A Study Guide in Organic Retrosynthesis: Problem Solving Approach

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Lecture – 54
Stereochemical Strategies (Contd.)

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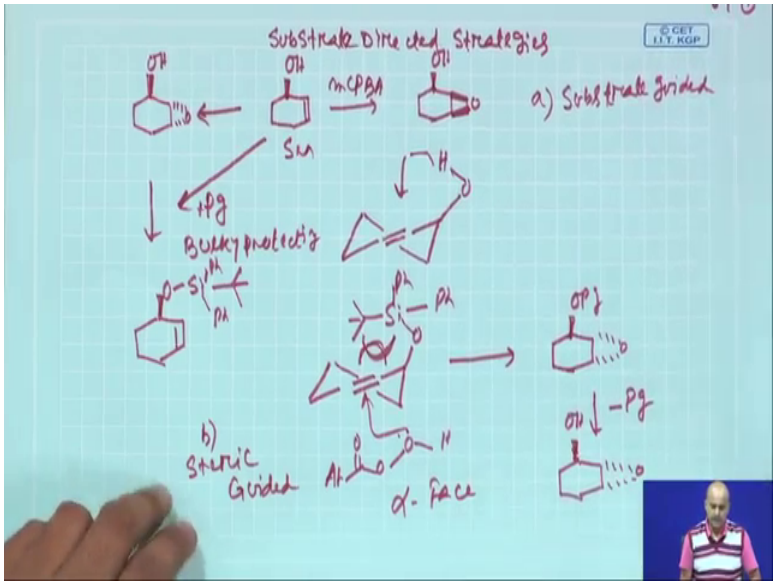

So, welcome students we are basically discussing stereo chemical based strategies and, on that particular point, we are mainly focusing on substrate directed strategies we said substrate directed strategies are those where, you have a pre existing stereo centres in your substrate. So, the pre existing stereo centre in the substrate that basically controls the incoming reagent, in such a way that your existing stereo centre is now determining from which phase the incoming reagent will attack.

So, we already explained that, if you have this kind of cyclo hexane in all system, in a as a beta alcohol you can control the epoxynation through a substrate directed mode and you can get this beta epoxyte, those 3 stereo centres you can basically fix. Now I am giving a similar kind of approach can you synthesize the other diastereomer starting from the same starting material, in a weird will be little bit seems to be little bit awkward because, substrate directed probably you cannot have the hydrogen bonding thing, initially what we said we said your substrate does have a well defined geometry in the

ground state, then your MCPBA the whole thing it is basically attacking on the top phase.

Now, here you are basically instructing that we need this epoxyte from forms to be the bottom phase. And this case the main way is first you make sure the alcohol is been protected with a suitable protecting group. The more bulky the protecting group it is better bulky protecting group.

So, what you do you first protect this compound as a bulky protecting group like tertiary butyl diphenyl silyl Si P h P h P h P h means that, now try to draw it is ground state half chair form, now you are basic basically having this Si this tertiary butyl is there, this phenyl this phenyl. The in earlier case that free hydrogen that basically makes the hydrogen bonding with the reagent so, here this free hydrogen is now missing and eventually this presence of this bulky silyl protection group effectively blocks the top phase.

So, then now MCPBA Ar C double bond O O OH will now effectively attack from this alpha phase and, this is very obvious you react with this fashion you get this alpha epoxyte. Now simply remove this Pg to get the require diastereomer which is desired. So, this kind of so, the initial approach is the first one where you have a hydrogen bonded, it is called substrate guided substrate guided, second one which is just now talked is basically a steric guided approach. So, these two parameter is very important and in one case you are having this hydrogen bonding instruction which basically directs the incoming electrophile in another case you are having this steric directed approach.

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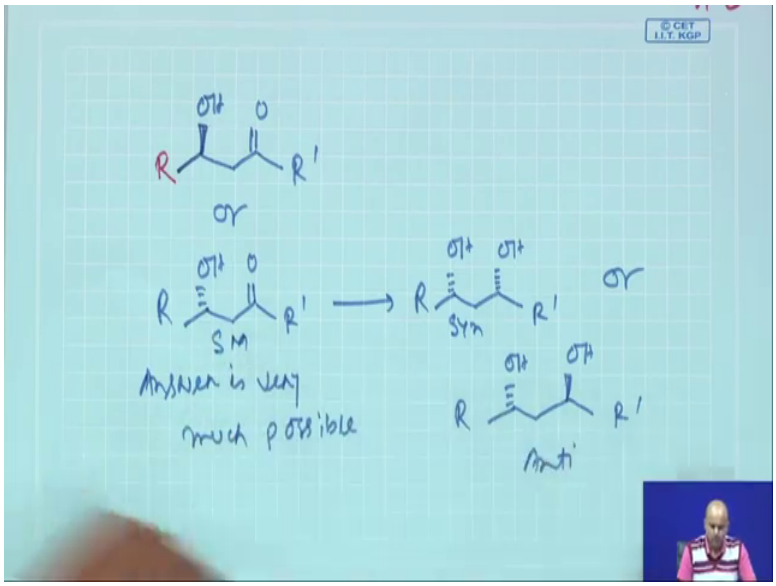

The substrate directed approach, next we will try to try to focus on a similar kind of problem which is also very interesting I am now saying that I am having this compound, or this compound any of this enantiomer pure compound. Now I am saying that is it possible from this compound to prepare a 1 3 dihydroxy compound either this or thus 1 case syn isomer another case is the anti isomer. So, is it possible I am saying it that syn and this is anti the answer is very much possible, the answer is very much possible very much possible and you have to take care of this initial configuration of this starting material.

So, now what I am trying to do, we will explain this scenario and this is basically example of a 13 induction.

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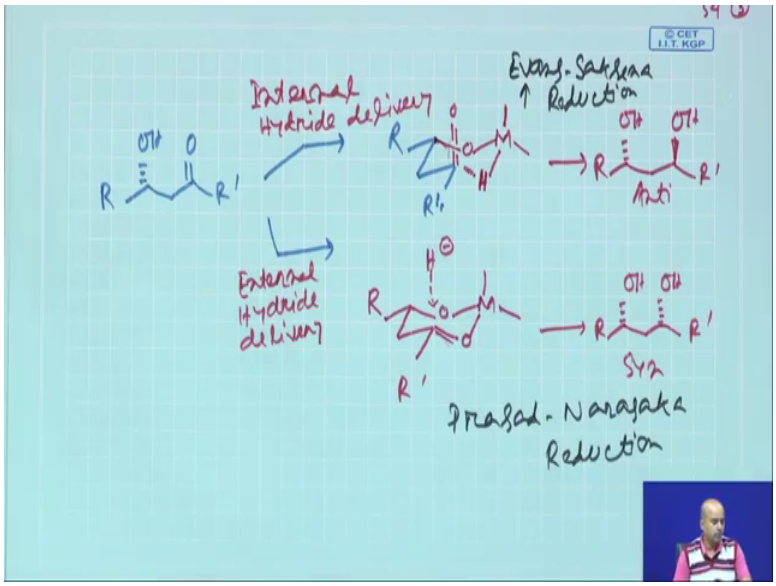

Now 1 to the starting material with then now right the starting material is so, you are basically trying to reduce this carbonyl, now this carbonyl is 1 2 3. Now existing stereo centre is 2 carbon away. So, is a 1 3 induction now, what I am saying that you basically device the reaction pathway, some saying that if the pathway it is follow a 6 member transition state and, where R 1 and R prime will try to having a equatorial kind of orientation, then you this OH we will put it here and, then I am saying if this OH is available for some coordination, with some reagent something like some reagent which will now simplify later on and, if this reagent is having a metal centre as well as hydride, probably these one can give you the this is the carbonyl ok.

So, I am saying that if. So, this is the compound it in here OH is below OH is below and, then you write the 6 member transition state, were R and R 1 is put in the most able equatorial form carbonyl, we fix it like this and then if this OH is available for this code reagent with metal centre I mean if you have a metal containing reducing agent, as well as this metal containing reducing reagent can give a internal hydride stores.

So, this hydride can only attack from this side and then the relative OH is this is below this is above. So, basically we will get the anti alcohol, this is we called internal hydride delivery, internal hydride delivery. The same line you may have a another scenario, what you can now design the carbonyl we now put it in this way, then put this oxygen here

and, then I say that if some reagents are here where carbonyl oxygen as well as alcohol oxygen both can coordinate.

Now, if you use a external hydride source this hydride will only have this option to attack. So, this is a external hydride; hydride delivery, in this case now the reaction goes both are syn this is below this is below. So, this is you get anti this you get syn. The first reaction the syn reaction now is known as Evans Saksena reduction it is a kind of a now very famous name reaction, the substrate directed reduction. The second one is now named as this external hydride delivery Prasad Narasaka reduction.

Now, the reagent system now will be talking about what are the reagents exactly you need to use.

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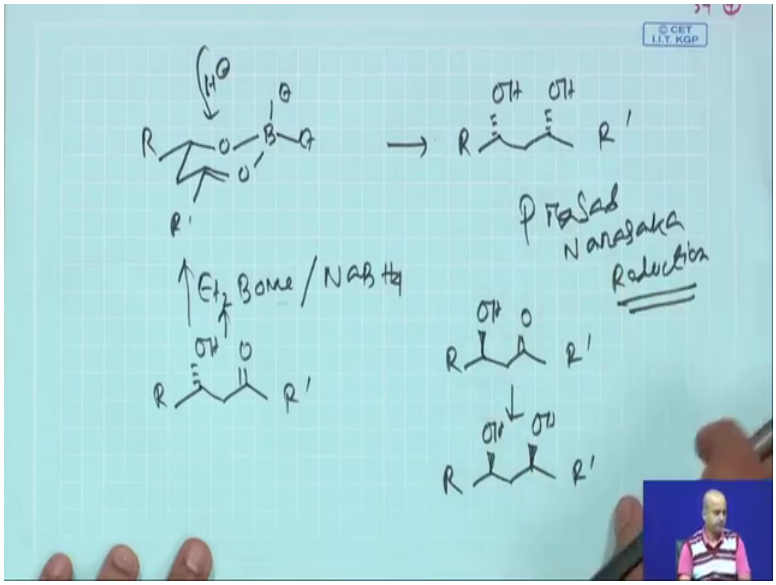

In case of the Prasad one, if you now draw the transition state again, the reagent system basically which was used say Et 2 Bome. Now this Et 2 Bome basically, Et Et say Et 2 Bome and sodium borohydride was used as a reagent, if you want to do the external hydride delivery for this reduction. So, now this reduction Et 2 Bome is boron 1 methoxy is there. So, this methoxy is replaced by this alcohol or this boron coordinates with this carbonyl Lewis basic basic site and this Et Et is there, now this NaB H 4 transfer this hydride from this phase. So, now you get the syn alcohol.

Now if you have the parent alcohol is this way, you will definitely get the other syn enantiomers whose stereochemistry or syn diastereomer basically you will get this, as obvious the same way the mechanism will operate. So, this is the Prasad Narasaka reduction, Prasad Narasaka reduction is very famous the only thing is you basically a take this corresponding beta hydroxyl ketoner, or alpha hydroxyl ketone whatever you required you react with Et 2 Bome sodium borohydride. Now these reagents are not chiral, substrate is chiral.

So, now this kind of transition state will operate and give you a external hydride delivery to give you a enantio pure compound, where one 3 asymmetric induction will takes place fine.

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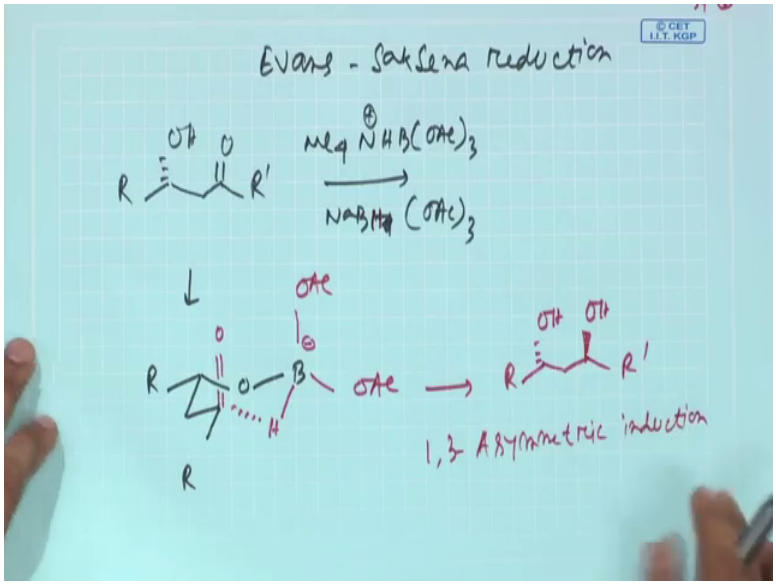

And now this next one this Evans Saksena 1 Evans Saksena Evans Saksena reduction is on the similar thing, only difference is you have a internal hydride delivery. The reagent which was now required should be producible or should be should be producing a hydride from internal sources.

Now, you basically use a tetra methyl sorry tetra methyl ammonium triacetoxy borohydride. So, Me 4 N plus or you can use sodium triacetoxy borohydride NaBH 4 OAC whole thrice NaBH; NaBH: so NaBH OAC whole thrice. Now the reaction basically goes through this kind of o a the same thing you put the oxygen here, the boron

is here now the carbonyl basically will here, now this boron is basically a negative charge here because, a tetra acetoxy borohydride.

And then it gives you this thing and one of this acetate was first replaced by this alcohol ok. So, then you are basically having a hydride, which was there in the initial reagent and, then you get the internal hydride delivery and you basically get the anti alcohol anti alcohol, and with in this particular case is very very useful and you get a absolute good stereo control absolute good stereo control for this kind of asymmetric induction that is a pure case of 1 1 3 asymmetric induction, pure case of 1 3 asymmetric induction.

Now our substrate directed approach probably ends here, there definitely many more examples, but please try to go through the assignments which will be supplying and try to get more knowledge from the assignments.

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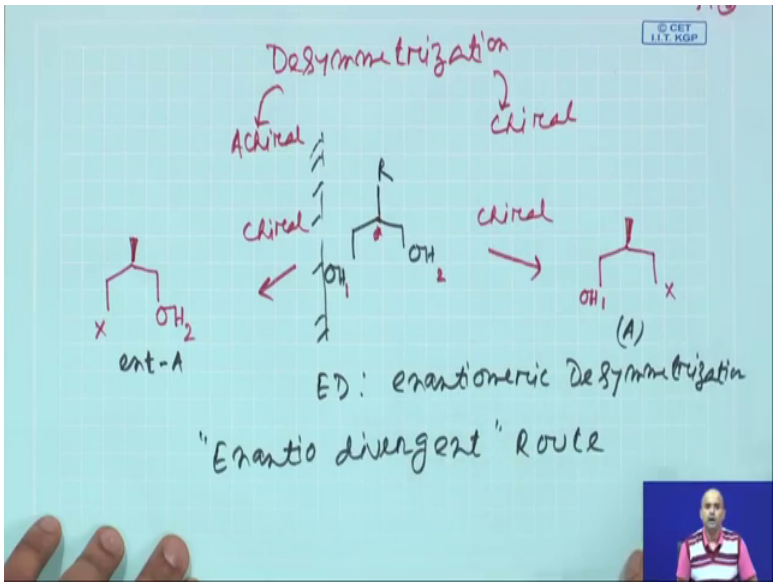

Next next guideline the stereo chemical strategies we said, will be now try to focus in what on desymmetrization, or desymmetrization we have earlier explained and at that time we only talked about achiral desymmetrization. Now we will be trying to focus it out on chiral desymmetrization, now desymmetrization is basically very important strategy, or you can find that if you having a molecule which can be a efficiently desymmetrized to give you 2 enantiomers, then it is absolutely useful we will come back to our simple example which we also earlier explained that if you have a compound like this, is a prochiral compound ok.

Now what I am saying that you have OH 1 OH 2 these are enantio topic, we explained earlier. Now I am saying that you try to first do some reaction in this OH 1 in a chiral fashion chiral fashion means this compound is a prochiral this compound is prochiral. Now I will try to put this prochiral compound in a chiral environment, same like chiral resolution or kinetic resolution takes place, what happen this OH 1 and this OH 2 are basically enantio topic.

So, they will they might interact with this chiral atmosphere in a different way, eventually just trying to give you the proof of concept probably the what exact reagent what a what exact catalyst system, is we are using it is only beyond beyond discussion of this particular this course work probably a very advanced level course work will help you, but and if you are if you wanted to know in detail, we can just supply use of study material.

Now, I am saying that you try to put a chiral environment for both this compound and, I am saying that one case OH 1 this enantio topic group reacts and one case this OH group reacts. Now if this compound reacts initially is a symmetric compound. Now you are basically having a this stereo centre now will be different. So, I am saying that this prochiral reacts and you get some compound which is now this. So, OH 1 reacts now in this case I am saying OH 2 reacts.

So, if OH 2 reacts now if OH 2 reacts you get this X and this OH 1. Now OH 1 and OH 2 basically is both are OH both are OH, now you try to analyse their relationship you can simply have a plane of I mean mirror plane, this 2 are basically enantiomer this 2 are ent, if it is ent A this will be simple a means enantiomer A and A are this a R enantiomer X O. So, basically this kind of reaction we called chiral desymmetrization. Now as this desymmetrization give you a enantiomeric compound, we call this a day enantiomeric desymmetrization enantiomeric desymmetrization.

Now enantiomeric desymmetrization sometimes also you guess very important, if you try to give you another terminology we will explain another terminology, which I am now saying is enantio divergent. Now this desymmetrization and enantio divergent are basically in principle very similar concept.

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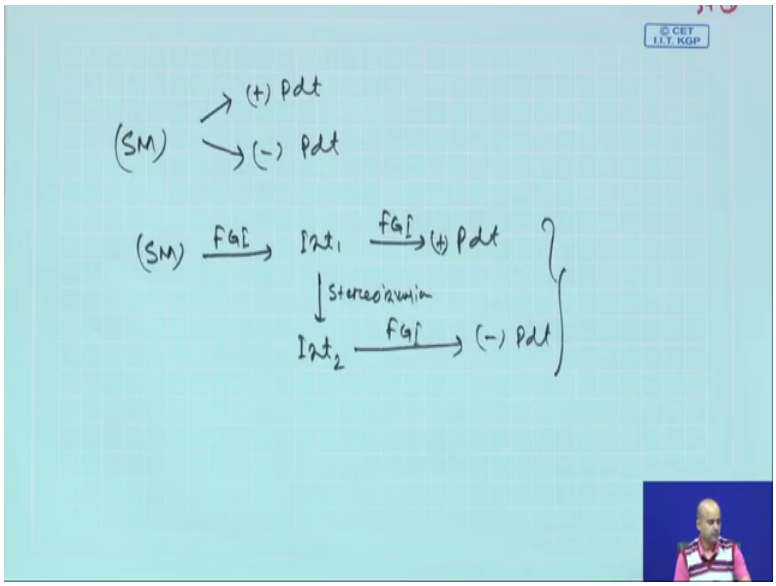

Now, what are enantio divergent route, the enantio divergent routes says that as the name implies diverge means this route is basically kind of a 2 different way, you start with a starting material you start with a starting material and, if you get both the enantiomers of a same product, then your route is called enantio divergent. Now in usually what was done you take the starting material. The starting material could be prochiral could be achiral, but as we are talking about desymmetrization it could be prochiral. So, you basically do a FGI do FGI you get some intermediate 1, you do another FGI you get the product, let say you get a plus product ok.

Now in this whole process if one of the intermediate, you can basically do some stereo chemical sense changing either by inversion, or by mutation, you may get another intermediate. Now this intermediate is basically will lead you to a negative or the minus product. So, in principle starting from same starting material, you can get both the enantiomeric product, that is why this is called divergent. And in principle this is very useful because depending on your need, if you need both the product both the enantiomeric product starting from a single starting material, you can basically reach to your final destination.

So, initially you will try to have a example to a very very simplified problem, I will say we will take a symmetrical compound, because the concept is desymmetrization.

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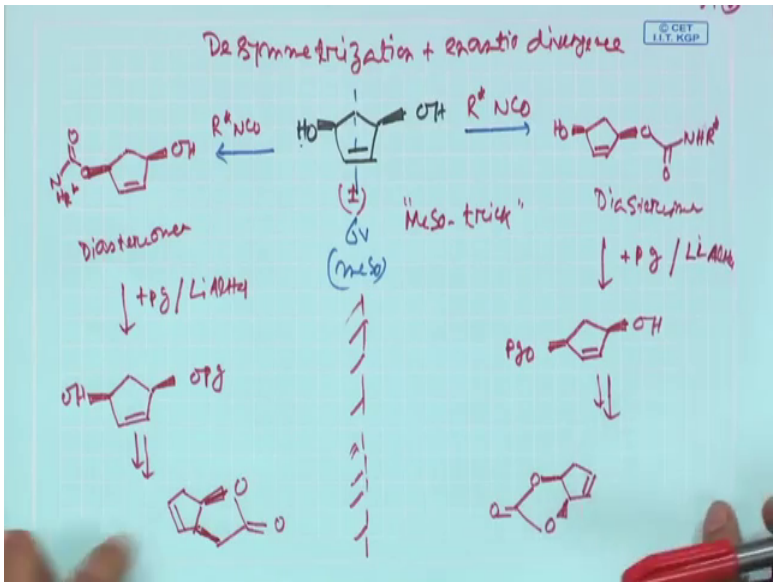

So, now this is a very nice example of desymmetrization coupled with divergent enantio divergent desymmetrization plus enantio divergent, the starting material which have taken is a recimacon. So, means the this isomer as well as it enantiomers are present. Now if you see this compound this compound is having nice sigma V, it is basically a meso compound or internally complete settled normally meso compound, we said those are optically inactive probably you cannot use meso compounds in some synthetic transformation because, they are regarded as a achiral, but you see closely this 2 OH groups are basically enantio topic to each other, because they are enantio topic, because they have a mirror image symmetry in between.

Now what I am saying already know that c d a technique, we have earlier explained ok. Now I am saying as both the OH or enantio topic and their reactivity's are almost similar, we will react with a chiral isocyanides with this one as well as this one fine. So, what will now get so for if you react with this OH we basically get O CO NH R prime R is basically chiral centre and, then for this one also you get the O CO NH R prime in your reaction mixture both the compounds are present ok. Now if you try to analyse this is the unique desymmetrization reaction because this compounds are now diastereomer because you put a chiral centre here R. So, these are no longer enantiomer ok.

So, enantiomers initial enantiomers or meso compound are now converted to the corresponding dash tumours. So, this is now Dia this are basically having diastereomeric

relationship diastereomer and diastereomer to each other, now as a we said that diastereomers having different physical properties. So, they can be in principle separated out. So, fine so, what we next do we do a simple protection here, OH you put a protecting group here we put a PgO, and then remove this carbonate while lithium aluminium, lithium aluminium hydride, basically get this OH.

And then here also it is the same thing you do a protection at this point and, you get the lithium aluminium hydride reduction now see what is this compounds are basically now mirror image. So, starting from a meso compound you have separated out this meso compound through a chiral desymmetrization, or a enantio selective desymmetrization just by making a chiral derivative reagent. So, this is a very useful technique and eventually this whole pathway can eventually lead to a series of reaction you can basically think about and, probably you can take it as a home assignment, how both of this enantiomer can be converted to this lactone from this compound, you get this lactone and from this compound you get this lactone.

And actually this lactones are basically mirror image to each other. So, this entire pathway is desymmetrization as well as divergent and actually this particular technique is often named as meso trick, meso trick means utilization the meso compound and it is internally compensated chirality to make to diastereomers, now this compounds are in reality these are not diastereomers these are basically pseudo enantiomers because, if you clip this NH R these are basically separated, the only thing is you need to react with a chiral reverising agent. So, that the diastereomers can be easily separated by physical separation, then you do a simple protection. So, you can basically get this 2 enantiomers.

So, this is a pure divergence on this method is called meso trick and in principle you can basically convert, this compounds to this lactone, this compound to this lactone, this lactones are enantiomeric to each other. Now I am not explaining it, but only one example I can one case I can show you the example how you can do it because the reaction we already know, I am saying that ok.

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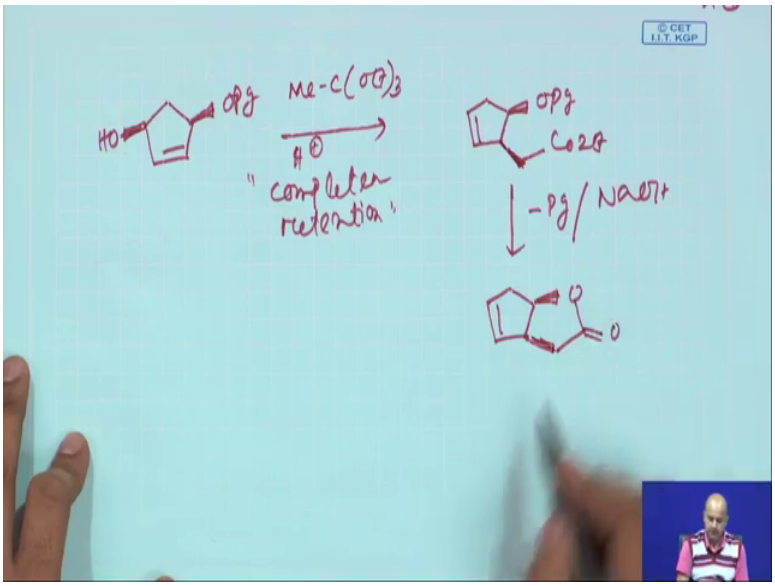

This first case you take a this OH this compound is aralic alcohol, the reagent which I will be now using all of you probably know, it this reaction we have explained many times, we will be using a Johnson Orthoester Claisen rearrangement and, Johnson Orthoester Claisen rearrangement the information it is a substrate directed reaction the 3 C sigmatropic reaction, whatever stereochemistry of the alcohol is having when you make this new carbon carbon bond by the Johnson Orthoester reagent basically you will get a this. This things after this Johnson Orthoester rearrangement and, this carbon carbon bond is now going to be formed newly and, this stereo centre is basically whatever stereo centre is there is alcohol has been retained is called complete retention of stereochemistry. Now as I am not explaining the mechanism of recyclic reaction and the stereo chemical features, we are not discussing it, but just remember.

So, once this has been done is very simple you remove this Pg hydrolyze this CO 2 e t by NaOH you can basically get one of this lactone which was here on the other enantiomer, you can get the same reaction sequences. So, basically what we did we take the meso compound, we take the meso compound and, we assume that the meso compounds have similar chemical reactivity not assume is sure, this compounds will have similar chemical reactivity.

Is basically we just reacted with this chiral derivative reagent to get the diastereomer, we separated out the diastereomer and, then we get this 2 compound which are basically

enantiomer to each other. So, meso compounds chirality has been internally compensated, but we use that internally compensated chirality to separate out to enantiomers, and this is basically a enantio divergent approach a through a desymmetrization pathway is very useful and you can we can subsequently see how this divergent is very helpful in our subsequent pathway.

So, will basically continuing our discussion on enantio divergent and, we will do it in the next lecture. So, please go through the slides and, have a clear cut idea about this divergent and try to go through the assignments, which will be supplied with this lecture. So, till then have a good time and goodbye.