A Study Guide in Organic Retrosynthesis: Problem Solving Approach

Prof. Samik Nanda
Department of Chemistry
Indian Institute of Technology, Kharagpur

Lecture – 37
Fg based Strategies

Welcome back students so, basically we were discussing a several strategies which includes a combination of starting material functional group as well as transformation in a combinative way.

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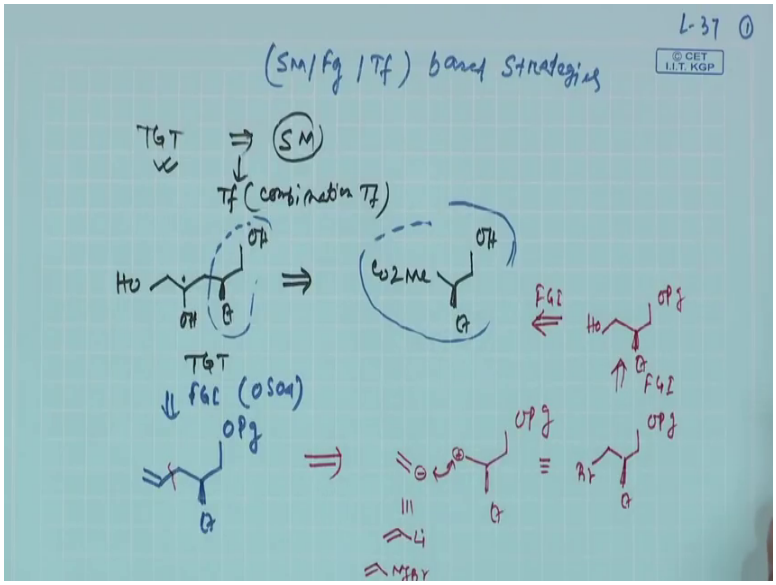

I said that if a target is given to you and the starting material also given to you, then you try to correlate the starting material structure with the given target and in between you need to take the help of several transformation based approaches. That what are the transformations you can think of you can design or you can you can basically visualize that this transformation will lead you from this starting material to this target.

Now, if your target is little bit complexed, then probably you need combination of transformation, a single transformation might not be sufficient combination of transformation is required. In addition you can also think of that what are the functional group where is in the target molecule and what are the functional group where is in the starting material. So, that functional group based analysis also will help you to disconnect a through a functional group based approaches and definitely the

transformation will be your key that this transformation will give this functional group and convert this functional group to other functional group which we were looking for so, we will try to continue our discussion on the initial problem.

This particular problem which the target molecule was given to you something like this and we said that this particular stereo center of ethyl, we have fixed it that this stereo centre is required. Now, this molecule does have a stereo center here and we are not concerned about that now basically why you are asking because this kind of transformation of this kind of chemistry we have already discussed in our lecture note. The starting material which was given to you having a structure is this structure, now see this target molecule having a stereo chemically pure ethyl appendages at this carbon as well having a hydroxyl methyl group here.

The starting material also having the same structure so, you can think of this starting material this part is basically similar this part is basically similar all the thing is you need to extend on its left end side left end side only basically you need to extend it.

Now, eventually the whole strategy will find that the initial starting material you are having a primary hydroxyl group. So, we will let us now do the disconnection now this left hand side you are having a Diol basically vicinal Diol so, vicinal Diol probably you can think off by preparing or disconnecting through a this kind of thing. Now I say that if you have this vicinal Diol which you can just convert through a FGI which is basically Osmium tetroxide mediated Dehydroxylation which is very well known and now why we put a protecting group, here the initial starting material having a hydroxyl group. So, as we will be experiencing multi state synthesis, which always better advisable the starting material hydroxyl group you first protect it I say you put a Pg here.

Now, we will again disconnect the molecule and now we will be doing a disconnection here and this disconnection basically you will give you a intermediate something like this. We say if you having a vinyl simple vinyl anion which in principle can be create it by vinyl lithium or vinyl magnesium bromide, which is a source of vinyl anion and then if you having any adjacent Carbocation kind of thing by simple substitution reaction you can correlate or you can connect this carbon carbon bond.

Now, this particular fragment will be visualizing in these way if you having a compound like CH2Br or CH2I, which you can visualize as CH2 plus remaining part are all are

similar. Now, try to correlate this how this Bromo you can convert, this Bromo you can easily prepare trough corresponding alcohol ok.

Now, see the starting material was given a ester methyl ester so, methyl ester can be converted through a reductive cleavage or its simple FGI to corresponding H o. The starting material is basically here now as I said initially we need to protect the Trihydroxy group.

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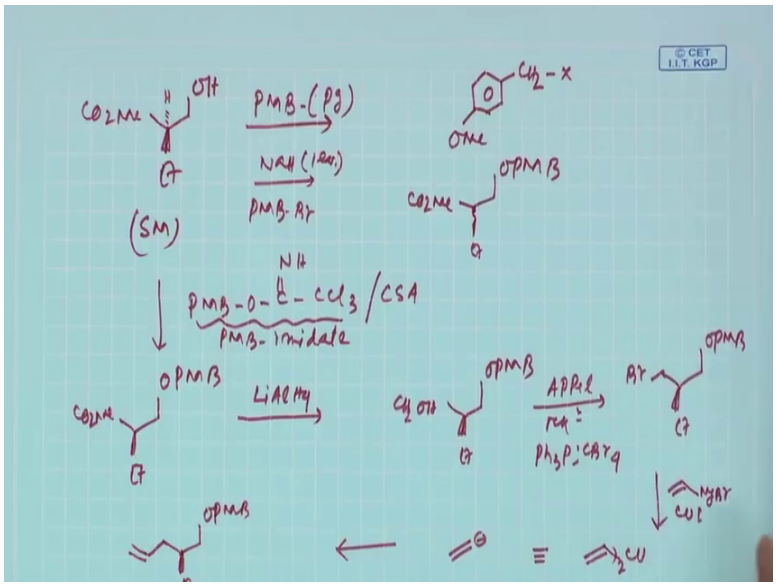

So, your starting material is this and you were having this hydroxyl methyl compound now you do a close analysis. I say will be trying to use a paramethoxy benzyl protection it definitely can do other protection this absolutely with no issues, but paramethoxy benzyl protection means basically you need to what is paramethoxy benzyl we have already explained earlier is basically paramethoxy benzyl group. Now, here if you analyze this compound in the stereo center having a hydrogen which seems to be acidic due to electro withdrawing effect of this CO 2 Me group.

So, normal if you try to protect by a standard base immediate reaction with one equivalent of sodium hydrate and PMB bromide, you will be definitely getting the getting the protected compound, but as I said as this hydrogen is acidic there is a enough possibility if you treat sodium hydrate then this hydrogen might undergo Ephemeralization because this centre is extremely acidic. So, stereo chemical purity of the final product you are not absolutely sure that it might undergo Ephemeralization.

Now, in this case we have already talked about you can use PMB imidate, the PMB imidate we have explained how we can prepare and basically you need a mild acidic condition. So, first is your PMB imidate who which will basically protect the primary hydroxyl group as it is and this PMB imidate. The chemistry of PMB imidate we have already explained to you in earlier lecture so, please try to refer that lecture.

Now, your remaining steps are absolutely similar you can reduce this aster to corresponding primary hydroxyl group something like this and then we have to convert this hydroxyl to the Bromo to generate the electrophile. The best way you can do is by apple reaction which was also thought to you the reagent is triphenylphosphine and CBr 4. So, then by this way you will end up with this compound and this compound is our one of the intermediate and then we say if you try to use a Vinylmagnesium bromide with little bit of Copper iodide, initially you will basically get a vinyl copper reagent.

Now, this vinyl copper reagent basically solved as a this minus it is basically minus copper plus and now you try to react with this vinyl anion with this electrophile. A normal ascend to fashion then basically what you will get your ethyl part will remain same here you have this OPMB, then you have a CH 2 here then you put this vinyl see you are almost close.

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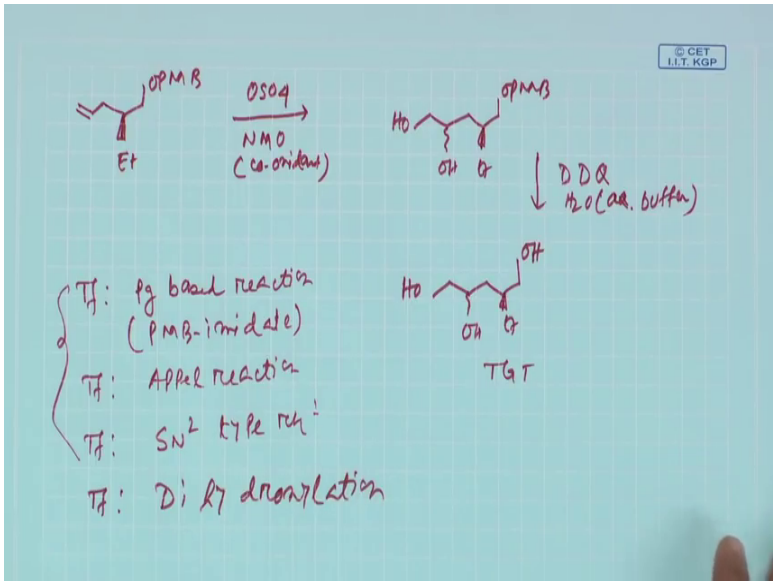

Now, if you write the intermediate which we have obtained in the earlier slide and then you find that you basically after this sn 2 reaction we obtained here. Now, here we

basically you need a diode oxidation per Osmium tetroxide is the preferred reagent you can use NMO as a co oxidant and this is very standard straight forward reaction and then now this will be basically giving you this vicinal Diol OPMB and the final target if you see the PMB group has been re producted.

So, PMB reproduction you can straight way use DDQ in a water medium or a aqua's buffer and then at PMB group will be deproducted, as discussed earlier by DDQ condition and you will get the final target molecule. So, what are the reaction we basically used here if you try to correlate you basically first do a protecting group based strategy protecting group based reaction and they are we used a PMB imidate to take care of the stereo centre take care of the stereo centre.

Then we use a apple reaction to generate the corresponding bromide from the alcohol and then also we are using a SN 2 type reaction SN 2 type reaction. So, this all this reactions have been combined together and eventually you can you can classify this particular retro synthetic pathway in the combination of all the three basically we are using functional group based chemistry.

So, this alcohol to bromide you know that this functional group transformation can be easily done with the help of apple reaction and this finally, also we used a Dihydroxylation reaction Dihydroxylation reaction through a Osmium tetroxide imidate at Dihydroxylation. So, those are the fine final aspects you need to always think about.

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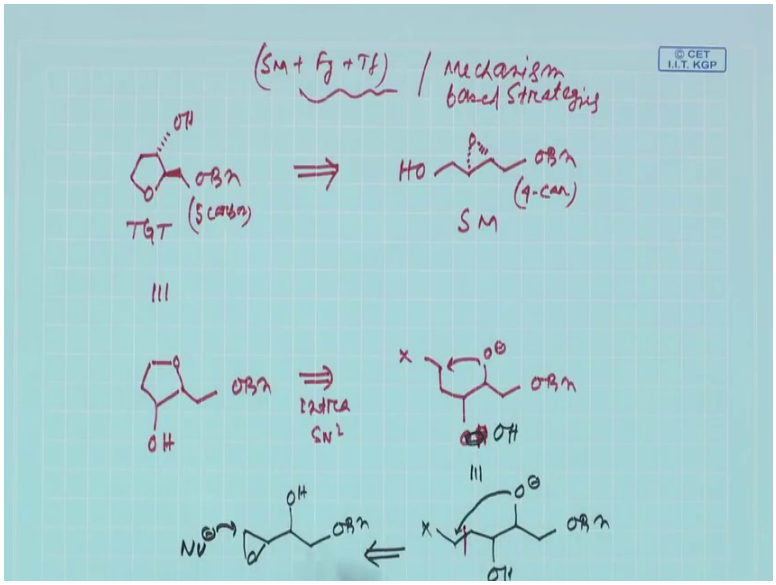

Now, in this starting material functional group class transformation based strategies sometimes we can talk about a another strategy which is basically similar its say that mechanism based strategies. Now, mechanism based strategies are basically extension of this transformation based strategies means if you are quite sure about what a particular mechanism of a key transformation or name reaction you can design, that if this mechanism operates through this way. Then this functional group might lead you to that target molecule will now explore this particular mechanism based strategies through a simple example, the example here which was given to you is this particular compound.

Now, eventually the stereo chemistry you can keep it or you can remove it if you want a simplified version. Now, I kept it because I said lets draw the stereo chemistry and then see how it can be the target molecule is this one, the starting material is this one BN stands for benzyl. Now, try to count the carbon atom 1, 2, 3, 4 the 4 is the basic skeleton in this tetrahydrofuran carbon there also 1, 2, 3, 4. So, no need to add any extra carbon as it is evident from the particular structure.

But here if you see the side seen of this tetrahydrofuran you have a one carbon extra CH 2 OBn so, this is basically 5 carbon and this part is 1, 2, 3, 4. So, the tetrahydrofuran though it is a 4 carbon its having a benzyl append h CH 2 OBn. So, these CH 2 initially we did not count so, basically we need to add one carbon extra. Now, I will just put the target molecule and I will see how this target can be made, now I write this target molecule little bit different way to have a, now for this part I say the stereo chemistry I just omit it. I said it will be written in this way this absolutely same compound same compound next to explain that how this mechanism is basically operating.

Now, I say if you can think of some intermediate something like this and here you are having a living group at this one of this end so, this can undergo a intramolecular SN 2 type reaction I said intra SN 2 to give you the 5 member ring. This is basically speculation and this O minus you can just keep it as a OH because that will give you a more convenient way more convenient way you can just put it as a OH fine.

Now, this we will just now rearrange the entire compound in a linear form, you just try to rearrange the compound in a linear form. I said x should be a living group in addition x can also give you a extra carbon, now you count 1, 2, 3, 4, 5 this is your OH so, this displacement we are basically talking about this basically talking about this

displacement. Now, try to correlate how this compound can be coming from this compound, now I say if you have a intramediete something like this you sit it is a OH. Now, I say if somehow you can try to open it up or you can just you can just open it up this epoxide by some nucleophile in this end the nucleophile must give you the extra carbon.

So, here basically opening up the epoxide here that this carbon as well as this x will be coming from the nucleophile, now see it is a get gave give you a CH 2 this CH 2 it will give you OH and these OH in the source of the O minus O minus and now this starting material this is the starting material which you can which go to the next slide.

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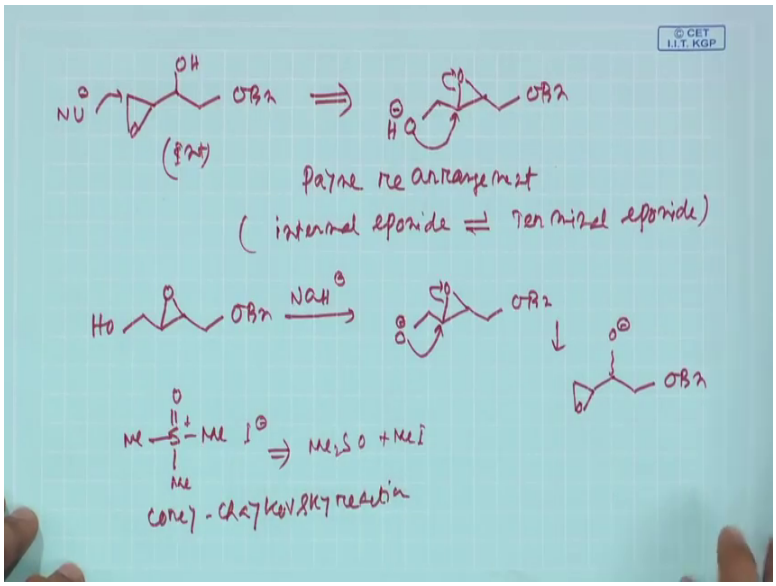

And then you see how this starting material of this intramediate which you are proposing, we said if you have a nucleophile which can basically give you that one carbon extra as was a living group you can get this intramediete this intramediete and this intramediete will undergo nucleophilic reopening and then intramolecular displacement. Now, do the analysis with the starting material that how this could be linked with the starting material.

The starting material is basically this OH this epoxy and initially we say if somehow you can protonate this epoxide hydrogen to give you a alkoxide. Now, this alkoxide serves as a very good nuclophile, if somehow this nucleophile attacks here to open the epoxide

you basically get this compound. So, this is basically a rearrangement of internal epoxide to a terminal epoxide.

Now, this particular reaction is named as Payne rearrangement so, a internal epoxide is basically rearranged to a terminal epoxide, that is the a main transformation in the Payne reaction. Now, we try to figure it out the problem which was given to you, stereo chemistry I did not mention so, first we take a equivalent of sodium hydrate, sodium hydrate as usually used as a base initially that basically will give you this alkoxide. As I said this undergoes intramolecular SN 2, open up the epoxide in this particular fashion. So, basically you will get you now a terminal epoxide and this terminal epoxide your O minus is here and CH 2 OBn is here.

Now, this terminal epoxide if you can treat some of the external nuclophile which can also give you a extra carbon. A this particular nuclophile which will be now talking about we have used this kind of nuclophile in the Corey Chaykovsky reaction if you remember.

Yes, Trimethylsulfoxonium actually is S plus and I minus basically it has been generated from Dimethyl sulfoxide or you refluxed with methyl iodide you will get this compound and this kind of similar compound we use trimethylsulfonium iodide in Corey Chaykovsky reaction. Now, I say this particular compound this particular compound we will be using as a internal nucleophile.

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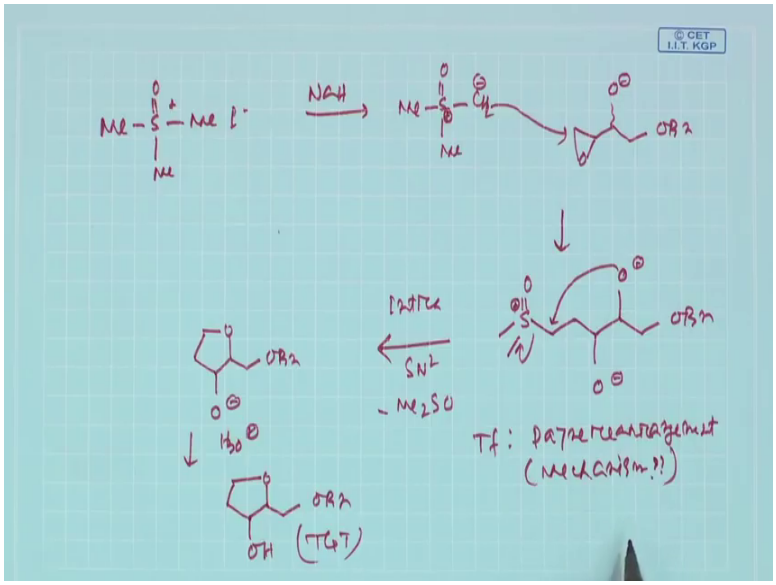

Now, this compound the structure is basically like this and this compound also if you subject it to a sodium hydrate this will immediately instantly give you the corresponding anion CH 2 minus. Now, this CH 2 minus will now attack to the terminal epoxide which have been generated after the Payne rearrangement. So, this epoxide will this nucleophile now will attack this statically less in their sight and now what will get we basically get this open, now one CH 2 will be now added to the CH 2, CH 2. This CH 2, this CH 2 your oxygen will now minus you can put this oxygen also minus it can be also cohinsed.

Now, what I say I say that if you now attack this things this O minus at this carbon that Dimethyl sulfoxide, will be now living as a living group now, Dimethyl sulphur containing compound have being a good living abstitute.

So, now a intra SN 2 will take part and that will basically leave your Dimethyl sulfoxide as it is and then basically you will get the you will get the 5 member compound which you are discussing in the initial your OBn will remain here because you are making this carbon carbon bond and your O minus is remaining here. We simply do a acidic work of and we end up with the target molecule.

Now, the original problem where from it was taken they basically give you a nice stereo chemical demonstration of the entire problem or simplicity have emitted the stereo chemistry part, but if you see the transformation which you have used it at a very beginning is a very nice reaction named as Payne rearrangement. Now, Payne rearrangement if you do not know the mechanism of Payne rearrangement probably this retro is there difficult to visualize. So, initial part as I said is a mechanism based strategies and if your sured about the mechanism of Payne rearrangement that by this kind of based mediated transformation a internal epoxide is converted to a terminal epoxide that gives you the main flavor.

And then finally, you need a nucleophile you need a nucleophile which will give you a one carbon as well as this the nucleophile having a living group. So, this criteria as been fulfilled by these trimethylsulfoxonium iodide this is acting as a good nucleophile, you can basically create the nucleophile the carbon and species by tending by base and then you react with this epoxide which have been generated after the Payne rearrangement.

So, this kind of transformation often give you a very nice clue or why very nice idea and as I said this is purely transformation based approaches, but in addition you can also the

as the starting material was given to you so, you can you can classify it in a starting material based approaches also.

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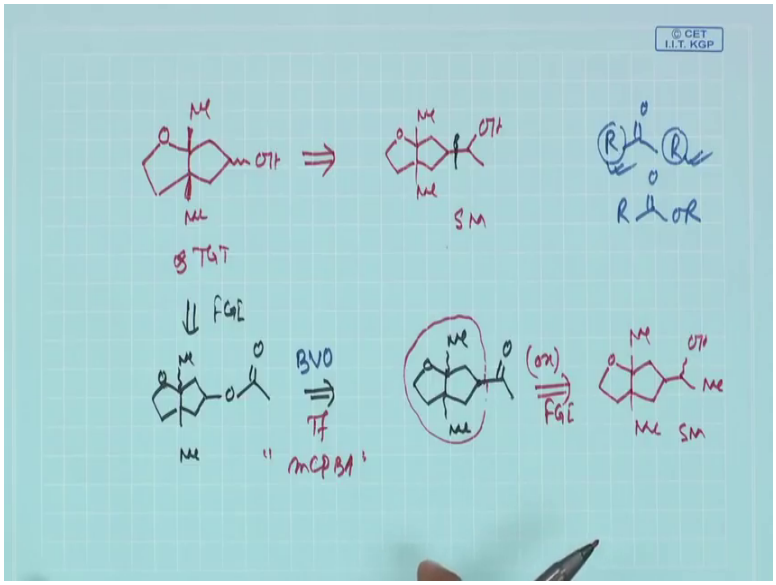

The next one will be time to have a similar kind of example it is basically a bicyclic compound the left hand compound is a tetrahydrofuran fused with a cyclopendant we have two angular methyl. Anyway the angular methyl stereo chemistry was given, but probably we would not talk about the stereo chemistry thing here the starting material was given. So, I have provided you the starting material I have provided you the starting material sorry this is the target and this is the starting material. Now, if you do a skeletal disconnection we will find that only thing is you need to remove something here and you need to introduce a oxygen with this carbon.

So, this part will be basically has to be vanished now what I do here I will follow a very classical retro based on very important reaction while all of you know this important reaction, but I will try to figure it out I will say that this alcohol will be bringing from a acetate by simple acetate hydrolysis which is a very classical FGI.

Now, I say that this alcohol or this sorry this acetate will be created through this reaction, now once I write this things that a ketone can be converted to a acetate the transformation which is initially come to your mind is a Baeyer Villiger oxidation. Now, Baeyer Villiger oxidation, we say if we having a ketone you can basically get a corresponding ester, now if your unsymmetrical ketone depending on which alkali group

having most tendency to migrate the most more migrating tendency is basically depending on its structure tertiary or more substituted alkali group will migrate to the towards the electro deficient oxygen.

So, this migrating tendency you should be familiar with that, now here this is basically ketone is having a this group and having a methyl group. Now, if you now think that this is the highly substituted group and methyl is a simple group so, definitely this group will migrate towards the oxygen that is what this carbon oxygen bond connection was there. Now, how you can convert this to this or correlate in the starting material by a simple oxidation so, now we are not doing the forward pathway.

I said this is a basically a oxidation based FGI starting material you do a oxidation based FGI you come here. Now, stop it here you do you will think about doing a Baeyer Villiger oxidation transformation and this transformation the your mechanism says that the more substituted alkali group the this group will basically migrate towards the electro deficient oxidant agent

In Baeyer Villiger reaction the reagent we used mCPBA the mechanism I am sure all of you know it. So, please if you are not sure about the mechanism again check the mechanism in from your standard text book and then you find that this group will basically migrate this group has more migrating aptitude then the methyl, now once it migrate we have this carbon oxygen bond your next is simple hydrolysis.

So, this kind of combination I have simple transformation in which you know the mechanism that we will basically give you a very clear cut idea that which pathway to choose and which pathway not to choose. So, probably we will keep on continuing the discussion on similar kind of problems where functional groups starting material and transformation all are combine together and has as of recently we have starting about some mechanism based strategies. Then basically that will also give you a flavor that how mechanism based strategies of a key transformation, will help you to design a certain retro synthetic pathway and root to a small molecular target will see you in the next lecture till then good bye.