A Study Guide in Organic Retrosynthesis: Problem Solving Approach

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Lecture –14
Tf/Fg/SM based strategies and its exploration

Welcome back. We are basically discussing several problem based approaches of a given target molecules.

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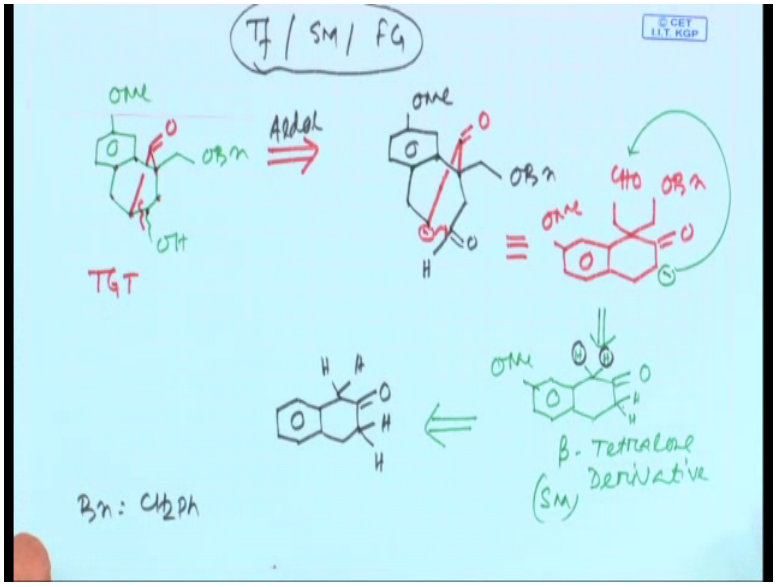

And we have talked that transformation based approaches starting material based approaches and functional group based approaches or the key core 3 strategies which can be combined together efficiently to solve numerous problems as discussed in the earlier lectures.

Now, in continuation with the same thing, we will now try to provide you a problem which is similar, but you need to figure it out the target structure in very closely. So, the 6 member ring is there and in addition you have a 7 member ring. Then, I am try to do 1 2 3 4. So, this is the target molecule, just try to draw the target molecule and then, this target molecule is bit complex; you have a bridge structure from here.

Now in reality the structure which was given here, it's a not a simple structure as it looked. The 6 member ring. Then, you have a 7 member ring; 1 2 3 4 5 6 7. Then, you are basically having a 5 member bridged; 1 2 3 4 5.

So, now there are cyclic structures connected in a different way. Probably a topological distinct molecule. But eventually, we will be just trying to analyze the molecule in a very straightforward retro by normal functional group based approaches. Let us first, do the very conventional retro and then, you will realize and how this retro's are so powerful; so, powerful.

The only thing if you check the molecule, you will find that a probably a Aldol kind of transformation is useful to make this target molecule. Now how? I will try to draw the structure. So, this is O Bn; Bn is benzyl. I am writing it Bn is basically benzyl; CH 2 Ph it's a abbreviated form.

Then, from this part you can fuse or you can hanging, you can make a hanging Alde Hyde; Alde Hyde appendages. Then, these things you can put something like this and then, you will try to make the bridge; try to make the bridge. Now we say that, we are doing a disconnection here. Now this is a Methylene compound adjacent to a carbonyl and a close proximity you have a Carbonyl or Alde Hyde group. So, basically is a Aldol Reaction, it is a Aldol Transformation.

Now, the structural simplicity is basically until and unless you draw the a Aldol retro it's not visible; does it mean sometimes you try to make a visible or visual communication with this target molecule and then, try to simplify the main target structure. Now this structure, we will write it in a simplified form.

If you write it, now you see the structure is basically nothing but a 6-6 molecule fused together is not it? See the analogy this is the Omethoxy; this is the fused, common fuse together, 1 2 3 4 5 6. So, the Ketone, this red color Ketone is basically this and then, you are doing it a Aldol reaction with this Alde Hyde to this. So, this is the Aldol reaction we are doing.

Now this compound has been rewritten in this way. So, that is what the structure looks pretty complex. Now once is simplified, now you are quite comfortable. Now it looks

quite comfortable and then, probably you can design a very straight forward retro based on a known starting material.

This starting material is known is a 1 2 3 4 5 6 7; 7 Methoxy Beta tetra lone. That was already known and probably this is a beta tetra lone derivative, it's a commercially also available; Beta tetra lone derivative. It could be sharp is a very good starting material. Now, what exactly you want to do it, you will be doing a successive round of alkylation to put these functional groups.

Now remember you are having a Methylene groups here as well as here, fine. Now out of this Methylene group, this Methylene group is most acidic because it is a Benzylic also, that gives you a things. So now you realize that. if you start with this compound again, we will draw the parent compound and you both the hydrogen's you will basically replaced by some carbon containing electrophile, that will be given you the this target. This target will the undergo intra molecular Aldol reaction to give you the final target, is not it.

So, let us start the forward synthesis.

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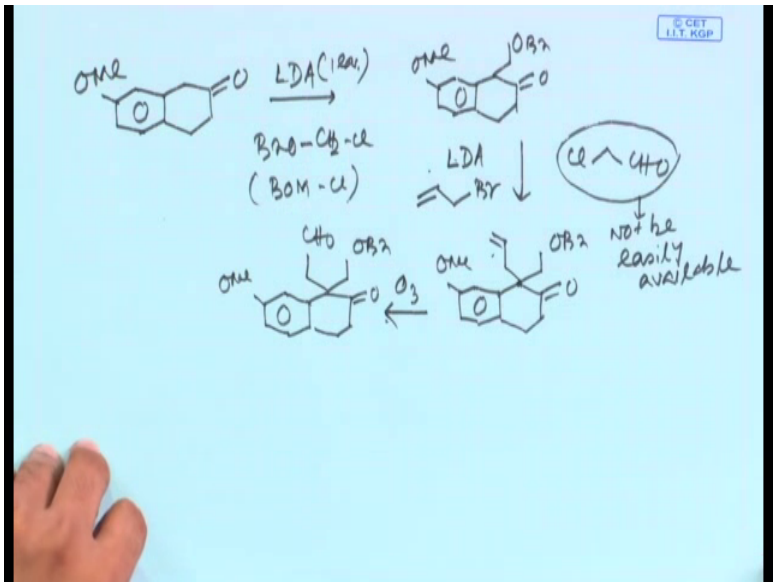

The 7 Methoxy, the tetra lone derivative, which you choose. As it doing the successive round of alkylation; so, LDA 1 equivalent. Now what are the groups need to be

introduced? The first one is Benzyl o B n o CH 2 Cl, this is called Benzyl Oxy Methyl Chloride or abbreviated as BOM Chloride.

So, first round of alkylation we get O Bn. The second group which you need to introduce must have a CH 2 CH o. In principle you can basically use this kind of chloro acetaldehyde, is possible definitely possible, but sometimes this reagent might not be easily available; might not be easily available.

So, what you do you can try to take a another source or another electrophile which will give you this particular functional group. So, alternatively we will be using this reagent condition, will be using LDA and Allyl Bromide; Allyl Bromide is very cheap material, cheap starting material and then, you will basically do another round of alkylation to get this all carbon quaternary center share, fine.

Then as the situation demands, you need to do a oxidative privilege here, to remove this one of this carbon to get a Alde Hyde. So, do a original analysis your own Methoxy group will be always there; you will do a original analysis and then, you basically getting this compound. Now this compound you can, now try to go back to the original retro it's nothing but this, you try to draw it in a this way and then, do a intra molecular Aldol. You can now finish it off the retro in a elegant way.

So, that was basically very useful simplification. So, once we have a complex structure that is why we always saying that the retro synthetic pathways are so powerful. So, you have to start communicating the, with the molecule in a visual way and once you try to finish the chemical logic. Then you simplify the starting material or the intermediate and then, you complete the forward synthesis is a very pleasing exercise.

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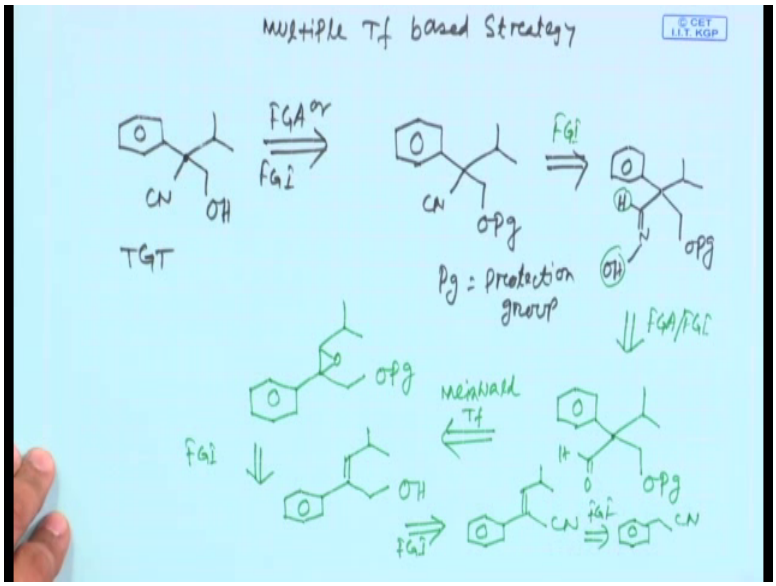

And next, we will be basically trying to use a similar kind of strategy would be using a multiple transformation based strategies. It is sometimes transformation which you required is to be combined, couple of transformation like 3- 4 transformation should be combined together. But till now, we have not discussed any complex structure. It is basically a simple structures where, you can just play with 2- 3 functional groups or 2- 3 transformation.

This particular target which is now, next we will be discussing, we will be using a 2- 3 transformations together and I am sure all the transformations have been known to you our earlier discussed. Is a target molecule which contains a Phenyl ring and here it's having a appendage which is having a Ciano CH to OH and a isopropyl group. So, this carbon is a quaternary carbon, with all carbon quaternary; the Phenyl Ciano CH to OH.

So, do the, I will do a functional groups addition or a functional group inter conversion is purely FGA based approach. In order to I have to do, will initially if we found some where the alcohol is given in the target molecule; means that the alcohol need to be protected.

Normally, Alcohol protection we have not discussed, but we will do it, little bit later on. But alcohol is not a good functional group which you can give as a free because acidic hydrogen a play some important role. So, alcohol free is always not recommended you can just protect it; the suitable protecting group. Pg stands for Protecting group; we will

be talking about many protecting groups little bit later on, when you talk about functional group based strategies in detail, Protection group.

The next you will try to figure it out other FGI based approach and then, we said that this compound can be potentially created from a Oxime; which can give you a cyanide. Now Oximes are basically having a with this is this command is Aldoxime means Alde Hyde Oxime. Now Aldoxime if you treat with a dehydrating agent, merely Phosphorus pent oxide, this water will be eliminating and you get the nitrile compound. So, what is this? This is basically a functional group inter conversion.

Now, Aldoxime means you need to have a Alde Hyde; otherwise, you won't get Aldoxime. So, this is again a FGA or FGI to come back to the parent aldehyde CH o. This isopropyl remains similar and this group is put it as is suitable protecting group. So, we are here. Now this carbon is all carbon quaternary carbon.

The next retro was again based on a very conventional reaction, which we discussed many time in our coursework. We said a manual kind of rearrangement will give you this Alde Hyde. So, is a manualed based rearrangement was used as a main transformation, manual transformation. Now you know the mechanism of manual rearrangement and you can ensured you can basically figure it out, how this transformation takes place.

So, next you need to make this epoxide, simple job. You can now, just make this alcohol free and then, if you have this kind of compound; this kind of allelic alcohol you can easily make it, this is a FGI. So the manual transformation as we discussed earlier, you know the mechanism, you can easily formulate.

So, now, this primary hydroxyl group we are putting in a different way, we will be accessing this primary hydroxyl group to a Ciano group. Some of the reactions we are not discussing, but we will discuss it when we talked about forward pathway and then, this Ciano will be discussing from a benzyl ciano through a intra molecular Aldol reaction. So, all are FGI, FGI based on couple of interesting transformation.

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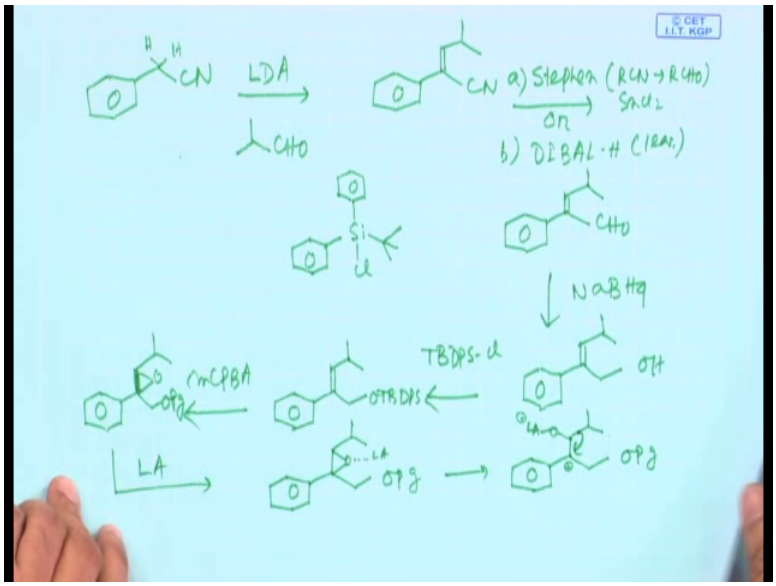

So, now let us go back to forward pathway. So, the forward pathway starts from very simple starting material Benzyl Cyanide. This compound is subjected to first LDA. The acidic compound, this hydrogen's are definitely acidic and then, you react this compound with this aldehyde. So, Aldol reaction will takes place and we definitely get these things. It is obvious means now, go back to the retro, you will find the cyanide now, needs to convert it to the corresponding aldehyde; you can basically do 2 different kind of formations. Probably you know Stephens reaction.

Stephen reaction is a very simple reaction in which you can convert a ciano to a aldehyde RCN to RCH o by SnCl 2. Otherwise if you donot like the Stephen reaction, you can simply using a DIBAL- dye isobutyl aluminium hydride, that will also selectively convert a ciano, the corresponding aldehyde. The beauty is the reaction will definitely stop in the aldehyde step, usually it if you use 1 equivalent of DIBAL, it usually stops at the aldehyde steps; otherwise you can use excess DIBAL to get the primary alcohol. Because in our synthetic experiences, synthetic exercises we need the primary alcohols.

Never the less, DIBAL is very expensive. So, what you do you put a DIBAL 1 equivalent to get the aldehyde. Then we use a cheap reagent sodium boro hydride to access this are allelic alcohols. Then this allelic alcohol needs to be protected. The protecting group, normally you can use any protecting group, but I am giving you protecting group whose name is TBDPS-Cl. The structure of TBDPS-Cl is Tertiary Butyl Diphenyl Silyl

Chloride. So, basically the oxygen will be replaced by this silyl ether and you will be having this O TBDPS. So, this is your these things.

You can do a mCPBA mediated epoxidation here, to get the corresponding epoxide, which will be next subjected to manual rearrangement. So, now, you are having this epoxide and this O, lets say Pg, O Pg. Manual arrangement this is say normally you treat with a Lewis Acid. It is Lewis acid.

So, the Lewis acid you add, I know obviously, make sure which way the carbons, carbon oxygen bond will be broken down. The most stable Carbonium iron will be definitely generated and I assume that this way you will be having this O L A things; because it is the Benzylic thing.

Now, the out of this, there is hydrogen. There is isopropyl; isopropyl group is secondary. It will basically migrate, isopropyl group will migrate here and then, once isopropyl group will migrate, let the isopropyl group migrate.

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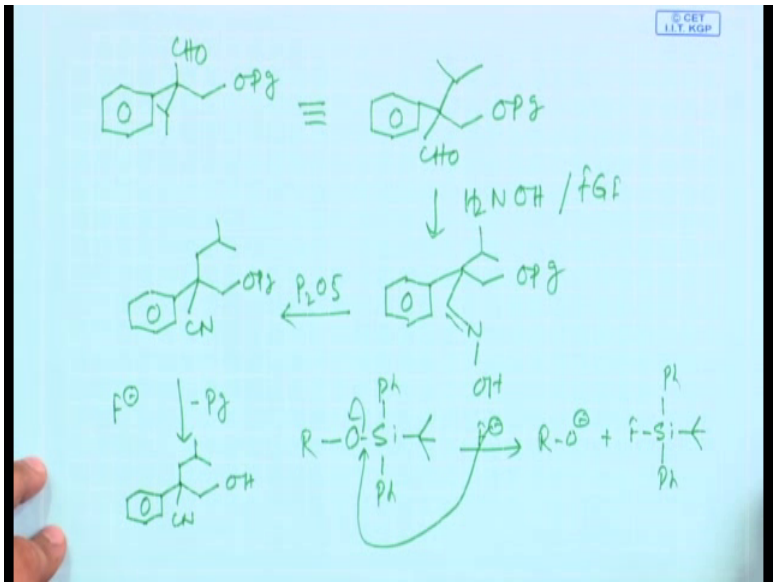

And then, you will basically get the all carbon quaternary center. This isopropyl group will definitely migrate and you are having this CHO after this rearrangement takes place which is basically nothing the compound. We said is a put the isopropyl group in the top this O Pg and your aldehyde.

Now, make this aldehyde oxime Aldoxime by hydroxylamine treatment, a very standard FGI. So what you will get? You get to this O Pg, O Pg remains similar; your isopropyl group remains similar and then, you get the corresponding oxime. Put a dehydrating agent may be P 2 O5, phosphorus pent oxide and you will get this O Pg ciano here and your isopropyl.

So, now we are almost close only thing is you need to remove the Pg. Now this Pg removal is a basically oxygen silicon bond. We will try to give some more information. Now this oxygen silicon bond is very labile under a fluoride condition; because you are going to form a new silicon florin bond. So, this will come here, you put a R - O minus and it will give you the silicon florin bond, silicon has a strong tendency or silicon is very much (Refer Time: 24:00).

The silicon florin bond energy is very high; that is why normally if you have a oxygen silicon bond or carbon silicon bond, the base to it clew is to (Refer Time: 24:12) fluoride source; fluoride source here will be giving fluoride source and then, basically you can access the target molecules which is required. You will get a OH here; you get a ciano, the target molecule.

Now, coming to the fluoride source, what kind of fluoride source you can think of using for silicon protection? Fluoride source.

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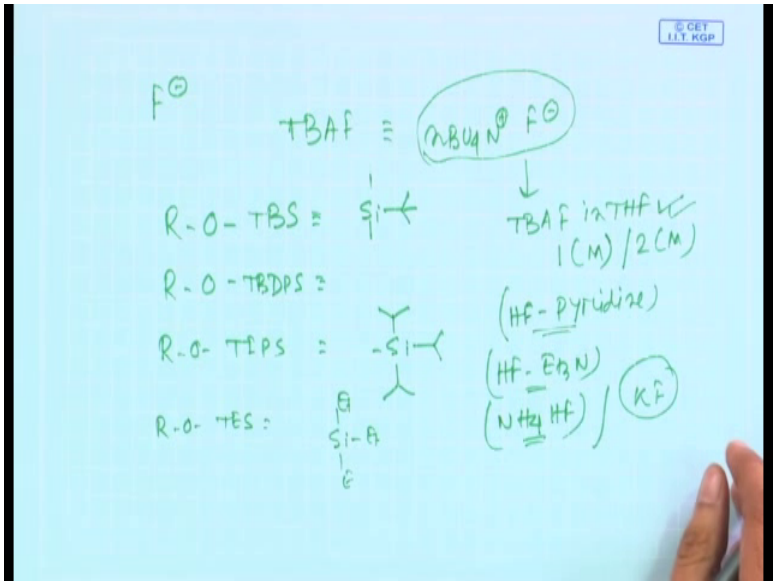

The best fluoride source, what we will be using is named as TBAF, Tetra Butyl Ammonium Fluoride, whose structure is nBU 4 N plus F minus. Normally all silicon containing protecting group has been cleaved in this way, say R - O - TBS stands for Tertiary Butyl dimethyle Silyl which is equivalent to Silicon methyl methyl this group.

TBDPS, which we just now talked, which are commonly used silicon reagent; silicon protecting group R – O – TIPS, TIPS stands for Silicon Try Isopropyl Silyl. There are other silicon containing protecting groups like R – O – TES, TES is Try Ethyl Silyl. When Silicon Ethyl Ethyl Ethyl. So, all the silicon containing protecting group can be cleaved with tetra butyl ammonium fluoride. These tetra butyl ammonium fluoride basically was commercially available TBAF solution.

So, you know try to buy it of conscious supplies you will find that TBAF in THF solution, Tetra Hydrofloro, Tetra hydro furan solution. So, normally 1 molar or 2 molar solution is commercially available and you can just use them in some cases, you can use HF. HF was very strong acidic and to minimize it's acidic nature sometimes HF was combined with Pyridine, HF Pyridine is a good reagent HF triethylamine is a good reagent to keep the silicon containing protecting group.

Simple ammonium fluoride NH 4 HF, ammonium bifloride was used. Potassium fluoride sometimes was used, but potassium fluoride is very much hydroscopic, is very difficult to handle. The potassium fluoride normally is not used, but you can use this all these compounds. TBAF was the most widely used compound to cleave any silicon containing oxygen silicon bonds or carbon silicon bonds. HF Pyridine also was used. HF triethylamine, ammonium fluoride, ammonium hydrogen fluoride all are used. So, what are these set of reagents, we will be using when you talk about protecting groups in detail.

So, we will just continue our discussion in the next week, till then, goodbye. Have a good time.