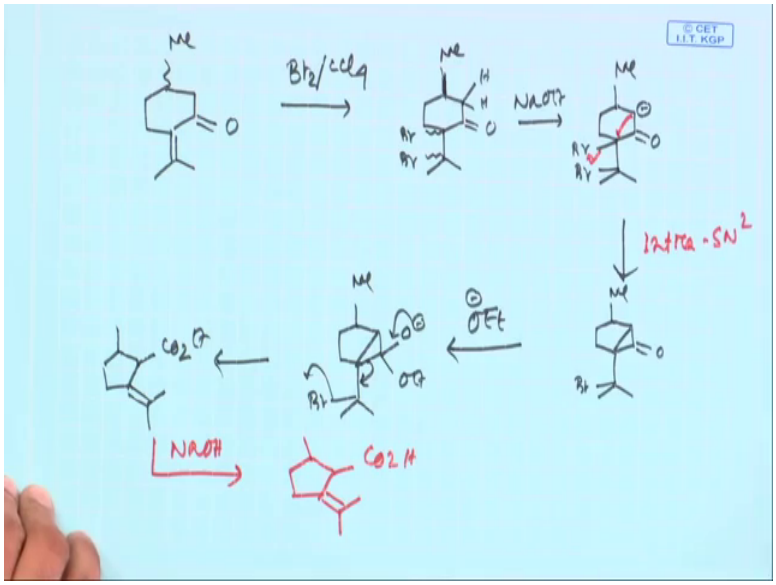

So, your study material which was given to you having structured like this.

Then to have a Favorskii Reaction, what you need? You need some Bromovar, leaving group adjacent to the carbonyl. So, first we will do the Electrophilic Bromination by treating this compound; as this compound is having aliphatic unsaturation. This Electrophilic Bromination, Bromin Carbon tetrachloride very standard textbook condition and then, what basically we will get you get a Bromo here, you get a Bromo here; Dye-Bromination. The remaining sorry, this part will be the same.

You subject this compound with the base which is normally Sodium Ethoxide. This Ethoxide will pick this acidic hydrogen, anyone of the acidic hydrogen and then, what you will get? You get a minus here and then, this part you are having this Dye Bromo 1 B r, 1 B r.

So, Favorskii now, can start. So, this a minus. Now basically can attack here. This through a intra SN 2 type reaction intra molecular SN 2. So, we will have this Favorskii in action and wrap this 5 member ring and 3 member ring and then, you see and then like this.

Now, eventually you have a Sodium Ethoxide in the reaction mixture. So, x is OE t minus is there and then, as a condition of Favorskii this, OE t minus will basically would

be here. Now when this O minus collapses; this particular bond has to be broken, as the normal Favorskii thing.

Now, entity when this bonds will try to break. This is find that instead of stopping this reaction here, if it can relate further that one of the B r is there which can act as a leaving group. That was the Favorskii Reaction followed by a nice elimination reaction or a fragmentation reaction. That is why the substrate was suitably designed and now, you see the ring has been contracted; the ring has been contracted and this methyl part is there. This Co 2 E t will be there and then here you will be having this double bond, this methyl methyl.

So, your product basically having a Co 2 H group here. So, you basically need to do a hydrolysis; you can do a acidic hydrolysis, you can do a basic hydrolysis and then finally, you will get the hydrolyzed product. Since the Favorskii Reaction we have represented by Favorskii reaction in a different perspective. We do the Favorskii Reaction, the same time we put a group here. This kind of group which basically helps the Favorskii when the ring collapses, starts taking place; it also equipped with a elimination. And the elimination is very facile and then, you get a double bond here. That was the Favorskii Reaction coupled with a elimination reaction and that gives you target molecules.

So, if you are familiar with Favorskii Reaction, I hope this problem you might be able to solve it.

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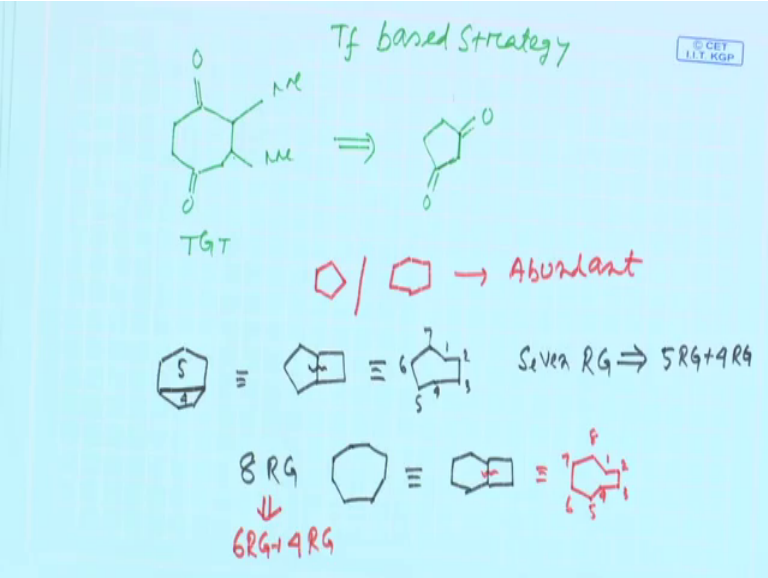

Next one is again, a Transformation based strategies; Transformation based strategy and this Transformation we have already discussed in the Chemquidge Retroquidge. But still we want to discuss it. The target molecule which was given to you is basically a 1 4 Dicarbonyl compound. This is methyl, this is a methyl. So, this is a 7 member compound 1 2 3 4 5 6 7, this is 7 number compound. This is the target molecule and the starting material; I will give it to you starting material. I say is a 1 3 Cyclopentane dione, this one.

Now, before we start analyzing this problem, I will try to give you a brief intro, that how 7 member rings, probably for this problem how you can think about doing a disconnection. Now 7 member rings are usually not a very good starting material. 7 members is not a good starting material, you probably won't get too many starting materials which is having 7 member ring.

On the contrary, Cyclopentane and Cyclohexane containing rings are Abundant in nature. Natures as well as you get many cheap starting materials which is having Cyclopentane and Cyclohexane. For the case of Cycloheptane rings if you draw the Cycloheptane; you know Cycloheptane sometimes you can think about doing a very adventurous retro.

Now, this top part is a 5 member ring and the bottom part is a 4 member ring. I will do it in a different way. I will draw it; this is a 5 member ring. This is a 4 member ring. Now

somehow if you can access this kind of ring and you break the middle ring, what will get? We will basically get a, what is this? Is a 7 member ring, 1 2 3 4 5 6 7.

So, in principle this kind of studies is very useful. So, 7 member ring, I said seven member ring RG can be a potential target, if you have a 5 member ring plus a 4 member ring fused together, fused together .

The similar way if you have a 8 member ring; let us say you are having a 8 member ring which might be target molecule. Then this 8 member ring, you can easily and you do this disconnection here. You will basically get, what is this 1 2 3 4 5 6 7 8. So, 8 member ring also can be possibly disconnected through 6 member ring plus 4 member ring together .

Now, this is very easy to pin down such retro, but if we have such kind of such transformation is known to you then, you can think about it and as I said 7 member rings sorry 8 member rings, 7 member rings are not abounded in the nature. You might have difficulties to find this kind of commercially available starting materials.

Now, what target is a seven member ring. So, based on our target we will figure the retro.

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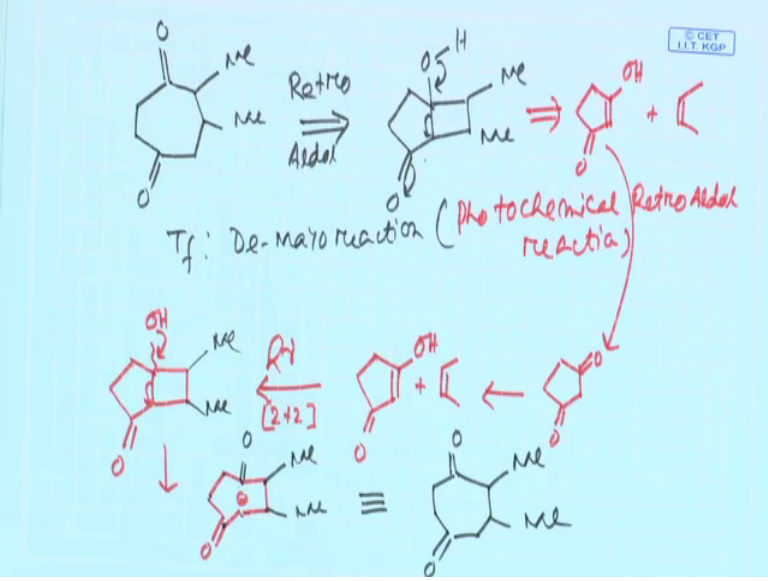

Now, first again draw the target. This is our target molecule. So, by keeping the mind 7 member ring; it is a combination of 5 member and 4 member ring. You possibly can do a retro, see the retro very carefully; you can possibly do a retro based on this kind of transformation.

Now, what is the transformation? Is basically nothing is a Retro Aldol reaction. Now how it goes? It basically goes through a this pathway, this and this and this and eventually you need to have a 1 4 Dicarbonyl things in your target structure.

Now, this is a what? This is a 5 and 4. Now this transformation which is crucial; we already talked about is a De-Mayo reaction. It is a De-Mayo reaction is a photochemical Retro Aldol reaction, is a Photochemical, we earlier discussed it during the retro (Refer Time: 15:06). It is a Photochemical Retro Aldol reaction. This is the main reaction will be now discussing.

So, now we have this starting material. So, find do another round of retro and then, try to simply get the simplify starting materials. So, this is this starting materials with these olefins. Now this starting material is nothing; this is a basically a simple 1 3 Cyclopentane dione.

So, what you do this compound is very easily analyzable. So, first you analyze in the reaction mixture. You will get this then you subject it to H nu mediated, 2 plus 2 H nu 2 plus 2 and then, we basically get a simple 2 plus 2 Cyclo addition which is the best way to make 4 member rings is there up to this absolutely clear, I guess.

Now, as I said 4 member rings are definitely not perished, stable. If there are possibilities the ring can open up; it will try to open up. Now see this is basically nothing and say further a Retro Aldol reaction can takes place. Now I will try to figure it out the how? So, this bond we have now, broken it up and then you put a negative charge here; this negative charge is definitely stabilized by this electro with strain.

Now, what is this? This ring is now, basically 7 member with a kitone group here which is arise on the Retro Aldol reaction. So, 1 2 3 4 is basically 1 4 Dicarbonyl compound. We have forgotten to put these 2 methyl group which will be definitely there. Now count the number of carbon 1 2 3 4. This side is 5 6 7. So, in principle this compound is nothing, where the target molecule which is the 7 member target which was initially desired for our synthetic sizes .

You see this kind of De-Mayo reaction; it is a very interesting reaction. And then, in principle very simple transformation, but give you little bit complex molecules the main take home message is if you know this De-Mayo reaction will be able to use this De-

Mayo reaction for synthesizing 7 member rings as well as 8 member rings starting from Cyclopentanone or Cyclohexanone. First generate the involves, then add the involve, take the olefin, do a 2 plus 2 cyclo addition reaction.

And now this you see this is basically perfectly fitted for a Retro Aldol reaction; because 4 member rings are strain. It will open it up and give you a carbonyl which is basically nothing, stabilized by this carbonyl group and then finally, you get this 7 member ring as a main product. That was the main essence of De-Mayo reaction which you have already discussed earlier in the retro (Refer Time: 18:59). The De-Mayo reaction is very useful very useful.

So, we will keep on, keep on discussing couple of more problems and eventually as I talked about De-Mayo reaction.

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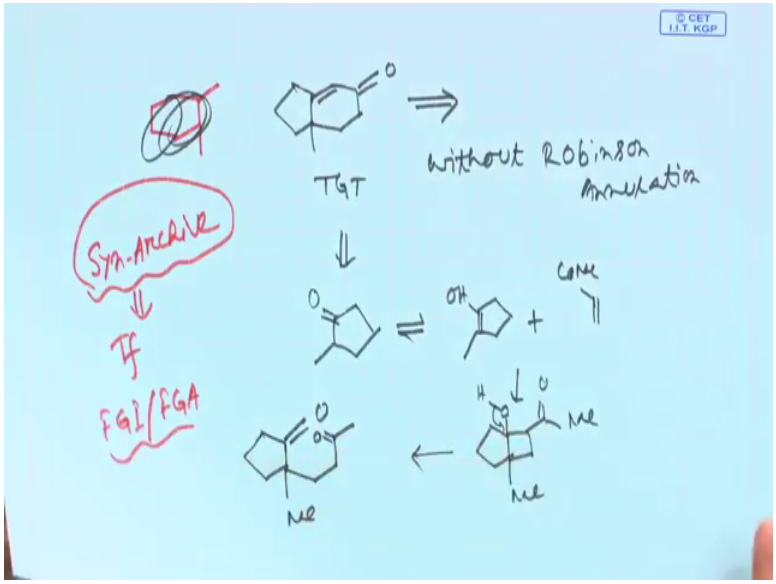

I will try to give you 1 assignment and I am sure this is (Refer Time: 19:25), earlier done this assignment basically was done earlier. So, this is not the correct thing, you can forget it. This assignment particularly was done earlier, I said you take this target molecule and synthesize it without Robinson Annulation reaction. And definitely in this case, your main option is to use a De-Mayo reaction.

So, De-Mayo reaction we have already talked about and this De-Mayo reaction is very simple, which is already discussed to you; you just take a Cyclopentene based compound

like this, which is basically will be analyzable and then, you get a Alkenol OH and then, you react with a methyl vinyl ketone to grid the corresponding 5 member as well as 4 member species. And then, if you can find a simple Retro Aldol reaction will now take space. Now this Retro is Retro Aldol is important because the ring will be now opening up in a different way, different way.

So, its opens up in a different way and once it opens up you basically have this methyl remains similar, CH 2 CH 2 CO CH 3. Then you figure it out through a intra molecular Aldol. So, this is similar kind of problems we already discussed and you will definitely having a excellent opportunity to go through solve the transformation which we talked in this lecture as well as you can go through the syn archive, I said syn archive is a very useful information; syn archive is a very good website that gives you loads of information for this kind of multiple transformation based approach. More and more you are familiar with several transformation. Then basically you can play with those transformations for normal functional group based inter conversion, functional group based addition.

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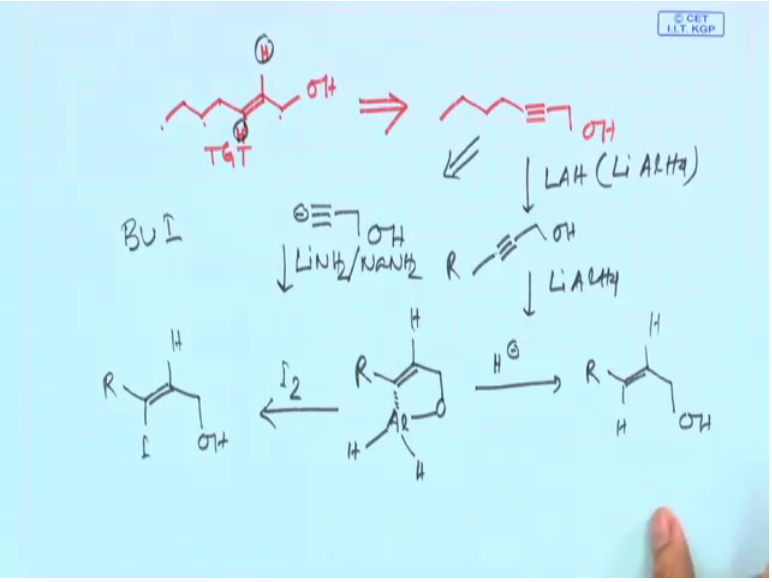

All those things you can; basically put your efforts to solve those problems. And that would basically really helpful.

We will try to figure it out some simple straightforward as it, let us this is the target molecule; we will just trying to do some or test some of your knowledges.

Now, this is 1 2 3 4 5 6 7, 7 carbon unit. So, it is very simple reaction. There are many ways you can basically do it. We will initially try to figure it out; 1 2 3 4. 1 2 3 4 then, we say if you have a Propargyl alcohol, you can easily do it. Now the target molecule you are having this double bond as a trans, trans geometry. It's not seize. So, Propargyl alcohol, if you subject to a reaction named as reducing agent named as Lithium Aluminum Hydride, Lithium Aluminum Hydride. It basically gives you the trans alcohol.

Now, how? We need to figure it out. Usually if you have such Propargylic alcohol as a starting material, normally with exposure on Lithium Aluminum Hydride you will basically end up with a initial step is the a it gives you a cyclic aluminates species and this cyclic aluminate species where, this particular triple bond the hydrogen one of the hydrogen from the LAH already had attacked .

Now, this cyclic aluminate is basically has to be on the same side, same side. That is why when next you are leaving this carbon aluminum bond by another round of hydride or another round of nucleophilic spices and electrophilic species; then, this particular hydrogen and this hydrogen become trans to each other, that is the main things.

So, you can now get this kind of allelic alcohol where, this are basically trans. Also you can treat this compound with iodine to make a carbon aluminum bond cleavage and that will basically give you compounds something like this. This is also a very good source of getting vinylic iron species.

But eventually, for our target molecule so, you need this compound do a LAH reduction and you will be getting this. Now how to access this particular compound? If you take this as a starting material and this is what? 1 2 3 4 Butyl Iodide; so, Butyl Iodide. Now this propargylic alcohol, you can basically generate this carbon ion here by using any base the bases which are preferred is Lithium amide or Sodium amide.

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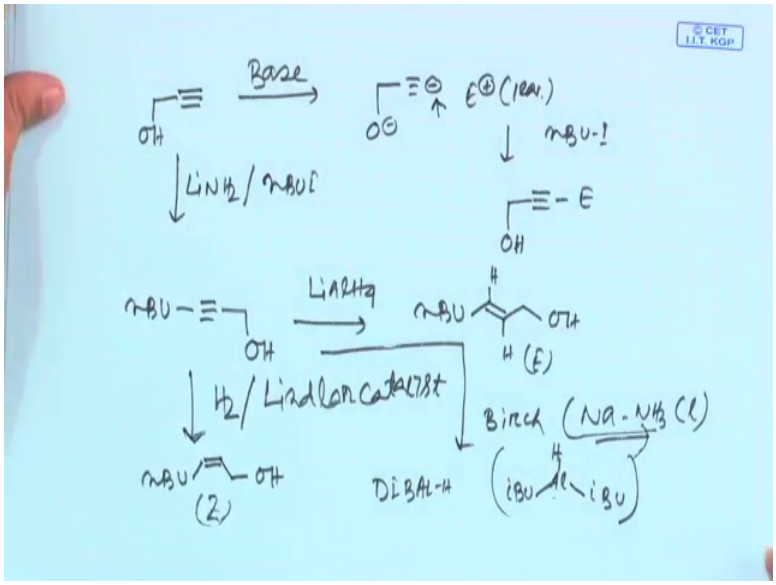

So, what exactly you will be using, take this starting propargyl alcohol, use a base and then, you get this anion as well as this O minus also. C minus O minus; C minus is much more Nucleophile because O minus is much more electronegative. So, this is much more Nucleophile. So, Electrophile if you now attack here definitely one equivalent then, we will find that this carbon Electrophile bonds we will know from here and you get a OH.

Now, in this case the Electrophile you are using basically n Butyl bromide or Iodide. So, lithium amide and n Butyl Iodide. So, you will basically getting this n Butyl this OH and then you use Lithium Aluminum Hydride to get this n Butyl; the double bond geometry is now Trans.

Now, I did not talked about a potentially other problems see, I say if we use this is starting material and doing a hydrogenation with a Lindlar catalyst conditions, Lindlar catalyst. Lindlar catalysts are very useful catalyst is basically paradium on calcium carbonate poisoned and then, this particular condition will give you a seize or Z double bond.

So, based on the particular reagent which you use, you can choose either Z, you can choose Z or you can choose either E. Now Lithium Aluminum Hydride as I said as a very interesting reaction. On the contrary, if we have this propargyl alcohol you can use other condition also to get the E geometry, you can use simple Birch reduction condition which is nothing but, the sodium liquid ammonia. This also gives you a E geometry try

to find it out the mechanism for this Birch reduction. How it gives you the E geometry and further reducing again something like aluminum base reducing agent let us say DIBAL. What is this? Di-isobutyl aluminum hydride. So, isobutyl aluminum hydride; it is a pretty sterically bulky hydride reagent and it is a pretty mind.

But this reagent also have the similar tendency to give you this E allelic alcohol starting from a propargyl alcohol. You can basically simply play a different kind of reaction conditions to tune the activity and then, you will see the original activity, we are basically looking for a compound something like this and there are other routes; there are definitely other routes and what are these routes? This is a n butyl, as it this is a route.

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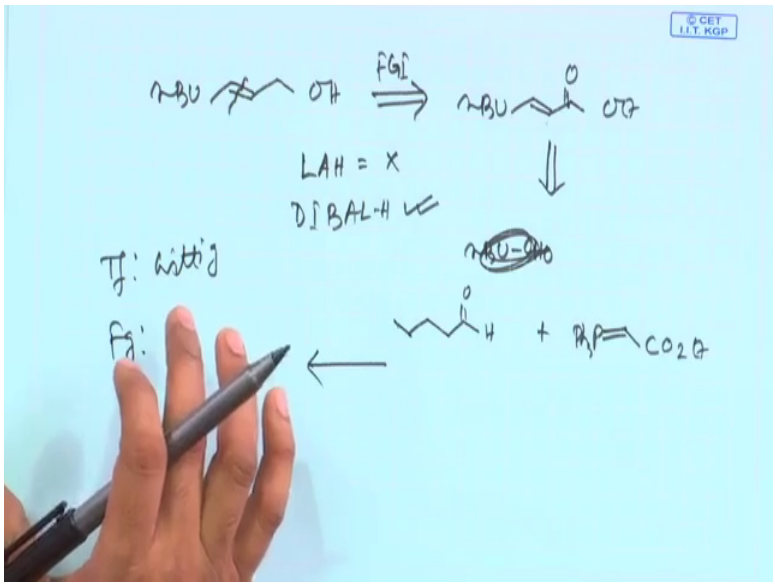

You can basically can simply think about other routes, do a functional group based retro. If we have a corresponding ester, you can definitely do it; esters.

Now, what is this is FGI. So, basically you need to reduce the alpha beta also you generate ester to its corresponding alcohol. LAH may not be the choice of reagent; LAH is good bad because it can reduce 1 2 as well as 1 4 the best choice the, of the reagent is this case is DIBAL, what I said just now. So, pretty mind and it won't touch the double bond, you reduce the only the ester to give you the alcohol.

So, fine. So, you can think about this. Then this compound how you can prepare? You can prepare a numerous way, one of this reagent, one of this condition I am giving you.

One of this condition I am giving you is basically, you take the corresponding aldehyde 1 2 3 yeah which you, now react with a basic condition (Refer Time: 32:19) that you can do.

So this, these are the different ways you can basically make the molecule and different ways. So, once you do this do this (Refer Time: 32:33) reaction; this is the thing and do general 1 2 3 4 react with wittig reaction and you get this product you do a DIBAL reduction then, you come to this.

So, transformation is wittig which is very useful for these things functional group based approach, you can start with propargyl alcohol, do a simple propargyl based coupling and then, you can react with electrophile. Then you can reduce the double triple bond the double bond.

So, it is basically combination of different reagents different functional groups and different strategies altogether. So, if you know a particular transformation which you can think can be fitted here, you can use it. If the starting material was given then, you can design your pathway that also could be very useful. The starting material is not given nevertheless you can think about to reducing the disconnection and then, you can straightaway design the pathway. So, we will keep on continuing our discussion and probably we will see you in the next week.

So, till then Good Bye.