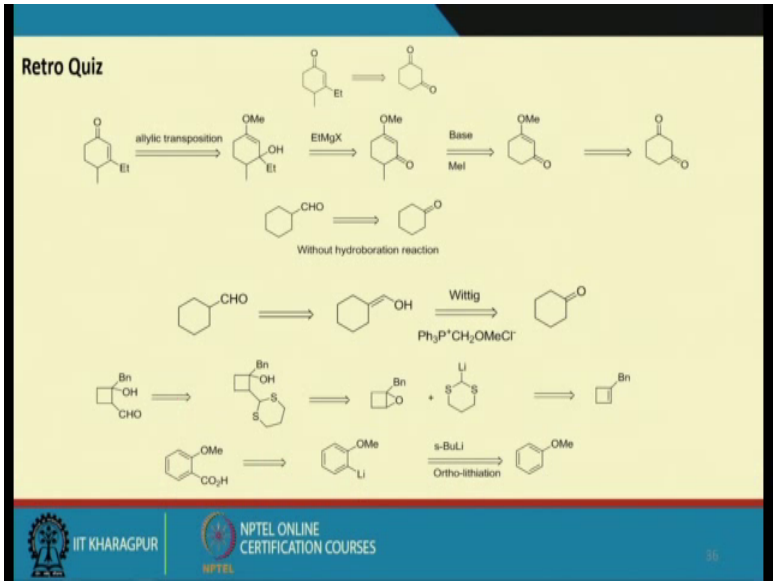
A Study Guide in Organic Retrosynthesis: Problem Solving Approach

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

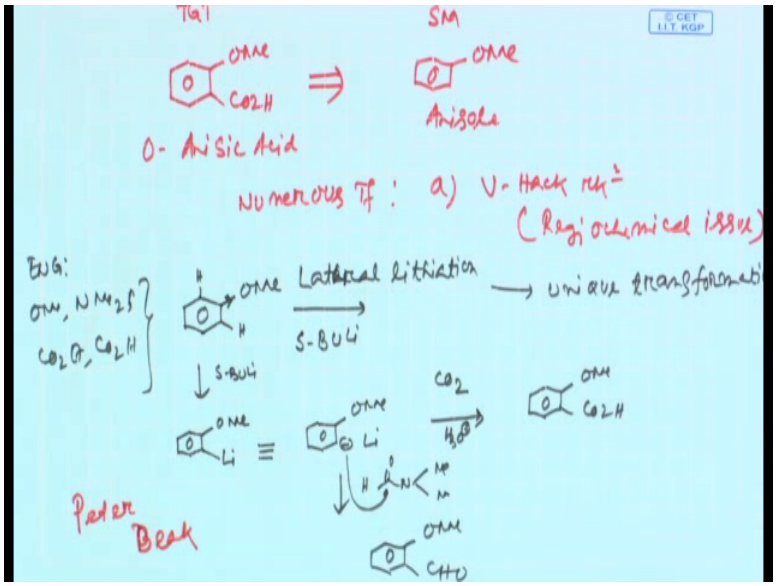
Lecture – 04
Retro Quiz based on Simple Transformation

(Refer Slide Time: 00:24)



[FL]. So, welcome back. So, if you just go through the end of the last weeks topic, we have discussed a. couple of retro quiz are a different kind of question answers based on very preliminary retrosynthesis disconnection, I hope that you are have gone through it and probably you will be able to solve it. So, in continuation with the earlier one let us talk about something a similar kind of problem which will basically give you a flavor that what kind of problems we will be dealing throughout this entire coursework.

(Refer Slide Time: 00:56)



So, the next one as you see we have chosen a particular compound which is very simple it is a anisic acid or ortho anisic acid means to methoxy benzyl benzoic acid. Now, this compound was given you as a target and the starting material I have given. So, starting material is basically what I am looking for is anisole ortho methoxy benzyl. Now, so this is your target molecule in the left hand side and this is your starting material or the precursor. In principal you can do it by numerous transformations. And I am just trying to figure it out what are the transformations you can think about, probably all of you know it the very popular Vilsmeier-Haack reaction. So, what this will give this Vilsmeier-Haack reaction will be giving a aldehyde functionality at the ortho as well as para position. So, we have a regiochemical issue and that is a bit serious concern because we are only dealing with a single product. So, regio chemistry we are not going to talk.

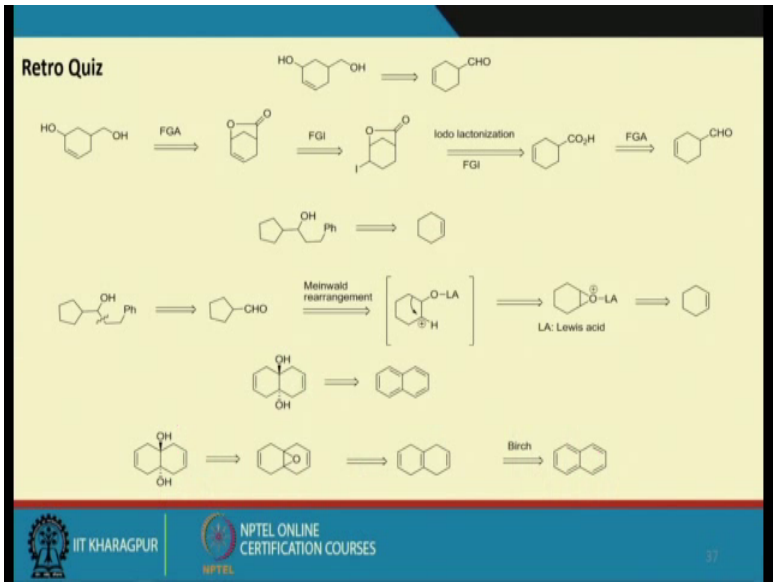
So, probably you can think about something very interesting transformation which I am not sure whether you are aware of that, but we will be talking about some reaction which is named as lateral lithiation. Now, what is that I said when you are having a an anisole as a compound and you subject this an anisole with a base. Now, normally we use base something like secondary butyl lithium or sec butyl lithium and ome group is basically electron withdrawing group and that is why the ortho hydrogens seems to be a little bit acidic on their attached to a vinylic or aril system.

And eventually if we subject this compound is sec butyl lithium or tertiary butyl lithium we expect that one of these ortho hydrogen will be removed and you get a lithirate spaces and that is called lateral lithiation or ortho lithiation. Now, the main point is ortho group is in close proximity with the ome oxy group that is why the hydrogen ortho to the ome oxy group has much work kinetic acidity and that is why it has been picked up. And now this compound is basically nothing you can simply write it this compound as a this minus and lithium plus. Now, depending on the target, which was given to you, you can basically now quench it with different electrophile.

For this case in our parent case we will be trading this compound with carbon dioxide as a electrophile and we will find that after usual acidic workup you will be getting anisic acid as a main product. On the contrary you can do a different kind of electrophilic trapping let us say for instances if you use dimethylformamide as a electrophile, this case is this minus, we will come here, attack these things and finally, you will get a aldehyde as a main product ortho methoxy and its aldehyde.

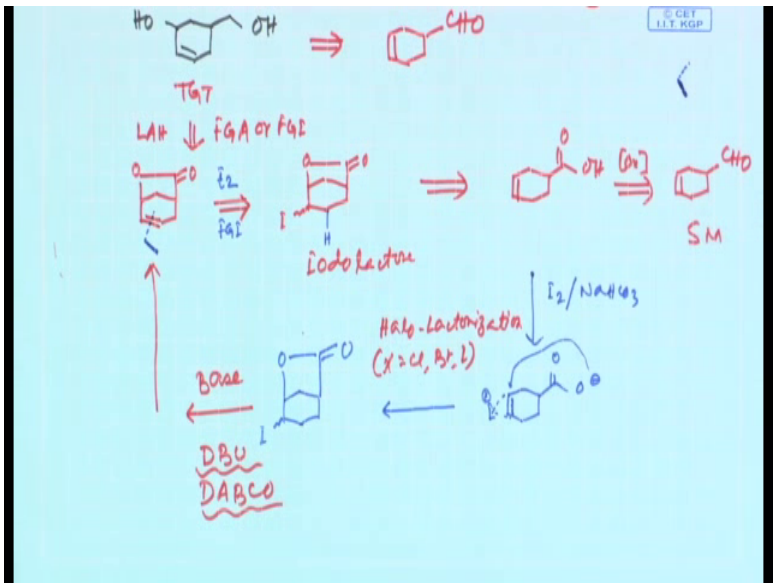
Now, this particular lateral lithiation is very unique transformation is a very unique transformation. And it will basically help you to functionalize aromatic nucleus when a electron withdrawing group groups like electron withdrawing group I say mainly o methoxy, n nme 2 or Nr 3 those kind of groups CO 2 et, CO 2 H those are essentially required to activate the aromatic nucleus and then you can do a lateral lithiation. This chemistry was first pioneered or explored by Prof. Peter Beak that is why it is called beak lithiation, peter beak is called beak lithiation and that is the very interesting transformation. So, we have just using the same thing through a retro arrow in the overall power point slide and we will find that this is our main target molecule.

(Refer Slide Time: 05:38)



So, coming to the next quiz or similar kind of quiz, we will next talk about a little bit of a different molecule as molecule which I am now next going to be write it down.

(Refer Slide Time: 05:49)



Let us say you need the structure here is a basically a cyclohexane based compound. And if you see a close structural view in this compound you will find there are two functional groups attached. It is basically a secondary hydroxy as well as you have a primary hydroxy, so both the groups are there. And the target molecule which was given to you is

a this one and the starting precursor or the starting material was a cyclohexane based carboxaldehyde.

Now, definitely the starting material was chosen very judiciously. So, you need to know certain transformation to carry out this kind of functional group interconversion. So, now, go back to the retro. So, draw a retro arrow like this. And then you can basically find it out the first step will be a functional group addition. And if you have access of this kind of compound which is basically nothing a cyclic ester then you can just do a reductive cleavage with lithium aluminum hydride kind of reagent that will basically lead you diol, this is a functional group addition reaction or you can say is a functional group interconversion.

So, these names are basically just to give you a flavor is in principle FGA, FGI its kind of similar fine. So, once you have this anhydride which you can cleave it. Now, next question is how to access this anhydride fine the next retro see it very carefully. We have put a halides group or a specifically aldo group to introduce or to bring the olefinic unsaturation in the given target molecule, the given target molecule is a having a olefinic unsaturation. So, what we trying to do the retro sometimes this kind of disconnection was used, which bond you want to disconnect you put a dotted line and based on that you put a bold line, this is called the retrosynthetic pathway to design that which bond to disconnect. So, this way this bond will be making a this pi bond. And how you can make this pi bond if you have a aido and you have a hydrogen here, you will basically doing a simple e two elimination by a FGI or even FGA fine.

Now, the next question we will be asking that why and where from you have to make this iodolactone, this compound is nothing is a iodolactone. So, this iodolactone essentially can be made by a very simple transformation which we will be now talking about is called iodolactone ionization. And now you can just try to correlate the starting material is almost similar you just now need a functional group interconversion. So, this is your starting material, you basically do a oxy transformation here to convert it to carboxylic acid.

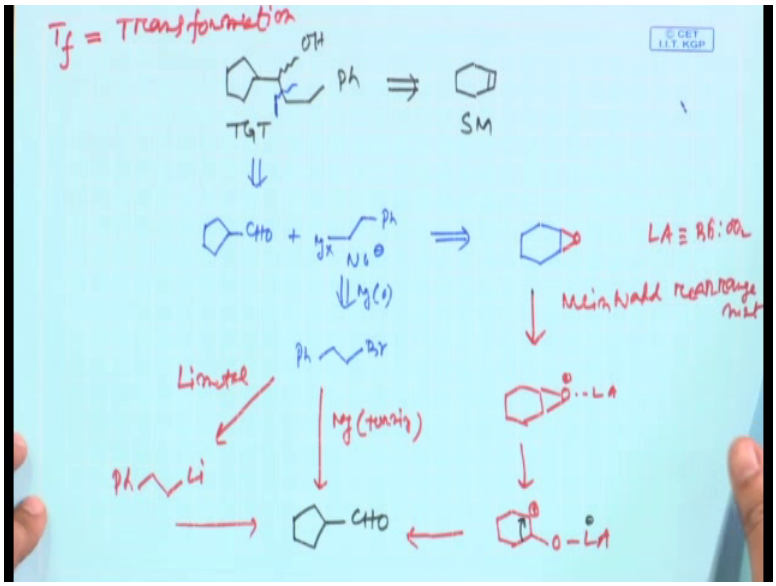
Now, here once this carboxylic acid you are having, now we would we will be doing the forward path. When you are having this corresponding carboxylic acid you keep it you put a or you subject it this carboxylic acid with iodine and sodium bicarbonate. Now,

what happen you are using sodium bicarbonate that basically will make a carboxylate salt or C double bond O O minus. And as this iodine is there you are trying to have a iodine man. So, this bond will be loose cyclic iodine ion. Now, this iodine man as I as you all know it will be internally attacked by a nucleophile and here O minus is basically iodoke to this carbon and then you will be getting this O C double bond O and iodine here.

So, in principle this is the main reaction which is which dictates that the synthetic pathway is very much viable and this kind of reactions are often regarded as a halo-lactonization, halo means any halogen species, you can use as a electrophile halo-lactonization. So, if you use x equal to chloro equal chlorolactonization. If you use x regard to bromo, it is called bromolactonization. If you use iodo, you can use you can call this a iodolactonization normally we prefer iodo because as we know that next step is a elimination reaction and hydro compounds are good living group. So, they can follow the subsequent pathway.

So, your next path is absolutely fine now you can do a simple elimination by standard base. The base basically you can use any non nucleophilic bases the preferred base are DBU or dabco which are basically sterically bulky non nucleophilic base. I mean just telling you the name dbu and dabco try to get their correct structure from any sources dbu stands for di as a diazabicyclo undec dabco is diazabicyclo octane. They are having a bicyclic nitrogen framework which are basically sterically bulky and non nucleophilic bases. And once you have this that basically give you this initial intermediate and then you and do a LH mediated reductive cleavage that will basically give you the target diol. So, these kind of synthetic pathway is very efficient very eventually the starting material this cyclohexane carboxylate is cheap. The other thing is if you know the iodo-lactonization method, I am sure you will be able to do it and that basically gives you the entire pathway.

(Refer Slide Time: 12:16)



So, coming to the another quiz based on similar thing. Now, first follow the slide what kind of structure was there for the target molecule. The target molecule basically having a cyclopentane structure as a core framework, and now we will try to explain certain terminologies which have already explained earlier. Now, see I said that this molecule is a cyclopentane framework having this long appendage. Now, appendage means basically hanging group now this appendage also contains a functional group it is having a secondary alcohol functionality and its having a CH 2 CH 2 ph as a alkyl chain.

The starting material which was given, it is pretty interesting a cyclohexane which was given to you as a starting material. So, now, you need to think that what kind of reaction you will be doing so that parent cyclohexane ring will undergo a ring contraction to give a one member less cyclopentane. Now, that things we need to find it out I do not know whether you will be familiar with couple of I mean it some interesting name reactions, but nevertheless we will do the retro we will do the retro first. For the standard pathway of retro, what we did we basically did a this kind of retro we and say that if you are having this aldehyde simple cyclopentane carboxaldehyde with this beginner.

This beginner we said M g x and Ph. So, Ph CH 2 CH 2 M g x, so it is basically grignard acting as a nucleophile to a electrophilic aldehyde that is very simple. Now, for the next step next step which was bit crucial bit crucial it is absolutely crucial this big naught is you can easily prepared from corresponding bromo compound. You take the

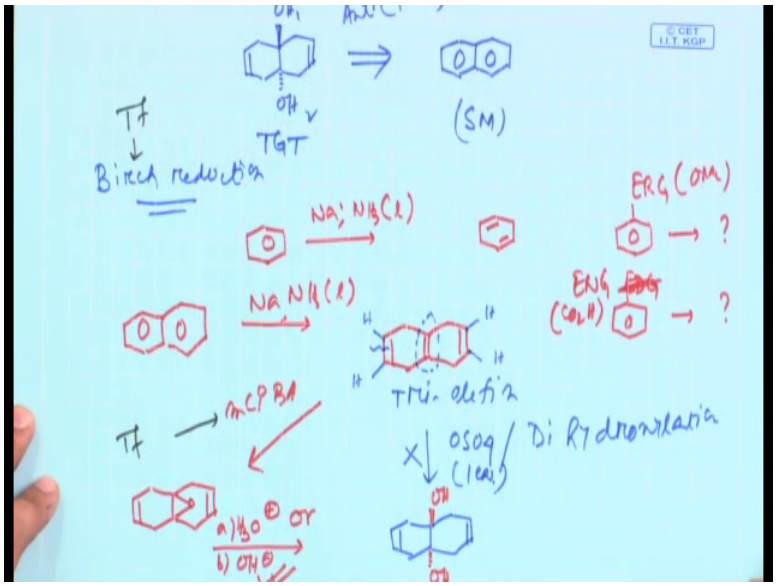
corresponding bromide heat with simple magnesium zero magnesium metal. Now, this particular compound cyclopentane carboxaldehyde in principle or in reality it can be accessed through a cyclohexane based epoxide through a rearrangement it is named as semi pinacol pinacolone rearrangement or a Meinwald type of rearrangement. It is a Meinwald it is a name reaction and this is the key transformation we are looking for.

Now, what exactly it is when you have cyclohexane epoxide, you treat with a lewis acid, lewis acid mainly you can take any lewis acid the preferred lewis acid we will take bf three thread. So, sake of simplicity we will just put it as a lewis acid. Now, lewis acid we will try to coordinate with this these things. And then you will find that once it is coordinates this carbon oxygen bonds are loosened up or loosened up once this carbon oxygen bonds are loosened up or kind of hazyl this is symmetrical epoxide. So, it will try to open off and will give you a carbonium ion here.

And once this carbonium ion is generated it basically undergoes a simple 1, 2-migration and that basically is the main factor to give you the corresponding once this basically migrates you have a ring contracted product here. And then lewis acid basically lewis acid will come back and give you the corresponding parent aldehyde. Now, once this parent aldehyde has been done, you do the corresponding reaction with magnesium turning that will be given you the corresponding grignard. Even we can do a other reaction, you just do a metallic lithium exchange lithium metal, which will basically give you corresponding lithiated species, which is also a good nucleophile and then it can react to this corresponding aldehyde it will give the product.

So, here this kind of this can a retro essentially you can fit it out in this category is a transformation based retro transformation, the main transformations we have talked here is a Meinwald rearrangement. So, Meinwald rearrangement is a synthetically very useful reaction when you have a epoxide ad you treat with lewis acid, now here we have taken a symmetrical epoxide. There are examples, so I can take unsymmetrical epoxide and based on the initial carbocation forming and the rearrangement also will be taking place. And the rearrangement basically depends on the most viablle carbocation which will be generated in the final reaction product that will be the major outcome of the main reaction. Now, synthetically it is very useful and I have used a very simple Meinwald rearrangement kind of a reaction, which will give your main target as we discussed here.

(Refer Slide Time: 17:37)



So, things we will just try to continue this similar kind of problem, but little bit difficult in the sense. And now we have chosen a molecule which is having a bicyclic framework and say its structure it is a interesting structural features if you look about it pena structure, it is kind of a symmetrical. You can have a nice plane of symmetry or major plane of symmetry through these two OH OH. As I said you have to take a two-dimensional structure fine. Now, the target molecule was this one which is basically a dihydroxy compound and having a naphthalene framework it is a naphthalene framework it is a tetrahedral naphthalene framework. And the target was this one and the starting precursor which was given to you is a naphthalene simple naphthalene molecule which is a cheap commercially available starting material.

Now, if you closely analyze the starting material is naphthalene the final product is basically not aromatic. So, you have to do a dearomatization reaction and to destabilize the aromaticity of the naphthalene. Now, can you name some reactions where a aromatic nucleus has been converted to a non aromatic compound? The very beginning of the reaction which will be which should come to your mind is a birch reduction. A birch reduction is principally very important reaction and probably during subsequent coursework, we will be talking this birch reduction in very detail.

Now, in a birch reduction, when you do a birch reduction, you will find this birch reduction is a pretty interesting reaction. And that will be a simple birch reduction of a

benzene system basically if you subject benzene with the sodium and liquid ammonia, the mechanism probably you can find it out you get a this kind of compound. And if the benzene has been substituted with electron releasing group, what will be the product; if the benzene is substituted with electron donating group what will be the product that is you just think it about what will be that relative product. If the benzene is substituted with electron releasing group like one methoxy, if it is subsume donating sorry electron withdrawing, it will be electron withdrawing group. One is electron releasing like O methoxy and electron withdrawing means CO 2 H kind of group and then you have to predict the which kind of product will finally form and that has a potential very good synthetic important.

Now, coming to the problem initial target was the molecule which was drawn here you have given naphthalene the subject to sodium ammonia or liquid ammonia. And then for naphthalene case, you basically will get this kind of compound. Now, the compound which was initial intermediate is a triolefin is a triolefin tri olefin. Now, if you see these olefins, the side olefin is disubstituted, because you are having two hydrogens here. This side olefin having again disubstituted, but this middle olefin the middle olefin is basically tetrasubstituted it does not have a hydrogen basically more of electron rich. And that is why when you are doing a diol reaction or some osmium tetroxide reaction dihydroxylation dihydroxylation. And the point is you have to do a dihydroxylation reaction with one equivalent of osmium tetroxide then you can absolutely control the geometry.

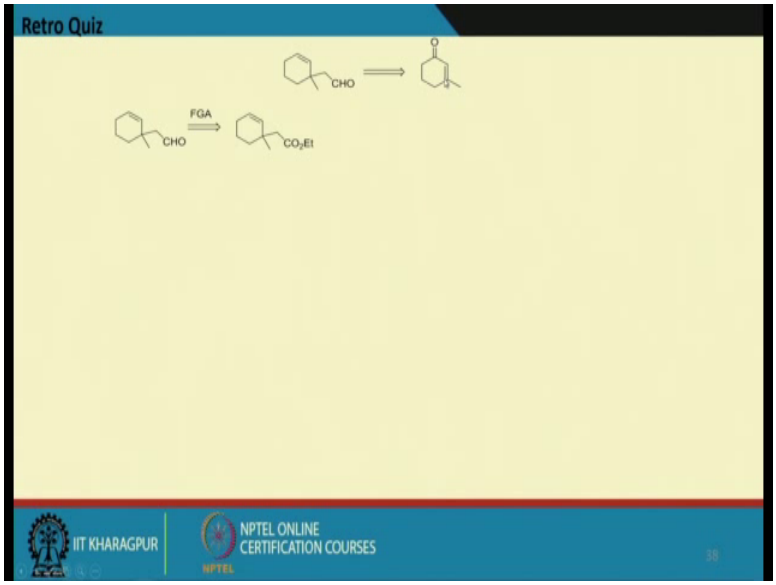
Now, if you do a dihydroxylation that basically do not give you the exact product, because here the relative geometries of OH and OH are anti to each other OH 1 and OH 2 are basically anti or trans to each other. And as you know the dihydroxylation often an gives a sis diol. So, probably a dihydroxylation would not be viable pathway as I said. So, you have to think about some alternative pathway, do not worry they are all alternative pathways. So, what you do you subject to these things with a m CPBA meta chloroperoxybenzoic acid do a corresponding epoxidation. And as this is a more electron rich olefin electron deficient oxidizing species all electron deficient oxidizing species will attack to electron rich species.

So, once you get the m CPBA epoxide opening will always give you antid diol by the standard Sn 2 condition, so that was pretty much known and now you will get the

product which is having anti geometry in the double bond. You can do a acid catalyzed cleavage even you can do a base catalyzed cleavage also, so that basically depending on your particular resources you can do a either acid catalysis or base catalysis. If you do a base catalysis means a stronger nucleophile (Refer Time: 23:14) chances are very high and in those cases normally you will get a always a antid diol, so that will solve the problem.

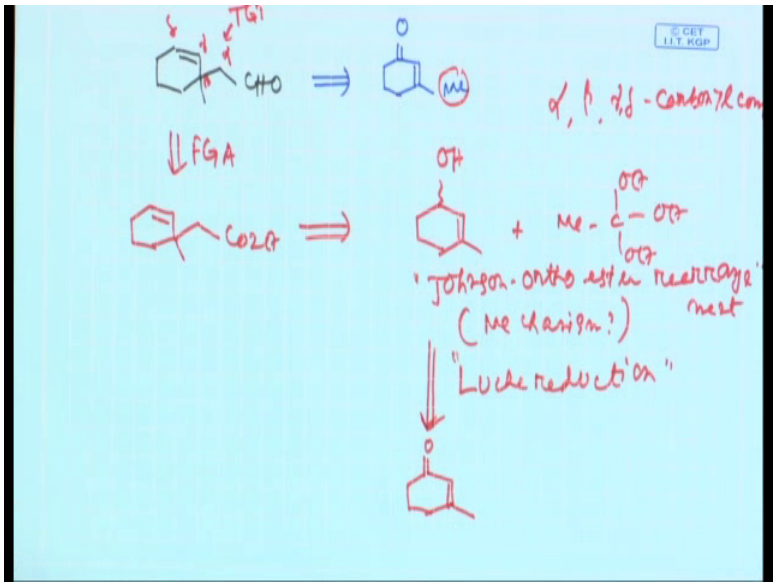
So, the particular transformation which is required here is a now I say transformation as a birch reduction is required and always also you required a epoxidation of a double bond by metachloro for a benzoic acid and then epoxide cleavage. So, these are the main transformation which we used eventually you can also said that the initial starting material does not have a functional the final target having a dihydroxy or bihydroxy functional group. So, it can be termed in that way also.

(Refer Slide Time: 24:03)



So, next we will be trying to figure it out a little bit complex system little bit complex.

(Refer Slide Time: 24:15)



Let us figure it out the structure. We have take a cyclohexane based compound. If you will see in the main lecture this one, and here you are having a corresponding the starting material, which was given to you is a cyclohexanone 3 methyl cyclohexanone. Do a close analysis, what are the groups are available to you. It is basically you are having a olefinic bond here and you are having alphabetical alpha generic carbon ion you are having a methyl this methyl might be this methyl. Now, this is it, this compound you can try to figure it out in a alpha, beta, gamma, delta. Basically this is a alpha beta gamma delta carbonyl compound that was the functional group analysis carbonyl compound.

For this compound this kind of compound let us do a simple straightforward analysis. We will be doing this analysis. We know that if you can convert this ester you can easily go back to the aldehyde by simple functional group addition. This is your target molecule fine. Now, here your main trick comes, how you can prepare this gamma delta unsaturated ester. The reaction which you were looking for is basically a very important name reaction named as Johnson-Ortho ester claisen rearrangement, Johnson-Ortho ester rearrangement. Probably in the next subsequent section we will talk about this rearrangement or this mechanism in detail, this mechanism we will be discussing in detail little bit later on.

So, once you are having these starting materials then you can do a Johnson-Ortho ester rearrangement and the exactly the reagent which is used here is trimethyl orthoacetate.

And once you have this Johnson-Ortho ester rearrangement this you basically can be synthesized from this starting material by a Luche reduction, it is again a transformation. Now, what is Luche reduction, what is Johnson-Ortho ester claisen rearrangement probably we can discuss all those things in the next week.

So, again we will see you in the next week, bye.