A Study Guide in Organic Retrosynthesis: Problem Solving Approach.

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Lecture – 57
Stereochemical Strategies (Contd.)

So, welcome back students last class basically.

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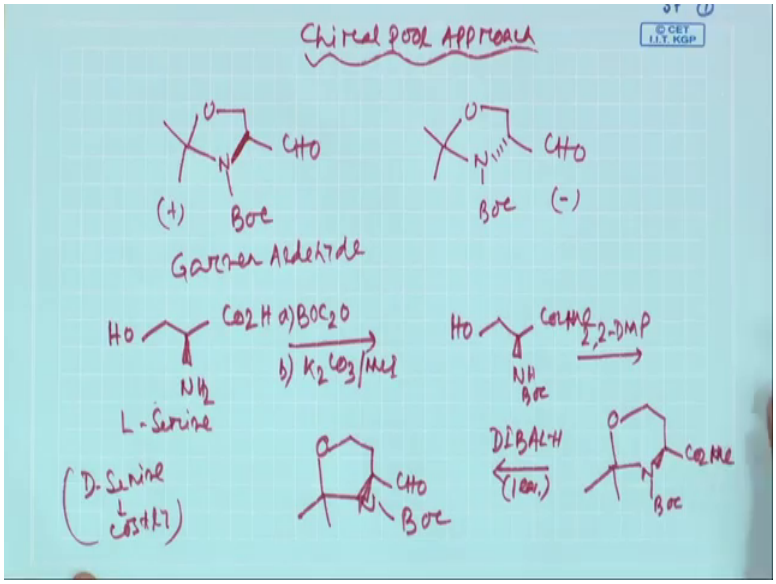

We were discussing the chiral pool approach and we said that we will be trying to complete this stereochemical strategies, and hopefully today we will we will be able to do it we will be just discussing the chiral pool approach and then we will give you one example were you start with the achiral compound, so and how to bring or how to create new stereo centres on that one.

Now, this particular particular problem which I am now going to pick up, it basically involves a kind of kind of divergency, but divergency is basically generated from the starting materials not with the reagent based divergency, this particular compound is a very good building block is named is garner aldehyde. Now garner aldehyde both the enantiomers you can you can prepare and you can use those as a very good synthetic intermediate. Now I have drawn both the enantiomers of garner aldehyde I say this is plus this is minus in reality I do not know what exactly this is, but this is plus and this is minus just the assumption.

Now, I am saying that this garner aldehyde can be prepared from amino acid as a chiral pool, first if you try to correlate probably you can figure it out this garner aldehyde can be easily made from a simple amino acid which is nothing, but a L serine because we said L serine L amino acids are plentily available in the nature these are very cheap easily commercial available material

Now, first we will be using a reagent which is often used for amino acid or Amin protecting agent, it is called BOC and hydride now BOC and hydride poly you can see structure BOC and hydride was usually used for Amin protecting group, and a mild base like potassium carbonate was used. So, initially if you use this one you get this N H BOC and CO 2 H fine.

Now, this as a acetonide protection is there in the target molecule. So, it was simply tethered with 2 2 DMP or 2 2 dimethoxy propane to basically, protect the alcohol and the Amin group as its acetonide the BOC remains same. And then you having this CO 2 H CO 2 H, now eventually if you use potassium carbon methyl iodide here, it will basically convert this carboxylic acid to carboxy methyl ester this also required.

Now, simple thing is you do a selective reduction with dibal which can reduce to ester to its corresponding aldehyde which is very well known in the literature. So, what exactly you are now having you are having one enantiomer of this garner aldehyde can easily be prepared starting from L serine.

Now I next question is for synthesizing the other enantiomer in principle you need D serine where the stereo centre has been inverted, but I am saying that D serine is extremely costly D serine is very costly, costly. So, can you use a similar kind of L amino acid because L amino acids are very cheap in nature my answer will be yes you can definitely do it, but if you know the structure of the amino acid in true sense.

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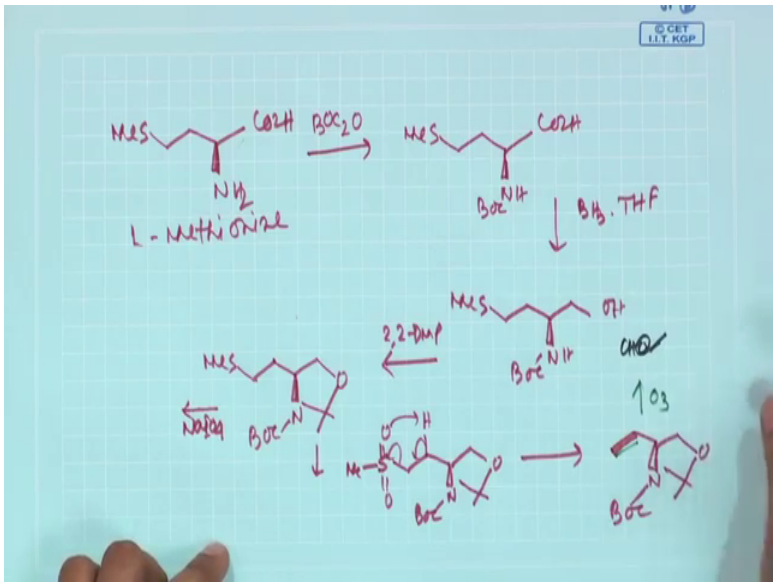

I am now trying to draw the structure of a another amino acid which also belongs to the L family, the amino acid which I am now drawing is named as L methionine is also L amino acids naturally occurring is very cheap.

Now, L methionine and L serine now if you do the structure analysis this is L methionine, and this is your L serine; now only difference is everything is similar you are having extra a semi group, now why this a semi group is required now I am basically discussing. So, first this L methionine you do the similar kind of reaction first you protect with BOC and hydride. So, you get this part is there your N H BOC and your CO 2 H.

Now as we need to construct the enantiomer, if you try to now go back to your original divergence concept I said that if you have a same starting material you want to create divergency you first pick up the left hand side keeping the right hand side intact in other operation you first do the right hand side reaction and keeping the left hand side intact. So, we will try to follow the same principle now here the carboxylic acid is there which now will reduce with a boron THF, and this reduction will be will give you the primary alcohol here.

Now, this primary alcohol will be now protected as it acetonide with 2 2 DMP. So, 2 2 DMP same way N BOC and this things, now in earlier case L serine already having hydroxyl group at the left hand side. Now here the hydroxyl group we are creating at the

right hand side to close the ring, now only thing you need to now convert to this group to a aldehyde. Now there are 2 carbons you basically need one carbon means that somehow down the line you need to cleave one carbon extra, now here what I do I will oxidize the sulphur with oxidizing agent sodium periodate to convert this sulphur to a highest oxidation state of sulphur to a sulfoxide N BOC.

Now, sulfoxides are very strong electron withdrawing group and this kind of sulfoxide elimination also available in the literature probably similar kind of reaction we explained when you talk about selenoxide syn elimination. Now this is also similar kind of reaction it basically goes through a 2 3 sigma tropic rearrangement and then basically give you a simple elimination. So, you now create a double bond here.

Now, this double bond definitely you can easily chop through a ozonolysis oxidative cleavage. If you do this ozonolysis you will basically get C HO at this end, we will write it in the separate page to have a better view, so you have a compound like this N BOC now what you do you just do a ozonolysis.

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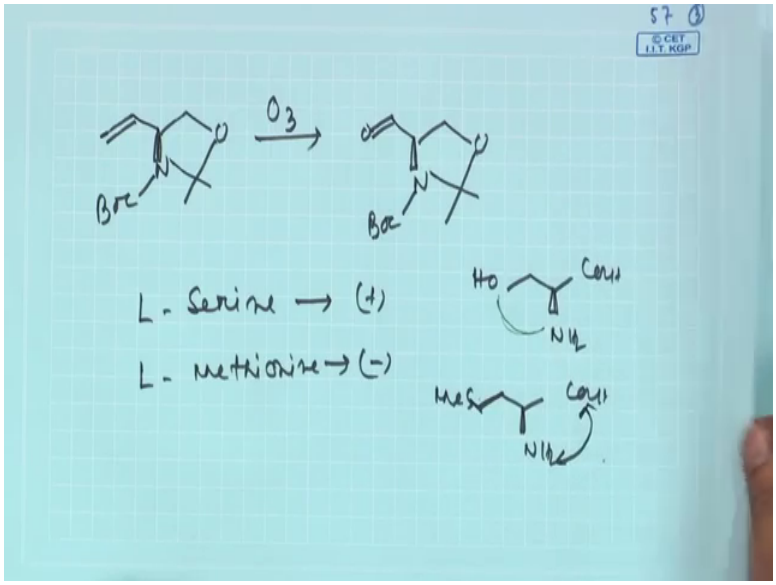

So, basically having this compound N BOC, so this is nothing the enantiomer of the garner aldehyde. So, some same starting material are similar kind of chiral sense, so you have now I saying that L serine gives you plus enantiomer and L methionine gives you the minus enantiomer.

So, the basically the divergency is coming from the starting material structure, though the absolutes absolute configuration on the stereogenic centre remains same the starting material serine is having this structure the starting material methionine having this structure. So, what we do we first in the case of serine do the acetonide protection at this stage, now in case of methionine we convert this CO 2 H to C H 2O H do this acetonide protection here.

So, this is your left hand side reaction this is right hand side reaction, so that is why we basically created the handedness in the final product the handedness is basically nothing, but your creation of 2 different enantiomers, but also you need to be very careful about the FGI, which will eliminate the SME group in from of sulfoxide then you do ozonolysis.

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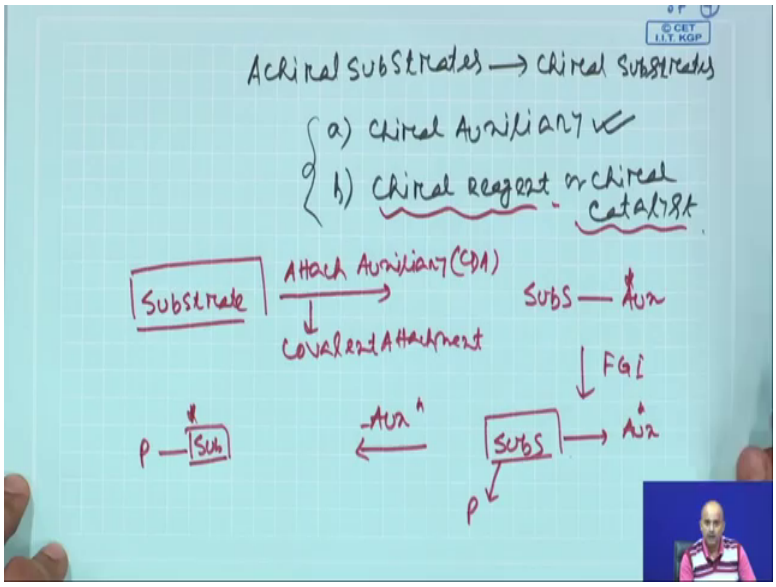

So, this kind of divergency is quite possible if you do a close analysis of the starting material structure, in the in the final part of this absolute asymmetry synthesis we will talk about if you having a achiral substrates, achiral substrates what is the usual way to create chiral substrates or to create asymmetric centre.

There are numerous ways the very earlier approaches or steel is very popular is chiral auxiliary based approaches, and the other things are basically you react with chiral reagent or chiral catalyst; this is the 2 principle ways you can start with achiral substrates and synthesize a chiral substrate. Now we will try to focus it at only the chiral auxiliaries

because we do not have enough time and for people who want to put more emphasis on this one can attend a basically advanced course on asymmetric synthesis. So, chiral auxiliary I will try to give you a schematic view if you have a substrate, which I am saying is achiral.

Now, first this substrate was you attach a auxiliary or a basically it is kind of a you basically do a derivatization with the help of C D a is basically extension of C D a technique, through a covalent attachment covalent attachment. Now this C D a having a stereochemical centre or stereo centre, now due to presence of this stereo centre now your new substrate is basically having substrate as well as auxiliary. Now this is basically chiral, now you do the necessary FGI, now this FGI will be doing it on the substrate part now the auxiliary part having a stereo centre this stereo centre will basically control the formation of the new stereo centre.

So, now, we will see that your substrate will be having some new bond formation and then the auxiliary remains here and now you get rid of the auxiliary. So, basically now we will be getting your substrate has a new bond. So, this is now substrate becomes chiral. So, starting from achiral substrate you can basically end up with a chiral substrate is a nothing, but extension of a chiral derivatization agent, so these things we called a auxiliary. Now, auxiliary similar like your if you have a if you have a C D a we said the auxiliary.

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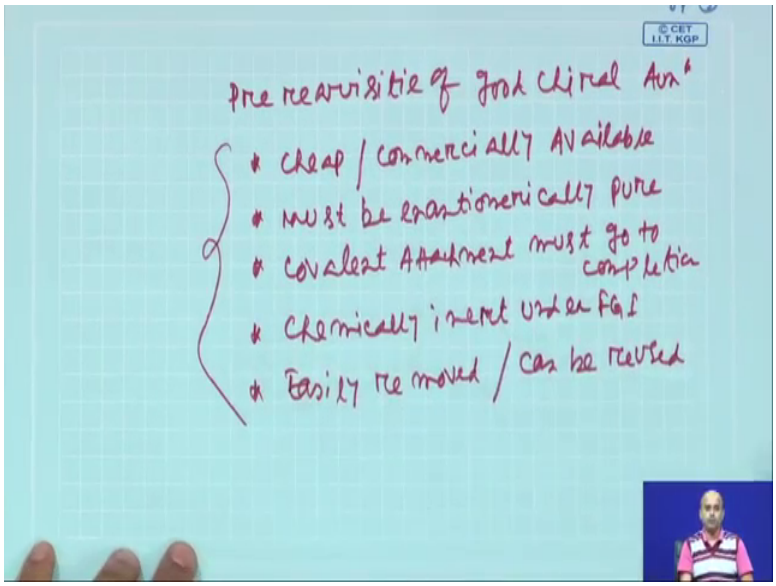

Have certain prerequisite the what are the prerequisite to be a good auxiliary, prerequisite of a good chiral auxiliary the prerequisites are this must be cheap and or commercially available or you can even make it in the lab, but it should be cheap ok.

The second point is very important it must be enantiomerically pure and it should be available in single enantiomeric form must be enantiomerically pure the covalent attachment by which you can basically attach the substrate of the auxiliary the covalent attachment must be complete.

Now the reaction should undergo completion covalent attachment must go to completion this is one of the essential criteria and finally, the auxiliary must be chemically inert under the reaction condition chemically inert under the FGI condition under FGI. And then the auxiliary can be easily removed easily removed and if necessary can be reused. So, these are the main five criteria's which we also discussed about the C D a your auxiliary suit fulfil this certain criteria, now next will be taking a example and we will try to try to try to formulate how this auxiliary is helping.

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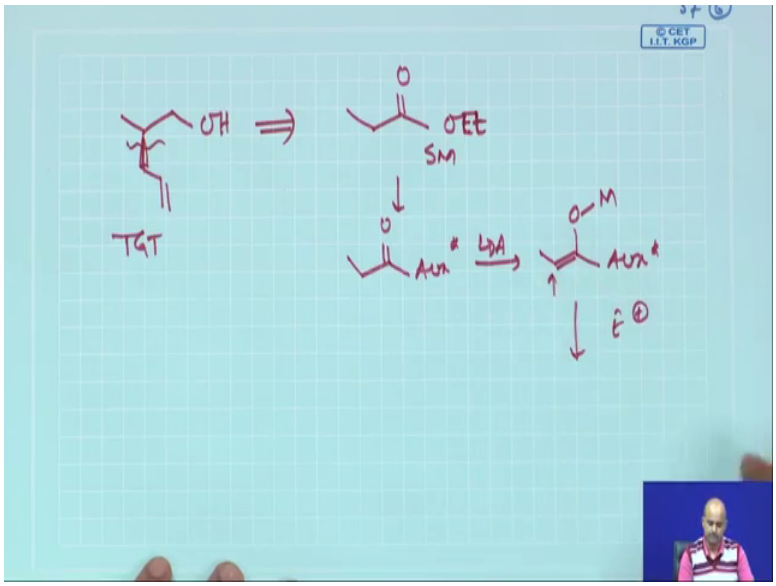

We say we will be trying to synthesize this compound; this compound the starting material is given to you, starting material what I am giving this ester. So, ethyl propionate ethyl propionate I am giving to you starting material, so it is a achiral compound. So, what basically you need to do you need to put a carbon, carbon bond here in stereo control fashion.

So, now your entire thing is probably will be now I am doing the doing the retro I am saying that, now if you take this starting material and if you can fuse it with a chiral auxiliary this auxiliary is there. Now this auxiliary is there, but the initial starting material have been carbonyl functionality. So, enolate chemistry can be used now if I treat with a base this compound will basically give you a enalote O metal and auxiliary remains here.

Now if you react with a electrophile this electrophile will now try to attack to this s p 2 trigonal carbon which is basically flat at this things you can attack from this top phase or bottom phase which could be re or psi depending on the C I P nomenclature, now I am saying that this auxiliary has its own chiral bias. So, auxiliary will now dictate from which phase the incoming electrophile is approaching. So, now, what auxiliaries are people mainly using there are many auxiliaries reported in the literature I will try to pick up one auxiliaries which is very often used named as evans oxazolidinone.

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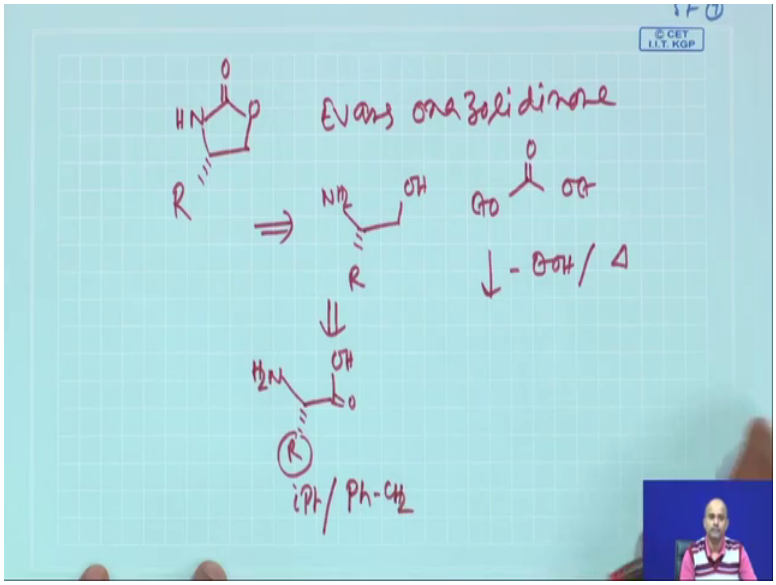

The evans oxazolidinone having this kind of structure, evans, oxazolidinone. Now as I said this oxazolidinones are commercially available or even you can make in the lab this oxazolidinone are best prepared starting from this corresponding, amino alcohol you react this amino alcohol with diethyl carbonate or other reagents you can basically remove to equivalent of ethanol by simply hitting to get this oxazolidinone this amino alcohol you can simply get it from the corresponding amino acid ok.

Now, once the oxazolidinone was done this R group should be little bit bulky. So, normally you prefer isopropyl means the blaine amino acid or P H C H 2, which is phenyl aladeine usually paper this compounds are commercially available, so now, how do you do the synthesis is lets first make this oxazolidinone.

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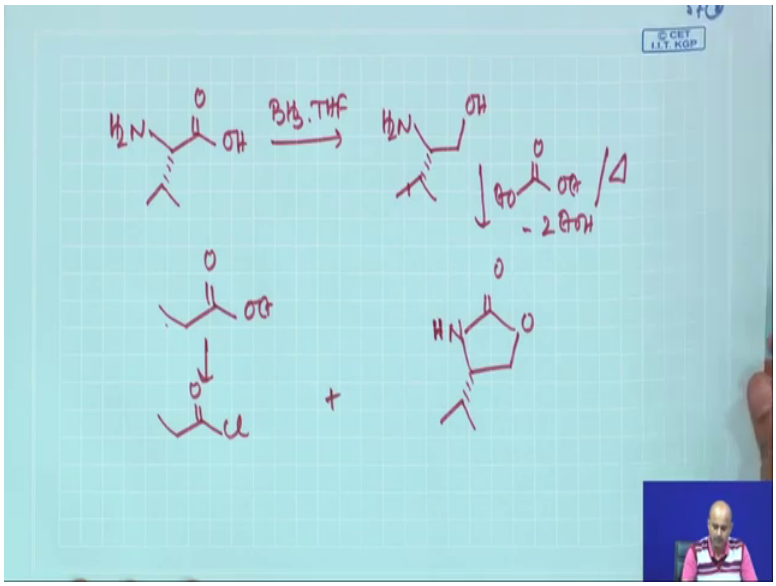

So, first we take this blaine, blaine carboxylic acid group first need to be reduced. So, do a boron reduction you basically get the corresponding amino alcohol. Now as I said react with the diethyl carbonate heat it 2 equivalent of ethanol will be releasing and you get this as this oxazolidinone, the oxazolidinone cyclic structure and the covalent attachment will be now possible through this mite nitrogen.

So, now, your compound is having basically I will I have given you a propionate this propionate you can easily convert it to corresponding propanel chloride. Now, chloride and Amin can easily be coupled easily be coupled. So, once you couple this chloride and Amin in presence of a base you can basically get.

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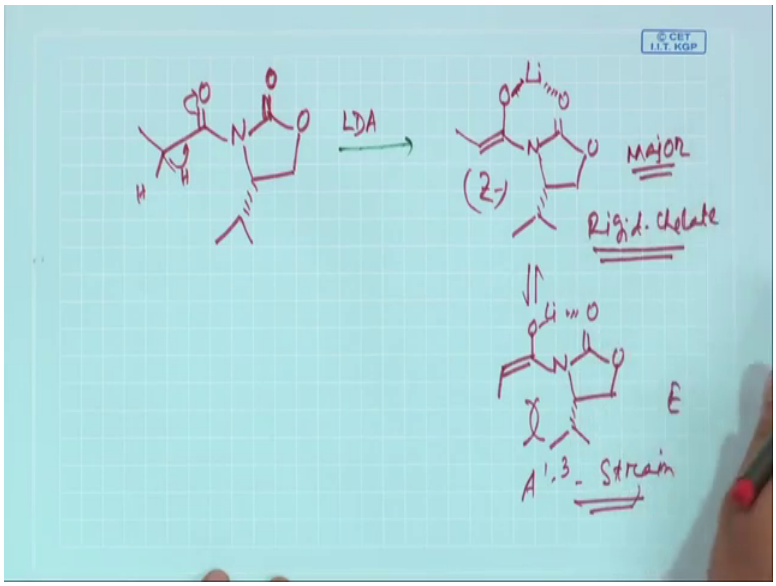

This CO N CO O this things, now oxazolidinone the structure has been very judiciously chosen it also fulfil certain other criteria. Now what I do you tray to it a base like L D A to abstract the hydrogen one of the hydrogen to generate the enolate. So, you will be now generating the enolate you have this O L I, now this oxazolidinone seems to be in a cyclic chelated form with this O L I this O L I basically makes this rigid chelate. So, this rigid chelate is very important.

Now, you can also think about having a possibility of another enolate in principle like this. So, one is basically Z this is oxygen (Refer Time: 23:38) this is Z enolate and this is E enolate, O L I thing. Now I am saying that normally z enolate basically forms in a predominant fashion because in case of e enolate you have a severe allylic 1 3 strain, allylic 1 3 strain if you are familiar you can understand. So, allylic 1 3 strain basically makes your Z enolate more predominant or major enolate now you have this, Z enolate in this reaction mixture.

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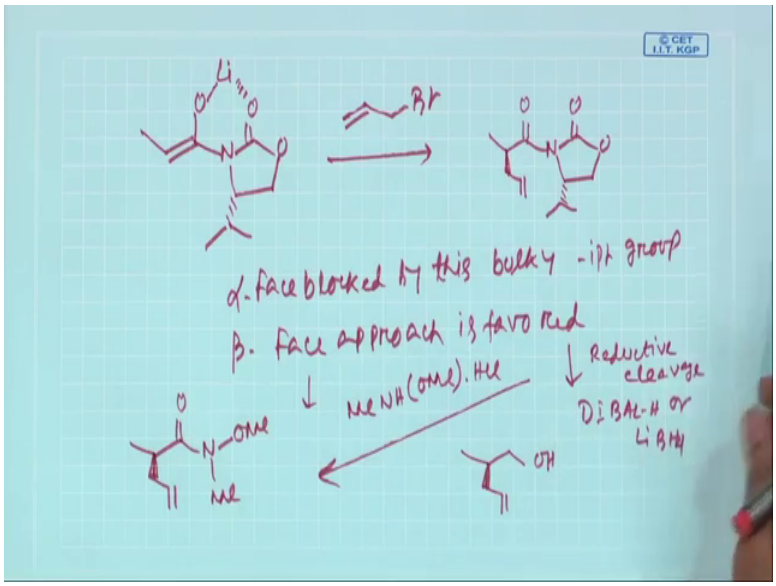

N C double bond O O lithium, now react with alyl bromide as your electrophile now see that this isopropyl globins oxazolidinone blocks this bottom phase. So, or the alpha face was basically blocked by this bulky isopropyl and that is very important. So, they your incoming electrophile only will get the beta face approach, now we can this explanation will be quite clear if you use a simple Bollen stick model. So, beta face approach is now favoured and then finally, if you now react this things you get you get this compound, now as I said the next prerequisite is your auxiliary removal.

So, auxiliary removal can be done by numerous ways the best way you can do a reductive cleavage you can do a reductive cleavage, reductive cleavage means you treat with dibal you can basically get the corresponding alcohol you can treat with same dibal or lithium borohydride you can get this compound, there also other ways you can cleave it, I am just giving you another approach you can treat this compound with this our old, old friend Weinreb Amin.

Now, once you treat this compound it is Weinreb Amin that will cleave to give you this Weinreb amide, now this Weinreb amide give you much more flexibility you can basically now convert this Weinreb amide to react with some other nucleophile so, that if you in your synthetic exercises if you need to put some other functional group.

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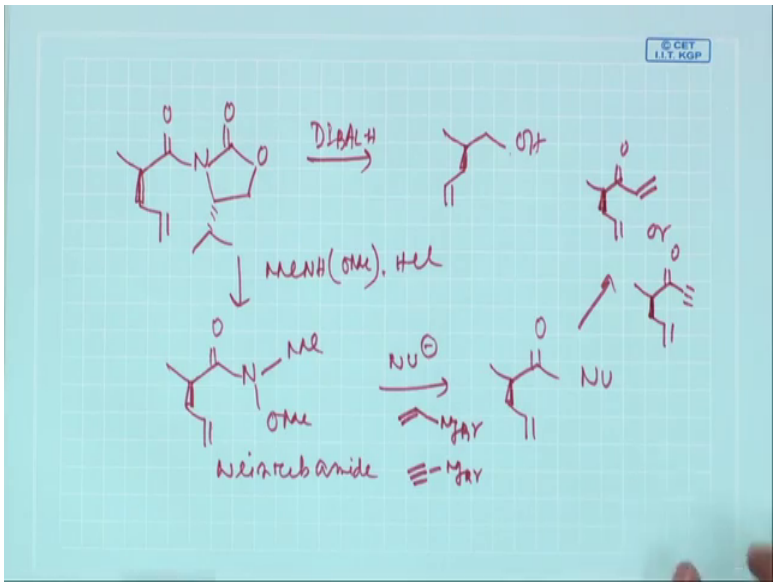

So we are basically discussing how this, oxazolidinone can be cleaved in a efficient way we say that reductive cleavage is very well known dibal or other things are can easily be done that will basically give you our target molecule that is fine. Now I said you can basically cleave it with the weinreb Amin like MENHO, MEHCL salt and then this cleavage will basically undergoing I mean this will basically undergoing transamination kind of reaction. And it will give you NME what is this, your weinreb amide now this weinreb amide basically react with any simple any profile.

So, that if your final target now has to be a this kind of compound. So, this kind of nucleophile could be your vinyl Grignard, could be your acetylenic Grignard and based on this you can basically get compounds like this kind of vinylic ketone or this kind of propargylic ketone based on your desired requirement. Now, the stereo centre which is our main target can be fixed very efficiently with the help of evans oxazolidinone methods.

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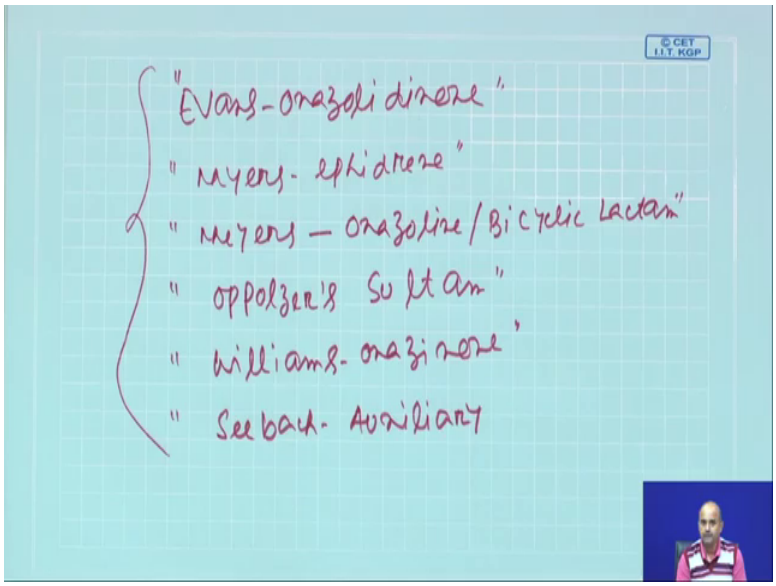

Now similar kind of auxiliaries are very old in the literature were not taking about, but I am just give you a couple of name evans oxazolidinone we have just discussed, there are reports which named as Myers ephedrine or pseudo ephedrine, based auxiliaries, then Meyers oxazoline these are not same Myers this is Myers this is Meyers Meyers oxazoline as well as bicyclic lactam.

Now, we are not talking about these auxiliaries due to time constraint and this is beyond of our scope this also have oppolzers sultam. So, there are many auxiliaries which are reported in the literature, there are auxiliaries named as Williams, Williams of oxazinone, oxazinone this is auxiliaries which probably you need to find it out in the literature there are see back auxiliaries. So, all the auxiliaries basically working in the similar kind of similar kind of principle you need to have a covalent attachment first and then you do the FGI, then you remove the auxiliaries the auxiliaries all having a in built chiralities. So, our stereochemical strategical stereochemical strategies ends here.

Next lecture will try to figure it out after all we will take a medium sized complex molecule. It is a natural product till now what are the strategical disconnection we have talked about we will try to apply those knowledge's and then we will see how a real problem can be tackled, we will take a real example of a natural product though in the study of this course we have talked about few natural products, now you take a real

natural product we will try to analyse through the knowledge's which you have acquired during our discussion. So, have a good time and see you in the next lecture.