A Study Guide in Organic Retrosynthesis: Problem Solving Approach

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Lecture - 15
Multiple Tf based strategy for small molecule disconnection

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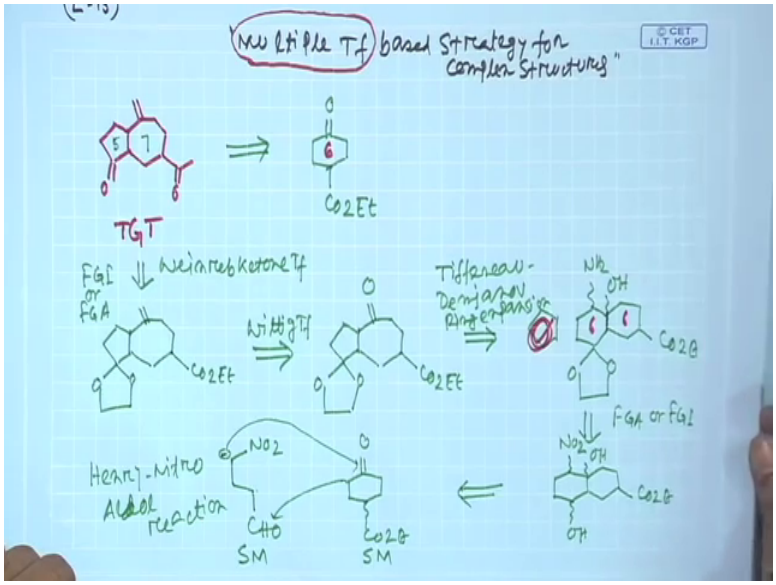

So welcome back everyone. So, we are basically discussing a multiple transformation based strategies and strategies related to functional group as well as starting material. We will try to continue our discussion on the same topic. And today we will have a little bit a different problems. And we will try to focus it on this particular theme multiple transformation based when couple of transformations will be used or to access a not a huge complex molecule a midsized complex structure. The initial target or initial problem, which I will be now drawing is based on a five member as well as seven member ring structure. Now, the structure of this target, if you switch structure, the structure is having diketone unit and one of these end is having a exocyclic methylene.

You see the structure, I have try to figure it out what are the functional groups available here the five member ring on the left hand side is a remembering one, two, three, four, five, six, seven. And then you are having two carbonyl of functional group as well as you are having a exocyclic methylene. So, this is our target molecule.

And for the sake of simplicity I will be also providing the starting material which you can take it and which is basically commercially available. Now, once I give the starting material, you are thinking will be little bit simplified because you know this is the starting material where from you have to make this target. So, you have options are basically kind of limited, you cannot have a random retro based on this. Now, as a starting material was given we will try to disconnect the molecule in its given form.

Now, see there are two carbonyl groups are there functional groups. So, it means that somewhere down the line you need to put it one of the carbonyl group based on the required transformation. In one case, you are having a ketone, which is part of the ring; in one case, you are having a ketone, which is basically kind of functional group the COCH three which is hanging. So, let us do the retro first and then we will try to analyze it. This ketone the ring ketone we are trying to put a protecting group. And then particularly this exocyclic methylene kept intact will be introduced in a latter part. We put ester group here to introduce the methyl ketone. And this chemistry we have already discussed you can do it by use of weinreb ketone synthesis.

So, this is this straight forwarded example of function of inter conversion or you can call it as a functional group addition because initially you are having a ester, your final target have a ketone fine. So, you keep on doing the retro and now we will try to introduce the exocyclic methylene group which we know that exocyclic methylene group can be installed through Wittig type of reaction. If we have a ketone like this and CO 2 E t ester groups normally would not interrupt in the Wittig reaction, so you are safe. So, we did a Wittig transformation here. So, initially is weinreb ketone transformation, a Wittig transformation.

I have tried to simplify the molecule the next step or next retro is crucial. Eventually, you see the target molecule having a five member and seven member and you are given a six member based starting material. So, you need some ring expansion or ring contraction kind of transformation because your initial starting with at a six member ring. So, based on this let us we will try to have a retro which will be for these particular things let us try to forget this and then we will put a retro which is very tricky, very tricky in the sense I will explain why it is very tricky. And I am sure this reactions or these kind of transformations globally all of you studied.

Now I say this five member and seven member ring, I will using transformation from this intermediate through way and this is a basically a six member ring and a six member ring. So, what basically you need to do, you need to do a such a transformation, where the left hand six member ring will undergoes ring contraction to give a five member ring and right hand six member ring will undergo ring expansion to give you the seven member ring. The functional groups, which was put here it is amino alcohol.

And if you try to remember a transformation which is basically named as Tiffeneau-Demjanov ring expansion. It is basically nothing it is a pinacole pinacolone type of reaction ring expansion reaction or you can call this Tiffeneau-Demjanov ring rearrangement. Now, how this reaction takes place, we are having amino alcohol, initially you put a nitrous acid HNO 2 that will make the diogenuim species and then it expels putting a positive charge here then one of this carbon basically migrates. Now, if this carbon, which I am now highlighting if it migrates the central carbon the right hand side ring is going to expand it, and the left hand side ring is going to be contracted. So, this is the main tricky transformation will be using here.

Now, next part is you have to now correlate that how this starting material can be correlated with this original given recursion. So, now, we put remaining all the fragments similar and here what we will put we put the alcohol to say that this alcohol will be oxidized to give the ketone and then this will be protected. Now, here you are having another alcohol, but there are differences, this is a secondary alcohol, this is a tertiary alcohol. And the amine group was thought to be prepare by reduction of a corresponding nitro group. So, this is a purely functional group addition or a functional group interconversion.

Now, let us try to correlate with the starting material. If the starting material will give you something now we say we have this starting material, which was given to you. Then if you have a compound like NO 2, we did to have 1, 2, 3, three carbon extra on this cyclohexanone site one two these things. Now, how this particular compound cyclohexanone based compound is basically having to alpha methylenec hydrogens, these are acidic. And now we were putting a nitro based aldehyde, one end having a nitro, and another end is having a aldehyde. Now, you can simply having a very important reaction named as Henry-Nitro aldol cascade transformation henry nitroaldol

reaction and this reaction basically we will give you the particular this bicyclic product, I will explain how.

If you see this nitro aldehyde, this is also one of the starting materials, which is commercially available or otherwise you can prepare in the lab. So, you basically need to functionalize here. Now, see this nitro is here and this aldehyde, which is also having this kind of alpha 1, 2, 3, 4. So, you can basically try to connect in this way and want to connect in this way that will basically give you the main thing. So, you just now try to follow the same analogy for the synthesis.

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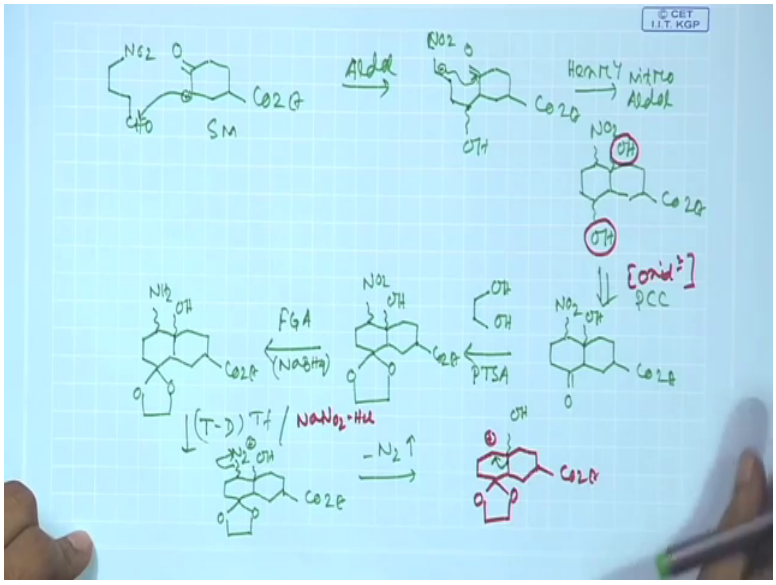

You pick the starting material which is basically your this starting material and then your reacting with this CH 2 CH 2 CH 2 CHO. So, the initial thing will be trying to have a simple aldol kind of reaction and that basically will be this would be generate in the carbonyl and that will attack this aldehyde first this is simple. CO 2 ET remains here we have this first aldol. Now, here you have this OH, which will be the OH, which we require at the later stage. So, 1, 2, 3, 4 they are having the nitro. Now, you see nitro compounds are basically electronic drawing group and so they can stabilize the carbonyl here. Now, the reaction is having basic medium we expect another carbonyl to be generated and that will the reacting in a intramolecular fashion to this carbonyl and then basically you would be getting the product which we earlier draw the structure. This is your bicyclic compound which we are expecting after this reaction is takes place.

Now this second reaction is namely named as henry nitroaldol reaction. Nitroaldol means a nitro species was taken as a precursor, to generate the carbonyl and that did not reacts with this electrophilic carbonyl group. So, this is your intermediate. And if you see the retro in the earlier slides, we have this intermediate which we said that this is the one of the intermediate in the synthetic pathway. So, this intermediate has been successfully generated.

Now see there are alcohols, this alcohol is a secondary alcohols this alcohol is tertiary alcohol. Now, you want to do the oxidation because next is this alcohol group will be oxidized. And in the final compound, it is the ketone. So, fine we will be just oxidizing this secondary alcohol by keeping the tertiary alcohol as intact. So, for oxidation you can basically use any known oxidizing reagent like PCC or other oxidizing agent let us say PCC pyridinium chlorochromate which is very known oxidizing reagent. Now, obviously now the ketone has been generated, we need to protect it. For the protection purpose you use the ethylene glycol to protect the ketone group and praetorian sulphonic acid which you already used earlier as a acids source.

So, try to write the structure as it is this ketone will be only now protected as it is as its ethylene glycol derivative cyclic ketone. The remaining part thus nitro will be same the OH will be remain same. Now, we will be doing a crucial Tiffeneau demjanow ring expansion for that the nitro group has to be reduced. So, we will be doing now a functional group addition. The nitro group can be reduced by a lithium aluminium hydride definitely, but lithium aluminium hydride we are not going to be use here. If you use lithium aluminium hydride that will also reduce the CO 2 ET because it is CO 2 ET.

So, the you need a predict mild reducing agent. Probably sodium borohydride might solves the purpose sodium borohydride will only reduce the nitro group and that will basically give you the nitro to corresponding amine compound the remaining part all remains same. So, nitro group is now reduced to amine. Now, your Tiffeneau-Demjanov reaction will be in action to set Tiffeneau-Demjanov cons formation. Now, what is the reaction condition the reaction condition will basically huge sodium nitrate and HCl, the (Refer Time: 15:34) condition. So, what exactly happens once this compound is subjected to sodium nitrate HCl will basically having this nitro this amine group will be converted to diaginium thing. So, it is there. Now, diaginium things we have a tendency to lose nitrogen as you guess. So, these things will now leap. Now, once the leaps we will

have a carbonium ion here we will basically having a carbonium ion here. Try to get the flavour of the mechanism, it basically having a carbonium ion here. You are having a oh here that adjacent OH. Now, this is a secondary carbonium ion and then the secondary carbonium on we will try to rearrange through this migration. This bond this sigma bond will have migrate to putting a more stable tertiary carbocation. We will explain in the next slide.

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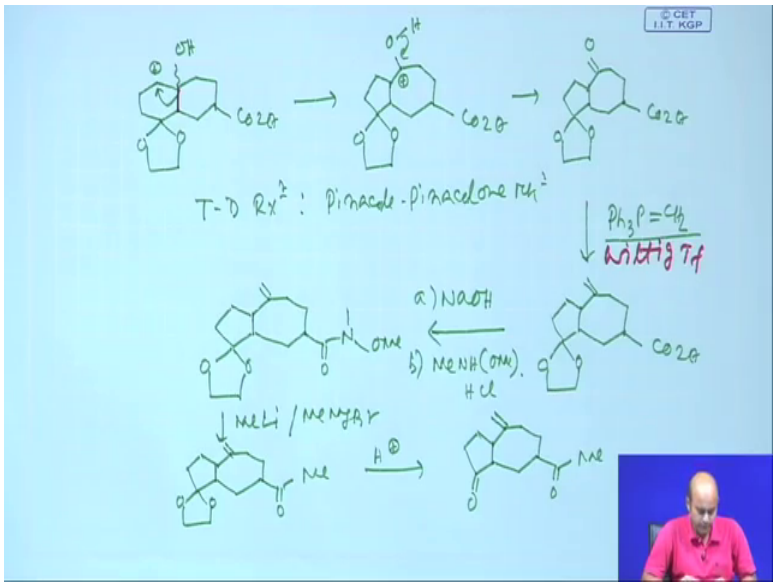

So, earlier slide we said we will having a carbocation, we will draw the carbocation again this is the carbocation and this is the OH. Now, this carbocation will be the rearranged carbocation or this particular sigma bond will basically migrate. And once this migrates, the left hand side ring will be now a five member ring. So, basically the contracted ring and then the right hand side ring is now the expanded. The carbon framework remains similar, now basically you will be having this carbonium ion.

And now this carbonium ion try to collapse to give you the five member and seven member ring as the main product in this reaction. This is basically nothing but a reaction where the ring expansion are one two migration takes place. So, Tiffeneau-Demjanov reaction basically is nothing it is like a pinacole-pinacoleone rearrangement pinacole-pinacoleone rearrangement, and it is just a pinacole-pinacoleone reaction. So, you known here well known here. And if you analyze the product structure we are very close. So, now, what would we have do, we just need to do a Wittig reaction Wittig reaction in

between one carbon Wittig ester does not hem path this Wittig reaction. So, ester you can keep as it is. So, this Wittig now takes place.

So, it is basically a Wittig transformation. So, we are doing it a Wittig transformation here. So, once this Wittig transformation was done, next you would try to analyze you only need to have a CO Me group in presence of this ester. So, what we do we basically do a basic hydrolysis to convert this ester to its corresponding carboxylic acid, step one. Step two you react to it (Refer Time: 19:32) of amine Me NH OMe is available as HCl solved and then you will basically converted it to corresponding amide which will be CO B Me OMe this chemistry we have already discussed. And now what you need to do you will need to have a methyl magnesium bromide or methyl lithium reacting with this weinreb amide, and then you get the corresponding methyl ketone you get the corresponding methyl ketone CO Me. And now you just remove this ketone functionality by simple H plus treatment and that will give your target molecule which was desired at the very beginning. So, as you can see throughout this synthetic pathway, we have used couple of interesting transformation.

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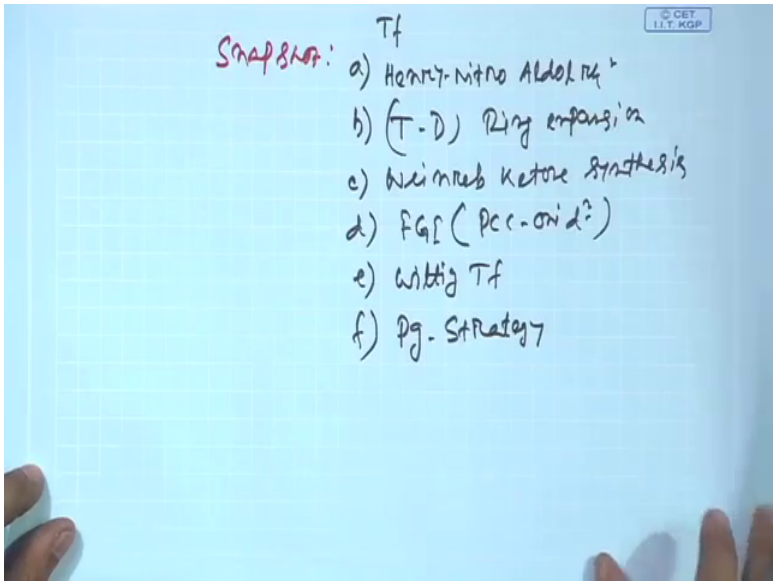

And if you do a snap shot or the summary you will find that this particular reaction or this particular pathway we used couple of interesting transformation. What are those you say that ketones formation at the very beginning is Henry nitroaldol reaction that was one of the very important reaction. We use Tiffeneau-Demjanov ring expansion reaction

that was very interesting reaction and you explained it in detail then at the end which is very known to all of us Weinreb ketone synthesis. And then also we use couple of functional group inter conversion like we do some PCC based oxidation. Also you used Wittig reaction Wittig transformation is very important. And then we also used protecting group based strategies PG strategy means we use some protecting group to protect the carbonyl compound one of the carbonyl compound which is not required or which is not touched during the synthetic values.

So, that basically gives you a very nice demonstration. And you can see the after this very powerful. After this very powerful means you have to execute the whole pathway by keeping the mind that the which transformation can lead to which kind of functional group. And as the starting material was given to you can basically correlate, if the starting material to the product, but definitely initial assumption is bit difficult. You have to disconnect the molecule step wise as we did in the very earlier slide, we have to discussed about the step wise. Once we have the step wise then you can correlate the target molecule and the starting material.

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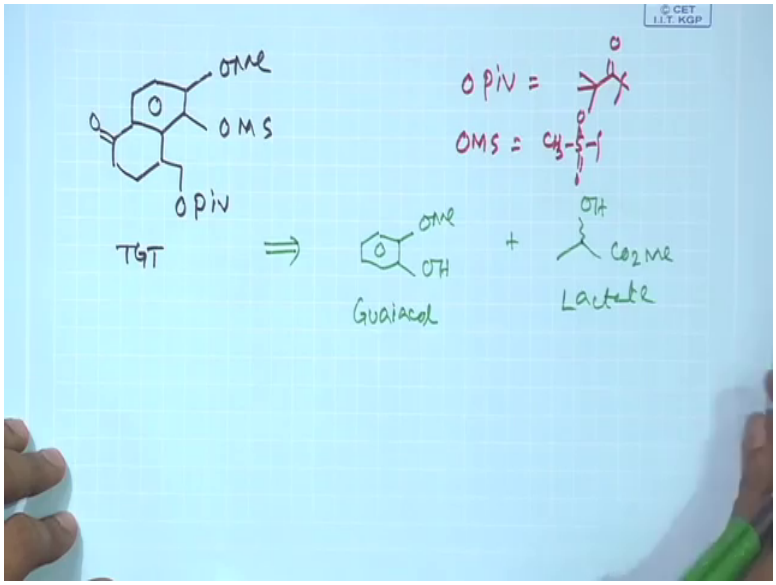

So, we will keep continuing our discussion based on the this kind of similar topic and probably we will touch another molecule which is bit complex. But eventually we can do it the molecule which are next going to draw it here that is basically having a structure a bicyclic structure having a bicyclic structure. And if you see the functional group will

explain what is this functional group this is one of the target molecule. Now, why I have chosen this target molecule this target molecule was basically chosen are to give a flavour of different transformation different functional group based interconversion. The transformation which you might aware of or which you might not the aware of.

So, those transformations which you are not sure we can discuss those transformations and the transformations which you know already. So, you can see that how this known transformation can be efficiently used to design a pathway where you can access the required target molecule. And this molecule if you see the target molecule couple of functions are goes probably it is non want to you to accept the you know pivoloil, pivoloil is the product the group actually pivoloil stands for this group. So, this is a alcohol productive group is a ester. So, O, CO this is tertiary butyl. OMS probably all of you know is a methane sulfonium group it was used as a alcohol producting group methane sulfonium ester. So, this is the target molecule.

And as I said definitely the starting material if you want the starting material I can give it to you it will a starting material the starting material was very simple starting material I will give you commercially available this compounds its name is guaiacol and a lactate derivative. So, this compound is O methoxy phenol guaiacol guaiacol and this is basically a lactate ester mythyle lactate. These two are the starting material which was given to you.

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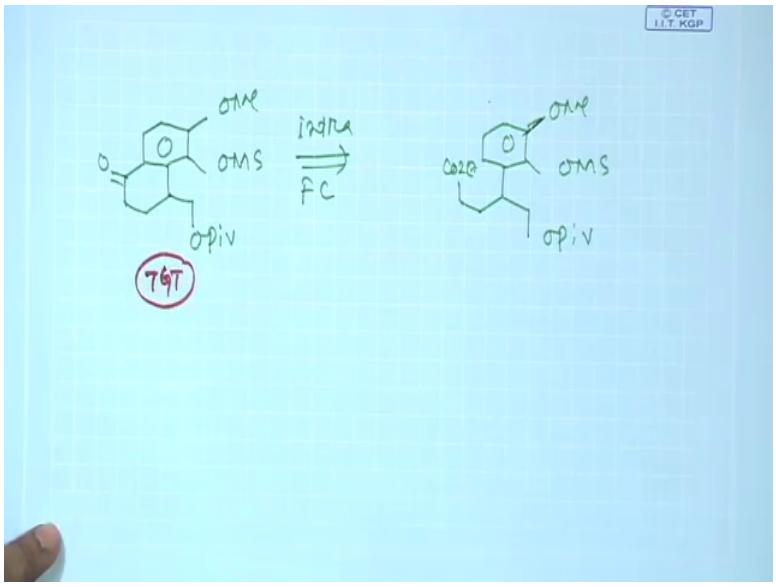

Now, if you try to do the retro, I try to do it the retro and eventually we will find that retro is pretty interesting but let us draw the retro. So, OME, OMS, opivloil is the target molecule the initial retro which was based on a intramolecular friedel crafts type of alkylation. And then we draw the intermediate which was required by keeping remaining structure similar. We say that if this is a carboxylic acid or ester, you can hydrolyze it and you can do an intramolecular friedel crafts reaction; now why, because you have a paramythoxy group. So, paramythoxy group I mean mythoxy is orthogon paradaidicting and as one vision is blocked probably the para position is much more facile and you can have an intramolecular friedel crafts reaction.

As the time is not sufficient probably we can discuss this particular problem in the next lecture. And please stay tuned with us, we will be back in next lecture.

Thank you.